ONCOLOGIC DRUGS ADVISORY COMMITTEE
BRIEFING DOCUMENT

NDA 21-600
Marqibo® (Vincristine Sulfate Liposomes Injection)

Indication : Treatment of Patients with Aggressive Non-Hodgkin's Lymphoma Previously Treated with at Least Two Combination Chemotherapy Regimens

Oncologic Drugs Advisory Committee
December 1, 2004

Inex Pharmaceuticals Corporation
(co-developed with
Enzon Pharmaceuticals Incorporated)

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

EXECUTIVE SUMMARY

Inex Pharmaceuticals Corporation (INEX) and Enzon Pharmaceuticals Incorporated (Enzon) are seeking an accelerated approval for the use of Marqibo® (Vincristine Sulfate Liposomes Injection) (VSLI) to treat patients with aggressive non-Hodgkin's lymphoma (NHL) previously treated with at least two combination chemotherapy regimens.

Unmet Medical Need

The incidence of aggressive NHL in the US is increasing and it is estimated that approximately 30,000 new cases will be diagnosed in 2004. At first presentation patients are generally offered CHOP-based combination chemotherapy, with the inclusion of rituximab for patients with B-cell disease. At first relapse the preferred treatment course includes high-dose chemotherapy with stem cell transplant. After second relapse there are no standard treatment options and patients have a very poor prognosis. Based on independent US market research, the prevalence in 2001 of patients with aggressive NHL being treated after 2 or more relapses was 10,000-15,000 patients.

As multiply relapsed patients usually have compromised bone marrow reserve from previous cytotoxic therapy and from the disease process itself, they have a very limited ability to withstand further myelosuppressive chemotherapy. Therefore, a relatively nonmyelosuppressive drug with good palliative efficacy would be of significant benefit for patients with multiply relapsed or refractory aggressive NHL.

Product Rationale

VSLI is a novel liposomal formulation of the cell-cycle-specific antineoplastic agent vincristine sulfate. In nonclinical studies, extending the duration of exposure to vincristine has been shown to increase antitumor activity. VSLI provides longer drug persistence in plasma and both higher and prolonged vincristine concentrations at tumor sites. This is the result of extravasation of the liposomes through "pores" present in immature tumor neovasculature and slow release of the encapsulated drug. These mechanisms provide an increased duration of drug exposure to tumor cells. In nonclinical studies VSLI shows increased antitumor activity compared to equivalent doses of vincristine in a wide range of tumor models, including lymphoma models.

The clinical development of VSLI has focused on establishing improved efficacy by maximizing dose intensity. While conventional vincristine is administered at 1.4 mg/m^2 every 3 weeks and the dose is often capped at 2 mg, VSLI is administered at a dose of 2 mg/m^2 every 2 weeks without dose capping. This represents at least a 2-fold increase in dose intensity for VSLI.

Clinical Efficacy

The two studies conducted to establish the efficacy of VSLI are the largest trials reported for patients with multiply relapsed aggressive NHL; primary data are provided from 119 patients in Study CA99002 (pivotal Phase IIb study) and supportive data are provided from 92 patients in Study DM97-162 (Investigator-sponsored Phase IIa study). Both of these studies were single-arm studies; as agreed with the FDA, the pivotal trial conducted without a concurrent control was considered to be acceptable to support an accelerated approval as it was acknowledged that there is no standard therapy for this population. Conventional vincristine is not typically used as a single-agent therapy in aggressive NHL and the physicians INEX approached were unwilling to conduct a trial in which patients would be randomized to single-agent conventional vincristine as a control arm. In the

Phase IIb study, the protocol required that patients had histologically confirmed aggressive NHL according to the WHO criteria and they had received at least two prior combination chemotherapy regimens, one of which must have been anthracycline-based. No limit was applied to the maximum number of prior regimens or to age. Objective response rate was the primary endpoint, with response defined according to the International Workshop Response Criteria for NHL. An Independent Review Panel (IRP) provided the primary efficacy evaluation in the Phase IIb study.

The majority of patients in both studies had extensive disease and a poor clinical prognosis and the goal of therapy was palliation. In the pooled data, the median age was 62 years, 53% were men, and 21% had ECOG or Zubrod performance status of 2 or worse. The median number of prior therapies was 3, with a mean of 3.7 regimens, thus defining a population that was predominantly receiving fourth- or fifth-line treatment. Twenty-eight percent of patients had received an autologous stem cell transplant. Two-thirds of the patients had resistant disease (refractory to or relapsed within 3 months of prior therapy) and 54% had refractory disease, defined as not having responded to the last therapy. In this heavily pretreated population with highly resistant disease, the objective response rate was 25% and 32% in the two studies, for a pooled rate of 28% based on intent-to-treat analyses. The majority of the responses were partial responses, with 7-8% complete responses in each study (Table 1).

The extent of prior therapy and sensitivity to last qualifying therapy were determined to be significant predictors of response. Therefore, the most informative presentation of the expected objective response rate for the intended population is for the four subgroups as shown in Table 1.

TABLE 1. Objective Response by Number of Prior Regimens and Sensitivity to Last Qualifying Therapy

Objective Response Rate (ORR)	Number (%) of Responders			
	Phase IIb Study		Phase IIa Study[a]	
Overall Objective Response	30/119	(25)	29/92	(32)
Complete Response	8/119	(7)	7/92	(8)
Partial Response	22/119	(18)	22/92	(24)
ORR by Number of Prior Regimens and Sensitivity to Prior Regimen				
≤2 Regimens	11/24[b]	(46)	13/25	(52)
Sensitive	7/11[b]	(64)	11/17	(65)
Resistant	4/13	(31)	2/8	(25)
>2 Regimens	19/95	(20)	16/66	(24)
Sensitive	9/28	(32)	7/15	(47)
Resistant	10/67	(15)	9/51	(18)

[a] One patient did not have prior therapy records to allow categorization into a subgroup.
[b] Includes one patient who had only one prior regimen and responded to VSLI.

In each study, the objective response rate varied considerably across the 4 subgroups based on extent of prior therapy and sensitivity to last qualifying therapy, ranging from 15% to 65%. The majority of patients enrolled were in the poorest prognosis group with >2 prior regimens and resistant disease. The overall objective response rates of 25% and 32% observed in these two studies were very much a result of the relative proportions of patients enrolled in the 4 subgroups.

Importantly, having had prior autologous stem cell transplant did not adversely affect response rates: 26% for patients who had prior transplant in both studies and 25% to 33% for those who did not.

The estimated median duration of response and time to progression were approximately 3 months in the Phase IIb study and time to progression was 4.3 months in the supportive study. Median estimated overall survival was 6.7 and 9.8 months, respectively, with an estimated 2-year survival probability of 25.5% and 27.0%.

Clinical Safety

VSLI was generally well tolerated and as expected based on the known safety profile of conventional vincristine, peripheral sensory neuropathy was the dose-limiting toxicity. No VSLI-related deaths occurred in the NHL studies and 12% of patients withdrew from treatment due to neuropathy. The gradual development of neuropathy is predictable and related to cumulative dose. The estimated median dose required to develop a Grade 3 or 4 neuropathy was 21 mg vincristine/m^2, which is a substantial amount of vincristine considering that 86% of the patients had previously received 2 or more neurotoxic chemotherapies. The limited data available on neurologic recovery from VSLI-induced neuropathy suggest that the clinical course is similar to that seen with conventional vincristine.

One-third of the patients in the Phase IIb study had poor hematologic status at study entry that would have precluded treatment with a standard myelosuppressive agent. VSLI was hematologically well tolerated. Severe gastrointestinal toxicity with VSLI was experienced by 10% of patients and 8% had alopecia. Severe constipation (5%) was easily managed with the use of stool softeners. Bowel obstruction or ileus attributed to VSLI therapy was reported in 5 patients (0.9%) in the total safety database of 537 patients from all clinical trials, which included patients with other cancers. A central line was not mandated for administration of VSLI in any of the study protocols. Injection site reactions occurred in 8 patients (1.5%) of the 537 patients. Preclinical data demonstrated the protective effect of the liposome against the vesicant effects of vincristine.

Potential adverse reactions from the liposome component do not appear to be a safety concern. The incidence of suspected infusion-related pyrexia was approximately 10% in the 434 patients treated with single-agent VSLI and most reactions were mild. Apart from pyrexia, no acute infusion-type reactions were observed and no other new toxicities were seen with VSLI compared to the clinical experience with conventional vincristine.

Clinical Benefit-Risk Evaluations of Individual Patients

In these two clinical trials, objective response rate is a surrogate endpoint for clinical benefit and the FDA requested that INEX prepare patient benefit summaries to facilitate their review of the data for responding patients and help identify other evidence that might suggest clinical benefit. There were 38 patients who were considered to be a responder by either the IRP or the Investigator and an additional 5 patients who achieved only minor responses (stable disease) but who appear to have had clinical benefit from VSLI treatment. Patient benefit summaries were provided to the FDA for these 43 patients. Abbreviated versions of these summaries are provided in Appendix D of this document for review. The data summarized for these 43 patients provide considerable evidence to support the conclusion that a 25% objective response rate is reasonably likely to predict clinical benefit in the indicated population. The 25% objective response rate was paralleled by documented improvement in patient-reported symptoms or ECOG performance status in 22% of patients.

Furthermore, the evaluation of these 43 patients revealed that evidence of antitumor activity, such as improved disease-related symptoms, improved ECOG performance status, decreased palpable

adenopathy, or improved disease-related laboratory parameter abnormalities (LDH, hematologic parameters), was usually clinically apparent well before the first radiologic evaluation of objective response at 6-8 weeks. In contrast, the development of neuropathy was gradual. The figure below displays the timing of the clinical evidence of antitumor activity/clinical benefit observed in these 43 patients. Each dot represents an individual patient. The timing of Grade 3 or 4 neuropathy and withdrawal for adverse events (not always Grade 3 or 4) is also shown.

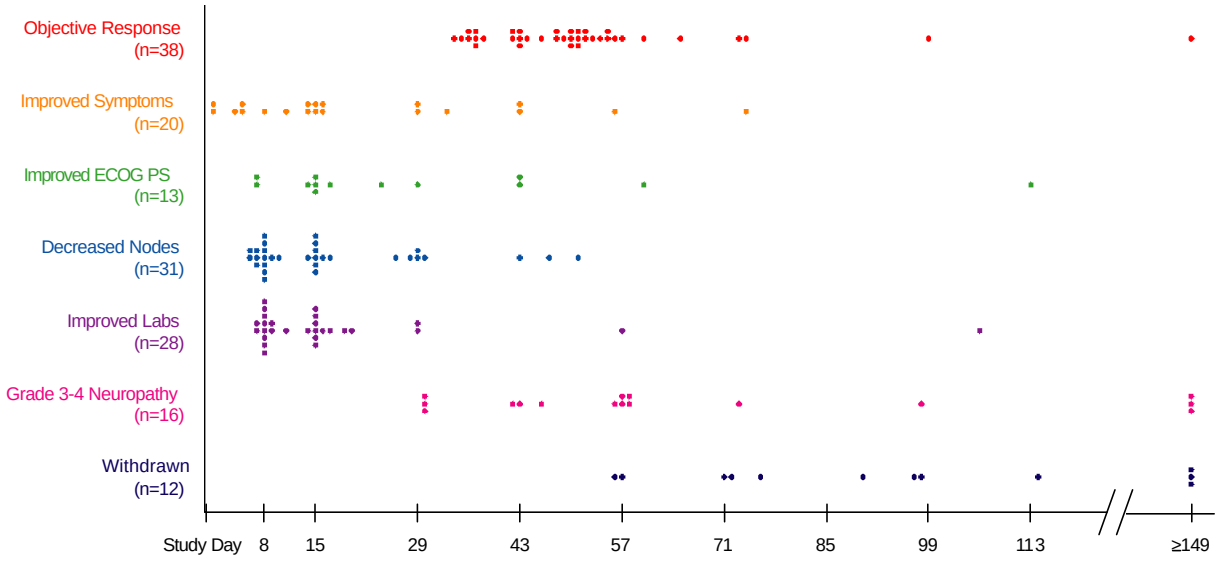

FIGURE 1. Timing of Symptom Improvement and Other Evidence of Antitumor Activity Compared to Timing of Grade 3-4 Neuropathy and Withdrawal due to Adverse Events in 43 Patients with Objective Response or Minor Response

Within the first 2 weeks, which is after only 1 dose of VSLI, some evidence of antitumor activity was evident in 34 of these 43 patients.

From the safety perspective it is interesting to note that there are more patients with Grade 3-4 neuropathy (only 1 had Grade 4) than actually withdrew from therapy. Therefore, reaching Grade 3 neuropathy was not necessarily a reason to stop treating patients who were responding to VSLI. Furthermore, the gradual development of neuropathy allows time for the physician to clinically assess if the patient's disease is responding to therapy.

From a benefit-risk perspective, given the relative timing of early evidence of antitumor activity in most cases versus the gradual development of neuropathy, the treating physician will know whether a patient's disease is responding to VSLI treatment long before significant neuropathy is experienced. At such time when neuropathy is becoming clinically important, the physician and patient can make an informed decision whether to modify or continue treatment.

In contrast, chemotherapeutic agents that cause significant myelosuppression, expose patients to greater risk after the first dose, before one is able to determine response to therapy. Consequently, VSLI provides a favorable profile for the palliation of patients with multiply relapsed aggressive NHL based on the anticipated benefits and manageable risks.

Alternative Therapies

INEX has provided a review of available literature for agents that are currently being used for the third-line or later treatment of aggressive NHL in the US. None of the three drugs most often used as single agents for this population (rituximab, gemcitabine, fludarabine), as identified by independent US market research, has an approved indication for aggressive NHL at any stage of treatment or is considered to be standard therapy in medical practice. Although there are marked difficulties in making scientifically rigorous comparisons with the literature, from a benefit-risk perspective VSLI compares favorably to these agents. Most other agents have shown greater myelotoxicity than VSLI. Moreover, the efficacy demonstrated with VSLI has been obtained in a large multicenter trial and assessed for an intent-to-treat population according to rigorous criteria applied by an external IRP. The supportive study showed consistent results. Therefore, the level of evidence supporting the efficacy and safety of VSLI is superior to that for any other agent reported in the literature.

Conclusions

VSLI is a rationally designed liposomal formulation that provides substantially increased and prolonged exposure to the cell-cycle-specific agent vincristine sulfate. Clinical studies conducted with VSLI allow the following conclusions:

- Consistent results were obtained in the two largest trials of any therapy in patients with multiply relapsed aggressive NHL.
- In this population of heavily pretreated patients with multiple adverse prognostic factors, clinically important objective response rates of 25% and 32% were observed.
- An objective response is likely to predict clinical benefit.
- Neuropathy is gradual and predictable.
- VSLI is hematologically well tolerated.
- VSLI compares favorably to single agents used in the US.
- The benefit-risk profile is favorable in this population with no standard treatment options.

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Appendix D – Patient Benefit Summaries

LIST OF ABBREVIATIONS

ABMT	Autologous bone marrow transplant
ALL	Acute lymphoblastic leukemia
AUC_{inf}	Area under the plasma concentration-time curve (h·ng/mL) from 0 h to infinity, calculated as $AUC_{last} + C_{last}/\lambda_1$, where C_{last} is the last total vincristine concentration.
BSA	Body surface area
CHOP	Cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin® (vincristine), and prednisone combination chemotherapy
CLL	Chronic lymphocytic leukemia
C_{max}	Observed maximum concentration (ng/mL)
CR	Complete response
CRu	Complete response unconfirmed
DLBCL	Diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
ESHAP	Etoposide, Solumedrol® (methylprednisolone), high-dose ara-C, and Platinol® (cisplatin) combination chemotherapy
IPI	International Prognostic Index
IRP	Independent Review Panel
MINE	Mesna, ifosfamide, Novantrone® (mitoxantrone), and etoposide
MPS	Mononuclear phagocyte system
MR	Minor response
NHL	Non-Hodgkin's lymphoma
ORR	Objective response rate
PD	Progressive disease
PK	Pharmacokinetics
PR	Partial response
ProMACE-CytaBOM	Prednisone, Adriamycin® (doxorubicin), cyclophosphamide, etoposide, cytarabine, bleomycin, Oncovin® (vincristine), and methotrexate
RICE	Rituximab, ifosfamide, carboplatin, and etoposide
SD	Stable disease
SM	Sphingomyelin
SPD	Sum of the products of the greatest diameters
$t_{½\lambda1}$	Circulation half-life (h) calculated as $\ln 2/\lambda_1$
TTP	Time to progression
VCR	Vincristine sulfate pharmaceutical product
VSLI	Vincristine Sulfate Liposomes Injection (0.16 mg/mL)
V_{ss}	Apparent volume of distribution (L) at steady state, calculated as mean resonance time multiplied by clearance
λ_1	Terminal phase rate constant (h^{-1}) determined as the slope of the apparent terminal phase of the natural log plasma concentration-time curve using linear regression analysis of selected time points (≥3 in most cases) at the terminal phase of the curve

1. INTRODUCTION

The indication for which this NDA will be seeking an accelerated approval is for the use of Marqibo® (Vincristine Sulfate Liposomes Injection) "for the treatment of patients with aggressive non-Hodgkin's lymphoma (NHL) previously treated with at least two combination chemotherapy regimens".

To support this marketing application, data for 537 patients from 13 studies in a variety of cancer types are included in the safety database and 211 patients from 2 studies in patients with multiply relapsed NHL are included in the efficacy database.

An Investigator-sponsored Phase IIa study (DM97-162) was the first NHL trial undertaken and it enrolled 132 patients, of whom 92 had aggressive refractory or relapsed NHL. The next NHL study was the pivotal Phase IIb study (CA99002), designed with input and agreement from the FDA. It was conducted in 119 patients at 42 multinational sites (Canada, Czech Republic, and US) and provides the primary efficacy and safety data in support of this NDA.

Document Organization

The main document is 70 pages and it contains the primary data analyses provided in support of this NDA review, focusing mainly on the pivotal Phase IIb study. This Briefing Document begins with a product rationale section, followed by a brief summary of the Phase IIa study, then a full presentation of the efficacy and safety of the pivotal Phase IIb study. Patients in the Phase IIb study with net clinical benefit from VSLI treatment are then discussed. Since patient benefit summaries are provided in Appendix D, specific patient numbers are sometimes referenced throughout this document. Benefit and risk conclusions are delineated and alternative therapies are discussed based on a review of the literature. The final section of the main document provides a summary of the regulatory requirements for an accelerated approval.

Several appendices provide additional information that may be of interest, such as the per-protocol population analyses for the pivotal Phase IIb study, additional details from the Phase IIa supportive study, as well as an integrated efficacy presentation combining the data from the Phase IIa and IIb studies.

1.1 Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma (NHL) represents a heterogeneous group of lymphoproliferative malignancies. NHL is one of the fastest rising cancers in both incidence and death rates in the US, second only to melanoma. The increase in incidence has been largest among NHL patients aged 65 years and older. NHL has a complex and evolving histopathological classification, however, it can be broadly divided into two distinct clinical groups, indolent (low-grade) lymphomas and aggressive (intermediate/high-grade) lymphomas. The aggressive NHLs constitute approximately half of all new cases of lymphoma in North America. It was estimated that approximately 30,000 new cases of aggressive NHL would be diagnosed in the US in 2004 (1, 7).

Patients with aggressive NHL are initially treated with CHOP-based combination chemotherapy regimens (cyclophosphamide, doxorubicin, vincristine, prednisone) with the inclusion of rituximab for B-cell disease. Upon relapse they usually receive a second-line combination regimen followed by high-dose chemotherapy and autologous bone marrow transplantation (ABMT) whenever possible. It is recognized that patients with aggressive NHL who relapse after ABMT or after other second-line therapy have a poor prognosis. These patients often have several adverse prognostic factors such as

advanced age, poor performance status, and chemoresistant disease. Long-term survival in these patients with aggressive histologies is bleak; median survival times of <8 months have been reported in patients who have not undergone ABMT (2-5). The data in Figure 1 are derived from Cabanillas et al. (1987); Dr. Cabanillas has provided this survival curve for the subset of patients who were receiving MIME therapy (mesna, ifosfamide, mitoxantrone, etoposide) as third-line or later therapy, which is a comparable population to those enrolled in our Phase IIa and IIb studies.

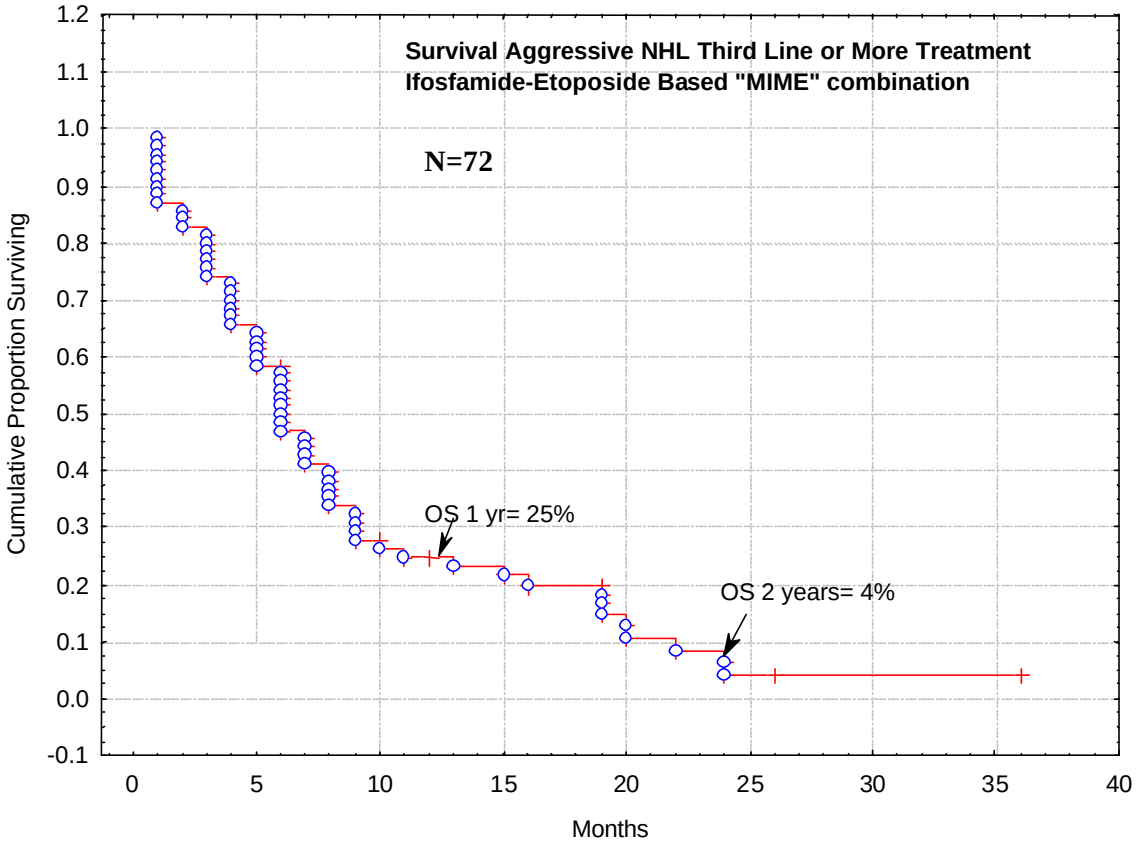

FIGURE 2. Survival in Aggressive NHL Patients Receiving Ifosfamide-Etoposide based MIME combination therapy as Third-line or Later Treatment

The median survival for this subgroup was approximately 6 months and <5% survived 2 years. By third-line treatment or beyond, aggressive NHL is an increasingly resistant disease, with lower response rates and shorter durations of response. Few complete responses are achieved even with combination regimens.

Patients who are in second or later relapse are incurable using present day conventional-dose therapies (6). These patients are generally treated in a palliative setting with single agents, with a variety of newer experimental drugs, or with low-dose combination therapies. These treatments are often associated with significant toxicity, especially myelotoxicity. As these multiply relapsed patients usually have compromised bone marrow reserve from previous cytotoxic therapy, including autologous stem cell transplant, and from the disease process itself, they have a limited ability to withstand further myelosuppressive chemotherapy. Since VSLI is a hematologically well-tolerated therapy, it can be a valuable therapeutic option for this population.

Based on independent US market research, the prevalence in 2001 of patients with aggressive NHL being treated after 2 or more relapses was 10,000-15,000 patients (7).

1.2 Rationale for Development of Vincristine Sulfate Liposomes Injection

Vincristine is a cell-cycle specific anticancer drug that arrests cell growth in the M-phase of mitosis by binding to tubulin and preventing formation of functional microtubules required for cell division. In view of vincristine's cell-cycle-specific mechanism of action, it was recognized that increased tumor cell killing could be achieved with longer duration of drug exposure as more tumor cells pass through mitosis (8-11). In developing a liposomal formulation of vincristine, INEX sought to increase the antitumor activity of this agent. Liposomes also have the potential to improve the safety profile of anticancer agents thereby allowing higher drug dosage without compromising patient safety (12-17). Nonclinical studies have shown that vincristine activity is dose-dependent, supporting the potential clinical benefit of increased dose intensity.

In VSLI vincristine is encapsulated in the aqueous interior of liposomes (115 nm mean diameter) composed of sphingomyelin and cholesterol (Figure 3). This novel lipid composition provides a highly stable bilayer that confers improved pharmacokinetic and pharmacodynamic characteristics to encapsulated vincristine compared to conventional liposome formulations.

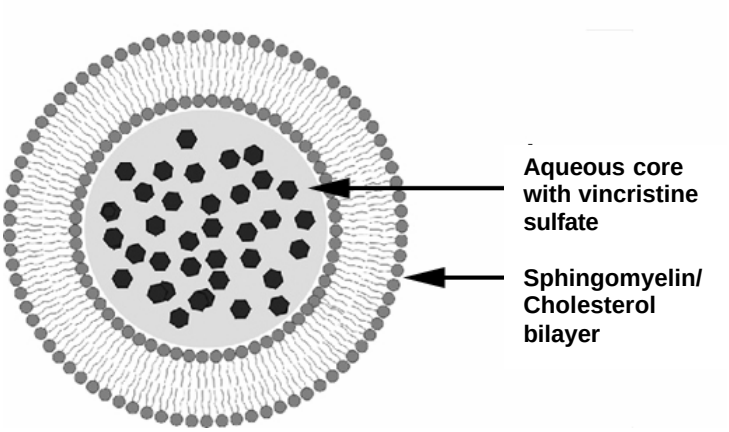

FIGURE 3. Diagrammatic Representation of VSLI

VSLI provides longer drug persistence in the plasma and higher and more prolonged vincristine concentrations at tumor sites, in part due to local release of drug from the liposomes. These mechanisms provide an increased duration of drug exposure to tumor cells.

Increased exposure to vincristine at tumor sites results from extravasation of the liposomes through "pores" present in immature tumor neovasculature (18-20); such fenestrated neovasculature is seen in NHL (21-23). A longer systemic persistence of the vincristine-containing liposomes increases the probability of liposome extravasation during their passage through the tumor neovasculature. In contrast to tumors, most normal tissues and organs have blood vessels with continuous endothelial linings and hence liposome extravasation would not be expected to occur. Exceptions to this are organs and tissues of the mononuclear phagocyte system (MPS) such as the liver, spleen, bone marrow, and lymph nodes where the capillaries are fenestrated or discontinuous. Phagocytic cells of the MPS are primarily responsible for the eventual uptake and removal of liposomes from the plasma.

Based on preclinical studies comparing VSLI to conventional vincristine (VCR) the following conclusions can be made:

- VSLI exhibits dramatically longer plasma persistence as depicted by circulation half-life (9-53 fold), greater AUC_{inf} (9-478 fold) for total vincristine which for VSLI predominantly represents the liposome-encapsulated drug, and a much smaller apparent volume of distribution (V_{ss}) which corroborates the limited distribution of the liposomal drug.
- Vincristine released from the liposomes undergoes the same distribution, metabolism and excretion as conventional vincristine, and has the same mechanism of action.
- VSLI provides higher drug exposure in tumors (6-fold greater AUC_{last} in mice) and in organs of the mononuclear phagocyte system (MPS), such as the liver (6-fold in mice, 5-fold in rats), spleen (7-fold in mice, 15-fold in rats) and lymph nodes (7-fold in mice, 6-fold in rats) compared to VCR.
- Release of vincristine from the liposomes after administration is relatively slow with approximately 50% of the encapsulated drug released by 24 hours and essentially complete release by 72 hours.
- VSLI shows increased antitumor activity compared to equivalent doses of VCR in a range of tumor models, including lymphoma models.
- The toxicity profile of VSLI is similar to that of VCR.

1.3 Clinical Pharmacology

Primary adult PK data were obtained from 26 patients in 3 studies. Twenty-five patients were from two studies conducted in metastatic melanoma and 1 patient was from the pivotal Phase IIb NHL study. Participation in the PK portion of the NHL trial was optional and only one patient consented to these additional procedures. The FDA agreed that primary PK data could be collected in patients with melanoma.

Mean plasma total vincristine concentrations over time for patients in the primary PK dataset are shown in Figure 4. For comparison, a mean plasma concentration-time curve for VCR is shown based on published data (24). In the primary PK studies for VSLI plasma levels of both total vincristine (encapsulated and released) and released vincristine were analyzed. A large majority of the released vincristine assay results (>91%) were below the lower limit of quantitation (2-4 ng/mL) and hence plasma total vincristine concentrations predominantly represent encapsulated drug.

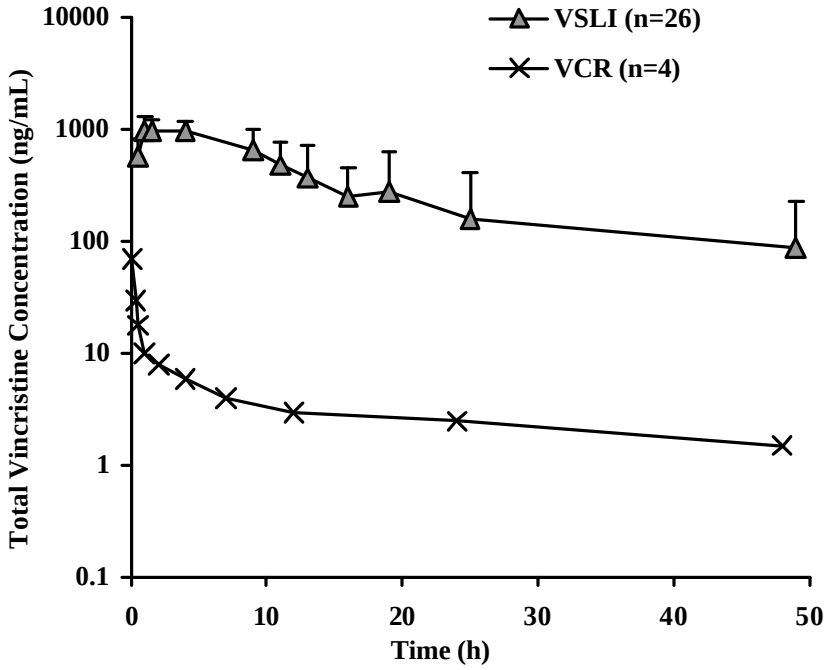

FIGURE 4. Mean (+SD) Plasma Total Vincristine Concentrations in Patients After VSLI 2.0 mg/m^2 or VCR 1.2 mg/m^2. VCR data are from Nelson, 1982 (24).

High drug concentrations are maintained in the circulation for extended periods after VSLI infusion compared to VCR. At most timepoints total vincristine concentrations are two orders of magnitude higher for VSLI. Further, patients treated with VSLI exhibit an initial phase after the end of infusion during which plasma total vincristine concentrations remain fairly constant before declining.

The primary PK dataset originally submitted in the NDA included 13 patients. PK data from an additional 13 patients are now available and were submitted to the FDA as part of the 120-Day Safety Update. Individual profiles for all 26 patients in the primary PK dataset are shown in Figure 5.

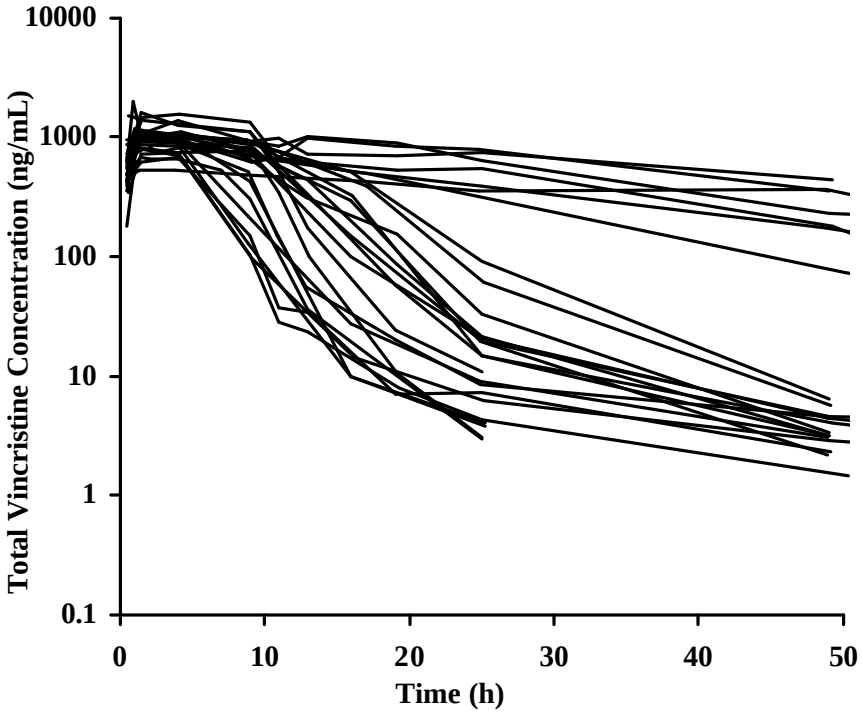

FIGURE 5. Individual Plasma Total Vincristine Concentration-Time Profiles for All Patients in the VSLI Primary PK Dataset (VSLI 2.0 mg/m^2) (n=26)

A range of profiles is seen with some patients exhibiting apparent biexponential profiles while other patients exhibit apparent monoexponential profiles. The NHL patient exhibited a PK profile falling within the range displayed by the melanoma patients. The continuum of profiles is believed to reflect interpatient differences in the rate of removal of vincristine-loaded liposomes from the plasma by cells of the MPS. This conclusion is supported by studies in dogs showing that animals exhibiting faster declines in plasma total vincristine concentration after VSLI administration show corresponding declines in plasma liposome concentrations. Further, published studies in animals with experimental liposome preparations (25, 26) also suggest that the more rapid removal phase seen in some patients likely corresponds to a capacity-limited, saturable process arising from phagocytosis of the liposomes by cells of the MPS, while the slower phase of the biexponential profile has been suggested to represent a first-order, nonsaturable process corresponding to uptake by a variety of tissues via fluid-phase endocytosis (25, 26). Another mechanism to account for the slower removal phase from plasma may be the recycling of MPS binding sites and/or recruitment of new MPS cells (27). Variations between individuals in the capacity of the saturable, rapid removal process might be due to differences in plasma protein binding and/or different levels of phagocytic activity giving rise to the observed interpatient variability in PK profiles (28). Finally, the variability seen for VSLI is similar to that observed for other liposomal products (29-31) consistent with a common mechanism involving interindividual differences in MPS activity or capacity.

Plasma profiles for any individual patient are similar upon repeated exposure to VSLI. There is no evidence of drug accumulation when VSLI is administered at 14-day intervals and there is no consistent alteration in pharmacokinetic parameters between Cycle 1 and Cycle 3. Due to the low rate of response in melanoma patients, the impact of PK profile on efficacy could not be evaluated;

however, no difference in tolerability was seen between patients exhibiting apparent biexponential or monoexponential plasma total vincristine concentration-time curves.

Pharmacokinetic parameters for total vincristine derived from the primary PK dataset are provided in Table 2.

TABLE 2. Summary of Pharmacokinetic Parameters (Mean ± SD) for VSLI

C_{max} (ng/mL)	Circulation Half-Life ($t_{1/2\ \lambda 1}$)[a] (h)	AUC_{inf} (h·ng/mL)	Clearance (mL/h)	Steady State Volume of Distribution (L)
1070 ± 323[b]	13.8 ± 7.2[c]	14785 ± 9535[c]	378 ± 212[c]	2.921 ± 1.121[c]

[a] Circulation half-life primarily represent the half-life of vincristine-loaded liposomes in plasma i.e. removal of liposomes from the plasma compartment to the tissues rather than elimination from the body

[b] n=26

[c] n=24, two patients not included in calculation because the proportion of extrapolated values in the calculation of AUC_{inf} was > 20%

Comparison of PK parameters for VSLI with published data for VCR (24, 32-41) shows a substantial increase in AUC_{inf} (21-778-fold) and circulation half-life ($t_{1/2?1}$) for VSLI and a corresponding reduction in clearance. Further, whereas the apparent volume of distribution for vincristine after VCR administration is very high suggesting widespread tissue distribution, the apparent volume of distribution for total vincristine after VSLI infusion is similar to plasma volume in all patients. This reflects the fact that liposome-encapsulated vincristine is largely restricted to the plasma compartment.

In summary, VSLI is a long circulating liposomal formulation of vincristine from which the encapsulated drug is slowly released. Vincristine is therefore removed from the circulation predominantly in an encapsulated form. Once released from the liposomes vincristine distributes, acts and is eliminated in the same way as the conventional drug. Compared with VCR, the AUC_{inf} and circulation half-life ($t_{1/2?1}$) of vincristine are substantially increased after VSLI administration. This is expected to increase tumor exposure to vincristine and thereby enhance antitumor efficacy of VSLI.

2. SUMMARY OF SUPPORTIVE PHASE IIA STUDY (DM97-162)

This section contains a brief summary of a supportive study, DM97-162, which was an Investigator-sponsored, Phase II, open-label, single-center, single-arm study conducted to evaluate VSLI in patients with relapsed or refractory NHL and acute lymphoblastic leukemia (ALL). The study was conducted by Dr. A.H. Sarris, Department of Lymphoma/Myeloma, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA and it was the first NHL study conducted with VSLI.

VSLI was administered as a single-agent at 2.0 mg/m^2 without dose capping (calculated based on the vincristine) and given as a 1-hour IV infusion every 2 weeks, which was intended to at least double the dose intensity of vincristine compared to the conventional regimen of 1.4 mg/m^2 every 3 weeks (often with dose capping at 2 mg). VSLI dose reductions of 10% were made for hematologic and nonhematologic toxicities. Patients received up to 12 treatment cycles until toxicity or progressive disease was documented.

Key inclusion and exclusion criteria included previously treated adult patients with relapsed low-grade NHL, relapsed or refractory intermediate-grade NHL, relapsed post-BMT intermediate-grade NHL, or relapsed or refractory ALL. Patients also had to have measurable disease, a Zubrod performance status score ≤3, neutrophil count ≥500/µL, platelet count ≥50,000/µL, and no central nervous system lymphoma, or serious neuropathy. Response to treatment was assessed by the Investigator using standard criteria for NHL and ALL. For the NHL response criteria, complete response was defined as complete disappearance of all known disease, partial response as a ≥50% decrease in tumor size, no response (NR) including stable disease as no significant change (i.e., lesions decreased by <50% or increased by <25%), and progressive disease as ≥25% increase in the size of existing lesions or the appearance of any new lesion.

The primary efficacy endpoint was objective response rate defined as the percentage of documented complete and partial responses in the intent-to-treat (ITT) population based on each patient's best response as determined by the Investigator.

2.1.1 Baseline Characteristics

One hundred thirty-five patients (135) were recruited into the study and 132 received at least one dose of VSLI and are included in the ITT population. The median age of the study ITT population was 62 years; 55% of the patients were men and 79% were Caucasian. Approximately 18% of the patients had Zubrod Performance Status of 2 or worse.

Overall, 116 of the 132 patients were diagnosed with NHL; 92 (79%) of these 116 patients had aggressive NHL and 24 (21%) had indolent disease. Sixteen of the 132 patients had ALL.

The patients enrolled had received many previous treatments. Overall, the median number of previous chemotherapy/immunotherapy regimens was 3, with a range of 1 to 12. In the aggressive NHL population, 45% of patients had previously received 4 or more different therapy regimens and another 27% had previously received 3 different regimens.

2.1.2 Exposure to Study Treatment

The median number of VSLI cycles administered to the 132 patients was 3. The median total dose of VSLI (as the sum across all cycles) was 6 mg/m^2, with a range of 1.9 to 24.0 mg/m^2. The median duration of exposure (months) was 1.5 months with a range of 0.5 to 4.8 months. The median dose

intensity of 1.0 mg/m^2/week among those 116 patients with NHL was identical to the target intensity (1.0 mg/m^2/week).

2.1.3 Efficacy Results

2.1.3.1 Objective Response Rate

Table 3 presents response rates for all 132 ITT patients and by subgroup including the 116 patients with NHL, the 92 patients with aggressive NHL and the 16 patients with ALL, as assessed by the Investigator.

TABLE 3. Objective Response Rates Across ITT Populations (Phase IIa Study)

	Number (%) of Patients			
Best Response on Study	**Study ITT (n=132)**	**NHL ITT (n=116)**	**Aggressive NHL ITT (n=92)**	**ALL[a] ITT (n=16)**
Objective Response Rate[b]	34 (25.8)	31 (26.7)	29 (31.5)	3 (18.8)
[95% CI][c]	[18.5, 34.1]	[18.9, 35.7]	[22.2, 42.0]	[4.1, 45.7]
Complete response (CR)	8 (6.1)	7 (6.0)	7 (7.6)	1 (6.3)
Partial response (PR)	26 (19.7)	24 (20.7)	22 (23.9)	2 (12.5)
Stable disease (SD)	38 (28.8)	30 (25.9)	18 (19.6)	8 (50.0)
Progressive disease (PD)	51 (38.6)	47 (40.5)	38 (41.3)	4 (25.0)
Ineligible (IN)[d]	6 (4.5)	6 (5.2)	6 (6.5)	0 (0.0)
Not evaluable (NE)	2 (1.5)	2 (1.7)	1 (1.1)	0 (0.0)
Missing	1 (0.8)	0 (0.0)	0 (0.0)	1 (6.3)

[a] ALL = Acute Lymphoblastic Leukemia.
[b] Objective response rate = CR + PR.
[c] 95% confidence intervals for the proportion of responders are based on the binomial distribution.
[d] 6 patients had primary refractory indolent NHL and were not eligible for the study.

The objective response rate was 26% in the Study ITT population, 27% in the NHL ITT population, and 32% in the aggressive NHL ITT population, which is the indicated population being requested in this NDA. The objective response rate was less in patients with ALL (19%).

An independent review of the images from patients reported by the Investigator to have achieved a CR or PR was conducted by an academic radiologist. This was not intended to be a formal, independent, blinded review panel process, but a review of available imaging data to confirm efficacy findings and to support a corporate decision to collect those data in support of this marketing application. A concordance rate of 71% was observed between the Investigator's and the Imaging Reviewer's determinations of responders versus nonresponders. All 7 patients who were assessed as having achieved CR by the Investigator were also assessed as CR by the independent review. Two patients assessed as achieving PR by the Investigator were reclassified as having achieved CR by the Imaging Reviewer.

Subgroup analyses of objective response rate for the 92 patients in the ITT population with aggressive NHL were conducted. Two factors distinguished VSLI responders from nonresponders; those with only 1 prior chemotherapy regimen (n=10) had a significantly higher response rate (80%) than those with >1 prior regimen (n=81) (26%). Patients who responded to their last chemotherapy (n=29) had a significantly higher response rate (55%) than nonresponders (n=55) (20%).

2.1.3.2 Time-to-Event Endpoints

Table 4 summarizes the median time-to-event parameters for the study populations.

TABLE 4. Time-to-Event Endpoints for ITT Population (Phase IIa Study)

	Study ITT	NHL ITT	Aggressive NHL ITT	ALL[a] ITT
Kaplan-Meier Estimates	**n=132**	**n=116**	**n=92**	**n=16**
Progression-free survival (days)				
Median	132	132	132	62
[95% CI]	[118, 189]	[118, 189]	[118, 243]	[44, –][b]
Survival (days)				
Median	299	349	299	166
[95% CI]	[246, 414]	[269, 457]	[246, 404]	[64, 213]

[a] ALL = Acute Lymphoblastic Leukemia.
[b] Upper limit of confidence interval not reached due to high number of censored patients.

The median progression-free survival was 132 days for the study ITT population, 132 days for the aggressive NHL ITT population and 62 days for patients with ALL included in the ITT population. The median overall survival was 299 days, 299 days, and 166 days for these populations, respectively.

2.1.4 Safety Results

Ten patients (8%) died within 30 days of the last VSLI dose, or from an adverse event that began within 30 days of the last dose; none of the deaths was assessed as treatment related. Thirteen patients (10%) were withdrawn from study due to adverse events (neuropathy in all cases).

The most commonly reported treatment-emergent adverse events in this study were peripheral sensory neuropathy (55% of ITT population, all grades), fatigue (26%), constipation (24%), pyrexia (20%), paresthesia (20%), alopecia (20%), nausea (18%), hypoesthesia (15%), weakness (14%), febrile neutropenia (13%), stomatitis (12%), and vomiting (10%). One patient had Grade 4 peripheral motor neuropathy. Common Grade 3 adverse events were peripheral sensory neuropathy (13%), fatigue (9%), weakness (5%), and limb pain (5%). The greatest change in laboratory parameters was for absolute neutrophil counts, with 31 patients (27%) experiencing a 3- or 4-grade worsening; 7 of whom were ALL patients.

2.1.5 Conclusions

VSLI showed a clinically important objective response rate of 26% overall in this study, with an objective response rate of 32% in patients with aggressive NHL, the indicated population. Despite the doubling of dose intensity compared to standard doses of conventional vincristine, VSLI was well tolerated in this heavily pretreated population.

The results in this study were consistent with those of the subsequent company-sponsored Phase IIb study, which will be discussed in detail in subsequent sections. Please refer to Appendix C for additional details for this supportive study as well as pooled efficacy results for this study combined with the pivotal Phase IIb study.

3. PIVOTAL PHASE IIB STUDY (CA99002)

The Phase IIb trial was a multicenter, international, single-arm, open-label study in patients with aggressive NHL that had been previously treated with at least two combination chemotherapy regimens. This trial evaluated the efficacy and safety of VSLI administered as a single agent at a dose of 2.0 mg/m^2 BSA every 2 weeks for up to a maximum of 12 cycles. The primary efficacy endpoint was the overall response rate, with time-to-event endpoints evaluated secondarily.

Key design features were incorporated to provide consistent and standard evaluation of efficacy endpoints and to ensure that the patient population met specific entry criteria .

- A central pathology review was conducted retrospectively for expert determination of each patient's histologic diagnosis according to the WHO criteria.
- The response criteria proposed in the "Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas" by Cheson et al. (47) were used to determine tumor response (See Appendix A); and
- An Independent Review Panel (IRP) was used for determination of efficacy to overcome the potential bias of efficacy determination by the treating Investigators in an open-label, single-arm trial and to apply tumor response criteria consistently across all sites.

This study enrolled 119 patients at 43 centers in Canada, the Czech Republic, and the US.

3.1 Dose Selection for Pivotal Study

A Phase I dose-escalation study of VSLI in patients with various cancers explored dosing regimens ranging from 0.5 to 2.8 mg/m^2 every 3 weeks; the recommended dose and schedule for subsequent studies was 2.0 mg/m^2 every 3 weeks. Early clinical experience in pancreatic and colorectal cancer patients indicated that VSLI was well tolerated at a dose of 2 mg/m^2 every 3 weeks. When the Phase IIa NHL study was initiated, the schedule was changed from 3 weeks to 2 weeks to account for the growth characteristics of aggressive NHL and ALL. Based on the positive results of the Phase IIa study where VSLI achieved an objective response rate of 32% in patients with aggressive NHL, the same dose and schedule of 2 mg/m^2 every 2 weeks was chosen for the subsequent Phase IIb study.

3.2 Key Eligibility Criteria

The study allowed inclusion of patients with:

- aggressive NHL that was refractory to or relapsed after second-line combination chemotherapy. One of the prior therapeutic regimens must have contained an anthracycline.
- histologically confirmed aggressive NHL (either diagnosed as aggressive NHL from first diagnosis [i.e. de novo] or transformed from indolent NHL), as defined by WHO classification. Specifically:
  - Diffuse large B-cell lymphoma.
    - primary mediastinal large B-cell lymphoma with sclerosis
    - intravascular large B-cell lymphoma
    - immunoblastic B-cell lymphoma
    - anaplastic large B-cell lymphoma

- Peripheral T-cell lymphoma, not otherwise specified.
- Anaplastic large null-/T-cell lymphoma.

- ECOG performance status ≤3.
- at least minor response (MR) to first-line therapy.
- measurable disease, as defined as at least 1 bidimensionally measurable lesion with clearly defined margins that was ≥2 cm in the largest dimension determined by physical examination or computed tomography (CT) scan.
- biochemistry values:
  - total bilirubin ≤2 times the upper limit of normal (ULN).
  - ALT and alkaline phosphatase ≤4 times ULN.
- hematology values:
  - granulocytes $\geq 0.5 \times 10^9$/L, unless lower due to lymphoma bone marrow involvement.
  - platelets $\geq 50 \times 10^9$/L, unless lower due to lymphoma bone marrow involvement.
- Age >18 years, with no upper limit.
- relapse after autologous bone marrow transplantation.

3.3 Independent Review Panel (IRP) for the Determination of Efficacy

The Independent Review Panel consisted of one radiologist and three medical oncologists who were specialized in the evaluation of response in NHL.

Name	**Affiliation**
Radiologist:	
Scott Gazelle, MD, MPH, PhD	Associate Professor Massachusetts General Hospital Boston, MA
Oncologists:	
Jonathan W. Friedberg, MD	Assistant Professor James P. Wilmot Cancer Center Rochester, NY
Bruce Peterson, MD	Professor of Medicine, University of Minnesota Minneapolis, MN
Michael Laurence Grossbard, MD	Associate Professor Beth Israel Medical Center New York, NY

The IRP process is depicted in Figure 6.

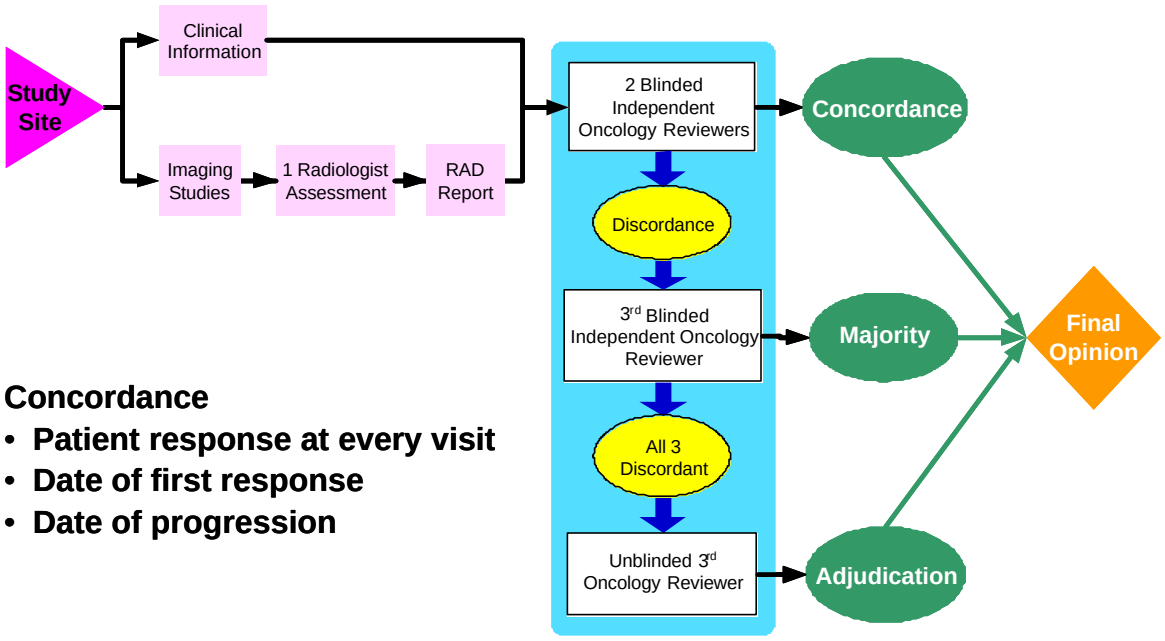

FIGURE 6. Independent Review Panel Flow Chart

IRP Process: Computed tomography (CT) scans and magnetic resonance images (MRIs) were provided to an independent radiologist who was a member of the IRP. The radiologist selected up to 6 indicator lesions (without knowing the indicator lesions chosen by the Investigator), recorded measurements of tumor dimensions, and created a radiology (RAD) report to document indicator lesion measurements and the percentage change during the course of the study. Two medical oncologists reviewed the radiology report as well as a redacted clinical report, which included physical examination findings and other relevant clinical information from the case report form. The 2 reviewing oncologists worked independently of one another and were blinded to each other's assessment as well as to the opinion of the Investigator. If concordant opinions were provided by the 2 reviewing oncologists, the process was complete for that patient and the final IRP opinion was recorded.

When discordance arose between these 2 oncologists, a third medical oncologist reviewed the case, blinded to the assessments of the initial 2 oncologists and the Investigator. At this step, if a majority occurred with agreement from any 2 of the 3 reviewers, it was accepted as the final opinion.

If all 3 opinions were discordant, then a final adjudication oncology review was performed. This review was done by the same third oncology reviewer who was now unblinded to the opinions of the other 2 reviewers, but never unblinded to the opinion of the Investigator. This adjudication opinion became the final IRP assessment. To be considered concordant the assessments by the medical oncologists needed to agree with respect to the following parameters: response category at each visit, date of first response, and date of progression.

In some instances, non protocol-specified images (e.g., PET scans, gallium scans, colonoscopy images) were obtained at the site and were used to declare disease progression (never for response).

These images were not reviewed by the IRP radiologist, but the findings of those images (as reported by the site) were provided to the IRP oncologists as part of the clinical information.

This IRP process was not managed by INEX, but by an independent contract research organization, Perceptive Informatics, that also performed site training for the collection of images in a standardized manner.

In the results section of this document, both the IRP and Investigator assessments of response and time to progression will be presented and compared. In some instances there were different opinions as to best response based on extent of tumor shrinkage and also the timing of disease progression. Several factors that may contribute to differences in opinion should be considered when reviewing the results and the level of agreement between the IRP and the Investigator:

- The IRP and the Investigator may have chosen different target lesions.
- Response to therapy was often a mixed response, with some tumors responding more than others. Therefore, the selection of different target lesions could lead to different conclusions.
- Small differences in absolute size can result in large differences in percentage change if small target lesions are chosen. This could lead to differences in categorization of PR versus SD based on minor differences in measurements (e.g., 55% versus 45% reduction), or what could be termed 'close calls'. Similarly, the difference between maintained stable disease (<50% increase) and progression (=50% increase) can be subject to 'close calls'.
- These patients had extensive disease, with approximately 60% having so many lesions that it was impractical to count them. Identifying a new lesion in that setting can be difficult.
- There can be a difference of opinion regarding whether lesions are sufficiently well demarcated to permit accurate measurements. This is particularly relevant for bulky amorphous masses of confluent lesions.
- There can be a difference of opinion in determining radiographically whether a small mass is a site of residual disease or only fibrotic tissue.

3.4 Response Criteria

Response to treatment was determined by both the IRP and the Investigator according to the criteria proposed in the "Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas" by Cheson et al. (47). Details of the criteria used are provided in Appendix A.

Response assessments included tumor response at each visit, date of first response, and date of progression. All patients were to have CT scans or MRIs of the chest, abdomen, and pelvis at baseline and at scheduled intervals.

3.5 Efficacy Endpoints

The primary efficacy endpoint was objective response rate, defined as the proportion of patients whose best response was complete response (CR), complete response unconfirmed (CRu) or partial response (PR) according to the IRP assessment of objective response. Secondary efficacy endpoints included time-to-event parameters (duration of response, time to progression and overall survival) analyzed using Kaplan-Meier methods.

The statistical objective was to assess the objective response rate to within 10% in the intent-to-treat population, which required a minimum enrollment of 100 patients.

3.6 Patient Populations for Analysis

The primary analyses were based on the intent-to-treat (ITT) population, i.e., those patients who had received at least one dose of VSLI. All 119 patients were included in the ITT population.

A per-protocol (PP) population of 77 patients was identified. The reasons why patients were not included in PP population are summarized in Appendix B; the most common reason was not having histologically confirmed aggressive de novo or transformed NHL (23 patients) as determined by the retrospective Central Pathology Review or not meeting the criterion of having at least 1 bidimensionally measurable lesion by physical examination or CT scan (8 patients) according to the IRP assessment (they had measurable lesions according to the Investigator).

The results of the per-protocol analyses were similar and consistent with the results of the ITT analyses. Therefore, the inclusion of some histologically ineligible patients in the ITT population did not favorably affect the objective response rate or secondary efficacy endpoints. Given the high degree of consistency in the ITT and PP results, the rest of this main document will present only the ITT data. The per-protocol analyses are provided in Appendix B.

3.7 Demographic and Baseline Characteristics

The population in this study was also assessed according to whether they had disease that was sensitive or resistant to their last qualifying chemotherapy/immunotherapy. The last chemo/immunotherapy was considered to be ‘qualifying’ if the regimen was appropriate with respect to doses and number of cycles. Sensitive patients were defined as those who had a response to their last therapy lasting 3 months or more. Resistant patients were defined as refractory patients who achieved no response to their last therapy or patients who relapsed within 3 months. Because patients’ resistance/sensitive status to last chemotherapy/immunotherapy was confirmed to be a strong prognostic factor, it is of interest to present data on these subgroups separately, in addition to the overall ITT population.

Age, gender, race, and ECOG performance status are summarized for the ITT, ITT-resistant and ITT-sensitive populations in Table 5.

TABLE 5. Demographics and Baseline Characteristics

	ITT (n=119)	ITT Resistant (n=80)	ITT Sensitive (n=39)
Gender [Number (%) of Patients]			
Men	64 (53.8)	44 (55.0)	20 (51.3)
Women	55 (46.2)	36 (45.0)	19 (48.7)
Age (Years)			
N	119	80	39
Median	60.0	60.5	60.0
Range	25-87	25-87	30-77
>70 years [Number (%) of Patients]	28 (23.5)	20 (25.0)	8 (20.5)
Race [Number (%) of Patients]			
Caucasian	98 (82.4)	64 (80.0)	34 (87.2)
African American	6 (5.0)	6 (7.5)	0 (0.0)
Hispanic	10 (8.4)	6 (7.5)	4 (10.3)
Other	5 (4.2)	4 (5.0)	1 (2.6)
ECOG Performance Status [Number (%) of Patients]			
0	35 (29.4)	20 (25.0)	15 (38.5)
1	59 (49.6)	41 (51.3)	18 (46.2)
2	18 (15.1)	12 (15.0)	6 (15.4)
3	6 (5.0)	6 (7.5)	0 (0.0)
Missing	1 (0.8)	1 (1.3)	0 (0.0)

In the ITT population, the median age was 60 years, with a range of 25-87 years. Fifty-four percent of patients were men and the majority of patients (82%) were Caucasian. ECOG performance status was 0 or 1 for the majority (79%) of the patients in keeping with patients willing to participate in clinical trials. The ITT-resistant and ITT-sensitive populations were comparable with respect to demographics but there was a slight shift towards a higher ECOG performance status score indicating a worse performance status in the ITT-resistant subgroup.

Recognizing the complex histology of aggressive NHL, a retrospective Central Pathology Review was conducted to determine eligibility for a per-protocol patient population. Enrollment into the study was based on the site pathology assessment. Patients deemed histologically ineligible by the Central Pathology Review were not withdrawn from the study.

With the exception of 1 patient with follicular large cell lymphoma, all patients were considered by the Investigator (based on the review by the pathologist at their site) to be eligible histologically. Final histologic diagnoses as determined by the Central Pathology Review are shown in Table 6.

TABLE 6. Histologic Type – Per Central Pathology Review

Histologic Type	Number (%) of Patients					
	ITT (n=119)		ITT Resistant (n=80)		ITT Sensitive (n=39)	
Eligible	96	(80.6)	69	(86.5)	27	(69.3)
Diffuse large B-cell lymphoma	68	(57.1)	48	(60.0)	20	(51.3)
Primary mediastinal large B-cell lymphoma with sclerosis	5	(4.2)	4	(5.1)	1	(2.6)
Immunoblastic B-cell lymphomas	1	(0.8)	1	(1.3)	0	(0.0)
T-cell rich B-cell lymphomas	2	(1.7)	2	(2.5)	0	(0.0)
Anaplastic large B-cell lymphomas	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral T-cell lymphoma	1	(0.8)	0	(0.0)	1	(2.6)
Anaplastic large null-/T-cell lymphoma	2	(1.7)	2	(2.5)	0	(0.0)
Composite lymphoma (DLBCL+)	7	(5.9)	5	(6.3)	2	(5.1)
Large cell lymphoma (FNA)	7	(5.9)	5	(6.3)	2	(5.1)
Other (large B-cell, PTLD, intermediate grade B-cell)	3	(2.5)	2	(2.5)	1	(2.6)
Ineligible	23	(19.4)	11	(14.0)	12	(31.0)
Follicular Grade 2	4	(3.4)	0	(0.0)	4	(10.3)
Follicular Grade 3	4	(3.4)	1	(1.3)	3	(7.7)
MALT	1	(0.8)	0	(0.0)	1	(2.6)
Mantle cell	2	(1.7)	1	(1.3)	1	(2.6)
SLL/CLL	2	(1.7)	2	(2.5)	0	(0.0)
Low grade B-cell	1	(0.8)	1	(1.3)	0	(0.0)
Small cell (FNA)	4	(3.4)	3	(3.8)	1	(2.6)
Indeterminate	3	(2.5)	2	(2.5)	1	(2.6)
Missing	2	(1.7)	1	(1.3)	1	(2.6)

Ninety-six patients (81%) were deemed to be histologically eligible by the Central Pathology Review. This rate is high considering the complex histology of aggressive NHL. Furthermore, this rate of histologic eligibility compares favorably with the 85% to 90% confirmatory diagnosis in the study by Coiffier et al. (2002) in newly diagnosed patients with diffuse large B-cell lymphoma (48). Gaynor et al. (2001) reported on three studies in similar newly diagnosed populations and the histologic eligibility rates were 79%, 81% and 90% (51).

Table 7 displays patients' lymphoma history.

TABLE 7. Lymphoma History

Characteristic	ITT (n=119)		ITT Resistant (n=80)		ITT Sensitive (n=39)	
Non-Hodgkin's lymphoma [Number (%) of Patients]						
Transformed	11	(9.2)	7	(8.8)	4	(10.3)
De novo aggressive	108	(90.8)	73	(91.3)	35	(89.7)
Ann Arbor staging classification at most recent relapse/failure[a] [Number (%) of Patients]						
I	6	(5.0)	3	(3.8)	3	(7.7)
II	23	(19.3)	16	(20.0)	7	(17.9)
III	35	(29.4)	23	(28.8)	12	(30.8)
IV	55	(46.2)	38	(47.5)	17	(43.6)
B symptoms at most recent relapse/failure [Number (%) of Patients]	33	(27.7)	20	(25.0)	13	(33.3)
International Prognostic Index (IPI Score) at Study Entry [Number (%) of Patients]						
0	6	(5.0)	5	(6.3)	1	(2.6)
1	29	(24.4)	19	(23.8)	10	(25.6)
2	24	(20.2)	14	(17.5)	10	(25.6)
3	38	(31.9)	29	(36.3)	9	(23.1)
4	17	(14.3)	10	(12.5)	7	(17.9)
5	3	(2.5)	2	(2.5)	1	(2.6)
Missing	2	(1.7)	1	(1.3)	1	(2.6)

[a] Ann Arbor staging imputed for 29 patients by INEX as not provided by Investigator.

The majority of the patients (91%) had de novo aggressive NHL; 11 patients (9%) had transformed disease according to the Investigators. Seven of the 11 transformed patients were confirmed to be histologically eligible by Central Pathology Review.

Three-quarters of the patients had Ann Arbor Stage III or IV at study entry indicating a population with extensive disease. Twenty-eight percent (28%) of patients had B symptoms.

At study entry, 69% of the patients had International Prognostic Index (IPI) scores of 2 or more and 49% had IPI scores of 3 or more, consistent with advanced aggressive disease. Please note that these IPI scores were determined at study entry in the patients with multiply relapsed disease and not at original diagnosis.

Bone marrow involvement, elevated LDH, and serum β_2-microglobulin are shown in Table 8.

TABLE 8. Tumor Burden

Number (%) of Patients

Characteristic	ITT (n=119)		ITT Resistant (n=80)		ITT Sensitive (n=39)	
Bone marrow involvement at most recent relapse/failure	20	(16.8)	14	(17.5)	6	(15.4)
Elevated LDH	78	(65.5)	52	(65.0)	26	(66.7)
Elevated serum β_2-microglobulin	71	(59.7)	45	(56.3)	26	(66.7)

The majority of patients (78%) did not have bone marrow involvement at study entry and 60% had elevated serum β_2-microglobulin. Sixty-six percent of the patients had elevated LDH indicating a high tumor growth potential, consistent with their poor prognosis.

The number and size of lesions at study entry were recorded by the IRP Radiologist (Table 9).

TABLE 9. Lesion Measurements At Study Entry – ITT Population

Characteristic	Number (%) of Patients					
	ITT (n=119)		ITT Resistant (n=80)		ITT Sensitive (n=39)	
Largest measured lesion diameter[a]						
<5 cm	58	(48.7)	38	(47.5)	20	(51.3)
≥5 cm	49	(41.2)	35	(43.8)	14	(35.9)
Missing	12	(10.1)	7	(8.8)	5	(12.8)
Total lesion count at study entry						
0-4	37	(31.1)	25	(31.3)	13	(33.3)
5-19	12	(10.1)	9	(11.3)	3	(7.7)
Multiple (“too many to count”)	70	(58.8)	46	(57.5)	24	(61.5)

[a] Based on Indicator lesions only.

The extent of disease as determined by lesion measurements and lesion counts is consistent with the Ann Arbor staging indicating a population with widespread disease and extensive tumor burden at study entry. The IRP radiologist performed a comprehensive documentation of tumor burden at study entry and it is noteworthy that 59% of patients had lesions that were too numerous to count by his assessment.

Table 10 displays prior lymphoma therapy.

TABLE 10. Prior Lymphoma Therapy

(Page 1 of 2)

Prior Therapy Variable	ITT (n=119)		ITT Resistant (n=80)		ITT Sensitive (n=39)	
Number of prior chemo/immunotherapy regimens [Number (%) of Patients][a]						
1	1	(0.8)	0	(0.0)	1	(2.6)
2	23	(19.3)	13	(16.3)	10	(25.6)
3	39	(32.8)	26	(32.5)	13	(33.3)
4	27	(22.7)	18	(22.5)	9	(23.1)
5-10	29	(24.4)	23	(28.8)	6	(15.4)
Mean (SD)	3.8 (1.67)		4.0 (1.78)		3.4 (1.35)	
Median	3.0		4.0		3.0	
ABMT [Number (%) of Patients]	39	(32.8)	22	(27.5)	17	(43.6)
ANC < 1.5 x 10^9/L or Platelets < 100 x 10^9/L [Number (%) of Patients]	40	(33.6)	27	(33.8)	13	(33.3)
Immunotherapy [Number (%) of Patients]	73	(61.3)	55	(68.8)	18	(46.2)

TABLE 10. Prior Lymphoma Therapy

(Page 2 of 2)

Prior Therapy Variable	ITT (n=119)		ITT Resistant (n=80)		ITT Sensitive (n=39)	
Response to first regimen of chemo/immunotherapy [Number (%) of Patients]						
CR	59	(49.6)	35	(42.5)	24	(61.5)
PR	51	(42.9)	38	(48.8)	13	(33.3)
SD or PD or Minor Response	7	(5.9)	6	(7.5)	1	(2.6)
Unknown	2	(1.7)	1	(1.3)	1	(2.6)
Duration of response to first regimen of chemo/immunotherapy						
N	101		66		35	
Median (months)	8.4		6.6		10.6	
Response to last regimen of chemo/immunotherapy [Number (%) of Patients]						
CR	16	(13.4)	1	(1.3)	15	(38.5)
PR	26	(21.8)	12	(15.0)	14	(35.9)
SD or PD or Minor Response	56	(47.1)	56	(70.0)	0	(0.0)
Unknown	21	(17.6)	11	(13.8)	10	(25.6)
Duration of response to last regimen chemo/immunotherapy						
N	42		13		29	
Median (months)	5.2		1.3		7.3	

[a] For prior ABMT, the chemotherapy given to facilitate collection of stem cells, subsequent conditioning chemotherapy, and eventual reinfusion of stem cells were counted together as one regimen.

All patients had been treated with prior chemotherapy and 61% also had prior immunotherapy; 51% of patients also had radiotherapy. The mean number of prior chemotherapy/immunotherapy regimens was 3.8 and the median was 3.0 with a range of 1 to 10. The majority of prior regimens were multidrug combinations, for example, CHOP, ESHAP, ProMACE, MINE, RICE, etc. Over 67% of patients had more than 2 combination drug regimens prior to entering this study. As expected, most patients (92%) responded to their first chemotherapeutic regimen but the median duration of response was only 8.4 months indicating a population with relatively poor response to treatment at the outset. Furthermore, only half of the patients achieved a CR to their first line of therapy.

