Oncology Division Advisory Committee (ODAC)

Briefing Document

Fulfillment of the Accelerated Approval Requirements for the Non-Small Cell Lung Cancer Indication:

"Ethyol® (Amifostine) Reduces the Cumulative Renal Toxicity Associated with Repeated Administration of Cisplatin in Patients with Advanced Non-Small Cell Lung Cancer"

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1 INTRODUCTION

ETHYOL® (amifostine) is an organic thiophosphate known chemically as ethanethiol, 2-[(3-aminopropyl)amino] dihydrogen phosphate (ester). It is a phosphorylated aminothiol prodrug exerting its effect as a selective cytoprotective agent for normal tissues against the toxicities of chemotherapy and/or radiation. The selective cytotoxic effect of amifostine has been demonstrated in preclinical and clinical trials of chemotherapy and/or radiotherapy with or without amifostine pretreatment.

The currently approved indications for intravenous administration of ETHYOL are:

ETHYOL (amifostine) is indicated to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small cell lung cancer.

ETHYOL (amifostine) is indicated to reduce the incidence of moderate to severe xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands.

The indication in non-small cell lung cancer (NSCLC) was approved under the Accelerated Approval Regulations on 15 March 1996. This approval was based on the results of a Phase II study of amifostine (740 and 910 mg/m^2), cisplatin (120 mg/m^2), and vinblastine (5 mg/m^2) in 25 patients with Stage IV NSCLC[1] (WR-0032) and on a commitment to the FDA by U.S. Bioscience, Inc. (West Conshohocken, PA) to conduct a controlled, clinical trial in patients with advanced NSCLC. WR-0053, a Phase III Trial of Intensive Cisplatin and Vinblastine ± Amifostine (Ethyol®) in Patients with Stage IIIB or IV NSCLC, was ongoing at this time and was offered by U.S. Bioscience, Inc. and accepted by the Agency, if positive, to fulfill the Accelerated Approval commitment.

WR-0053 was conducted from 16 December 1994 to 30 June 1999, with final results submitted to the Agency on 24 June 2002 as part of a pre-supplemental new drug application (sNDA) Briefing Package (Serial #493). Included in this submission was a meta-analysis of survival data from the Phase III experience of amifostine in controlled, clinical trials supporting the contention that amifostine did not affect the antitumor efficacy of anticancer therapy. On 26 July 2002, in a response to the sNDA Briefing Document submitted by MedImmune Oncology, Inc., the FDA concluded that, although study WR-0053 demonstrated nephroprotection, it did not appear to demonstrate that amifostine had no affect on antitumor efficacy. In light of this, the Agency stated that the completion of an appropriately sized, adequate and well-controlled study of cisplatin-based chemotherapy in NSCLC demonstrating that amifostine does not affect antitumor efficacy in addition to showing protection from cisplatin-induced nephrotoxicity should be performed. The elements of this trial design were discussed with the Agency on 23 January 2003 in a face-to-face meeting requested by the company. The purpose of this meeting was to seek the FDA's guidance for the design of a trial necessary to fulfill the Phase IV commitment.

This ODAC Briefing Document summarizes the results of the primary endpoints of WR-0053 (i.e., nephroprotection and no reduction in antitumor efficacy) as well as the results of the meta-

analysis of survival data from the Phase III experience of amifostine in randomized, controlled clinical trials. In addition, this document presents the trial design elements discussed at the 23 January 2003 meeting with the agency of a new, adequate and well-controlled trial of cisplatin-based chemotherapy ± amifostine in patients with advanced NSCLC. Also, some of the issues involved in the implementation of such a trial will be described.

