Technology Assessment

Technology Assessment Program

Agency for Healthcare Research and Quality
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REPORT ON THE RELATIVE EFFICACY OF ORAL CANCER THERAPY FOR MEDICARE BENEFICIARIES VERSUS CURRENTLY COVERED THERAPY:

PART 4

THALIDOMIDE FOR MULTIPLE MYELOMA

November 29, 2005

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Executive Summary

Multiple myeloma is a progressive, debilitating malignancy characterized by the proliferation and accumulation of cancerous plasma cells and the overabundance of monoclonal paraprotein. It is part of a spectrum of diseases ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukemia. Extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures is common, as well as anemia, hypercalcemia, and kidney dysfunction. Although treatable, multiple myeloma is considered incurable and accounts for approximately 2 percent of all cancer deaths.[1] Historically, intermittent oral melphalan and prednisone (MP) was standard therapy for untreated symptomatic multiple myeloma. In more recent years, newer combination chemotherapy regimens have been used both as initial first-line chemotherapy and as salvage chemotherapy, with better response rates but little effect on overall survival.

Example combination chemotherapy programs include VBCMP (vincristine, carmustine, cyclophosphamide, melphalan, and prednisone) and VAD (vincristine, doxorubicin, and dexamethasone). There is a survival benefit when patients responding to chemotherapy such as VAD are treated with high dose chemotherapy plus single or double autologous stem cell transplantation. Nonetheless, over 80 percent of patients still relapse within 7 years. Treatment programs that include transplantation have limited applicability due to toxicity and associated age, performance status, and organ function requirements. Nearly all patients with multiple myeloma will eventually relapse and become resistant to further treatment. Median survival remains approximately 4 years.

Thalidomide, a glutamic acid derivative, was used as sedative in the late 1950s until it was withdrawn from the market because it caused severe birth defects. Thalidomide's anti-angiogenic properties were appreciated in the 1990s and because bone marrow angiogenesis plays a substantial role in the development of multiple myeloma, thalidomide has been tried in multiple myeloma. Since the first publication documenting objective responses with thalidomide in patients with refractory myeloma was published in 1999, there has been a rapid proliferation of published and abstract reports on the use of thalidomide in multiple myeloma. In 1998, the Food and Drug Administration (FDA) approved thalidomide for use in treating leprosy (Hansen's disease); it is not currently FDA-approved for multiple myeloma. Thalidomide can only be prescribed under the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program, patented by Celgene Corporation.

Scope and Key Questions

The key questions for this review were developed with experts in the field of oncology, health economics, and health policy. The key questions are as follows:

1. For patients with relapsed or refractory multiple myeloma, what is the effect of thalidomide compared to standard chemotherapy regimens (e.g., VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, and prednisone) and VAD (vincristine, doxorubicin, and dexamethasone)) on 2-year survival, disease-free survival, CR, PR (m-protein), and quality of life?

2. For patients with relapsed or refractory multiple myeloma, what is the effect of thalidomide compared to standard chemotherapy regimens (e.g., VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, and prednisone) and VAD (vincristine, doxorubicin, dexamethasone)) on adverse effects, tolerability, and compliance?

3. What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy?

As there was emerging information regarding the role of thalidomide for newly diagnosed and smoldering multiple myeloma, these groups were also considered as part of this review.

Methods

Search Strategy

Primary studies were sought in a computerized bibliographic search of MEDLINE (1966 through September 2004, updated August 2005) and limited to articles published in the English language. Additional strategies included searching ancillary bibliographic databases, searching abstracts presented at the American Society of Clinical Oncology and American Society of Hematology professional meetings since 2004, querying experts, and checking references of included studies and review articles.

Selection Criteria

Each citation identified from the search strategies was evaluated according to the following selection criteria. Evaluations were performed by the authors.

Inclusion criteria were as follows:

Patients	Patients with multiple myeloma
Interventions	Thalidomide
Comparators	Any

Study designs:

- *For **efficacy** questions*: Prospective clinical trials; may be phase II uncontrolled, or phase III randomized controlled trials.

- *For studies of **adverse effects:*** May be retrospective or prospective case series, cohort studies, or clinical trials provided the number of patients treated (at risk for adverse effects) as well as the number with adverse effects can be ascertained.

- *For studies of **predictors** of response:* May be retrospective or prospective case series, cohort studies, case-control studies, or clinical trials provided the response can be ascertained for patients with and without the predictor.