Only 35% of patients had a response to their last chemotherapy/immunotherapy regimen prior to the study and the median duration of response was shorter at 5.2 months compared to the duration of response to the first chemotherapy regimen (8.4 months). The CR rate of 13% was considerably lower than seen with first-line therapy (50%), demonstrating that, as one would expect, these patients were developing more resistant disease with successive relapses.

The median duration of response of 5.2 months to the last chemotherapy/immunotherapy should be considered with the fact that 89 patients (75%) had a combination chemotherapy/immunotherapy regimen as their last treatment. Of these 89 patients, 16 patients had a complete response and 20 patients had a partial response, giving an overall response rate of 40% to their last combination chemotherapy regimen. Of the 30 patients (25%) who had a single agent as their last treatment prior to the study, only 6 patients responded (partial response), giving a response rate of 20%. Most of these 30 patients (20 patients, 67%) had rituximab as their single agent. It should also be noted that the response determinations to the first regimen and last regimen of chemotherapy/immunotherapy were based on the Investigators' assessments and not upon an independent review.

Of note in this study, 39 patients (33%) had prior autologous bone marrow transplantation. In this subgroup, 19 patients went directly on to receive single agent VSLI and 7 patients had another single agent as their last therapy prior to entering the study; the remaining 13 patients received another combination regimen prior to entering the study. This treatment pattern suggests that the majority of these patients were not able to tolerate further treatment with combination chemotherapeutic regimens. At study baseline, 34% of the patients enrolled were not eligible to receive another myelotoxic agent due to poor hematologic status, defined as having an absolute neutrophil count of $< 1.5 \times 10^9$/L or platelets $< 100 \times 10^9$/L.

When the criteria of sensitivity or resistance to last qualifying therapy were applied, 80 patients (67%) were deemed to be resistant to their last chemotherapy/immunotherapy regimen and 39 patients (33%) were deemed to be sensitive. Of the 80 patients with resistant disease, 60 patients were deemed to have refractory disease, having achieved no response to their last qualifying regimen (assumptions were made regarding those few patients with unknown responses to their last therapy and 4 were counted as refractory).

The ITT-sensitive population had slightly fewer prior chemotherapy/immunotherapy regimens compared with the ITT-resistant population (median 3 versus 4 regimens, respectively) and also had less immunotherapy (46% of patients versus 69%, respectively). Although the response rates to first therapy were similar between the ITT-sensitive and ITT-resistant populations, the duration of response was longer in the ITT-sensitive population (median 10.6 months versus 6.6 months).

3.8 Exposure to VSLI

All 119 patients received at least 1 dose of VSLI. The number of cycles received and extent of exposure to VSLI for all patients is presented in Table 11.

TABLE 11. Extent of Exposure to VSLI

(Page 1 of 2)

Extent of Exposure Variable	ITT (n=119)	ITT Resistant (n=80)	ITT Sensitive (n=39)
Number of cycles received			
Mean (SD)	4.6 (3.4)	3.9 (3.08)	6.3 (3.45)
Median	4.0	3.0	6.0
Minimum, maximum	1–20	1-20	1-16
Total number of cycles received [Number (%) of Patients]			
1	15 (12.6)	12 (15.0)	3 (7.7)
2	19 (16.0)	17 (21.3)	2 (5.1)
3	16 (13.4)	13 (16.3)	3 (7.7)
4	25 (21.0)	18 (22.5)	7 (17.9)
5	13 (10.9)	10 (12.5)	3 (7.7)
≥6	31 (26.1)	10 (12.5)	21 (53.8)
Total dose received (mg/m^2)[a, b]			
Mean (SD)	9.13 (6.78)	7.59 (6.16)	12.30 (6.96)
Median	7.90	6.05	11.80
Minimum, maximum	1.9-39.8	1.9-39.8	2.0-33.7

TABLE 11. Extent of Exposure to VSLI

(Page 1 of 2)

Extent of Exposure Variable	ITT (n=119)	ITT Resistant (n=80)	ITT Sensitive (n=39)
Dose intensity ($mg/m^2/wk$)[b, c]			
Mean (SD)	0.96 (0.07)	0.97 (0.05)	0.95 (0.08)
Median	0.98	0.98	0.98
Minimum, maximum	0.6-1.1	0.8-1.1	0.6-1.1
Full Doses Given (No reductions)	90 (75.6)	65 (81.3)	25 (64.1)
No Dose Delays	95 (79.8)	65 (81.3)	30 (76.9)

[a] Total dose vincristine received (mg/m^2) = sum of total doses administered per cycle.
[b] Median BSA (range) was 1.85 (1.28-2.61) m^2 for ITT population, 1.86 (1.36-2.43) m^2 for the ITT resistant population, and 1.80 (1.28-2.61) m^2 for the ITT sensitive population.
[c] Dose intensity ($mg/m^2/wk$) = total dose received (mg/m^2)/(duration of exposure in days/7).

For the ITT population, the median number of treatment cycles was 4.0, with a mean of 4.6 and a range of 1 to 20. The sensitive population received more cycles of VSLI than the resistant population. The median number of cycles for the sensitive population was 6.0, compared to a median of 3.0 for the resistant group. Three patients who wished to continue therapy were allowed to receive more than 12 cycles of VSLI.

The median total dose of VSLI (as the sum of total dose across cycle) for the entire safety population was 7.9 mg/m^2, with a mean of 9.1 mg/m^2 and a range of 1.9 to 39.8 mg/m^2.

Most patients had no dose reductions or delays. Single dose reductions of 10% (i.e., 1.8 mg/m^2 VSLI) were implemented for 21 patients (18%), 6 patients (5%) had 2 dose reductions, and 2 patients (2%) had the maximum 3 dose reductions. Dose delays were implemented in 24 patients (20%). For the ITT population, the median dose intensity was 0.98 $mg/m^2/wk$, compared to a target intensity of 1.0 $mg/m^2/wk$. Similar dose intensity was observed in both the resistant and sensitive groups.

During the development of VSLI, the intent has been to deliver a higher dose intensity of vincristine than one can achieve with conventional vincristine. The typical schedule for conventional vincristine is 1.4 mg/m^2 every 3 weeks often with dose capping at 2 mg for each dose. Without a dose cap, this regimen would give a dose intensity of 0.47 mg/m^2/week for conventional vincristine. If a dose cap were applied this would mean that anyone with a BSA greater than 1.43 m^2 would receive a lower dose intensity. The schedule of VSLI used in the NHL trials reported here was 2.0 mg/m^2 every 2 weeks without dose capping. Thus, without adjusting for dose capping of vincristine, the VSLI schedule has achieved a doubling of the dose intensity at 1.0 mg/m^2/week. Calculations based on the actual BSA values in this trial indicate that on average the patients received 2.7 times the dose of vincristine they would have received as vincristine with dose capping. Published studies have indicated that higher total dose or higher rate of delivery of vincristine may be associated with higher response rates in patients with lymphomas (42-46). Nonclinical investigations with VSLI in human tumors grown as xenografts in mice revealed dose-dependent antitumor activity. The higher dose intensity and the increased exposure time achieved with VSLI compared with conventional vincristine are expected to improve efficacy.

3.9 Efficacy Results

3.9.1 Primary Efficacy Endpoint – Objective Response Rate

Objective response rates (ORR) and 95% confidence intervals (CIs) for the ITT population are provided for both the IRP review and the Investigator assessments in Table 12.

TABLE 12. Objective Response – ITT Population

Best Tumor Response During Study	IRP Review		Investigator Assessment	
	Number (%) of Patients (n=119)	95% CI[a]	Number (%) of Patients (n=119)	95% CI[a]
Objective response rate (ORR)[b]	30 (25.2)	[17.7, 34.0]	29 (24.4)	[17.0, 33.1]
Complete response (CR)	4 (3.4)	[0.9, 8.4]	7 (5.9)	[2.4, 11.8]
Complete response unconfirmed (CRu)	4 (3.4)	[0.9, 8.4]	0 (0.0)	[0.0, 2.5]
Partial response (PR)	22 (18.5)	[12.0, 26.7]	22 (18.5)	[12.0, 26.7]
Stable disease (SD)	31 (26.1)		31 (26.1)	
Progressive disease (PD)	32 (26.9)		51 (42.9)	
Unable to evaluate (UE)	26 (21.8)		8 (6.7)	

[a] 95% CI for the proportion based on the binomial distribution.
[b] ORR = CR + CRu + PR, based on patient's best documented response.

The ORR for the ITT population was 25% with a 95% CI of [18%, 34%] according to the IRP review and 24% [17%, 33%] based on the Investigator assessment. The confidence intervals for both assessments indicate that the ORR was estimated to within ±9% and thus the study achieved its statistical objective of estimating the ORR to within ±10% for the ITT population.

The IRP assessed 8 patients (6.7%) as having a complete response (4 were CR, 4 were CRu) and the Investigator identified 7 (5.9%) complete responders (all CRs). The rate of partial response was also consistent between the IRP and Investigator reviews (19%), as was the rate of stable disease as the best outcome (26%).

Overall, the IRP and Investigator reviews concluded that approximately 25% of the patients achieved a response to VSLI treatment and another 26% of patients had disease stabilization.

Concordance of IRP and Investigator Response Assessments

With such a high level of consistency between the IRP and Investigator reviews with respect to the objective response categories, an important question to ask is whether they are the same patients. The answer is that in most cases they are the same patients. Figure 7 depicts the responders by either IRP or Investigator assessment.

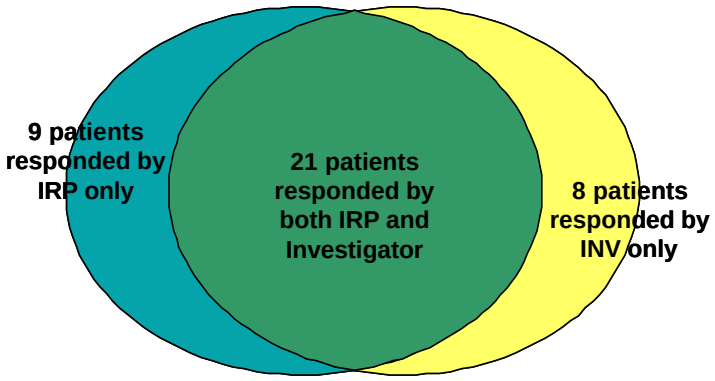

FIGURE 7. Responders by Either IRP or Investigator Assessment

The concordance between the IRP and Investigator determinations of response is provided in Table 13. In this concordance analysis, patients are grouped as responders (CR, CRu, or PR) or nonresponders (SD, PD, or UE).

TABLE 13. Concordance of Response Assessments Between IRP and Investigator Reviews – ITT Population

Concordance	Number (%) of Patients (n=119)	
Total concordant assessments	102	(85.7)
IRP and Investigator responder	21	
IRP and Investigator nonresponder	81	

The IRP and Investigator agreed on whether a patient was a responder or not in all but 17 cases, for an overall concordance rate of 86% (102/119). This is an excellent rate of concordance despite the fact that the IRP and Investigator often chose different indicator lesions.

It is common for independent panels to find an objective response rate that is lower than the rate determined by the treating Investigators. In this study, 8 patients considered to be responders by the Investigator were assessed as nonresponders by the IRP. It is interesting to note, however, that the reverse also occurred and the IRP declared response in 9 patients considered to be nonresponders by the Investigator. Accordingly, it does not appear that the Investigator opinions were biased in favor of the study drug. Instead, this balanced pattern of discordance reflects the complexity of determining response in multiply relapsed aggressive NHL patients with extensive disease.

If both the IRP and Investigator assessments are considered, 38 patients (32%) were a responder by one assessment or the other. All 38 patients were evaluated for evidence of clinical benefit (See Section 4).

One point of difference between the two assessments was the number of patients with progressive disease as their only outcome to treatment. The Investigator reported 43% of the patients with progression, whereas the IRP was unwilling to declare progression as frequently based on the evidence provided to them for their blinded review. As a result, the IRP review concluded that 27% of the patients experienced disease progression and that response outcome could not be evaluated for 22% of the patients. For the 26 patients with response outcome of UE by the IRP, 7 were also UE by the Investigator and the other 19 had an Investigator best response of PR (2), SD (6), and PD (11). The

Investigator assessed response for these 19 patients by physical examination for 12 patients, by CT scans for 5 patients, and by other imaging modalities for 2 patients. The use of physical examination evidence is appropriate according to the criteria described in the protocol and the IRP charter, which were based on the International Workshop criteria published by Cheson et al. (47). However, it appears that the IRP occasionally considered the physical examination evidence to be inconclusive, which resulted in a lower rate of PD in the IRP review.

Responders with Confirmatory Assessments

According to the International Workshop criteria confirmation of response at least 4 weeks later is not required for a patient to be considered a responder. Nevertheless, this additional confirmation of response is of interest. Of the 29 responders by the Investigator assessment, 20 (69%) had confirmatory CTs that documented continued response; 4 of the 9 patients without confirmatory CTs had progressive disease identified by physical examination at 4 to 6 weeks after the first documentation of response. The remaining 5 patients had progression documented on the subsequent CTs taken 6 to 8 weeks after the first documentation of response.

For those 30 patients considered to be responders by the IRP, 17 (57%) had confirmatory CTs documenting continued response at 4 weeks or later. For the 13 IRP responders without confirmatory CTs, 5 had documented PD 2 to 8 weeks later and 8 were taken off study by the Investigator precluding further assessment by the IRP. Even without confirmatory assessments, these 13 patients were considered to be responders by the IRP in accordance with the International Workshop criteria.

Patterns of Clinical Benefit

Achieving complete resolution of all evidence of disease, as required for CR and CRu responses, is clearly the easiest response outcome to interpret from a clinical benefit perspective. Of the 8 patients with CR or CRu by the IRP review, 3 patients went on to receive a potentially curative therapy with allogeneic bone marrow/stem cell transplants after leaving the study (Patients 01-12, 01-20, and 22-01). Having achieved a significant response to VSLI and having maintained a good performance status, these patients were considered for transplant therapy, a potentially curative therapy. Patient 01-12 never had a recurrence of his NHL, but he died of acute myelogenous leukemia 1.8 years after his first VSLI dose. Patients 01-20 and 22-01 were alive with no evidence of disease at the last survival follow-up, with survival periods of >2.4 and >2.5 years, respectively, since their first VSLI dose. The IRP radiologist had assessed a CR for Patient 01-05, although the IRP oncology panel concluded that her response could not be evaluated; she was also transferred off study to receive an allogeneic stem cell transplant and was alive with no evidence of disease and a survival of >3.2 years. Lastly, a fifth patient (12-01) who achieved a CR was alive with no evidence of disease at >3.1 years survival, having received no other anticancer therapies after VSLI. Five of these 8 patients also had resolution of B symptoms or an improvement in other disease-related symptoms or ECOG performance status; the remaining 3 patients were asymptomatic at study entry. Each patient is described further in Appendix D.

A partial response requires at least a 50% reduction in the sum of the products of the greatest diameters (SPD) of the indicator lesions from the value at study entry to the best value on study. One would expect that such a large reduction in tumor burden would be associated with an improvement of any symptoms that were tumor-specific, such as localized pain or dyspnea, or with an improvement in constitutional symptoms, such as B symptoms, that were caused by the presence of extensive disseminated disease. Of the 22 patients who achieved a PR according to the IRP review, 15 had

symptomatic improvement (B symptoms or other disease-related symptoms) or had an improvement in ECOG performance status after treatment with VSLI. One of the patients (22-03) also received an allogeneic stem cell transplant after the VSLI study, as she had demonstrated a response with VSLI and was then considered eligible for this potentially curative therapy. Additional details and descriptions of net clinical benefit for individual patients are provided in Appendix D for all patients considered to be responders.

Disease stabilization is also important from a patient's perspective as disease progression is typically associated with a worsening of disease-related symptoms, a decline in overall performance status, and finally death. Thirty-one patients (26%) had disease stabilization following VSLI treatment. The definition of SD is tumor response not meeting the criteria for a CR, CRu, or PR, nor the criteria for PD, and hence the patients with SD could have experienced <50% decreases (less than a PR) or <50% increases in tumor burden (not PD). Figure 8 shows the percentage change in SPD of the indicator lesions from the study entry value to the nadir value according to the IRP review for patients who achieved SD as their best objective response outcome; 29 patients are represented in this figure because SD was assessed without exact tumor measurements for 2 patients.

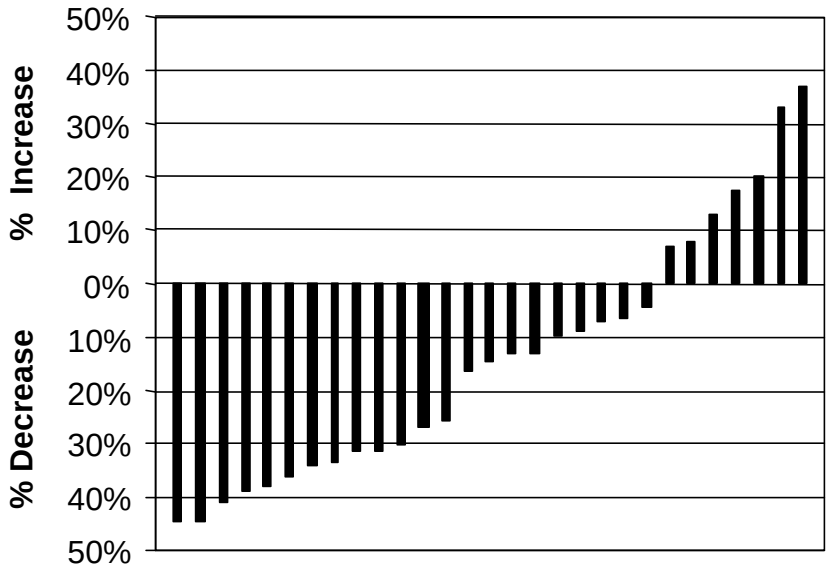

FIGURE 8. Rank Order Presentation of Percentage Change from Study Entry to Nadir in Tumor SPD for Patients with Stable Disease

From Figure 8 it is apparent that the majority of the patients with SD (22 of the 29 patients in the figure) had decreases in their tumor burden and only 7 had increases. Of the 22 patients with decreases, 13 patients had at least a 25% reduction in tumor burden and could be considered to have achieved a 'minor response'. In total, 6 of the 13 patients with a 'minor response' had either an improvement in B symptoms or an improvement in ECOG performance status after treatment with VSLI. Tumor-specific symptoms were not collected prospectively in this study, but these examples demonstrate that symptomatic improvement occurred for some of the patients who had disease stabilization as their best outcome to treatment with VSLI. One of these patients (01-23) was considered to have achieved a CR by the Investigator; this patient went off study to receive an

allogeneic BMT and was alive with no evidence of disease at last contact (26.7 months after first VSLI dose).

Timing of Responses

It is also of interest to understand the timing of the responses observed in this study. The first scheduled evaluation of tumor response was after 3-4 cycles of VSLI, which was therefore at 6-8 weeks. According to the IRP assessments, 27 of the 30 responders had a documented response at that first evaluation. Similarly, according to the Investigator assessments, 25 of the 29 responders were identified at the first assessment. Review of the case studies presented in Section 4 and Appendix D reveals even earlier evidence of treatment effect in patients who were responders; improvements in LDH and clinical evidence of lymph node regression on physical examination and disease-related symptom improvements were often recorded within the first 2 weeks of treatment, i.e., after a single injection. Therefore, the ability to respond to treatment with VSLI is established quickly for most patients.

3.9.2 Secondary Efficacy Endpoints

3.9.2.1 Duration of Response

Duration of response, calculated as the time from first documentation of response until first documentation of relapse/progression, is summarized in Table 14 for the ITT population based on the IRP and Investigator reviews. Only patients with a response of CR, CRu, or PR are included in this analysis.

TABLE 14. Duration of Response – ITT Population

Kaplan-Meier Analysis	IRP Review (n=30)		Investigator Review (n=29)	
Number (%) of patients relapsed/progressed	10	(33.3%)	22	(75.9%)
Number (%) of patients censored	20	(66.7%)	7	(24.1%)
Median duration of response in days[a]	>85[b]		72.0	
95% confidence interval	[72.0, –][b]		[65.0, 128.0]	

[a] Kaplan-Meier estimates of median duration of response. Data for patients not relapsing or progressing were censored in the analysis at date of last contact for progression. Death on study was counted as progression.
[b] The median duration of response was not reached and upper limit of the 95% CI could not be calculated.

Based on the IRP review, two-thirds of the patients did not progress and therefore their data were censored in the analysis at last contact. With this high amount of censoring, the median duration of response was not reached and the upper limit of the confidence interval could not be calculated. The last event of documented progression occurred at 85 days, when the probability of remaining in response was 51.9%.

According to the Investigator review, one-quarter of the patients did not have documented progression and the median duration of response was estimated to be 72 days with a 95% CI of [65, 128].

Having such a large discrepancy in the level of censored data between the IRP and the Investigator analyses (67% vs 24%), raises concerns about the quality of the duration of response analyses and the ability to draw conclusions. Therefore, additional analyses were performed in which the earliest assessment (IRP or Investigator) of PD was used as the date of failure to establish the “worst case”

boundary for estimated median duration of response. Using this approach, the estimated median duration of response for the IRP responders was 63 days, with a 95% CI of [38, 116].

A similar worst-case analysis was undertaken for the Investigator responders, and using this approach, the estimated median duration of response for the Investigator responders was 71 days, with a 95% CI of [65, 128].

Both of these analyses provide point estimates of median duration of response (63 and 71 days) that are very similar to what was previously reported for the original analysis by the Investigator review (72 days). It can be concluded, therefore, that the Investigator assessments are consistent with the most conservative or worst-case opinion.

All patients who went off study were followed for long-term survival as required by protocol. Additional data were collected regarding time to progression on all patients who had gone off study while still in response or with stable disease according to the Investigator. These additional data were not available for the IRP reviews, which had been conducted earlier based on the data available up to the time that patients went off study. Therefore, longer durations of response for a few patients are reflected only in the Investigator analyses. The patients achieving these long-lasting responses did not receive any intervening therapy during the follow-up period.

As assessed by the Investigator, 11 of the 29 responders had durations of response lasting longer than 3 months. Three patients had responses to single-agent VSLI alone (without subsequent bone marrow transplant) that were still ongoing after more than 2 years (Patient 12-01 with a CR lasting >3 years, Patient 33-06 with a CR lasting >2.2 years and Patient 40-01 with a PR lasting >2.4 years).

Prior therapy data show that the median duration of response to first regimen combination chemotherapy was 8.4 months for the ITT population. The median duration of response to the last regimen of therapy was shorter, as would be expected, at 5.2 months; this last regimen of therapy was a combination regimen for approximately 75% of the patients. Therefore, the median duration of response to VSLI of approximately 3 months based on the IRP review and approximately 2.5 months based on the Investigator assessment, is a good outcome with this single-agent therapy.

3.9.2.2 Time to Progression

Time to progression (TTP), calculated as the time from initial day of dosing until first documentation of relapse/progression, is summarized in Table 15 for the ITT population based on the IRP and Investigator reviews. All patients are included in this analysis.

TABLE 15. Time to Progression – ITT Population

Kaplan-Meier Analysis	IRP Review (n=119)		Investigator Review (n=119)	
Number (%) of patients relapsed	56	(47.1%)	98	(82.4%)
Number (%) of patients censored	63	(52.9%)	21	(17.6%)
Median time to progression in days[a]	89.0		57.0	
95% confidence interval	[64.0, 217.0]		[50.0, 72.0]	

[a] Kaplan-Meier estimates of median time to progression. Data for patients not relapsing or progressing were censored in the analysis at date of last contact for progression.

Based on the IRP review, approximately half of the patients had disease progression at some time on study. The median TTP was estimated to be 89 days with a 95% CI of [64, 217].

Based on the Investigator review, 82% of patients had disease progression; the estimated median TTP was shorter at 57 days with a narrow 95% CI of [50, 72]. There was substantially more censoring in the IRP review (53%) than by the Investigator (18%).

This difference in the proportion of patients considered to have documented progression between the IRP and Investigator assessments (47% vs 82%) might lead one to question whether the IRP review was appropriately conducted and whether they received adequate information to allow determination of PD. A review of the reasons for discordance confirmed that the IRP review was appropriately conducted. Of the 63 patients without documented progression by the IRP assessment (i.e., their data were censored at last contact in the TTP analysis), 21 were lost to follow-up without documented PD by the Investigator as well. For the remaining 42 patients without documented PD by the IRP review, the Investigator had declared PD most often based on evidence from CT scans (26 patients, 62%); for 16 patients the Investigator had declared PD based on evidence from other non protocol-specified imaging modalities (6 patients) or from physical examination findings (10 patients). Therefore, for the majority of the cases with a discrepancy in assessment of progression between the IRP and Investigator, the discrepancy was due to a difference in interpretation of the protocol-specified CT scans. For 18 of these patients, the Investigator noted new lesions on CT scans that were not identified as new by the IRP radiologist.

Twenty-one patients were lost to follow-up for progression in both the IRP and Investigator reviews. Seven of these 21 patients were withdrawn due to adverse events, 5 withdrew consent, 2 patients were removed by physician discretion, and 1 patient was determined to have been misdiagnosed and had no cancer (apparent liver lesions were later considered to be cysts). Importantly, 4 patients were removed from study to receive bone marrow/stem cell transplants, and 2 patients had completed the protocol-specified additional 2 cycles of VSLI beyond documented CR.

Figure 9 provides the Kaplan-Meier plots of TTP in the ITT population for both the IRP and Investigator assessments.

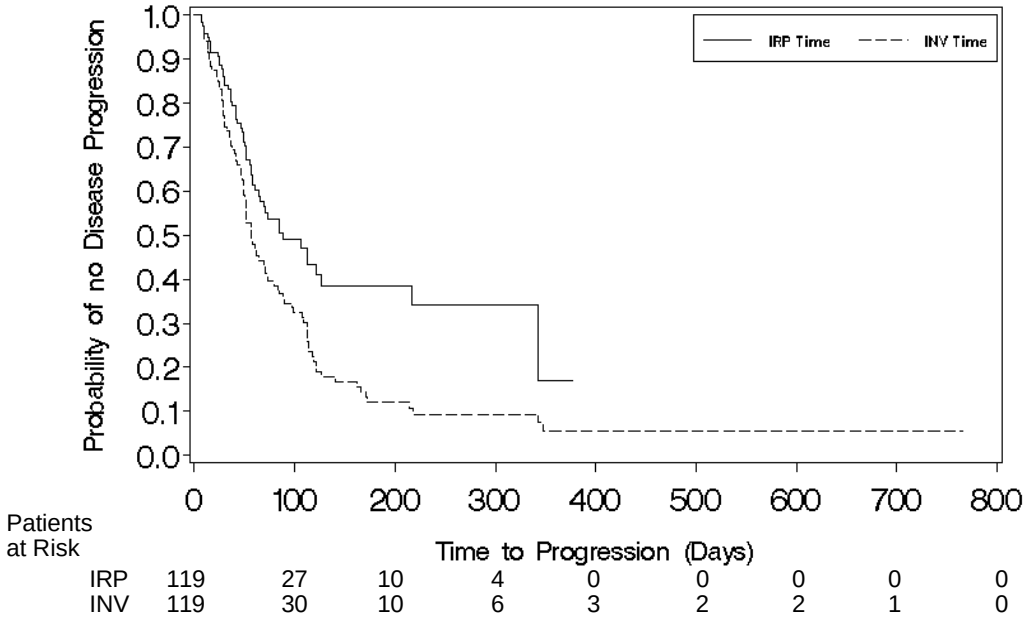

FIGURE 9. Kaplan-Meier Curve of Time to Progression – ITT Population

Additional data were collected regarding TTP on all patients who had gone off study while still in response or with stable disease according to the Investigator. These additional data were available only for the Investigator review. These longer follow-up data are evident in the tail of the Kaplan-Meier plot for the Investigator data.

Kaplan-Meier plots were generated for TTP for the responding patients (CR, CRu, PR). Figure 10 displays these plots for both the IRP and Investigator ITT analyses.

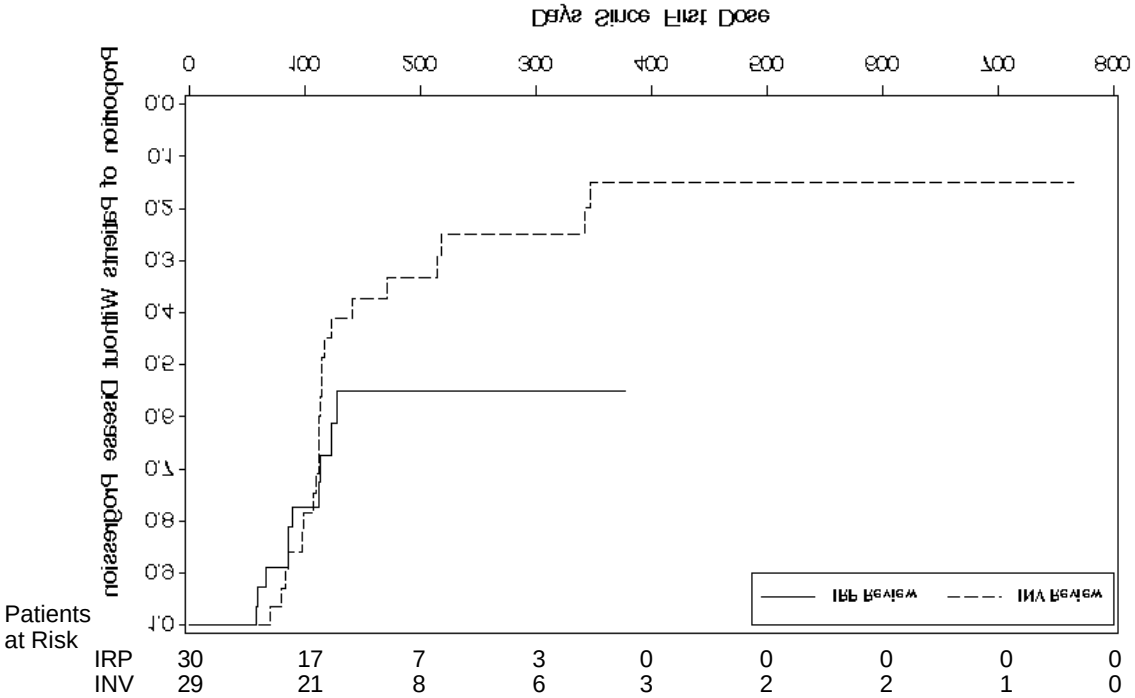

FIGURE 10. Time to Progression for Responders

The median TTP for responding patients based on the Investigator review was 114 days. The corresponding median based on IRP review had not been reached, but the probability of progression after 4 months was estimated to be .45.

From Figure 10 it can be seen that the curves for the IRP and Investigator reviews are quite close up to approximately the median time to progression. The difference in the tails of the curves is due to the difference in the proportion of patients with censoring (lack of progression) in the two reviews.

The median TTP of approximately 4 months is likely to be a conservative estimate of the duration of time that a responding patient had less tumor burden than at study entry. The definition of PD required a 50% increase in SPD from nadir measurements or the appearance of a new lesion.

3.9.2.3 Survival

Survival, calculated as the time from initial day of dosing until death or last contact, is summarized in Table 16 for the ITT population using the updated survival data collected in May and June of 2004 and submitted to the NDA in July 2004. The original NDA filed in March 2004 had approximately 1.25 years less follow-up for survival. The estimated median survival did not change with the updated survival data.

Figure 11 provides the Kaplan-Meier plot of survival for the ITT population.

TABLE 16. Survival – ITT Population

Kaplan-Meier Analysis[a]	ITT Population (n=119)
Number (%) of patients dead	92 (77.3)
Number (%) of patients alive	27 (22.7)
Median survival time in months[a]	6.7
95% confidence interval	[4.6, 9.7]

[a] Kaplan-Meier estimates of median survival time. Data for patients alive or lost to follow-up were censored in the analysis at the date of last contact for survival.

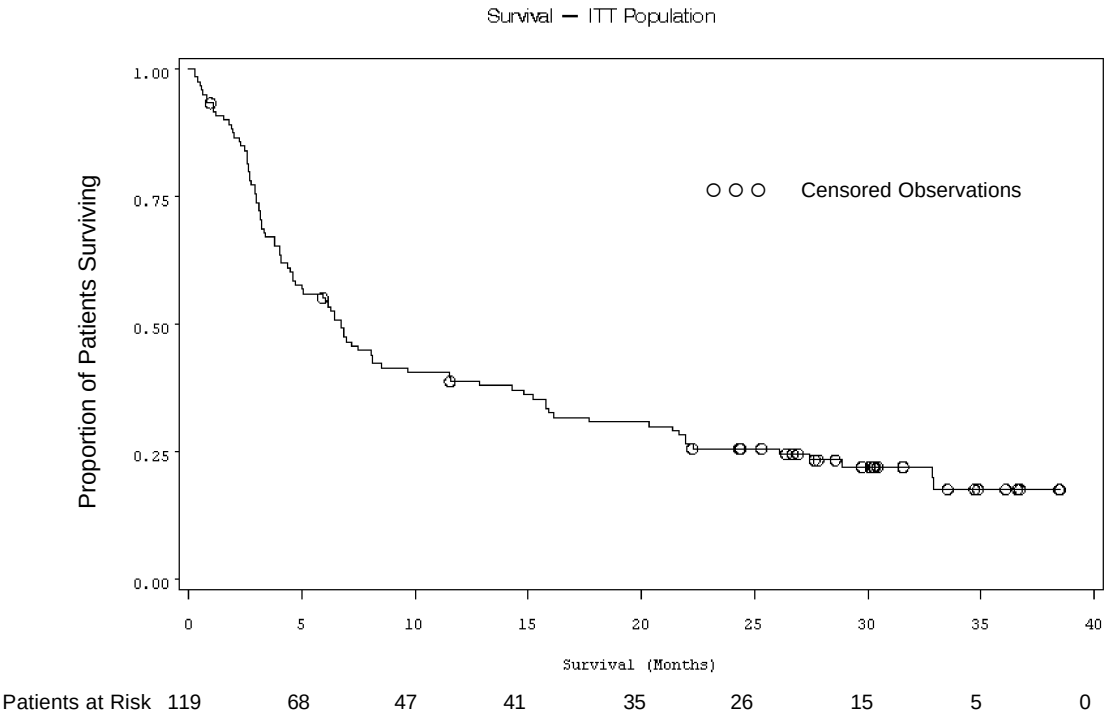

FIGURE 11. Kaplan-Meier Curve of Overall Survival

All patients were to be followed for long-term survival even after they went off study. As of the last survival update, 77% of patients had died. The median survival time was estimated to be 6.7 months with a 95% CI of [4.6, 9.7]. The 2-year survival probability was estimated to be 25.5%.

This short median survival time is an indication of the very advanced disease status of these patients and it is consistent with the extent of prior chemotherapy/immunotherapy regimens (median 3, mean 4), the proportion of patients with resistant disease (67%), and poor IPI status at study entry (49% with IPI of 3 or higher).

3.9.3 Univariate Subgroup Analyses

Fifteen prospective subgroup analyses (age, gender, race, NHL history, lymphoma cell type, bone marrow involvement at study entry, β_2-microglobulin level at study entry, International Prognostic Index (IPI) at study entry, number of prior regimens, prior ABMT, prior radiation therapy, response to first regimen of therapy, duration of response to first regimen of therapy for those who had CR or CRu, response to most recent therapy, and time from last regimen) were performed on objective response rate based on the IRP review for the ITT population. An additional subgroup analysis was included based on sensitivity or resistance to last qualifying chemo/immunotherapy using the 3-month criterion. Table 17 provides a summary of selected subgroup analyses of interest.

TABLE 17. Objective Response Rate by Subgroup Based on IRP Review – ITT Population

Subgroup	Number (%) of Responders		95% CI[a]	
NHL history				
De novo aggressive NHL (n=108)	30	(27.8)	[19.6,	37.2]
Transformed NHL (n=11)	0	(0.0)	[0.0,	28.5]
Difference: de novo – transformed		(27.8)*	[19.3,	36.2]
Number of prior regimens				
≤2 (n=24)	11	(45.8)	[25.6,	67.1]
3 (n=39)	8	(20.5)	[9.3,	36.5]
4 (n=27)	6	(22.2)	[8.6,	42.2]
>4 (n=29)	5	(17.2)	[5.8,	35.7]
Difference: (≤2) – (>2)		(25.8)*	[4.3,	47.3]
Prior ABMT				
Yes (n=39)	10	(25.6)	[13.0,	42.1]
No (n=80)	20	(25.0)	[16.0,	35.9]
Difference: yes – no		(0.6)	[-16.0,	17.3]
Sensitivity to last chemo/immunotherapy with 3-month criterion				
Sensitive (n=39)	16	(41.0)	[25.6,	57.9]
Resistant (n=80)	14	(17.5)	[9.9,	27.6]
Difference: sensitive – resistant		(23.5)*	[6.0,	41.1]
Subcategories of resistant:				
Refractory (n=60)	11	(18.3)	[9.5,	30.4]
Relapsed (n=13)	2	(15.4)	[1.9,	45.5]
Unknown (assumed resistant) (n=7)	1	(14.3)	[0.4,	57.9]
Difference: sensitive – refractory		(22.7)*	[4.4,	41.0]
Difference: refractory – relapsed		(2.9)	[-19.0,	24.9]

[a] 95% CIs for the proportions of responders are based on the binomial distribution. 95% CIs for the differences in proportions between subgroups are based on the normal approximation to the binomial distribution.

* The confidence interval on the difference in response rates excludes zero, indicating that the difference is statistically significant.

Univariate subgroup analyses of age, gender, race, lymphoma cell type, β_2-microglobulin at study entry, IPI at study entry, prior radiation therapy, response to first regimen therapy, duration of response to first regimen therapy for those who had CR or CRu, and response to most recent therapy showed no statistical differences in ORR.

Subgroups showing statistical differences in objective response rate were number of prior regimens, de novo NHL versus transformed NHL history, and sensitivity to last qualifying chemotherapy/immunotherapy.

The number of prior regimens was a strong predictor of objective response based on this subgroup analysis. The objective response rate was 46% in patients who had received 2 prior regimens (one patient had received a single prior regimen) and this was consistently higher than for all other groups who had received more prior regimens (ranging from 17% to 22%). It is noteworthy that the response rate was consistent for patients who had received 3, 4, or more than 4 chemotherapy/immunotherapy regimens before entering the study. That is an important finding as typically the response rate drops with each subsequent line of therapy. Patients who have relapsed many times are in need of effective therapies that are not myelotoxic and these results have demonstrated that VSLI can achieve a response rate of approximately 20% in multiply relapsed patients with primarily resistant disease.

The objective response rate was higher in patients who had de novo aggressive NHL compared with those who had transformed NHL (28% vs 0%), but this analysis is limited by the small number of patients with transformed NHL (n=11).

Having had prior ABMT did not adversely impact the capacity to respond to VSLI, which is also an important finding. Of the 39 patients who had undergone ABMT before entering the trial, 21 had received the transplant as their most recent therapy. Patients who are post-transplant frequently have compromised marrow reserve and a therapy such as VSLI that is not severely myelotoxic offers an important treatment option.

In the protocol-specified subgroup analysis by response to most recent therapy, the objective response rate was numerically higher in patients who had achieved a response to their last therapy compared with those who were nonresponders (29% versus 18%), but the difference did not reach statistical significance (data not shown in table). This original approach had not factored in the duration of response to last therapy. An additional subgroup analysis by sensitivity or resistance to the last qualifying therapy was introduced to factor in the quality of the previous response using a response duration criterion.

Sensitivity to the last qualifying therapy was highly predictive of response; 39 patients were considered to have sensitive disease and the objective response rate in this subgroup was 41%. This is noteworthy, having been achieved with single-agent VSLI.

Clearly, the clinical need is higher in patients who have resistant disease. The resistant subgroup of 80 patients achieved an objective response rate of 18%. For three-quarters of the resistant patients (58 patients) the last therapy was a combination regimen and they achieved a VSLI response rate of 17%.

Within the resistant subgroup, 60 patients (50% of the ITT population) had disease that was clearly refractory to the last therapy (SD or PD as the only outcome to last therapy) and the objective response rate in this subgroup was also 18%. An objective response rate of 18% in refractory and resistant patients is a clinically important rate of response, demonstrating that VSLI has significant clinical activity.

3.9.4 Multivariate Subgroup Analyses

The 2 strongest predictors of objective response rate identified in the univariate analyses were the number of prior regimens and sensitivity to last therapy. Recognizing that it was possible that these 2 variables could be highly correlated and that other characteristics linked to advanced stage of disease, such as bone marrow involvement, may also be impacting the outcome, additional exploratory multivariate regression analyses were undertaken to understand the relative contribution of the apparent prognostic factors.

Logistic regressions were conducted for objective response rate using both the IRP and the Investigator data. Potential prognostic variables included prior therapy regimens, sensitivity to last therapy, center, prior ABMT, per-protocol status, gender, and IPI score.

Results showed that the extent of prior therapy and sensitivity to last qualifying therapy were important predictors of response. Sensitivity to last qualifying therapy was also important for time to progression. Furthermore, sensitivity to last qualifying therapy and IPI score had an impact on overall survival. No factors were prognostic for duration of response.

Given that the extent of prior therapy and sensitivity to last qualifying therapy are such important predictors of response, the most informative presentation of the expected ORR for the intended population is presented in Table 18 for the 4 subgroups.

TABLE 18. Objective Response by Number of Prior Regimens and Sensitivity to Last Qualifying Therapy

Number of Prior Regimens Sensitivity to Prior Regimen	Number (%) of Responders	
≤2 Regimens[a] (n=24)	11	(46)
Sensitive[a] (n=11)	7	(64)
Resistant (n=13)	4	(31)
>2 Regimens (n=95)	19	(20)
Sensitive (n=28)	9	(32)
Resistant (n=67)	10	(15)

[a] Includes one patient (sensitive) who had only one prior regimen and responded to VSLI.

The objective response rate varied considerably across the 4 subgroups based on extent of prior therapy and sensitivity to last qualifying therapy, ranging from 15% in the poorest prognosis subgroup to 64% in the best prognosis subgroup. Therefore, the overall objective response rate of 25% observed in this study was very much a result of the relative proportions of patients enrolled in the 4 subgroups.

3.9.5 Efficacy by Sensitivity or Resistance to Last Qualifying Therapy

Table 19 provides a summary of all efficacy endpoints for the sensitive- and resistant-disease subgroups of patients according to the IRP and Investigator assessments.

TABLE 19. Efficacy by Sensitivity to Last Therapy – ITT Population

Efficacy Endpoint	IRP Review		Investigator Review	
	Sensitive (n=39)	Resistant (n=80)	Sensitive (n=39)	Resistant (n=80)
ORR: Number (%) of responders [95% CI]	16 (41.0) [26, 58]	14 (17.5) [10, 28]	20 (51.3) [35, 68]	9 (11.3) [5, 20]
Median[a] duration of response (days) [95% CI]	>77[b] [63, –][c]	85 [30, –][c]	71 [57, 99]	109 [71, 249]
Median[a] TTP (days) [95% CI]	217 [85, 342]	64 [51, 122]	98 [70, 114]	50 [40, 58]
Median[a] survival (months) [95% CI]	–	–	12.9 [7.0, 21.9]	4.6 [3.3, 6.9]

[a] Median estimate from Kaplan-Meier analysis.
[b] Median not reached.
[c] Upper limit of 95% CI not estimable.

From the data summarized in Table 19, the profound effect of resistant disease is apparent. According to the IRP review, patients with resistant disease achieved an ORR of 18%, with an estimated median duration of 85 days; the estimated median was 64 days for TTP. In contrast, the sensitive-disease patients had efficacy outcomes approximately twice the magnitude shown for the resistant-disease patients: an ORR of 41% versus 18% and an estimated median of 217 days versus 64 days for TTP.

The Investigator assessments provided similar outcomes to the IRP assessments on all efficacy parameters except TTP for the sensitive patients. Survival was more than twice as long for the patients with sensitive disease with a median estimate of 12.9 months versus 4.6 months for the patients with resistant disease.

The majority of the patients in the trial had resistant disease (67% using the 3-month criterion). Therefore, the overall efficacy outcomes for the ITT population are strongly influenced by the high proportion of patients with resistant disease in this trial.

3.9.6 Landmark Survival Analysis

The traditional method of testing for survival differences between responders and nonresponders using the log-rank test contains two significant biases; one is introduced by defining early death as nonresponse and the second is caused by including the time before response as part of the survival time for responders (lead-time bias). The Landmark technique offers a method for reducing these two biases, as described by Anderson, Cain and Gelber (50). Using this method, an appropriate landmark time point on the study is selected, for example at the first evaluation for response. Those patients still on study at the landmark time are divided into two groups based on whether they have responded before that time. The survival curves are then calculated from the landmark time point onwards and the two groups are compared to determine if survival from the landmark depends on the patient's response status at the landmark. Patients who die or are lost to follow-up before the landmark do not contribute to the analysis and patients who respond after the landmark are analyzed as nonresponders.

Even with this improved methodology, the Landmark method cannot support a definitive conclusion regarding causality, namely that response prolongs survival. The ability to achieve response may simply be a marker for favorable prognosis patients who would have lived longer anyway. One approach used to try to examine causality is to add covariates that are correlated with both response and survival into the model. If a significant relationship between response and survival disappears

when these covariates are taken into account, then the evidence for a causal relationship between response and survival is reduced.

In this landmark analysis, selection of the landmark point was done empirically to maximize the number of responders while at the same time minimize the loss of survival information. Using this approach a landmark time point of 57 days was selected. Given that the first scheduled assessment of objective tumor response was after 3 cycles of therapy (42 days) this is a reasonable landmark. In this study, sensitivity to last qualifying therapy was found to be a significant prognostic factor for ORR and for overall survival. IPI score was a highly significant factor for overall survival, but not for ORR.

Landmark analyses were conducted using Day 57 as the landmark without stratification and also with stratification based on sensitivity to last qualifying therapy and IPI score at study entry (Table 20, Figure 12).

TABLE 20. Summary of Landmark Survival Analysis by IRP Responder Status at Day 57

Statistic	Responders (n=25)	Nonresponders (n=80)
Non-stratified Analysis		
Number (%) of Patients Alive	9 (36.0)	17 (21.3)
Number (%) of Patients Dead	16 (64.0)	63 (78.8)
Median survival from Day 57 (months)	19.8	4.9
95% CI (months)	[7.8, –][a]	[2.8, 6.7]
Hazard ratio[b]	0.57	
95% CI	[0.33, 0.99]	
Log rank *P*-value	.043	
Wilcoxon *P*-value	.019	
Stratified Analysis[c]		
Hazard ratio[b]	0.48	
95% CI	[0.27, 0.86]	
P-value	.013	

[a] Upper limit of 95% CI not estimable.
[b] Hazard ratio of responder:nonresponder.
[c] Sensitivity to last qualifying therapy and baseline IPI score were included as covariates.

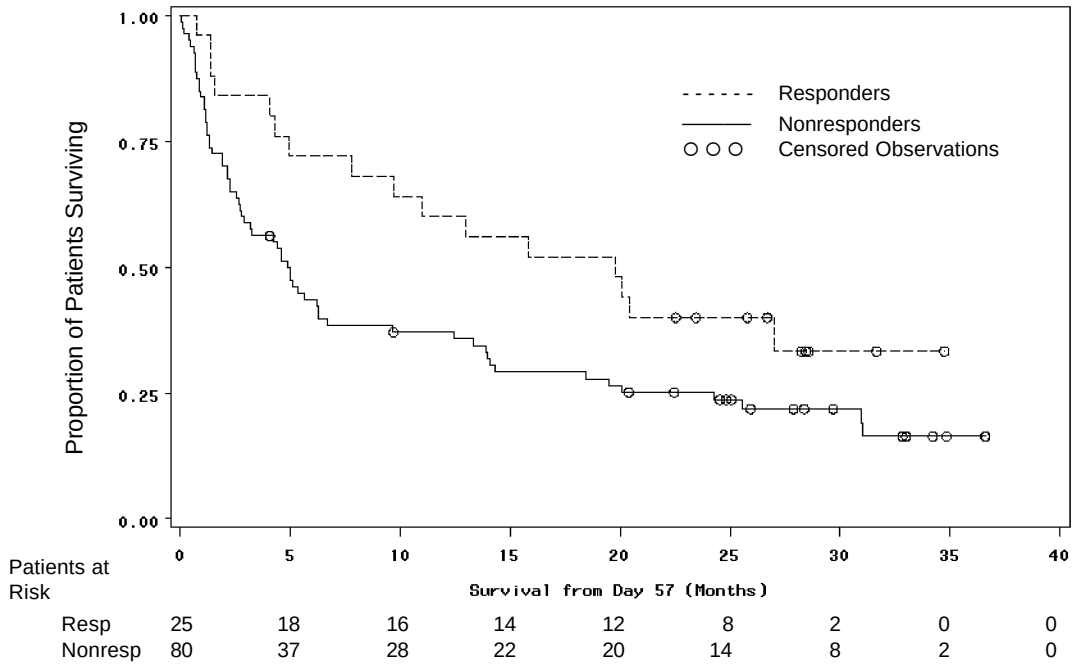

FIGURE 12. Landmark Analysis Survival Curves

Responders had a median survival of 19.8 months from the landmark (Day 57) while nonresponders had a median survival of 4.9 months. The hazard ratio of responders versus nonresponders is 0.57 with a 95% CI of [0.33, 0.99] indicating that responders are approximately half as likely to die after the landmark as nonresponders. To determine whether this correlation of survival with response can be accounted for by other covariates, the landmark analysis was conducted including stratification for sensitivity and IPI score. Using this stratified model the hazard ratio of responders versus nonresponders was 0.48 (95% CI of [0.27, 0.86]).

The significant correlation between response to VSLI and survival is at least maintained and possibly even stronger with the addition of the covariates, indicating that even after consideration of the factors that were identified as predictors of survival (IPI and disease sensitivity), response to VSLI is correlated with overall survival.

It is acknowledged that the ability to achieve response may simply be a marker for favorable prognosis patients who would have lived longer anyway. However, the IPI score encompasses the 5 factors internationally recognized as being important contributors to survival outcome (Age, Ann Arbor stage, ECOG performance status, LDH levels, and extent of extranodal disease) (49, 52). Furthermore, the sensitivity or resistance of the patient's disease to previous therapy should also encompass these and many other unidentified factors that might predict responsiveness to therapy. Therefore, the statistically significant correlation of response and survival in the stratified analysis in which both IPI and sensitivity to therapy were included as covariates, although only an exploratory analysis in this uncontrolled trial, is consistent with the hypothesis that response to VSLI has contributed to extended survival.

3.10 Safety Results

3.10.1 Deaths, Withdrawals and Other Serious Adverse Events

A summary of the key safety endpoints is provided in Table 21 based on the 119 patients in the pivotal Phase IIb study. All adverse events (AEs) occurring within 30 days of the last VSLI dose or AEs beginning during this period that resulted in withdrawal from study treatment or death have been summarized.

TABLE 21. Summary of Key Safety Endpoints

Category[a]	Number (%) of Patients (n=119)			
	All Adverse Events		Associated[b] Adverse Events	
Patients with any adverse event	117	(98)	113	(95)
Unique Patients with a Serious AE[c]	50	(42)	21	(18)
All deaths within 30 days of Last VSLI Dose	16	(13)	0	(0)
Withdrawal due to an adverse event	18	(15)	17	(14)
Other serious adverse events[d]	41	(34)	19	(16)

[a] Patients may be reported in more than one category.
[b] Associated was defined as possibly, probably, or definitely related to study treatment.
[c] Unique patients who died, withdrew due to a serious adverse event, or experienced at least 1 other serious adverse event.
[d] Serious adverse events other than those leading to death or withdrawal from treatment.

At least 1 AE was reported for 98% of patients and 95% of patients reported associated AEs. No deaths were associated with VSLI. Sixteen patients (13%) died within 30 days of the last VSLI dose: 14 from disease progression and 2 from worsening of a preexisting comorbidity (cardiac-related deaths in patients with ischemic heart disease).

Withdrawals Due to Adverse Events

Table 22 lists the 18 patients who withdrew from study treatment due to a treatment-emergent AE shown according to the last cycle of VSLI received. Patient numbers are given to provide a reference to patient summaries included in Appendix D.

TABLE 22. Patients Withdrawn from Treatment Due to Adverse Events by Cycle

C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15
	73-02	12-09	14-03[a]	01-09[a]	01-01[a]		21-02[a]			01-12[a]				13-01[a]
		12-10	16-06	01-22[a]	12-06[a]					12-04[a]				
			21-03[a]	22-01[a]										
			22-02[a]	27-01										
			66-01[a]											
	1	2	5	4	2		1			2				1

The colors denote the worst grade of AE that caused withdrawal from VSLI therapy:
Grade 1, Grade 2, Grade 3, Grade 4.
[a] Additional details are provided in patient summaries in Section 4 or Appendix D.

Of the 18 patients withdrawing from study treatment due to AEs, 17 patients had AEs that were associated with VSLI treatment. Neurologic AEs, all of which were associated with VSLI treatment,

were the primary reasons for withdrawal for 16 patients. Since 86% of patients had 2 or more prior regimens of neurotoxic agents, this incidence of withdrawals due to neurologic AEs is not unexpected.

The two patients who were withdrawn for non-neurologic AEs were Patients 73-02 and 01-12 and both experienced Grade 4 adverse events.

Patient 73-02 was withdrawn from VSLI therapy on Day 29 (Cycle 2, Day 16) having experienced a Grade 4 duodenal obstruction due to lymphoma that was considered to be not associated with VSLI therapy.

Patient 01-12 was withdrawn from therapy on Day 328 (Cycle 11, Day 85) due to progressive cytopenias (Grade 4 neutropenia and Grade 3 thrombocytopenia) that were considered to be possibly associated with VSLI therapy. This patient had previously received 6 chemotherapy/immunotherapy regimens (3 were combination regimens) including ABMT and radioimmunotherapy (Bexxar®). Two days after he was withdrawn from study, he was diagnosed with AML, which was considered to be unrelated to VSLI therapy. More details are provided in Appendix D.

All other patients were withdrawn for neuropathy considered to be due to VSLI therapy. The remaining patient who had a Grade 4 event was Patient 14-03.

Patient 14-03 was withdrawn from therapy on Day 56 (Cycle 4, Day 15) due to Grade 3 cachexia (not related to VSLI) and Grade 4 proximal muscle weakness (possibly related). Prior to study entry, he had received 2 classes (3 regimens) of chemotherapies that cause peripheral neuropathy; vinca alkaloid (1 regimen) and platinum (2 regimens). He entered the trial with Grade 2 generalized and right hand weakness, Grade 2 constipation, Grade 2 generalized pain, Grade 1 generalized and hand numbness and paresthesia, and chronic Grade 3 right hand weakness due to syringomyelia. More details are provided in Appendix D.

The color coding in Table 22 indicates that two patients were withdrawn for Grade 1 neuropathy. Both were elderly patients: Patient 12-06 (age 76 years) developed Grade 1 leg weakness and Patient 21-02 (age 74 years) had absent knee, bicep, and brachioradialis reflexes.

Other Serious Adverse Events

Forty-one patients had other SAEs not leading to death or withdrawal from treatment. Of these 41 patients, 10 patients had SAEs leading to death and are included in the death category; 6 patients had AE/SAEs leading to withdrawal from study treatment and are included in the withdrawal category.

Of these 41 patients who had other SAEs not leading to death or withdrawal from treatment, 19 patients had associated SAEs. No clinical pattern emerged from the associated serious adverse events that were reported. Non-neutropenic fever was reported in 6 patients and thrombocytopenia was reported in 3 patients, followed by anemia, febrile neutropenia, and dehydration in 2 patients each. Other Grade 3 or 4 associated SAEs were single occurrences of Grade 4 atrial fibrillation, cranial neuropathy, confusion, cellulitis and pneumonia and Grade 3 esophageal ulcer and deep vein thrombosis. Only 2 severe infections were reported, confirming that severe neutropenia was not a common consequence of VSLI treatment.

3.10.2 All Adverse Events

Individual adverse events at the preferred term level (all grades) reported in =5% of patients for all AEs are summarized in Table 23, grouped by System Organ Class (SOC) and rank ordered from highest to lowest frequency. The display in Table 23 includes all AEs and associated AEs, with a total column and the incidence of Grade 3 and Grade 4 events for each category. AEs are counted once per occurrence in the number of events summary. Patients are counted once at the highest severity for each preferred term if they had multiple occurrences of the same AE. Patients are also counted once within SOC by worst grade if they experienced multiple AEs within that SOC.

TABLE 23. Adverse Events Reported in 35% of Patients

(Page 1 of 3)

		Number (%) of Patients (n=119)					
		All Adverse Events			Associated[a] Adverse Events		
SYSTEM ORGAN CLASS Preferred Term	No. of Events	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
AT LEAST 1 AE		117 (98)	54 (45)	33 (28)	113 (95)	54 (45)	16 (13)
NERVOUS SYSTEM DISORDERS	593	110 (92)	39 (33)	5 (4)	105 (88)	34 (29)	5 (4)
Areflexia	66	58 (49)	6 (5)	0 (0)	57 (48)	5 (4)	0 (0)
Ataxia	6	6 (5)	1 (1)	1 (1)	6 (5)	1 (1)	0 (0)
Dizziness (excl vertigo)	10	10 (8)	1 (1)	0 (0)	4 (3)	1 (1)	0 (0)
Dysgeusia	7	7 (6)	0 (0)	0 (0)	7 (6)	0 (0)	0 (0)
Gait Abnormal	26	21 (18)	1 (1)	0 (0)	19 (16)	1 (1)	0 (0)
Headache	22	16 (13)	0 (0)	0 (0)	9 (8)	0 (0)	0 (0)
Hypoesthesia	82	76 (64)	17 (14)	0 (0)	74 (62)	17 (14)	0 (0)
Hyporeflexia	61	51 (43)	2 (2)	0 (0)	50 (42)	2 (2)	0 (0)
Insomnia	22	22 (19)	2 (2)	0 (0)	11 (9)	2 (2)	0 (0)
Paresthesia	86	75 (63)	14 (12)	0 (0)	74 (62)	14 (12)	0 (0)
Peripheral Neuropathy	12	12 (10)	5 (4)	0 (0)	12 (10)	5 (4)	0 (0)
Peripheral Sensory Neuropathy	56	45 (38)	3 (3)	0 (0)	45 (38)	3 (3)	0 (0)
Weakness	80	71 (60)	22 (19)	3 (3)	60 (50)	20 (17)	3 (3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	256	95 (80)	13 (11)	7 (6)	63 (53)	7 (6)	1 (1)
Chest Pain	17	15 (13)	1 (1)	0 (0)	7 (6)	0 (0)	0 (0)
Fatigue	70	56 (47)	8 (7)	0 (0)	32 (27)	5 (4)	0 (0)
Edema	7	7 (6)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Edema Peripheral	10	10 (8)	2 (2)	0 (0)	2 (2)	0 (0)	0 (0)
Pain	37	32 (27)	3 (3)	1 (1)	15 (13)	0 (0)	1 (1)
Pyrexia	62	42 (35)	2 (2)	0 (0)	32 (27)	1 (1)	0 (0)
Rigors	18	17 (14)	0 (0)	1 (1)	11 (9)	0 (0)	1 (1)

[a] Associated was defined as possibly, probably, or definitely related to study treatment as assessed by the Investigator.

TABLE 23. Adverse Events Reported in ³5% of Patients

(Page 2 of 3)

SYSTEM ORGAN CLASS Preferred Term	Number (%) of Patients (n=119)						
		All Adverse Events			Associated[a] Adverse Events		
	No. of Events	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
GASTROINTESTINAL DISORDERS	297	92 (77)	13 (11)	3 (3)	76 (64)	12 (10)	0 (0)
Abdominal Pain	22	22 (19)	3 (3)	2 (2)	11 (9)	1 (1)	0 (0)
Abdominal Pain Upper	7	7 (6)	1 (1)	0 (0)	4 (3)	0 (0)	0 (0)
Constipation	82	67 (56)	6 (5)	0 (0)	47 (40)	6 (5)	0 (0)
Diarrhea	33	26 (22)	2 (2)	0 (0)	13 (11)	1 (1)	0 (0)
Dyspepsia	6	6 (5)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Dysphagia	6	6 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea	52	40 (34)	4 (3)	0 (0)	30 (25)	2 (2)	0 (0)
Vomiting	34	26 (22)	3 (3)	0 (0)	17 (14)	1 (1)	0 (0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	147	73 (61)	8 (7)	1 (1)	49 (41)	5 (4)	0 (0)
Arthralgia	29	26 (22)	3 (3)	0 (0)	17 (14)	2 (2)	0 (0)
Back Pain	25	21 (18)	0 (0)	0 (0)	11 (9)	0 (0)	0 (0)
Bone Pain	6	6 (5)	1 (1)	0 (0)	4 (3)	0 (0)	0 (0)
Myalgia	12	11 (9)	1 (1)	0 (0)	7 (6)	1 (1)	0 (0)
Pain in Jaw	6	6 (5)	1 (1)	0 (0)	6 (5)	1 (1)	0 (0)
Pain in Limb	47	38 (32)	5 (4)	1 (1)	27 (23)	2 (2)	0 (0)
Peripheral Swelling	6	6 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	144	61 (51)	29 (24)	8 (7)	49 (41)	24 (20)	8 (7)
Anemia	48	41 (35)	12 (10)	3 (3)	30 (25)	11 (9)	3 (3)
Leukopenia	13	11 (9)	4 (3)	0 (0)	8 (7)	4 (3)	0 (0)
Lymphopenia	10	6 (5)	3 (3)	0 (0)	5 (4)	3 (3)	0 (0)
Neutropenia	41	32 (27)	21 (18)	5 (4)	27 (23)	17 (14)	5 (4)
Thrombocytopenia	25	22 (19)	9 (8)	2 (2)	18 (15)	9 (8)	2 (2)
METABOLISM AND NUTRITION DISORDERS	97	59 (50)	13 (11)	4 (3)	26 (22)	6 (5)	0 (0)
Anorexia	16	16 (13)	3 (3)	0 (0)	10 (8)	1 (1)	0 (0)
Appetite Decreased	15	15 (13)	0 (0)	0 (0)	4 (3)	0 (0)	0 (0)
Dehydration	11	11 (9)	5 (4)	0 (0)	6 (5)	2 (2)	0 (0)
Hypokalemia	13	11 (9)	5 (4)	0 (0)	5 (4)	2 (2)	0 (0)
Hypomagnesemia	8	7 (6)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	119	57 (48)	6 (5)	8 (7)	15 (13)	0 (0)	1 (1)
Cough	16	15 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dyspnea	28	24 (20)	2 (2)	3 (3)	8 (7)	0 (0)	1 (1)
Hoarseness	7	6 (5)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)
Pharyngolaryngeal Pain	7	7 (6)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Rhinorrhea	12	10 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a] Associated was defined as possibly, probably, or definitely related to study treatment as assessed by the Investigator.

TABLE 23. Adverse Events Reported in ³5% of Patients

(Page 3 of 3)

SYSTEM ORGAN CLASS Preferred Term	Number (%) of Patients (n=119)						
		All Adverse Events			Associated[a] Adverse Events		
	No. of Events	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
SKIN AND SUBCUTANEOUS DISORDERS	56	43 (36)	1 (1)	0 (0)	25 (21)	1 (1)	0 (0)
Alopecia	11	11 (9)	1 (1)	0 (0)	10 (8)	1 (1)	0 (0)
Night Sweats	7	7 (6)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)
Pruritus	10	9 (8)	0 (0)	0 (0)	5 (4)	0 (0)	0 (0)
Rash	7	6 (5)	0 (0)	0 (0)	4 (3)	0 (0)	0 (0)
INFECTIONS AND INFESTATIONS	57	38 (32)	9 (8)	2 (2)	9 (8)	0 (0)	2 (2)
Urinary Tract Infection	12	8 (7)	2 (2)	0 (0)	1 (1)	0 (0)	0 (0)
INVESTIGATIONS	58	30 (25)	8 (7)	2 (2)	12 (10)	5 (4)	0 (0)
Blood LDH Increased	8	8 (7)	2 (2)	1 (1)	0 (0)	0 (0)	0 (0)
Weight Decreased	16	15 (13)	1 (1)	0 (0)	6 (5)	1 (1)	0 (0)
RENAL AND URINARY DISORDERS	27	21 (18)	1 (1)	0 (0)	9 (8)	0 (0)	0 (0)
Nocturia	9	8 (7)	0 (0)	0 (0)	5 (4)	0 (0)	0 (0)
PSYCHIATRIC DISORDERS	38	19 (16)	1 (1)	1 (1)	5 (4)	0 (0)	1 (1)
Anxiety	14	12 (10)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Depression	10	7 (6)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
CARDIAC DISORDERS	19	18 (15)	3 (3)	2 (2)	3 (3)	0 (0)	1 (1)
Tachycardia	11	11 (9)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
EAR AND LABYRINTH DISORDERS	11	9 (8)	0 (0)	0 (0)	4 (3)	0 (0)	0 (0)
Tinnitus	6	6 (5)	0 (0)	0 (0)	4 (3)	0 (0)	0 (0)

[a] Associated was defined as possibly, probably, or definitely related to study treatment as assessed by the Investigator.

The most frequent adverse events reported were observed in the Nervous System, and included hypoesthesia (64% of patients), paresthesia (63%), weakness (60%), areflexia (49%), and hyporeflexia (43%). Gastrointestinal Disorders that were seen most often were constipation (56%), nausea (34%), diarrhea (22%), vomiting (22%), and abdominal pain (19%). General Disorders that were observed frequently included fatigue (47%), pyrexia (35%), and pain (27%).

Although severe events were reported at a high incidence overall, in most of the system organ classes, the majority of adverse events were Grade 1 or 2. Most Grade 3 or 4 events were isolated occurrences. Many of these events were disease related or due to other comorbidities. Disease progression, multi-organ failure, duodenal obstruction, hepatic failure and jaundice were all disease-related events, as were the majority of the severe events in the Respiratory Disorders (airway obstruction, cardio-respiratory arrest, dyspnea, respiratory distress and respiratory arrest). Severe infections, including bacteremia, catheter-related infection, fungemia, and pneumonia, were primarily considered unrelated to study drug and were likely complications of progressive disease (data not shown in table).

Although the majority of patients (59%) reported at least 1 Grade 3 or 4 associated event, at the level of individual events most patients had associated events of Grade 1 or 2 as their worst severity.

When adverse events were assessed by association to study drug, the majority of Nervous System Disorders were associated. Nervous Disorders were reported as associated and Grade 3 in 29% of patients and Grade 4 in 4% (56% were Grade 1 or 2). Approximately half of the patients who experienced a Grade 3 neurologic event continued to receive VSLI. Frequently reported neurologic associated adverse events were generally mild or moderate in severity. Hypoesthesia, reported as associated in 62% of patients, was seen as Grade 3 in 14% of patients and paresthesia (also associated in 62%) was reported as Grade 3 in 12% of patients; no Grade 4 events were reported for hypoesthesia or paresthesia. Weakness (associated in 50%) was seen as Grade 3 in 17% of patients and as Grade 4 in 3%.

In the Blood and Lymphatic System, most of the reported events were considered to be associated with VSLI. Blood and Lymphatic Disorders were reported as Grade 3 in 20% of patients and Grade 4 in 7% (14% were Grade 1 or 2). The severity of hematologic events showed that neutropenia (associated in 23% of patients) was reported as Grade 3 in 14% of patients and as Grade 4 in 4%. No Grade 3 infections were reported and only 2 Grade 4 infections were seen (cellulitis and pneumonia) (data not shown in table). This low percentage (2%) of Grade 3 and 4 infections suggests the neutropenia that occurred did not result in significant clinical consequences. The incidence of febrile neutropenia was also low (3 patients overall, 2 patients with association; 1 was Grade 3 and the other was Grade 4). Anemia (associated in 25%) and thrombocytopenia (associated in 15%) were reported as Grade 3 in 9% and 8% of patients, respectively. Anemia was reported as Grade 4 in 3% and thrombocytopenia was reported as Grade 4 in 2% of patients.

Most other frequently reported associated adverse events were graded as mild (Grade 1) or moderate (Grade 2) in severity. Areflexia (associated in 48%), constipation (40%), and fatigue (27%) were reported as Grade 3 in 4-5% of patients; peripheral sensory neuropathy (associated in 38%), nausea (25%), pain in limb (23%), and arthralgia (14%) were reported as Grade 3 in 2-3%; pyrexia (associated in 27%), vomiting (14%), and diarrhea (11%) were reported as Grade 3 in 1% of patients. None of these associated adverse events were reported as a Grade 4 event.

The number of events (number of episodes) is also provided in Table 23 for each specific adverse event preferred term. The ratio of number of events to number of patients was generally between 1:1 and 2:1. This low ratio indicates that multiple occurrences of the same events were reported infrequently.

3.11 Neurotoxicity Data

3.11.1 Prior Exposure to Neurotoxic Agents

The extent of prior neurotoxic agent exposure is presented in Table 24.