2 WR-0053: A PHASE III TRIAL OF INTENSIVE CISPLATIN AND VINBLASTINE ± AMIFOSTINE (ETHYOL®) IN PATIENTS WITH STAGE IIIB OR IV NON-SMALL CELL LUNG CANCER

WR-0053 was a Phase III, open-label, randomized, two-arm, parallel-group, multicenter, multinational study designed to determine if pretreatment with amifostine increases the therapeutic index of comparable cisplatin doses when combined with vinblastine in the treatment of patients with advanced NSCLC. Eligible patients included men or women, 18 years of age or older, with histologically or cytologically verified Stage IIIB or IV NSCLC. Other eligibility criteria included measurable or evaluable disease, no prior chemotherapy or biological therapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate bone marrow, renal, and hepatic function. In this study, patients were randomized to receive cisplatin (120 mg/m^2) and vinblastine (3.75 mg/m^2) ± amifostine (740 mg/m^2) every 4 weeks until disease progression, unacceptable toxicity, or other reasons for patient withdrawal. Stratification factors at randomization included treatment center, histology (adenocarcinoma vs. squamous vs. other), disease stage (IIIB vs. IV), ECOG performance status (0 vs. 1), and prior radiation therapy (yes vs. no).

WR-0053 was conducted between 16 December 1994 and 30 June 1999. A total of 366 patients from 28 study centers in the United States of America (15 centers), Europe (10 centers), and Africa (3 centers) were randomized to receive cisplatin and vinblastine ± amifostine in this study. Of these patients, 185 patients were randomized to receive amifostine, cisplatin, and vinblastine (amifostine arm) and 181 patients (180 of which were included in the intent-to-treat data set) and were randomized to receive cisplatin and vinblastine (control arm). Both treatment arms were well balanced in terms of baseline demographic and tumor characteristics, and both treatment arms received comparable doses of cisplatin and vinblastine. The median dose intensity of amifostine was 100%.

The primary endpoint of this study was an improved therapeutic index defined as follows:
1. No reduction in antitumor efficacy with a reduction in cisplatin-related nephrotoxicity; or
2. Increase in antitumor efficacy.

- No reduction in antitumor efficacy was based on the following conditions:
  a. No more than 7% reduction in tumor response rate;
  b. >0.7 two-sided 95% lower confidence limit of hazard ratio for time to progression; and
  c. >0.7 two-sided 95% lower confidence limit of hazard ratio for survival time.

- Cisplatin-related nephrotoxicity was defined as 25% or more decrease from baseline in creatinine clearance at the completion of therapy.

2.1 Nephrotoxicity Endpoint

WR-0053 demonstrated that the addition of amifostine to the cisplatin and vinblastine regimen resulted in a statistically significant reduction of cisplatin-related nephrotoxicity defined as ≥25% decrease in creatinine clearance from baseline to completion of therapy.

As shown in Exhibit 1, the incidence of protocol-defined cisplatin-related nephrotoxicity was statistically significantly lower in patients treated with amifostine as compared with control patients ($p<0.001$). Nephrotoxicity occurred in 49 (28%) patients in the amifostine arm and 87 (49%) patients in the control arm. When stratified by cisplatin dose, the incidence of cisplatin-related nephrotoxicity was statistically significantly lower in the amifostine arm versus the control arm ($p<0.001$). Moreover, the cumulative dose to onset of cisplatin-related nephrotoxicity was statistically significantly higher in the amifostine arm (240 mg/m^2) versus the control arm (120 mg/m^2) ($p<0.001$). When nephrotoxicity was analyzed by cycle (a secondary endpoint), the incidence was statistically significantly lower in the amifostine arm versus the control arm at the end of each cycle for cycles 1 through 5 ($p<0.02$) and over all cycles ($p<0.001$).