Outcomes:

- *For **efficacy** questions*: Survival, quality of life (QOL), and the following intermediate outcomes:
    - Complete response
        - Lack of detectable M-protein in serum or urine by immunoelectrophoresis & immunofixation, maintained for a minimum of 6 weeks
        - Bone marrow biopsy with <5 percent plasma cells
        - No increase in size or number of bone lesions
        - Disappearance of plasmacytomas
    - Partial response
        - Reduction in serum M-protein by at least 50 percent, maintained for at least 6 weeks
        - Reduction in urine Bence Jones protein by at least 90 percent or <200 mg, maintained for at least 6 weeks
        - If non-secretory, reduction in bone marrow plasma cells by at least 50 percent, maintained for at least 6 weeks
        - No increase in size or number of bone lesions

- *For studies of **adverse effects**:* Adverse effects, tolerability, and compliance with treatment.

- *For studies of **predictors** of response:* Predictive value of patient or tumor characteristics that are associated with clinically important differences in treatment response that are:

    - related to the mechanism of action of the drug (i.e., molecular target); and
    - candidates for diagnostic testing (even if not commercially or clinically available currently [e.g., Polymerase Chain Reaction]).

The Evidence

1. *For patients with relapsed or refractory multiple myeloma, what is the effect of thalidomide compared to standard chemotherapy regimens (e.g., VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, and prednisone) and VAD (vincristine, doxorubicin, and dexamethasone)) on 2-year survival, disease-free survival, CR, PR (m-protein), and quality of life (QOL)?*

While the original question was about relapsed or refractory multiple myeloma, we expanded our review of the topic to include untreated myeloma because many of the newer studies of thalidomide focused on this setting. Also, we included some studies of asymptomatic myeloma

although the current standard is not to treat this group but rather adopt an approach of "watchful waiting." The breadth of studies, myeloma treatment settings (first-line, relapsed, asymptomatic, peri-transplantation), and drug combinations highlights the many ways that thalidomide is quickly becoming incorporated into myeloma treatment regimens. Key clinical issues include the mechanism of this prototype drug, managing toxicity, and finding the most effective dose, schedule, and medication combinations. Nonetheless, thalidomide's most critical contribution to the array of anti-myeloma treatments is as an oral medication with a tolerable side effect profile that has efficacy in the relapsed or refractory setting and can be administered to the elderly and/or debilitated patients typical of the multiple myeloma population.

VBCMP and VAD are the comparators. No studies have randomized patients to thalidomide versus these interventions. As such, historical rates and survival estimates from previous trials including these agents must be used as the comparison group. Two-year survival rates were rarely reported except in the Samson et al. study of VAD for untreated patients where 83 percent of responders were alive at 2 years. In the Mineur et al. trial of bolus VAD vs. VDD for untreated myeloma, median time to progression was 24 months. Median overall survival had not been reached and was expected to exceed 40 months with both arms.

It is difficult to directly compare numbers between categories as response criteria for the various studies vary widely and very few of the thalidomide data presented are from randomized studies (only thalidomide-dexamethasone vs. dexamethasone or MP in untreated myeloma). Our use of PPR 25 percent as the summary response criteria for thalidomide is supported in another recent literature review for multiple myeloma. This is notably different than the PPR 50 percent criteria described for most of the older trials. It can be misleading to compare the PPR 50 percent, as some studies report PPR 50 percent to mean all responses that were greater than 50 percent (i.e., 50-100 percent) and others indicate just those reflected in that response level (e.g., 50-74 percent with next response level at 75 percent). Response ranges for thalidomide are broad, reflecting heterogeneity among studies and study populations, including the volume and intensity of previous myeloma treatments, study quality, and study size. Also, participant populations may be represented multiple times in the different published analyses of these studies; it is difficult to determine.

The most notable findings are the following:

- Thalidomide has activity in both the untreated and resistant/refractory settings.
- Generally, survival and responses are better when dexamethasone has been added.
- Response rates and survival estimates do not appear to be substantially different from that seen with VBCMP or VAD.

Thalidomide's place in the multiple myeloma therapeutic armamentarium is clarified as these similar response rates are considered in terms of the comparative adverse events, ease of administration, and ability to be combined with other treatments.

- First, thalidomide (or thalidomide plus dexamethasone) has a different toxicity profile than the combination chemotherapy regimens. Until head to head studies are done, it will be difficult to be certain; however thalidomide appears to have less intense toxicity with fewer treatment-related deaths. Deaths such as those related to neutropenic fever from VBCMP and VAD and cardiotoxicity with VAD are not reported for thalidomide.

The unexpected thromboembolic risk of thalidomide can be mitigated by adding enoxaparin. Thalidomide's peripheral neuropathy is cumulative and will need further consideration. Sedation can be minimized by slowly escalating the dose.