TABLE 24. Prior Exposure to Neurotoxic Agents

	Percentage of Patients (n=119)
Prior Neurotoxic Agents	
Any Prior Neurotoxic Agent	100
Vinca Alkaloids	98
Platinums	67
Taxanes	14
Number of Prior Regimens Containing Neurotoxic Agents	
1	14
2	56
3-5	30

All patients had prior exposure to at least 1 neurotoxic agent; almost always a vinca alkaloid. The vinca alkaloid used was almost exclusively vincristine except for 3 patients who also had vinblastine. The majority of patients (69%) had been exposed to at least 2 classes of neurotoxic agents, predominantly vinca alkaloids and platinums. The platinum used was mostly cisplatin; only 14 patients used carboplatin and another 7 used cisplatin and carboplatin. The other class of neurotoxic agent was the taxanes where paclitaxel was exclusively used. Furthermore, the majority of patients (86%) had prior exposure to 2 or more regimens containing neurotoxic agents. As a consequence, 85% had some neurological deficit (abnormal reflexes or neurological symptoms) at study entry.

3.11.2 Neurological Symptoms

Neurological symptoms at study entry and on study are displayed in Table 25.

TABLE 25. Neurological Symptoms at Study Entry and On Study

	Percentage of Patients				
Neurological Symptom	**Normal**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Study Entry					
Any Neurological Symptom (n = 110)	35	42	19	3	1
Numbness (n = 108)	66	28	6	1	0
Paresthesia (n = 104)	68	27	4	1	0
Constipation (n = 106)	83	12	5	0	0
Pain (n = 108)	71	17	9	3	0
Weakness (n = 104)	79	10	9	2	1
Worst Grade on Study					
Any Neurological Symptom (n =112)	3	21	41	32	4
Numbness (n = 111)	23	40	23	14	1
Paresthesia (n = 111)	23	41	23	13	1
Constipation (n = 111)	35	37	25	3	0
Pain (n = 112)	36	24	31	8	1
Weakness (n = 111)	42	19	18	19	2

Grading based on NCI Common Toxicity Criteria

At study entry, 65% of patients presented with at least 1 neurological symptom. The majority of symptoms present were mild or moderate (Grade 1 or 2).

The incidence of each neurological symptom increased while patients were on study, however, the majority remained mild or moderate.

Worst grade change from study entry for each neurologic symptom is presented in Table 26.

TABLE 26. Change from Study Entry to Worst Toxicity Grade for Neurological Symptoms

	Percentage of Patients				
	Grade Change[a]				
Neurological Symptoms	**No Change**	**1 Grade**	**2 Grades**	**3 Grades**	**4 Grades**
Numbness (n=103)	44	29	18	9	0
Paresthesia (n=100)	36	34	20	7	0
Constipation (n=101)	48	32	18	1	0
Pain (n=102)	47	27	18	3	0
Weakness (n=98)	48	22	12	12	2

[a] Grading based on NCI Common Toxicity Criteria

Approximately 40-45% of the patients experienced no grade changes on study for each specific neurologic symptom. Of the patients who did have a grade change, most were 1-grade changes (22-34%), followed by a smaller percentage (12-20%) with 2-grade changes.

Figure 13 displays the mean (±SEM) changes in numbness of the hand from study entry to Cycle 6 for the 23 patients who completed therapy to that point. Hand numbness was the symptom most affected by VSLI treatment.

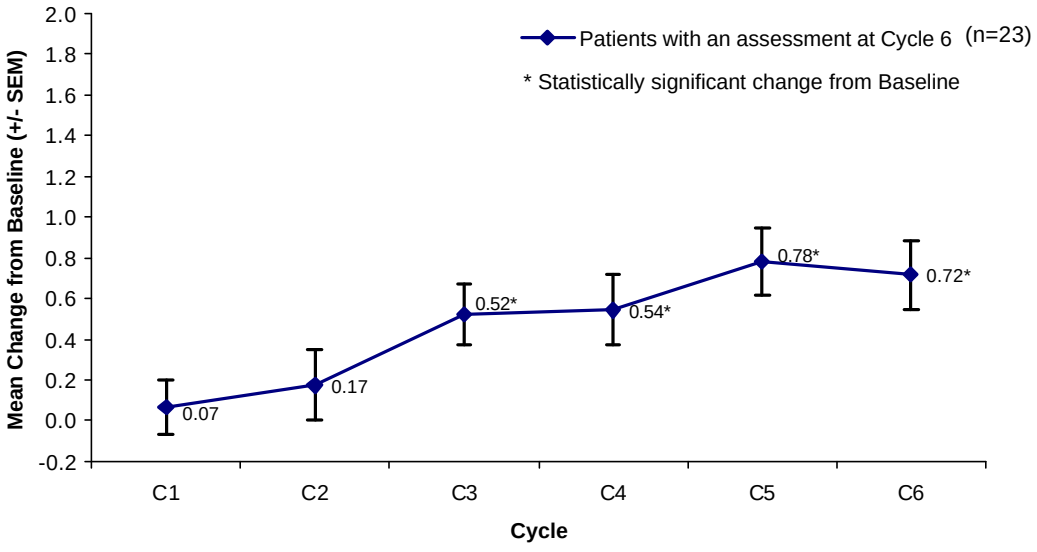

FIGURE 13. Mean Change in Hand Numbness Scores from Study Entry to Cycle 6 (n=23)

As shown in Figure 13 above, there was a gradual cumulative increase in hand numbness scores during the study. At the maximum change, there is just under a 1-grade change in severity after 5-6 cycles of VSLI treatment. An analysis based on all available patients by cycle showed a similar pattern.

3.11.3 Time and Cumulative Dose to Grade 3 or 4 Neurological Symptoms

Table 27 summarizes the data for the time and cumulative dose to Grade 3 or 4 neurological symptoms.

TABLE 27. Time and Cumulative Dose to Grade 3 or 4 Neuropathy – ITT Population

Kaplan-Meier Analysis	**n=115**		
Number (%) of patients with Grade 3 or 4 neuropathy	37	(32)	
Number (%) of patients censored	78	(68)	
Reason for censoring			
No Grade 3 or 4 neuropathy	74	(95)	
Death (not disease specific)	4	(5)	
Median time[a] in days to Grade 3 or 4 neuropathy [95% CI][b]	169.0	[85.0,	--]
Median cumulative dose (mg/m^2)[a] to Grade 3 or 4 neuropathy [95% CI][b]	21.2	[10.2,	31.2]

[a] Time/dose to Grade 3 or 4 neuropathy was defined as the time/total dose from the initial day of dosing to the first Grade 3 or 4 neuropathy symptom (pain, paresthesia, numbness, weakness, or constipation).

[b] Kaplan-Meier estimates of median time (days)/median cumulative dose (mg/m^2) to Grade 3 or 4 neuropathy. Patients not experiencing Grade 3 or 4 neuropathy were censored in the analysis at date of last contact on study.

In Table 27, only 115 patients were included in this analysis as 4 patients with Grade 3 or 4 neurological symptoms at study entry were not included. Thirty-seven patients developed Grade 3 or 4 neurological symptoms (constipation, numbness, pain, paresthesia or weakness) during the study. The estimated median time to Grade 3 or 4 neuropathy was 169 days or approximately 24 weeks. The estimated median cumulative dose to Grade 3 or 4 neuropathy was 21.2 mg/m^2 [95% CI: 10.2, 31.2], which is approximately 11 cycles. This is a substantial amount of vincristine considering that almost all of the patients would have received treatment regimens containing VCR, usually the standard CHOP regimen, and other neurotoxic agents.

Although neurologic recovery data were not prospectively collected, 13 of the 37 patients who developed a Grade 3 or 4 neurologic symptom had additional neurologic assessments performed after their symptoms reached this level of severity. Of these 13 patients, 5 continued treatment with VSLI and had attenuation of their neurologic symptoms by dose reductions and/or dose delays; details are provided in the patient summaries in Appendix D for Patients 01-12, 12-04, 22-01, 66-01, and 74-02.

Twelve (40%) of the 30 responding patients (based on the IRP assessments) developed Grade 3 or 4 neurological symptoms. Therefore, the majority of responders did not develop clinically significant neurological effects with VSLI treatment.

3.11.4 Neurologic Recovery

With conventional vincristine, severe neuropathy is usually prevented with dose adjustment and neurologic symptoms are eventually reversed when treatment is suspended or discontinued, although some neurologic abnormalities may persist for prolonged periods in some patients (57, 58).

The majority of patients in the Phase IIa and IIb studies were not followed for neuropathy recovery after they withdrew from treatment for disease progression as they were quickly started on a new therapy. Thus, the amount of neurological recovery data was minimal for patients in those trials. A few patients in the Phase IIb study have data available that document an improvement in their neuropathy after dose reductions or dose delays and these situations are described in the Patient Summaries for Patients 01-12, 12-04, 22-01, 66-01, and 74-02 (Appendix D).

However, there is one trial where neurological assessment is performed as part of the long-term follow-up, Study CA00004, in which VSLI was substituted for conventional VCR in the CHOP or R-CHOP regimen in patients with previously untreated aggressive NHL. VSLI was given at the same dose as in the relapsed NHL studies of 2.0 mg/m^2 without dose capping, but the schedule was every 3 weeks to be consistent with the dosing schedule of the other agents in the R-CHOP regimen. The median number of cycles of VSLI administered to 72 treated patients was 6, with a range of 1 to 8 cycles. These patients responded well to this first-line regimen (93% objective response in 68 evaluable patients) and they continue to be followed.

Numbness was the symptom most affected and was chosen to illustrate neurologic recovery. No Grade 3 neuropathy of any kind occurred in any patient; 9 patients (13%) developed Grade 2 numbness and 49 patients (68%) developed Grade 1 numbness.

Figure 14 shows the change from baseline in mean scores for numbness, based on the 37 patients who developed neuropathy and who also had follow-up assessments out to 9 or 12 months to allow evaluation of neurologic recovery.

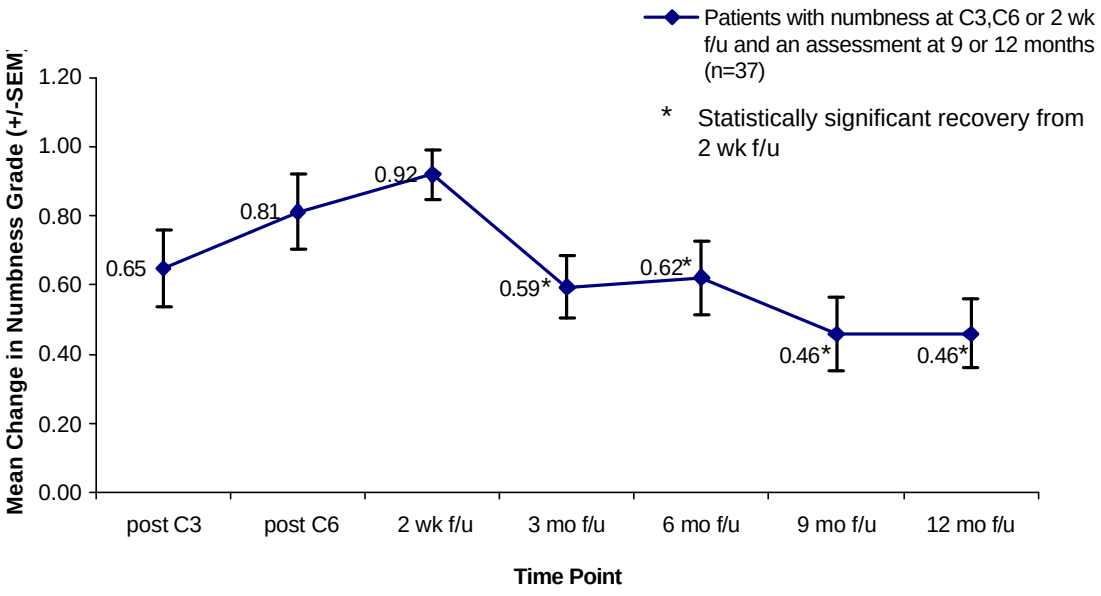

FIGURE 14. Neurologic Recovery for Patients who Developed Numbness in First-Line NHL Study

As shown in Figure 14, for patients who developed neuropathy, the change from baseline in mean severity grade for numbness was small, averaging approximately a 1-grade change at its maximum at the Week 2 post-treatment follow-up visit. Upon cessation of treatment, there was a statistically significant improvement in neuropathy noted at the next evaluation 3 months later. This was the period

of greatest recovery. Thereafter, the change in mean score gradually diminished indicating continued improvement in numbness. This gradual improvement is consistent with the pattern seen with conventional vincristine (58).

3.12 Laboratory Data

3.12.1 Hematology Results

Common Toxicity Criteria grades are shown for study entry and worst grade on study for hematology parameters in Table 28.

TABLE 28. Hematology Grades at Study Entry and On Study

	Percentage of Patients				
Parameter	**Normal**	**Grade 1[a]**	**Grade 2**	**Grade 3**	**Grade 4**
Study Entry					
Hemoglobin (n=119)	22	42	35	2	0
WBC count (n=119)	71	16	10	3	0
Neutrophils (n=118)	86	3	10	2	0
Platelet count (n=119)	61	26	8	5	0
Worst Grade on Study					
Hemoglobin (n=118)	6	34	46	13	2
WBC count (n=118)	38	21	26	13	2
Neutrophils (n=118)	51	7	15	19	8
Platelet count (n=118)	41	35	12	12	<1

[a] Grading based on NCI Common Toxicity Criteria

At study entry, patients had a profile consistent with the extensive prior therapies received and advanced disease in that 78% of patients had some level of anemia and 39% had thrombocytopenia. One-third of the patients were not eligible to receive another myelotoxic agent as they had neutrophil counts $<1.5 \times 10^9$/L or platelets $<100 \times 10^9$/L.

For the patients who had abnormal hemoglobin values on study, most (34-46%) had a Grade 1 or 2 hemoglobin value as their worst grade on study, with a few Grade 3 (13% of patients) and Grade 4 values (2% of patients) observed. For WBC counts, most patients (21-26%) had Grade 1 or 2 abnormalities as their worst grade on study. Similarly for platelet counts, most abnormalities (35% of patients) were Grade 1 on study.

The hematologic parameter with the greatest change on study was neutrophil counts. Normal neutrophil counts were seen in 86% at study entry; half of the patients never had a neutrophil abnormality on study. The worst grades on study were predominantly Grade 2 or Grade 3 (15% and 19% of patients, respectively). Grade 4 neutropenia was reported in 8%.

The treatment-emergent impact on hematologic parameters can be assessed by examining the maximum worsening that occurred on study. Hematology parameters summarized by worst grade change from study entry are presented in Table 29.

TABLE 29. Change from Study Entry to Worst Toxicity Grade for Hematology Parameters

	Percentage of Patients				
	Grade Change[a]				
Parameter	**No Change**	**1 Grade**	**2 Grades**	**3 Grades**	**4 Grades**
Hemoglobin (n=118)	47	40	9	1	0
WBC count (n=118)	49	25	14	9	0
Neutrophils (n=117)	52	15	11	15	5
Platelet count (n=118)	56	32	6	1	0

[a] Grading based on NCI Common Toxicity Criteria

For each hematologic parameter, about half of the patients had no change in toxicity grade with VSLI treatment. Approximately 38-49% of patients had worsening of specific hematologic parameters but most of them were 1-grade (15-40%) or 2-grade (6-14%) changes. The greatest change was seen in neutrophil counts, with 15% having a worsening of 3 grades and 5% have a worsening of 4 grades. Filgrastim was used prophylactically in only 2% of patients. Bone marrow involvement at study entry and prior transplant were risk factors for development of severe neutropenia. A worsening of 3 grades was reported in WBC counts for 9% and hemoglobin and platelet counts for 1% of patients. Overall, VSLI was well tolerated hematologically in these patients who had received several previous chemotherapy regimens.

3.12.2 Biochemistry Results

At study entry, the majority of the biochemistry parameters were normal. The greatest abnormality at study entry was observed in albumin levels. At study entry, albumin level was normal in 76 patients (64%); 16% had a Grade 1 abnormality, 17% were Grade 2, and 2% were Grade 3.

On study, no CTC grade change in biochemistry parameters was observed in most patients (62-93%). The greatest changes were observed in albumin and GGT, with a worsening observed in approximately 30% of patients. Abnormalities were mainly 1-grade worsenings (21-25%); 3-7% had a 2-grade worsening and 1-2% of patients had a 3-grade worsening. These abnormalities were likely related to the patient's disease or comorbidities.

3.13 Safety Conclusions from Integrated Safety Database of 537 Patients

To support this NDA, an integrated safety database included 537 patients from all studies conducted with VSLI across several types of cancer, including NHL, Hodgkin's Disease, ALL, small cell lung cancer, melanoma, pancreatic cancer, colorectal cancer, and sarcoma. In most of these studies VSLI was given at the same dose and schedule as in the NHL studies, but some studies included other chemotherapy or immunotherapy agents. Of the 537 patients, 434 patients were treated with single-agent VSLI and 103 patients were treated with VSLI in combination with other agents. Based on the analyses of this integrated safety database, it was concluded that VSLI has a similar spectrum and severity of toxicities as reported in the literature for conventional vincristine, despite at least a doubling of the dose intensity.

Three associated deaths occurred in the total safety database of 537 treated patients (0.6%) and in two of the three cases, the death was not fully attributed to VSLI but was also attributed to disease. A patient with infiltrating duct carcinoma in the Phase I dose-escalation study received 2.8 mg/m^2 and was hospitalized for increasing shortness of breath and pancytopenia on Day 4 (Cycle 1, Day 4) and died shortly thereafter; these events were considered possibly related to VSLI therapy. A patient with

small cell lung cancer died on Day 13 (Cycle 1, Day 13) of exacerbation of chronic obstructive pulmonary disease, considered to be probably related to VSLI therapy and to underlying relapsed lung cancer. A patient with pancreatic cancer died on Day 9 (Cycle 1, Day 9) of ascending cholangitis and sepsis that were considered possibly related to VSLI and to metastatic disease.

Bowel obstruction or ileus attributed to VSLI therapy was reported in 5 patients (0.9%) in the total safety database of 537 patients. A central line was not mandated for administration of VSLI in any of the study protocols. Mild to moderate injection site reactions occurred in 8 patients (1.5%). Preclinical data demonstrated the protective effect of the liposome against the vesicant effects of vincristine.

Potential adverse reactions due to the liposome did not appear to be a safety concern. Hand-foot syndrome has been well described with liposomal doxorubicin (55, 56). Two patients (0.4%) among the 537 in the safety database experienced mild desquamation of the skin that was attributed to VSLI. The incidence of suspected infusion-related pyrexia was approximately 10% in the 434 patients treated with single-agent VSLI and most reactions were mild. Apart from pyrexia, no acute infusion-type reactions were observed with VSLI administration and no other new toxicities were seen with VSLI compared to the clinical experience with vincristine.

Although no trials have been conducted in which VSLI and conventional vincristine were compared directly, the Kaplan-Meier analysis of the cumulative dose required to develop a Grade 3 or 4 neuropathy in the pivotal Phase IIb study estimated a median cumulative dose of 21 mg/m^2. This is a substantial amount of vincristine for these patients who have received numerous prior neurotoxic agents and this suggests that the liposomal encapsulation has enhanced the tolerability of vincristine.

4. PATIENTS WITH NET CLINICAL BENEFIT FROM VSLI TREATMENT

The results in the previous sections were presented for the whole population treated in the Phase IIb study and selected subgroups. Descriptions of group efficacy and safety outcomes are helpful for understanding the outcomes in the broad population and for statistical comparisons with minimal bias. In the setting of multiply relapsed NHL where palliation is the goal of therapy, it is also helpful to evaluate individual patients for their net clinical benefit, considering the reduction in tumor burden achieved, the resolution of disease-related symptoms and other evidence of patient benefit, while also considering the toxicities of the therapy. This section summarizes the evidence of clinical benefit described in individual patient benefit summaries (Appendix D) to allow further understanding of the clinical importance of the responses achieved with VSLI treatment.

A total of 38 patients were considered to be responders by either the IRP or the Investigator. In response to a request from the FDA, summaries of clinical benefit have been written for these 38 individual patients, as well as for 5 additional patients who achieved disease stabilization (SD) and who appear to have had clinical benefit from VSLI therapy, for a total of 43 patients. As most of the responders achieved partial responses, but not complete responses, the FDA expressed an interest in understanding the value of these partial responses and whether there was other evidence that the patients likely achieved clinical benefit. Patients were considered by INEX to have achieved net clinical benefit (a favorable benefit-risk ratio) if they achieved at least one of the following and did not have significant VSLI-related toxicity.

- Clinically meaningful period of disease-free survival (durable CR)
- Tumor response to VSLI that permitted subsequent stem cell transplant, a potentially curative therapy
- Improvement in tumor-related symptoms or ECOG performance status
- Better response or time to progression than achieved with previous standard chemotherapy regimen
- Clinically meaningful period of progression-free survival (durable PR or prolonged SD)
- Improvement in anemia, neutropenia, or thrombocytopenia present at study entry

Patients may have experienced more than one of the above categories of clinical benefit. The evaluation of net clinical benefit is admittedly a subjective evaluation conducted by INEX, and therefore the patient benefit summaries are provided in Appendix D for review.

Clinically Meaningful Period of Disease-Free Survival

The following 5 patients were considered by INEX to have experienced clinically meaningful periods of disease-free survival due to VSLI therapy alone (i.e., did not receive transplant post VSLI).

- Patient 01-12 achieved a CR that lasted >9.0 months; he then developed acute myelogenous leukemia and required other treatment. His NHL never recurred, but he died of leukemia.
- Patient 12-01 achieved a CR and is alive with no evidence of disease at >36.6 months.
- Patient 33-06 achieved a CR and is alive with no evidence of disease at >26.9 months.

- Patient 35-01, with highly refractory disease, achieved a CRu that lasted almost 1 year.
- Patient 40-01 achieved a PR that is ongoing for >28 months with no subsequent therapies (unchanged residual pulmonary nodules suspected to be fibrotic tissue).

Tumor Response to VSLI that Permitted Subsequent Stem Cell Transplant

Six patients are described who received stem cell transplants after treatment with VSLI established that they had responsive disease. With the updated survival data, all 6 patients had survival times greater than 2 years and VSLI may have contributed to these long survival times by enabling them to be considered for transplant.

- Patient 01-05, >38.5 months (alive, no evidence of disease)
- Patient 01-19, 28.9 months (died)
- Patient 01-20, >28.6 months (alive, no evidence of disease)
- Patient 01-23, >26.7 months (alive, no evidence of disease)
- Patient 22-01, >30.5 months (alive, no evidence of disease)
- Patient 22-03, >27.7 months (alive, no evidence of disease)

Improvement in Tumor-Related Symptoms or ECOG Performance Status

It is important to note that the Phase IIb study had no formal symptom improvement endpoint. Thus the symptom improvements described in the patient benefit summaries are based on patient-reported evidence collected on the case report form, mostly as improvements to baseline signs and symptoms, not on prospectively assessed outcomes using validated symptom scores or quality-of-life instruments. Therefore, the level of evidence for symptom improvement is not of the standard expected for prospective efficacy endpoints. Nevertheless, these data were collected the same way as adverse events were collected and therefore can be helpful in assessing whether patients likely experienced symptomatic benefit from treatment with VSLI. These baseline symptoms were graded according to the CTC grading scale and improvements of at least 1 grade or total resolution were noted. Performance status was reported by the Investigator after assessing and interviewing the patient during the clinical visit.

Table 30 provides a summary of the symptomatic and ECOG performance status improvement observed in the 43 patients.

TABLE 30. Summary of Symptomatic and ECOG Performance Status Improvements

Category of Improvement	Number (%) of Patients (n=43)	
Symptomatic or ECOG PS Improvement	26	(60.5)
ECOG PS Improved	13	(30.2)
Both Symptomatic and ECOG PS Improvements	7	(16.3)
Symptomatic Improvement	20	(46.5)
B Symptoms	12	(27.9)
Night Sweats	8	(18.6)
Fever	4	(9.3)
Weight Loss	3	(7.0)
Unspecified	1	(2.3)
Other Tumor-Related Symptoms	11	(25.6)
Pain	7	(16.3)
Dyspnea/Shortness of Breath	3	(7.0)
Itching	1	(2.3)
Fatigue	1	(2.3)
Pneumonia	1	(2.3)
Cough	1	(2.3)

Twenty-six of these 43 patients (60%) had documented improvement in either ECOG performance status (30%) or a disease-related symptom (47%). Symptomatic improvements were due to B symptoms (night sweats, fever, weight loss) in 12 patients (28%) and other tumor-related symptoms, mostly pain, in 11 patients (26%). Most symptoms were totally resolved. All of these patients who presented with B symptoms experienced an improvement with VSLI therapy.

It is of interest to summarize the other evidence of clinical benefit noted in the patients who achieved CR, CRu, or PR. Five of the 8 patients with CR or CRu by the IRP review had resolution of B symptoms or other disease-related symptoms or ECOG performance status; the remaining 3 were asymptomatic at study entry. Additionally, improvements in symptoms or performance status were documented in 15 of the 22 patients who achieved a PR according to the IRP review.

Other evidence of clinical benefit/antitumor activity described in the summaries includes resolution of pleural effusions and atelectasis caused by tumor obstruction, and resolution of ascites associated with liver involvement.

Better Response or Time to Progression (TTP) than Achieved with Previous Standard Chemotherapy

In addition to the patients who received stem cell transplants after VSLI and some who achieved long-lasting CRs, the following 9 patients were considered by INEX to have achieved better outcomes than they achieved with previous standard therapies.

- Patient 07-01, PR, a better response than achieved on his last 4 regimens
- Patient 01-13, SD with TTP >5.6 months, which was better than achieved with 2nd-line salvage regimen (ESHAP) and 3rd-line regimen of paclitaxel and topotecan
- Patient 12-04, PR lasting longer than with rituximab and comparable to that achieved with transplant
- Patient 13-01, SD with TTP >7 months, which was better than achieved with rituximab and comparable to that achieved with transplant

- Patient 21-03, PR with TTP >3.7 months in patient with highly refractory disease, which was better than achieved with last 2 therapies, one of which was transplant
- Patient 22-02, CR, a better response than achieved with rituximab
- Patient 26-01, PR, a better response than achieved with ProMACE-CytaBOM regimen
- Patient 66-01, PR with TTP >5.6 months, better than achieved with previous transplant
- Patient 72-01, PR with TTP >7.2 months, better than achieved with last two regimens (cisplatin, cytarabine; RICE)

Clinically Meaningful Period of Progression-Free Survival

In addition to those patients listed in several categories described above, the following 2 patients were considered by INEX to have achieved clinically meaningful periods of progression-free survival.

- Patient 21-02, SD with TTP >5.7 months in elderly patient with refractory disease after 6 prior regimens
- Patient 33-04, SD with TTP of 11.2 months, comparable to what was achieved with previous ESHAP regimen

Improvement in Anemia, Neutropenia, or Thrombocytopenia

Table 31 provides a summary of the improvements in disease-related hematologic and other laboratory parameter abnormalities observed in the 43 patients without the use of supportive therapies. Improvement was defined as at least a 1-grade change according to the CTC grading scale.

TABLE 31. Improvement in Disease-Related Hematologic and Other Laboratory Parameter Abnormalities[a]

Hematologic or Other Laboratory Parameter Abnormality	Number (%) of Patients (n=43)	
Resolution/Improvement of Baseline Anemia, Neutropenia, or Thrombocytopenia	15	(34.9)
Anemia Resolved/Improved	7	(16.3)
Neutropenia Resolved	2	(4.7)
Thrombocytopenia Resolved/Improved	8	(18.6)
Liver Function Tests Normalized/Improved	5	(11.6)
Hypoalbuminemia Resolved/Improved	10	(23.3)

[a] Selected parameters of clinical interest.

Fifteen (35%) of the 43 patients had documented resolution or improvement in anemia (7 patients), neutropenia (2), or thrombocytopenia (8) that had been present at study entry. These improvements were achieved with VSLI therapy and no other supportive growth factors. Improvement of anemia has been linked with improved quality of life, although no formal assessment of quality of life was performed in this study (53, 54).

Several of the 43 patients had very poor hematologic status at study entry, such that they could not have been treated with standard myelosuppressive chemotherapeutic agents. VSLI treatment was generally well tolerated, causing very little myelosuppression in these patients. A few patients required on-study support with erythropoietin, filgrastim, or transfusions and these details are provided in the patient summaries.

Elevated liver function tests normalized or improved in 5 patients who had lesions in the liver. Improved nutritional/metabolic status was documented with resolution or improvement in 10 of the 14 patients who presented with hypoalbuminemia at study entry.

Other evidence of clinical benefit/antitumor activity included resolution of tumor-related hypercalcemia.

Patient Benefit Summaries

Patient benefit summaries for all 43 patients were provided to the FDA and abbreviated versions are provided with this document in Appendix D for 40 patients; 2 patients considered to have achieved PR according to the Investigator (but not the IRP) did not appear to have any other evidence of clinical benefit according to the INEX review and are not included in Appendix D. One sample summary is provided below for Patient 35-01.

Each graphic contains a graph of the key efficacy and safety data, as well as an overall summary of the patient's case. At the top of each figure, there is a time scale and along this scale a gray bar indicates a period of 'antitumor activity' and a black bar indicates a period of 'clinical benefit' according to the INEX review. This relative assessment of activity versus benefit is admittedly a highly subjective assessment. Please note, however, that for most patients, there is evidence of antitumor activity or benefit well before the first documented objective response. This is relevant for the interpretation of the formal analysis of duration of response presented in Section 3.9.2.1.

FIGURE 15. Graphical Presentation of Efficacy and Safety for Patient 35-01

3 Prior Systemic Therapies	56-year-old woman	Best Response: CRu SPD Change: -100%
1. CHOP x6; PR of 2.8 mo.	Stage IV Primary mediastinal LBCL with sclerosis, IPI 1	Duration of Response: >10.6 mo
2. ESHAP x2; PD.	Per Protocol Eligible	Time to Progression: >12.4 mo
3. RICE x4; PD.	Refractory to Last Qualifying Therapy	Survival: >30.3 mo, alive with no evidence of disease

This 56-year-old Caucasian woman with refractory Stage IV primary mediastinal large B-cell lymphoma with sclerosis had received 3 combination chemotherapy regimens within her 1.3 years since first diagnosis. Her best response to previous therapy was a PR to CHOP that lasted less than 3 months and she had no response to her subsequent regimens (ESHAP, RICE). At study entry she had "unstable anemia" post chemotherapy. She had B symptoms and extensive disease in her chest and abdomen, including a pleural effusion, and numerous axillary, porta hepatis, and retroperitoneal nodes that were considered to be "too numerous to count" by the IRP.

The first evidence of VSLI antitumor activity was improvement in her Grade 2 hemoglobin level at Day 8 after the first cycle of VSLI, with normalization achieved by Day 57 after 4 cycles without the use of erythropoietin. Her B symptoms had resolved after 4 cycles of VSLI, with no further episodes of fever, night sweats or weight loss. Her weight had started to increase after 3 cycles and she had a 9% increase in her body weight after 5 cycles.

She achieved a best response of CRu per the IRP, with complete resolution of her extensive tumor burden, but without a repeated bone marrow biopsy until the end of the study. Her marrow involvement was indeterminate at baseline and negative at the end of the study, supporting the possibility that the CRu could have been a CR. The Investigator assessed her best response as a PR (lasting 8.2 months) due to a residual small axillary node, also noting complete resolution of all other disease. At Day 347, the Investigator noted 5 lesions by PET scan and declared PD. One of the IRP oncologists accepted this as evidence of PD, but the other two did not and thus the final IRP assessment was UE at this visit.

She tolerated treatment extremely well, receiving 20 cycles of VSLI (39.8 mg/m^2 total) without delays or reductions and only minimal neurotoxicity (Grade 1 numbness, paresthesia in hands and feet) and maintained an ECOG PS of 1 throughout the study.

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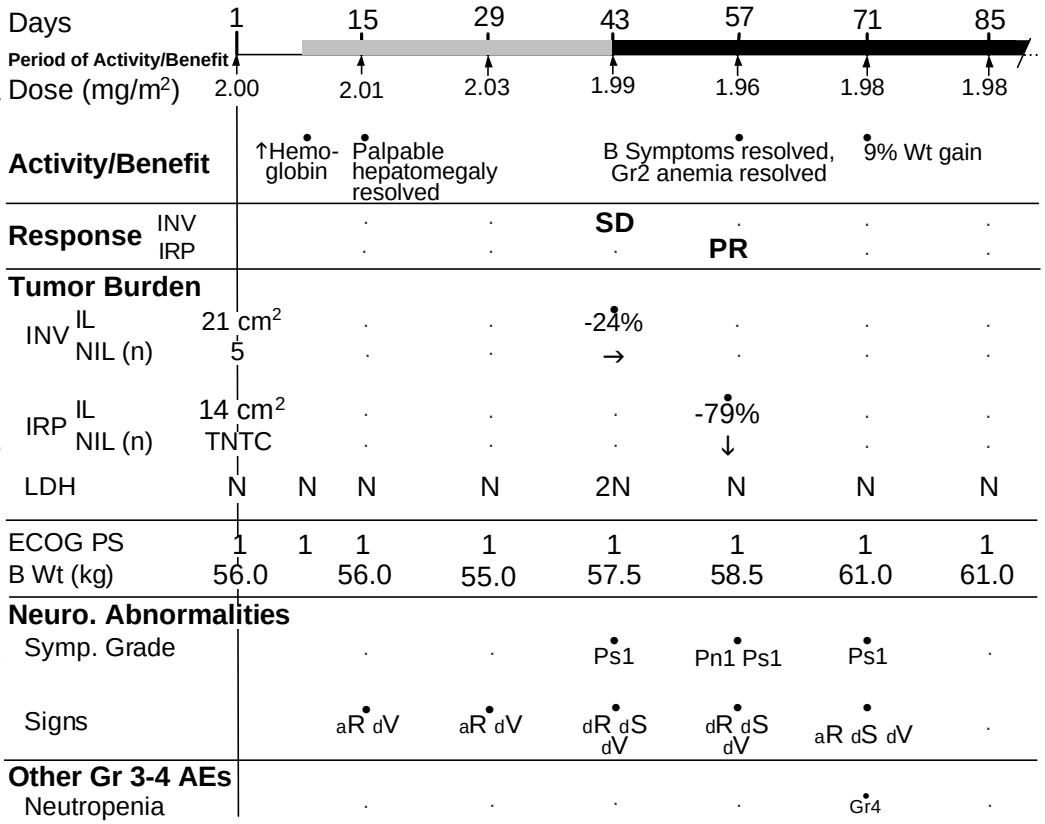

Legend: ↓Decrease ↑Increase →Stable **a** Absent **C** Constipation **CR** Complete Response **CRu** Complete Response Unconfirmed **d** diminished **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **UE** Unable to Evaulate

FIGURE 15. Graphical Presentation of Efficacy and Safety for Patient 35-01 (continued)

3 Prior Systemic Therapies 1. CHOP x6; PR of 2.8 mo. 2. ESHAP x2; PD. 3. RICE x4; PD.	56-year-old woman Stage IV Primary mediastinal LBCL with sclerosis, IPI 1 Per Protocol Eligible Refractory to Last Qualifying Therapy	Best Response: CRu SPD Change: -100% Duration of Response: >10.6 mo Time to Progression: >12.4 mo Survival: >30.3 mo, alive with no evidence of disease

Patient 35-01 continued

She reported constipation only once and had no nausea or vomiting. She did have transient neutropenia after the 5th cycle, which recovered without therapy. Her anemia resolved and her platelet count was almost always above 100.

The IRP assessed her CRu duration as >10.6 months with a time to progression of >12.4 months. She was alive with no evidence of disease (Investigator assessment) at 30.3 months after her first dose of VSLI, having received other chemotherapy and immunotherapy to achieve a CR again after VSLI.

Her response to VSLI, whether a CRu or a PR, is notable as her only previous response was to 1st-line CHOP, with a PR lasting <3 months. She had no response to two other prior regimens. Thus, VSLI alone produced a better response (in terms of duration, if not quality as well), than prior combination chemotherapy including non-liposomal vincristine.

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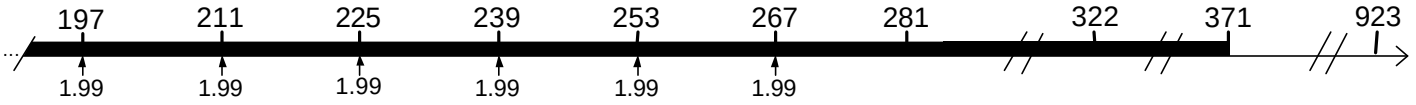
Days	99	113	127	141	155	169	183
Period of Activity/Benefit	↑	↑	↑	↑	↑	↑	↑
Dose (mg/m²)	1.98	1.98	1.98	1.98	1.98	1.99	1.99
Activity/Benefit							
Response INV	**PR**	.	.	.	**PR**	.	.
IRP	. **UE**	.	.	.	. **CRu**	.	.
Tumor Burden							
INV IL	-100%	.	.	.	-100%	.	.
INV NIL (n)	↓	.	.	.	↓	.	.
IRP IL	-100%	.	.	.	-100%	.	.
IRP NIL (n)	resolved	.	.	.	resolved	.	.
LDH	N	N	N	N	N	N	N
ECOG PS	1	1	1	1	1	1	1
B Wt (kg)	61.0	61.0	61.0	61.0	61.0	61.0	60.0
Neuro. Abnormalities							
Symp. Grade	C1 Ps1	Ps1	Ps1	Ps1	Ps1	Ps1	Ps1
Signs	aR dS aV	dR dS aV	dR dS aV	dR dS aV	dR dS aV	dR aV	dR aV
Other Gr 3-4 AEs							
None	.	.	.	.	.	.	.

Legend: ↓Decrease ↑Increase →Stable **a** Absent **C** Constipation **CR** Complete Response **CRu** Complete Response Unconfirmed **d** diminished **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **UE** Unable to Evaluate

FIGURE 15. Graphical Presentation of Efficacy and Safety for Patient 35-01 (continued)

3 Prior Systemic Therapies 1. CHOP x6; PR of 2.8 mo. 2. ESHAP x2; PD. 3. RICE x4; PD.	56-year-old woman Stage IV Primary mediastinal LBCL with sclerosis, IPI 1 Per Protocol Eligible Refractory to Last Qualifying Therapy	Best Response: CRu SPD Change: -100% Duration of Response: >10.6 mo Time to Progression: >12.4 mo Survival: >30.3 mo, alive with no evidence of disease



Activity/Benefit

Response	INV			**PR**			**PR**		**PR**	**PD**		
	IRP		**CRu**				**UE**	**CRu**	**UE**	**UE**		
Tumor Burden												
INV IL				-100%			-100%		-100%			
INV NIL (n)				→			→		↓	new		
IRP IL			-100%				-100%					
IRP NIL (n)			resolved				resolved					
LDH	N	N	N	N	N	N	N	N	N			
ECOG PS	1	1	1	1	1	1	1	1	1	1		
B Wt (kg)	60.0	60.0	60.0	60.0	60.0	60.0	61.0	60.0	60.0	60.0		
Neuro. Abnormalities												
Symp. Grade	Ps1	Ps1	Ps1	Ps1	Nu1 Ps1 W1	Nu1 Pn1 Ps1	Pn1 Ps1	Ps1 W1				
Signs	dR aV	dR aV	dR aV	dR aV	dR aV	dR aV	dR aV	dR aV				
Other Gr 3-4 AEs												
None												

Legend: ↓Decrease ↑Increase →Stable **a** Absent **C** Constipation **CR** Complete Response **CRu** Complete Response Unconfirmed **d** Diminished **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **UE** Unable to Evaluate

5. BENEFITS AND RISKS CONCLUSIONS

Patients with aggressive NHL who are in second or later relapse are incurable using present day conventional-dose therapies (6). There is no standard therapy for relapsed aggressive lymphomas aside from high-dose chemotherapy with stem cell transplant. Many patients do not qualify for transplantation and furthermore, following relapse after autologous stem cell transplant there are no standard options and certainly no curative therapies. Not only are there limited options available that are effective in treating patients with multiply relapsed aggressive NHL, but the primary toxicity typically associated with these agents is myelosuppression. As these patients usually have compromised bone marrow reserve from previous cytotoxic therapy and the disease process itself, they have a very limited ability to withstand further myelosuppressive chemotherapy. New therapies are urgently needed. Therefore, a relatively nonmyelosuppressive drug with good palliative efficacy would be of significant benefit for patients with multiply relapsed or refractory aggressive NHL.

5.1 Clinical Efficacy with VSLI Therapy

The efficacy of VSLI has been demonstrated in the two largest studies in patients with multiply relapsed aggressive NHL. In these single-arm studies, the majority of patients had extensive disease and a poor clinical prognosis. Thus, the goal of therapy was palliation. In both studies, the rate of objective response was influenced by the number of prior therapy regimens a patient had received (2 or >2 regimens), as well as whether they had achieved a response of at least 3 months duration to their last therapy (sensitive or resistant disease). Two-thirds of the patients had resistant disease and 54% had refractory disease, defined as not having responded to the last therapy. The median number of prior therapies was 3 in the pooled population, with a mean of 3.7 regimens, thus defining a population that was predominantly receiving fourth- or fifth-line treatment. Twenty-eight percent of patients had received an autologous bone marrow transplant. In this heavily pretreated population with highly resistant disease, the rate of objective response was 25% and 32% in the two studies, for a pooled rate of 28% based on the intent-to-treat analyses (see Appendix C).

The objective response rate was not affected by age (within adults), gender, or very importantly, having had a prior autologous bone marrow transplant. Patients who are post transplant will frequently have compromised marrow reserve and VSLI, which is not severely myelotoxic, offers an important treatment option with an objective response rate in this population of 26%.

The ITT objective response rate of 25% was paralleled by documented symptomatic or ECOG performance status improvement in 22% of patients in the Phase IIb study. This was based on patient-reported symptoms as there was no prospectively defined collection of disease-related symptoms in that study. Even some patients who had only a minor response to VSLI (stable disease with at least a 25% reduction in tumor burden) had symptomatic or performance status improvement. Therefore, the objective response point estimate of 25% may be an underestimate of the true proportion of patients who achieved clinical benefit from VSLI.

The timing of achieving response and clinical benefit from VSLI therapy and its duration are important considerations. In the Phase IIb study, the first formal evaluation of objective response was at 6-8 weeks after the first dose of VSLI and the median duration of response of ~3 months is calculated from that assessment. However, from the review of individual patient data in the patient benefit summaries, it is apparent that the antitumor activity and clinical benefit from VSLI therapy often manifest before this first formal evaluation of response. Therefore, the period of clinical benefit may be underestimated by the formal analysis of duration of objective response.

5.2 Clinical Risks Associated with VSLI Therapy

In the 235 previously treated patients with NHL in the Phase IIa and IIb studies, 13% of patients withdrew from VSLI therapy due to a treatment-associated adverse event, which was mostly neuropathy; treatment-associated serious adverse events, including any that led to withdrawal, occurred in 12% of the patients. No treatment-associated deaths occurred in those two studies.

The evolution of sensorimotor neuropathy with VSLI is gradual and predictable. Initially, diminished reflexes, peripheral sensory neuropathy and constipation develop. Motor difficulties and neuritic pain may occur with continued treatment. The severity of neuropathy appears to be related to the total cumulative dose of VSLI although there was considerable variation in tolerability, with some patients receiving more than 10 cycles of VSLI and experiencing only mild or moderate peripheral sensory neuropathy and others experiencing Grade 3 sensory neuropathy after 3 or 4 cycles.

Almost all patients had residual neuropathy from previous chemotherapy. The estimated median cumulative dose of VSLI required to develop Grade 3 neuropathy in these patients was 21 mg/m^2 or approximately 11 doses of VSLI.

Overall, VSLI is well tolerated in the indicated population of patients with aggressive NHL previously treated with at least two combination therapies.

5.3 Individual Patient Benefit-Risk Evaluations

In these two clinical trials, objective response rate is a surrogate endpoint for clinical benefit and the FDA requested that INEX prepare patient benefit summaries to facilitate their review of the data for responding patients and help identify other evidence that might suggest clinical benefit. There were 38 patients who were considered to be a responder by either the IRP or the Investigator and an additional 5 patients who achieved only minor responses (stable disease) but who appear to have had clinical benefit from VSLI treatment. Patient benefit summaries were provided to the FDA for these 43 patients.

The data for these 43 patients were examined for evidence of net clinical benefit. This review considered the reduction in tumor burden achieved; the resolution of disease-related symptoms and signs; as well as other evidence of antitumor activity/patient benefit, such as improved ECOG performance status, decreased palpable adenopathy, or improved disease-related laboratory parameter abnormalities (LDH, hematologic parameters); as well as the toxicities of the therapy. The improvements reported for these patients have been summarized in Section 4 and the individual patient benefit summaries are in Appendix D.

In essence, individual patient benefit-risk assessments were made for these 43 patients and INEX identified 41 patients (34% of the ITT population) who had favorable benefit-risk outcomes from VSLI therapy.

Furthermore, the evaluation of these 43 patients revealed that evidence of antitumor activity was usually clinically apparent well before the first radiologic evaluation of objective response at 6-8 weeks. In contrast, the development of neuropathy was gradual. The figure below displays the timing of the clinical evidence of antitumor activity/ clinical benefit observed in these 43 patients. Each dot represents an individual patient. The timing of Grade 3 or 4 neuropathy and withdrawal for adverse events (not always Grade 3 or 4) is also shown.

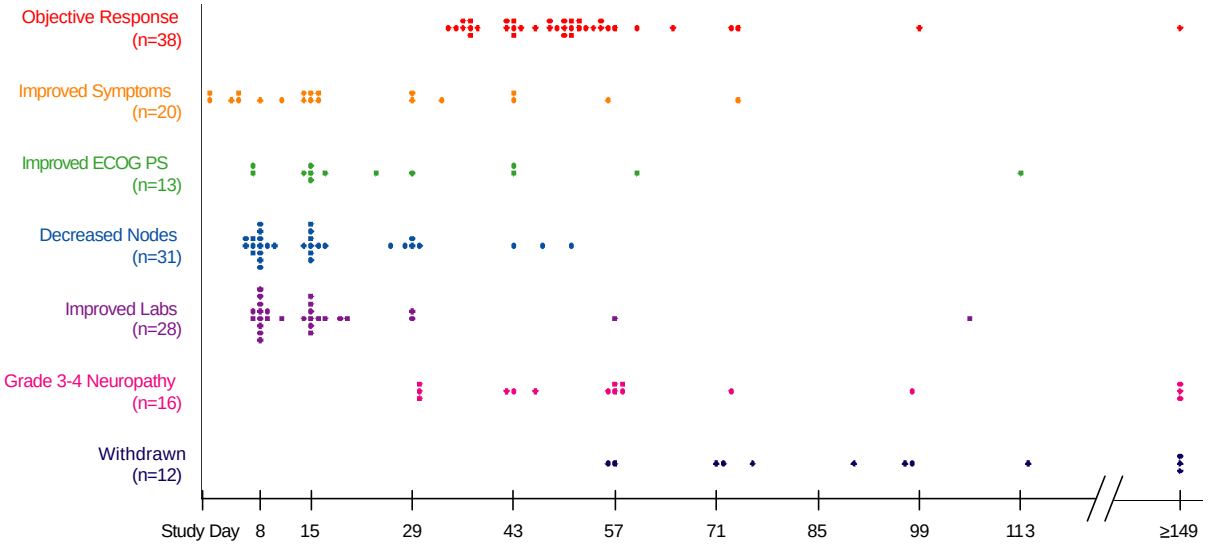


FIGURE 16. Timing of Symptom Improvement and Other Evidence of Antitumor Activity Compared to Timing of Grade 3-4 Neuropathy and Withdrawal due to Adverse Events in 43 Patients with Objective Response or Minor Response

Within the first 2 weeks, which is after only 1 dose of VSLI, some evidence of antitumor activity was evident in 34 of these 43 patients.

From the safety perspective it is interesting to note that there are more patients with Grade 3-4 neuropathy (only 1 had Grade 4) than actually withdrew from therapy. Therefore, reaching Grade 3 neuropathy was not necessarily a reason to stop treating patients who were responding to VSLI. Furthermore, the gradual development of neuropathy allows time for the physician to clinically assess if the patient's disease is responding to therapy.

From a benefit-risk perspective, given the relative timing of early evidence of antitumor activity in most cases versus the gradual development of neuropathy, the treating physician will know whether a patient's disease is responding to VSLI treatment long before significant neuropathy is experienced. At such time when neuropathy is becoming clinically important, the physician and patient can make an informed decision whether to modify or continue treatment.

In contrast, chemotherapeutic agents that cause significant myelosuppression, expose patients to greater risk after the first dose, before one is able to determine response to therapy. Consequently, VSLI provides a favorable profile for the palliation of patients with multiply relapsed aggressive NHL based on the anticipated benefits and manageable risks.

5.4 Overall Benefit-Risk Conclusion

VSLI is an active agent that provides clinically important palliation for patients with multiply relapsed aggressive NHL and it does so with a distinctly different safety profile than other agents that are currently used. The dose-limiting toxicity of VSLI is neuropathy, which is gradual and predictable. VSLI is hematologically well tolerated.

As these multiply relapsed patients usually have compromised bone marrow reserve from previous cytotoxic therapy and from the disease process itself, they have a very limited ability to withstand further myelosuppressive chemotherapy. Therefore, as an active agent that is not severely myelosuppressive, VSLI offers a favorable benefit-risk profile for this population with no standard treatment options.

6. COMPARISON TO OTHER SINGLE-AGENT THERAPIES REPORTED IN THE LITERATURE

As these clinical trials did not have control arms, one must rely on published literature for the perspective of other therapies that might be used to treat this population. An extensive review of the use of a single agent for the treatment of multiply relapsed aggressive NHL was published based on a review of the literature from 1966 through 2001 (59). Reported response rates varied between 0 and 67%. The majority of the published trials were uncontrolled single-institution Investigator-initiated studies in a small number of patients with a broad diversity of histologic diagnoses, extent of prior treatment, and other key parameters. Response rates >30% were mostly in trials of fewer than 20 patients and reported on an evaluable-patients analysis, not an intent-to-treat analysis. The only agents with sufficient reproducible evidence to suggest a response rate greater than 30% in patients at second or greater relapse were etoposide, vincristine, vinorelbine, and possibly rituximab.

INEX has subsequently updated that literature review to include new publications from 2002 and 2003. In addition to the literature review, a review of drug prescribing patterns in the United States was undertaken for the period October 2000 through September 2001 (7). This independent market research identified that the most commonly used single-agent therapies for relapsed intermediate- and high-grade NHL patients who were receiving third-line or later therapy were rituximab (13% of patients), gemcitabine (10%), fludarabine (7%), and cyclophosphamide (4%).

Key publications for each of the agents of interest were selected and study design details and response and safety outcomes are tabulated in Table 32. No studies with single-agent cyclophosphamide in a relapsed/refractory NHL population were found in the published literature. The response rates in all of these trials in Table 32 were determined by the Investigators without external review (except Coiffier 1998 where the drug sponsor confirmed the responses) and are reported on the basis of evaluable patients. Furthermore, the patients often had fewer previous therapies than the patients in the VSLI studies, which would lead to higher reported response rates in the less heavily pretreated populations. Overall, they may represent higher estimates of response than would be reported on an intent-to-treat basis in an externally reviewed trial conducted for regulatory approval purposes. Additionally, histologic classification was not confirmed through an expert histology panel. Even the adverse event rates in Table 32 are reported more thoroughly in the VSLI trials, compared to the literature reports.

TABLE 32. Efficacy vs Percentage (³5%) of Patients with Grade 3 or 4 Adverse Events of Single-Agent Chemotherapy or Immunotherapy in Relapsed NHL

(Page 1 of 2)

Study (Reference)	Agent (n)[a]	ORR in Aggressive NHL Patients	Prior Regimens Median (Range)	Grade 3-4 Myelotoxicity (%)		Grade 3-4 Neurotoxicity (%)		Grade 3-4 Other (%)		WD/ Associated Deaths (%)
Phase IIb Study										
CA99002	VSLI			Anemia	14	Numbness	14[c]	Fatigue	7	15/0
	(n=119)	25%	3 (1-10)	Leukopenia	14	Paresthesia	13[c]	Infections	9	
	(n=24)[a]	46%	2	Neutropenia	27	Pain	8[c]	Alopecia	9[d]	
	(n=95)[b]	20%	>2	Thrombocytopenia	13	Weakness	20[c]			
Phase IIa Study										
DM97-162	VSLI			Anemia	25	Sensory		Pain in limb	5	10/0
	(n=132)	32%	3 (1-10)	Leukopenia	23	neuropathy	13	Fatigue	9	
	(n=25)[e]	52%	≤2	Neutropenia	35	Weakness	5			
	(n=66)[b]	24%	>2	Thrombocytopenia	29					
Jackson, 1984 (60)	VCR infusion (n=25)	40% of 15 pts.	NR	Leukopenia Thrombocytopenia	12 12	48 (all grades)		NR		NR/NR
Rule, 1998 (61)	Vinorelbine (n=17)	44% of 9 pts.	2 (1-8)	NR		NR		Constipation Hepatic toxicity Phlebitis	6 6 6	NR/NR
Sarris, 1998 (62)	Vinorelbine infusion (n=44)	18% of 22 pts.	3 (1-11)	Neutropenia Thrombocytopenia	61[f] 8[f]	0		Mucositis Neutropenic fever	18[f] 10[f]	NR/NR
Balzarotti, 1996 (63)	Vinorelbine (n=23)	46% of 13 pts.	2 (1-6)	Leukopenia	12	0		None		NR/NR

WD = Withdrawals.
NR = Not recorded.
[a] Number of patients who had 2 prior regimens. Includes one patient who had only one prior regimen.
[b] Number of patients who had more than 2 prior regimens.
[c] Based on prospective neurologic assessments on 115 patients (4 patients excluded due to Grade 3-4 neuropathy at study entry).
[d] Alopecia = all grades.
[e] Number of patients who had ≤2 prior regimens.
[f] Based on number of cycles given

TABLE 32. Efficacy vs Percentage (³5%) of Patients with Grade 3 or 4 Adverse Events of Single-Agent Chemotherapy or Immunotherapy in Relapsed NHL

(Page 2 of 2)

Study (Reference)	Agent (n)[a]	ORR in Aggressive NHL Patients	Prior Regimens Median (Range)	Grade 3-4 Myelotoxicity (%)		Grade 3-4 Neurotoxicity (%)	Grade 3-4 Other (%)		WD/ Associated Deaths (%)
Bruno, 1994 (64)	Vinorelbine (n=20)	50% of 10 pts.	2.2 (NR)	Anemia Neutropenia	10 40	NR	Infection	5	5/NR
Niitsu, 1997 (66)	Etoposide (n=29)	59% of 17 pts.	>1 (NR)	Anemia Leukopenia Neutropenia Thrombocytopenia	24 83 86 17	0	Nausea and vomiting Alopecia	7 48[g]	0/NR
Hainsworth, 1993 (67)	Etoposide (n=25)	50% of 10 pts.	2.3[h] (NR)	Leukopenia	28	0	Alopecia	100[g]	NR/NR
Coiffier, 1998 (6863)	Rituximab (n=54)	31%	1 (0-2)	0		0	Rigors	7	4/0
Package Insert (69)	Rituximab (n=356)	NA	NA	Lymphopenia Neutropenia	40 6	0	Grade 3 and 4 AEs	57	NR/NR
Savage, 2000 (70)	Gemcitabine (n=15)	23% of 13 pts.	3 (1-4)	Anemia Leukopenia Thrombocytopenia	7 33 60	0	Fever Stomatitis Vomiting Diarrhea Dehydration	7 7 7 7 7	13/0
Fossa, 1999 (71)	Gemcitabine (n=31)	19%	2 (1-3)	Anemia Leukopenia Neutropenia Thrombocytopenia	11 7 9 22	0	Infections Hepatic toxicity	7 13	NR/3
Redman, 1992 (72)	Fludarabine (n=76)	0% of 17 pts.	3 (NR)	NR		0	Fever or Infection	62	9/NR

WD = Withdrawals.
NR = Not recorded.
[g] Alopecia = all grades.
[h] Mean.
NA = Not applicable.

Infusional Vincristine

Jackson et al. (1984) studied vincristine given as a 5-day continuous infusion regimen (60). Patients in these studies had previously received multiple chemotherapy drugs, although the number of regimens was not specified. An objective response rate of 40% was seen in 15 patients with aggressive NHL with 7% complete response. The confidence interval is very wide on this point estimate of response [16%, 67%], which certainly encompasses the response rate demonstrated in these trials with VSLI. The rate of neuropathy (48% all grades) is reasonably consistent with what was reported in the VSLI studies. According to the independent US market research, vincristine is not used as a single-agent in this population, either as a bolus injection or as an infusion.

Vinorelbine

Four studies with vinorelbine have been published (61-64). All were small single-institution studies and the study by Sarris et al. (1998) used an infusional regimen. Objective response rates from 18 to 50% were seen in these studies, with complete response rates from 4.5 to 23%. The 3 studies with response rates of 44%, 46%, and 50% had patients who had received a median of 2 prior regimens; the rate of response seen with VSLI, 46% in patients with 2 prior regimens in the Phase IIb study and 52% in patients with ≤2 prior regimens in the Phase IIa study, was comparable. In the study by Sarris et al. (1998), the patients had received a median of 3 prior chemotherapy regimens and the response rate with vinorelbine was 18%, which is slightly lower than the VSLI response rate of 25% in a similar population with respect to amount of previous therapy.

The infusional regimen of vinorelbine was associated with higher toxicity than reported in the 3 other studies, with 61% of the cycles associated with Grade 3-4 neutropenia. Grade 3 or 4 leukopenia or neutropenia was seen in 12% and 40% of patients in the noninfusional studies, respectively. These data are consistent with the 15% Grade 4 leukopenia and 36% Grade 4 neutropenia reported in patients with other malignancies treated with vinorelbine (65).

VSLI appears to have achieved a similar rate of response as reported in the literature for vinorelbine and with a similar level of myelotoxicity as the noninfusional regimens of vinorelbine, but with the addition of neurotoxicity. A definitive conclusion cannot be made comparing these agents, however, as the vinorelbine publications are based on very small numbers of patients, ranging from only 9 to 13 patients with aggressive NHL receiving the non-infusional regimens. According to the US market research, single-agent vinorelbine is not used for this population.

Oral Etoposide

Published studies of oral etoposide in the treatment of relapsed/refractory lymphoma included patients with a wide variety of lymphomas (Hodgkin's disease, low-, intermediate-, and high-grade NHL, and CLL). Two papers were identified that have sufficient details on patient characteristics (histology, prior treatment, disease resistance status) to allow comparisons; however, both were small single-institution studies. Niitsu et al. (1997) reported a response rate with etoposide of 59% in 17 evaluable patients with aggressive NHL, most of whom were either at first relapse or previously untreated (66). Hainsworth et al. (1993) reported a response rate of 50% in 10 patients with aggressive NHL who had a mean of 2.3 prior regimens (67); the median duration of response was 3 months. These 2 publications demonstrate consistent response rates, although each study had a small number of patients. The response rates were higher than what was observed with VSLI, but the patients in the etoposide studies were less heavily pretreated than the VSLI patients; nevertheless, the median duration of response was the same at 3 months.

Oral etoposide was, however, associated with significant myelotoxicity (86% Grade 3-4 neutropenia in the Niitsu study with 28% Grade 4) and alopecia in half the patients in the Niitsu study and in all patients in the Hainsworth study.

By comparison, VSLI demonstrated similar rates of response (46% in patients with 2 prior regimens with VSLI in Phase IIb study or 52% in patients with ≤2 prior regimens in Phase IIa study vs 50-59% with etoposide), but with considerably less myelotoxicity. According to the US market research, single-agent etoposide is used in <1% of the patients receiving third-line or later therapy.

Rituximab

Rituximab is a relatively new agent of particular clinical interest. It has demonstrated excellent effectiveness in indolent NHL, with less activity in the aggressive NHL histologies. In a multicenter Phase II study of 54 patients with aggressive lymphoma, single-agent rituximab therapy achieved an ITT response rate of 31% (9% CR, 22% PR) (68). The reported response rate of 31% with rituximab was similar to that demonstrated with VSLI (25-32%). However, it is important to note that 91% of the patients in the rituximab study were at first or second line of therapy (17% at first diagnosis, 74% at first relapse), compared to the VSLI study populations with a median of 3 prior regimens. The response rate for VSLI was 46% in 24 patients who had received two prior regimens in the Phase IIb study and 52% in patients with ≤2 prior regimens in the Phase IIa study. The median progression-free survival for the entire group in the rituximab study was >3.5 months.

From a safety perspective, rituximab was a well-tolerated therapy in this study, with a low incidence of Grade 3-4 adverse events. In summary, VSLI appears to be more efficacious than rituximab in aggressive NHL, but with more toxicity.

Safety data from the US Package Insert for rituximab shows 40% of patients with Grade 3 or 4 lymphopenia (66). This is not unexpected and is related to the mode of action of rituximab. Grade 3-4 neutropenia was seen in 6% of patients. A Grade 3-4 adverse event of any nature was experienced by 57% of patients. In the combined VSLI studies, where a population with more advanced aggressive NHL was studied, 57% of patients had a Grade 3-4 AE of any nature. These were isolated events and were mostly related to the patients' disease or comorbid conditions.

The US market research indicated that rituximab is the most commonly used single-agent for third-line or later treatment of relapsed aggressive NHL (13% of patients). It is anticipated that with the increased use of rituximab as part of first-line therapy with CHOP and also as part of salvage therapy regimens, that its use in patients who are receiving third-line or later therapy will decline, as patients will not likely be given multiple regimens of rituximab immunotherapy.

Gemcitabine

In a small two-institution study, Savage et al. (2000) reported a response rate with gemcitabine of 23% in 13 patients that were similar in histology and extent of prior chemotherapy to the patients in the VSLI studies (70). In a slightly larger multicenter study, Fossa et al. (1999) reported a response rate of 19% to gemcitabine in 31 patients with aggressive relapsed or refractory NHL, 29% of whom had only 1 prior regimen and 35% of whom had 2 prior regimens (71). The median TTP was 6 months in responders and 2.2 months in nonresponders. In comparison, VSLI achieved an objective response rate of 46-52% in patients who had ≤2 prior regimens and a median TTP of at least 4 months in all responding patients (whether they had 2 or more prior regimens).

These two studies with gemcitabine used slightly different regimens, but achieved essentially the same dose intensity overall. The Savage study used weekly doses of 1000 mg/m^2 for 7 weeks followed by 1 week of rest, whereas the Fossa study used a weekly doses of 1250 mg/m^2 for 3 weeks followed by 1 week of rest. The level of toxicity was considerably different in the two studies, with about 3 times the rate of myelosuppression in the study reported by Savage (60% Grade 3-4 thrombocytopenia, 33% Grade 3-4 leukopenia). Severe nonhematologic toxicities were observed at low frequencies. Severe hepatic toxicity (liver function test abnormalities) was reported in 13% of patients.

In comparison, VSLI achieved comparable efficacy to that reported in the Savage study, but with much less toxicity. VSLI efficacy appears to be superior to that reported in the Fossa study, when one adjusts for the amount of prior therapy, with a similar rate of myelosuppression. Gemcitabine is used as a single-agent in 10% of patients with third-line or later relapsed aggressive NHL.

Fludarabine

Redman et al. (1992) reported the use of fludarabine in 67 evaluable patients with relapsed lymphoma (72). High response rates were observed for follicular lymphoma and other low-grade lymphomas, but no responses occurred in 17 patients with diffuse large B-cell lymphoma. Although specific hematologic AEs were not presented, a high rate of fever or infection (62%, all grades) was seen. Grade 4 neutropenia have been reported in 59% of patients with CLL treated with fludarabine (73). Fludarabine is used as single-agent therapy in approximately 7% of the indicated population in the US. VSLI appears to be superior with respect to both efficacy and safety in relapsed aggressive lymphoma based on these limited data.

Conclusions from Literature Comparisons

Although there are marked difficulties in making scientifically rigorous comparisons with the literature, from a benefit-risk perspective VSLI compares favorably to agents currently used as single agents in relapsed aggressive NHL (rituximab, gemcitabine, fludarabine). Most other agents have shown greater myelotoxicity than VSLI. None of these drugs has an approved indication for aggressive NHL or is considered to be standard therapy in medical practice.

The efficacy demonstrated with VSLI has been obtained in a large multicenter trial and assessed for an intent-to-treat population according to rigorous criteria applied by an external IRP. The supportive study showed consistent results. Moreover, the two studies conducted with VSLI are the largest trials reported for patients with multiply relapsed aggressive NHL. Therefore, the level of evidence supporting the efficacy and safety of VSLI is superior to that for any other agent reported in the literature.

7. OVERALL CONCLUSIONS

VSLI is a rationally designed liposomal formulation that provides substantially increased and prolonged exposure to the cell-cycle-specific agent vincristine sulfate. Clinical studies conducted with VSLI allow the following conclusions:

- Consistent results were obtained in the two largest trials of any therapy in patients with multiply relapsed aggressive NHL.
- In this population of heavily pretreated patients with multiple adverse prognostic factors, clinically important objective response rates of 25% and 32% were observed.
- An objective response is likely to predict clinical benefit.
- Neuropathy is gradual and predictable.
- VSLI is hematologically well tolerated.
- VSLI compares favorably to single agents used in the US.
- The benefit-risk profile is favorable in this population with no standard treatment options.

8. REGULATORY BASIS FOR ACCELERATED APPROVAL OF VSLI

In accordance with 21 CFR 314.510, an accelerated approval of a new drug that provides meaningful therapeutic benefit over existing treatments to patients with a serious or life-threatening illness may be granted on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.

Primary efficacy and safety data are provided from 119 patients enrolled and treated in Study CA99002 (pivotal Phase IIb study). Supportive data from 92 patients are provided from Study DM97-162 (Phase IIa study). These studies satisfy the criteria for adequate and well controlled studies as defined in the FDA regulations.

The FDA agreed that the development program for VSLI met the criteria for Fast Track status as the indicated population of patients with aggressive NHL previously treated with at least two combination chemotherapy regimens is a population of patients with a serious and life-threatening condition, for whom there is no standard therapy.

Meaningful Therapeutic Benefit Over Existing Treatments

According to the draft FDA guidance of February 2002 on Available Therapy, “existing treatments” should be interpreted as therapy that is reflected in the approved labeling of regulated products. Drug products that have been in clinical use for many years, such as doxorubicin hydrochloride, cyclophosphamide, and vincristine have broad labeled indications using general terms such as “non-Hodgkin’s malignant lymphomas”. The Package Inserts for vincristine and cyclophosphamide suggest that these drugs are useful in combination with other oncolytic agents.

The draft guidance further allows that in unusual cases, compelling literature evidence could be used to establish available therapy. It was agreed with the FDA when the Fast Track status was granted to the VSLI development program, that there was no therapy that was recognized as standard therapy for the indicated population of patients with aggressive NHL requiring third-line or later treatment.

INEX has provided a review of available literature for agents that are currently being used for the third-line or later treatment of aggressive NHL in the US, even though these are not considered to be standard treatment. None of the three drugs most often used as single agents for this population (rituximab, gemcitabine, fludarabine), as identified by independent US market research, has an approved indication for aggressive NHL at any stage of treatment or is considered to be standard therapy in medical practice.

The analysis of net clinical benefit for individual patients in the Phase IIb study provides considerable evidence to support the conclusion that a 25% objective response rate in a population of patients who were receiving primarily fourth- or fifth-line treatment is reasonably likely to predict clinical benefit in the indicated population. Clinical benefit was demonstrated in at least one of the following ways, in the absence of significant VSLI-related toxicity:

- Clinically meaningful period of disease-free survival
- Tumor response to VSLI that permitted subsequent stem cell transplant, a potentially curative therapy
- Improvement in tumor-related symptoms or ECOG performance status

- Better response or time to progression than achieved with previous standard chemotherapy regimen
- Clinically meaningful period of progression-free survival
- Improvement in anemia, neutropenia, or thrombocytopenia present at study entry

Additionally, the statistically significant correlation of response and survival in a landmark survival analysis using IPI score and sensitivity to last qualifying therapy as covariates is consistent with the hypothesis that response to VSLI contributed to extended survival.

In conclusion, VSLI is an active agent that provides clinically important palliation for patients with multiply relapsed aggressive NHL and it does so with a distinctly different safety profile than other agents that are currently used. These conclusions are drawn from the two largest studies reported for patients with multiply relapsed aggressive NHL and thus based on a higher level of evidence than provided by any other agent as reported in the literature. As these multiply relapsed patients usually have compromised bone marrow reserve from previous cytotoxic therapy, including autologous stem cell transplant, and from the disease process itself, they have a very limited ability to withstand further myelosuppressive chemotherapy. Therefore, as an active agent that is not severely myelosuppressive, VSLI offers an important new treatment option for patients with aggressive NHL previously treated with at least two combination chemotherapy regimens, a population for whom treatment options are limited.

Postapproval Phase III Study Commitment

An accelerated approval based on clinical studies using a surrogate endpoint usually requires that the Sponsor conduct a postapproval trial to confirm clinical benefit. FDA and INEX have discussed Phase III study designs and protocol finalization is underway.

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10. APPENDICES

APPENDIX A – RESPONSE CRITERIA

Response to treatment was determined by both the IRP and the Investigator according to the criteria proposed in the International Workshop. INEX noted areas where the published criteria were potentially ambiguous and could have presented opportunities for inconsistent application during the conduct of this trial. Therefore, some wording clarifications were introduced by INEX to ensure consistent application of response criteria. The wording clarifications were accepted by the FDA as part of the protocol review prior to study enrollment.