Exhibit 1 Summary of Cisplatin-Related Nephrotoxicity (ITT Data Set)

	Amifostine + Cisplatin/Vinblastine (N=185)		Cisplatin/Vinblastine (N=180)		P-value
Incidence of Nephrotoxicity[a]					
Yes	49	(28%)	87	(49%)	<0.001[b]
No	128	(72%)	89	(51%)	
Nephrotoxicity by Total Cisplatin Dose					<0.001[c]
≤360 mg/m^2	24/89	(27%)	46/102	(45%)	
361-480 mg/m^2	10/41	(24%)	14/ 25	(56%)	
>480 mg/m^2	15/47	(32%)	27/ 49	(55%)	
Cumulative Cisplatin Dose to Onset of Nephrotoxicity					
Median	240 mg/m^2		120 mg/m^2		<0.001[d]
Range	(107.8-803.4)		(111.1-710.2)		

[a] 12 patients (8 in the amifostine arm and 4 in the control arm) had missing nephrotoxicity data.
[b] P-value based on Fisher's exact test
[c] P-value based on Mantel-Haenszel test
[d] P-value based on log rank test.

2.2 No Reduction in Antitumor Efficacy Endpoint

2.2.1 Tumor Response Rate

Exhibit 2 summarizes the tumor response of patients treated with cisplatin and vinblastine ± amifostine for advanced NSCLC. As shown in this exhibit, 56 (30%) patients in the amifostine arm and 58 (32%) patients in the control arm achieved an objective response (CR or PR) to therapy; this difference was not statistically significant (p=0.735). The difference in tumor response was -2.0%, with a 95% confidence interval of -11.5% to 7.6%. Thus, the protocol-defined criterion of no more than 7% reduction in tumor response rate was met.

Additional analyses of tumor response (i.e., time to objective response and duration of response) were also comparable between the two treatment arms. The median time to objective response was 57 days in the amifostine arm and 58 days in the control arm (p=0.134), and the median duration of response was 118 days in the amifostine and 159 days in the control arm (p=0.268).

Exhibit 2 Tumor Response (ITT Data Set)

	Amifostine + Cisplatin/Vinblastine (N=185)		Cisplatin/Vinblastine (N=180)		P-value
Objective Response					
CR + PR	56	(30%)	58	(32%)	0.735[a]
Difference of Tumor Response	-2.0%				
95% CI (2-Sided)	(-11.5%-7.6%)				
Best Response					
CR	1	(1%)	4	(2%)	
PR	55	(30%)	54	(30%)	
Stable Disease	69	(37%)	48	(27%)	
Progressive Disease	31	(17%)	40	(22%)	
Not Assessable	29	(16%)	34	(19%)	
Time to Objective Response (Days)					
N	56		58		
Median	56.5		57.5		0.134[b]
Range	(32.0-163.0)		(49.0-168.0)		
Duration of Objective Response (Days)					
Median	118		159		0.268[c]
Range	(0.0-589.0)		(4.0-625.0)		

[a] P-value based on Fisher's exact test
[b] P-value based on Wilcoxon rank sum test
[c] P-value based on log-rank test
CR: Complete Response; PR: Partial Response; CI: Confidence Interval

2.2.2 Progression-Free Survival

Exhibit 3 summarizes the progression-free survival results of this study. The median progression-free survival was 4.14 months in the amifostine arm and 4.73 months in the control arm, with a hazard ratio of 0.91 and a 95.2% confidence interval of 0.72-1.15. This difference was not statistically significant (p=0.852, based on Wilcoxon test or p=0.417, based on the log-rank test). Given the lower bound of the two-sided 95.2% confidence interval of 0.72, the

protocol-defined criterion of >0.7 two-sided 95% LCL of hazard ratio for time to progression was met.

Exhibit 3 Progression-Free Survival (ITT Data Set)

	Amifostine + Cisplatin/Vinblastine (N=185)	Cisplatin/Vinblastine (N=180)	P-value
Progression-Free Survival			
Median (months)	4.14	4.73	0.852[a]
Range	(0.0-27.2)	(0.0-22.4)	(0.417)[b]
Hazard Ratio	0.91		
95.2% CI of Hazard Ratio	(0.72-1.15)		

[a] P-value based on Wilcoxon test.
[b] P-value based on log-rank test.