- Second, thalidomide is oral and can be managed in the outpatient setting. It does not require venous access or central venous catheters. This is balanced by the increased burden of the S.T.E.P.S. program, an important reminder and safeguard for the known teratogenicity of thalidomide.
- Third, thalidomide can be administered in elderly, immunocompromised patients and those with renal or cardiac dysfunction. It is unlikely that the true magnitude of this advantage is represented across the efficacy studies, as such ill patients are often excluded from the study populations.
- Fourth, it has activity even when patients have been heavily pretreated with VAD, VBCMP, or high dose chemotherapy plus autologous stem cell transplant. Hence, thalidomide can be added to the list of appropriate options for treatment of multiple myeloma and the timing of its use is considered based upon the needs of the individual.
- Fifth, evidence of maximal response is seen early so thalidomide does not need to be continued for long periods if it is not effective. In the 2001 Barlogie et al. study of thalidomide only in refractory/relapsed myeloma, 70 percent of patients achieving a PPR >25 percent did so within 2 months and 90 percent within 4.5 months.
- Sixth, it can be combined with other agents with additive effect. In particular, lack of severe myelosuppression with thalidomide makes this possible. Thalidomide plus MP appears to be superior to MP alone and there are many promising combinations.
- Seventh, thalidomide can be used in the pre- and post-transplantation settings although some recent data suggest that it may be better not to use thalidomide for post-transplant maintenance but rather save the intervention for future relapse states.

Should thalidomide always be combined with dexamethasone? Pre-clinical data suggests synergistic effects when thalidomide is combined with dexamethasone. Dexamethasone is the main active agent in VAD. Weber et al. reported that thalidomide restored the sensitivity of myeloma cells to dexamethasone-induced apoptosis. Generally, survival and responses are better when dexamethasone has been added, with fewer side effects. Thalidomide doses are generally lower when dexamethasone is added. Dexamethasone dosing is variable across studies. Unless a patient has a contraindication to high dose dexamethasone (e.g., severe labile diabetes, history of steroid psychosis), the addition of dexamethasone is quickly becoming standard when thalidomide is used.

The ideal dose of thalidomide is unclear. The 2001 Barlogie et al. study demonstrated that patients who received >42 g of thalidomide in the first 3 months had significantly better response rates and survival. Similar findings were noted in both of the predictors study on the topic. Recent studies have looked to decreasing the thalidomide dose though, predominantly in an effort to decrease adverse effects. This is most noticeable across the range of thalidomide plus dexamethasone studies, some of which start at 50 mg and many of which fix the thalidomide dose at 200 mg.

The role of thalidomide in soft tissue plasmacytomas is also unclear. Some authors report poorer responses in this setting. More data are needed.

Only one study specifically evaluated QOL outcomes. In an abstract presented at the American Society of Clinical Oncology meeting in May 2005, Mileshkin and colleagues investigated the effect of thalidomide plus celecoxib in 66 patients with relapsed multiple myeloma. The EORTC QLQ-C30 was used to measure QOL. Overall response to thalidomide (PPR 25 percent) was 42 percent. Global health on the QLQ-C30 decreased (lower is worse) for 80 percent of participants over the first month of thalidomide treatment. Among responders, QOL on this sub-scale increased for 29 percent of individuals. Responders were more likely to have improvement in QOL than non-responders (61 percent vs. 27 percent, p=0.024). Health-related QOL was also reported in a study of 65 patients with refractory/relapsed myeloma treated with thalidomide only. The QLQ-C30 was again used as the measurement instrument. Pain improved and constipation worsened with thalidomide, but otherwise it was difficult to determine the impact of thalidomide on QOL from this report.

2. *For patients with relapsed or refractory multiple myeloma, what is the effect of thalidomide compared to standard chemotherapy regimens (e.g., VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, and prednisone) and VAD (vincristine, doxorubicin, dexamethasone)) on adverse effects, tolerability and compliance?*

The two most notable adverse effects with thalidomide are peripheral neuropathy and thromboembolism. Bradycardias, skin toxicity, constipation, and neutropenia are also well described. Using data from studies of thalidomide only, thalidomide side effects include constipation (3-11 percent grade 3 and 4), neurotoxicity predominantly evident as peripheral neuropathy (1-7 percent grade 3 or 4) and sedation (3-13 percent grade 3 or 4), cardiac insufficiency due to bradycardia (2-6 percent grade 3 or 4), leukopenia (2-31 percent grade 3 and 4), and blood clots (2-10 percent grade 3 or 4). Side effects are dose dependent as evidenced in studies by Singhal et al., Hus et al., and Rajkumar et al. that escalated thalidomide up to 800 mg with exaggeration of side effects including somnolence, neuropathy, and constipation.