The wording clarifications were based on the following principles:

1. Some lesions would not be able to be measured accurately. Percentage increases or decreases (as used for some response categories) can only be calculated when accurate bidimensional measurements are possible.
2. A minimum of 1 and a maximum of 6 lesions (called "indicator" lesions) were to be identified and measured accurately throughout the study and used for all subsequent comparisons. For this study, 1.5 cm was defined as the normal lymph node size and, to optimize measurement reliability in determining response, indicator lesions had to have a minimum size of 2 cm.
3. The maximum of 6 lesions were to be chosen from the largest dominant nodes or nodal masses, splenic or hepatic nodules.
4. Measurements were not required for all other lesions ("non-indicator" lesions), but these lesions were to be "assessable" and were to be tracked for changes in status (increased, decreased, stable, resolved).

Tumor response was determined according to 5 categories: complete response (CR) which required complete disappearance of all disease; complete response unconfirmed (CRu) which was similar to a CR but allowed an indeterminate bone marrow or a residual lymph node or nodal mass that was greater than 1.5 cm but that had regressed by more than 75% or; partial response (PR) which required ≥50% reduction in tumor burden; stable disease (SD) which was a response that did not fulfill the criteria for CR, CRu, or PR, but was not progressive disease; and progressive disease (PD) which was a ≥50% increase in tumor burden or the appearance of a new lesion.

A.1 Evaluation of Tumor Response as per Phase IIb Protocol

A.1.1 Standard Procedures

Response to the study treatment was determined according to the criteria proposed in the "Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas" by Cheson *et al.* (47). (The text has been clarified with reference to this Phase IIb study.) All patients were to undergo a CT of the chest, abdomen and pelvis at baseline and follow-up visits. Additional MRI of selected regions could be required at baseline and were likewise to be obtained on all follow-up visits.

All tumor measurements were recorded in centimeters. For the purposes of this study, 1.5 cm was accepted as the normal lymph node size. Lymph nodes that were 1.1 cm to 1.5 cm in size at study entry CT scanning were not used to determine response. The ability of CT scans to reliably distinguish abdominal or pelvic nodes involved with lymphoma from non-involved nodes in this size range remains controversial (74, 75).

During the study, measurable disease was to be measured using the same modality as that employed at study entry. Tumor response was determined on the basis of measurable disease quantified using the sum of the products of the largest perpendicular dimensions. A minimum of one, and a maximum of six, defined indicator lesions was employed to determine tumor measurements in the case of partial responses or stable disease (no response). A minimum of 2 cm in at least one dimension was used for indicator lesions to optimize reliability in determining response. These measurements could not be in areas that had been treated with radiation therapy. The number and location of all other lesions was to be recorded at study entry to provide an estimate of overall tumor burden. The Sponsor provided specific guidelines for tumor measurement. Due to the fact that this is a non-randomized study, an independent assessment by a centralized Independent Review Panel (IRP) was employed to evaluate all scans in a blinded fashion.

Any patient with a Complete or Partial Response was defined as a tumor responder.

A.1.2 Criteria for Tumor Response

All responses were documented. The following criteria was utilized to judge response:

A.1.2.1 Complete Response (CR)

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of lactate dehydrogenase (LDH) if definitely assignable to NHL.
2. All lymph nodes and nodal masses had to have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter).
3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, had to have regressed in size and could not be palpable on physical examination. However, no normal size was specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determination of splenic volume or splenic index by CT scan are cumbersome and not widely used. Any macroscopic nodules in any organs detectable on imaging techniques could no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, had to have decreased in size.
4. If the bone marrow was involved by lymphoma before treatment, the infiltrate had to be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination was made had to be adequate (≥ 20 mm biopsy core). Flow cytometric, molecular, or cytogenetic studies were not considered part of routine assessment to document persistent disease at the present time.

CR/unconfirmed (CRu) included those patients who fulfilled Criteria 1 and 3 above, but with one or more of the following features:

1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that had regressed by more than 75% in the SPD. Individual nodes that were previously confluent had to have regressed by more than 75% in their SPD compared with the size of the original mass.
2. Indeterminate bone marrow (increased number or size of aggregate without cytologic or architectural atypia).

A.1.2.2 Partial Response (PR)

1. ≥ 50% decrease in SPD of the 6 indicator lesions (largest dominant nodes or nodal masses, splenic or hepatic nodules). These were to be selected according to the following features: (a) they were to be clearly measurable in at least two perpendicular dimensions, (b) they were to be ≥ 2 cm in at least one dimension, (c) they were to be from as disparate regions of the body as possible, and (d) they were to include mediastinal and retroperitoneal areas of disease whenever these sites are involved, and (e) were not be in areas treated with radiation therapy.
2. No increase in the size of the non-indicator lesions (other nodes or splenic or hepatic nodules).
3. Non-indicator lesions of the spleen or liver or any nodules in other organs were considered assessable and not measurable disease.
4. Bone marrow assessment is irrelevant for determination of a PR.
5. No new sites of disease of measurable or assessable disease.

A.1.2.3 Stable Disease (SD)

Stable disease was defined as not fulfilling the criteria for CR, CRu or PR but was not progressive disease (see below).

A.1.2.4 Progressive Disease (PD)

1. ≥ 50% increase from nadir in the SPD of indicator lesions for CRs, PRs, or stable disease.
2. Appearance of new sites of disease.

A.1.3 Response Assessment

Response was assessed on the basis of clinical, radiologic, and pathologic (i.e., bone marrow) criteria.

1. CT scans remained the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans were required for all patients even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. Studies were to be performed within 3 weeks prior to the initiation of therapy and every 8 weeks (or 4 cycles) until first documented response.
2. A bone marrow aspirate and biopsy were only to be performed to confirm a CR if they were initially positive or if it was clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

3. Response was to be confirmed by repeat assessment (including CT scans) 4 weeks following the first documentation of response.
4. Duration of response was to be defined as the time from the first documentation of response in patients that had achieved a PR or CR until progression.
5. Time to progression was to be defined as the time from the initial day of dosing to the first documentation of progression or relapse.
6. Survival was defined as the time from the first administration of drug until date of death from any cause.

APPENDIX B – PER-PROTOCOL ANALYSES

The criteria for patient exclusion from the per-protocol (PP) population are summarized below. Patients excluded for each criterion are not mutually exclusive.

Criteria Not Met	Number (%) of Patients Excluded (n=119)	
Histologically confirmed (by Central Pathology Review) aggressive de novo or transformed NHL.	23	(19)
By IRP assessment, measurable disease with at least 1 bidimensionally measurable lesion (at least 2 cm in largest dimension) by physical examination or CT scan.	8	(7)
Must have baseline and at least 1 postbaseline tumor assessment (from physical examination or CT scan).	6	(5)
Two or more prior combination chemotherapy from time of diagnosis of aggressive de novo or transformed NHL.	5	(4)
Anthracycline-based chemotherapy regimen for their aggressive de novo or transformed NHL.	4	(3)
At least a minor response to first-line chemotherapy.	3	(3)
Must not have received radiotherapy, chemotherapy, immunotherapy, and/or alternative anticancer treatment or corticosteroids (at dose >10 mg/day prednisone or equivalent) within the past 4 weeks.	1	(1)

The PP population consisted of 77 patients, with approximately one-half of the exclusions from PP being due to ineligible histologic diagnosis based on the Central Pathology Review (23 patients).

Demographic and Baseline Characteristics

For the PP population, the demographic characteristics were similar to the ITT population. The median age was 62 years for the PP population and 60 years for the ITT population. The percent of men was similar between the populations (55% for PP and 54% for ITT). In both populations, the majority of patients were Caucasian (88% in PP and 82% in ITT). ECOG performance status was 0 or 1 for 78% of the PP population and 79% for the ITT population.

The PP population was similar to the ITT population for lymphoma history except for a lower proportion of transformed disease (4% vs. 9%). Tumor burden was also similar in both populations, with bone marrow involvement at baseline seen in 16% of the PP population and 17% of the ITT population. Elevated LDH levels were seen in 66% of each population, and elevated serum β_2 microglobulin was present in 60% of each population.

For prior lymphoma history, the PP and ITT populations were also similar. Both populations had a median of 3 prior chemo/immunotherapy regimens, and 33% of each population had previously received an ABMT. Over 90% of each population had an objective response to the first regimen of chemo/immunotherapy, with median durations of response of approximately 8.5 months. Response to last regimen of chemo/immunotherapy was approximately 35% in both the PP and ITT populations, with a median duration of response of about 5 months.

Primary Efficacy Endpoint – Objective Response Rate

The objective response outcomes for the ITT and PP populations based on the IRP review only are provided in Table 33. As prespecified in the statistical analysis plan, PP population analyses were not performed using the INV assessments.

TABLE 33. Objective Response Based on IRP – PP Population

Best Tumor Response During Study	ITT		PP	
	Number (%) of Patients (n=119)	95% CI[a]	Number (%) of Patients (n=77)	95% CI[a]
Objective response rate (ORR)[b]	30 (25.2)	[17.7, 34.0]	21 (27.3)	[17.7, 38.6]
Complete response (CR)	4 (3.4)	[0.9, 8.4]	1 (1.3)	[0.0, 7.0]
Complete response unconfirmed (CRu)	4 (3.4)	[0.9, 8.4]	3 (3.9)	[0.8, 11.0]
Partial response (PR)	22 (18.5)	[12.0, 26.7]	17 (22.1)	[13.4, 33.0]
Stable disease (SD)	31 (26.1)	–	22 (28.6)	–
Progressive disease (PD)	32 (26.9)	–	21 (27.3)	–
Unable to evaluate (UE)	26 (21.	–	13 (16.9)	–

[a] 95% CI for the proportion based on the binomial distribution.
[b] ORR = CR + CRu + PR, based on patient's best documented response.

Based on IRP review, the ORR for the PP population was 27% [18%, 39%], which is almost identical to the ORR for the ITT population of 25%. The ORR in the patients who were eliminated from the PP population was 21% (9/42). The distribution of patients by response category in the PP population is very similar to what was seen in the ITT analysis, with only slight changes in the proportions of patients with PR (increased by 3%), SD (increased by 3%), and UE (decreased by 5%). Confirmatory CTs taken at least 4 weeks after the first documentation of response were available for 13 (62%) of the 21 responders.

Note that despite the smaller number of patients in the PP population, the confidence interval width of 20.9% was close to the statistical design criterion of 20% for the ITT population. Therefore, the sample size of 77 PP patients was sufficient to achieve an adequate estimate of the primary endpoint of ORR.

The consistent objective response rates for the ITT and PP populations demonstrate that the eligibility deviations, approximately half of which were due to ineligible histology, did not favorably affect the outcome to VSLI treatment on this endpoint. The ORR in the 23 patients with histologies deemed to be ineligible by the Central Pathology Review was 26% by the IRP review and 22% by the INV review.

Correct histologic diagnosis of aggressive NHL is recognized to be problematic in routine clinical practice, which is why a Central Pathology Review was conducted in this trial. With few exceptions, the treating INV believed that these patients were histologically eligible, and therefore, the ITT results reflect the outcome that would be expected in treating relapsed aggressive NHL with VSLI in clinical practice.

Secondary Efficacy Endpoints

Duration of Response

Duration of response for the ITT and PP populations based on the IRP review is summarized in Table 34.

TABLE 34. Duration of Response Based on IRP Review – ITT and PP Populations

Kaplan-Meier Analysis	ITT Population (n=30)	PP Population (n=21)
Number (%) of patients relapsed	10 (33.3)	8 (38.1)
Number (%) of patients censored	20 (66.7)	13 (61.9)
Median duration of response in days[a]	>85[b]	85.0
95% confidence interval	[72.0, –][b]	[63.0, –][b]

[a] Kaplan-Meier estimate of median duration of response. Data for patients not relapsing or progressing were censored in the analysis at date of last contact for progression.

[b] Upper limit of the confidence interval could not be estimated.

According to the IRP review, 21 of the 30 responders were eligible for the PP population. As was seen in the ITT analysis, a high rate of censoring (62%) was observed in the Kaplan-Meier analysis of the PP population, but in this analysis the median duration of response was reached at 85 days. The lower limit of the 95% CI was 63 days, but the upper limit was not reached. There were 5 of the 21 responders who had responses lasting longer than 3 months and all were censored in the analysis; 2 patients had responses that were ongoing longer than 6 months.

Time to Progression

Time to progression for the ITT and PP populations based on the IRP review is summarized in Table 35.

TABLE 35. Time to Progression Based on IRP Review – ITT and PP Populations

Kaplan-Meier Analysis	ITT Population (n=119)	PP Population (n=77)
Number (%) of patients relapsed	56 (47.1)	36 (46.8)
Number (%) of patients censored	63 (52.9)	41 (53.2)
Median time to progression in days[a]	89.0	89.0
95% confidence interval	[64.0, 217]	[64.0, –][b]

[a] Kaplan-Meier estimate of median time to progression. Data for patients not relapsing or progressing were censored in the analysis at date of last contact for progression.

[b] Upper limit of the confidence interval could not be estimated.

The estimated median TTP for the PP population (89 days) was identical to that estimated for the ITT population. The lower limit of the 95% CI was also identical, but the CI was broader for the PP population with an upper limit that could not be calculated.

Survival

Survival, calculated as the time from initial day of dosing until death or last contact, is summarized in Table 36 for the ITT and PP populations. Figure 17 provides the Kaplan-Meier plots of survival for the ITT and PP populations.

TABLE 36. Survival – ITT and PP Populations

Kaplan-Meier Analysis[a]	ITT Population (n=119)	PP Population (n=77)
Number (%) of patients dead	73 (61.3)	49 (63.6)
Number (%) of patients alive	46 (38.7)	28 (36.4)
Median survival time in days[a]	206.0	197.0
95% confidence interval	[144.0, 352.0]	[144.0, 392.0]

[a] Kaplan-Meier estimates of median survival time. Data for patients alive or lost to follow-up were censored in the analysis at the date of last contact for survival.

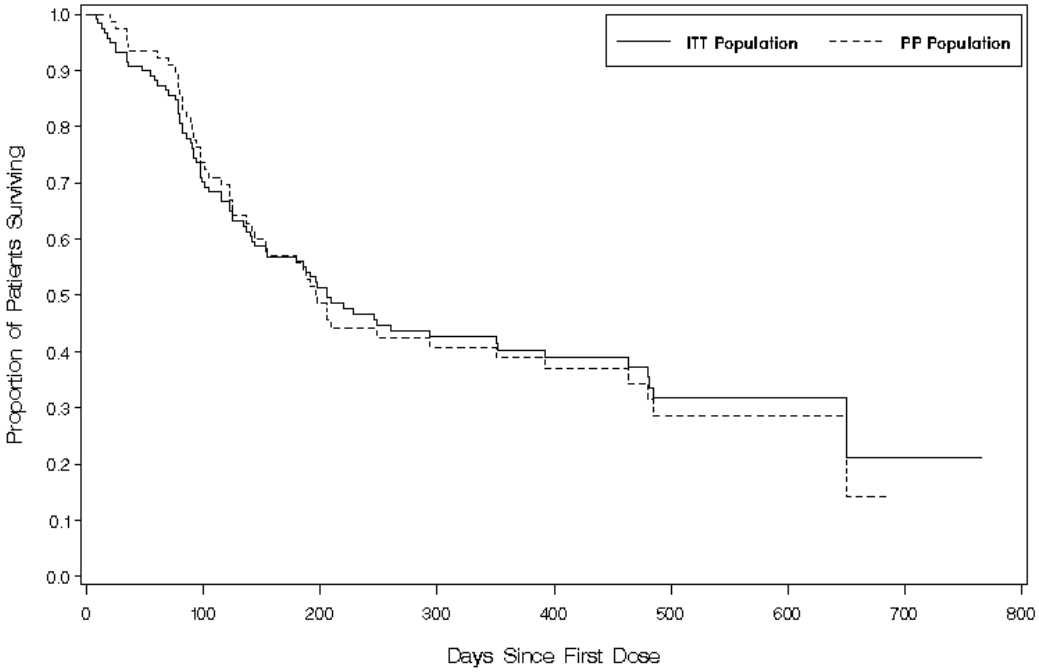


FIGURE 17. Kaplan-Meier Curve of Overall Survival

The PP population had a similar estimated median survival (197 days). The virtually identical overall survival experiences of the ITT and PP groups further indicates their similarity and the likelihood that observations and outcomes were not affected by the inclusion of the additional patients in the ITT group.

Subgroup Analysis: Efficacy by Sensitivity to Last Therapy

Table 37 provides a summary of all efficacy parameters for the per-protocol patients with sensitive and resistant disease as assessed by the IRP.

TABLE 37. Efficacy by Sensitivity to Last Therapy Based on IRP Review ITT and PP Populations

Efficacy Endpoint	ITT		PP	
	Sensitive (n=39)	Resistant (n=80)	Sensitive (n=21)	Resistant (n=56)
ORR: Number (%) of Patients	16 (41.0)	14 (17.5)	11 (52.4)	10 (17.9)
[95% CI]	[26, 58]	[10, 28]	[30, 74]	[9, 30]
Median[a] duration of response (days)	>77[b]	85	77	>85[b, c]
[95% CI]	[63, –][c]	[30, –][c]	[38, –][c]	[30, –][c]
Median[a] TTP (days)	217	64	113	66
[95% CI]	[85, 342]	[51, 122]	[85, –][d]	[50, 127]
Median[a] survival (days)[e]	–	–	392	153
[95% CI]			[206, –][d]	[115, 209]

[a] Median estimate from Kaplan-Meier analysis.
[b] Median not reached.
[c] Last event was at 85 days with probability of remaining in response of .56.
[d] Upper limit of 95% CI not estimable.
[e] Survival data provided by Investigator assessment.

The per-protocol population had similar results to those observed in the ITT population, once again confirming that the results in the ITT population are good estimates of the true outcomes for the intended protocol population. As was shown for the ITT population, the response rate and durations of time-to-event parameters for the sensitive per-protocol patients were twice the values observed for the resistant patients.

Summary

For the objective response rate and each secondary efficacy parameter, the results in the PP population were consistent with the results of the ITT population. When sensitivity to last treatment was evaluated, the results of the PP population were also similar to the ITT population.

APPENDIX C – COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES CA99002 AND DM97-162

A total of 211 patients with relapsed and refractory aggressive NHL were treated with single-agent VSLI, 119 in the pivotal Phase IIb Study CA99002 and 92 in the supportive Phase IIa Study DM97-162. This section provides additional details for the Phase IIa analyses and those based on the combined data from the two trials.

Pooling and Tabulation of Data

The efficacy data from the Phase IIb pivotal study and from the subgroup of patients with aggressive NHL enrolled in the Phase IIa supportive study were pooled based on several factors:

- A similar patient population based on review of demographic and baseline disease characteristics including histologic diagnosis and prior therapies.
- The dosing regimen and extent of exposure to VSLI were the same in both studies.
- The primary endpoint in both studies was ORR with secondary endpoints that were similar.
- The response assessments for both studies were based on comparable criteria.

Tabulations of the results for the primary endpoint ORR and secondary endpoints are presented by study. Within the Phase IIb study, results are presented for both the IRP and Investigator evaluations and for the Phase IIa study results are presented for those patients with aggressive disease (n=92). A pooled column of results is provided for all 211 patients with aggressive NHL that were treated in these studies. The pooled data includes the primary endpoints for both studies: the IRP results for the Phase IIb study and the Investigator results for the Phase IIa study. Similar tabulations are presented for the PP population.

Patient Populations for Analysis

TABLE 38. Patient Populations for Analysis

Population	Number (%) of Patients		
	Phase IIb (n=119)	Phase IIa Aggressive NHL (n=92)	Combined Aggressive NHL (n=211)
Treated (safety population)	119 (100.0)	92 (100.0)	211 (100.0)
ITT population	119 (100.0)	92 (100.0)	211 (100.0)
Per-protocol population	77 (64.7)	38 (41.3)	115 (54.5)

The primary tabulations of data in both the Phase IIa and Phase IIb studies were based on the ITT population, i.e., those patients who had received at least one dose of VSLI. In the Phase IIb study, additional analyses were conducted on the PP population, which was comprised of a subset of patients in the ITT population who had received at least 50% of the intended first dose of VSLI, had an evaluation of tumor response conducted post-baseline (but prior to start of any dinically relevant concomitant therapy) and who had satisfied key inclusion and exclusion criteria, as described in Appendix B.

The criteria from the Phase IIb study for inclusion in the PP population were retrospectively applied to the patients from the Phase IIa study. As a consequence of the differences in data available for the

Phase IIa study, only certain criteria used for selecting the PP population for the Phase IIb study could be applied to the Phase IIa study. The criterion for requiring measurable disease at baseline could not be applied to the Phase IIa study as no tumor measurements were documented. Furthermore, differences in the application of some criteria were necessitated by differences in the type and nature of data collected for the Phase IIa study. Thus, histologic diagnoses were based on the Investigators' site diagnoses and not on a Central Pathology Review. The criterion for requiring post-baseline measurement was interpreted to allow patients where a post-baseline tumor response assessment was made, irrespective of whether data from post-baseline imaging studies or physical examination of tumor lesions were available.

A total of 38 (41%) of the 92 patients with aggressive NHL in the Phase IIa study were included in the PP population.

Table 39 summarizes the number of patients excluded from the PP population for each criterion in both the Phase IIb and the Phase IIa study. Note that the patients excluded for each criterion are not mutually exclusive.

TABLE 39. Reasons for Exclusion from the PP Population

Reason for Exclusion	Number (%) of Patients					
	Phase IIb (n=119)		Phase IIa Aggressive NHL (n=92)		Combined Aggressive NHL (n=211)	
Excluded from PP population	42	(35.3)	54	(58.7)	96	(45.5)
Reasons for exclusion:[a]						
Histologic diagnosis not aggressive NHL	23	(19.3)	22	(23.9)	45	(21.3)
Received only one prior therapy	5	(4.2)	17	(18.5)	22	(10.4)
Did not achieve at least minor response to first line	3	(2.5)	19	(20.7)	22	(10.4)
Did not receive anthracycline-based chemotherapy	4	(3.4)	8	(8.7)	12	(5.7)
Did not have baseline and at least one post-baseline tumor assessment	6	(5.0)	5	(5.4)	11	(5.2)
Received radio-, chemo-, immunotherapy or alternate treatment or corticosteroids within 4 weeks	1	(0.8)	10	(10.9)	11	(5.2)
Did not have measurable disease	8	(6.7)	NA		8	(3.8)

[a] More than one reason for exclusion could be recorded for an individual patient.
NA = Not available.

A higher proportion of patients in the Phase IIa study were excluded as they had not received 2 or more prior combination chemotherapies from the time of diagnosis of aggressive NHL to study entry and they did not achieve at least a minor response to first-line therapy; this is not unexpected as the patients enrolled in this study were only required to have been previously treated, with no further qualifiers.

Exposure to Study Drug

TABLE 40. Extent of Exposure

Extent of Exposure Variable	ITT Population			PP Population
	Phase IIb (n=119)	Phase IIa Aggressive NHL (n=92)	Combined Aggressive NHL (n=211)	Combined Aggressive NHL (n=115)
Number of cycles received				
n	119	92	211	115
Mean (SD)	4.6 (3.4)	4.2 (2.8)	4.5 (3.1)	4.5 (3.1)
Median	4.0	4.0	4.0	4.0
Minimum, maximum	1, 20	1, 12	1, 20	1, 20
Number of cycles received [Number (%) of Patients]				
1	15 (12.6)	10 (10.9)	25 (11.8)	9 (7.8)
2	19 (16.0)	21 (22.8)	40 (19.0)	23 (20.0)
3	16 (13.4)	10 (10.9)	26 (12.3)	16 (13.9)
4	25 (21.0)	24 (26.1)	49 (23.2)	25 (21.7)
5	13 (10.9)	7 (7.6)	20 (9.5)	14 (12.2)
6	6 (5.0)	3 (3.3)	9 (4.3)	5 (4.3)
7	4 (3.4)	3 (3.3)	7 (3.3)	5 (4.3)
8	6 (5.0)	7 (7.6)	13 (6.2)	6 (5.2)
9	4 (3.4)	1 (1.1)	5 (2.4)	4 (3.5)
10	3 (2.5)	1 (1.1)	4 (1.9)	3 (2.6)
11	3 (2.5)	0 (0.0)	3 (1.4)	0 (0.0)
≥12	5 (4.2)	5 (5.4)	10 (4.7)	5 (4.3)
Total dose received (mg/m^2)[a]				
n	119	91	210	115
Mean (SD)	9.13 (6.76)	8.37 (5.44)	8.80 (6.22)	8.96 (6.16)
Median	7.87	8.00	7.94	7.97
Minimum, maximum	1.9, 39.6	2.0, 24.0	1.9, 39.6	2.0, 39.6
Dose intensity ($mg/m^2/wk$)[b]				
n	119	91	210	115
Mean (SD)	0.96 (0.07)	0.98 (0.12)	0.97 (0.09)	0.98 (0.08)
Median	0.98	1.00	0.99	0.99
Minimum, maximum	0.6, 1.1	0.5, 1.4	0.5, 1.4	0.7, 1.3

[a] Total dose received (mg/m^2) = sum of total doses administered/BSA per cycle.
[b] Dose intensity ($mg/m^2/wk$) = total dose received (mg/m^2)/(duration of exposure in days/7).

Patients with NHL treated in the Phase IIa and IIb studies had similar exposure to VSLI with a median of 4 cycles of VSLI administered in both studies. A total of 120 (57%) of the 211 ITT patients received 4 or more cycles of therapy, including 10 patients (5%) who received 12 or more cycles of VSLI.

The median total dose of VSLI administered (as the sum of total dose across all cycles) in the 211 patients in the combined aggressive NHL ITT population was 7.9 mg/m^2, with a range of 1.9 to 39.6 mg/m^2; the median dose intensity was 0.99 mg/m^2/week, compared to a target intensity of 1.0 mg/m^2/week.

Demographic and Other Baseline Characteristics

TABLE 41. Demographics and Baseline Characteristics

Characteristics	ITT Population			PP Population
	Phase IIb (n=119)	Phase IIa Aggressive NHL (n=92)	Combined Aggressive NHL (n=211)	Combined Aggressive NHL (n=115)
Age (years)				
n	119	92	211	115
Mean (SD)	58.6 (14.1)	59.5 (14.3)	59.0 (14.2)	59.0 (14.3)
Median	60.0	62.5	61.8	62.0
Minimum, maximum	25, 87	19, 86	19, 87	20, 81
Age (years) [Number (%) of Patients]				
≤40	16 (13.4)	11 (12.0)	27 (12.8)	17 (14.8)
>40-50	20 (16.8)	9 (9.8)	29 (13.7)	13 (11.3)
>50-60	24 (20.2)	20 (21.7)	44 (20.9)	23 (20.0)
>60-70	31 (26.1)	31 (33.7)	62 (29.4)	33 (28.7)
>70-80	26 (21.8)	20 (21.7)	46 (21.8)	28 (24.3)
>80	2 (1.7)	1 (1.1)	3 (1.4)	1 (0.9)
Gender [Number (%) of Patients]				
Men	64 (53.8)	48 (52.2)	112 (53.1)	60 (52.2)
Women	55 (46.2)	44 (47.8)	99 (46.9)	55 (47.8)
Race [Number (%) of Patients]				
Caucasian	98 (82.4)	75 (81.5)	173 (82.0)	98 (85.2)
African American	6 (5.0)	3 (3.3)	9 (4.3)	2 (1.7)
Asian	3 (2.5)	2 (2.2)	5 (2.4)	4 (3.5)
Hispanic	10 (8.4)	7 (7.6)	17 (8.1)	8 (7.0)
Other	2 (1.7)	0 (0.0)	2 (0.9)	2 (1.7)
Missing	0 (0.0)	5 (5.4)	5 (2.4)	1 (0.9)
ECOG/Zubrod [Number (%) of Patients]				
0	35 (29.4)	10 (10.9)	45 (21.3)	28 (24.3)
1	59 (49.6)	54 (58.7)	113 (53.6)	58 (50.4)
2	18 (15.1)	17 (18.5)	35 (16.6)	19 (16.5)
3	6 (5.0)	2 (2.2)	8 (3.8)	6 (5.2)
4	0 (0.0)	1 (1.1)	1 (0.5)	1 (0.9)
Missing	1 (0.8)	8 (8.7)	9 (4.3)	3 (2.6)

There were no apparent differences between the Phase IIa and Phase IIb studies.

NHL Histology

Table 42 presents histologic type of NHL; the table depicts those diagnoses that were eligible for entry into the Phase IIb study and those that were not eligible. The histologic eligibility criteria for the Phase IIb study were retrospectively applied to the Phase IIa for this analysis.

TABLE 42. Histologic Type

Histologic Type	Number (%) of Patients							
	ITT Population						PP Population	
	Phase IIb (n=119)		Phase IIa Aggressive NHL (n=92)		Combined Aggressive NHL (n=211)		Combined Aggressive NHL (n=115)	
Histologic type eligible [a]								
Diffuse large B-cell lymphoma (DLBCL)	68	(57.1)	61	(66.3)	129	(61.1)	85	(73.9)
Primary mediastinal large B-cell lymphoma with sclerosis	5	(4.2)	0	(0.0)	5	(2.4)	4	(3.5)
Immunoblastic B-cell lymphoma	1	(0.8)	0	(0.0)	1	(0.5)	1	(0.9)
T-cell rich B-cell lymphoma	2	(1.7)	0	(0.0)	2	(0.9)	2	(1.7)
Peripheral T-cell lymphoma	1	(0.8)	5	(5.4)	6	(2.8)	5	(4.3)
Anaplastic large null-/T-cell lymphoma	2	(1.7)	0	(0.0)	2	(0.9)	2	(1.7)
Composite lymphoma (DLBCL+)	7	(5.9)	4	(4.3)	11	(5.2)	8	(7.0)
Large cell lymphoma (FNA)	7	(5.9)	0	(0.0)	7	(3.3)	6	(5.2)
Other (large B-cell, PTLD, aggressive B-cell)	3	(2.5)	0	(0.0)	3	(1.4)	2	(1.7)
Histologic type ineligible [a]								
Follicular, not otherwise specified	0	(0.0)	2	(2.2)	2	(0.9)	0	(0.0)
Follicular Grade 2 lymphoma	4	(3.4)	1	(1.1)	5	(2.4)	0	(0.0)
Follicular Grade 3 lymphoma	4	(3.4)	11	(12.0)	15	(7.1)	0	(0.0)
MALT lymphoma	1	(0.8)	0	(0.0)	1	(0.5)	0	(0.0)
Mantle cell lymphoma	2	(1.7)	8	(8.7)	10	(4.7)	0	(0.0)
SLL/CLL	2	(1.7)	0	(0.0)	2	(0.9)	0	(0.0)
Low-grade B-cell lymphoma	1	(0.8)	0	0.0)	1	(0.5)	0	(0.0)
Small cell lymphoma (FNA)	4	(3.4)	0	(0.0)	4	(1.9)	0	(0.0)
Indeterminate	3	(2.5)	0	(0.0)	3	(1.4)	0	(0.0)
Missing	2	(1.7)	0	(0.0)	2	(0.9)	0	(0.0)

[a] Phase IIb study histologic diagnosis according to independent Central Pathology Review. Phase IIa study histologic diagnosis according to site.

In keeping with the usual presentation of aggressive NHL, the most common histologic diagnosis across all 211 patients included in the combined aggressive NHL ITT population was diffuse large B-cell lymphoma (DLBCL): 61% of patients, including 57% of patients in the Phase IIb study and 66% of patients with aggressive NHL in the Phase IIa study. In selecting the subgroup of 92 patients with "aggressive" NHL from the Phase IIa study, follicular Grade 3 lymphoma was considered to be an aggressive NHL subtype in keeping with the clinical working criteria applied at this single center. The 2 patients with follicular NOS lymphoma were patients with follicular lymphoma with large cleaved cells; the patients with the follicular Grade 2 lymphoma had a transformed mixed follicular lymphoma. Furthermore, mantle cell lymphoma, an aggressive lymphoma subtype, was also permitted in the Phase IIa study (8 patients), although not considered eligible in the Phase IIb study.

Lymphoma History

TABLE 43. Lymphoma History

Characteristics	ITT Population			PP Population
	Phase IIb (n=119)	Phase IIa Aggressive NHL (n=92)	Combined Aggressive NHL (n=211)	Combined Aggressive NHL (n=115)
Non-Hodgkin's lymphoma [Number (%) of Patients]				
Transformed	11 (9.2)	19 (20.7)	30 (14.2)	6 (5.2)
De novo aggressive	108 (90.8)	73 (79.3)	181 (85.8)	109 (94.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Time since original diagnosis (years)				
n	119	92	211	115
Mean (SD)	3.57 (2.90)	2.64 (2.41)	3.17 (2.73)	2.99 (2. 50)
Median	2.63	1.82	2.09	2.05
Minimum, maximum	0.6, 13.6	0.1, 13.3	0.1, 13.6	0.1, 13.6
Elevated LDH at Baseline				
Yes	78 (65.5)	51 (55.4)	129 (61.1)	74 (64.3)
No	40 (33.6)	37 (40.2)	77 (36.5)	40 (34.8)
Missing	1 (0.8)	4 (4.3)	5 (2.4)	1 (0.9)

A total of 14% of patients in the combined studies had transformed disease; a higher proportion of patients in the Phase IIa study (21%) compared to the Phase IIb study (9%). The median time since original diagnosis was 2.1 years across all 211 patients, with a range of <6 months to ~14 years. The patients in the Phase IIb study had a longer time since diagnosis (2.6 years) compared with the Phase IIa study (1.8 years).

Elevated LDH was noted in 61% of the 211 patients included in the combined aggressive NHL ITT population indicating a high tumor growth potential.

Prior Therapy for NHL

TABLE 44. Prior Therapy for Non-Hodgkin's Lymphoma

Prior Therapy Variable	ITT Population			PP Population
	Phase IIb (n=119)	Phase IIa Aggressive NHL (n=92)	Combined Aggressive NHL (n=211)	Combined Aggressive NHL (n=115)
Type of prior therapy [Number (%) of Patients]				
Chemotherapy	119 (100.0)	91 (98.9)	210 (99.5)	115 (100.0)
Immunotherapy	73 (61.3)	40 (43.5)	113 (53.6)	63 (54.8)
Radiation	61 (51.3)	35 (38.0)	96 (45.5)	56 (48.7)
ABMT	39 (32.8)	19 (20.7)	58 (27.5)	36 (31.3)
ABMT with total body irradiation	8 (6.7)	1 (1.1)	9 (4.3)	4 (3.5)
Surgery	34 (28.6)	0 (0.0)	34 (16.1)	26 (22.6)
Other	5 (4.2)	0 (0.0)	5 (2.4)	5 (4.3)
Missing	0 (0.0)	1 (1.1)	1 (0.5)	0 (0.0)
Number of prior chemotherapy and immunotherapy regimens				
n	119	91	210	115
Mean (SD)	3.78 (1.67)	3.67 (1.92)	3.73 (1.78)	3.67 (1.69)
Median	3.0	3.0	3.0	3.0
Minimum, maximum	1, 10	1, 10	1, 10	2, 10
Number of prior chemotherapy and immunotherapy regimens [Number (%) of Patients]				
1	1 (0.8)	10 (10.9)	11 (5.2)	0 (0.0)
2	23 (19.3)	15 (16.3)	38 (18.0)	27 (23.5)
3	39 (32.8)	25 (27.2)	64 (30.3)	39 (33.9)
4	27 (22.7)	15 (16.3)	42 (19.9)	25 (21.7)
5	13 (10.9)	11 (12.0)	24 (11.4)	10 (8.7)
6	8 (6.7)	9 (9.8)	17 (8.1)	8 (7.0)
7	4 (3.4)	2 (2.2)	6 (2.8)	2 (1.7)
8	1 (0.8)	1 (1.1)	2 (0.9)	0 (0.0)
9	1 (0.8)	2 (2.2)	3 (1.4)	1 (0.9)
10	2 (1.7)	1 (1.1)	3 (1.4)	3 (2.6)
Missing	0 (0.0)	1 (1.1)	1 (0.5)	0 (0.0)
Prior neurotoxic agents [Number (%) of Patients]				
Any prior neurotoxic agent	119 (100.0)	87 (94.6)	206 (97.6)	115 (100.0)
Vinca alkaloids	116 (97.5)	86 (93.5)	202 (95.7)	112 (97.4)
Taxanes	17 (14.3)	20 (21.7)	37 (17.5)	16 (13.9)
Platinums	80 (67.2)	49 (53.3)	129 (61.1)	76 (66.1)
Missing	0 (0.0)	1 (1.1)	1 (0.5)	0 (0.0)

The median number of prior chemotherapy/immunotherapy regimens across all 211 patients included in the combined aggressive NHL ITT population was 3 with a range of 1 to 10; similar results were noted in the Phase IIb and Phase IIa aggressive NHL ITT populations. Prior therapy was missing for one patient in the Phase IIa study; all other patients had been treated with prior chemotherapy and 54% also had received prior immunotherapy; 61% in the Phase IIb study and 44% in the Phase IIa study. Notably, over one-fourth of the 211 patients (28%) had undergone prior autologous bone marrow transplant (ABMT), including 33% of patients in the Phase IIb study and 21% of patients with aggressive NHL in the Phase IIa study.

TABLE 45. Response to Prior Therapy

Response to Prior Therapy Variable	ITT Population			PP Population
	Phase IIb (n=119)	Phase IIa Aggressive NHL (n=92)	Combined Aggressive NHL (n=211)	Combined Aggressive NHL (n=115)
Response to first-line therapy [Number (%) of Patients]				
CR or PR	110 (92.4)	74 (80.4)	184 (87.2)	110 (95.7)
MR	5 (4.2)	3 (3.3)	8 (3.8)	4 (3.5)
SD or PD or NR	2 (1.7)	10 (10.9)	12 (5.7)	0 (0.0)
Unknown	2 (1.7)	1 (1.1)	3 (1.4)	1 (0.9)
Missing	0 (0.0)	4 (4.3)	4 (1.9)	0 (0.0)
Duration of response to first-line therapy (months)				
n	101	24	125	84
Mean (SD)	15.2 (19.6)	18.8 (20.0)	15.9 (19.6)	15.7 (19.8)
Median	8.4	13.4	8.6	8.6
Minimum, maximum	0.03, 98.69	1.50, 73.50	0.03, 98.69	0.03, 98.69
Best response to last therapy [Number (%) of Patients]				
CR or PR	42 (35.3)	29 (31.5)	71 (33.6)	35 (30.4)
MR	5 (4.2)	4 (4.3)	9 (4.3)	5 (4.3)
SD or PD or NR	51 (42.9)	49 (53.3)	100 (47.4)	60 (52.2)
Unknown	21 (17.6)	2 (2.2)	23 (10.9)	11 (9.6)
Missing	0 (0.0)	8 (8.7)	8 (3.8)	4 (3.5)
Number (%) of patients with resistant disease to last-line therapy per 3-month criterion	80 (67.2)	59 (64.1)	139 (65.9)	83 (72.2)

As expected based on eligibility criteria in the two trials, the majority of all patients with aggressive NHL (87%) achieved a CR or PR to their first chemotherapy/immunotherapy regimen with a median duration of response of 8.6 months (data available for 125 of the 184 responders). A higher proportion of patients in the Phase IIb study achieved a CR or PR to first-line therapy (92%) compared to patients with aggressive NHL in the Phase IIa study (80%). This difference is because the Phase IIa study allowed enrollment of patients with primary refractory disease.

In contrast to the high level of response reported for first-line therapy, only 34% of the patients included in the combined aggressive NHL ITT population achieved a CR or PR to their last chemotherapy/immunotherapy regimen received prior to the study. The proportion of patients achieving a response to their last regimen was similar for patients in the two studies (Phase IIb 35%, Phase IIa 32%).

Patients were grouped into sensitive and resistant disease classifications based on response and timing of response to last prior therapy. Specifically, sensitivity to last chemotherapy/immunotherapy was defined as having achieved a response of CR, CRu, or PR to the prior qualifying therapy that lasted at least 3 months. With this definition, the subgroup defined as resistant is unquestionably a subgroup of patients with very difficult-to-treat disease.

Based on the 3-month criterion, a total of 139 (66%) of the 211 patients in the combined aggressive NHL ITT population were deemed to be resistant to their last qualifying regimen. Results were similar in the two studies (Phase IIb 67%, Phase IIa 64%).

Summary of Demographic and Baseline Disease Characteristics

In summary, the demographic and the baseline disease characteristics for the patients with aggressive NHL enrolled in the Phase IIb and Phase IIa studies were comparable, providing support for the pooling of data across these two studies. The only notable differences were a shorter time since original diagnosis observed in the Phase IIa study (mean 2.6 years) compared to the Phase IIb study (mean 3.6 years) that was consistent with a higher proportion of patients having received only one prior therapy (11%, first relapse patients) in the supportive study compared to the pivotal study (1%). These results are expected based on the entrance criteria of the studies.

The combined aggressive NHL ITT population had a baseline presentation consistent with a heavily pretreated population with extensive resistant or refractory disease.

This was predominantly a fourth- and fifth-line population with difficult-to-treat disease; a median of 3 prior regimens had been administered in both studies. A total of 66% of the 211 patients were deemed to be resistant to their last regimen.

Overall Response Rate

Objective tumor response rates and 95% confidence intervals among patients with aggressive NHL in the Phase IIb and IIa studies are displayed graphically for the ITT population in Figure 18 and for the PP population in Figure 19.

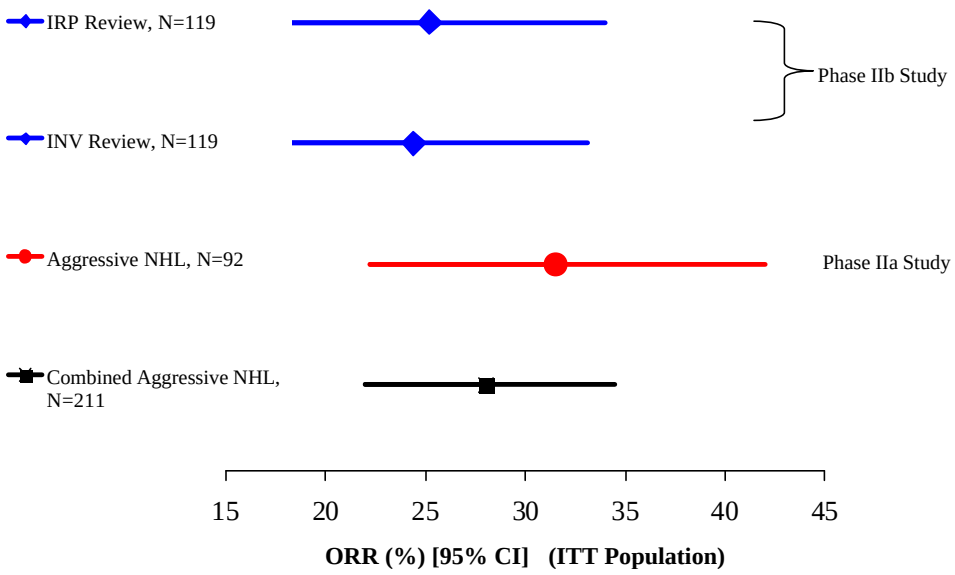


FIGURE 18. Comparison of Overall Response Rates [Point Estimates, 95% Confidence Limits] in Phase IIb and Phase IIa Studies (ITT Population)

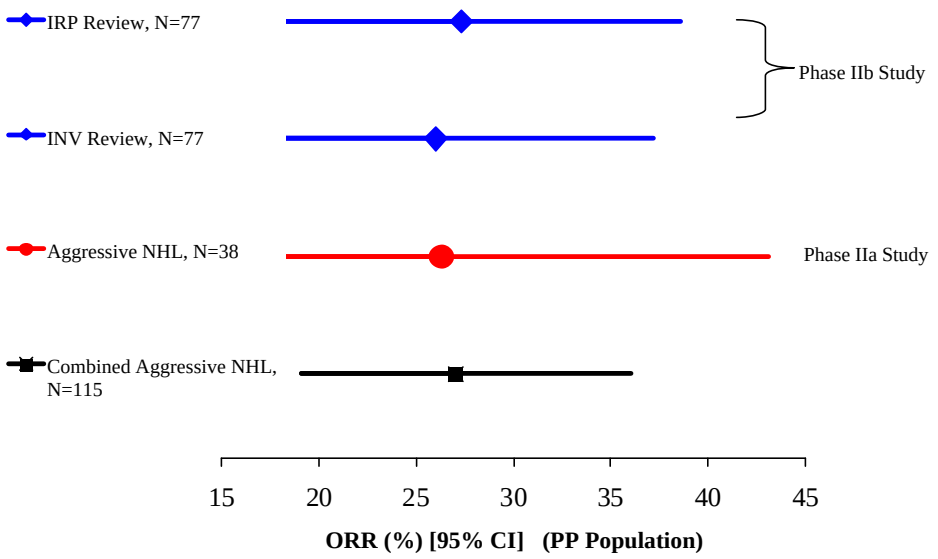


FIGURE 19. Comparison of Overall Response Rates [Point Estimates, 95% Confidence Limits] in Phase IIb and Phase IIa Studies (PP Population)

It is clear in Figure 18 that the point estimates of the rates of response and confidence intervals are similar for the ITT populations in both studies, using all opinions. Figure 19 shows the same concordance for the PP populations. Further details of the ORR results are presented in Table 46 for the ITT populations and in Table 47 for the PP populations.

TABLE 46. Objective Tumor Response (ITT Population)

Best Response During Study	Number (%) of Patients			
	Phase IIb (n=119)		Phase IIa Aggressive NHL (n=92)	Combined Aggressive NHL (n=211)
	IRP	INV		
Objective response rate (ORR)[a] [95% CI][b]	30 (25.2) [17.7, 34.0]	29 (24.4) [17.0, 33.1]	29 (31.5) [22.2, 42.0]	59 (28.0) [22.0, 34.5]
Complete response (CR) [95% CI][b]	4 (3.4) [0.9, 8.4]	7 (5.9) [2.4, 11.8]	7 (7.6) [3.1, 15.1]	11 (5.2) [2.6, 9.1]
CR unconfirmed (CRu) [95% CI][b]	4 (3.4) [0.9, 8.4]	0 (0.0) [0.0, 2.5]	0 (0.0) [0.0, 3.9]	4 (1.9) [0.5, 4.8]
Partial response (PR) [95% CI][b]	22 (18.5) [12.0, 26.7]	22 (18.5) [12.0, 26.7]	22 (23.9) [15.6, 33.9]	44 (20.9) [15.6, 27.0]
Stable disease (SD)	31 (26.1)	31 (26.1)	18 (19.6)	49 (23.2)
Progressive disease (PD)	32 (26.9)	51 (42.9)	38 (41.3)	70 (33.2)
Unable to evaluate (UE)	26 (21.8)	8 (6.7)	7 (7.6)	33 (15.6)

[a] ORR = CR + CRu + PR.
[b] 95% CI is an exact confidence interval on the proportion, based on the binomial distribution.

The ORR for the combined aggressive NHL ITT population was 28.0% with a 95% CI of [22.0%, 34.5%]. ORR was similar across the two Phase II studies including the relative proportions of CRs and PRs.

TABLE 47. Objective Tumor Response (Per-protocol Population)

Best Response During Study	Number (%) of Patients			
	Phase IIb (n=77)		Phase IIa Aggressive NHL (n=38)	Combined Aggressive NHL (n=115)
	IRP[a]	INV		
Objective response rate (ORR)[b]	21 (27.3)	20 (26.0)	10 (26.3)	31 (27.0)
[95% CI][c]	[17.7, 38.6]	[16.6, 37.2]	[13.4, 43.1]	[19.1, 36.0]
Complete response (CR)	1 (1.3)	4 (5.2)	2 (5.3)	3 (2.6)
[95% CI][c]	[0.0, 7.0]	[1.4, 12.8]	[0.6, 17.7]	[0.5, 7.4]
CR unconfirmed (CRu)	3 (3.9)	0 (0.0)	0 (0.0)	3 (2.6)
[95% CI][c]	[0.8, 11.0]	[0.0, 4.7]	[0.0, 9.3]	[0.5, 7.4]
Partial response (PR)	17 (22.1)	16 (20.8)	8 (21.1)	25 (21.7)
[95% CI][c]	[13.4, 33.0]	[12.4, 31.5]	[9.3, 37.3]	[14.6, 30.4]
Stable disease (SD)	22 (28.6)	21 (27.3)	10 (26.3)	32 (27.8)
Progressive disease (PD)	21 (27.3)	35 (45.5)	17 (44.7)	38 (33.0)
Unable to evaluate (UE)	13 (16.9)	1 (1.3)	1 (2.6)	14 (12.2)

[a] IRP = Independent Review Panel.
[b] ORR = CR + CRu + PR.
[c] 95% CI is an exact confidence interval on the proportion, based on the binomial distribution.

The ORR for the 115 patients included in the combined aggressive NHL PP population was 27.0% with a 95% CI of [19.1%, 36.0%]; results were remarkably similar for the IRP (27.3%) and INV (26.0%) assessments in the Phase IIb study and for patients with aggressive NHL in the Phase IIa study (26.3%). As well, the ORR noted in the PP population of 27.0% was similar to that observed in the ITT population (28.0%) for the pooled data from both studies.

The consistent objective response rates for the ITT and PP populations demonstrate that eligibility deviations, most of which were due to ineligible histology, did not favorably affect the outcome to VSLI treatment for this primary endpoint.

Time-to-Event Analyses

The following sections present results of the secondary efficacy endpoints of time to progression and overall survival. Duration of response was not calculated for the Phase IIa study as dates of response were not recorded. All results were analyzed using Kaplan-Meier methods.

Time to Progression

Time to progression was calculated as the duration from day of first dose until first documentation of relapse/progression; death on study was considered progression for these analyses.

TABLE 48. Time to Progression (Days) (ITT Population)

Kaplan-Meier Analysis	Phase IIb (n=119)		Phase IIa Aggressive NHL (n=92)	Combined Aggressive NHL (n=211)
	IRP[a]	INV[b]		
Number (%) of patients progressed/ relapsed	56 (47.1)	98 (82.4)	30 (32.6)	86 (40.8)
Number (%) of patients censored	63 (52.9)	21 (17.6)	62 (67.4)	125 (59.2)
Median time to progression (days) [95% CI]	89 [64, 217]	57 [50, 72]	132 [118, 243]	122 [89, 155]

[a] Based on IRP assessment. Data for patients not relapsing were censored in the analysis at the date of last contact on study.

[b] Based on INV assessment. Data for patients not relapsing were censored in the analysis at the date of last contact including post study follow-up.

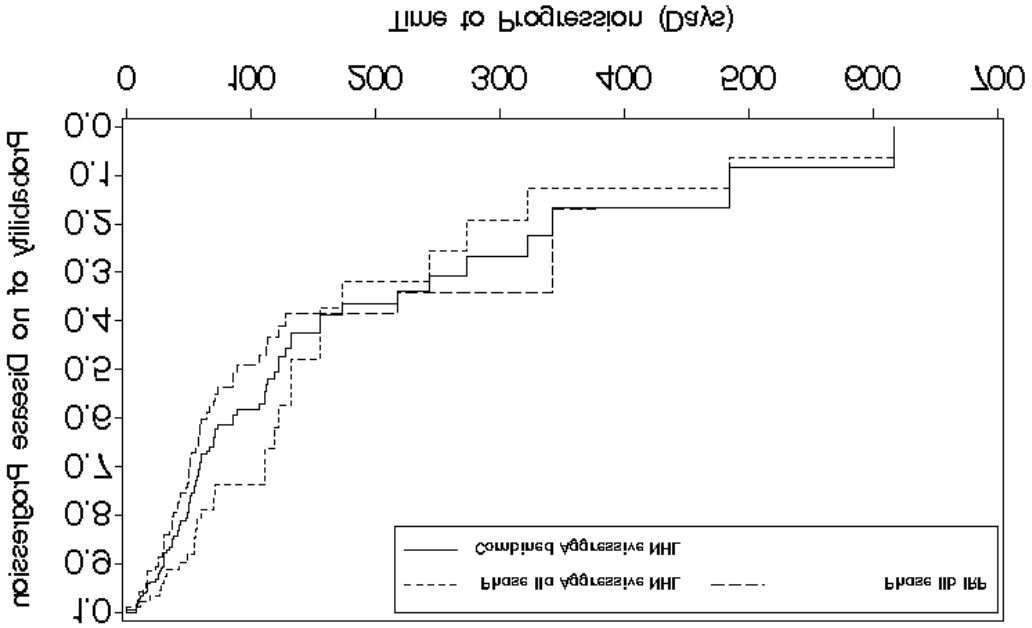


FIGURE 20. Kaplan-Meier Curve of Time to Progression for Patients with Aggressive NHL by Study and Overall (ITT Population)

Median TTP for the combined aggressive NHL ITT population of 211 patients was 122 days (~4.0 months) with a 95% CI of [89, 155]. Median TTP for patients with aggressive NHL was longer in the supportive Phase IIa study (132 days) as compared to the pivotal Phase IIb study (89 days for IRP review). However, the confidence intervals for these 2 determinations were wide and overlapping.

TABLE 49. Time to Progression (Days) (PP Population)

Kaplan-Meier Analysis	Phase IIb (n=77)		Phase IIa Aggressive NHL (n=38)	Combined Aggressive NHL (n=115)
	IRP[a]	INV[b]		
Number (%) of patients progressed/ relapsed	36 (46.8)	66 (85.7)	14 (36.8)	50 (43.5)
Number (%) of patients censored	41 (53.2)	11 (14.3)	24 (63.2)	65 (56.5)
Median time to progression (days) [95% CI]	89 [64, –][c]	60 [49, 89]	122 [56, 243]	111 [71, 155]

[a] Based on IRP assessment. Data for patients not relapsing were censored in the analysis at the date of last contact on study.
[b] Based on INV assessment. Data for patients not relapsing were censored in the analysis at the date of last contact including post study follow-up.
[c] Upper limit of the 95% CI could not be calculated.

Similar results were noted for analysis of the PP population as was observed for the ITT population. Median TTP across the combined aggressive NHL PP population of 115 patients was 111 days (3.6 months) with a 95% CI of [71, 155].

Survival

Overall survival in the Phase IIb and IIa studies was calculated as date of first dose to date of death.

TABLE 50. Overall Survival (ITT Population) – Phase IIb Survival Update Not Included

Kaplan-Meier Analysis	Phase IIb[a] (n=119)	Phase IIa Aggressive NHL (n=92)	Combined Aggressive NHL (n=211)
Number (%) of patients dead	73 (61.3)	48 (52.2)	121 (57.3)
Number (%) of patients alive	46 (38.7)	44 (47.8)	90 (42.7)
Median survival (days) [95% CI]	206 [144, 352]	299 [246, 404]	260 [205, 352]

[a] Data per original NDA submission, not updated. The median survival did not change with the second survival update.

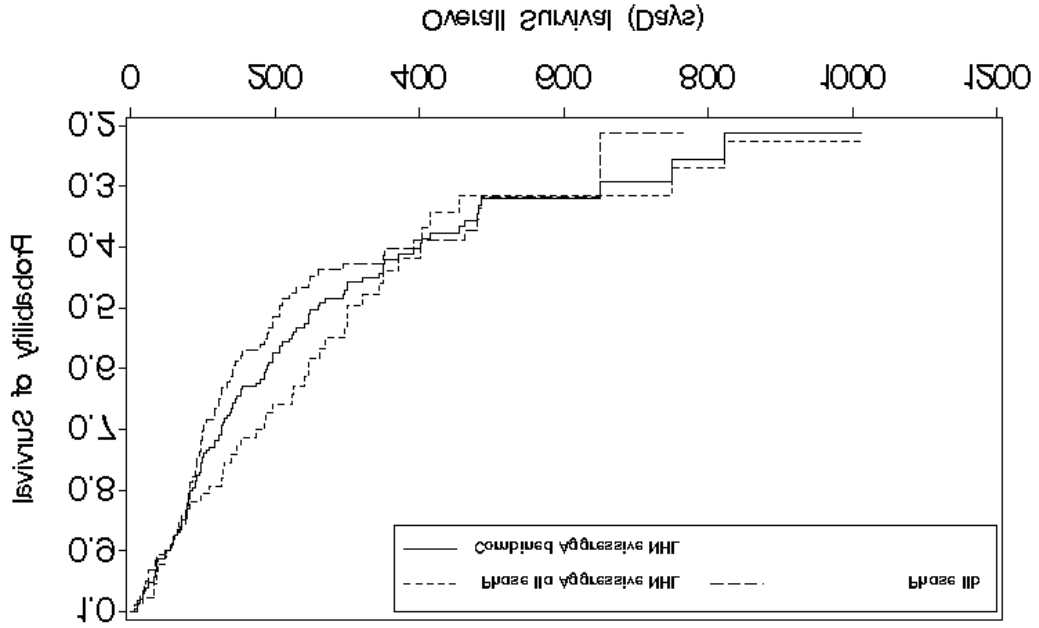


FIGURE 21. Kaplan-Meier Curve of Overall Survival for Patients with Aggressive NHL by Study and Overall (ITT Population) – Phase IIb Survival Update Not Included

All patients were to be followed for long-term survival. As of the original NDA survival follow-up, 57% of the 211 patients in the combined aggressive NHL ITT population had died. The median survival time was estimated to be 260 days (8.5 months) for these 211 patients with a 95% CI of [205, 352]. Median survival was ~3 months shorter for those patients in the pivotal Phase IIb study (median of 206 days, 6.8 months) compared to those with aggressive NHL in the supportive Phase IIa study (median of 299 days, 9.8 months). However, the confidence intervals for these 2 determinations were wide and overlapping.

TABLE 51. Overall Survival (PP Population) – Phase IIb Survival Update Not Included

Kaplan-Meier Analysis	Phase IIb[a] (n=77)	Phase IIa Aggressive NHL (n=38)	Combined Aggressive NHL (n=115)
Number (%) of patients dead	49 (63.6)	20 (52.6)	69 (60.0)
Number (%) of patients alive	28 (36.4)	18 (47.4)	46 (40.0)
Median survival (days)	197	321	209
[95% CI]	[144, 392]	[185, 414]	[180, 349]

[a] Data per original NDA submission, not updated.

Median survival across all 115 patients with aggressive NHL included in the PP population was slightly shorter than that observed in the ITT population at 209 days (6.9 months) compared to 260 days (8.5 months); however the 95% CI was broad [180, 349], overlapping that for the ITT

population. Note that comparison of median overall survival for the ITT and PP populations for the Phase IIb pivotal study revealed similar results of 206 and 197 days, respectively.

Comparison of Results in Patient Subpopulations

The following sections present the primary efficacy endpoint, objective response rate, for various patient subpopulations based on demographic and baseline disease characteristics, type and number of prior therapies, and response to prior therapy.

Objective Response Rate by Demographic and Baseline Disease Characteristics

TABLE 52. Objective Response Rate by Demographic and Baseline Disease Characteristics (ITT Population)

Subgroup	Phase IIb IRP Review (n=119)[b] r/n[a] (%)	Phase IIa Aggressive NHL (n=92)[b] r/n[a] (%)	Combined Aggressive NHL (n=211)[b] r/n[a] (%)
Age			
≤60 years	15/60 (25.0)	11/40 (27.5)	26/100 (26.0)
>60 years	15/59 (25.4)	18/52 (34.6)	33/111 (29.7)
?[c] % [95% CI ?][d]	-0.4 [-16.0, 15.2]	-7.1 [-26.1, 11.8]	-3.7 [-15.8, 8.4]
Gender			
Men	16/64 (25.0)	15/48 (31.3)	31/112 (27.7)
Women	14/55 (25.5)	14/44 (31.8)	28/99 (28.3)
?[c] % [95% CI ?][d]	-0.5 [-16.1, 15.2]	-0.6 [-19.6, 18.4]	-0.6 [-12.7, 11.5]
Race			
Caucasian	28/98 (28.6)	22/75 (29.3)	50/173 (28.9)
Non-Caucasian	2/21 (9.5)	7/17 (41.2)	9/38 (23.7)
?[c] % [95% CI ?][d]	19.0 [3.6, 34.5]*	-11.8 [-37.4, 13.7]	5.2 [-9.9, 20.3]
NHL History			
De-novo aggressive NHL	30/108 (27.8)	22/73 (30.1)	52/181 (28.7)
Transformed NHL	0/11 (0.0)	7/19 (36.8)	7/30 (23.3)
?[c] % [95% CI ?][d]	27.8 [19.3, 36.2]*	-6.7 [-30.8, 17.4]	5.4 [-11.1, 21.9]

* The confidence interval on the difference in response rates excludes zero, indicating that the difference is statistically significant.

[a] r = number of patients with objective response in the category, n = total number of ITT patients in the category.

[b] Objective response rate (ORR).

[c] Difference in ORR rates between subgroups.

[d] 95% CI based on the normal approximation of the binomial distribution.

There were no statistically significant differences in ORR for patient subgroups based on age, gender, or race, or NHL history (de novo aggressive versus transformed disease) for the analysis of data across all 211 patients included in the combined aggressive NHL ITT population.

Objective Response Rate by Type, Number and Response to Prior Therapy

TABLE 53. Objective Response Rate by Type and Number of Prior Therapy and Response to Prior Therapy (ITT Population)

Subgroup	Phase IIb IRP Review (n=119) r/n[a] (%)[b]	Phase IIa Aggressive NHL (n=92) r/n[a] (%)[b]	Combined Aggressive NHL (n=211) r/n[a] (%)[b]
Prior ABMT			
Yes	10/39 (25.6)	5/19 (26.3)	15/58 (25.9)
No	20/80 (25.0)	24/72 (33.3)	44/152 (28.9)
?[c] % [95% CI ?][d]	0.6 [-16.0, 17.3]	-7.0 [-29.6, 15.6]	-3.1 [-16.5, 10.3]
Number of prior therapy regimens			
1 or 2	11/24 (45.8)	13/25 (52.0)	24/49 (49.0)
≥3	19/95 (20.0)	16/66 (24.2)	35/161 (21.7)
?[c] % [95% CI ?][d]	25.8 [4.3, 47.3]*	27.8 [5.6, 49.9]*	27.2 [11.9, 42.6]*
Resistant/sensitive to last-qualifying therapy			
Resistant	14/80 (17.5)	11/59 (18.6)	25/139 (18.0)
Sensitive	16/39 (41.0)	18/32 (56.3)	34/71 (47.9)
?[c] % [95% CI ?][d]	-23.5 [-41.1, -6.0]*	-37.6 [-57.5, -17.8]*	-29.9 [-42.3, -16.6]*

* The confidence interval on the difference in response rates excludes zero, indicating that the difference is statistically significant.
[a] r = number of patients with objective response in the category, n = total number of ITT patients in the category.
[b] Objective response rate (ORR).
[c] Difference in ORR rates between subgroups.
[d] 95% CI based on the normal approximation of the binomial distribution.

Having had prior ABMT did not adversely impact the ability to respond to VSLI. Patients who are post transplant will frequently have compromised marrow reserve and a therapy such as VSLI that is not severely myelotoxic could offer an important treatment option. The ORR for the combined aggressive NHL ITT population was 25.9% among patients who had undergone prior ABMT and 28.9% among patients who had not. Results were consistent in the Phase IIb and Phase IIa studies.

The number of prior therapy regimens was a strong predictor of ORR. The ORR was statistically significantly higher at 49.0% in patients who had received one or two prior regimens compared to 21.7% for patients who had received 3 or more prior regimens. This was consistently observed in both the Phase IIb and Phase IIa study results.

Sensitivity to the last qualifying therapy was highly predictive of ORR. The ORR for sensitive-disease patients in the combined aggressive NHL ITT population was statistically significantly higher at 47.9% compared to 18.0% for the resistant disease subgroup. Results were consistent across the Phase IIb and Phase IIa studies.

For the PP population, the analysis according to the number of prior therapy regimens was not significantly different between patients who had ≤2 prior regimens (ORR 41%) and those who had received ≥3 prior regimens (ORR 23%).

Analysis of Results Based on Sensitive and Resistant Disease Categories

Based on the univariate and multivariate analyses in both the Phase IIb and Phase IIa studies, it was apparent that the sensitivity or resistance to last qualifying therapy was a significant prognostic factor. The sensitive-disease patients had efficacy outcomes approximately twice the magnitude shown for the resistant-disease patients.

TABLE 54. Efficacy Endpoints by Sensitive and Resistant Disease Categories (ITT Population)

Efficacy Endpoint	Phase IIb		Phase IIa Aggressive NHL		Combined Aggressive NHL	
	Sensitive (n=39)	Resistant (n=80)	Sensitive (n=32)	Resistant (n=59)	Sensitive (n=71)	Resistant (n=139)
ORR						
[Number (%) of Patients]	16 (41.0)	14 (17.5)	18 (56.3)	11 (18.6)	34 (47.9)	25 (18.0)
[95% CI]	[25.6, 57.9]	[9.9, 27.6]	[37.7, 73.6]	[9.7, 30.9]	[35.9, 60.1]	[12.0, 25.4]
Median TTP (days)	217	64	155	122	155	89
[95% CI]	[85, 342]	[51, 122]	[111, 273]	[118, 616]	[111, 243]	[60, 132]
Median survival (days)[a]	392	153	>823	246	823	187
[95% CI]	[228, --][b]	[104, 220]	[299, --][b]	[138, 344]	[299, --][b]	[134, 247]

[a] Survival data per original NDA submission, not updated for Phase IIb.
[b] Upper limit of the 95% CI could not be calculated.

From the data summarized in Table 54, the profound effect of resistant disease is apparent. In the combined aggressive NHL ITT population, patients with resistant disease achieved an ORR of 18%, with an estimated median TTP of 89 days (3 months) and a median survival of 187 days (6 months). In contrast, the sensitive-disease patients had better efficacy outcomes with an ORR of 48% and an estimated median TTP of 155 days (5 months) and an estimated median survival of 823 days (27 months).

Similar results were noted for comparison of sensitive- and resistant-disease patients for the PP population. ORR was 18% for resistant-disease patients compared to 50% for sensitive-disease patients. Median TTP was 71 days compared to 113 days for resistant- and sensitive-disease patients, respectively, and median survival was 185 days and was not reached, respectively, for resistant- and sensitive-disease patients.

APPENDIX D – OTHER PATIENTS WITH NET CLINICAL BENEFIT FROM VSLI TREATMENT

Patient benefit summaries for 41 patients are provided with this Briefing Document; the summary for Patient 35-01 (CRu) was provided in Section 4 of the main document and the other 40 are provided in this appendix. The figures are ordered by best response as determined by the IRP: CR, CRu, PR, SD and UE. Within each response category, patients are listed in numeric order by patient number.

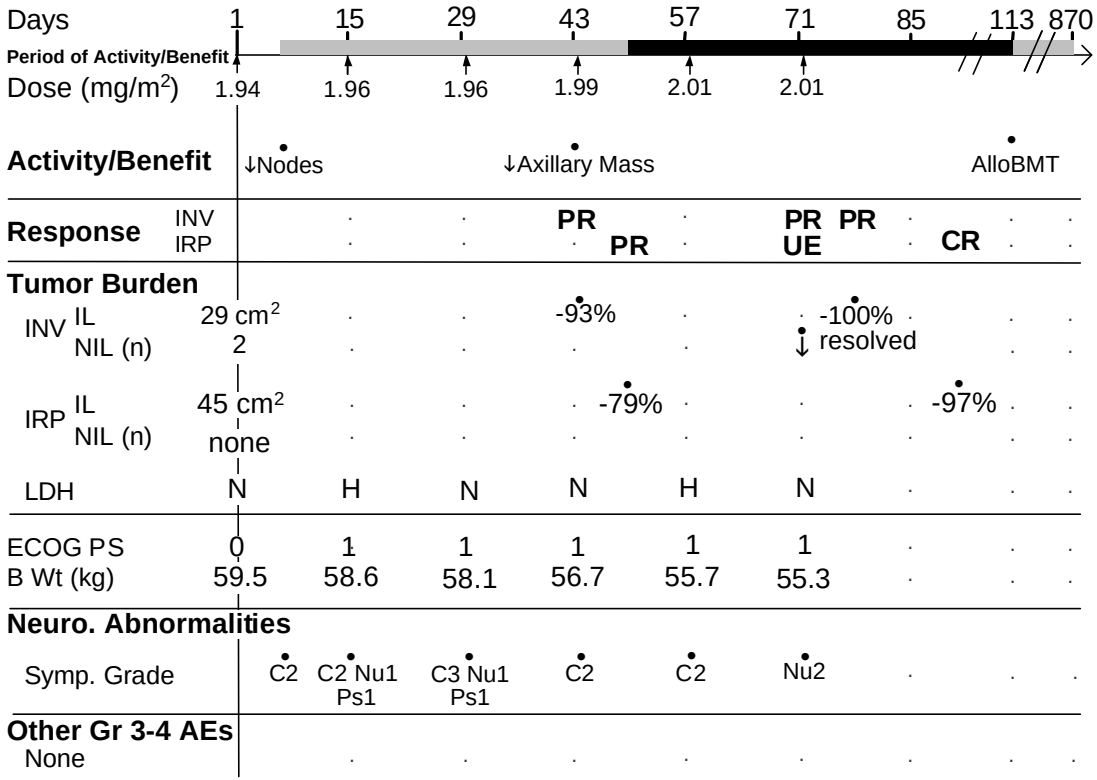
FIGURE 22. Graphical Presentation of Efficacy and Safety for Patient 01-20

3 Prior Systemic Therapies		
1. CHOP x6; CR of 2-3 mo; salvaged by XRT. CR of 2 yr. 2. (ifosfamide, etoposide, mesna) x2; methylprednisolone x1; (ifosfamide, mitroxantrone, mesna) x1. PR → transplant. 3. BEAM + transplant; CR of 1.3 yr.	47-year-old woman Stage I DLBCL, IPI 0 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: CR SPD Change: -97% Duration of Response: >1.4 mo Time to Progression: >3.1 mo Survival: >28.6 mo, alive with no evidence of disease

This 47-year-old Caucasian woman had Stage I diffuse large B-cell lymphoma that relapsed after 3 combination chemotherapy regimens including XRT at 1st line and transplant at 3rd line. Her disease was sensitive to the last qualifying therapy (autologous transplant), having attained a CR lasting 1.3 years. At study entry, her measured tumor burden was 45.2 cm^2, which decreased by 79% to 9.7 cm^2 after 4 cycles of VSLI according to the IRP (Day 51). She was declared to be in CR by the IRP after 6 cycles (Day 93). The Investigator declared her response to be PR with a 93% reduction in measured tumor burden after 4 cycles. After 6 cycles the Investigator assessed her response to be a PR again, based on a clinical review of the CTs. A retrospective radiology assessment at the site documented that all disease had resolved, but the response designation was not permitted to be changed from a PR to a CR.