2.2.3 Overall Survival

As shown in Exhibit 4, the median survival was 8.75 months in the amifostine arm and 9.93 months in the control arm, with a hazard ratio of 0.83 and a 95.2% confidence interval of 0.67-1.04. This difference was not statistically significant (p=0.288, based on Wilcoxon test or p=0.097, based on the log-rank test). Given the lower bound of the two-sided 95% confidence interval of 0.67, the protocol-criterion of >0.7 two-sided 95% LCL of hazard ratio for survival time was not met.

Exhibit 4 Overall Survival (ITT Data Set)

	Amifostine + Cisplatin/Vinblastine (N=185)	Cisplatin/Vinblastine (N=180)	P-value
Overall Survival			
Median (months)	8.75	9.93	0.288[a]
Range	(0.1-50.5)	(0.1-61.5)	(0.097)[b]
Hazard Ratio	0.83		
95.2% CI of Hazard Ratio	(0.67-1.04)		

[a] P-value based on Wilcoxon test.
[b] P-value based on log-rank test.

Stratified analyses of overall survival including age, gender, and the stratification factors used at randomization showed the survival of the subset of ECOG Performance Status of 0 (ECOG PS=0) patients as having the most impact on overall survival. Analysis of survival among patients with ECOG PS=0 (75 patients in the amifostine arm and 72 patients in the control arm) showed a median survival of 9.8 months in the amifostine arm versus 17.2 months in the control arm (p=0.026). Since the stratification factors at randomization were well balanced between the two treatment arms, no explanation for this observation has been identified.

The finding of 17.2 months survival among ECOG PS=0 patients in the control arm is not consistent with other randomized trials. In a large randomized trial comparing four platinum-

based chemotherapy regimens in 1,207 patients with advanced NSCLC, the median survival for all 1,207 patients was 8 months and among PS=0 patients, the median survival was 10.8 months.[2] In an earlier randomized trial (EST 1581) of the most active regimens between 1981 and 1985, in which three treatment arms were platinum-based and one arm was a combination of mitomycin C, vinblastine, and cisplatin, the median survival of PS=0 patients was 9 months.[3]

The risk of potential tumor protection in WR-0053 is inconclusive. Objective response rates, progression-free and overall survival did not show any statistically significant differences between the two treatment arms. Objective response rates were 30% in the amifostine arm versus 32% in the control arm (p=0.735), and median progression-free survival was 4.14 months in the amifostine arm and 4.73 months in the control arm (p=0.417, log-rank test), with a hazard ratio of 0.91 and a 95% confidence interval of 0.72-1.15. The tumor response and progression-free survival results met the protocol-defined criteria for no reduction in tumor efficacy. Median survival was 8.75 months in the amifostine arm versus 9.93 months in the control arm. However, analysis of overall survival in the amifostine arm did not meet the protocol-defined criterion for non-inferiority, namely >0.7 two-sided 95% lower confidence limit of hazard ratio.

3 ANTITUMOR EFFICACY DATA FROM THE PHASE III EXPERIENCE WITH AMIFOSTINE

Including WR-0053, five Phase III randomized, controlled studies of amifostine have been completed to date. These trials consist of 1,326 patients with various cancers, including head and neck (WR-0038), rectal (WR-9001), ovarian (WR-0001), and NSCLC (WR-0053 and WR-0056). Final study reports for each of these trials have been submitted to the FDA. In each of these trials, preservation of antitumor efficacy was assessed using the parameters of tumor response, progression-free survival, and overall survival.

3.1 Tumor Response, Progression-Free Survival, and Overall Survival

Exhibit 5 summarizes the tumor response data from the Phase III randomized, controlled trials of amifostine.

Exhibit 5 Summary of Tumor Response Data

	Response Rate (%)			
	Amifostine Arm	Control Arm	Difference in Rates	95% CI (2-sided)
WR-0053: NSCLC (N=365)[a]	30%	32%	–2%	–11.5%, 7.6%
WR-0056: NSCLC (N=300)[a]	37%	34%	3%	–7.2%, 14.4%
WR-0001: Ovarian (N=242)[b]	37%	28%	9%	–2.9%, 20.5%
WR-0038: Head & Neck (N=315)[c]	54%	58%	–4%	–16.1%, 7.9%
WR-9001: Rectal (N=104)[d]	16%	8%	8%	–4.2%, 21.2%

[a] Tumor response based on objective response rate (CR + PR)
[b] Tumor response based on pathologic tumor response rate (CR + PR)
[c] Tumor response based on locoregional tumor control.
[d] Tumor response based on complete response rate.

Exhibit 6 summarizes the progression-free survival data from the Phase III randomized, controlled trials of amifostine. As seen in this exhibit, the progression-free survival hazard ratios appear close to 1.0.

Exhibit 6 Summary of Progression-Free Survival Data

	Median (months)			
	Control Arm	Amifostine Arm	Hazard Ratio	95% CI (2-sided)
WR-0053: NSCLC (N=365)	4.73	4.14	0.91	0.72 - 1.15
WR-0056: NSCLC (N=300)	3.95	4.27	1.12	0.85 - 1.48
WR-0001: Ovarian (N=242)	18.1	15.8	0.98	0.64 - 1.4
WR-0038: Head & Neck (N=315)	8.7	10.8	1.00	0.70 - 1.42
WR-9001: Rectal (N=104)	5.8	6.8	1.12	0.73 - 1.71

Exhibit 7 summarizes the overall survival data for the five Phase III randomized, controlled trials of amifostine. As seen in this exhibit, the overall survival hazard ratios for four of the five studies appear close to 1.0. In WR-0053, the protocol-defined criterion for the survival endpoint, namely >0.7 lower bound of the two-sided 95% CI for the survival hazard ratio, was not met.

Exhibit 7 Summary of Overall Survival Data

	Median (months)			
	Control Arm	Amifostine Arm	Hazard Ratio	95% Confidence Interval
WR-0053: NSCLC (N=365)	9.9	8.8	0.831	0.666 - 1.037
WR-0056: NSCLC (N=300)	9.2	9.7	1.014	0.795 - 1.292
WR-0001: Ovarian (N=242)	31.8	31.3	0.971	0.688 - 1.372
WR-0038: Head & Neck (N=315)	15.1[a]	21.7[a]	1.327	0.873 - 2.107
WR-9001: Rectal (N=104)	12.6	15.0	1.000	0.647 - 1.546

[a] Time to 75% survival (median survival has not been reached).

3.2 Meta-Analysis of Phase III Survival Data

A meta-analysis was performed on the survival data from the five Phase III randomized, controlled trials. This analysis contained a total of 1,326 patients. The different weighting schemes used in the meta-analysis for summarizing the trials and estimating mean hazard ratios and corresponding confidence intervals as well as the results of this meta-analysis are summarized in Exhibit 8. Overall, regardless of how the analysis was weighted, the hazard ratio estimates were in proximity of 1.0 with lower limits of the two-sided 95% confidence interval of >0.84. These findings do not suggest that antitumor efficacy of cytotoxic therapy is altered in cancer patients receiving amifostine.

Exhibit 8 Meta-Analysis of Survival Data From Phase III Experience of Amifostine (N=1,327 Patients)

Weight of Studies	Hazard Ratio	95% Confidence Intervals	
		Lower Limit	Upper Limit
Equal Weight	1.017	0.872	1.185
Weight of Sample Size	1.014	0.875	1.175
Weight of 1/SE	0.988	0.861	1.133
Weight of $1/SE^2$	0.962	0.843	1.098

SE: standard error

The Phase III experience and the meta-analysis described above were previously submitted to the FDA as part of the pre-sNDA Briefing Document on July 26, 2002.