Her hemoglobin fell (Grade 2) but was maintained at acceptable levels with erythropoietin. Grade 2 leukopenia and thrombocytopenia did not require treatment. She developed Grade 2 numbness of her hands and toes on study. Her only Grade 3 AE was constipation after 2 cycles, which improved to Grade 2. These adverse events were tolerable and her dose and schedule of study drug were not altered. Her ECOG PS was 0 at study entry and maintained at 1 throughout the study.

Her excellent response with VSLI allowed her to receive an allogeneic transplant on Day 113. At last contact, she was alive with no evidence of disease at 28.6 months after her first VSLI treatment. The response achieved with VSLI and subsequently maintained with AlloBMT provided >25.6 months of disease-free survival for this patient.



Legend:
↓Decrease **AlloBMT** Allogeneic Bone Marrow Transplant **C** Constipation **CR** Complete Response **Gr** Grade **H** High **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **PR** Partial Response **Ps** Paresthesia **UE** Unable to Evaluate **XRT** Radiation

FIGURE 23. Graphical Presentation of Efficacy and Safety for Patient 12-06

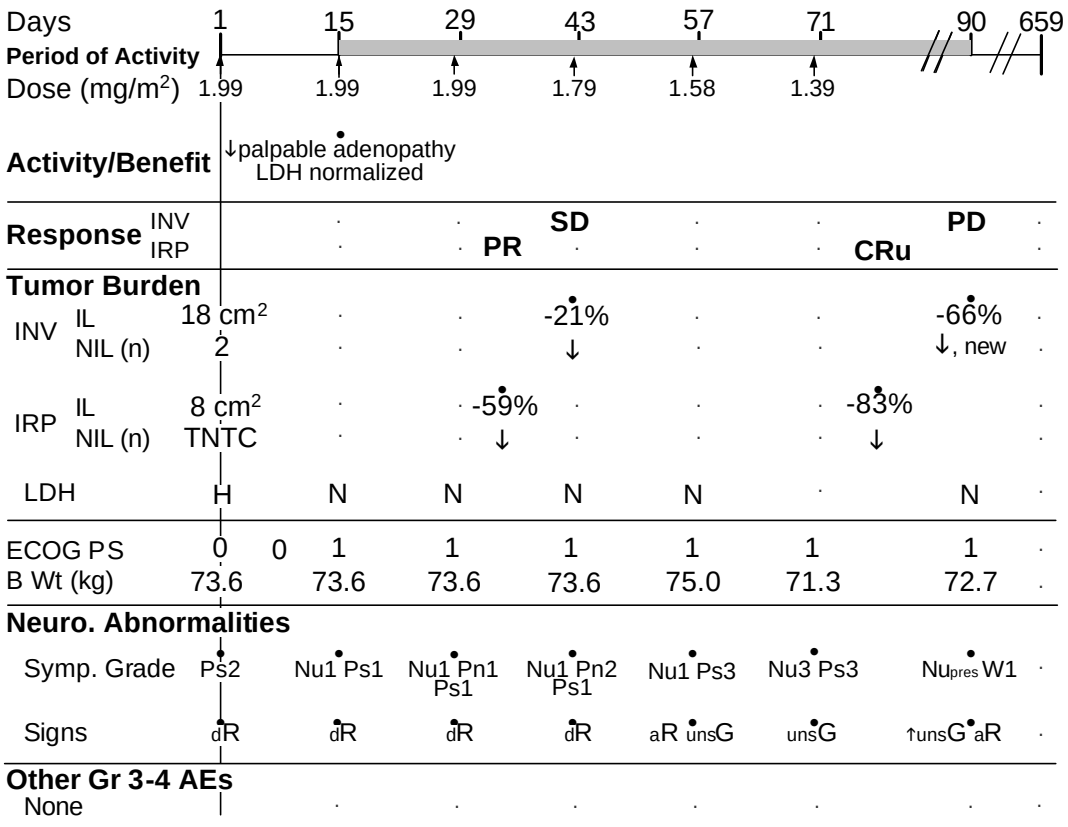
4 Prior Systemic Therapies	76-year-old man	IRP Best Response: CRu SPD Change: -83%
1. CHOP x10; PR → laparotomy with excisional biopsy + XRT; CR. 2. ESHAP x1; UE. 3. COMLA; CR of ~1 yr. 4. MINE x6; unknown response + XRT; PR of 5 mo.	Stage IIE Composite Lymphoma, IPI 2 Per Protocol Eligible Sensitive to Last Qualifying Therapy	Duration of Response: >1.9 mo Time to Progression: >3.0 mo Survival: 21.7 mo

This 76-year-old Caucasian man with chemosensitive Stage IIE DLBCL had received 4 prior combination chemotherapy regimens and 2 courses of radiation therapy. He had extensive axillary nodes that were "too numerous to count" according to the IRP, plus cervical and supraclavicular nodes identified by physical examination.

His slightly elevated LDH level normalized after the 1st cycle of VSLI and his palpable nodes were smaller. On Day 34 (Cycle 3, Day 7), the IRP assessed his response as a PR based on a 59% reduction in his indicator lesions from 8.2 to 3.4 cm^2. The Investigator declared his response to be SD; one of the indicator lesions was not measured. By Day 78, the Investigator noted a 66% decrease in the indicator lesions from 17.8 to 6.0 cm^2, but also noted a new lesion in the pectoralis muscle region by CT, and therefore declared PD. The IRP radiologist, however, did not note any new lesions on the CTs. The IRP oncology review concluded that his response was a CRu, citing a ">75% decrease with very minimal remaining disease".

Three of the prior regimens contained neurotoxic agents (2 with vincristine, 1 with cisplatin) and he had residual Grade 2 neuropathy in his right hand and feet at study entry. He received a total of 6 cycles of VSLI, with 3 dose reductions due to progressive sensory neuropathy that reached Grade 3 and he withdrew from further treatment when he developed Grade 1 motor neuropathy (leg weakness and unsteady gait - Day 90). However, he never experienced constipation and his ECOG PS diminished only to 1 from his baseline of 0. His hematologic parameters were stable, with intermittent Grade 2 leukopenia and Grade 1 anemia, all from study entry and one occurrence of Grade 2 neutropenia. Transient thrombocytopenia occurred after the 1st two cycles only. His weight was stable and he had no nausea or vomiting.

This elderly patient with extensive disease after 4 prior combination regimens achieved a good objective response (CRu) and a time to progression of >3.0 months, with minimal incremental toxicity from VSLI. He had no disease-related symptoms at study entry and therefore symptomatic benefit could not be demonstrated. He died due to disease progression on Day 659, 21.7 months after his first dose of VSLI.



Legend: ↓Decrease ↑Increase **a** Absent **abn** Abnormal **CR** Complete Response **CRu** Complete Response Unconfirmed **G** Gait **Gr** Grade **H** High **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **pres** Present **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to evaluate **uns** Unsteady **W** Weakness **XRT** Radiation

FIGURE 24. Graphical Presentation of Efficacy and Safety for Patient 22-04

3 Prior Systemic Therapies	68-year-old woman	IRP Best Response: CRu SPD Change: -90%
1. CHOP x3; PR then next therapy immediately.	Stage III Composite Lymphoma, IPI 4	Duration of Response: 2.5 mo
2. CVP x4 (first 2 cycles w/o prednisone); UE.	Per Protocol Eligible	Time to Progression: 3.7 mo
3. (Ritux./dex.) x4; PR of 12 mo.	Sensitive to Last Qualifying Therapy	Survival: >24.4 mo, alive with disease

This 68-year-old Caucasian woman with Stage III composite lymphoma (>75% DLBCL, <25% follicular Grade 3 lymphoma) had received 3 systemic therapy regimens in the 1.9 years from her initial diagnosis. Her disease was sensitive to her last qualifying therapy (rituximab and dexamethasone), with a PR that lasted 12 months.

The first evidence of antitumor activity and patient benefit was the resolution of her Grade 1 abdominal (RLQ) pain by Day 8, after only 1 dose of VSLI; she had bilateral inguinal and iliac lesions. Her bilateral palpable axillary nodes resolved at Day 29 visit, after 2 cycles. Her Grade 1 anemia and Grade 2 hypoalbuminemia improved steadily from the first cycle of VSLI; her hemoglobin level improved from 10.1 to 12.7 g/dL without erythropoietin or transfusions and her albumin level improved from 24 to 34 g/L.

On Day 37 after 3 cycles, the IRP considered her response to be a CRu based on an 84% reduction in the indicator lesions from 38.9 to 6.2 cm^2. The Investigator declared a PR based on a 71% reduction in the indicator lesions from 68.3 to 19.5 cm^2. Her response was confirmed with additional CTs on Days 71 and 113 according to the Investigator review. The IRP confirmed her response on Day 71, but declared PD due to a new axillary node on Day 113. By Day 127, the new right axillary node was palpable and the CTs on Day 141 documented PD for the Investigator.

She tolerated 10 cycles of VSLI (19.0 mg/m^2 total) well, with no dose delays or decreases. Despite prior exposure to vincristine twice (13 mg total), her preexisting Grade 1 neuropathy did not worsen on study and she had only minimal GI complaints of Grade 1 nausea, constipation, and diarrhea. Her course was complicated by an L4 vertebral collapse due to tumor present since study entry. She maintained her ECOG PS at 0 until the last two visits, when it worsened to 1 concurrent with increased back pain, Grade 3 leg weakness, and PD. She had no other Grade 3-4 AEs.

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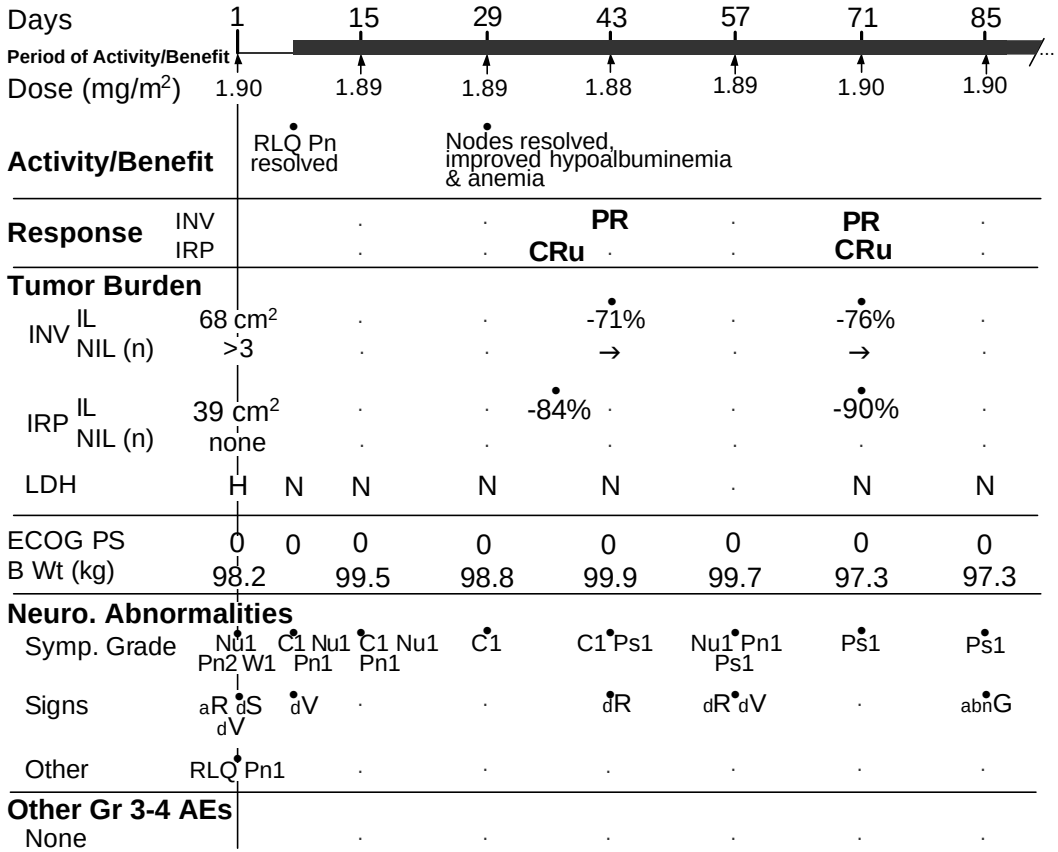


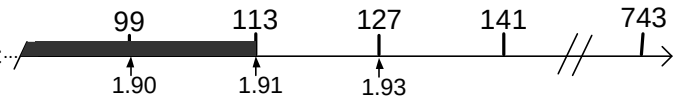
Legend: ↓Decrease →Stable **abn** Abnormal **a** Absent **CR** Complete Response **CRu** Complete Response Unconfirmed **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 24. Graphical Presentation of Efficacy and Safety for Patient 22-04 (continued)

3 Prior Systemic Therapies	68-year-old woman	IRP Best Response: CRu	SPD Change: -90%
1. CHOP x3; PR then next therapy immediately. 2. CVP x4 (first 2 cycles w/o prednisone); UE. 3. (Ritux./dex.) x4; PR of 12 mo.	Stage III Composite Lymphoma, IPI 4 Per Protocol Eligible Sensitive to Last Qualifying Therapy	Duration of Response: 2.5 mo Time to Progression: 3.7 mo Survival: >24.4 mo, alive with disease	

Patient 22-04 continued

According to the IRP, her best response was a CRu, with a documented duration of 2.5 months and a time to progression of 3.7 months. The Investigator assessed her response as a PR, with a duration of 3.3 months and a time to progression of 4.6 months. She was alive with disease on Day 743, more than 2 years after her first VSLI dose.



Activity/Benefit

Response	INV	·	·	**PR**	**PD**	·
	IRP	·	**PD**		**PD**	·
Tumor Burden						
INV	IL	·	·	-68%	-65%	·
	NIL (n)	→	·	→	→	·
IRP	IL	·	·	-76%	-85%	·
	NIL (n)	·	·	·	·	·
LDH		N	N	N	N	·
ECOG PS		0	0	1	1	·
B Wt (kg)		98.2	96.8	95.0	·	·
Neuro. Abnormalities						
Symp. Grade		C1 Pn2 Ps1	Nu1	Nu1 Pn2 Ps1 W3	·	·
Signs		abnG dR	dR	abnG dR dS dV	·	·
Other		·	·	·	·	·
Other Gr 3-4 AEs						
None		·	·	·	·	·

Legend: ↓Decrease →Stable **abn** Abnormal **a** Absent **CR** Complete Response **CRu** Complete Response Unconfirmed **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 25. Graphical Presentation of Efficacy and Safety for Patient 01-19

2 Prior Systemic Therapies	71-year-old woman Stage IV DLBCL, IPI 4 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: PR Duration of Response: >3.1 mo Time to Progression: >4.8 mo Survival: 28.9 mo	SPD Change: -92%
1. CHOP; CR of 4.5 yr. 2. CHOP; presumed CR of 2.3 yr.			

This 71-year-old Caucasian woman had estimated Stage IV chemosensitive DLBCL that relapsed after 2 courses of CHOP. She entered the study with ECOG PS of 1-2, no B symptoms, and extensive tumor involvement in the neck, lung, spleen and paracaval area, with an IPI score of 4.

Clinical evidence of tumor response (decreased adenopathy, reduced LDH) was apparent after 1 cycle of VSLI. She received 10 cycles in total (20.5 mg/m^2 total) and achieved a confirmed best response of CR per the Investigator, PR per the IRP (92% reduction in measurable tumors) lasting more than 3 months and ongoing at the last evaluation.

Following the first dose of study drug, she developed an upper extremity DVT, considered to be possibly related to VSLI, which was treated with anticoagulation, and had no further thromboses. She developed up to Grade 3 neutropenia during the study, which responded to filgrastim, and had no other clinically significant cytopenias or associated infections. VSLI was well tolerated without dose modifications. Her worst neurotoxicity was transient Grade 2 numbness and paresthesia. She had baseline GI problems with few on-study complaints, all Grade 1. Her weight remained stable. Her ECOG PS was improved at 0-1, with only two scores of 2. Her final ECOG PS was 0.

Her excellent response to VSLI allowed her to be considered for transplant. On Day 147, she was transferred for autologous BMT, which she received on Day 190 and remained in response for 5.5 months afterwards, with relapse on Day 357. The response achieved with VSLI and subsequently maintained with BMT provided 8.4 months of disease-free survival for this patient, according to the Investigator. She died on Day 879, 28.9 months after her first VSLI dose, due to progressive disease.

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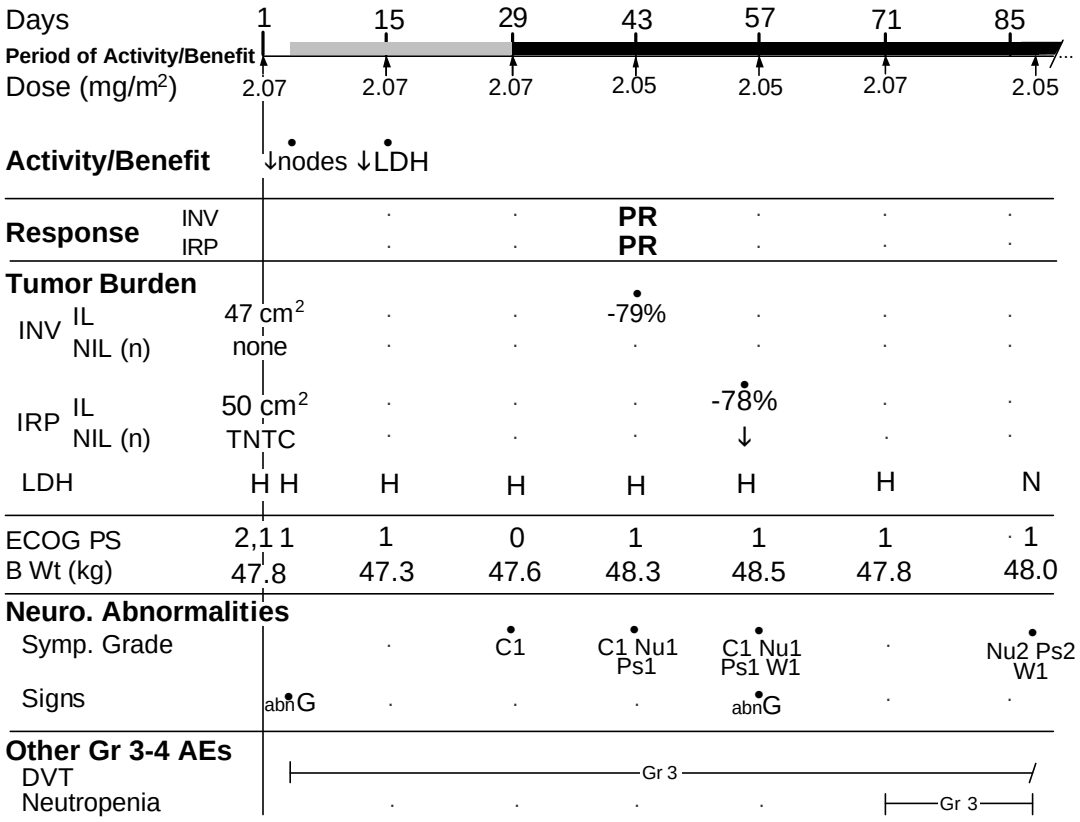
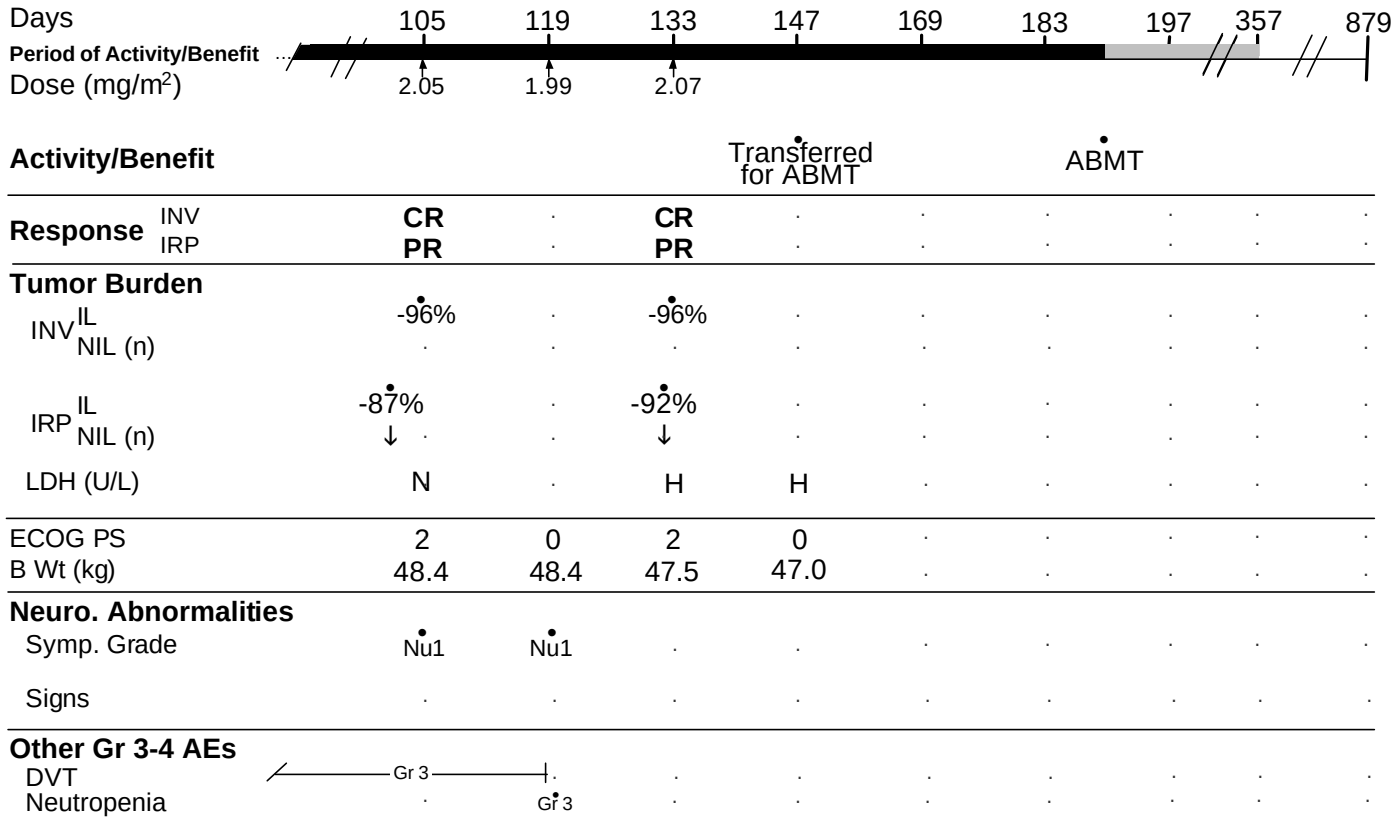


Legend:
↓Decrease **ABMT** Autologous Bone Marrow Transplant **abn** Abnormal **C** Constipation **CR** Complete Response **DVT** Deep Vein Thrombosis **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PR** Partial Response **Ps** Paresthesia **TNTC** Too numerous to count **W** Weakness

FIGURE 25. Graphical Presentation of Efficacy and Safety for Patient 01-19 (continued)

2 Prior Systemic Therapies 1. CHOP; CR of 4.5 yr. 2. CHOP; presumed CR of 2.3 yr.	71-year-old woman Stage IV DLBCL, IPI 4 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: PR Duration of Response: >3.1 mo Time to Progression: >4.8 mo Survival: 28.9 mo SPD Change: -92%

Patient 01-19 continued



Legend:
↓Decrease **ABMT** Autologous Bone Marrow Transplant **abn** Abnormal **C** Constipation **CR** Complete Response **DVT** Deep Vein Thrombosis **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PR** Partial Response **Ps** Paresthesia **TNTC** Too numerous to count **W** Weakness

FIGURE 26. Graphical Presentation of Efficacy and Safety for Patient 01-22

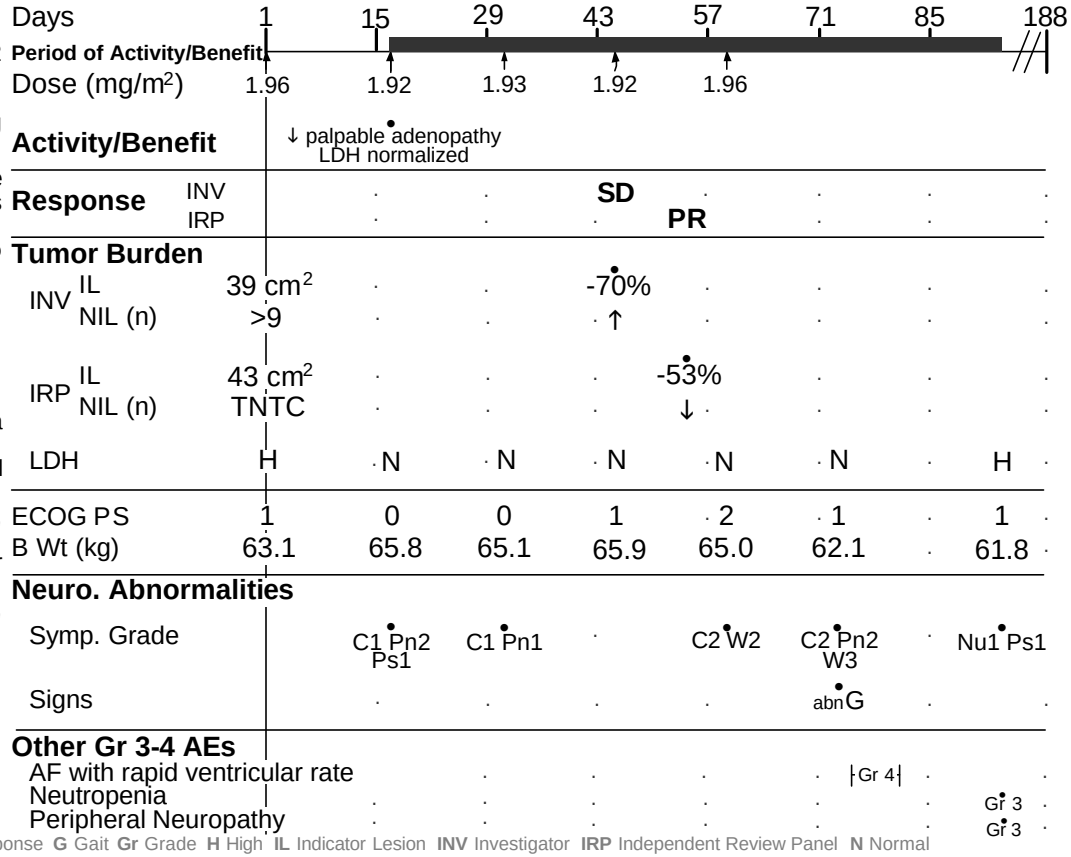
2 Prior Systemic Therapies 1. CHOP x6; CR. 2. MINE x5; likely refractory.	74-year-old woman Stage III Intermediate-grade LBCL, IPI 3 Per Protocol Eligible Refractory to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -53% Duration of Response: >1.6 mo Time to Progression: >3.4 mo Survival: 6.2 mo

This 74-year-old Caucasian woman with refractory Stage III intermediate-grade large B-cell lymphoma had received 2 combination chemotherapy regimens in the 1.8 years since her original diagnosis. She had widespread disease, with cervical and retroperitoneal nodes that were "too numerous to count" according to the IRP.

The first evidence of antitumor activity was a decrease in the palpable adenopathy and normalization of her LDH levels documented on Day 17, after a single dose. By Day 55 (Cycle 4, Day 11) the IRP assessed her response to be a PR, with a 53% decrease in indicator lesions from 43.4 cm^2 to 20.3 cm^2. The Investigator assessed her response to be SD, based on a clinical review of the CTs. A retrospective radiology review of the CTs at the treating site documented a 70% decrease from 38.7 cm^2 to 11.8 cm^2, which would have supported a PR assessment.

At study entry she had a significant history of cardiac disease and a CVA, and was on multiple medications. Her tachyarrhythmia recurred during the trial. She tolerated the first 4 cycles of VSLI well, with minimal neuropathy, but developed Grade 3 peripheral neuropathy after the 5th cycle and was withdrawn from the study on Day 97. Her hematologic parameters were stable throughout, with Grade 3 neutropenia only after 5 cycles. Her chronic constipation worsened to Grade 2, but she had no nausea or vomiting. Her ECOG PS improved for the first month on study, from 1 to 0, and then it returned to 1 for the remainder of the study, with one transient score of 2.

The IRP concluded that she had a best response of PR that lasted >1.6 months, with a time to progression of >3.4 months. She died 6.2 months after her first dose of VSLI from an unknown cause, with disease status unknown.



Legend: ↓Decrease ↑Increase **abn** Abnormal **C** Constipation **CR** Complete Response **G** Gait **Gr** Grade **H** High **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **Pn** Pain **PR** Partial Response **Ps** Paresthesia **PD** Progressive Disease **TNTC** Too numerous to count **W** Weakness

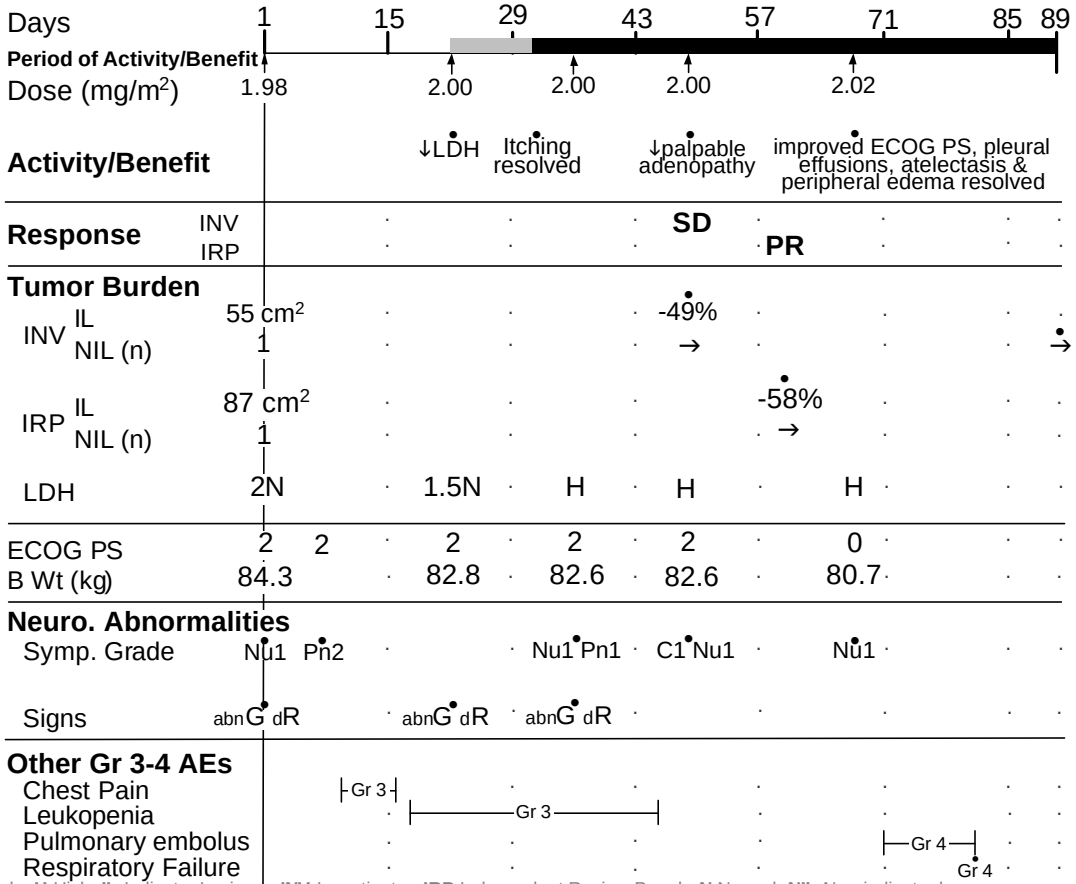
FIGURE 27. Graphical Presentation of Efficacy and Safety for Patient 04-01

2 Prior Systemic Therapies	77-year-old woman	IRP Best Response: PR SPD Change: -58%
1. CHOP x6 with Ritux. x4; PR consolidated by XRT. PR of 15 mo. 2. (Mitroxantrone & fludarabine) x4; PR of <2 mo.	Stage IIE DLBCL, IPI 3 Per Protocol Eligible Resistant to Last Qualifying Therapy	Duration of Response: 1.0 mo Time to Progression: 2.9 mo Survival: 2.9 mo

This 77-year-old Caucasian woman with resistant DLBCL entered the study after failing two courses of combination chemotherapy, including one with immunotherapy and salvage radiation. Her best response had been a PR to all previous therapies and she relapsed within 2 months of completing her most recent regimen. She had a poor prognosis, with an IPI score of 3, bulky disease, and an extensive medical history that included an MI and 2 episodes of recurrent pulmonary emboli. Unstable persistent herpes zoster infections would have made immunosuppressive treatment with standard chemotherapeutic agents dangerous.

The first evidence of antitumor activity was improvement of her elevated LDH by Day 19. Clinical benefit was documented with the total resolution of her lymphoma-related itching by Day 33 after 2 cycles of VSLI. The IRP assessed her response after 4 cycles as PR, based on a 58% reduction in the measured tumors from 87 cm^2 to 37 cm^2. The Investigator documented a similar level of reduction (49%), which met the criteria for SD only. A comment indicated that the Investigator considered her response to be a PR, but strictly according to the criteria, it had to be SD. The right-sided pleural effusion and right lower lobe atelectasis resolved. Her 4% weight loss was partly due to the resolved pleural effusions and peripheral edema. Her ECOG improved from 2 to 0.

She received 5 doses of VSLI with only minimal neurologic side effects and only one episode of gastrointestinal side effects (Grade 1 constipation). During therapy she developed Grade 2 neutropenia and Grade 3 leukopenia that resolved without therapy and Grade 1 anemia that was treated with blood transfusion. Unfortunately, while maintaining her response and clinical benefit she expired on Day 89 of her third pulmonary embolus. The IRP assessed her best response to be a PR with a documented duration of 1 month and a survival of 2.9 months.



Legend:
↓Decrease →Stable **abn** Abnormal **C** Constipation **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **Pn** Pain **PR** Partial Response **pres** Present **R** Reflexes **SD** Stable Disease **XRT** Radiation

FIGURE 28. Graphical Presentation of Efficacy and Safety for Patient 05-01

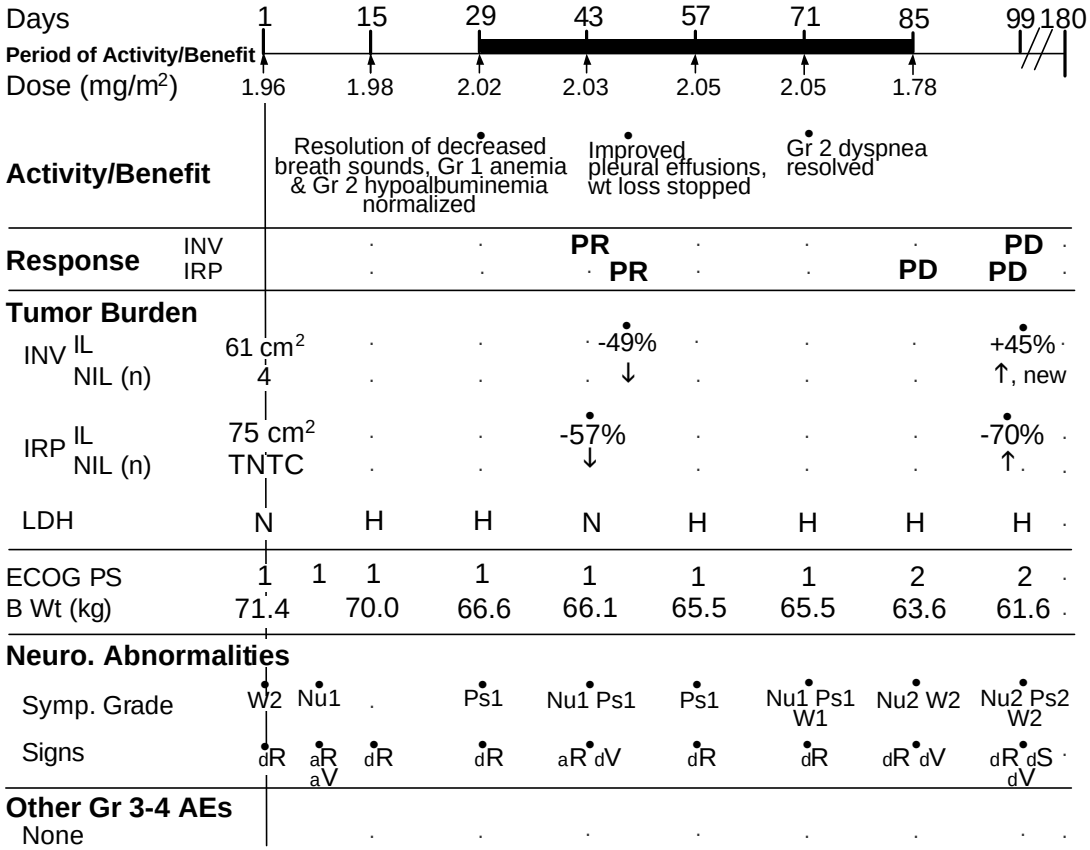
2 Prior Systemic Therapies	76-year-old woman Stage II DLBCL, IPI 1 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: PR Duration of Response: 1.3 mo Time to Progression: 2.8 mo	SPD Change: -70% Survival: 5.9 mo
1. CHOP x6; CR of 2.3 yr. 2. CHOP; assume CR of 2.6 yr.			

This 76-year-old Caucasian woman with sensitive Stage II DLBCL relapsed after 2 courses of CHOP, with multiple lesions in the lungs, hilum, mediastinum, mesentery and retroperitoneal areas that were "too numerous to count". She also had a left pleural effusion and disease-related Grade 2 dyspnea and fatigue, as well as B symptoms.

Several parameters improved early, some even before a measurable response was documented. Her dyspnea improved and her anemia and albumin levels normalized after 2 cycles of VSLI. Her B symptom (weight loss) improved on study. An abrupt body weight loss of 3.4 kg (5%) over 2 weeks may have been partly due to the resolution of her pleural effusion and hypoalbuminemia. Her weight started to decrease again around the time of disease progression. Her Grade 2 fatigue improved to Grade 1 as well for 1 month during the period of documented response, which is also when her Grade 2 dyspnea resolved completely. She achieved a PR after 4 cycles of VSLI according to the Investigator and the IRP.

Despite having residual neuropathy from her 2 prior regimens containing vincristine, she tolerated VSLI well, with only 1 dose decrease for her 7th and final dose. Her worst neurotoxicity was Grade 2 numbness and paresthesia after 6 cycles. She had stable or improved hematologic parameters and no GI complaints or Grade 3-4 AEs of any nature. Her ECOG PS was stable at 1 until the time of relapse.

She was removed from study due to PD. The IRP assessed her PR as lasting 1.3 months, with a time to progression of 2.8 months. She experienced considerable symptomatic improvement during her 2.8 months of progression-free survival, which was approximately half of her survival period from study entry. She died of progressive disease 5.9 months after her first dose of VSLI.



Legend:
↓Decrease ↑Increase **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 29. Graphical Presentation of Efficacy and Safety for Patient 07-01

10 Prior Systemic Therapies		40-year-old man Stage IV Composite Lymphoma, IPI 3 Per Protocol Eligible Refractory to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -68% Duration of Response: could not be assessed Time to Progression: >1.2 mo Survival: 3.4 mo
1. CHOP x6; CR salvaged by XRT; CR or PR of 8 mo.	6. ICE x4; PR of <1 mo.		
2. XRT; ESHAP x2; PR of 2 mo.	7. (Vinc., dox., dex.) x1; Unknown response.		
3. BCNU, cisplatin + transplant; CR of 28 mo.	8. (Ritux., DaunoXome) x2; SD.		
4. Rituximab x8; PR of <4 mo.	9. Thalidomide, (dex.) x1; UE.		
5. Rituximab x4; PD.	10. INE x1; rapid PD.		

This 40-year-old Caucasian man had refractory Stage IV composite lymphoma (>90% DLBCL) and had received 10 prior chemotherapeutic regimens plus 3 courses of radiation therapy and a stem cell transplant. In the previous year, he had received 7 different therapies in an unsuccessful attempt to achieve a meaningful response. He had extensive abdominal disease that included the liver, spleen, and mesenteric and periaortic nodes that were "too numerous to count" according to the IRP. His baseline IPI score was 3.

The first evidence of antitumor activity was an immediate resolution of his Grade 1 abdominal pain (by Day 5), a decrease in his LDH values, improvement/resolution of his liver function tests abnormalities, and resolution of his baseline Grade 2 hypoalbuminemia and Grade 1 thrombocytopenia after 1 cycle of VSLI. He was removed from the study due to the Investigator's assessment of PD (a new lesion) after receiving only 3 doses of VSLI, although the IRP determined that he had achieved a PR (Day 35), with a 68% decrease in measured lesions from 101 cm^2 to 32 cm^2 and no new lesions. His duration of response could not be assessed by the IRP as he was removed from study 2 days later.

On Day 3, he experienced an infection of his indwelling catheter and required hospitalization. Grade 3 neutropenia was recorded on Day 8. Grade 2 anemia was treated with PRBCs. Despite having received 6 prior regimens containing neurotoxic agents, he maintained his baseline level of neuropathy (Grade 1) after 3 cycles of VSLI. His ECOG PS was 1 throughout the study, slightly worsened from his baseline score of 0. His weight was stable. He died on Day 104 of metastatic disease.

According to the IRP assessment, he achieved a better response (PR) with single-agent VSLI than he had achieved on his 4 most recent combination chemotherapy regimens, documenting clinically useful activity of VSLI in a situation where no response to any available therapeutic agent would have been expected.

Legend:
↓Decrease ↑Increase **a** Absent **abd** abdominal **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to evaluate **XRT** Radiation

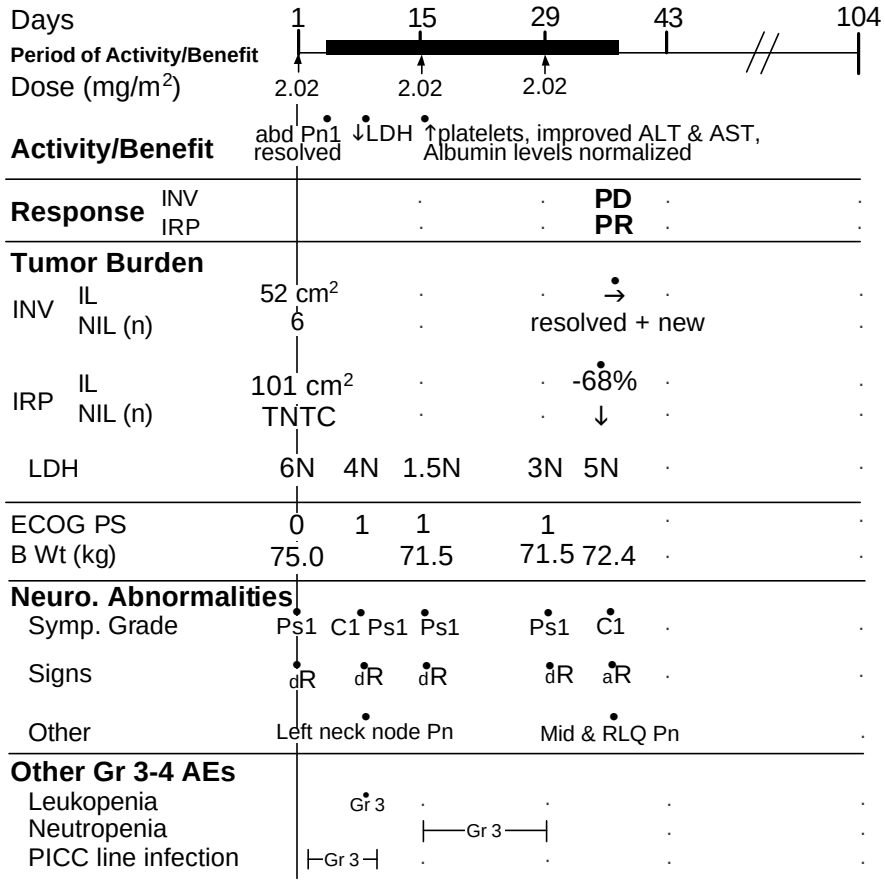


FIGURE 30. Graphical Presentation of Efficacy and Safety for Patient 11-02

4 Prior Systemic Therapies 1. CHOP x6; CR of <9 mo. 2. (DHAP/rituximab) x2; CRu of <2 mo. 3. Ribavirin + interferon; PR of <3 mo. 4. MINE x6; PR of ~4.5 mo.	47-year-old man Stage III DLBCL, IPI 3 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: PR Duration of Response: 0.26 mo Time to Progression: 1.9 mo SPD Change: -48% to -51% Survival: 6.8 mo

This 47-year-old Caucasian man with chemosensitive Stage III DLBCL had received 4 prior combination regimens in the 2.7 years since his initial diagnosis. He achieved a PR to his last qualifying therapy (MINE) that lasted 4.5 months. His medical history included diabetes, hypothyroidism secondary to Grave's disease, kyphoscoliosis, and chronic hepatitis C. At study entry, he had bulky cervical nodes on physical examination and numerous small lesions in the liver that were "too numerous to count" according to the IRP. The IRP Radiologist did not identify any indicator lesions as the liver lesions were too small to characterize and no neck CTs were done for the bulky neck lesions.

The first evidence of antitumor activity was the reduction in his palpable bulky indicator lesion by 32% from 36.5 to 25 cm^2 by Day 8 and by Day 43 after 3 cycles, it reached nadir measurements with an area of 19 cm^2. By Day 43, his preexisting B symptom (fever) had resolved, with no further episodes reported on study. Additionally, his Grade 1 elevated GGT from study entry normalized by Day 57 (after 4 cycles).

At Day 43, the Investigator assessed his response as a PR based on a 48% reduction in the indicator lesion by physical examination. In the physical examination notes, the bulky lesion was inconsistently recorded as 36.5 cm^2 and 37.5 cm^2 at study entry. Using the larger size, the reduction was 51%.The IRP assessed his response as a PR based on the physical examination data and stable or decreased nonmeasurable disease by CT. The date of response assigned by the IRP was Day 50, the date of the CTs. The next evaluation by physical examination on Day 57 documented an increase in the large neck mass from a nadir of 19 cm^2 to 33 cm^2 and the IRP declared PD at this time. The Investigator declared PD on Day 70, when the mass was further increased to 45 cm^2.

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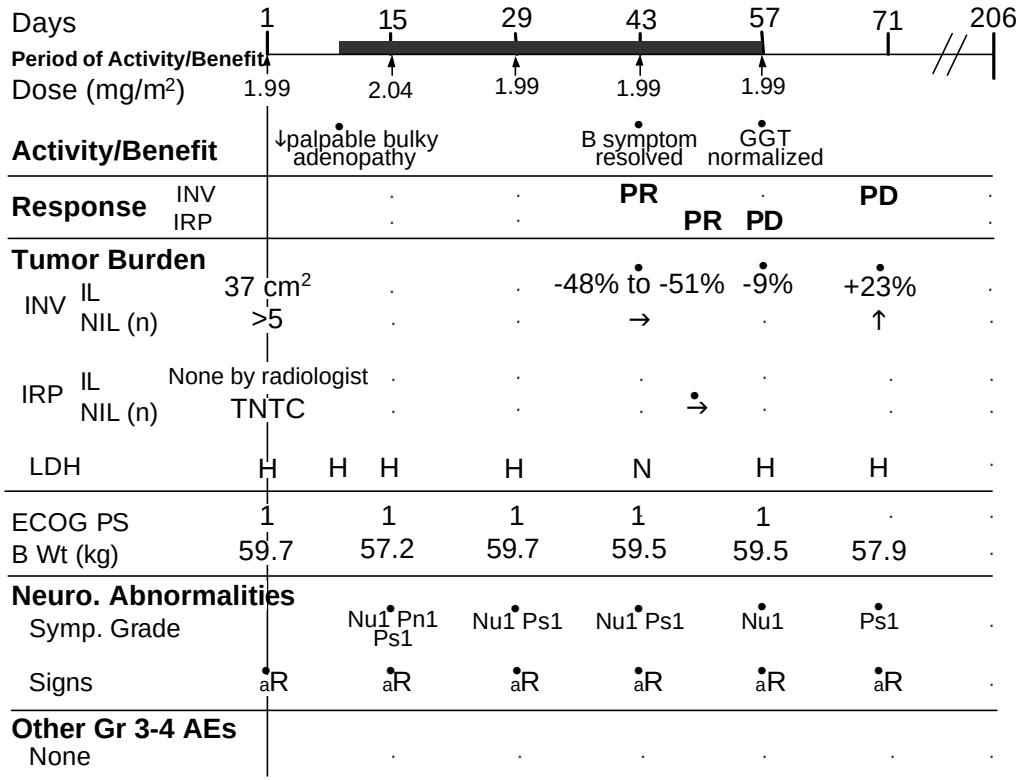

Legend: ↓Decrease ↑Increase →Stable **a** Absent **CR** Complete Response **CRu** Complete Response Unconfirmed **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **PS** Paresthesia **R** Reflexes **TNTC** Too numerous to count

FIGURE 30. Graphical Presentation of Efficacy and Safety for Patient 11-02 (continued)

4 Prior Systemic Therapies 1. CHOP x6; CR of <9 mo. 2. (DHAP/rituximab) x2; CRu of <2 mo. 3. Ribavirin + interferon; PR of <3 mo. 4. MINE x6; PR of ~4.5 mo.	47-year-old man Stage III DLBCL, IPI 3 Per Protocol Eligibile Sensitive to Last Qualifying Therapy	IRP Best Response: PR Duration of Response: 0.3 mo Time to Progression: 1.9 mo	SPD Change: -48% to -51% Survival: 6.8 mo

Patient 11-02 continued

He tolerated 5 cycles of VSLI well with no dose decreases or delays, no weight loss, no hematologic toxicities, only minimal Grade 1 neuropathic complaints, despite having received both vincristine and cisplatin previously. He had no GI side effects or Grade 3-4 AEs of any nature. His ECOG PS remained at the baseline level of 1.

According to the IRP assessment, his best response was a PR that was documented as lasting only 1 week, with a time to progression of 1.9 months. The Investigator assessed his PR as starting 1 week earlier and progressing 2 weeks later, for a duration of response of 0.9 months and a time to progression of 2.3 months. By either assessment, the duration of documented response was short, but it was accompanied by resolution of his fever and a stable ECOG performance status and his period of benefit may have been longer, given the early improvement in his bulky submandibular/cervical adenopathy documented at Day 8.

He died of progressive disease 6.8 months after the first VSLI dose.

Legend: ↓Decrease ↑Increase →Stable **a** Absent **CR** Complete Response **CRu** Complete Response Unconfirmed **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **PS** Paresthesia **R** Reflexes **TNTC** Too numerous to count

FIGURE 31. Graphical Presentation of Efficacy and Safety for Patient 14-03

3 Prior Systemic Therapies		56-year-old man Stage IV DLBCL, IPI 4 Per Protocol Eligible Refractory to Last Qualifying Therapy	IRP Best Response: PR Duration of Response: >0.5 mo Time to Progression: >1.8 mo	SPD Change: -53% Survival: 2.6 mo
1. CHOP x8; PR + XRT; CR of ~11 mo.				
2. XRT; PR of ~7 mo.	4. DHAP x1; SD.			
3. DHAP x1; PR of 1 mo.	5. XRT; PR of ~1 mo.			

This 56-year-old Caucasian man with refractory Stage IV DLBCL had received 3 prior chemotherapy regimens and 3 courses of radiation in the 2.7 years since his first diagnosis. He entered the study with significant medical problems including syringomyelia since childhood (with muscle wasting and right hand weakness), a partial gastrectomy, tachycardia, and residual peripheral neuropathy (Grade 1-2). The IRP identified extensive disease for this patient in the chest and abdomen with numerous lesions in the lungs, liver, spleen, and celiac regions that were "too numerous to count", as well as a pleural effusion (with chest tube), lower lobe atelectasis, and ascites. His IPI score at study entry was 4.

The first evidence of antitumor activity and clinical benefit was an improvement in his ECOG performance status from 3 to 2 after 1 cycle of VSLI; this improvement was maintained for about 6 weeks. His palpable adenopathy resolved by Day 28, after 2 cycles. He had improvement in his Grade 1 hemoglobin level of 10.4 to 12.3 g/dL after 1 cycle and he maintained levels >11.0 g/dL without transfusions or erythropoietin until the end of the study. His Grade 3 hypoalbuminemia improved from 19 g/L at study entry to 25-26 g/L (Grade 2) after 3 cycles of VSLI. Marked improvement was seen after 1 cycle of VSLI in his elevated LDH, alkaline phosphatase, and AST levels, with continued improvement over the study period. His AST level normalized after 3 cycles.

The Investigator identified 3 indicator lesions by physical examination and numerous non-indicator lesions by CT. The first CTs after baseline were taken on Day 42 (Cycle 3 Day 15). By this visit, all indicator lesions were resolved by physical examination, but the Investigator could not assess the outcome for all of the non-indicator lesions because measurements were not recorded at study entry. Therefore, the Investigator made a conservative response assessment of SD.

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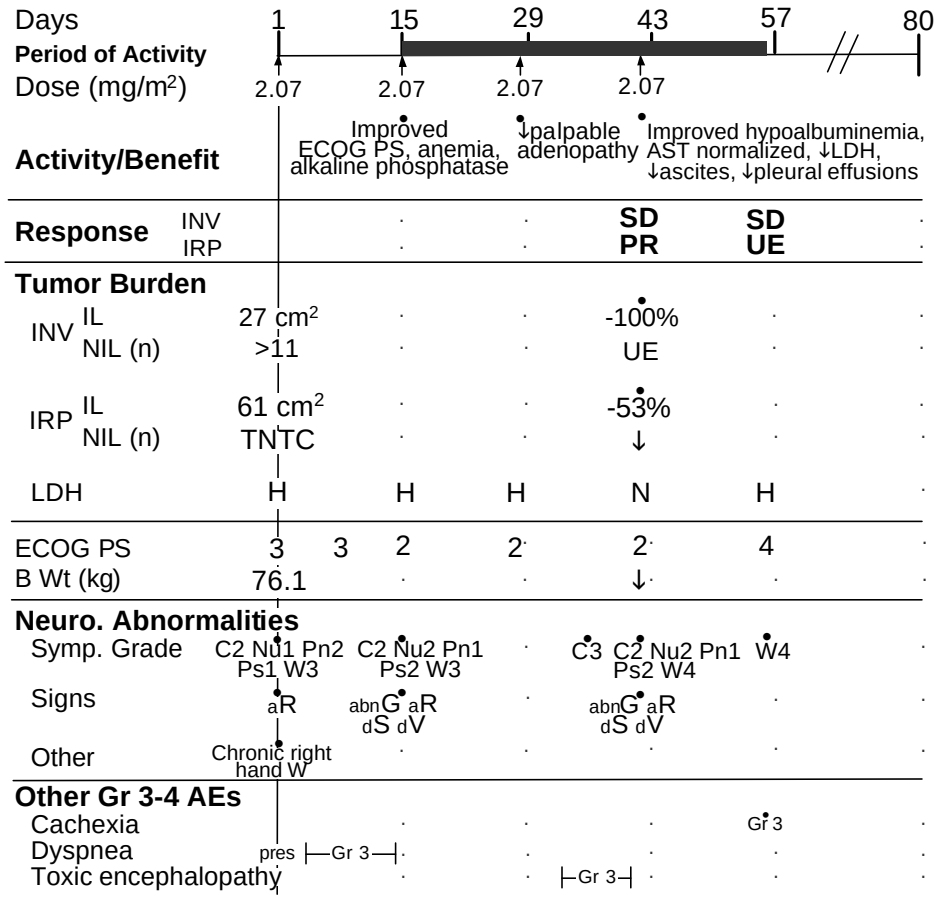

Legend:
↓Decrease ↑Increase →Stable **a** Absent **abn** Abnormal **C** Constipation **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **Pn** Pain **PR** Partial Response **pres** Present **R** Reflexes **S** Strength **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to evaluate **V** Vibration **W** Weakness **XRT** Radiation

FIGURE 31. Graphical Presentation of Efficacy and Safety for Patient 14-03 (continued)

3 Prior Systemic Therapies 1. CHOP x8; PR + XRT; CR of ~11 mo. 2. XRT; PR of ~7 mo. 4. DHAP x1; SD. 3. DHAP x1; PR of 1 mo. 5. XRT; PR of ~1 mo.	56-year-old man Stage IV DLBCL, IPI 4 Per Protocol Eligible Refractory to Last Qualifying Therapy	IRP Best Response: PR Duration of Response: >0.5 mo Time to Progression: >1.8 mo	SPD Change: -53% Survival: 2.6 mo

Patient 14-03 continued

The IRP had identified extensive disease as described above and the non-indicator lesions were many of the same lesions that the Investigator could not assess at Day 42. The IRP opinion was that his response was a PR, based on a 53% decrease in the indicator lesions from 61 to 28.5 cm^2, with a decrease in all non-indicator lesions.

Most of the lung lesions had resolved completely and his pleural effusion had decreased. The decrease in the numerous liver lesions was accompanied by an improvement in his ascites and his liver function tests and albumin level.

His preexisting Grade 1 peripheral sensory neuropathy worsened slightly to Grade 2 and his constipation worsened from Grade 2 to 3. His only other GI complaint was Grade 1 nausea early in the study. He had no myelotoxicity from VSLI. He received a total of 4 cycles of VSLI, with no dose reductions or delays, even though his course was complicated by numerous medical events. On Day 4 he was hospitalized for a hydropneumothorax, unrelated to VSLI, and his dyspnea worsened to Grade 3. This resolved by Day 15 and his dyspnea improved to Grade 2. He was hospitalized a second time on Day 34 for a Grade 3 toxic encephalopathy, considered unrelated to VSLI, and although it resolved by Day 42, he could not be discharged as his wife was unable to care for him. He withdrew consent for participation in the study on Day 56 as his clinical condition declined with Grade 3 cachexia, Grade 4 generalized weakness, and an ECOG performance status of 4. No further CTs were performed.

According to the IRP, he achieved a PR, with a time to progression of >1.8 months. He withdrew consent 2 weeks after the first documentation of response and his clinical condition deteriorated rapidly after that, as he died of metastatic disease 3 weeks later.

Legend:
↓Decrease ↑Increase →Stable **a** Absent **abn** Abnormal **C** Constipation **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **Pn** Pain **PR** Partial Response **pres** Present **R** Reflexes **S** Strength **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to evaluate **V** Vibration **W** Weakness **XRT** Radiation

FIGURE 32. Graphical Presentation of Efficacy and Safety for Patient 16-01

4 Prior Systemic Therapies	64-year-old man Stage IV DLBCL, IPI 4 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -79% Duration of Response: >2.0 mo Time to Progression: >3.7 mo Survival: 9.7 mo

1. MACOP x8 (1 cycle w/o vinc.); CR of ~2 mo.
2. XRT; CR of ~2 yr.
3. DHAP x2; CR → transplant.
4. Cyclophos. x1; UE; (Etop., melphalan) x1 + transplant; CR of ~18 mo.
5. Rituximab x4; PR of 6 mo.

This 64-year-old Caucasian man with sensitive Stage IV, marrow positive, DLBCL had received 4 prior systemic regimens including a stem cell transplant and 1 course of radiation therapy since his initial diagnosis 5.6 years before study entry. He had an IPI score of 4 at study entry, with extensive nodes in the axillary, mediastinal, and retroperitoneal regions that were "too numerous to count" according to the IRP, plus periaortic, iliac, and hilar nodes. In addition, the Investigator noted cervical nodes, a pericardial effusion, and an iliac bone metastasis. He had a history of coronary artery disease, significant residual neuropathies, Grade 2 anemia, lymphopenia, and thrombocytopenia, Grade 1 leukopenia, and hypoglobulinemia (globulins 20 g/L).

His B symptom (night sweats) resolved immediately with VSLI treatment. Other early evidence of antitumor activity was decreased palpable nodes at Day 15 after 1 cycle of VSLI. His palpable adenopathy was within normal limits of node size after 3 cycles and completely resolved after 5 cycles. Other abnormal laboratory parameters (LDH, leukopenia, lymphopenia, thrombocytopenia, hypoglobulinemia) normalized after 2-6 cycles. His Grade 2 anemia improved to Grade 1, initially with transfusions, but steadily improved over the last 2 months of the study without transfusion support. His weight was stable throughout the study.

On Day 52, after 4 cycles, the IRP assessed his response as a PR based on a 64% reduction in 6 indicator lesions. The Investigator also declared a PR with a 95% decrease in 5 indicator lesions; 3 nodes in the neck, axillary, and inguinal regions had totally resolved and the pericardial effusion was resolved.

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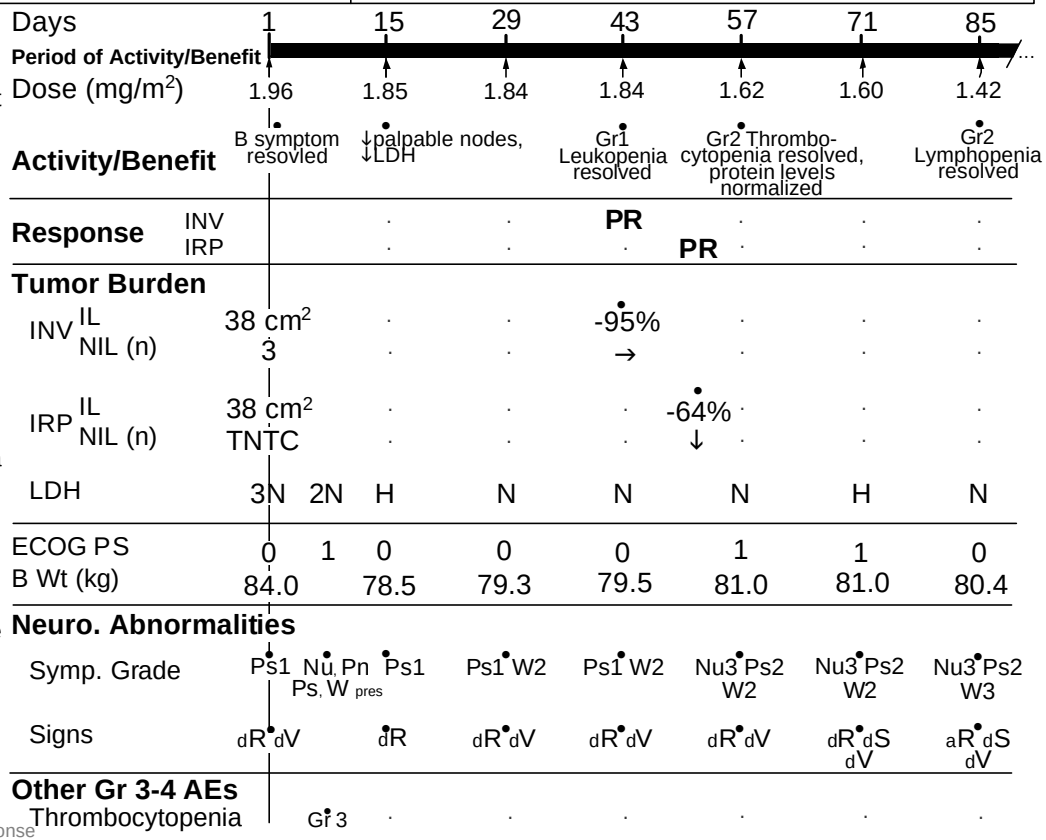

Legend: ↓Decrease ↑Increase →Stable **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **pres** Present **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **UE** Unable to Evaluate **V** Vibration **W** Weakness

FIGURE 32. Graphical Presentation of Efficacy and Safety for Patient 16-01 (continued)

4 Prior Systemic Therapies	64-year-old man Stage IV DLBCL, IPI 4 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -79% Duration of Response: >2.0 mo Time to Progression: >3.7 mo Survival: 9.7 mo
1. MACOP x8 (1 cycle w/o vinc.); CR of ~2 mo. 2. XRT; CR of ~2 yr. 3. DHAP x2; CR → transplant. 4. Cyclophos. x1; UE; (Etop., melphalan) x1 + transplant; CR of ~18 mo. 5. Rituximab x4; PR of 6 mo.		

Patient 16-01 continued

On Day 107, the IRP continued with an assessment of PR, based on a further reduction in the indicator lesions (a 79% reduction from baseline). The Investigator noted a sustained 92% reduction in the original indicator lesions, but also recorded a new inguinal lymph node by CT scan and a rise in his LDH levels and accordingly declared PD at this time. The IRP did not identify any new lesions using the same CTs.

He received 8 cycles of VSLI, with an initial dose reduction due to his preexisting Grade 2 thrombocytopenia that worsened to Grade 3 after the 1st dose, and two additional dose reductions for worsening neuropathy. He had Grade 1 paresthesia in his hands and feet at study entry; he developed Grade 2 generalized paresthesia and Grade 3 hand and generalized numbness and weakness on study. He had only 1 occurrence of constipation, Grade 1, and no other GI complaints. Despite his neuropathy, he maintained a good ECOG PS of 0 or 1 throughout the study.

According to both the IRP and the Investigator, his best response was a PR. The IRP assessed his response duration as >2.0 months, with a time to progression of >3.7 months. The Investigator assessed his PR as lasting 2.1 months, with a time to progression of 3.5 months. He died Day 294 of metastatic disease, with a survival of 9.7 months after his first dose of VSLI.

Activity/Benefit

Response INV / IRP	**PD**	**PR**	**PD UE**
Tumor Burden			
INV IL	-92%		
INV NIL (n)	new		
IRP IL		-79%	
IRP NIL (n)		↓	
LDH	H		H
ECOG PS	1		1
B Wt (kg)	82.5		80.0
Neuro. Abnormalities			
Symp. Grade	Nu3 Ps2 W3		C1 Nu3 Ps2 W3
Signs	aR aS dV		aR dS dV
Other Gr 3-4 AEs			
Thrombocytopenia			

Legend: ↓Decrease ↑Increase →Stable **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **pres** Present **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **UE** Unable to Evaluate **V** Vibration **W** Weakness

FIGURE 33. Graphical Presentation of Efficacy and Safety for Patient 21-03

4 Prior Systemic Therapies	69-year-old man	IRP Best Response: PR	SPD Change: -77%
1. CHOP x8; CR of ~6 mo. 2. DHAP x2; unknown response. 3. (Etoposide, busulfan, cyclophophamide) x1 + transplant; unknown response. 4. (Gemcitabine, rituximab) x4; no response.	Stage III DLBCL, IPI 3 Per Protocol Eligible Resistant to Last Qualifying Therapy	Duration of Response: >1.8 mo Time to Progression: >3.7 mo Survival: 14.8 mo	

This 69-year-old Caucasian man with Stage III refractory DLBCL and an IPI score of 3, had received 4 prior chemotherapy/immunotherapy regimens, including a stem cell transplant. His most recent therapy had been gemcitabine and rituximab, with progressive disease.

He had extensive disease at study entry, all in the liver. After 4 cycles (Day 57), the IRP assessed his response to be a PR with a 76% reduction in his liver lesions that was confirmed on Day 112. His elevated liver function tests (attributed to liver metastases) normalized, with improvements noted as early as Day 15 (after 1 cycle). The Investigator also assessed PR at Day 57, but noted increased lesions at Day 112 and declared PD at that time.

He had a baseline ECOG PS of 1 and no residual neuropathy from prior vincristine and cisplatin. He developed progressive sensory neuropathy (Grade 2), requiring pain medications, which ultimately resulted in withdrawal from the study on Day 71. The pain medications may have contributed to the Grade 2 constipation (baseline Grade 1). Extensive liver involvement with lymphoma and documented reduction in liver function may have contributed to increased or more sustained levels of vincristine and, in turn, neurotoxicity. Some of the neuropathies were improving after withdrawal from VSLI therapy, and his ECOG PS improved from 3 to 2. The abrupt change in his ECOG PS from 1 to 3 was not clearly linked to neuropathy which was Grade 1-2 at that time, although the Grade 2 pain may have contributed. He maintained stable hematologic parameters on study. The Grade 2 neutropenia and leukopenia at study entry normalized for most of the study.

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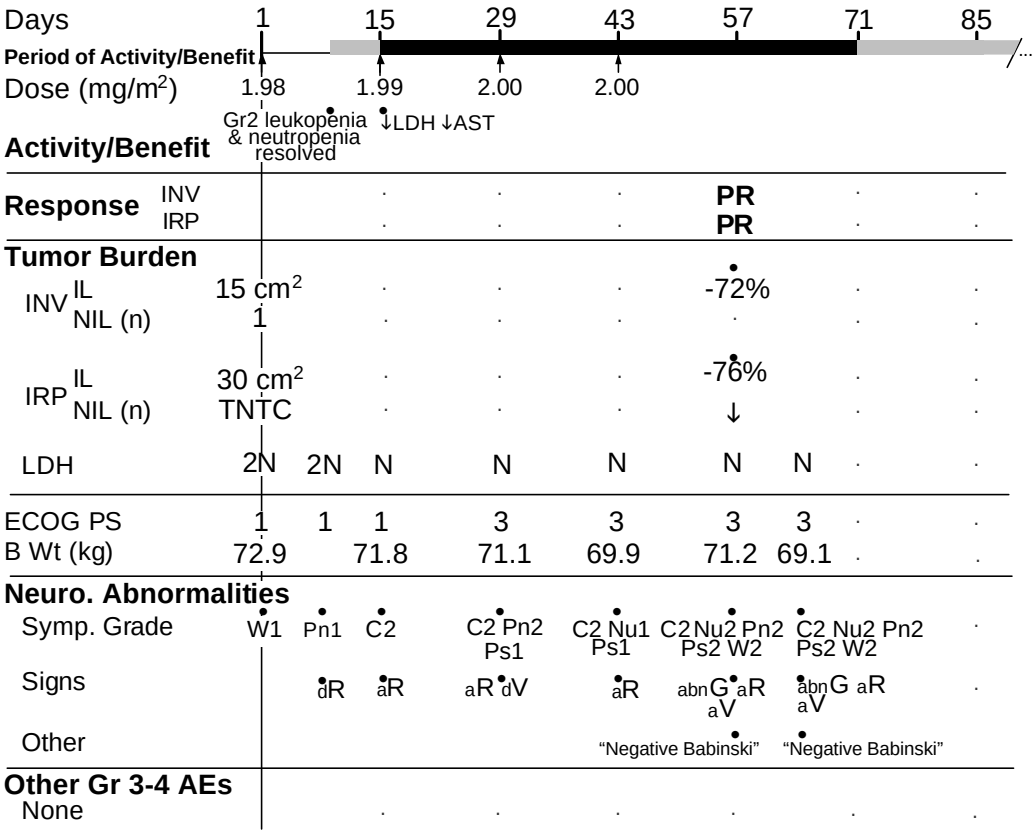


Legend:
↓Decrease ↑Increase **a** Absent **abn** Abnormal **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **Pn** Pain **PR** Partial Response **Ps** Paresthesia **PD** Progressive Disease **R** Reflexes **W** Weakness

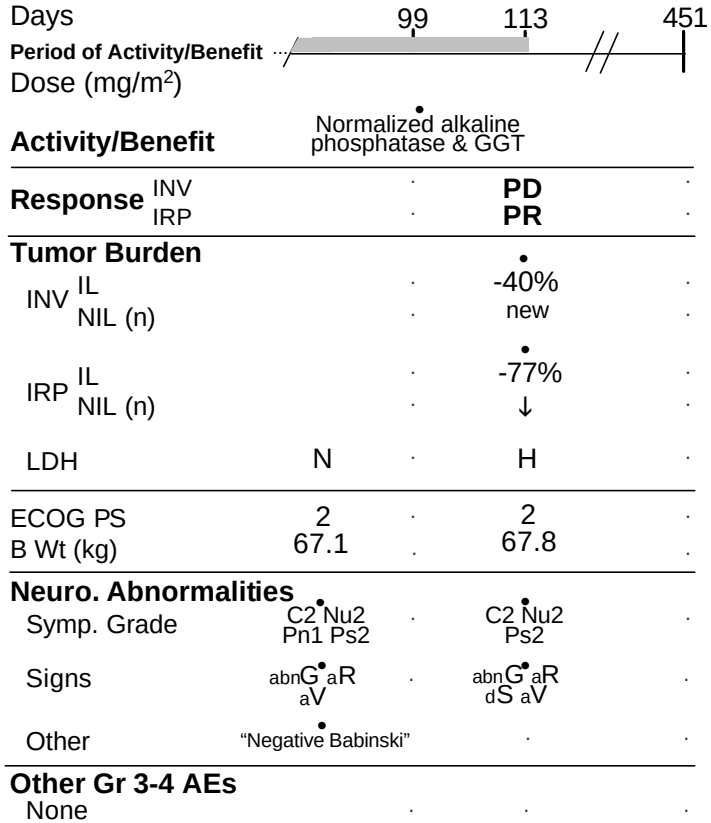
FIGURE 33. Graphical Presentation of Efficacy and Safety for Patient 21-03 (continued)

4 Prior Systemic Therapies	69-year-old man	IRP Best Response: PR	SPD Change: -77%
1. CHOP x8; CR of ~6 mo. 2. DHAP x2; unknown response. 3. (Etoposide, busulfan, cyclophophamide) x1 + transplant; unknown response. 4. (Gemcitabine, rituximab) x4; no response.	Stage III DLBCL, IPI 3 Per Protocol Eligible Resistant to Last Qualifying Therapy	Duration of Response: >1.8 mo Time to Progression: >3.7 mo Survival: 14.8 mo	

Patient 21-03 continued

According to the IRP, he achieved a PR after 4 doses of study drug, lasting >1.8 months with a time to progression of >3.7 months, which was a better response than he had achieved with his previous gemcitabine and rituximab therapy (immediate PD). His prior therapy before that (etoposide, busulfan and cyclophosphamide with stem cell transplant) had resulted in either no response or a short-lived response, as the next therapy was given 3 months later.

Therefore, VSLI provided an important response with a significant decrease in extensive liver disease and normalization of liver function tests in this patient with highly refractory disease in a disease site that is usually difficult to treat effectively. He died from progressive disease on Day 451, 14.8 months after starting VSLI treatment.



Legend:
↓Decrease ↑Increase **a** Absent **abn** Abnormal **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **Pn** Pain **PR** Partial Response **Ps** Paresthesia **PD** Progressive Disease **R** Reflexes **W** Weakness

FIGURE 34. Graphical Presentation of Efficacy and Safety for Patient 22-03

4 Prior Systemic Therapies	27-year-old woman	IRP Best Response: PR SPD Change: -66%
1. CHOP x4; brief PR. 2. ESHAP x2; PR requiring XRT; PR. 3. ESHAP x4; UE. 4. Rituximab; UE, TTP ~2-2.5 mo.	Stage III anaplastic lg null-/T-cell lymphoma, IPI 1 Per Protocol Eligible Resistant to Last Qualifying Therapy	Duration of Response: 2.8 mo Time to Progression: 4.2 mo Survival: >27.7 mo, alive with disease

This 27-year-old Caucasian woman with resistant Stage III anaplastic large null-/T-cell lymphoma entered the study having never achieved a CR with any of her 4 previous systemic therapies plus radiation therapy, all given within 1.5 years before study.

Reductions in lung and mediastinal lesion led to resolution of tumor-related apparent pneumonia by Day 43 (per CT), after 3 cycles of VSLI. The Investigator assessed SD with a 44% reduction in tumor area. According to the IRP, she achieved a PR after 3 cycles of VSLI (Day 43) with a 66% reduction in tumor area, which was maintained for 2.8 months with a time to progression of 4.2 months.

Despite 3 prior regimens with neurotoxic agents, she tolerated VSLI well, able to receive 10 full doses (20.0 mg/m^2 total) with no GI complaints and minimal neurotoxicity (Grade 1). She had no Grade 3-4 AEs of any nature. Her weight and lab values were stable and her ECOG PS was always 0.

Having demonstrated responsive disease with VSLI, she received an allogeneic bone marrow transplant on Day 190, 2 months after withdrawing from study and was alive with disease at 27.7 months after her first dose of VSLI.

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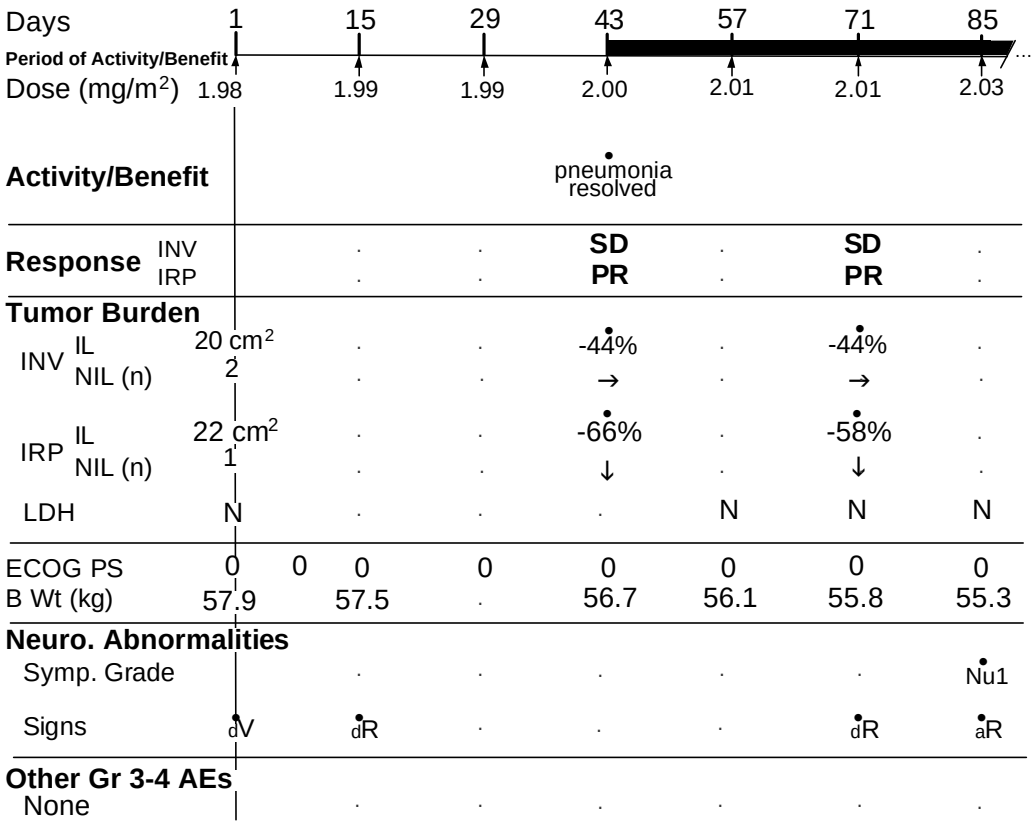
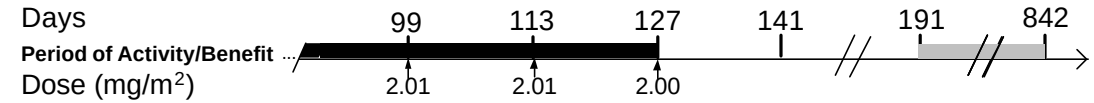


Legend:
↓Decrease ↑Increase →Stable **a** Absent **AlloBMT** Allogeneic Bone Marrow Transplant **CR** Complete Response **d** Diminished **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **UE** Unable to Evaluate **V** Vibration **XRT** Radiation

FIGURE 34. Graphical Presentation of Efficacy and Safety for Patient 22-03 (continued)

4 Prior Systemic Therapies 1. CHOP x4; brief PR. 2. ESHAP x2; PR requiring XRT; PR. 3. ESHAP x4; UE. 4. Rituximab; UE, TTP ~2-2.5 mo.	27-year-old woman Stage III anaplastic lg null-/T-cell lymphoma, IPI 1 Per Protocol Eligible Resistant to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -66% Duration of Response: 2.8 mo Time to Progression: 4.2 mo Survival: >27.7 mo, alive with disease

Patient 22-03 continued



Activity/Benefit

AlloBMT

Response INV	**SD**	·	**PD**	·	·	·
IRP	**UE**	·	**PD**	·	·	·
Tumor Burden						
INV IL	·	·	-27%	·	·	·
NIL (n)	·	·	↑	·	·	·
IRP IL	·	·	-20%	·	·	·
NIL (n)	·	·	↓	·	·	·
LDH	N	N	N	·	·	·
ECOG PS	0	0	0	0	·	·
B Wt (kg)	55.5	55.9	56.4	·	·	·
Neuro. Abnormalities						
Symp. Grade	Nu1	Nu1	Ps1	·	·	·
Signs	aR	dR	aR	·	·	·
Other Gr 3-4 AEs						
None	·	·	·	·	·	·

Legend:
↓Decrease ↑Increase →Stable **a** Absent **AlloBMT** Allogeneic Bone Marrow Transplant **CR** Complete Response **d** Diminished **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **UE** Unable to Evaluate **V** Vibration **XRT** Radiation

FIGURE 35. Graphical Presentation of Efficacy and Safety for Patient 22-05

2 Prior Systemic Therapies 1. CHOP x6; PR of 4.7 mo. 2. ESHAP x4 + rituximab; PR of 2 mo.	74-year-old woman Stage III LBCL, IPI 3 Per Protocol Eligible Resistant to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -63% Duration of Response: 1.0 mo Time to Progression: 2.2 mo Survival: >25.3 mo, alive with disease

This 74-year-old Caucasian woman with resistant Stage III large B-cell lymphoma, having relapsed after 2 combination chemotherapy regimens, including immunotherapy, in the previous 1.6 years. Her best response had been a PR, with her last PR lasting about 2 months.

By the Investigator assessment, she achieved a PR after 3 cycles of VSLI, and a CR after 5 cycles, with an overall duration of response of 2.3 months and a time to progression of 3.7 months. She withdrew her consent 1 week after a PET scan on Day 113 suggested progression of her disease. The IRP assessed her best response as a PR lasting only 1 month due to a transient increase in the indicator lesions that was not seen on subsequent CTs. Although the IRP radiologist indicated that her PR was re-established at the next visit, the earlier progression date was the final opinion. Using the first and last CT measurements available, her PR lasted at least from Day 37 to beyond Day 104, or >67 days. She was last known to be alive with disease on Day 771, for a survival of >25.3 months.

She tolerated 6 cycles of VSLI well, with mostly Grade 1 neurotoxicities, and maintained an ECOG score of 0 throughout the study. She had minimal, sporadic complaints of constipation and no Grade 3-4 AEs of any nauture.

By the Investigator assessment, her response to single-agent VSLI was comparable in duration to what she achieved with her last therapy, which was ESHAP plus rituximab. She achieved this without developing hematologic toxicities and with only minimal neuropathies.

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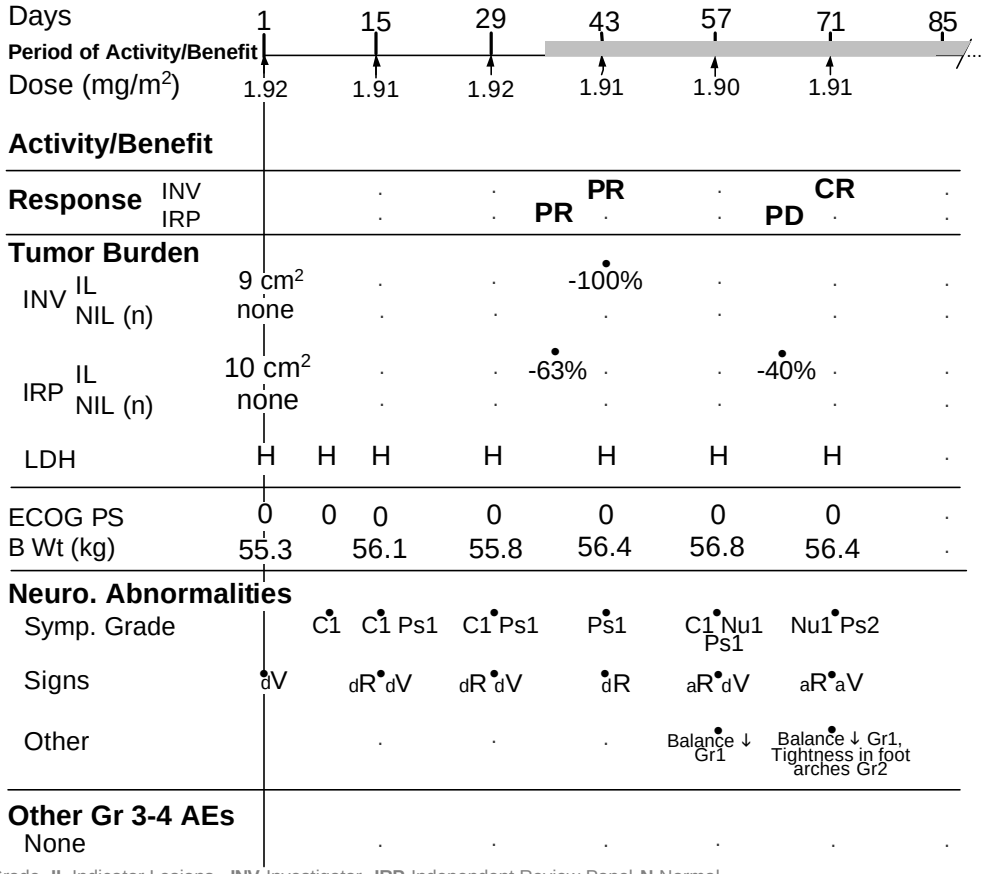
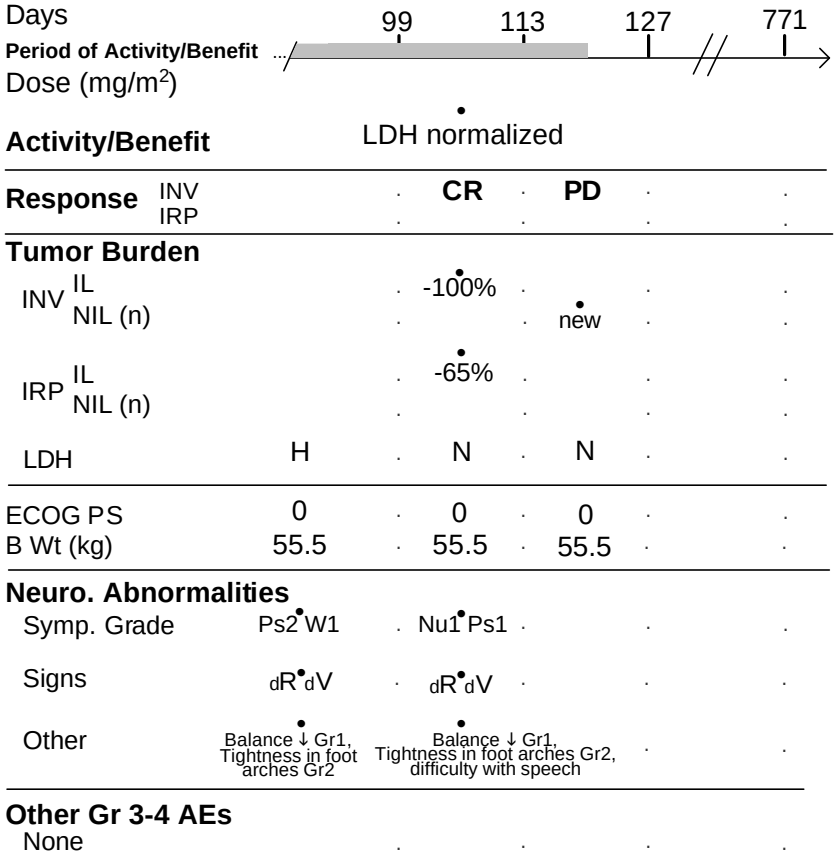


Legend:
↓Decrease ↑Increase **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **PR** Partial Response **PS** Paresthesia **R** Reflexes **SD** Stable Disease **V** Vibration **W** Weakness

FIGURE 35. Graphical Presentation of Efficacy and Safety for Patient 22-05 (continued)

2 Prior Systemic Therapies 1. CHOP x6; PR of 4.7 mo. 2. ESHAP x4 + rituximab; PR of 2 mo.	74-year-old woman Stage III LBCL, IPI 3 Per Protocol Eligible Resistant to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -63% Duration of Response: 1.0 mo Time to Progression: 2.2 mo Survival: >25.3 mo, alive with disease

Patient 22-05 continued



Legend:
↓Decrease ↑Increase **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **PR** Partial Response **PS** Paresthesia **R** Reflexes **SD** Stable Disease **V** Vibration **W** Weakness

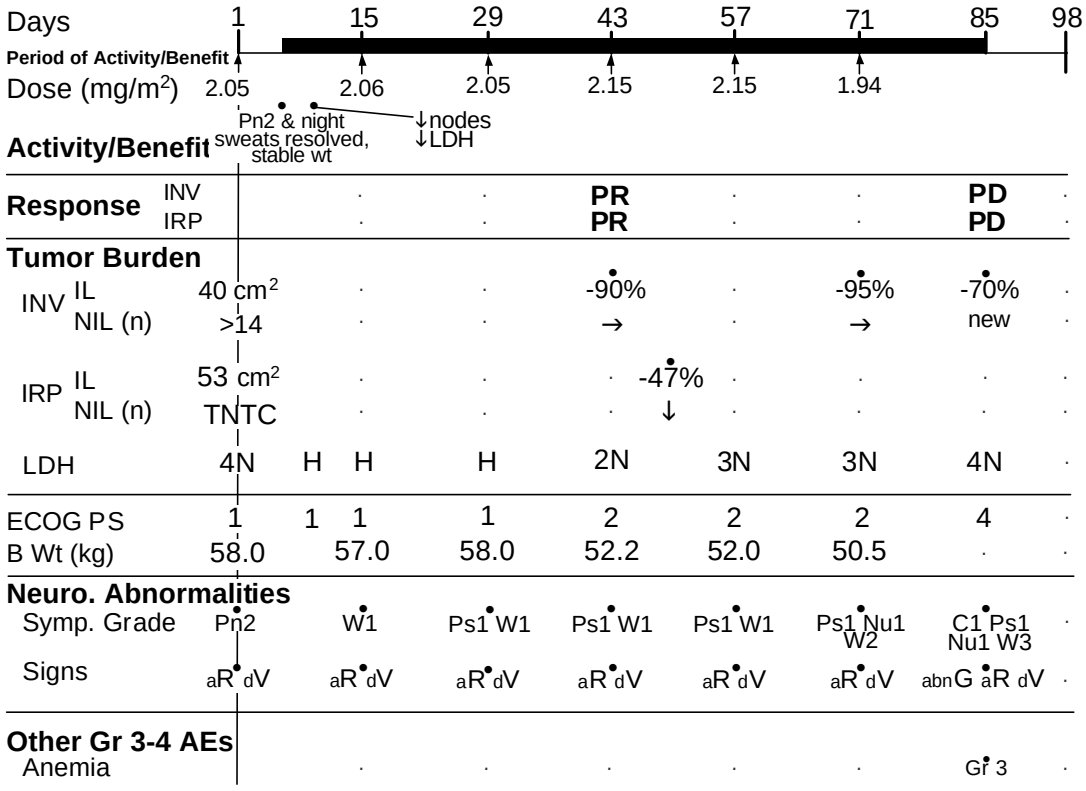
FIGURE 36. Graphical Presentation of Efficacy and Safety for Patient 31-01

3 Prior Systemic Therapies	51-year-old woman Stage IV DLBCL, IPI 3 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -54% Duration of Response: 1.2 mo Time to Progression: 2.8 mo Survival: 3.2 mo
1. (Adriamycin, cyclophos., vinc.) x3; CR + XRT; CR of <4 mo. 2. Cyclophos. x1; minor response. 3. Cytosine arabinoside x5, etop. x4, carmustine x1, melphalan x1 + transplant; CR of 5 mo.		

This 51-year-old Caucasian woman with Stage IV DLBCL relapsed after having been treated over 1.4 years with 2 courses of combination chemotherapy, plus radiation and an autologous stem cell transplant. She had achieved CRs to previous therapies lasting less than 6 months. At enrollment, she had significant tumor burden including lesions in the liver, lung and spine, and residual problems from previous therapy including anemia requiring transfusions and leukopenia.

She had residual neuropathy and generalized pain that required narcotics. The narcotics were discontinued 4 days after the first dose of VSLI, and the pain did not recur. Both the IRP and Investigator assessed her response as PR at Day 43 (Cycle 3 Day 15) and during this period she had approximately 6 weeks without night sweats (through Day 43) and 1 month with stable body weight. By Day 43, she had a sudden 10% weight loss. Subsequently, she developed progressive weakness, her ECOG PS declined as her LDH increased, and relapse was documented on Day 85 (Cycle 6 Day 15). Her night sweats were occurring frequently by Day 85. By the IRP assessment, she achieved a PR lasting 1.2 months with a time to progression of 2.8 months.

She tolerated VSLI well with only minimal neuropathy (Grade 1 paresthesia, numbness and constipation). She developed Grade 3 generalized weakness on Day 85 and died of progressive disease on Day 98 (Cycle 6, Day 28), with a survival of 3.2 months.



Legend:
↓Decrease →Stable **a** Absent **abn** Abnormal **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Parethesia **R** Reflexes **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 37. Graphical Presentation of Efficacy and Safety for Patient 33-07

2 Prior Systemic Therapies 1. (Doxorubicin, cyclophosphamide, predisone) x8; vincristine x3; vinblastine x5; PR of <6 mo. 2. ESHAP x4; PR of ~5 mo.	68-year-old man Stage III DLBCL, IPI 3 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -80% Duration of Response: >2.6 mo Time to Progression: >3.8 mo Survival: 22.3 mo

This 68-year-old Caucasian man with sensitive Stage III DLBCL relapsed after achieving PRs lasting 5-6 months with his 2 previous combination chemotherapy regimens. He had extensive periaortic disease and retroperitoneal and mesenteric lesions that were "too numerous to count" according to the IRP, with an elevated LDH and a high $ß_2$-microglobulin level (2xULN).

The first evidence of antitumor activity was seen after 1 cycle of VSLI with normalization of anemia and hypoalbuminemia, improvement in LDH levels, and resolution of palpable adenopathy. After 2-5 cycles, his LDH levels and liver function tests (AST, ALT, alkaline phosphatase) normalized. After only 3 doses of VSLI, he achieved a documented PR. Following an additional 2 doses of therapy, he achieved a CR per the Investigator, and improved his PR per the IRP. He received 2 more cycles after his CR, and at the next evaluation, the Investigator declared PD based on new lesions detected by CT, despite complete resolution of all previously noted disease. The IRP felt he had no new disease and remained in PR with a duration of >2.6 months and a time to progression of >3.8 months when taken off study.

He maintained an ECOG PS of 1 throughout the study, with minimal neurotoxicities (Grade 2 paresthesia at Cycle 6). He had only one episode of mild (Grade 1) constipation and no hematologic toxicities. He was removed from study at Day 114 due to progression as assessed by the Investigator and was treated with chlorambucil and steroids. He achieved a CR and was alive with no evidence of disease on Day 416, 13.7 months after his first dose of VSLI. However, he subsequently died due to progressive disease on Day 678, 22.3 months after commencing VSLI treatment.

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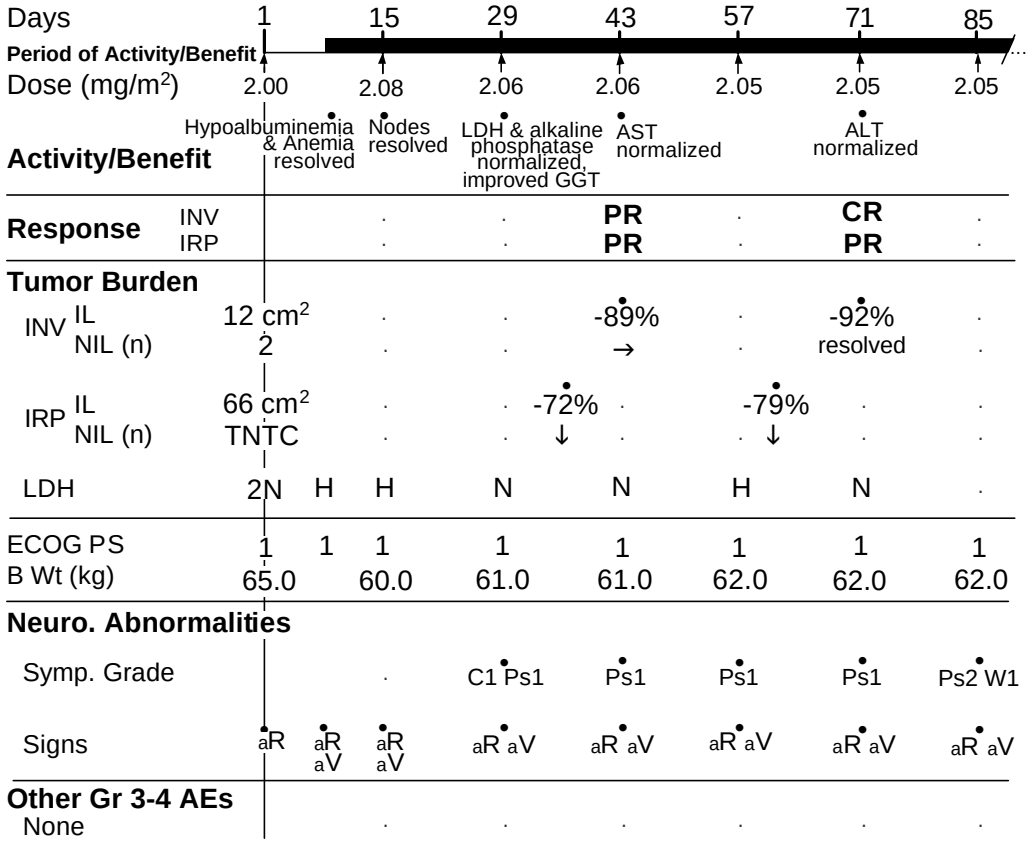

Legend: ↓Decrease →Stable **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **PD** Progressive Disease **PR** Partial Response **Ps** Paresthesia **R** Reflexes **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 37. Graphical Presentation of Efficacy and Safety for Patient 33-07 (continued)

2 Prior Systemic Therapies 1. (Doxorubicin, cyclophosphamide, predisone) x8; vincristine x3; vinblastine x5; PR of <6 mo. 2. ESHAP x4; PR of ~5 mo.	68-year-old man Stage III DLBCL, IPI 3 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -80% Duration of Response: >2.6 mo Time to Progression: >3.8 mo Survival: 22.3 mo

Patient 33-07 continued

Activity/Benefit

Response	INV		**PD**		
	IRP		**PR**		
Tumor Burden					
INV	IL		-100%		
	NIL (n)		new		
IRP	IL		-80%		
	NIL (n)		→		
LDH		N			
ECOG PS		1			
B Wt (kg)		61.0			
Neuro. Abnormalities					
Symp. Grade		Ps2 W1			
Signs		aR aV			
Other Gr 3-4 AEs					
None					

Legend: ↓Decrease →Stable **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **PD** Progressive Disease **PR** Partial Response **Ps** Paresthesia **R** Reflexes **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 38. Graphical Presentation of Efficacy and Safety for Patient 40-01

2 Prior Systemic Therapies	76-year-old woman	IRP Best Response: PR SPD Change: -94%
1. CHOP x6; CR of ~10 mo (including idiotype vaccine; UE). 2. (Rituximab, cyclophosphamide, etoposide, dacarbazine, predisone) x5; CR of 6 mo.	Stage III DLBCL, IPI 3 Per Protocol Eligible Sensitive to Last Qualifying Therapy	Duration of Response: >8.3 mo Time to Progression: >10.0 mo Survival: >30.1 mo, alive with disease

This 76-year-old Caucasian woman with sensitive Stage III DLBCL, relapsed after 2 prior combination chemotherapy regimens and an idiotype vaccine. She achieved a CR to her last chemotherapy regimen, but relapsed within 6 months. She entered the study with residual Grade 1 neuropathy, Grade 2 thrombocytopenia, an IPI score of 3, and ECOG PS of 0, multiple pulmonary nodules, and large inguinal nodes.

Early evidence of antitumor activity was noted after the first cycle with reduced palpable adenopathy and resolution of the thrombocytopenia. Her LDH normalized after 3 cycles. She achieved a PR according to both the Investigator and IRP after 4 cycles of VSLI. Her PR was confirmed with 4 additional sets of CTs taken over the next 8 months, with the last set on Day 304. Her pulmonary disease remained stable, and her inguinal indicator lesion measurement (per the IRP) decreased by 94%.

She received 8 cycles of VSLI (16.0 mg/m^2 total) without dose delays or decreases. She had minimal worsening of her neuropathy, and her worst ECOG PS was 1 (maintained throughout most of the study).

Her PR was documented as lasting over 8.3 months by the IRP, longer than her CR to her last course of combination chemotherapy. Having completed the required 6 months of follow-up after her last dose, she was removed from the study and no further CTs were available for IRP review. Additional follow-up obtained from the Investigator confirmed an ongoing PR with residual stable pulmonary nodules, lasting >28.7 months without additional therapy; given this unusually long duration of PR for aggressive NHL without further treatment, the residual pulmonary nodules may have been fibrotic tissue only, in which case, she would have achieved a CR. Her time to progression and survival from first dose of VSLI were >30.1 months. Importantly, the durable ongoing response from VSLI, which was achieved with minimal toxicity despite her advanced age, has allowed her to be free from chemotherapy for >26.7 months, a longer interval than she achieved with either of her previous combination therapies.

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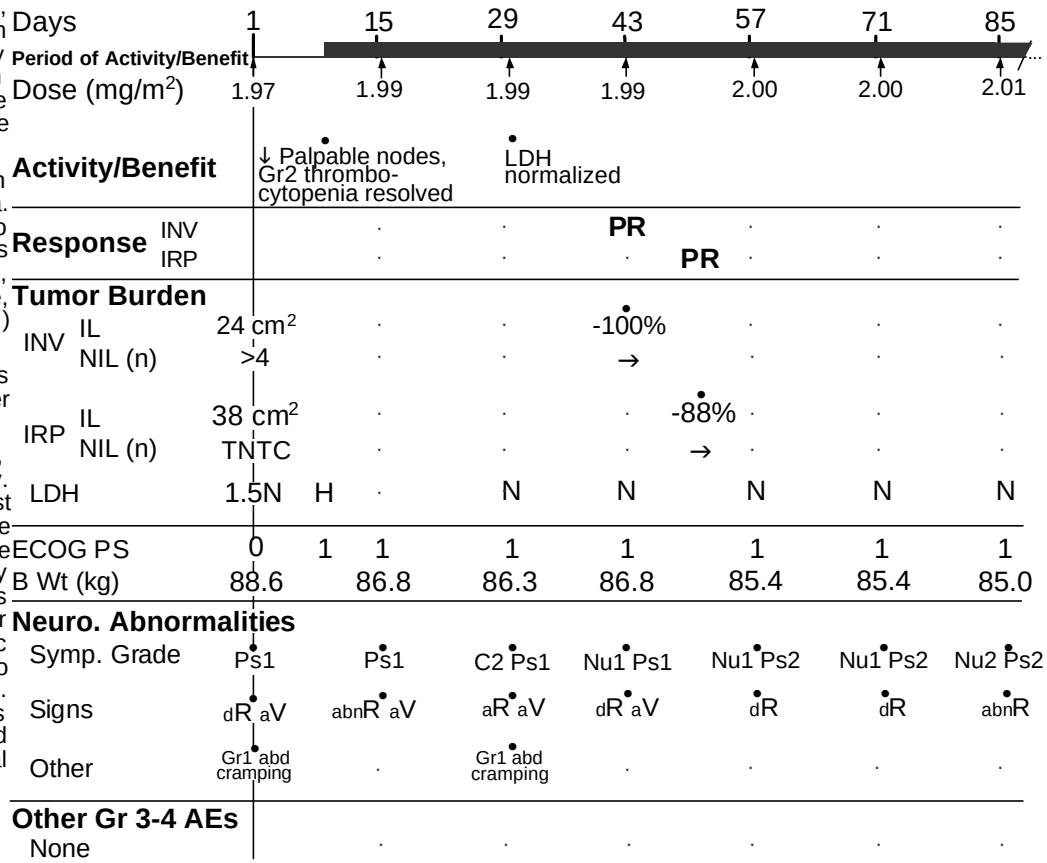
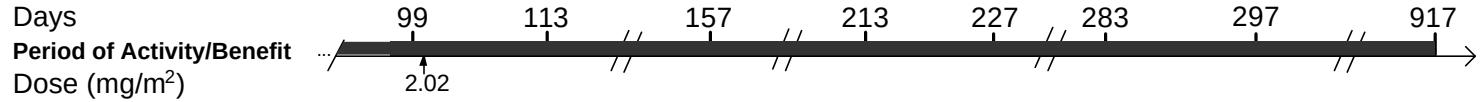


Legend:
↓Decrease →Stable **abd** Abdominal **abn** Abnormal **a** Absent **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PR** Partial Response **Ps** Paresthesia **R** Reflexes **TNTC** Too numerous to count **UE** Unable to Evaluate **V** Vibration

FIGURE 38. Graphical Presentation of Efficacy and Safety for Patient 40-01 (continued)

2 Prior Systemic Therapies	76-year-old woman	IRP Best Response: PR SPD Change: -94%
1. CHOP x6; CR of ~10 mo (including idiotype vaccine; UE).	Stage III DLBCL, IPI 3	Duration of Response: >8.3 mo
2. (Rituximab, cyclophosphamide, etoposide, dacarbazine, predisone) x5; CR of 6 mo.	Per Protocol Eligible	Time to Progression: >10.0 mo
	Sensitive to Last Qualifying Therapy	Survival: >30.1 mo, alive with disease

Patient 40-01 continued



Activity/Benefit

Response INV / IRP										
		PR / **PR**			**PR** / **PR**	**PR**		**PR**		**PR**
Tumor Burden										
INV	IL	-100%			-100%	-100%		-100%		
	NIL (n)	→			→	→		→		
IRP	IL	-91%			-92%		-91%			-94%
	NIL (n)	→			→		→			→
LDH		N	N		N	N		N		
ECOG PS		1	1		1	1		0		
B Wt (kg)		83.6	84.1		87.3			86.4		
Neuro. Abnormalities										
Symp. Grade		Nu1 Ps2	Ps2		Nu2 Ps1	Nu2		Nu2		
Signs		dR			dR aV					
Other										
Other Gr 3-4 AEs										
None										

Legend: ↓Decrease →Stable **abd** Abdominal **abn** Abnormal **a** Absent **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PR** Partial Response **Ps** Paresthesia **R** Reflexes **TNTC** Too numerous to count **UE** Unable to Evaluate **V** Vibration

FIGURE 39. Graphical Presentation of Efficacy and Safety for Patient 66-01

3 Prior Systemic Therapies	58-year-old man	IRP Best Response: PR SPD Change: -34%
1. (Ritux., cyclophos., vinc.) with doxorubicin x4; PR of 6.6 mo.	Stage IV Composite Lymphoma, IPI 1	Duration of Response: >4.2 mo
2. (Mesna, ifosfamide, carboplatin, VP-16) x2; PR.	Per Protocol Eligible	Time to Progression: >5.6 mo
3. Cyclophos. x4, VP-16 x6, BCNU x1 + transplant; SD of 5 mo.	Refractory to Last Qualifying Therapy	Survival: >33.5 mo, alive with disease

This 58-year-old Caucasian man had refractory Stage IV composite lymphoma (Grade 1 follicular lymphoma with focal areas of DLBCL) that had been treated with 3 prior combination chemotherapy regimens over a period of 1.9 years. He achieved only stable disease with his last regimen that included an autologous stem cell transplant. He had a large left supraclavicular lesion of 36 cm^2 and multiple small periaortic nodes that were "too numerous to count".

The first evidence of VSLI antitumor activity was resolution of the Grade 1 neck pain associated with the large neck node after only 1 cycle of VSLI (Day 14); the node was completely resolved after 2 cycles by Day 30. The Investigator assessed that he had achieved a PR by Day 44, after 3 cycles of VSLI with an 88% reduction in indicator lesions. The IRP radiologist assessed SD based on a 34% decrease in the indicator lesion but the IRP oncologists also considered physical examination findings and declared PR.

At study entry, he had Grade 1 paresthesia of his thigh. On study he developed Grade 3 numbness and paresthesia in his hands and feet and Grade 3 hand pain by Day 58. He received gabapentin treatment from Day 58 onwards and was withdrawn from therapy after 4 cycles of VSLI (Day 72). Some recovery was noted 1 month after his last dose of VSLI. As an insulin-dependent diabetic with hypothyroidism and previous exposure to neurotoxic agents (vincristine and carboplatin), he may have been at higher risk of developing significant neuropathies than other patients. He had no significant GI toxicities with only Grade 1 constipation.

Both the IRP and Investigator confirmed his continuing PR on Day 83. The IRP was unable to assess his response at Day 171, as the CTs were lost. According to the Investigator, his PR was maintained for 4.2 months, with a time to progression of 5.6 months. This was a better response than he had achieved on his last systemic therapy (transplant).

He was alive, with disease, 33.5 months from the start of therapy.

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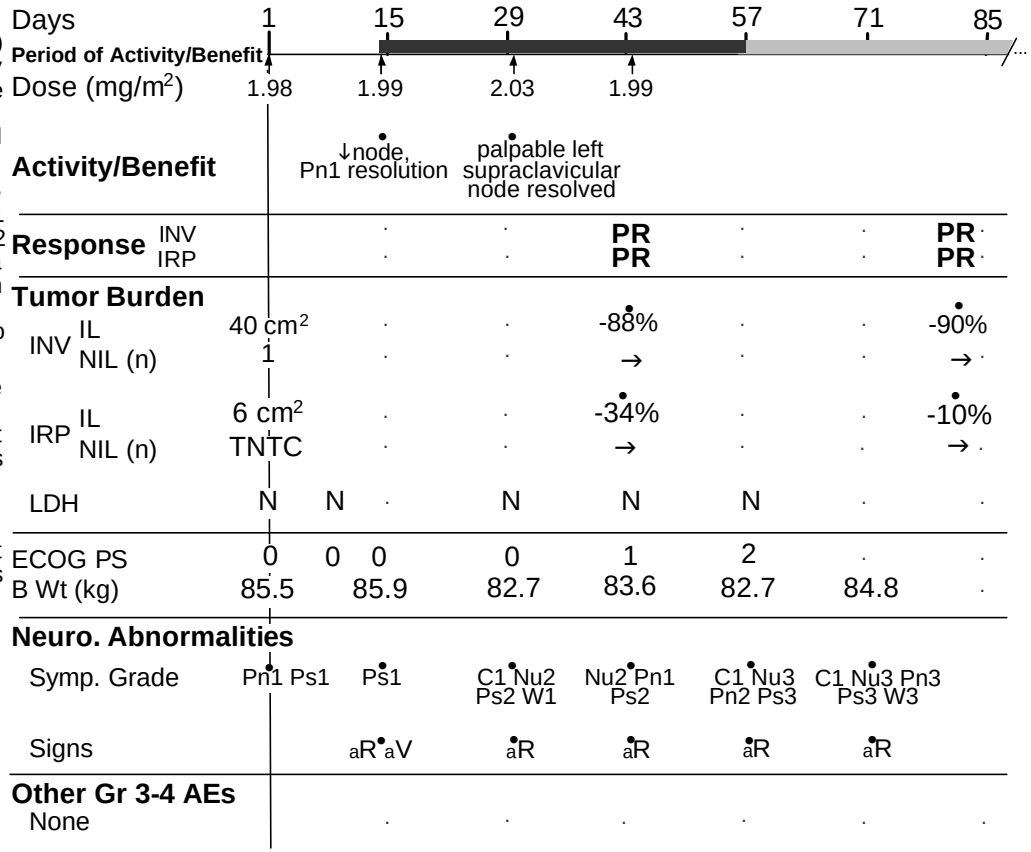
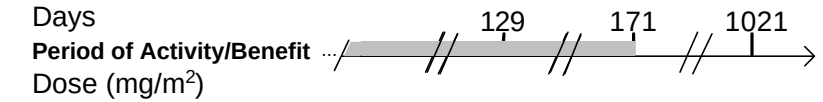


Legend:
↓Decrease →Stable **a** Absent **C** Constipation **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to Evaluate **V** Vibration **W** Weakness

FIGURE 39. Graphical Presentation of Efficacy and Safety for Patient 66-01 (continued)

3 Prior Systemic Therapies 1. (Ritux., cyclophos., vinc.) with doxorubicin x4; PR of 6.6 mo. 2. (Mesna, ifosfamide, carboplatin, VP-16) x2; PR. 3. Cyclophos. x4, VP-16 x6, BCNU x1 + transplant; SD of 5 mo.	58-year-old man Stage IV Composite Lymphoma, IPI 1 Per Protocol Eligible Refractory to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -34% Duration of Response: >4.2 mo Time to Progression: >5.6 mo Survival: >33.5 mo, alive with disease

Patient 66-01 continued



Activity/Benefit

Response	INV IRP	. .	**PD** **UE**	. .
Tumor Burden				
INV	IL	.	.	.
	NIL (n)	.	.	.
IRP	IL	.	.	.
	NIL (n)	.	.	.
LDH		N	.	.
ECOG PS		.	.	.
B Wt (kg)		84.8	.	.
Neuro. Abnormalities				
Symp. Grade		Nu3 Pn3 Ps3	Nu3 Pn3 Ps3	.
Signs		aR	aR	.
Other Gr 3-4 AEs				
None		.	.	.

Legend:
↓Decrease →Stable **a** Absent **C** Constipation **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to Evaluate **V** Vibration **W** Weakness

FIGURE 40. Graphical Presentation of Efficacy and Safety for Patient 72-01

3 Prior Systemic Therapies	45-year-old woman Stage III DLBCL, IPI 2 Per Protocol Eligible Refractory to Last Qualifying Therapy	IRP Best Response: PR Duration of Response: >3.9 mo Time to Progression: >7.2 mo Survival: 20.3 mo	SPD Change: -64%
1. (Doxil, cyclophos., etop.) x8; PR of 8.4 mo. 2. (Cisplatin, cytarabine) x2; SD. 3. Ritux. ~x3, (ifosfamide, carboplatin, etop.) x1; PD.			

This 45-year-old Caucasian woman with refractory Stage III DLBCL had received 3 combination chemotherapy regimens over 1.4 years and did not respond to her last two regimens. She had achieved only a PR to her 1st-line therapy. She had extensive disease with numerous mesenteric, periaortic, and iliac nodes that were "too numerous to count" according to the IRP.

A decrease in a palpable node and resolution of hypoalbuminemia by Day 8 visit were the first evidence of activity after a single dose of VSLI. Her Grade 2 anemia (hemoglobin 8.4 g/dL) improved to Grade 1 (10.4 g/dL) after 1 cycle and resolved after 6 cycles, without transfusions or erythropoietin, remaining above 11 g/dL until progression. Improvement in anemia is generally associated with an improved quality of life for patients, although no formal assessment was performed in this study.

The first CTs taken after 3 cycles indicated a tumor reduction of 48%, which was declared SD by both the Investigator and the IRP. After 7 cycles (Day 99), her response was a PR by both assessments and this was confirmed again after 11 cycles. At the final assessment on Day 214, the Investigator noted progression on the CTs, but the IRP did not.

She received 12 cycles of VSLI (23.6 mg/m^2 total), with one dose decrease at Cycle 10 due to Grade 3 neutropenia, which subsequently resolved with the lower dose of VSLI. She had a 3-week period with worsened ECOG PS of 2 and 3 in the first month on study. She developed Grade 3 numbness, paresthesia, and weakness in her hands and feet at the end of her treatment, but maintained an ECOG PS of 1 from Day 43 onward. Her weight drifted down throughout the study, with a loss of 16% over 7 months.

The IRP assessed her PR as having a duration of >3.9 months, with a time to progression of >7.2 months. This was a better response than she had achieved with her last two combination chemotherapy regimens (cisplatin and cytarabine; RICE). She died due to progressive disease on Day 619, with a survival of 20.3 months.

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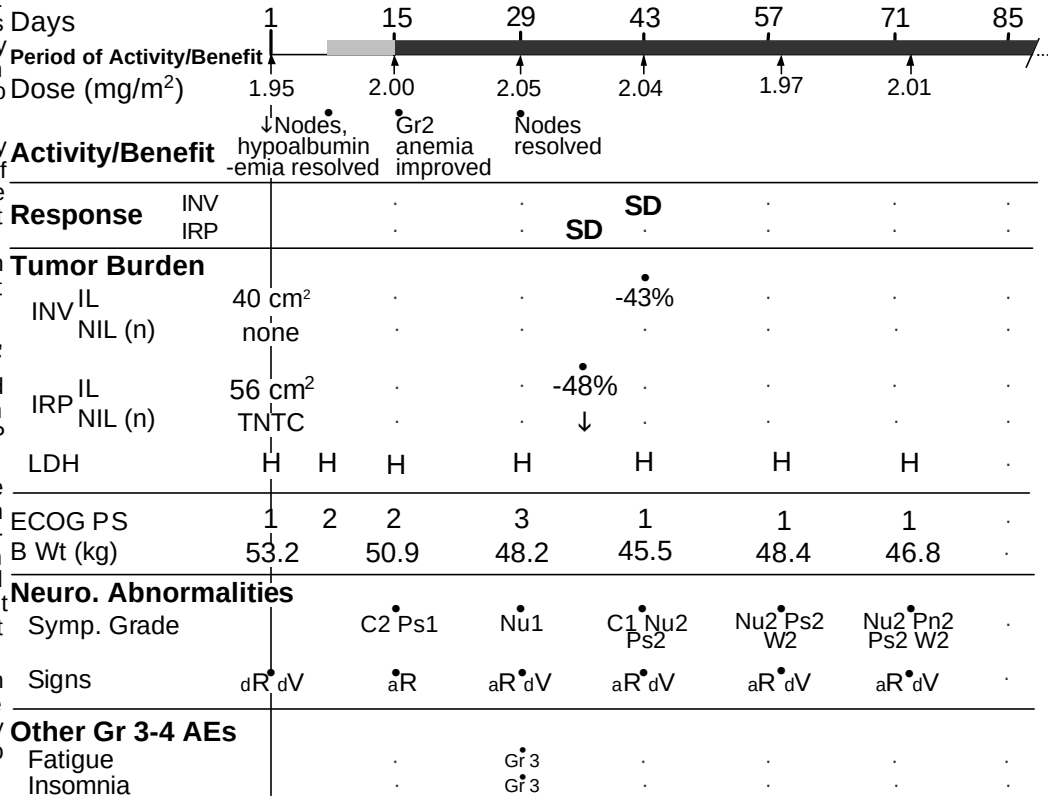
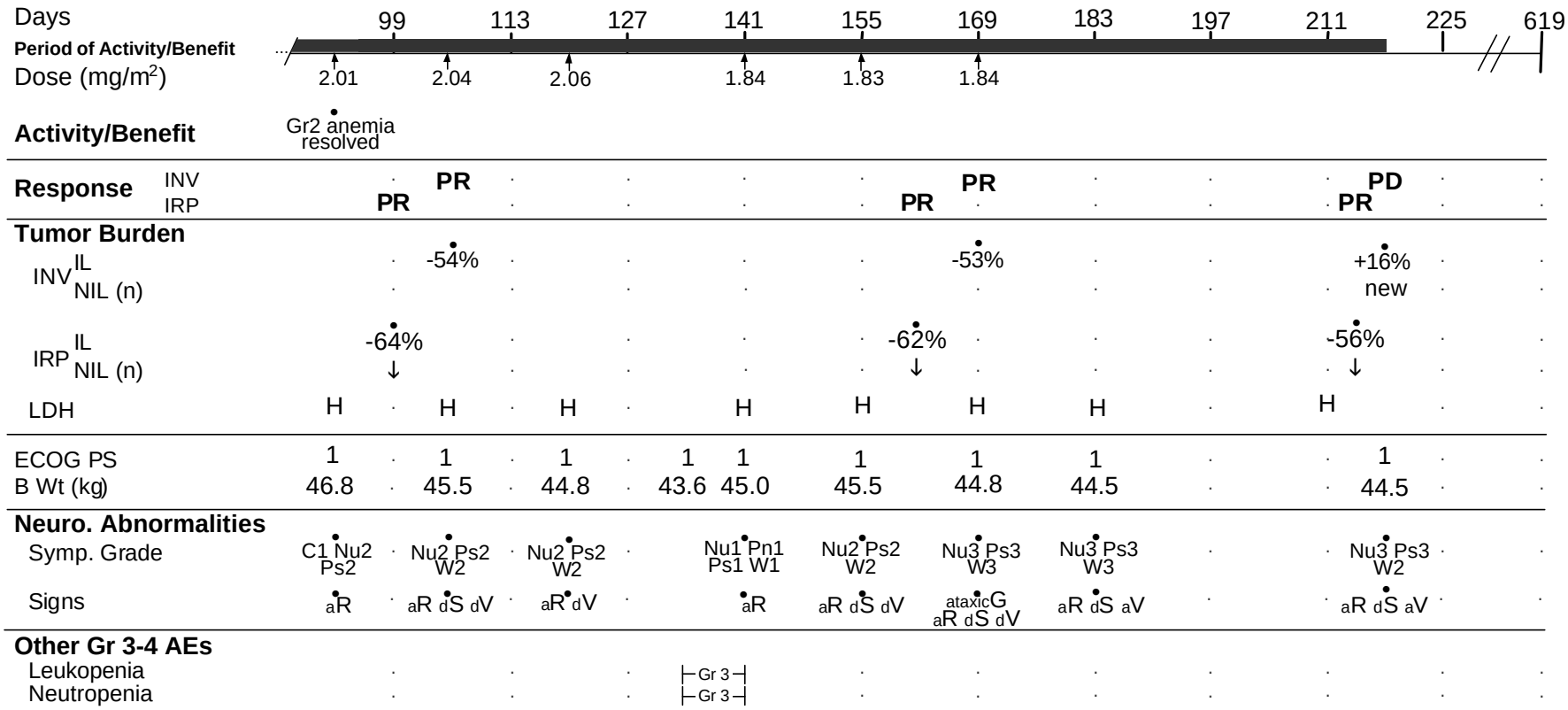


Legend: ↓Decrease ↑Increase **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 40. Graphical Presentation of Efficacy and Safety for Patient 72-01 (continued)

3 Prior Systemic Therapies	45-year-old woman	IRP Best Response: PR	SPD Change: -64%
1. (Doxil, cyclophos., etop.) x8; PR of 8.4 mo. 2. (Cisplatin, cytarabine) x2; SD. 3. Ritux. ~x3, (ifosfamide, carboplatin, etop.) x1; PD.	Stage III DLBCL, IPI 2 Per Protocol Eligible Refractory to Last Qualifying Therapy	Duration of Response: >3.9 mo Time to Progression: >7.2 mo Survival: 20.3 mo	



Legend: ↓Decrease ↑Increase **a** Absent **C** Constipation **CR** Complete Response **d** diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 41. Graphical Presentation of Efficacy and Safety for Patient 74-02

2 Prior Systemic Therapies	75-year-old man	IRP Best Response: PR	SPD Change: -95%
1. CHOP x6; CR of 6.3 mo. 2. (Cisplatin, cytarabine and etoposide) x5; PR then 4 mo later, resection of a neck mass and splenectomy; relapsed 1.3 yr later.	Stage IV DLBCL, IPI 2 Per Protocol Eligible Sensitive to Last Qualifying Therapy	Duration of Response: 2.1 mo Time to Progression: 3.7 mo	Survival: 12.9 mo

This 75-year-old Caucasian man had a 3-year history of chemosensitive DLBCL, treated with 2 regimens of combination chemotherapy, resection of a neck mass, and a splenectomy. He had Stage IV disease at study entry with bilateral neck masses and a skull lesion that were palpable, a bulky mediastinal mass, a RUL lesion, and numerous axillary nodes that were "too numerous to count" according to the IRP.

The first evidence of antitumor activity was the resolution of his palpable adenopathy and normalization of his Grade 2 hypercalcemia after the 1st cycle of VSLI. Both the IRP and the Investigator assessed his response to be a PR after 3 cycles of VSLI, which was maintained for over 2 months. His significant tumor burden decreased by 95%, accompanied by an improvement in his B symptoms. He reported no fevers or night sweats, but he lost 7% of his body weight over the 4 months on study.

At study entry he had Grade 2 neuropathies that progressed to Grade 3 after 3 cycles of VSLI and he was treated with gabapentin thereafter. He received 8 doses of VSLI in total, the last 5 doses decreased due to neuropathy, which showed some improvement by the end of the study. His ECOG PS worsened from 1 to 2 in the middle of the study, but improved again despite his Grade 3 neuropathy. His baseline anemia responded well to erythropoietin and his other hematologic parameters were stable.

He developed new lesions after Cycle 8 with a time to progression of 3.7 months according to the Investigator and the IRP. He died on Day 392 of progressive lymphoma, with a survival of 12.9 months.

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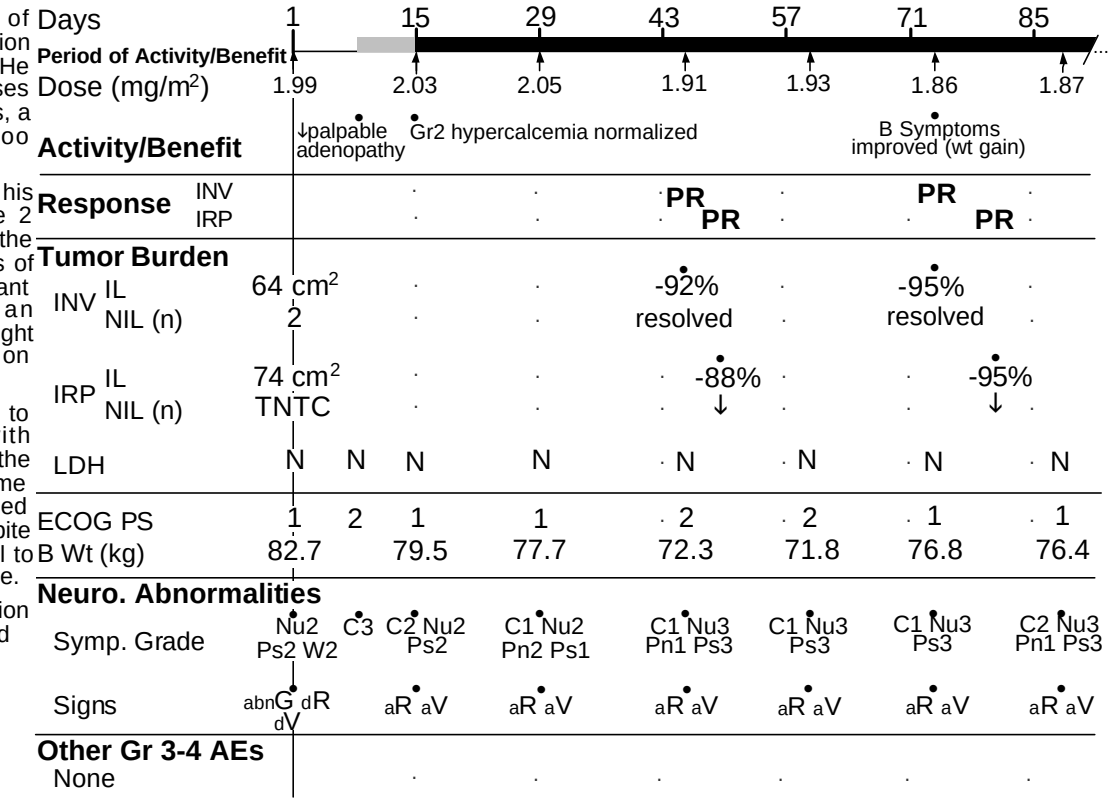


Legend: ↓Decrease ↑Increase **abn** Abnormal **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **Pn** Pain **PR** Partial Response **Ps** Paresthesia **PD** Progressive Disease **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 41. Graphical Presentation of Efficacy and Safety for Patient 74-02 (continued)

2 Prior Systemic Therapies 1. CHOP x6; CR of 6.3 mo. 2. (Cisplatin, cytarabine and etoposide) x5; PR then 4 mo later, resection of a neck mass and splenectomy; relapsed 1.3 yr later.	75-year-old man Stage IV DLBCL, IPI 2 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: PR Duration of Response: 2.1 mo Time to Progression: 3.7 mo	SPD Change: -95% Survival: 12.9 mo

Patient 74-02 continued

Activity/Benefit

Response	INV		**PD**
	IRP		**PD**
Tumor Burden			
INV	IL		-98%
	NIL (n)	resolved	new
IRP	IL		-94%
	NIL (n)		↓, new
LDH		N	N
ECOG PS		1	1
B Wt (kg)		72.0	76.8
Neuro. Abnormalities			
Symp. Grade		C2 Nu3 Ps3	Nu2 Ps2
Signs		aR aV	aR aS
Other Gr 3-4 AEs			
None			

Legend: ↓Decrease ↑Increase **abn** Abnormal **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **Pn** Pain **PR** Partial Response **Ps** Paresthesia **PD** Progressive Disease **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **W** Weakness

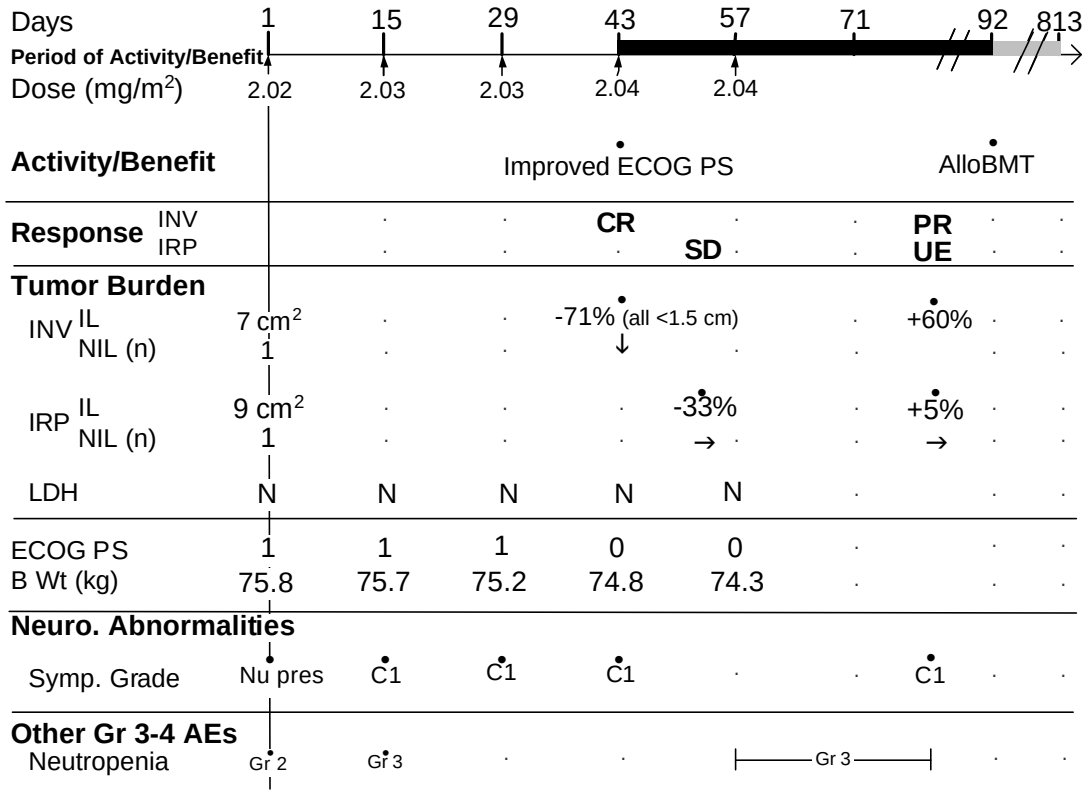
FIGURE 42. Graphical Presentation of Efficacy and Safety for Patient 01-23

2 Prior Systemic Therapies 1. CHOP x6; CR of 10 mo. 2. ESHAP x2 + transplant; CR of 14 mo.	59-year-old woman Stage IIIE DLBCL, IPI 1 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: SD SPD Change: -33% Duration of Response: n/a Time to Progression: >2.6 mo Survival: >26.7 mo, alive with no evidence of disease

This 59-year-old Caucasian woman had Stage IIIE chemosensitive DLBCL that had relapsed after complete responses to CHOP and salvage therapy with ESHAP and autologous stem cell transplant. After 3 cycles this patient experienced benefit with an improvement of ECOG PS from 1 to 0. After 4 cycles, her tumor burden decreased 33% from 9.0 to 6.0 cm^2 resulting in SD as declared by IRP. However, one of the lesions reviewed by the IRP was in the spleen and they questioned whether it was a cyst instead of a tumor. Removing this cyst from the IRP review would have made her response a PR. The Investigator declared CR (based on clinical CT review) after 4 cycles of VSLI. The site radiologist documented a 71% decrease in tumor burden to 1.9 cm^2 and all lesions were within normal size limits. At Day 79, the Investigator changed the response assessment to PR, based on a slight increase above normal size limits in one of the lesions. The neck CT was not done at Day 79, and as the cervical lesion could not be assessed, the IRP was unable to evaluate her response.

Although her neurologic evaluations were not formally assessed after baseline, Grade 1 constipation and numbness of fingers were the only neurotoxicities reported as adverse events. She entered the study with baseline Grade 2 anemia, Grade 2 neutropenia, and Grade 1 thrombocytopenia. These parameters remained reasonably stable throughout the study (neutropenia increased to Grade 3) and she maintained her weight as well. Her ECOG PS improved from 1 to 0.

She received a total of 5 cycles of VSLI and her response to VSLI allowed her to be transferred for an allogeneic BMT which she received on Day 92. At last contact on Day 813 (26.7 months), she was alive with no evidence of disease.



Legend:
↓Decrease →Stable **AlloBMT** Allogeneic Bone Marrow Transplant **C** Constipation **CR** Complete Response **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PR** Partial Response **pres** Present **SD** Stable Disease **UE** Unable to Evaluate

FIGURE 43. Graphical Presentation of Efficacy and Safety for Patient 08-02

2 Prior Systemic Therapies 1. CNOP x7; CR of 8.2 yr. 2. CNOP x6; PR of 5 mo.	77-year-old man Stage IV DLBCL, IPI 5 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: SD SPD Change: -16% Duration of Response: n/a Time to Progression: 3.5 mo Survival: 6.5 mo

This 77-year-old Caucasian man with diabetes and a 9-year history of DLBCL was treated with CNOP twice, first with a long-lasting CR, then with a PR lasting 5 months. At study entry he had Stage IV marrow positive disease, an IPI score of 5, and a large tumor burden, with extensive disease in the chest, abdomen, and bulky disease in the neck causing jaw and variable ear pain.

He experienced a number of clinical benefits during the study. The bulky disease in his neck improved rapidly and his jaw pain resolved after 1 cycle of VSLI. His ECOG PS of 2 improved to 1 on Day 7 and remained 1 until it became 0 at Day 113. His weight remained stable. His Grade 2 hypoalbuminemia normalized for most of the study, until relapse. The Investigator and IRP chose different indicator lesions; the Investigator included the bulky mandibular and neck lesions (166 cm^2) measured only by physical examination, whereas the IRP chose only CT-imaged lesions including a chest wall muscle mass. He achieved a PR per the Investigator that lasted 2.3 months, SD per the IRP with a time to progression of 3.5 months.

He received a total of 9 doses of VSLI (17.9 mg/m^2) without decreases or delays. Despite having received 13 doses of vincristine (22 mg total), 6 within the last 8 months, he developed minimal neurotoxicities, primarily limited to Grade 1 numbness of hands and feet and diminished/absent reflexes and vibration perception. He had no GI complaints other than 1 episode of Grade 1 nausea and constipation. Two weeks after his last dose he developed Grade 3 pulmonary edema (unrelated to VSLI), possibly related to his preexisting cardiac disease, but recovered completely. He had no other Grade 3-4 AEs of any nature. He died of progressive lymphoma 3 months later (Day 197).