4 FDA ASSESSMENT OF THE RESULTS FOR WR-0053

The final results for WR-0053 were submitted to the Agency on 24 June 2002 as part of a pre-sNDA Briefing Package (Serial #493). On 26 July 2002, in a response to this submission, the FDA concluded that, although study WR-0053 demonstrated nephroprotection, it did not appear to demonstrate that amifostine had no affect on antitumor efficacy. In light of this, the Agency stated that the completion of an appropriately sized, adequate and well-controlled study of cisplatin-based chemotherapy in NSCLC demonstrating that amifostine does not affect antitumor efficacy in addition to showing protection from cisplatin-induced nephrotoxicity should be performed.

5 ELEMENTS OF A TRIAL DESIGN REQUIRED BY THE FDA FOR FULFILLMENT OF THE POST-APPROVAL COMMITMENT FOR THE NSCLC INDICATION

Based on the finding that WR-0053 did not meet the criteria for no affect on antitumor efficacy (although it did demonstrate protection from cisplatin-induced nephrotoxicity), the FDA is asking that MedImmune Oncology conduct an appropriately sized, adequate and well-controlled study of cisplatin-based chemotherapy in NSCLC demonstrating that amifostine does not affect antitumor efficacy in addition to showing protection from cisplatin-induced nephrotoxicity to fulfill the Accelerated Approval requirements of the NSCLC indication.

In light of the request for this new trial, MedImmune Oncology met with the FDA on 23 January 2003 to seek the guidance of the Agency regarding the appropriate trial design elements for such a trial. The main focus of this discussion was the non-inferiority endpoint of the trial and its effect on the sample size determination. Other issues discussed included overall study design, patient population, primary endpoints, and treatment regimens. One important outcome of the meeting was that the FDA encouraged the use of a surrogate for survival such as response rate or

time to progression (TTP) as the primary endpoint of the trial, and that overall survival could be a secondary endpoint, although both endpoints need to be met for the trial to be positive. Thus, rather than sizing the trial to meet a non-inferiority of survival endpoint, the trial could be sized primarily to meet a non-inferiority of response rate or TTP. Moreover, the FDA stated that using a fixed cutoff for the hazard ratio confidence interval (e.g., fixed cut-off of 0.8) for the non-inferiority endpoint was no longer acceptable to the agency, and that a 50% retention of treatment effect defined in the literature should be used to calculate the lower bound of the confidence interval and therefore the sample size.

A summary of the trial design elements discussed with the Agency is presented below along with supportive literature.

Study Design:	Randomized, double-blind, placebo-controlled, multicenter, multinational study
Objectives:	
Primary:	Compare the effect of amifostine versus placebo on the incidence of nephrotoxicity in patients with NSCLC receiving cisplatin-based chemotherapy. Nephrotoxicity is defined as a 25% or more decrease from baseline in creatinine clearance at the completion of therapy. Compare the effect of amifostine versus placebo on tumor response rate to demonstrate non-inferiority in this patient population. Non-inferiority in tumor response rate will be determined if the lower limit of the 97.5% confidence interval of the difference in response rate between the two treatment arms is equal to or above -8%,based on a treatment effect determined from the literature. Tumor response will be assessed using RECIST criteria.[4]
Secondary:	Non-inferiority in survival will be defined as the point estimate of the hazard ratio of survival is not lower than 0.95.
Patient Population:	Histologically or cytologically verified Stage IIIB or IV NSCLC; Measurable or evaluable disease (based on RECIST criteria); ECOG performance status of 0 or 1; No prior therapy for NSCLC
Study Drugs:	
Amifostine:	740 mg/m^2 as a 15-minute IV infusion given 15-30 minutes prior to cisplatin
Placebo:	Identical in appearance to amifostine and given at same schedule

Cisplatin-Based Chemotherapy: Patients will be stratified by cisplatin-based chemotherapy regimen at randomization

Cisplatin/Paclitaxel: Paclitaxel: 135 mg/m^2 over a 24-hour period on day 1,
Cisplatin: 75 mg/m^2 over 30 minutes on day 2,
Cycle repeats every 3 weeks

Cisplatin/Gemcitabine: Gemcitabine: 1000 mg/m^2 over 30 to 60 minutes on days 1, 8, 15
Cisplatin: 100 mg/m^2 over 30 to 120 minutes on day 1
Cycle repeats every 4 weeks

Cisplatin/Docetaxel: Docetaxel: 75 mg/m^2 over 60 minutes on day 1
Cisplatin: 75 mg/m^2 over 60 minutes on day 1
Cycle repeats every 3 weeks

Cisplatin/Vinorelbine: Vinorelbine 25 mg/m^2 on days 1, 8, and 15
Cisplatin: 100 mg/m^2 over 60 minutes on day 1
Cycle repeats every 4 weeks

Patients will be treated until disease progression, unacceptable toxicity, or other reasons for patient withdrawal.

Primary Endpoints:

Nephroprotection: Compare the incidence of nephrotoxicity in patients with NSCLC receiving cisplatin-based chemotherapy. Nephrotoxicity is defined as a 25% or more decrease from baseline in creatinine clearance at the completion of therapy. A 40% reduction is assumed in the incidence of nephrotoxicity between the placebo (35%) and amifostine (21%) arms. Based on the sample size of this trial (1,150 patients, see below), the statistical power is >99%.

Non-Inferiority: Compare the effect of amifostine versus placebo on tumor response rate to demonstrate non-inferiority in this patient population. Non-inferiority in tumor response rate will be determined if the lower limit of the 97.5% confidence interval of the difference in response rate between the two treatment arms is equal to or above -8% based on a treatment effect determined from the literature. Based on the sample size of this trial (1,150 patients, see below), the statistical power is 85%.

Secondary Endpoint:

Survival: Compare the effect of amifostine versus placebo on survival to demonstrate non-inferiority in this patient population. Non-inferiority in survival will be defined as the point estimate of the hazard ratio of survival is not lower than 0.95. Based on the sample size of this trial (1,150 patients, see below), the statistical power is 85%.

Endpoint Assumption: The primary endpoints of nephroprotection and non-inferiority in response rate and the secondary endpoint of survival must all be positive for this study to fulfill the requirements of the Accelerated Approval obligation.

The sample size of this study is estimated at 1,150 patients, and is based on the treatment effect of cisplatin derived from randomized studies of singlet non-platinum chemotherapy and doublet cisplatin-based chemotherapy in the first-line treatment of patients with advanced NSCLC. This approach to the determination of the treatment effect was recommend by the FDA. A review of the literature resulted in only one randomized study (with complete data) comparing singlet non-platinum therapy (vinorelbine) with doublet cisplatin-based chemotherapy (cisplatin/vinorelbine) in the first-line treatment of advanced NSCLC.[5] In this study, the tumor response rate of cisplatin/vinorelbine was 30% versus 14% for vinorelbine alone ($p<0.01$) for a treatment size of 16% and a 50% retention rate (mandated by the FDA) of 8%. With a justified lower bound of -8%, a statistical power of 85%, and a lower limit of one-sided confidence interval of 97.5%, the sample size was estimated at 1,150 patients. In comparison, the calculation of sample size based on non-inferiority of survival as the primary endpoint, using survival data from this same study (40 weeks for cisplatin/vinorelbine vs. 31 weeks for vinorelbine) yielded an estimated sample size of 2,600 patients. There was no sample size estimate based on time to progression data since these data were not analyzed in the cisplatin study.

Exhibit 9 summarizes the published randomized trial experience of singlet non-platinum therapy and doublet cisplatin-based chemotherapy reviewed for determining the sample size of the study. Note, all of these studies were for first-line treatment of advanced NSCLC.