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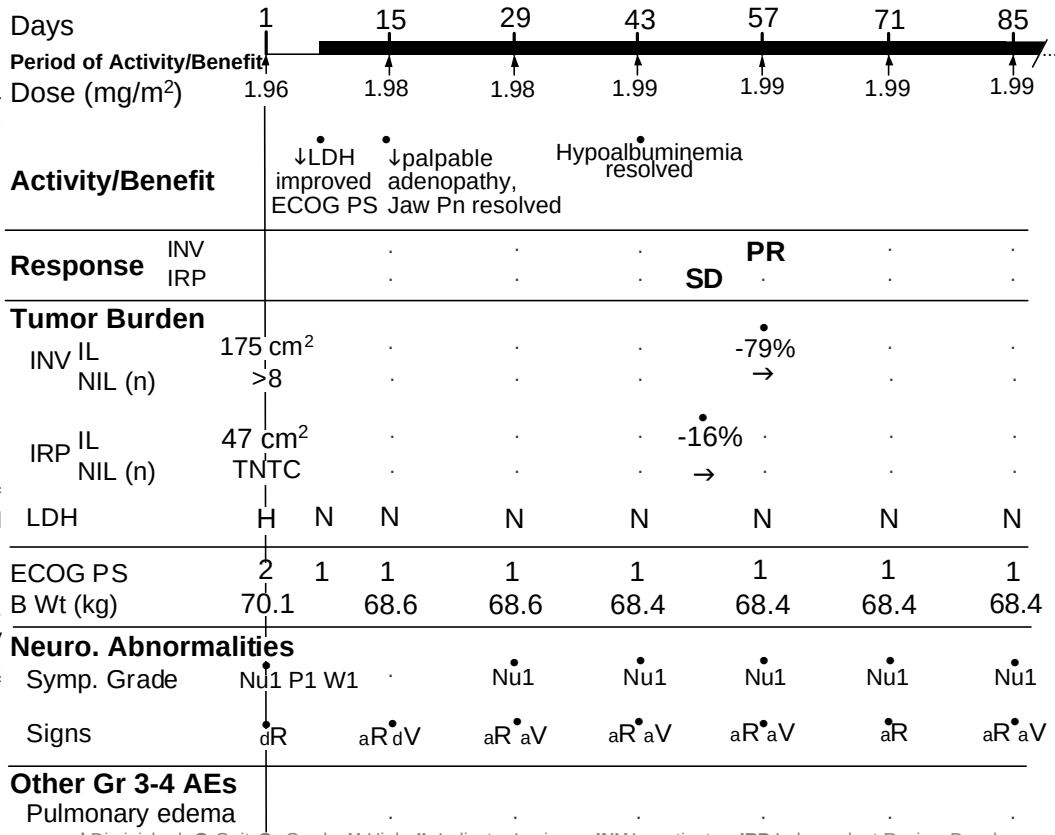


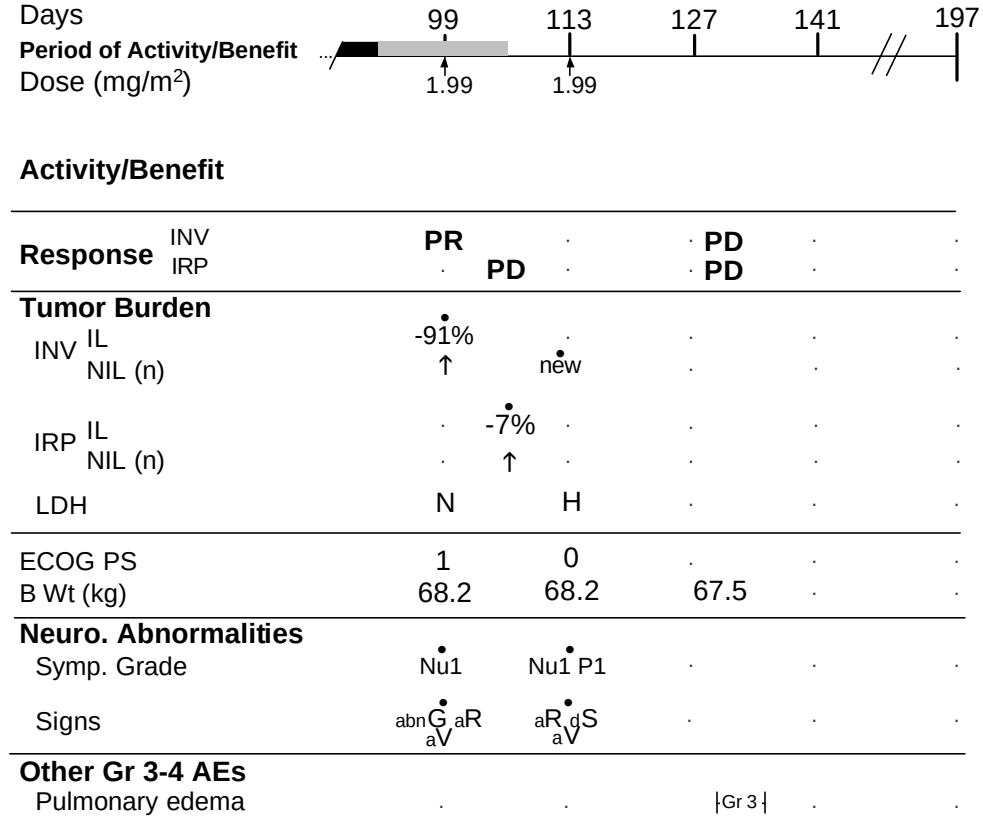
Legend: ↓Decrease ↑Increase →Stable **a** Absent **abn** Abnormal **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **SD** Stable Disease **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 43. Graphical Presentation of Efficacy and Safety for Patient 08-02 (continued)

2 Prior Systemic Therapies 1. CNOP x7; CR of 8.2 yr. 2. CNOP x6; PR of 5 mo.	77-year-old man Stage IV DLBCL, IPI 5 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: SD SPD Change: -16% Duration of Response: n/a Time to Progression: 3.5 mo Survival: 6.5 mo

Patient 08-02 continued

VSLI provided an important response with symptomatic improvement for a period of ~3 months in this elderly patient with extensive bulky disease and a poor IPI score. The 3-month period of symptomatic improvement was about half of his remaining survival from study entry.



Legend: ↓Decrease ↑Increase →Stable **a** Absent **abn** Abnormal **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **SD** Stable Disease **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 44. Graphical Presentation of Efficacy and Safety for Patient 13-01

5 Prior Systemic Therapies	62-year-old woman	Best Response: SD SPD Change: -13%
1. CHOP x6; PR of <4 mo. 2. ESHAP x2; SD. 3. (Etop., cyclophos.) x1; UE. 4. (Etop., cyclophos., dacarbazine) x1 + transplant; PR of <5 mo. 5. Rituximab x4; PD.	Stage IIA Composite lymphoma, IPI 1 Per Protocol Eligible Refractory to Last Qualifying Therapy	Duration of Response: n/a Time to Progression: >7.4 mo Survival: >29.8 mo, alive with disease

This 62-year-old Caucasian woman with refractory Stage IIA composite lymphoma (50% DLBCL, 50% follicular Grade 3A lymphoma) had received 5 systemic regimens including an autologous stem cell transplant in the 1.6 years since her first diagnosis. She had several periaortic nodes and retroperitoneal nodes that were "too numerous to count" according to the IRP, as well as renal lesions according the Investigator.

The first evidence of antitumor activity was the normalization of Grade 1 thrombocytopenia at Day 20. The Investigator and the IRP assessed her best response to VSLI to be stable disease, which was documented by CT imaging on 4 occasions after baseline. According to both the IRP and the Investigator, her disease was stable for >7 months with VSLI treatment.

She tolerated VSLI therapy well, developing mild to moderate neuropathies that remained stable for 14 cycles. She developed Grade 3 numbness and paresthesia in her hands after 15 cycles of VSLI (31.2 mg/m^2 total) and was withdrawn from further treatment due to increasing neuropathy and lack of response to VSLI. Her only dose delay was due to her hospitalization for febrile neutropenia and she had no dose decreases. Her ECOG performance status was maintained at 0 throughout the study. Her weight was stable and she had only one episode of Grade 1 constipation early in the study.

She had Grade 2 neutropenia at study entry and experienced an episode of Grade 4 febrile neutropenia after the first dose of VSLI, which required hospitalization for IV antibiotics. She maintained a normal or elevated neutrophil count on filgrastim for the duration of the study. She had Grade 1 anemia for most of the study, possibly related to VSLI therapy.

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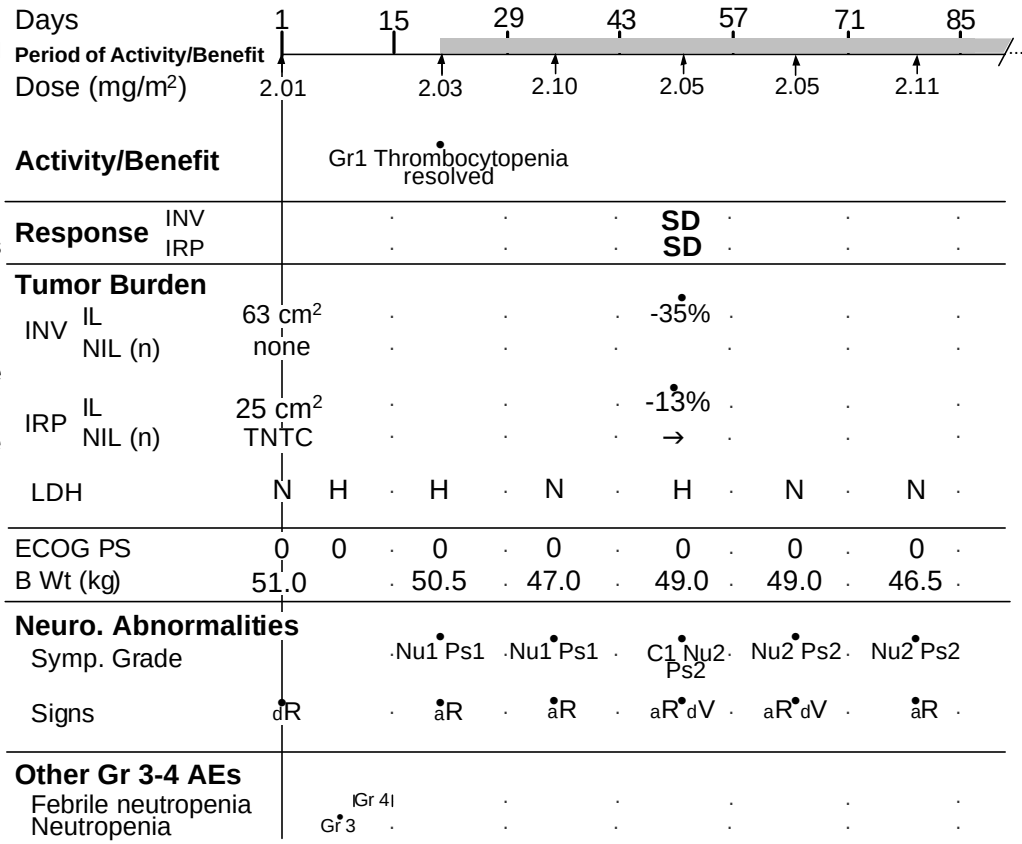

Legend: →Stable **a** Absent **C** Constipation **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to evaluate **V** Vibration

FIGURE 44. Graphical Presentation of Efficacy and Safety for Patient 13-01 (continued)

5 Prior Systemic Therapies	62-year-old woman	Best Response: SD SPD Change: -13%
1. CHOP x6; PR of <4 mo. 2. ESHAP x2; SD. 3. (Etop., cyclophos.) x1; UE. 4. (Etop., cyclophos., dacarbazine) x1 + transplant; PR of <5 mo. 5. Rituximab x4; PD.	Stage IIA Composite lymphoma, IPI 1 Per Protocol Eligible Refractory to Last Qualifying Therapy	Duration of Response: n/a Time to Progression: >7.4 mo Survival: >29.8 mo, alive with disease

Patient 13-01 continued

Through post-study communication with the Investigator, it was learned that she started gemcitabine therapy 1 week after leaving the VSLI study and was treated from Day 233 until Day 367, with an unknown response. She subsequently received a nonmyeloablative allogeneic transplant on Day 444 from an HLA-matched sibling. The last formal survival update, on Day 906 indicated that she still had active lymphoma.

No direct evidence of symptom improvement, but her disease was stable for >7 months with minimal toxicity, which was a better outcome that she had achieved with her last therapy (rituximab). This time to progression was comparable to what she achieved with ABMT (~8 months). The extended period of treatment with VSLI (15 cycles, 3 cycles beyond the protocol-specified 12 cycles) is evidence that the patient and physician assessed the benefit (potential or realized) to outweigh the toxicity from the therapy and thus they elected to continue VSLI therapy.

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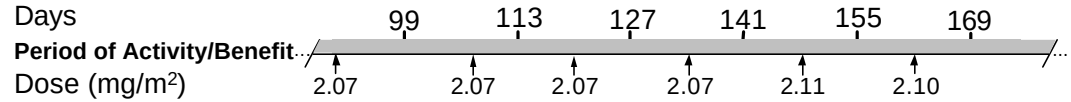


Activity/Benefit

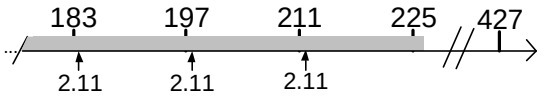
Response	INV		**SD**							**SD**				
	IRP	**SD**							**SD**					
Tumor Burden														
INV	IL		-45%							-49%				
	NIL (n)													
IRP	IL	+9%							-4%					
	NIL (n)	→							→					
LDH		N		N		H		H		H		N		N
ECOG PS		0		0		0		0		0		0		0
B Wt (kg)		48.0		48.5				48.5		46.5		47.0		47.0
Neuro. Abnormalities														
Symp. Grade		Nu2Ps2		Nu2Ps2		Nu2Ps2		Nu2Ps2		Nu2Ps2		Nu2Ps2		Nu2Ps2
Signs		aRdV		aRdV		aRdV		aRdV		aRdV		aRdV		aRdV
Other Gr 3-4 AEs														
None														

Legend: → Stable **a** Absent **C** Constipation **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to evaluate **V** Vibration

FIGURE 44. Graphical Presentation of Efficacy and Safety for Patient 13-01 (continued)

5 Prior Systemic Therapies	62-year-old woman	Best Response: SD SPD change: -13%
1. CHOP x6; PR of <4 mo. 2. ESHAP x2; SD. 3. (Etop., cyclophos.) x1; UE. 4. (Etop., cyclophos., dacarbazine) x1 + transplant; PR of <5 mo. 5. Rituximab x4; PD.	Stage IIA Composite lymphoma, IPI 1 Per Protocol Eligible Refractory to Last Qualifying Therapy	Duration of Response: n/a Time to Progression: >7.4 mo Survival: >14.0 mo, alive with disease

Patient 13-01 continued



Activity/Benefit

Response	INV	.	.	.		**SD**	.
	IRP	.	.	.	**SD**	.	.
Tumor Burden							
INV	IL	.	.	.		-26%	.
	NIL (n)	.	.	.		.	.
IRP	IL	.	.	.	-2%	.	.
	NIL (n)	.	.	.	→	.	.
LDH		N	H	H		H	.
ECOG PS		0	0	0		.	.
B Wt (kg)		47.5	49.0	46.0		.	.
Neuro. Abnormalities							
Symp. Grade		Nu2 Ps2	Nu2 Ps2	Nu2 Ps2		Nu3 Ps3	.
Signs		aR dV	aR dV	aR dV		aR dV	.
Other Gr 3-4 AEs							
None		.	.	.		.	.

Legend: →Stable **a** Absent **C** Constipation **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to evaluate **V** Vibration

FIGURE 45. Graphical Presentation of Efficacy and Safety for Patient 14-06

3 Prior Systemic Therapies	63-year-old man	IRP Best Response: SD SPD Change: -45%
1. CHOP x6; CR of ~8 yr.	Stage IIIS DLBCL, IPI 3	Duration of Response: n/a
2. DHAP x2; PR.	Per Protocol Eligible	Time to Progression: >4.6 mo
3. High-dose etop., melphalan + transplant; CRu of 1 yr.	Sensitive to Last Qualifying Therapy	Survival: 7.0 mo

This 63-year-old Caucasian man with sensitive Stage IIIS DLBCL relapsed after 3 combination chemotherapy regimens and a stem cell transplant as his most recent therapy. His disease responded well to all previous therapies.

Early evidence of antitumor activity of VSLI was noted by decreased LDH levels and improved leukopenia by Day 8, decreased palpable adenopathy by Day 15, and resolution of B symptoms (night sweats) by Day 29. He achieved a PR (per Investigator) on Day 48 (Cycle 4 Day 6) with a 75% reduction in tumor size, but was felt to have only SD by the IRP, having documented a 44% reduction in tumor size. After 9 cycles of VSLI, the Investigator noted almost total resolution of original disease, but 4 new lesions constituted PD. Thus the PR lasted 2.5 months, with a time to progression of 3.8 months. The IRP continued to declare SD, with no new disease and a time to progression of >4.6 months.

He had a history of chronic cytopenias and his baseline counts, consistent with persistent myelotoxicity from previous extensive treatment, were too low for standard cytotoxic therapy. He also presented with elevated creatinine and BUN. While on the study these parameters remained stable or improved and his anemia responded to erythropoietin. He had only 1 episode of Grade 3 neutropenia.

He tolerated 9 cycles of VSLI well (18.0 mg/m^2 total), with no dose decreases. His 10th dose of VSLI was held due to neuropathy for 14 days, at which time PD was noted. His ECOG PS remained stable at 1. His sensory neuropathies were mild, with only sporadic reports of Grade 2 generalized weakness. His gait remained normal and his baseline Grade 1 constipation did not worsen. He died due to progressive disease on Day 212, 7 months after his first dose of VSLI.

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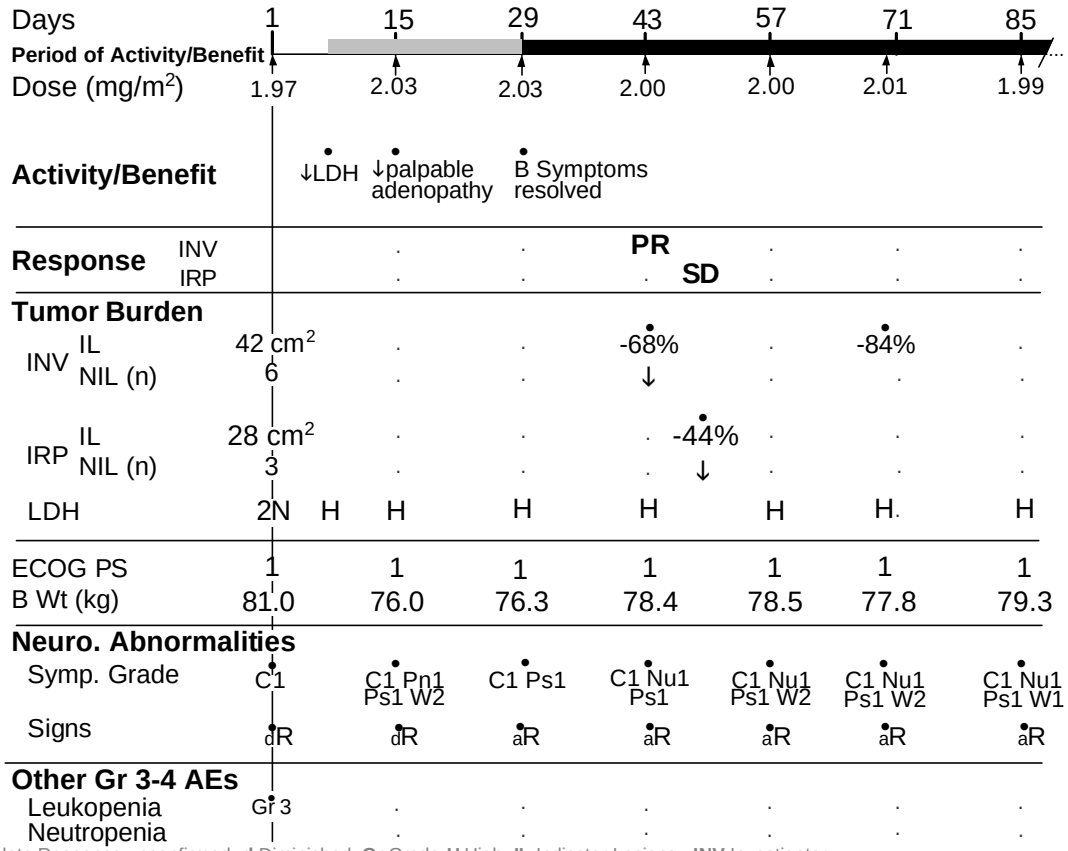


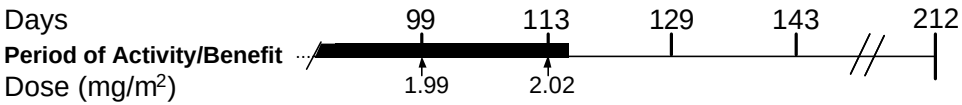
Legend: ↓ Decrease **a** Absent **C** Constipation **CR** Complete Response **CRu** Complete Response unconfirmed **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **PR** Partial Response **Ps** Paresthesia **S** Strength **W** Weakness **UE** Unable to Evaluate

FIGURE 45. Graphical Presentation of Efficacy and Safety for Patient 14-06 (continued)

3 Prior Systemic Therapies	63-year-old man	IRP Best Response: SD SPD Change: -45%
1. CHOP x6; CR of ~8 yr. 2. DHAP x2; PR. 3. High-dose etop., melphalan + transplant; CRu of 1 yr.	Stage IIIS DLBCL, IPI 3 Per Protocol Eligible Sensitive to Last Qualifying Therapy	Duration of Response: n/a Time to Progression: >4.6 mo Survival: 7.0 mo

Patient 14-06 continued

This patient sustained clinically meaningful benefit with reduction of palpable disease and elimination of lymphoma-related symptoms (night sweats), with minimal toxicity or myelotoxicity despite compromised bone marrow function due to extensive prior treatment.



Activity/Benefit

Response INV / IRP		**PD SD**	**PR UE**	**PD UE**	
Tumor Burden					
INV	IL: -100%	-93%	-97%	-90%	
	NIL (n)	new			
IRP	IL	-45%			
	NIL (n)	↓			
LDH	H	H	2N	2N	
ECOG PS	1	1	1	1	
B Wt (kg)	79.7	77.5	77.5	76.0	
Neuro. Abnormalities					
Symp. Grade	C1 Nu1 Ps1	Nu1 Ps1	C1 Nu1 Ps1 W2	C1 Nu1 Ps1 W1	
Signs	aR	aR dS	aR dS	aR dS	
Other Gr 3-4 AEs					
Leukopenia					
Neutropenia	Gr 3				

Legend: ↓Decrease **a** Absent **C** Constipation **CR** Complete Response **CRu** Complete Response unconfirmed **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **PR** Partial Response **Ps** Paresthesia **S** Strength **W** Weakness **UE** Unable to Evaluate

FIGURE 46. Graphical Presentation of Efficacy and Safety for Patient 21-02

6 Prior Systemic Therapies	74-year-old man	Best Response: SD SPD Change: -34%
1. CHOP x6; CR of almost 7 mo. 2. IL-4 x1; PD. 3. (Mitroxantrone, fludarabine) x4; PR of ~10 mo. 4. (Cyclophos., vinc., dex.) x2; UE. 5. VP-16 x1; SD. 6. Rituximab; SD. Progressed ~13 mo later.	Stage II LBCL, IPI 1 Per Protocol Eligible Refractory to Last Qualifying Therapy	Duration of Response: n/a Time to Progression: >5.7 mo Survival: >38.5 mo, alive with disease

This 74-year-old Caucasian man with refractory Stage II large B-cell lymphoma had received 6 prior systemic regimens over the 4.7 years since his initial diagnosis. He had achieved only one CR lasting approximately 6 months. He achieved only stable disease with his last two regimens. His medical history was remarkable for a right thoracotomy with pleurodesis, right hydronephrosis with placement of a stent, stable cardiomegaly, anemia, fatigue, right chest wall discomfort, and GERD.

He had bulky disease (>7 cm) in the right kidney and near the right ureter, as well as numerous celiac nodes that were "too numerous to count" according to the IRP. The first evidence of antitumor activity was the resolution of small inguinal nodes by Day 15. On Day 52, after 4 cycles, the CTs showed a 31-32% decrease in indicator lesions by both the IRP and the Investigator assessments and his response was declared to be SD. This assessment was maintained at Day 107 and at Day 165 by the IRP. The Investigator declared PD based on the Day 165 CTs.

Despite having received vincristine twice before (16 mg total), he experienced relatively minor neuropathy with 8 cycles of VSLI (16.0 mg/m^2 total); his worst were Grade 2 paresthesia in his hands and feet, and Grade 1 constipation. He was withdrawn from further treatment on Day 113 after a fall that was considered possibly cause by VSLI. He had isolated treatment-emergent hematologic abnormalities, mostly Grade 1. His only GI toxicity was Grade 1 abdominal bloating, transient burning, and 1 episode of Grade 2 vomiting. He had no Grade 3-4 adverse events and his ECOG PS was maintained at 0 throughout the study until disease progression.

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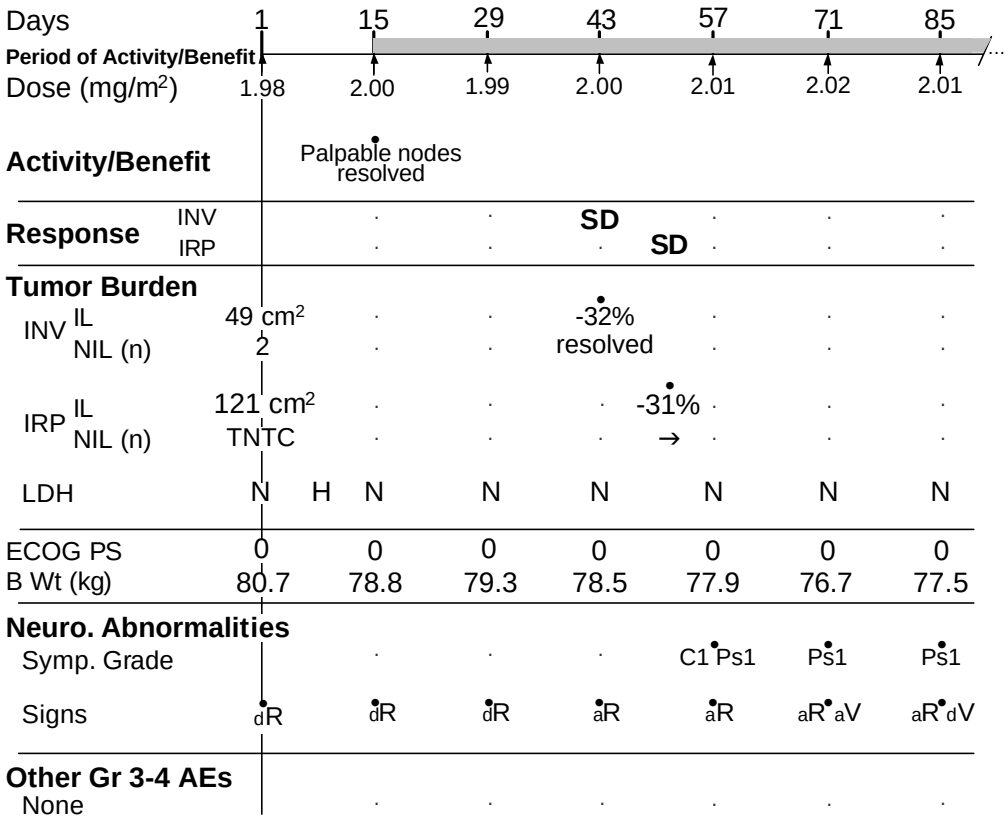


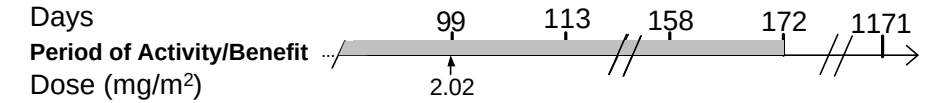
Legend: ↑Increase →Stable **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **PD** Progressive Disease **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to Evaluate **V** Vibration

FIGURE 46. Graphical Presentation of Efficacy and Safety for Patient 21-02 (continued)

6 Prior Systemic Therapies 1. CHOP x6; CR of almost 7 mo. 2. IL-4 x1; PD. 3. (Mitroxantrone, fludarabine) x4; PR of ~10 mo. 4. (Cyclophos., vinc., dex.) x2; UE. 5. VP-16 x1; SD. 6. Rituximab; SD. Progressed ~13 mo later.	74-year-old man Stage II LBCL, IPI 1 Per Protocol Eligible Refractory to Last Qualifying Therapy	Best Response: SD SPD Change: -34% Duration of Response: n/a Time to Progression: >5.7 mo Survival: >38.5 mo, alive with disease

Patient 21-02 continued

His time to progression was 5.7 months according to the Investigator and >5.7 months by the IRP assessment, reflecting a difference in review of the same CTs. This important period of progression-free survival was achieved in this elderly patient with refractory disease after 6 prior regimens. He was alive, with disease, at the last survival follow-up on Day 1171, 38.5 months after his first dose of VSLI.



Activity/Benefit

Response	INV	**SD**					**PD**		
	IRP		**SD**			**SD**			
Tumor Burden									
INV	IL	-47%					+3%		
	NIL (n)	resolved					new		
IRP	IL		-34%			-19%			
	NIL (n)		→			→			
LDH		N		H		H			
ECOG PS		0		1					
B Wt (kg)		77.0		75.1			76.7		
Neuro. Abnormalities									
Symp. Grade		Ps1		Ps2			Ps2		
Signs		aRaV		aRdV			aRdV		
Other Gr 3-4 AEs									
None									

Legend: ↑Increase →Stable **a** Absent **C** Constipation **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **PD** Progressive Disease **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to Evaluate **V** Vibration

FIGURE 47. Graphical Presentation of Efficacy and Safety for Patient 25-01

3 Prior Systemic Therapies	77-year-old woman	IRP Best Response: SD SPD Change: -31%
1. CHOP x6; minor response lasting 5 mo. 2. (Lomustine, etoposide) x1; UE. 3. (DHAP) x2; SD with immediate progression.	Stage IV Composite lymphoma, IPI 5 Per Protocol Eligible Refractory to Last Qualifying Therapy	Duration of Response: n/a Time to Progression: >2.5 mo Survival: 5.0 mo

This 77-year-old Caucasian woman with refractory Stage IV marrow positive composite lymphoma (DLBCL and follicular Grade 3 lymphoma) had received 3 combination chemotherapy regimens in the 1.4 years since her original diagnosis and had never achieved a meaningful response. She achieved only a minor response to first-line CHOP, so she had primary refractory disease, which is usually associated with failure to respond to subsequent salvage therapies. Her medical history included congestive heart failure, coronary artery bypass surgery, a prosthetic mitral valve, hypertension, steroid-requiring drug-induced pneumonitis, and hypothyroidism. She entered the study with B symptoms, an ECOG PS of 2-3, and an IPI of 5, indicating a very poor prognosis. She had numerous mediastinal lymph nodes, bilateral pleural effusions, as well as paratracheal, supraclavicular, axillary, and retroperitoneal adenopathy and splenomegaly.

Early evidence of antitumor activity and clinical benefit after the 1st cycle of VSLI included the resolution of her palpable splenomegaly, Grade 1 fever, Grade 2 night sweats, and Grade 1 thrombocytopenia, and improvement in her ECOG PS from 3 to 1. Her hypoalbuminemia resolved after 3 cycles. On Day 42, after 3 cycles, the IRP declared her response to be SD, with a 29% decrease in the 2 indicator lesions. The Investigator also declared SD with minimal changes in the indicator lesions and decreases in all of the non-indicator lesions, including the pleural effusions. On Day 70, the IRP noted no change from the previous evaluation. The Investigator noted that the bilateral pleural effusions had resolved completely and numerous other lesions were stable; however, the size of the spleen was increased and she had multiple new lesions. Accordingly, the Investigator declared PD. Her night sweats resumed on Day 63.

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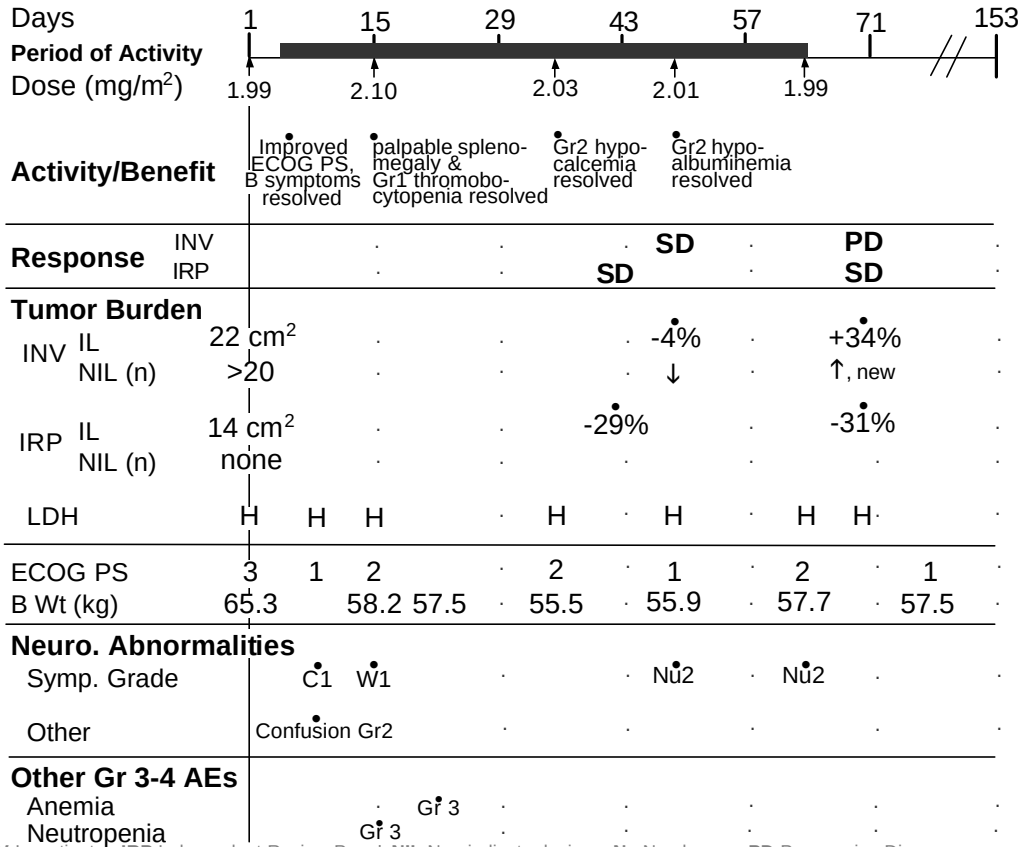

Legend: ↓Decrease ↑Increase **C** Constipation **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **SD** Stable Disease **UE** Unable to Evaluate **W** Weakness

FIGURE 47. Graphical Presentation of Efficacy and Safety for Patient 25-01 (continued)

3 Prior Systemic Therapies 1. CHOP x6; minor response lasting 5 mo. 2. (Lomustine, etoposide) x1; UE. 3. (DHAP) x2; SD with immediate progression.	77-year-old woman Stage IV Composite lymphoma, IPI 5 Per Protocol Eligible Refractory to Last Qualifying Therapy	IRP Best Response: SD SPD Change: -31% Duration of Response: n/a Time to Progression: >2.5 mo Survival: 5.0 mo

Patient 25-01 continued

She tolerated 5 cycles of VSLI well, with no dose reductions and only 1 delay due to hospitalization for Grade 3 anemia. Her chronic anemia of about 4 years required support with PRBC transfusions and erythropoietin on study. Her weight decreased 15% in the first month, but stabilized in the latter half of the study; some of the weight loss may have been due to resolution of her bilateral pleural effusions and resolution of her Grade 2 hypoalbuminemia and peripheral edema. She developed minimal neuropathy and maintained an improved ECOG PS of 1-2 throughout the study.

Both the IRP and the Investigator assessed her best response to be stable disease, with a time to progression of >2.5 months (IRP) and 2.3 months (Investigator). She died on Day 153, 5.0 months after her first dose of VSLI, of respiratory decompensation, likely related to her preexisting drug-induced pneumonitis.

Legend: ↓Decrease ↑Increase **C** Constipation **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **SD** Stable Disease **UE** Unable to Evaluate **W** Weakness

FIGURE 48. Graphical Presentation of Efficacy and Safety for Patient 35-02

3 Prior Systemic Therapies 1. CHOP x6; CR of ~1 yr. 2. ESHAP x4; CR → transplant. 3. BEAM + transplant; CR of 20 mo.	49-year-old man Stage III Peripheral T-cell Lymphoma, IPI 1 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: UE SPD Change: stable Duration of Response: n/a Time to Progression: >3.9 mo Survival: 16.2 mo

This 49-year-old Caucasian man with sensitive Stage III T-cell lymphoma had received 3 combination chemotherapy regimens, including an autologous stem cell transplant as his last therapy. He achieved CRs to all previous therapies. He had residual neuropathy (diminished and absent reflexes) at study entry and no significant comorbidites. According to the Investigator he had 3 axillary nodes at study entry, two measured by physical examination and 1 by CT, whereas the IRP could not identify any indicator lesions due to the poor quality of the images. As a result, the IRP could not evaluate his response throughout the study.

The first evidence of antitumor activity was the resolution of one of the two axillary nodes by physical examination on Day 8 and a decrease in the other by Day 15. On Day 46 (Cycle 4, Day 4), the Investigator declared his response to be a PR, with a 75% decrease in the indicator lesions from 8.0 to 2.0 cm^2. The Investigator maintained a response assessment of PR on Days 71 and 105. The IRP radiologist declared SD and PD based on a qualitative review of the CTs on Days 46 and 105, but the IRP oncology reviewers were unable to evaluate (UE) his response, although they noted regression of tumors based on clinical evidence.

On Day 109, 5 new lesions were noted on a PET scan and the Investigator declared PD accordingly. The unresolved axillary lesion had also increased in size by the next clinical evaluation on Day 120 and his LDH level was elevated for the first time on study on Days 113 and 120, consistent with PD. The PET scan was not reviewed by the IRP radiology reviewer in accordance with the Charter, but the information was provided in the clinical evidence for the IRP oncology reviewers. They noted the progression in the clinical notes, but maintained that his response was UE.

His clinical course on VSLI was remarkable for stable weight, ECOG scores of 0 for most of the study (worsened to 1 for about 1 month in the middle of the study), stable laboratory values, and no GI complaints.

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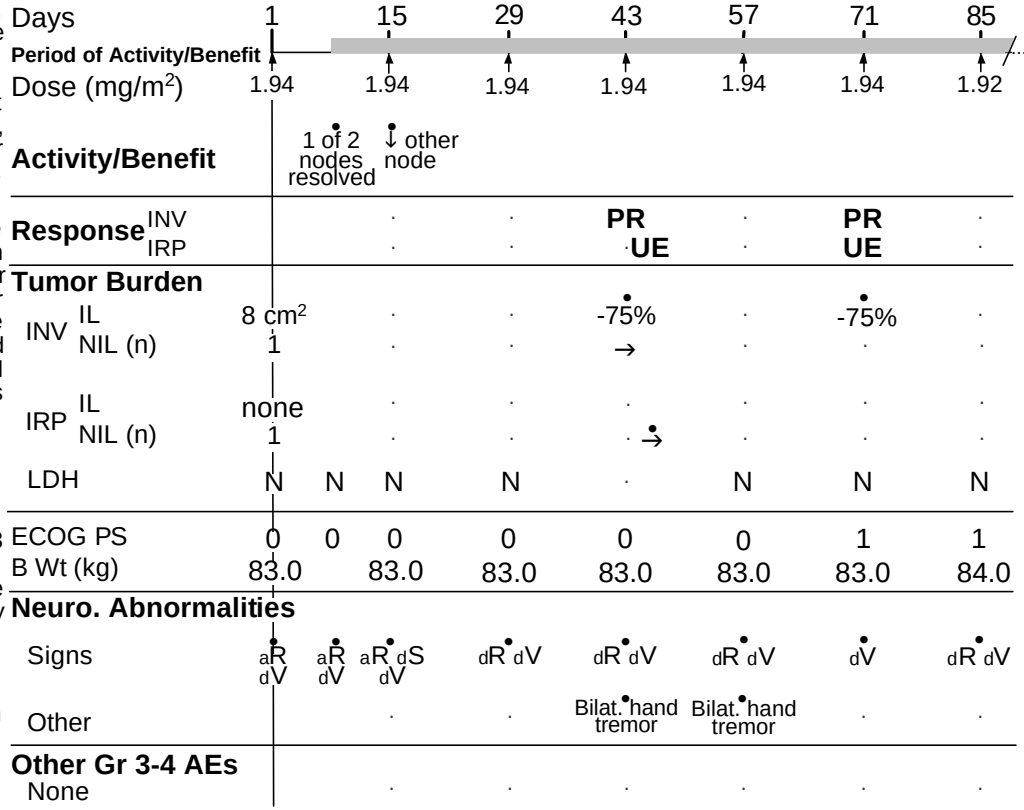


Legend: ↓Decrease ↑Increase →Stable **a** Absent **bilat.** Bilateral **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **PD** Progressive Disease **PR** Partial Response **R** Reflexes **S** Strength **V** Vibration **UE** Unable to Evaluate

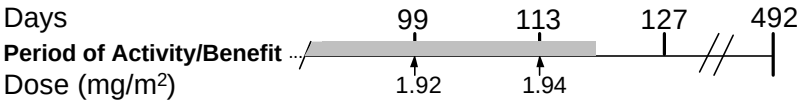
FIGURE 48. Graphical Presentation of Efficacy and Safety for Patient 35-02 (continued)

3 Prior Systemic Therapies 1. CHOP x6; CR of ~1 yr. 2. ESHAP x4; CR → transplant. 3. BEAM + transplant; CR of 20 mo.	49-year-old man Stage III Peripheral T-cell Lymphoma, IPI 1 Per Protocol Eligible Sensitive to Last Qualifying Therapy	IRP Best Response: UE Duration of Response: n/a Time to Progression: >3.9 mo Survival: 16.2 mo SPD Change: stable

Patient 35-02 continued

He received 9 cycles of VSLI (17.4 mg/m^2 total) with no dose reductions or delays. This patient was unusual in that he entered the study with evidence of residual neuropathies (limited to absent reflexes and vibration perception) that improved during the study and vanished completely as of 2 weeks after the last dose of VSLI.

According to the Investigator, his best response was a PR, with a duration of 2.2 months and a time to progression of 3.6 months. He died due to progressive disease on Day 492, 16.2 months after his first dose of VSLI.



Activity/Benefit

Response	INV	**PR**		**PD**		
	IRP		**UE**	**UE**		
Tumor Burden						
INV	IL	-75%		+13%		
	NIL (n)	→		new		
IRP	IL					
	NIL (n)		↑			
LDH		N		H	H	
ECOG PS		1		0	0	
B Wt (kg)		84.0		83.0	82.0	
Neuro. Abnormalities						
Signs		dV		dV		
Other						
Other Gr 3-4 AEs						
None						

Legend: ↓Decrease ↑Increase →Stable **a** Absent **bilat.** Bilateral **CR** Complete Response **d** Diminished **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **PD** Progressive Disease **PR** Partial Response **R** Reflexes **S** Strength **V** Vibration **UE** Unable to Evaluate

Per-Protocol Ineligible Patients

FIGURE 49. Graphical Presentation of Efficacy and Safety for Patient 01-12

6 Systemic Prior Therapies

1. Alternating (CHOP/BLEO +OPEN) x9; CR of 22 mo.
2. ESHAP x2; PD→transplant; CR ~2 yr.
3. Rituximab; CR of >1.5 yr.
4. Rituximab; CR of <1 mo.
5. Bexxar; PD. Next therapy 2.5 yr later.
6. (MINE + rituximab) x6; CR of 8 mo.

60-year-old man
Stage IV Follicular lymphoma Gr 3A, IPI 1
Per Protocol Ineligible (Histology)
Sensitive to Last Qualifying Therapy

IRP Best Response: CR SPD Change: resolved
Duration of Response: >9.0 mo
Time to Progression: >10.8 mo
Survival: 21.9 mo

This 60-year-old Hispanic man had sensitive Stage IV Follicular Grade 3A lymphoma that had relapsed after 6 previous regimens of combination chemotherapy, immunotherapy, radioimmunotherapy, and an autologous stem cell transplant. The baseline CT scan documented pulmonary nodules that were "too numerous to count." Additional CT scans were taken on Days 54 and 152, which documented that these nodules completely resolved with VSLI therapy. Both the Investigator and the IRP stated that he had achieved a CR, with a duration of response of >9.0 months and a time to progression of >10.8 months. Overall lymphoma-free survival attributed to VSLI was >9 months.

He had preexisting Grade 1 neuropathies on study entry and received 11 doses of VSLI (20.94 mg/m^2 total), with 1 dose reduction and 6 dose delays. His worst neuropathy on study was Grade 4 numbness and paresthesia after the 2nd dose of VSLI, which recovered rapidly to Grade 2 after a delay and reduction of the next dose. Thereafter, he tolerated VSLI well and his ECOG PS was maintained consistently at 0 or 1. His neuropathies were primarily peripheral with mention of constipation only on Days 27 and 30. His neuropathies diminished near the end of the study and his final two recorded ECOG PS scores were both 0. He received gabapentin daily after the 5th dose and his 8th, 9th, 10th, and 11th doses of VSLI were given at intervals of 21-42 days rather than the protocol-mandated 14 days. The increase in interval may be related to the improvement in neurologic status.

He developed progressive cytopenias and was withdrawn from treatment on Day 328 due to progressive thrombocytopenia and was diagnosed with AML 2 days later. He received subsequent chemotherapy for his AML, achieved a short-lived CR, and eventually underwent an allogeneic stem cell transplant. He was alive with no evidence of disease on Day 624, 20.5 months after entering the study. However, he died due to progression of his AML on Day 668, 21.9 months after his first dose of VSLI.

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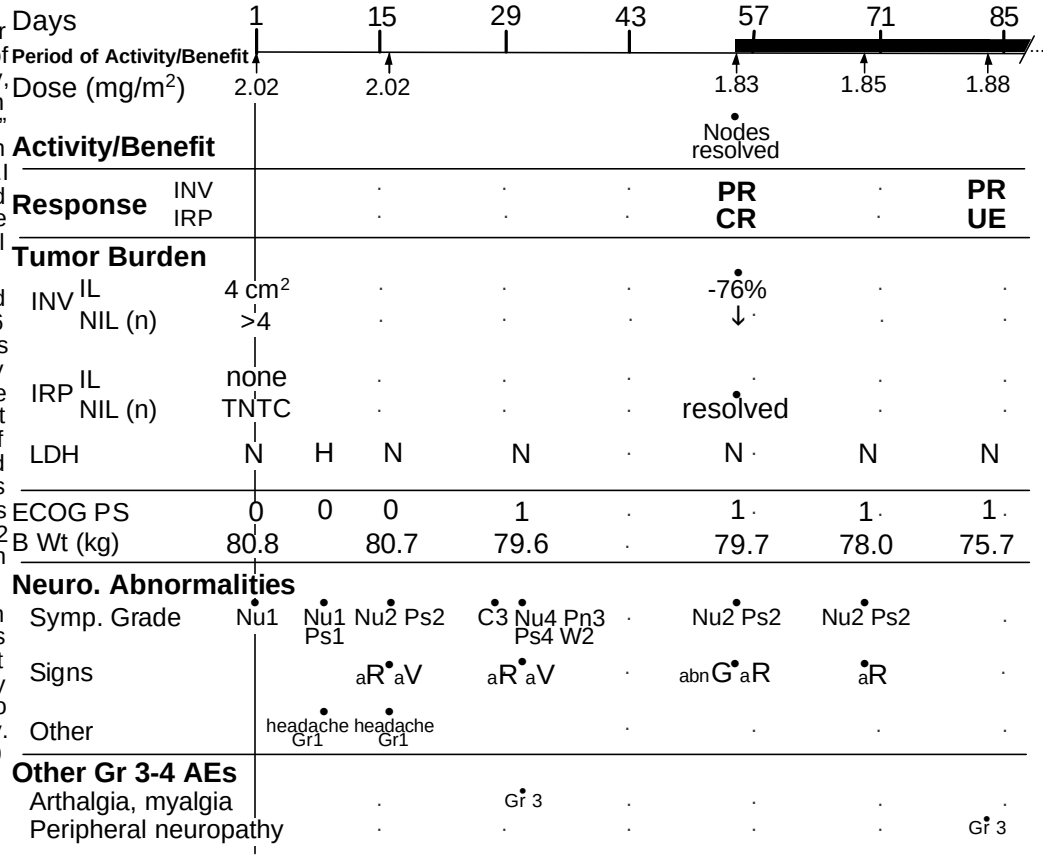
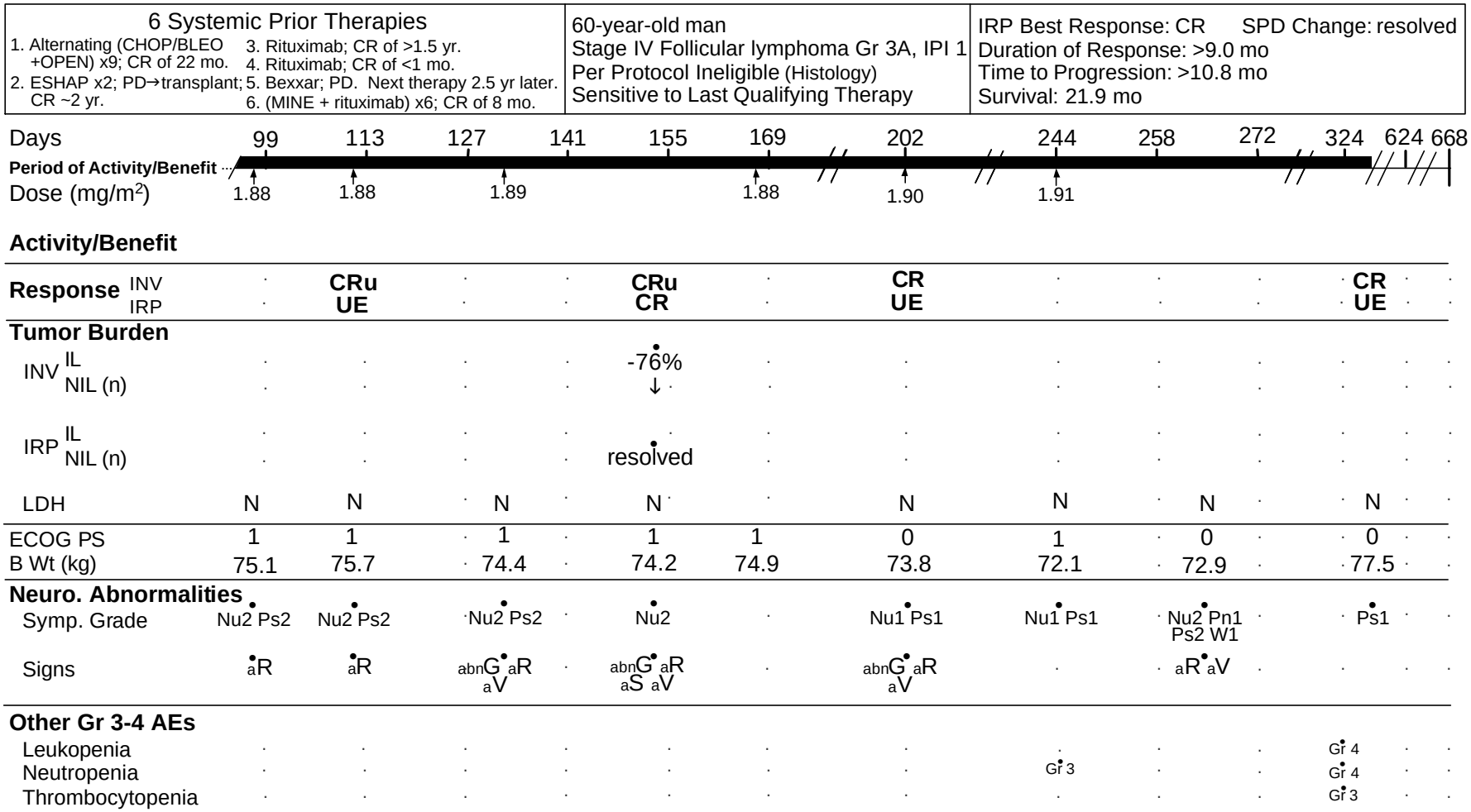


Legend:

↓Decrease **abn** Abnormal **a** Absent **C** Constipation **CR** Complete Response **CRu** Complete Response Unconfirmed **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **W** Weakness **UE** Unable to Evaluate

FIGURE 49. Graphical Presentation of Efficacy and Safety for Patient 01-12 (continued)



Legend: ↓Decrease **abn** Abnormal **a** Absent **C** Constipation **CR** Complete Response **CRu** Complete Response Unconfirmed **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **TNTC** Too numerous to count **V** Vibration **W** Weakness **UE** Unable to Evaluate

FIGURE 50. Graphical Presentation of Efficacy and Safety for Patient 12-01

3 Prior Systemic Therapies 1. CNOP x6; CR of 6.2 mo. 2. Fludarabine x6; CR of ~15 mo. 3. Rituximab x3; PD.	53-year-old man Stage III Composite Lymphoma, IPI 3 Per Protocol Ineligible (1 prior combination therapy) Refractory to Last Qualifying Therapy	IRP Best Response: CR SPD Change: -100% Duration of Response: >7.2 mo Time to Progression: >8.4 mo Survival: >36.6 mo, alive with no evidence of disease

This 53-year-old Caucasian man had refractory Stage III composite lymphoma (25% DLBCL, 75% Grade 3A follicular lymphoma), an ECOG PS of 2, and an IPI score of 3. He had received only 1 prior combination chemotherapy regimen and was technically ineligible for the study although he had received 3 prior regimens in total. His history included COPD, CAD with bypass, and exposure to dioxin-containing Agent Orange, which is a controversial product believed to cause peripheral neuropathy.

At study entry, he had B symptoms and other clinical symptoms consistent with his extensive chest disease that included a large hilar mass and numerous small mediastinal nodes that were "too numerous to count". He achieved a durable CR after 3 doses of VSLI according to the Investigator. The IRP assessed his response as a CRu at this time, and eventually as a CR after 6 cycles. His LDH normalized by Day 8. His B symptoms (fever, night sweats) were improved immediately (reported Day 16) and resolved by Day 30 and his chest symptoms (cough, pain, and shortness of breath) improved or resolved with complete response to VSLI.

He tolerated 6 doses of VSLI well, with no delays or decreases. His hematologic parameters remained relatively stable; Grade 1 anemia at study entry worsened to Grade 2 intermittently and he had 1 episode of Grade 1 thrombocytopenia. His GI toxicities were limited to Grade 1 loss of appetite and heartburn. At study entry, he had Grade 2 paresthesia, which continued on study but did not worsen. He developed Grade 2 numbness in his feet and hands and eventually an unsteady gait by Day 128 (Cycle 6 Day 57). He received gabapentin for his neuropathies from Day 58 onwards. He had no Grade 3 or 4 AEs of any nature. His ECOG status was 2 at study entry and throughout the study, until the final visit when it improved to 1.

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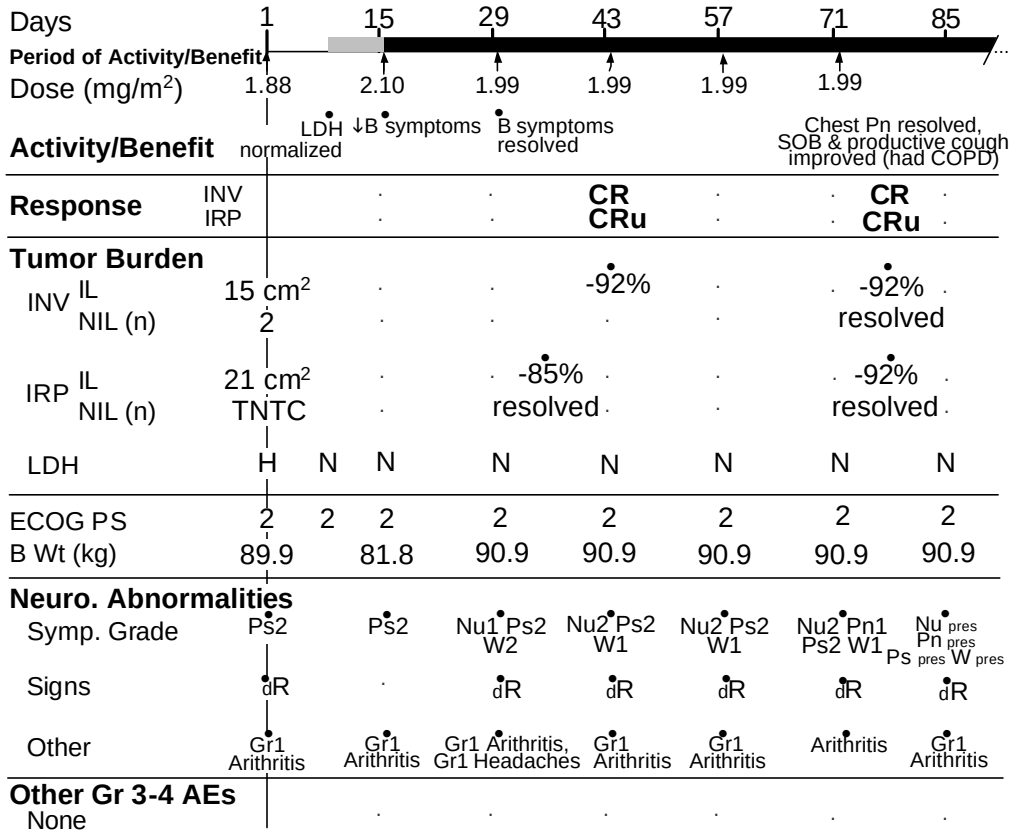


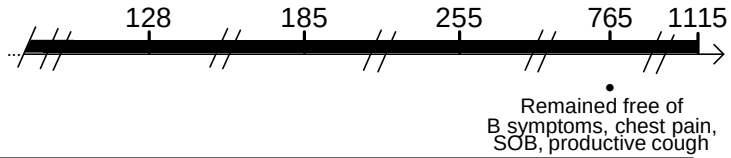
Legend: ↓Decrease **a** Absent **abn** Abnormal **CR** Complete Response **CRu** Complete Response Unconfirmed **dim** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **PD** Progressive Disease **Pn** Pain **pres** Present **Ps** Paresthesia **R** Reflexes **S** Strength **SOB** Shortness of Breath **TNTC** Too numerous to count **W** Weakness

FIGURE 50. Graphical Presentation of Efficacy and Safety for Patient 12-01 (continued)

3 Prior Systemic Therapies 1. CNOP x6; CR of 6.2 mo. 2. Fludarabine x6; CR of ~15 mo. 3. Rituximab x3; PD.	53-year-old man Stage III Composite Lymphoma, IPI 3 Per Protocol Ineligible (1 prior combination therapy) Refractory to Last Qualifying Therapy	IRP Best Response: CR SPD Change: -100% Duration of Response: >7.2 mo Time to Progression: >8.4 mo Survival: >36.6 mo, alive with no evidence of disease

Patient 12-01 continued

The last CTs read by the IRP were from Day 252, confirming a duration of response >7.2 months, with a time to progression of >8.4 months. Follow-up data obtained on Day 765 indicated he remained in CR and continued to be free of his B symptoms and chest symptoms. At the last survival follow-up, symptom data was not provided. However, he remained in CR as of Day 1115 with >3 years of progression-free survival attributable to VSLI therapy and a CR lasting 3 years. This is a longer CR than he obtained with his first-line therapy (CNOP), which contained conventional vincristine.



Activity/Benefit					
Response	INV IRP	**CR** **CRu**	**CR** **CR**	**CR** **CR**	
Tumor Burden					
INV	IL	-100%	-100%	-100%	
	NIL (n)				
IRP	IL	-89%	-100%	-100%	
	NIL (n)	resolved	resolved	resolved	
LDH		N		N	
ECOG PS		2	2	1	
B Wt (kg)		88.4	90.9	95.4	
Neuro. Abnormalities					
Symp. Grade		Nu2	Nu2	Nu pres Pn pres Ps pres W pres	
Signs		abn G a R	abn G d R	abn G d R d S	
Other		Arithritis	Arithritis	Arithritis	
Other Gr 3-4 AEs					
None					

Legend: ↓Decrease **a** Absent **abn** Abnormal **CR** Complete Response **CRu** Complete Response Unconfirmed **dim** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesion **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesion **Nu** Numbness **PD** Progressive Disease **Pn** Pain **pres** Present **Ps** Paresthesia **R** Reflexes **S** Strength **SOB** Shortness of Breath **TNTC** Too numerous to count **W** Weakness

FIGURE 51. Graphical Presentation of Efficacy and Safety for Patient 22-02

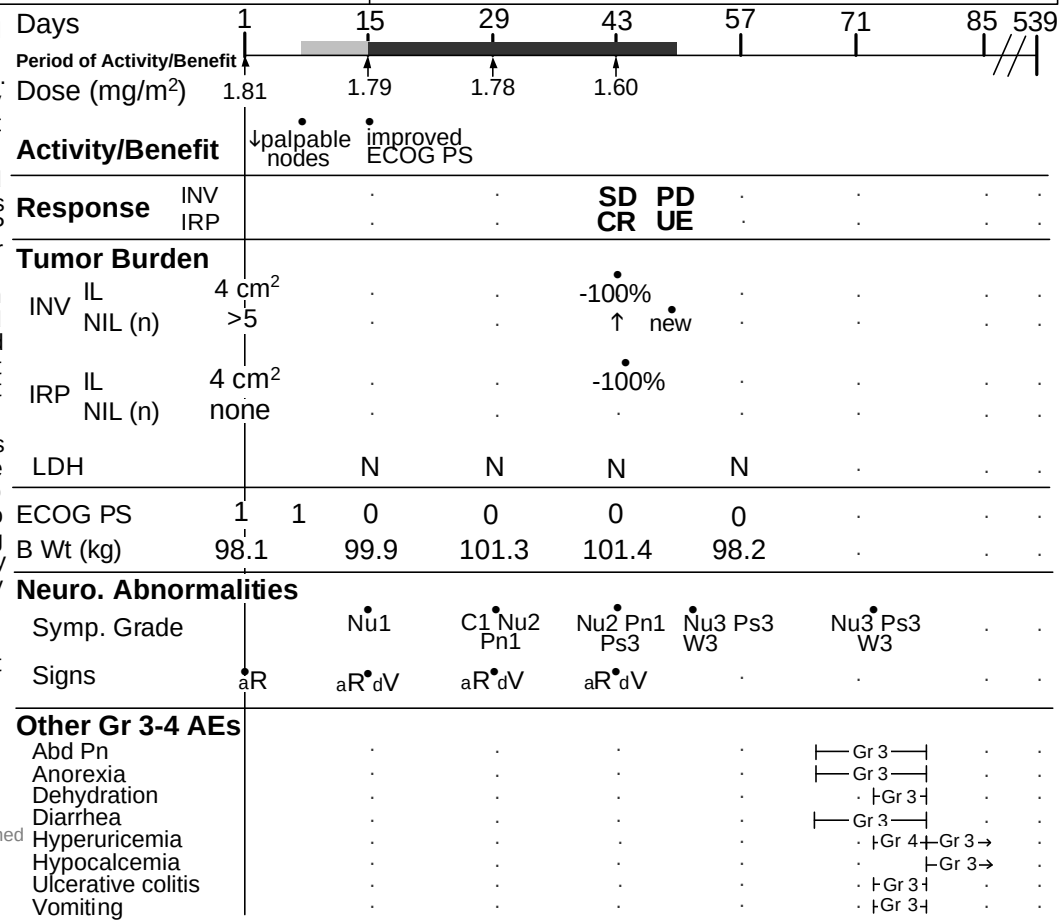
4 Prior Systemic Therapies	51-year-old man	IRP Best Response: CR	SPD Change: -100%
1. CHOP x8; CR of 6 yr. 2. XRT + (cytarabine, dex., platinum) x5; UE. 3. Cytarabine, etoposide + transplant + irradiation; assume CR of ~15 mo. 4. Rituximab x8; PR of 8 mo.	Stage IV Small Cell lymphoma, IPI n/a Per Protocol Ineligible (Histology) Sensitive to Last Qualifying Therapy	Duration of Response: >0.5 mo Time to Progression: >1.9 mo Survival: 17.7 mo	

This 51-year-old Caucasian man with sensitive Stage IV small cell lymphoma had received 4 prior systemic treatments, plus local radiotherapy and a stem cell transplant with total body irradiation. He had a history of ulcerative colitis and chronic renal insufficiency with associated anemia that required erythropoietin treatment at study entry.

Evidence of antitumor activity was seen by Day 8 with decreased palpable adenopathy. The Investigator and IRP disagreed about his response at the first CT evaluation on Day 44, with the IRP declaring a CR, but the Investigator declaring SD. The Investigator declared PD based on a PET scan taken 5 days later, citing progression in his ribs and pelvis. The pelvic mass may have been related to the development of recurrent ulcerative colitis, diagnosed 2 weeks later. He was hospitalized for his colitis and required multiple medical therapies. As per the Charter, the IRP radiologist did not review the PET scan and the IRP oncologists did not accept the PET scan findings as sufficient evidence of progression.

He had preexisting Grade 1 peripheral sensory neuropathy and was treated prophylactically with gabapentin from Day 1. While on the study, he was diagnosed with hypothyroidism, which is known to cause peripheral neuropathy, and the contribution of this disorder to his neurotoxicity is unclear. He received 4 doses of VSLI, starting with a reduced dose, and had 1 further reduction. His neuropathy worsened to Grade 3 and he chose to withdraw from further therapy on Day 57. Despite his significant neuropathies, his ECOG PS improved from 1 to 0 and remained normal.

The IRP determined that he had achieved a CR, with a duration that could not be assessed because he was withdrawn from study follow-up; he had a time to progression of >1.9 months. A CR after four doses of VSLI is a better response than he had achieved with his most recent therapy (8 cycles of rituximab). He died from progressive disease on Day 539, 17.7 months after his first dose of VSLI.



Legend: ↓Decrease ↑Increase **abd** Abdominal **a** Absent **C** Constipation **d** Diminished **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **PS** Paresthesia **R** Reflexes **SD** Stable Disease **UE** Unable to Evaluate **V** Vibration **W** Weakness

FIGURE 52. Graphical Presentation of Efficacy and Safety for Patient 22-01

5 Prior Systemic Therapies	37-year-old man	IRP Best Response: CRu SPD Change: -84%
1. CHOP x6; CR of <6 mo. 2. (Mitroxantrone, fludarabine, dex.) x3; CR of ~2.2 yr. 3. (Ifosfamide, etoposide, carboplatin) x2; PR of ~2 mo. 4. 2-CDA; UE and next treatment 5 mo later. 5. Ritux. x4; minor response. PD noted 6 wk later.	Stage II Low grade BCL, IPI 0 Per Protocol Ineligible (Histology) Refractory to Last Qualifying Therapy	Duration of Response: 2.4 mo Time to Progression: 4.0 mo Survival: >30.5 mo, alive with no evidence of disease

This 37-year-old Caucasian man with refractory Stage II low grade B-cell lymphoma had received 5 systemic regimens in the last 4 years before study entry with only a minor response to his last therapy, rituximab, and progression within 6 weeks. He had a 20-cm^2 ilio-psoas node and associated night sweats at study entry.

The first evidence of antitumor activity was resolution of his B symptoms after 1 cycle of VSLI. His last episode of night sweats was on Day 14 and he had no further episodes until Day 100, approximately 3 weeks before PD was documented by CT scans. After 4 cycles, the IRP assessed an 84% reduction in his indicator lesion from 20.0 to 3.3 cm^2 and declared his response to be a CRu. The Investigator measured the same lesion as having a 67% reduction from 16.0 to 5.3 cm^2 and declared his response to be a PR. Using the Day 86 CTs, the IRP and Investigator maintained their respective opinions of CRu and PR. Both declared PD on Day 122.

With Grade 2 neutropenia and leukopenia at study entry, he was not considered for standard cytotoxic chemotherapy. He was treated with filgrastim from baseline and his neutrophil counts improved and remained normal throughout the study without additional filgrastim, through 5 doses of VSLI. His other laboratory parameters were stable on study, as was his body weight. He had few GI complaints with Grade 2 intermittent nausea, one episode of Grade 1 vomiting, Grade 1 constipation, and intermittent Grade 1 diarrhea. He did, however, develop progressive neuropathy, reaching Grade 3 numbness in his left foot and Grade 2 paresthesia in his hands and feet. His VSLI dose was reduced once and he received gabapentin therapy. He eventually withdrew from VSLI therapy on Day 114 due to neurotoxicity, even though he had some improvement over a 7-week delay in dosing. He had no other Grade 3-4 AEs. Despite his neuropathy, his ECOG PS was maintained at 0 throughout, except for one transient score of 1.