Exhibit 9 Summary of Published Randomized Trials of Single and Doublet Therapy in Patients with Advanced NSCLC

Study	Treatment	N	Response Rate
Le Chevalier, et al.[5]	Cisplatin (100 mg/m^2)/ Vinorelbine	206	30%
	Vinorelbine	206	14%
*Georgoulias, et al.[6]	Cisplatin (80 mg/m^2)/ Docetaxel	140	35%
	Docetaxel	139	18%
Schiller, et al.[2]	Cisplatin (75 mg/m^2)/ Paclitaxel	288	21%
	Cisplatin (100 mg/m^2)/ Gemcitabine	288	22%
	Cisplatin (75 mg/m^2)/ Docetaxel	289	17%
Gatzemeier, et al.[7]	Cisplatin (80 mg/m^2)/ Paclitaxel	207	26%
Sandler, et al.[8]	Cisplatin (100 mg/m^2)/ Gemcitabine	260	30.4%
Wozniak, et al.[9]	Cisplatin (100 mg/m^2)/ Vinorelbine	216	26%
Sederholm C.[10]	Gemcitabine	137	12%
Anderson, et al.[11]	Gemcitabine	150	19%
* Results based on preliminary data.			

6 IMPLEMENTATION AND CHALLENGES OF A NEW CLINICAL TRIAL TO FULFILL THE ACCELERATED APPROVAL REQUIREMENTS OF THE NSCLC INDICATION

There are several challenges in performing this new trial, the most important of which is accrual of the required sample size to adequately conduct the trial. The estimated sample size of the study is 1,150 patients. Assuming an accrual rate of 20 patients per month, the enrollment period is estimated at 57.5 months or approximately 5 years, with an added 8 months for the follow-up period. To speed accrual, multiple cisplatin-based regimens will be investigated in this trial, all of which have shown comparable effects on overall survival in this patient population. However, many researchers are shying away from high-dose cisplatin-based regimens and focusing on non-cisplatin-based regimens such as carboplatin/paclitaxel for the treatment of advanced NSCLC. In addition, with the advent of newer chemotherapy agents, there will be several higher priority protocols in this patient population competing against this trial. Therefore, accrual to this study may be slowed, prolonging the overall duration of the trial and preventing its completion within a reasonable period of time.

7 CONCLUSION

Cumulative renal toxicity associated with cisplatin administration is severe and a major dose-limiting toxicity of cisplatin-based therapy. This toxicity becomes more prolonged and severe with repeated doses of cisplatin, and can limit the ability to deliver full doses and cycles of cisplatin. In light of the known effects of dose response on the activity of cisplatin, this may have a significant and negative effect on the efficacy of cisplatin administration to patients. Dose reductions, treatment delays, and treatment discontinuation after 4 to 6 cycles of therapy are typical ways to manage cisplatin-induced nephrotoxicity in addition to vigorous hydration and osmotic diuresis. Despite these measures, life-threatening and sometimes fatal renal toxicity still occurs. Cumulative irreversible nephrotoxicity can also limit the ability to treat recurrent disease with other therapeutic agents that require renal elimination such as carboplatin as well as hampering the ability to administer supportive therapies such as antibiotics.

Ethyol (amifostine) represents an important advance in the care of oncology patients. It is the only cytoprotective agent that has been shown to reduce the cumulative renal toxicity associated with repeated administration of cisplatin, having done so in patients with both advanced ovarian cancer and NSCLC. Although there is a decrease in the use of high-dose cisplatin regimens for the treatment of NSCLC with a shift toward non-cisplatin containing regimens, there is still a cohort of patients in whom these regimens are used effectively, as evidenced by the recent approval of docetaxel and cisplatin for the primary treatment of patients with advanced NSCLC. In addition, cisplatin-based regimens are still being used in patients who are unable to tolerate alternative treatment or meet the expense of the more sophisticated new regimens. In these patients, there still exists a need to ameliorate the nephrotoxicity associated with the administration of cisplatin.

The completion of a second Phase III study in 1,150 patients for fulfillment of the Accelerated Approval faces challenges, including slow patient accrual and timeliness of results. In view of these challenges, it will be helpful if the ODAC can suggest any alternative solutions for approaches to the completion of the Accelerated Approval requirement for Ethyol in NSCLC.

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