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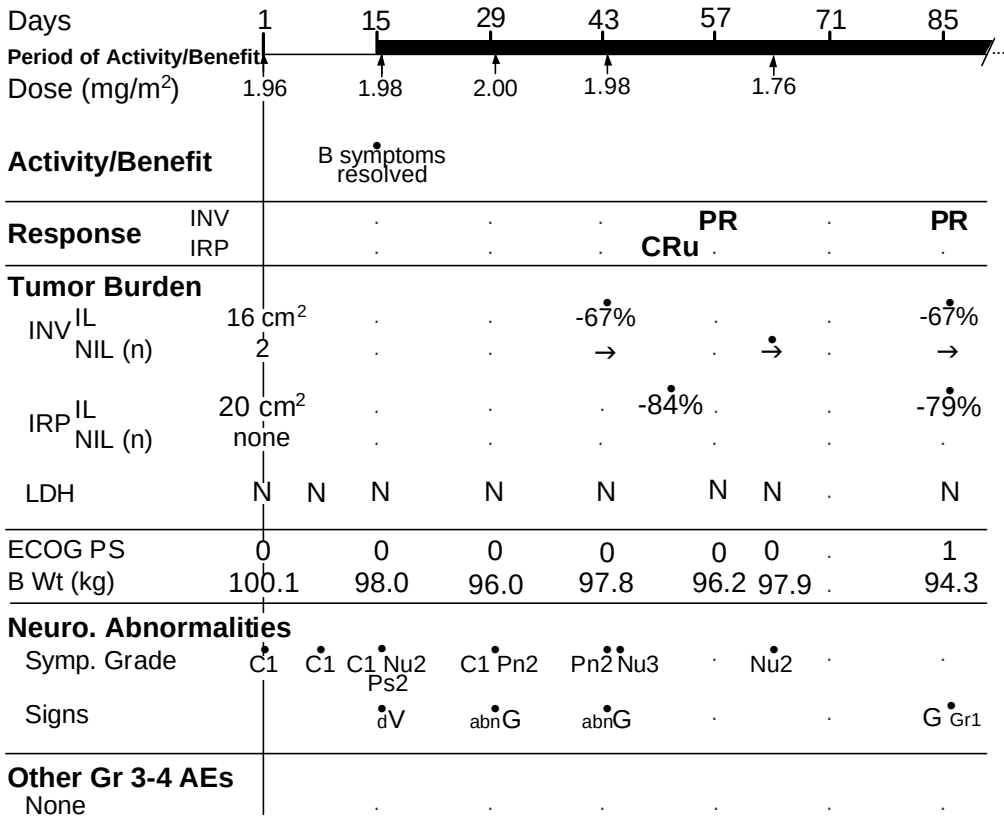


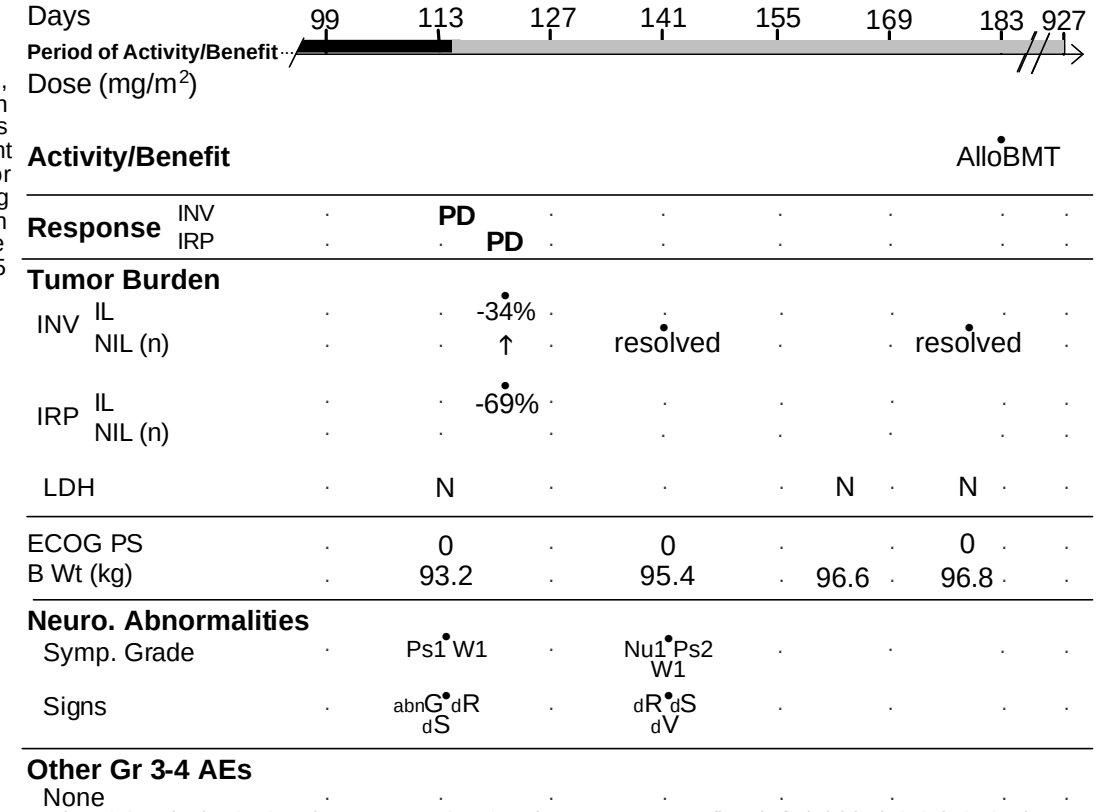
Legend: ↑Increase →Stable **abn** Abnormal **AlloBMT** Allogeneic Bone Marrow Transplant **C** Constipation **CR** Complete Response **CRu** Complete Response Unconfirmed **d** Diminished **G** Gait **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **UE** Unable to Evaluate **V** Vibration **W** Weakness

FIGURE 52. Graphical Presentation of Efficacy and Safety for Patient 22-01 (continued)

5 Prior Systemic Therapies	37-year-old man	IRP Best Response: CRu SPD Change: -84%
1. CHOP x6; CR of <6 mo. 2. (Mitroxantrone, fludarabine, dex.) x3; CR of ~2.2 yr. 3. (Ifosfamide, etoposide, carboplatin) x2; PR of ~2 mo. 4. 2-CDA; UE and next treatment 5 mo later. 5. Ritux. x4; minor response. PD noted 6 wk later.	Stage II Low grade BCL, IPI 0 Per Protocol Ineligible (Histology) Refractory to Last Qualifying Therapy	Duration of Response: 2.4 mo Time to Progression: 4.0 mo Survival: >30.5 mo, alive with no evidence of disease

Patient 22-01 continued

According to the IRP, he achieved a CRu after 4 cycles of VSLI, which was maintained for 2.4 months with a time to progression of 4.0 months, a better outcome than had been achieved with his last rituximab therapy (minor response). This was an important response in a patient who was considered not eligible for standard myelotoxic chemotherapeutic agents. Having demonstrated responsive disease with VSLI, he received an allogeneic bone marrow transplant 2 months after his disease progressed and he was alive with no evidence of disease at 30.5 months.



Legend: ↑Increase →Stable **abn** Abnormal **AlloBMT** Allogeneic Bone Marrow Transplant **C** Constipation **CR** Complete Response **CRu** Complete Response Unconfirmed **d** Diminished **G** Gait **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **UE** Unable to Evaluate **V** Vibration **W** Weakness

FIGURE 53. Graphical Presentation of Efficacy and Safety for Patient 01-01

1 Prior Systemic Therapy	75-year-old man	IRP Best Response: PR SPD Change: -95%
1. XRT to left temple; CR of ~11 mo. 2. CHOP x6; assume CR or PR of ~11 mo. 3. XRT to right groin; PD.	Stage III DLBCL, IPI 3 Per Protocol Ineligible (only 1 prior combination therapy) Sensitive to Last Qualifying Therapy	Duration of Response: >1.1 mo Time to Progression: >3.2 mo Survival: 7.5 mo

This 75-year-old Caucasian man with sensitive Stage III DLBCL had received 1 course of CHOP and 2 courses of radiation in his 2.6 years since diagnosis. He had extensive and bulky disease with a marked elevation of both LDH (1093, ULN 618) and $ß_2$-microglobulin (5.1, ULN 2.0), as well as an intermediate-high risk IPI of 3. He had coronary artery disease with atrial fibrillation, having undergone angioplasty and stent placement.

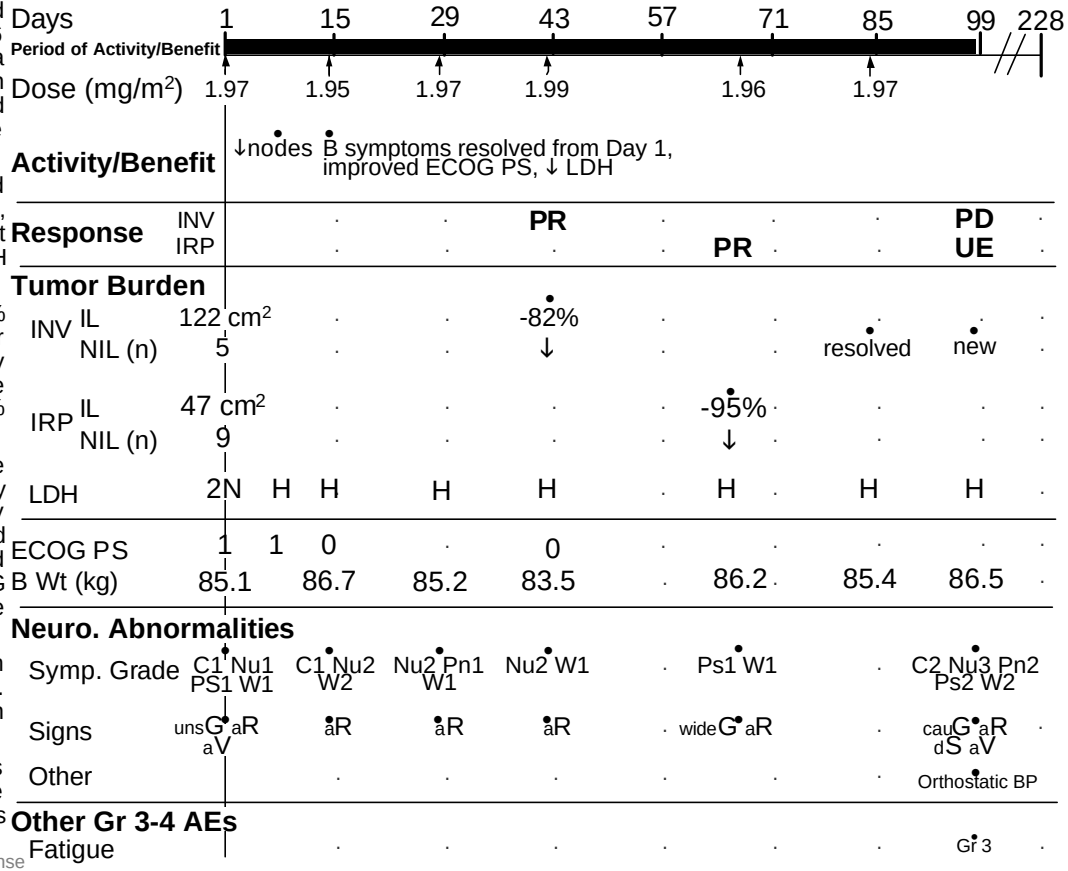
Evidence of antitumor activity after the 1st cycle of VSLI included reduction in his palpable adenopathy, resolution of his night sweats, and an improved ECOG PS from 1 to 0. His last episode of night sweats was the day before his first VSLI dose. His elevated LDH levels also showed rapid decreases.

On Day 65 after 4 cycles, the IRP declared a PR based on a 95% decrease in tumor burden from 46.9 to 2.3 cm^2, with all indicator lesions either totally resolved or within normal size limits; his slightly elevated LDH precluded a CRu response assessment. The Investigator also assessed his response as a PR, with an 82% reduction in his indicator lesions from 122.0 to 21.5 cm^2.

His residual Grade 1 neuropathy at study entry progressed to Grade 2 after his 1st cycle of VSLI. Gabapentin therapy was started on Day 28 and by Day 98, after 6 cycles, he was withdrawn from study therapy due to progressive neuropathy and Grade 3 fatigue. He had no notable hematologic or GI toxicity, no other Grade 3-4 AEs, and his weight was stable. Despite his increasing neuropathy, his ECOG PS remained improved at 0, although it was not assessed when he was withdrawn from therapy.

Also on Day 98, the Investigator noted new right 1.0-cm posterocervical nodes by physical examination and declared PD. The IRP did not accept this as sufficient evidence of progression and they were "unable to evaluate" his response at this final visit.

According to the IRP, he achieved a PR with a duration >1.1 months and a time to progression >3.2 months. He died on Day 228 (Cycle 6, Day 145) from an unknown cause, with his disease status unknown. His survival was 7.5 months from his first dose of VSLI.



Legend: ↓Decrease **a** Absent **C** Constipation **cau** Cautious **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **UE** Unable to Evaluate **uns** Unsteady **V** Vibration **W** Weakness

FIGURE 54. Graphical Presentation of Efficacy and Safety for Patient 01-09

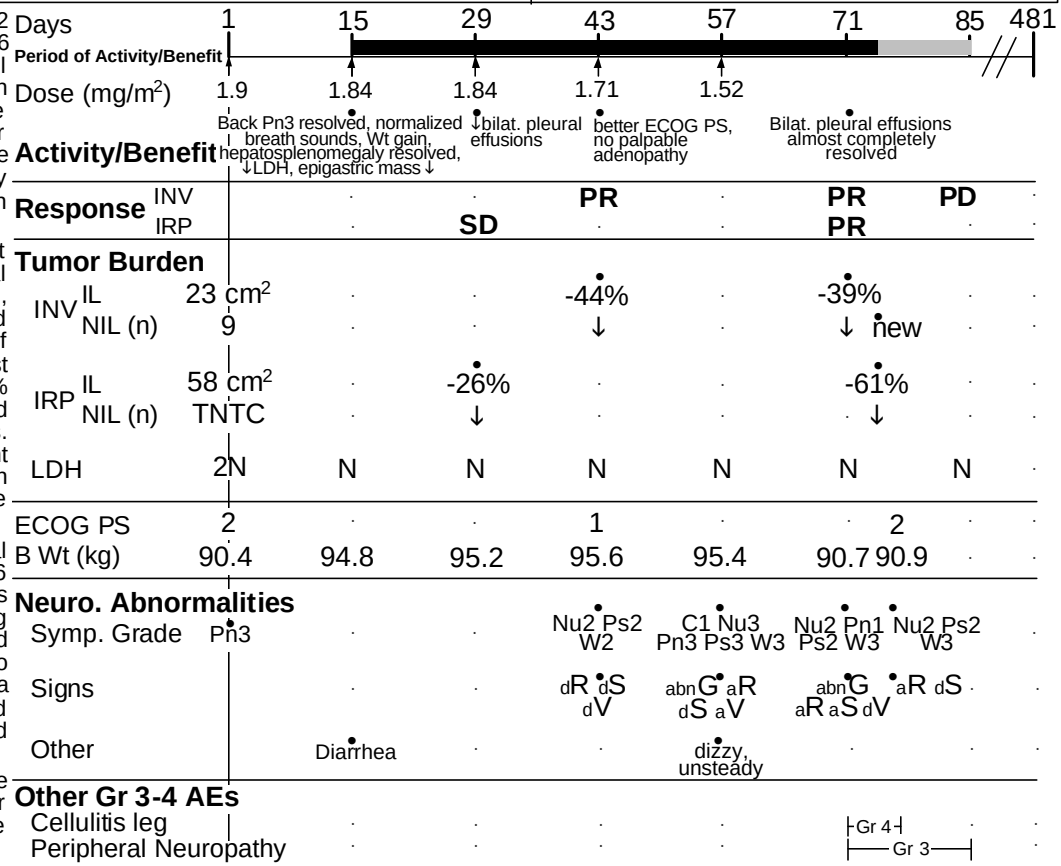
6 Prior Systemic Therapies		50-year-old man Stage IV Follicular Gr 2 lymphoma, IPI 4 Per Protocol Ineligible (Histology) Presumed Sensitive to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -61% Duration of Response: unknown Time to Progression: >2.5 mo Survival: 15.8 mo
1. (ProMACE-CytaBOM) x8; PR + XRT; CR of <3 mo.	3. ESHAP x2; PD.		
2. Etoposide, cyclophosphamide + transplant; PR; through XRT, CR of 4.5 yr.	4. Paclitaxel & topotecan; PD. 5. CHOP x4; PR of 8 mo. 6. Ritux. x4; assume SD of 13 mo.		

This 50-year-old Caucasian man with Stage IV follicular Grade 2 lymphoma, an IPI score of 4, and an ECOG PS of 2, relapsed after 6 prior chemotherapy/immunotherapy regimens, including stem cell transplant and 2 courses of radiation, having achieved CR only with radiotherapy. Nevertheless, he was considered to have sensitive disease as his response to rituximab given approximately 1 year before study was unknown. He was histologically ineligible for the study according to the Central Pathology Review, but his significantly elevated LDH and ß$_2$-microglobulin at study entry suggest an aggressive lymphoma histology.

He had extensive retrocrural, mesenteric, and periaortic nodes that were "too numerous to count", hepatosplenomegaly, and bilateral pleural effusions. Evidence of response (5% weight gain, normalization of LDH, disappearance of hepatosplenomegaly and palpable epigastric mass, normalized breath sounds, and resolution of Grade 3 back pain due to tumor) was seen within 2 weeks of the first dose of VSLI. After 2 cycles, the IRP declared SD based on a 26% reduction in tumor burden. His pleural effusions had decreased and the Investigator declared PR based on a clinical review of the CTs. After 3 cycles, his ECOG PS improved to 1 and he had no significant palpable adenopathy. After 5 cycles, the IRP and Investigator both declared his response to be PR, with almost total resolution of the pleural effusions.

He had 4 prior neurotoxic regimens and developed Grade 3 peripheral neuropathy with VSLI and was withdrawn from treatment on Day 76 after 5 cycles. He had no significant GI or hematologic toxicities. His course was complicated by the development of a Grade 4 leg cellulitis, considered unlikely related to VSLI. When he was removed from the study for Grade 3 neuropathy, his ECOG PS had returned to the baseline score of 2. The Investigator noted new disease by a gallium scan a week later and considered this to be PD. The IRP did not review the gallium scan, as this was not a protocol-specified imaging modality.

His time to progression was >2.5 months and his duration of response was unknown as he was lost to further efficacy follow-up 3 days after response was documented by the IRP. He died of pneumonia more than a year later on Day 481, with a survival of 15.8 months.



Legend: ↓Decrease **abn** Abnormal **a** Absent **Bilat.** Bilateral **C** Constipation **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **SD** Stable Disease **TNTC** Too numerous to count **V** Vibration **W** Weakness **XRT** Radiation

FIGURE 55. Graphical Presentation of Efficacy and Safety for Patient 12-04

4 Prior Systemic Therapies		
1. Resection of small bowel and mesentery. 2. CHOP x6; CR of 11 mo. 3. ESHAP x3; CR of ~3 mo. 4. Rituximab, BEAM, (indium chloride & yttrium) + transplant; PR of ~5.5 mo. 5. Rituximab x1; UE then relapsed ~6 mo later.	69-year-old woman Stage IV MALT Lymphoma, IPI 3 Per Protocol Ineligible (Histology) Sensitive to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -100% Duration of Response: >5.4 mo Time to Progression: >6.8 mo Survival: 11.6 mo

This 69-year-old Caucasian woman with sensitive Stage IV MALT lymphoma, had been previously treated with resection at first diagnosis, followed by 4 systemic therapies that included a stem cell transplant. She achieved a 5.5-month PR after transplant and then received single-agent rituximab as her last therapy, with an unevaluable response and a 6-month time to progression.

She had an 8.4 cm duodenal lesion and numerous mesenteric lymph nodes that were "too numerous to count" according to the IRP. The Investigator and the IRP oncology reviewers chose colonoscopy as the primary imaging modality for monitoring disease outcome. The IRP radiology reviewer received only the CTs for review (not the colonoscopies) and he measured the extensive duodenal involvement to be 43 cm^2 at baseline. The first evidence of VSLI antitumor activity and clinical benefit was the improvement in her ECOG PS from 1 to 0 by Day 15 (after 1 cycle) and the normalization of her LDH and albumin levels after 2 cycles of VSLI. The IRP determined that she had achieved a PR on Days 43, 92 and 175, with the only evidence of disease being the biopsies that continued to show lymphoma in the duodenum. The Investigator could not obtain accurate measurements of her primary lesion and therefore assessed her best response to be SD.

She received 11 doses of VSLI (21.9 mg/m^2 total) with 1 dose reduction and 2 delays. She had preexisting Grade 1 hand paresthesia and numbness and her worst sensory neuropathy on study was Grade 2 numbness, paresthesia, and weakness. Her Grade 1 constipation recurred sporadically but did not worsen. Her baseline Grade 2 anemia worsened to Grade 3 and was treated with erythropoietin. Grade 2 neutropenia resolved without treatment and she had no infections. She developed thromboses in both iliac veins with ovarian infarct, not associated with VSLI, which resolved with anticoagulants. Her weight dropped markedly at Day 164 and afterwards when she had new onset of loose stools and hypoalbuminemia.

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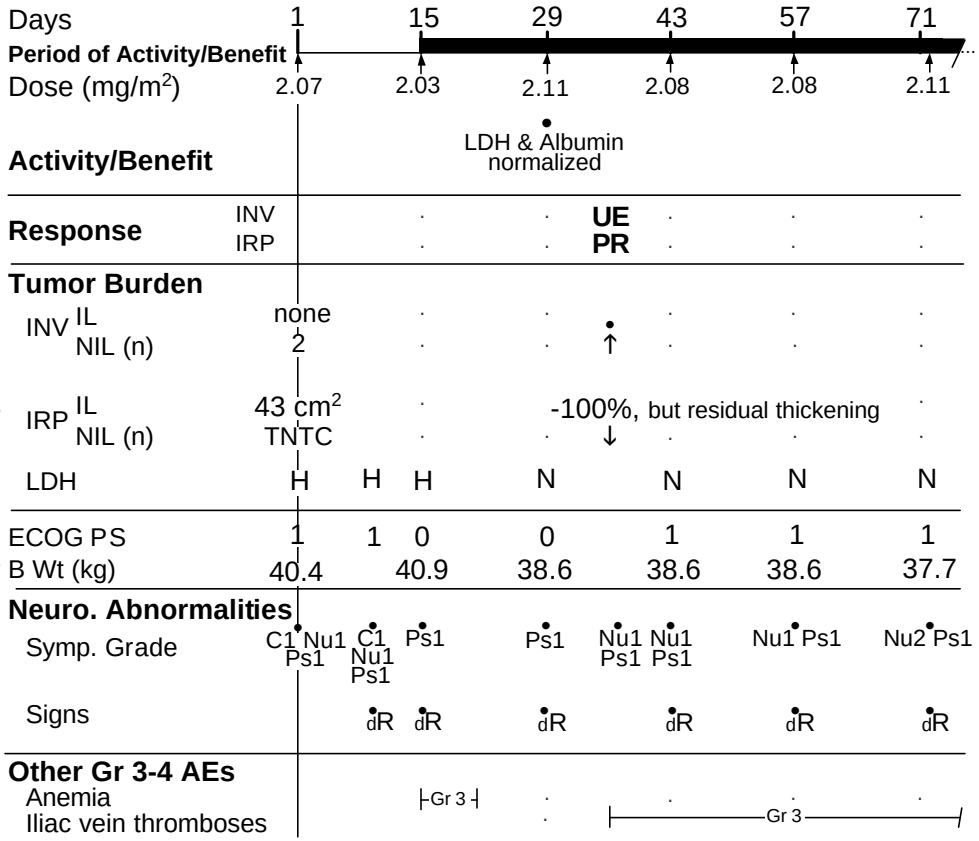


Legend:
↓Decrease ↑Increase →Stable **a** Absent **abn** Abnormal **C** Constipation
CR Complete Response **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **Pn** Pain
PR Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to Evaluate **W** Weakness

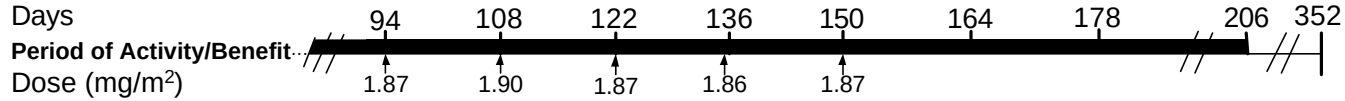
FIGURE 55. Graphical Presentation of Efficacy and Safety for Patient 12-04 (continued)

4 Prior Systemic Therapies		
1. Resection of small bowel and mesentery. 2. CHOP x6; CR of 11 mo. 3. ESHAP x3; CR of ~3 mo. 4. Rituximab, BEAM, (indium chloride & yttrium) + transplant; PR of ~5.5 mo. 5. Rituximab x1; UE then relapsed ~6 mo later.	69-year-old woman Stage IV MALT Lymphoma, IPI 3 Per Protocol Ineligible (Histology) Sensitive to Last Qualifying Therapy	IRP Best Response: PR SPD Change: -100% Duration of Response: >5.4 mo Time to Progression: >6.8 mo Survival: 11.6 mo

Patient 12-04 continued

Despite her progressive neuropathy and thrombotic complication, her ECOG PS remained 1 until Day 164, when it worsened to 2 when her gastrointestinal complaints worsened. She withdrew from treatment on Day 206 (Cycle 11, Day 57), due to persistent gastrointestinal problems and increased neuropathy. She died on Day 352, from sepsis due to lymphoma.

Her best response to VSLI was a PR that lasted >5.4 months, with a time to progression of >6.8 months. This response was better than she had achieved most recently with rituximab and comparable to (and possibly better than) what she achieved with BEAM, radioimmunotherapy, and stem cell transplant. After treatment with VSLI, her residual disease was detectable only by pathology, not by CT.



Activity/Benefit

Response	INV	**SD**							**UE**	
	IRP	**PR**						**PR**	**UE**	
Tumor Burden										
INV	IL								•	•
	NIL (n)		↑						→	→
IRP	IL	•						•	•	
	NIL (n)	-100%, but +ve biopsy →						-100% Resolved, biopsy not done	+ve Biopsy	
LDH (U/L)		N	N	N	N	N	H		N	
ECOG PS			1	0	1	1	2		1	
B Wt (kg)		38.6	37.7	38.6	39.6	38.6	36.3		34.0	
Neuro. Abnormalities										
Symp. Grade			Nu2 Ps2	Nu2 W2	Nu2 W1	C1 Nu2 W1			Nu1 Pn1 W1	
Signs			aR	abnG aR dS	dR	abnG aR	abnG dR		abnG aR dS	
Other Gr 3-4 AEs										
Anemia										
Iliac vein thromboses		⊢Gr 3⊣								

Legend:
↓Decrease ↑Increase →Stable **a** Absent
abn Abnormal **C** Constipation **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions
Nu Numbness **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **SD** Stable Disease **TNTC** Too numerous to count **UE** Unable to Evaluate **W** Weakness

FIGURE 56. Graphical Presentation of Efficacy and Safety for Patient 26-01

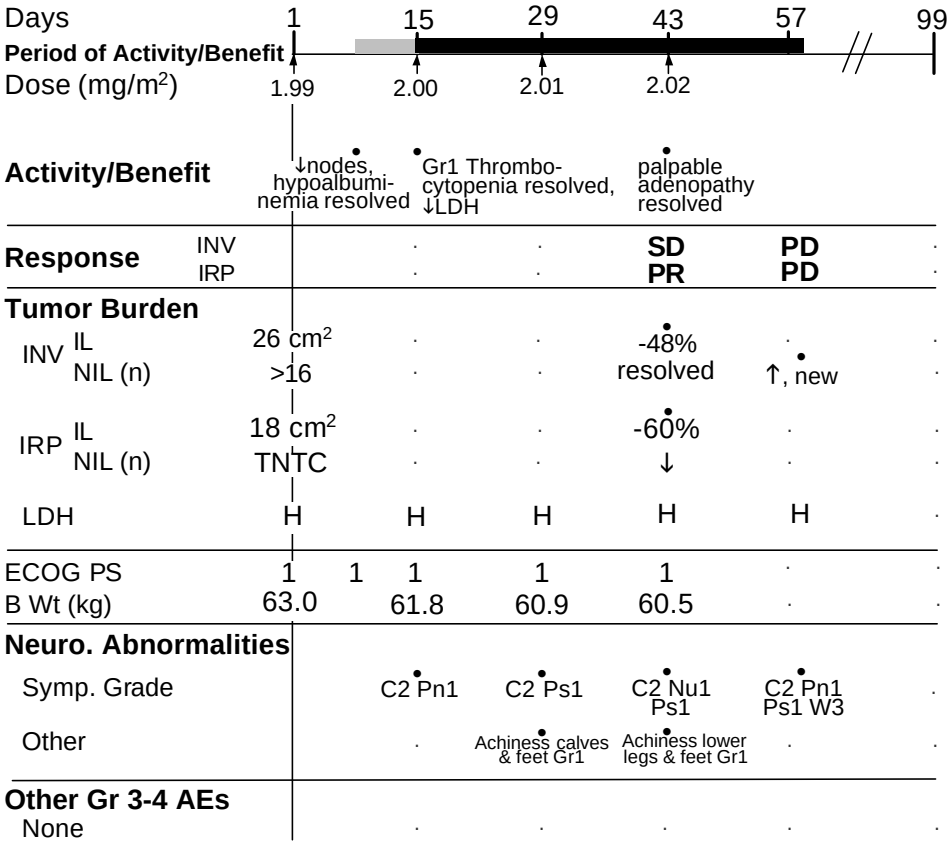
3 Prior Systemic Therapies	73-year-old woman	IRP Best Response: PR SPD Change: -60%
1. CHOP x8; CR of ~4 yr. 2. ProMACE-CytaBOM x4; PD. 3. Rituximab x1; PD. 4. XRT; unknown response.	Stage III Composite Lymphoma, IPI 3 Per Protocol Ineligible (no slides for Central Pathology Review) Refractory to Last Qualifying Therapy	Duration of Response: 0.5 mo Time to Progression: 1.9 mo Survival: 3.3 mo

This 73-year-old African-American woman with refractory Stage III composite lymphoma (diffuse mixed small and large B-cell lymphoma) had received 2 prior combination chemotherapy regimens, immunotherapy, and radiation. She did not respond to salvage ProMACE-CytaBOM therapy or rituximab. At study entry she had extensive disseminated disease with axillary and retroperitoneal nodes that were "too numerous to count" according to the IRP and an IPI score of 3. She had significant comorbidities that included CHF, COPD, and prior atelectasis of the RLL.

The first evidence of antitumor activity on Day 8 included the decrease in palpable adenopathy, resolution of her Grade 1 hypoalbuminemia, and by Day 15 a marked reduction in her elevated LDH and normalization of her Grade 1 thrombocytopenia. The palpable adenopathy was fully resolved after 3 cycles. Based on the CTs taken Day 43 (Cycle 3, Day 15), the IRP noted a 60% reduction in the indicator lesions from 17.8 to 7.1 cm^2, with decreased non-indicator disease, for an overall assessment of PR. The Investigator noted a 48% reduction in the indicator lesions from 25.5 to 13.2 cm^2, with complete resolution of all non-indicator disease, and concluded that her response was SD. The difference in response between the IRP and the Investigator assessments was due to the selection of different indicator lesions and tumor reductions that were close to the definition of PR. At the next clinical visit 2 weeks later, physical examination detected multiple new nodes and the Investigator and the IRP declared PD on this basis.

Despite a total of 12 doses of vincristine (~24 mg total) with her previous therapies, she tolerated 4 cycles of VSLI well, maintaining an ECOG PS of 1 throughout, with relatively minimal neurotoxicities until the last visit when she developed Grade 3 generalized weakness at the time of disease progression. She had Grade 1 numbness and paresthesia in her hands and feet, Grade 1 limb pain, Grade 2 constipation, and no other Grade 3 adverse events.

According to the IRP she achieved a documented PR with a documented duration of 2 weeks and a time to progression of 1.9 months. This response was better than that achieved with her previous standard therapy (ProMACE-CytaBOM). She died on Day 99 (Cycle 4, Day 57) of disease progression, 3.3 months after her first dose of VSLI.



Legend:
↓Decrease ↑Increase →Stable **C** Constipation **CR** Complete Response **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **SD** Stable Disease **TNTC** Too numerous to count **W** Weakness **XRT** Radiation

FIGURE 57. Graphical Presentation of Efficacy and Safety for Patient 33-06

2 Prior Systemic Therapies	47-year-old man	IRP Best Response: PR SPD Change: resolved
1. CHOP x4; minor response. 2. ICE x3 + Rituximab x4; PD. 3. XRT to neck & Waldeyer's ring; PR of 4 mo.	Stage IV DLBCL, IPI 1 Per Protocol Ineligible (Bulky disease not measurable per IRP) Refractory to Last Qualifying Therapy	Duration of Response: n/a Time to Progression: >8.8 mo Survival: >26.9 mo, alive with no evidence of disease

This 47-year-old Caucasian man with refractory Stage IV DLBCL had received 2 combination chemotherapy regimens, including immunotherapy, plus 1 course of radiation therapy, all within 1.3 years since diagnosis. His response to first-line CHOP was only a minor response and he had PD to RICE salvage therapy. His only PR was to radiation.

He tolerated 8 cycles of VSLI well, with no delays or reductions. Despite prior exposure to vincristine and carboplatin, his on-study neurologic complaints were minimal, mostly Grade 1 (paresthesia in hands and feet, numbness in feet, unstable gait). He had no hematologic or GI toxicity. His ECOG PS worsened from a score of 0 to 1 after 4 cycles, with one score of 2 at Day 99. The reason for his changed ECOG PS is unclear as his neuropathies were minimal. His weight was stable.

Both the Investigator and IRP identified a mediastinal nodal mass and he had a positive marrow at study entry. The Investigator measured the nodal mass to be 9.8 cm^2, whereas the IRP radiology reviewer stated that it was confluent and impossible to measure, which complicated the IRP review and created considerable discordance among the IRP oncologists in assigning the correct response.

According to the Investigator, his nodal mass resolved completely by the first CT assessment after 3 cycles of VSLI (Day 43). He was also bone marrow negative for tumor. Accordingly, the Investigator assessed that he had achieved a CR. The Investigator confirmed his CR with additional CTs taken on 4 separate occasions over a period of 7.5 months. The IRP radiologist considered his response to be a PR from Day 43 until Day 267, at which time he declared it to be a CR. One IRP oncologist agreed with the PR assessment, but the final IRP opinion after 4 oncology reviews was that in the absence of exact measurements of the mediastinal disease, the correct response was SD for most of the study.

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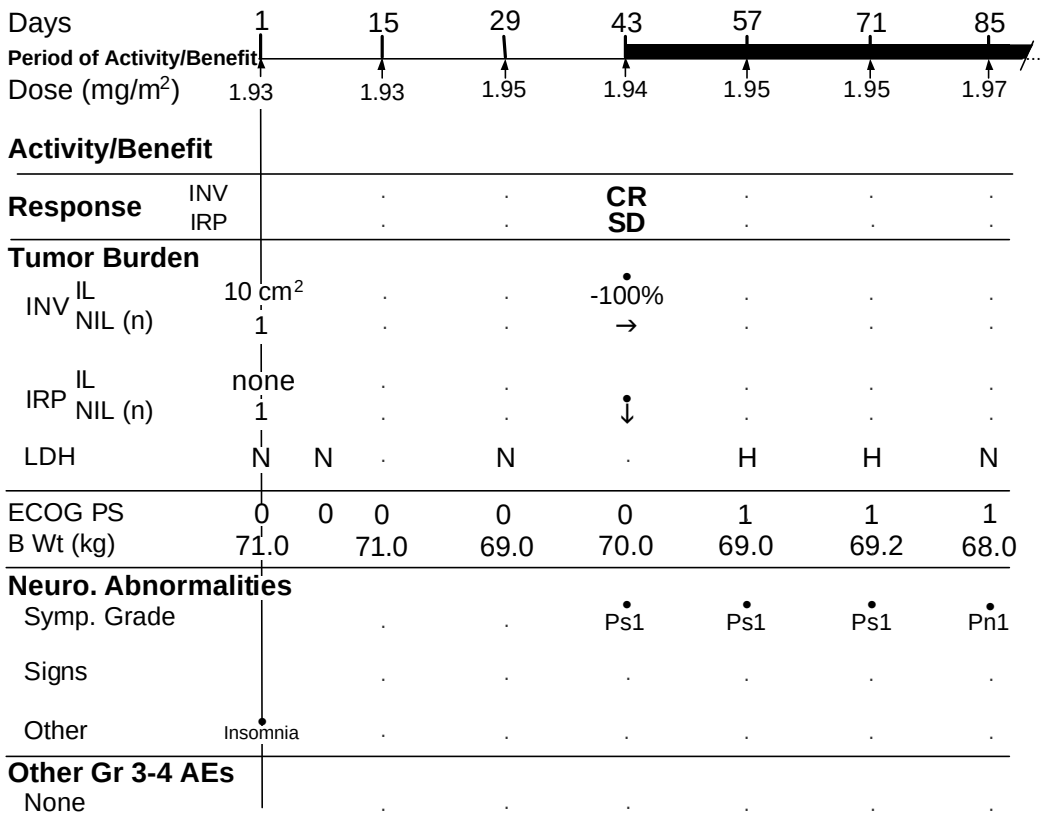


Legend: ↓Decrease →Stable **a** Absent **CR** Complete Response **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **UE** Unable to Evaulate **uns** Unstable **W** Weakness

FIGURE 57. Graphical Presentation of Efficacy and Safety for Patient 33-06 (continued)

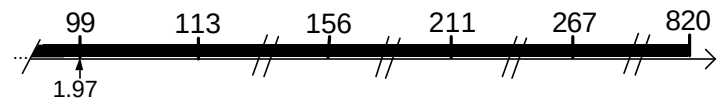
2 Prior Systemic Therapies	47-year-old man Stage IV DLBCL, IPI 1 Per Protocol Ineligible (Bulky disease not measurable per IRP) Refractory to Last Qualifying Therapy	IRP Best Response: PR SPD Change: resolved Duration of Response: n/a Time to Progression: >8.8 mo Survival: >26.9 mo, alive with no evidence of disease
1. CHOP x4; minor response. 2. ICE x3 + Rituximab x4; PD. 3. XRT to neck & Waldeyer's ring; PR of 4 mo.		

Patient 33-06 continued

By the final evaluation on Day 267, they acknowledged that the mediastinal disease was totally resolved, but declared it to be a PR only, stating that the repeat bone marrow biopsy had been taken from the opposite iliac crest as tested at study entry.

Despite the discordance among the IRP oncologists, all reviewers agreed that there was no evidence of the mediastinal mass on Day 267, his last day on study. Given that the Investigator considered this mass to have resolved completely from Day 43 and that the IRP radiologist considered it to be at least a PR from that visit as well, it is likely that the residual disease was minimal throughout the trial. Moreover, his last dose of VSLI was on Day 99 (2 doses after CR) and he was followed on study for an additional 6 months without any evidence of progression.

At his last survival follow-up (post study), the Investigator confirmed that he remained free of disease on Day 820, having received no other lymphoma therapies after the VSLI study. Therefore, considering the full weight of evidence, INEX believes that this case manifested objective evidence of a major response to VSLI, but in view of the fact that the bone marrow biopsy was not repeated, it can't be classified as a CR. Nonetheless, the patient was continuously free of recurrent disease for >26 months. This important response occurred in a patient with refractory disease that did not respond to any previous chemotherapy. VSLI therapy provided >2.1 years of disease-free survival for this patient with refractory DLBCL.



Activity/Benefit

Response	INV	**CR**	·	**CR**	**CR**	**CR**	·
	IRP	**SD**	·	**SD**	**SD**	**PR**	·
Tumor Burden							
INV	IL	-100%	·	-100%	-100%	-100%	·
	NIL (n)	→	·	→	→	→	·
IRP	IL	·	·	·	·	·	·
	NIL (n)	→	·	→	→	resolved	·
LDH		N	N	H	·	N	·
ECOG PS		2	1	1	1	1	·
B Wt (kg)		68.0	68.0	71.0	72.0	74.0	·
Neuro. Abnormalities							
Symp. Grade		Ps1 W1	Nu1 Ps1 W2	Nu1 Ps1 W1	Nu1 Ps1	Nu1 Ps1 W2	·
Signs		·	·	·	unsG Gr1 aR	unsG Gr1 aR	·
Other		Polyneuropathy Gr1	Polyneuropathy, insomnia	·	·	Polyneuropathy Gr1, insomnia	·
Other Gr 3-4 AEs							
None		·	·	·	·	·	·

Legend: ↓Decrease →Stable **a** Absent **CR** Complete Response **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **SD** Stable Disease **UE** Unable to Evaulate **uns** Unstable **W** Weakness

FIGURE 58. Graphical Presentation of Efficacy and Safety for Patient 01-13

4 Prior Systemic Therapies	50-year-old man	IRP Best Response: SD SPD Change: decreased
1. CHOP x8; PR of 5 mo. 2. XRT; unknown response. 3. (ESHAP + ritux.) x4; PD. 4. (Paclitaxel + topo.) x4; PR of 1 mo. 5. (Ritux. + cyclophos.); unknown response.	Stage I DLBCL, IPI 2 Per Protocol Ineligible (Bulky disease not measurable per IRP) Sensitive to Last Qualifying Therapy	Duration of Response: n/a Time to Progression: >5.6 mo Survival: 8.5 mo

This 50-year-old Caucasian man with Stage I DLBCL had received 4 combination regimens and 1 course of radiation therapy in the 2.9 years since his first diagnosis. His disease was categorized as sensitive to last qualifying therapy, given that progression was noted >3 months later. But he clearly had difficult-to-treat disease from the time of diagnosis and never achieved a CR. He had a complicated history at study entry, with discitis treated with chronic antibiotics and significant cytopenias from his previous chemotherapies.

He had bulky gastrohepatic and retroperitoneal adenopathy and a bony metastasis in his spine. The IRP radiologist declared the bulky disease to be assessable, but not measurable and therefore could not identify any lesions to be tracked as indicator lesions. The first evidence of antitumor activity was the immediate normalization of his LDH after the 1st cycle of VSLI and resolution of the palpable abdominal mass after 2 cycles. His rapid weight loss slowed after the 1st cycle and stopped after 2 cycles. CT evaluations were provided on Days 56, 105, and 166 and although the IRP radiologist qualitatively assessed SD, PR and PD on those days, respectively, the IRP oncologists assessed his response as SD throughout. The Investigator chose the bulky gastrohepatic nodal mass as the indicator lesion (55 cm^2) and also concluded that his response was SD on Days 56 and 105 based on a clinical review of the CTs, but subsequent tumor measurements by the site radiologist recorded a 56% reduction from baseline size, which would have supported a PR at Day 105. By Day 166, the Investigator declared PD due to new disease noted on the abdominal CT, despite a continued decrease in the indicator lesion (a 68% reduction from baseline). His weight loss resumed and his LDH was elevated again, consistent with PD.

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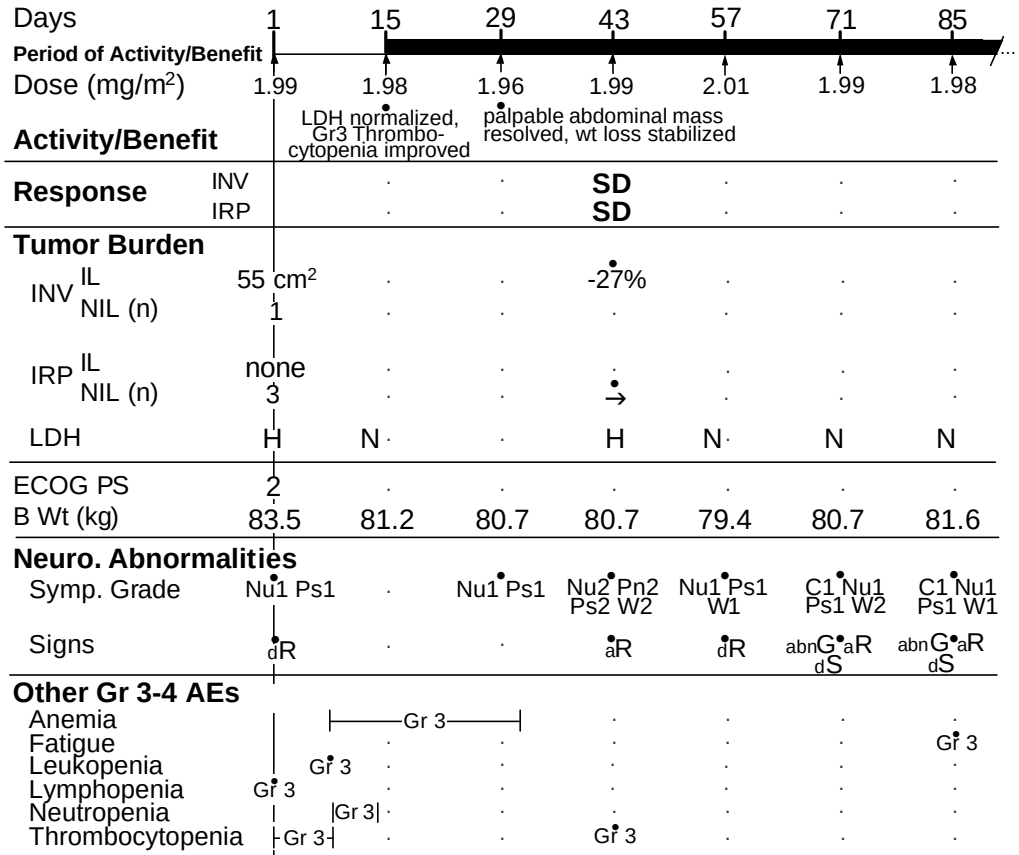


Legend: ↓Decrease ↑Increase →Stable **a** Absent **abn** Abnormal **C** Constipation **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **SD** Stable Disease **UE** Unable to Evaluate **V** Vibration **W** Weakness

FIGURE 58. Graphical Presentation of Efficacy and Safety for Patient 01-13 (continued)

4 Prior Systemic Therapies 1. CHOP x8; PR of 5 mo. 2. XRT; unknown response. 3. (ESHAP + ritux.) x4; PD. 4. (Paclitaxel + topo.) x4; PR of 1 mo. 5. (Ritux. + cyclophos.); unknown response.	50-year-old man Stage I DLBCL, IPI 2 Per Protocol Ineligible (Bulky disease not measurable per IRP) Sensitive to Last Qualifying Therapy	IRP Best Response: SD SPD Change: decreased Duration of Response: n/a Time to Progression: >5.6 mo Survival: 8.5 mo

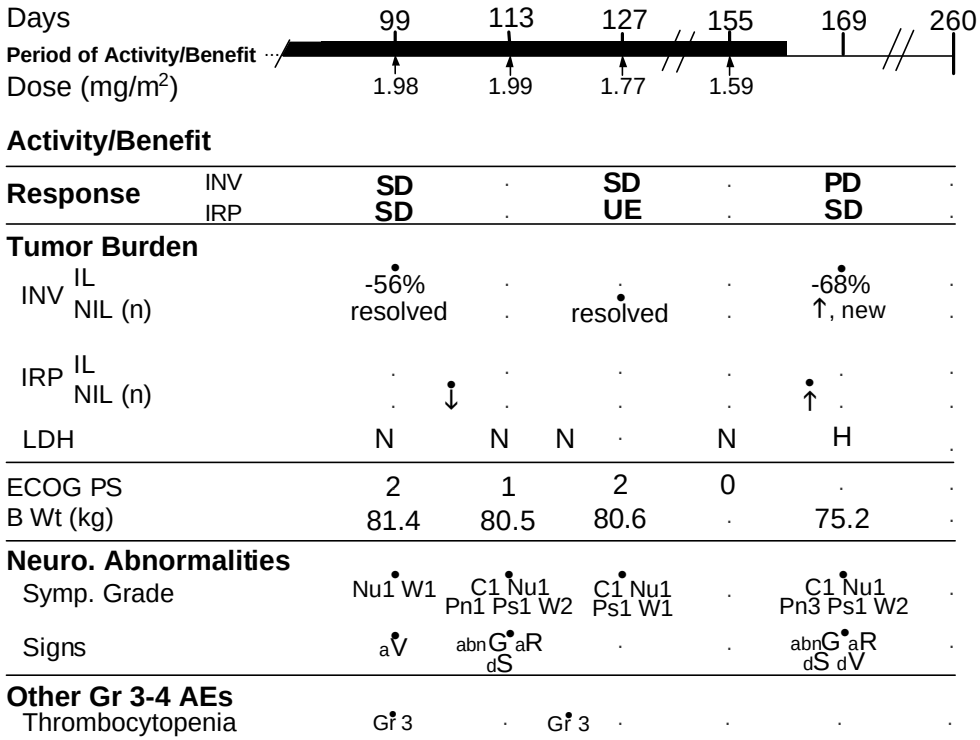
Patient 01-13 continued

He received 11 cycles of VSLI (21.2 mg/m^2 total), the last two at reduced doses. His unstable anemia from study entry, worsened to Grade 3 after the first dose and required transfusion and erythropoietin support throughout the study. Similarly, his preexisting Grade 2 neutropenia worsened to Grade 3 and required treatment with filgrastim. He had Grade 3 thrombocytopenia at study entry and this improved to Grade 2 for most of the study.

Despite having had 3 prior neurotoxic agents (vincristine, cisplatin, and paclitaxel), he tolerated VSLI well, with minimal changes to his preexisting residual Grade 1 neuropathy. He experienced no significant GI toxicity. His ECOG PS improved from 2 to intermittent scores of 1 and 0.

According to both the IRP and the site radiologist evaluations, this patient probably achieved a PR, although the reported best response by the IRP oncologists and the Investigator (based on a clinical review of CTs) was SD only. His time to progression was 5.5 months by the Investigator assessment and >5.6 months by the IRP. This was a longer time to progression than had been achieved with his 2nd-line salvage regimen of ESHAP and rituximab, or with his 3rd-line regimen of paclitaxel and topotecan.

He died on Day 260 (Cycle 11, Day 106) with disease status unknown for an overall survival of 8.5 months after his first dose of VSLI.



Legend: ↓Decrease ↑Increase →Stable **a** Absent **abn** Abnormal **C** Constipation **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **SD** Stable Disease **UE** Unable to Evaluate **V** Vibration **W** Weakness

FIGURE 59. Graphical Presentation of Efficacy and Safety for Patient 01-14

3 Prior Systemic Therapies	75-year-old woman	IRP Best Response: SD SPD Change: -38%
1. (IDSHAP, MBIDCOS, MINE) x7; CR of 14 mo.	Stage III Follicular lymphoma Gr 2, IPI 3	Duration of Response: n/a
2. ASHAP, M-BACOS; CR of ~3.5 yr.	Per Protocol Ineligible (Histology)	Time to Progression: 7.1 mo
3. MINE; CR of ~2.8 yr.	Sensitive to Last Qualifying Therapy	Survival: >36.1 mo, alive with no evidence of disease

This 75-year-old Caucasian woman with sensitive Stage III follicular lymphoma (Grade 2) had relapsed after 3 intensive courses of combination chemotherapy including 2 with vincristine and 2 with cisplatin. She achieved a CR three times. She had an IPI score of 3 at study entry with numerous axillary nodes that were "too numerous to count" as well as mediastinal, cervical, inguinal nodes, and a measurable bone lesion. She was histologically ineligible for the study according to the Central Pathology Review, however the elevated LDH and ß$_2$-microglobulin levels at study entry suggest an aggressive lymphoma. The IRP chose 5 lesions as indicator lesions and the Investigator chose 2.

The first evidence of VSLI antitumor activity was a decrease in the size of the palpable nodes noted after 2 doses of VSLI (Day 26). After 3 cycles of VSLI, the nodes were no longer palpable or were within normal size limits. Based on physical examination findings and a clinical review of the CTs, the Investigator determined her response to be a PR. Retrospective tumor measurements by the site radiologist documented a 26% reduction in the indicator lesions, which would have supported only SD. The IRP evaluated her response throughout the study as SD, with a 38% reduction in her measured lesions from 52.8 to 32.8 cm^2.

She tolerated 12 doses of VSLI (24.3 mg/m^2 total) extremely well, despite significant previous exposure to neurotoxic agents, with ECOG scores almost always 0. Her worst neurotoxicity was Grade 2 numbness of her hands and feet, beginning at Cycle 9. She had minimal GI complaints, with only Grade 1 constipation and no Grade 3-4 AEs of any nature. Her lab values were stable, with only a small fall in hemoglobin and white blood cell count in the middle of the study. Her body weight drifted down slowly over the 7 months on study (6% loss in total).

Her disease progressed 2 months after the last dose of VSLI, with a time to progression of 7.1 months. She was alive with no evidence of disease at the last survival follow-up 36.1 months after her first VSLI dose, presumably having received some additional therapy.

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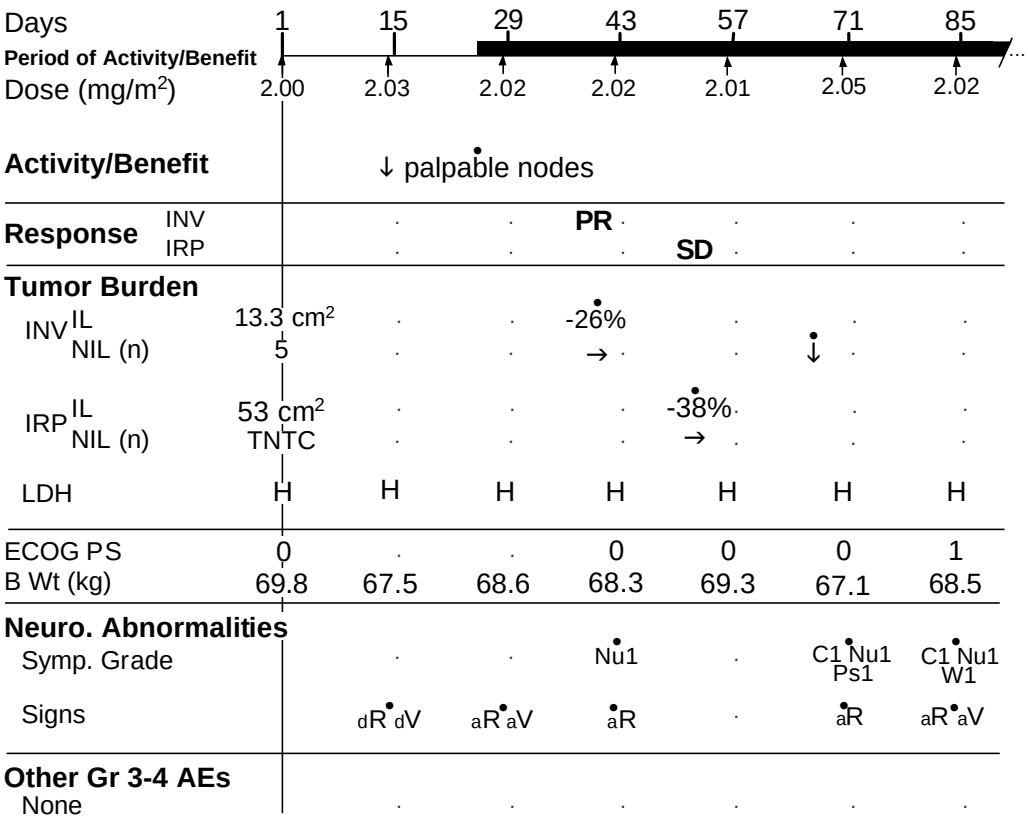
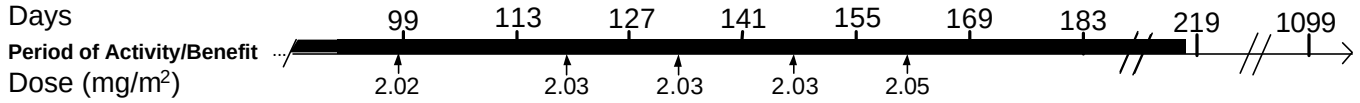


Legend: ↓Decrease ↑Increase →Stable **a** Absent **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **SD** Stable Disease **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 59. Graphical Presentation of Efficacy and Safety for Patient 01-14 (continued)

3 Prior Systemic Therapies	75-year-old woman	IRP Best Response: SD SPD Change: -38%
1. (IDSHAP, MBIDCOS, MINE) x7; CR of 14 mo.	Stage III Follicular lymphoma Gr 2, IPI 3	Duration of Response: n/a
2. ASHAP, M-BACOS; CR of ~3.5 yr.	Per Protocol Ineligible (Histology)	Time to Progression: 7.1 mo
3. MINE; CR of ~2.8 yr.	Sensitive to Last Qualifying Therapy	Survival: >36.1 mo, alive with no evidence of disease

Patient 01-14 continued



Activity/Benefit

Response	INV	PR		SD				SD		PD
	IRP			SD				SD		PD
Tumor Burden										
INV	IL	-38%				resolved		→		-44%
	NIL (n)	→			→			→		↑, new
IRP	IL			-35%				-38%		+14%
	NIL (n)			→				→		→
LDH		H		H		H		H		H
ECOG PS		0		0	0	0	0	0		0
B Wt (kg)		68.0		67.9	67.2	67.8	66.5	65.7		66.9
Neuro. Abnormalities										
Symp. Grade		Nu1		Nu1	Nu2	Nu2	Nu2			
Signs		aR aV		aR aV	aR dV	aR dV	aR dV			
Other Gr 3-4 AEs										
None										

Legend: ↓Decrease ↑Increase →Stable **a** Absent **CR** Complete Response **d** Diminished **G** Gait **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **Pn** Pain **PR** Partial Response **Ps** Paresthesia **R** Reflexes **S** Strength **SD** Stable Disease **TNTC** Too numerous to count **V** Vibration **W** Weakness

FIGURE 60. Graphical Presentation of Efficacy and Safety for Patient 33-04

3 Prior Systemic Therapies	42-year-old woman Stage III DLBCL, IPI 1 Per Protocol Ineligible (only 1 combination chemotherapy regimen after transformation) Sensitive to Last Qualifying Therapy	IRP Best Response: SD SPD Change: -30% Duration of Response: n/a Time to Progression: 11.2 mo Survival: >27.8 mo, alive with disease
1. ProMACE-CytaBOM x6; CR of ~6 mo. 2. (Dex., etop., ifos., cisplatin) x4; PR followed immediately by next treatment. 3. XRT x2; PR of ~7 mo. 4. XRT; PR of 16 mo. 5. ESHAP x6; PR of ~8 mo, TTP of 12 mo.		

This 42-year-old Caucasian woman with follicular lymphoma that had transformed to chemosensitive Stage III DLBCL, had received 3 combination chemotherapy regimens and 3 courses of radiation, and relapsed with bulky retroperitoneal and mesenteric disease. At study entry, she had Grade 2 thrombocytopenia that precluded treatment with standard myelotoxic chemotherapeutic events.

Her best response was a PR per the Investigator and SD per the IRP and both documented a time to progression of 11.2 months, which was the same as she achieved with her most recent prior chemotherapy (ESHAP).

Despite having received 3 prior neurotoxic therapies, she tolerated 16 cycles of VSLI well (33.7 mg/m^2 total), with no dose reductions or delays and neurotoxicities limited to Grade 1-2 paresthesias of the hands and feet. She had no constipation. Her ECOG PS dropped from 0 to 1 for four assessments (Cycles 4-7) and was normal for the remaining 9 months on study. She had no notable hematologic toxicity and her only significant adverse event was Grade 3 alopecia.

At last contact she was alive, with disease, with a survival of >27.8 months. VSLI provided 1 year without documented progression, in a patient who could not have been treated with standard myelosuppressive chemotherapeutic agents.

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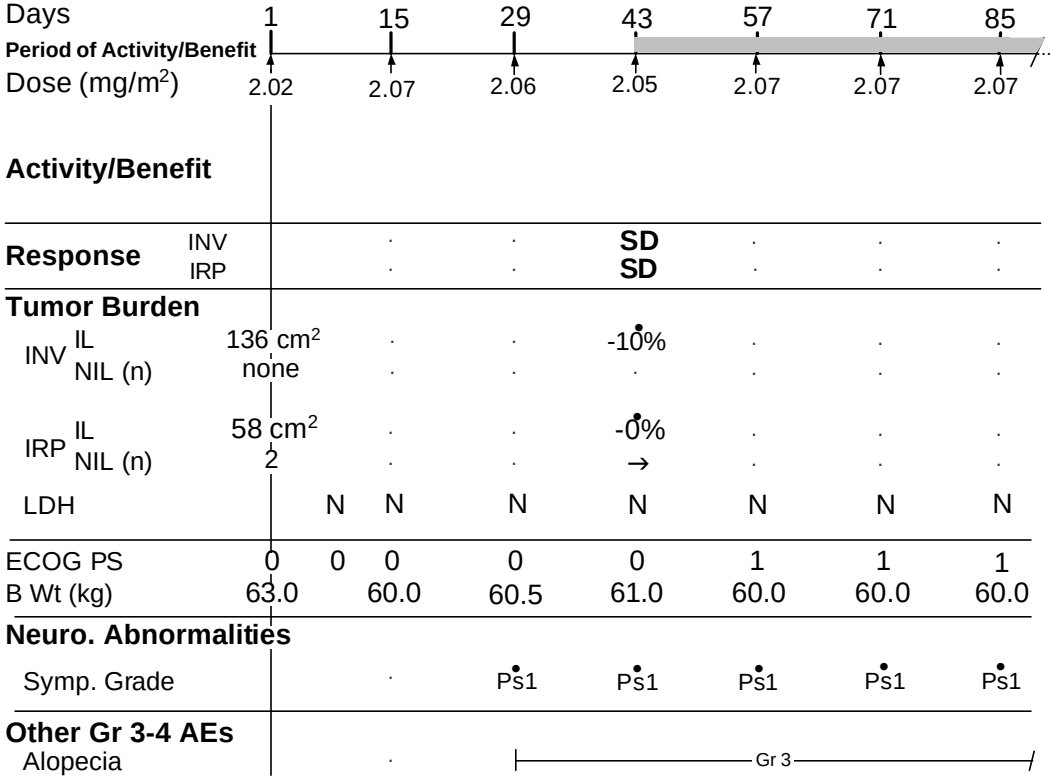
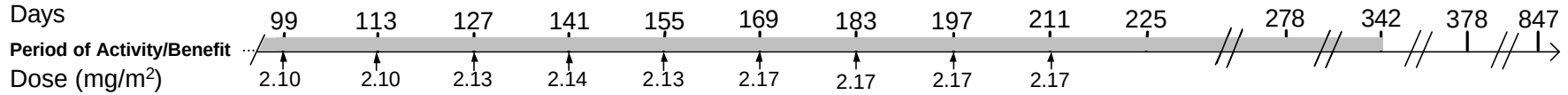


Legend:
↑Increase →Stable **CR** Complete Response **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **PD** Progressive Disease **PR** Partial Response **Ps** Paresthesia **SD** Stable Disease **UE** Unable to Evaulate

FIGURE 60. Graphical Presentation of Efficacy and Safety for Patient 33-04 (continued)

3 Prior Systemic Therapies	42-year-old woman	IRP Best Response: SD SPD Change: -30%
1. ProMACE-CytaBOM x6; CR of ~6 mo. 2. (Dex., etop., ifos., cisplatin) x4; PR followed immediately by next treatment. 3. XRT x2; PR of ~7 mo. 4. XRT; PR of 16 mo. 5. ESHAP x6; PR of ~8 mo, TTP of 12 mo.	Stage III DLBCL, IPI 1 Per Protocol Ineligible (only 1 combination chemotherapy regimen after transformation) Sensitive to Last Qualifying Therapy	Duration of Response: n/a Time to Progression: 11.2 mo Survival: >27.8 mo, alive with disease



Activity/Benefit			Improved ECOG PS											
Response	INV	**SD**				**PR**				**SD**		**SD**	**PD**	**PD**
	IRP	**SD**			**SD**						**UE**	**SD**	**PD**	**PD**
Tumor Burden														
INV	IL	-4%				-59%				-43%		-45%	-31%	-4%
	NIL (n)													
IRP	IL	-10%			-23%					-30%		-12%	+12%	+24%
	NIL (n)	→			→					→		→	→	↑
LDH		N	N	N	N	N	N	N	N	N	N	N	N	N
ECOG PS		1	0	0	0	0	0	0	0	0	0	0	0	0
B Wt (kg)		58.5	58.0	57.0	56.0	57.0	56.0	56.0	56.0	55.0	55.0	56.0	57.0	57.0
Neuro. Abnormalities														
Symp. Grade		Ps1	Ps1	Ps1	Ps1	Ps1	Ps1	Ps1	Ps1	Ps2	Ps2	Ps2	Ps2	Ps2
Other Gr 3-4 AEs														
Alopecia		Gr 3												

Legend:
↑Increase →Stable **CR** Complete Response **Gr** Grade **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **PD** Progressive Disease **PR** Partial Response **Ps** Paresthesia **SD** Stable Disease **UE** Unable to Evaulate

FIGURE 61. Graphical Presentation of Efficacy and Safety for Patient 01-05

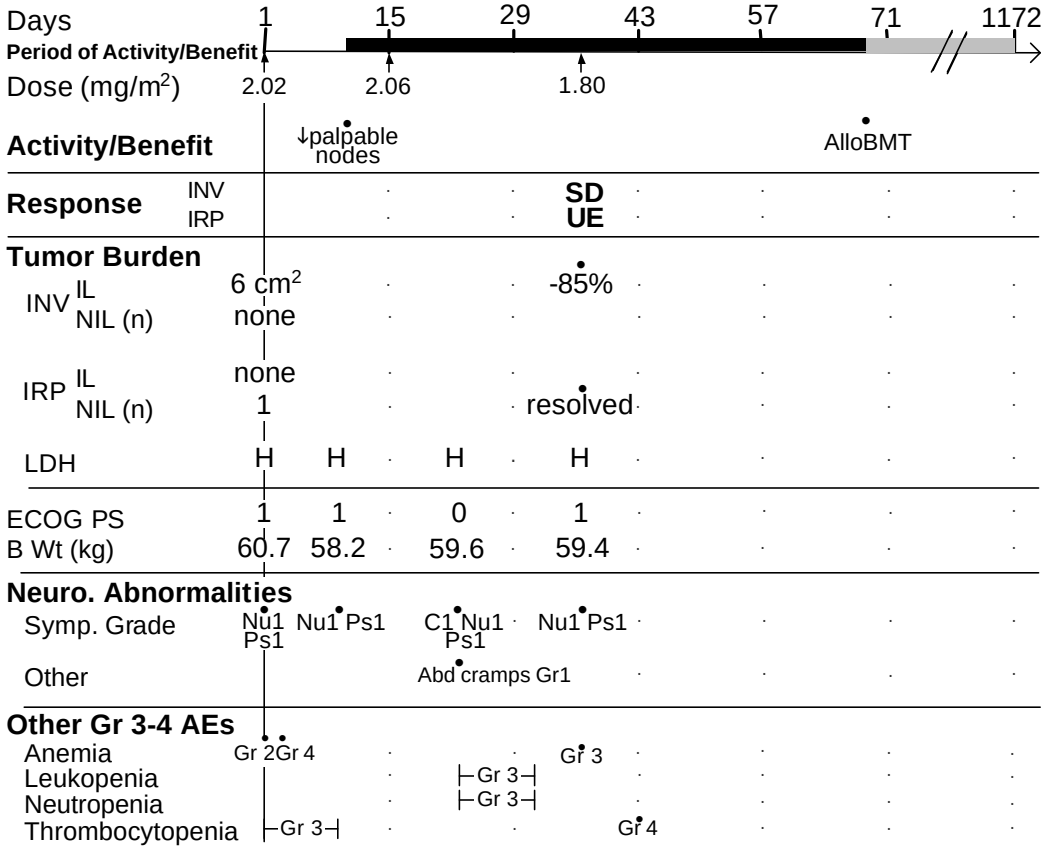
4 Prior Systemic Therapies	47-year-old woman	IRP Best Response: UE SPD Change: -100%
1. CHOP x3; minor response. 2. ESHAP x1; PD. 3. (MINE/rituximab) x3; PR 4. Cyclophos. x1, BEAM → transplant; CR of 5 mo.	Stage I Follicular Gr 3B lymphoma, IPI 1 Per Protocol Ineligible (Histology, only lesion <2.0 cm per IRP) Sensitive to Last Qualifying Therapy	Duration of Response: n/a Time to Progression: >1.5 mo Survival: >38.5 mo, alive with no evidence of disease

This 47-year-old Hispanic woman with Stage I sensitive follicular Grade 3B lymphoma had received 4 prior systemic therapies and an autologous stem cell transplant. She had primary refractory disease, with only a minor response to 1st-line CHOP. The transplant was her most recent therapy, to which she achieved a CR that lasted 5 months. She had significant Grade 3 cytopenias at study entry and was technically ineligible because of her poor hematologic status.

The final IRP oncology opinion was that she was not evaluable for response, as her only lesion was <2.0 cm. The IRP radiologist, however, documented that her disease had totally resolved by Day 31 and considered her response to be a CR. Her palpable axillary node was reduced by Day 10 and completely resolved by Day 24, but her LDH remained elevated. The Investigator assessed her response as SD based on this information plus a clinical review of the CTs. Measurements provided retrospectively by the site radiologist would have supported a response assessment of PR, with total resolution of her two axillary nodes and an elevated LDH.

She received 3 cycles of VSLI, with 1 dose reduction, and was supported on study with filgrastim and RBC and platelet transfusions. It is not clear that the transfusion requirement was a change during VSLI treatment, as the Investigator noted that she had had persistent cytopenias since receiving her 1st-line CHOP therapy. Her residual Grade 1 peripheral neuropathy remained stable during the study. She had only one episode of Grade 1 constipation and abdominal cramping. Her ECOG PS improved transiently from 1 to 0.

After response to VSLI, she was eligible for and received an allogeneic bone marrow transplant on Day 65. As a result, her time to progression is underestimated at >1.5 months. As of Day 1172, she was alive with no evidence of disease. Her survival was >38.5 months from her first dose of VSLI and >36.4 months after her post-study transplant.



Legend: ↓Decrease **abd** Abdominal **AlloBMT** Allogeneic Bone Marrow Transplant **C** Constipation **CR** Complete Response **Gr** Grade **H** High **IL** Indicator Lesions **INV** Investigator **IRP** Independent Review Panel **N** Normal **NIL** Non-indicator lesions **Nu** Numbness **PD** Progressive Disease **PR** Partial Response **PS** Paresthesia **SD** Stable Disease **UE** Unable to Evaluate