In the 1998 Mineur et al. randomized trial of VAD vs. VBCMP, toxicities described included neutropenic infections that led to four deaths (VAD 2 and VMBCP 2), corticosteroid effects in two cases both in the VAD arm (pancreatitis and diabetes mellitus for one case, candidal esophagitis for the other), cardiotoxicity after three cycles of VAD, and hematological toxicity after VAD requiring treatment modification. In the 2003 Dimopoulos et al. randomized trial of VAD administered as intravenous bolus injection vs. VDD for patients with previously untreated myeloma, toxicities in the bolus VAD and VDD arms respectively were Grade 2 neutropenia (20 percent vs. 15 percent, p=0.7), Grade 2 thrombocytopenia (10 percent vs. 5 percent, p=0.2), Grade 2 nausea/vomiting (4 percent vs. 5 percent, p=0.8), Grade 1 alopecia (55 percent vs. 37 percent, p<0.001), Grade 2 mucositis (7 percent vs. 15 percent, p=0.3), Grade 2 erythrodysesthesia (2 percent vs. 13 percent, p=0.03), and Grade 2 neurotoxicity (13 percent % vs. 15 percent, p=0.9). Steroid-related side-effects occurred with equal frequency in both arms; Cushingoid features were noted in approximately one-fifth of patients, hyperglycemia in 15 percent of patients treated with bolus VAD bolus and in 12 percent treated with VDD, mood changes in <10 percent of patients in either arm and peptic ulcer disease, hiccups and proximal muscle weakness each occurred in <5 percent of patients. Infections, which required antibiotics, including neutropenic fever, were noted in 17 percent of patients treated with bolus VAD and 18

percent treated with VDD. Eleven patients (9 percent) in the bolus VAD and 14 (11 percent) in the VDD arm died within the first 4 months of treatment. Among the 11 patients treated with bolus VAD, three deaths were due to infections and two were due to heart failure and/or myocardial infarction. Of the 14 early deaths in the VDD arm, four were due to infections and three were due to heart failure and/or myocardial infarction.

There are no prospective comparative studies between thalidomide and VAD/VBCMP to specifically answer this question. However, Cavo et al. recently presented a retrospective review that compared the experience of 200 patients receiving thalidomide plus dexamethasone or VAD as preparative regimens for SCT. Patients were matched on age, disease stage, and B_2 microglobulin. Grade 3/4 toxicity was presented. Among patients receiving thalidomide plus dexamethasone, 15 percent developed DVT, 0 percent granulocytopenia, 9 percent constipation, 4 percent infections, 4 percent neuropathy, and 6 percent deaths during treatment. Among patients receiving VAD, 2 percent developed DVT, 12 percent granulocytopenia, 3 percent constipation, 5 percent infections, 7 percent neuropathy, and 6 percent deaths during treatment.

A more complete review of the differences in administration and tolerability is provided in the previous section. Compliance data were not identified during this review.

3. *What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy?*

Thus far, despite myriad studies reporting predictors of response, little consistent data support the use of any specific tests related to the mechanism of the disease. TNFα polymorphisms at position -238 of the gene promoter were correlated with response and survival in the one study of the topic, but, as was seen across this group of studies, often a single study was positive but subsequent confirmations were negative. Two studies of TNFα as a predictor suggested that TNFα correlated with survival, but one did not. The same studies reported similar findings for IL6. Studies of Vascular Endothelial Growth Factor (VEGF), Vascular Endothelial Growth Factor (VEGF), and other substances had very few consistent positive findings. Taken together, these studies suggest that we have a lot to learn about the mechanism of action of thalidomide, that predictors related to angiogenesis are likely to be less helpful, and that cytokine like TNFα and IL-6 play may be more predictive after future study.

Other clinical and demographic factors that predict response include age and beta-2 microglobulin. These findings do not substantially add to current care, as the findings were fairly consistent with the previously known predictors for myeloma.

Once large randomized trials are available, predictor analyses should be repeated to see if any new patterns or predictors emerge.

Current State of Clinical Use

The National Cancer Institute (NCI) guidelines at www.cancer.gov lists thalidomide as a treatment option within the array of current options, without specifying where in the treatment

order it should fall. The guidelines argue that the choice of first-line and subsequent therapies should be individualized based upon patient age, general health, and patient preference. A dose of thalidomide is not recommended and the guideline argues that more data are needed until clear recommendations about the role of dexamethasone and enoxaparin can be provided. The NCCN does not have a guideline for multiple myeloma.

Implications for Future Research

As has been highlighted throughout this review there is much work to be done on both the clinical and basic science levels. Clinically, randomized data are needed. The final results of the ongoing phase III trials are anxiously awaited. These will guide subsequent directions for therapy. It is unclear whether a randomized study of VAD versus thalidomide (or thal-dex) will be possible, as the older patient profile ideal for thalidomide may be able to tolerate the standard chemotherapy arm. If the study is limited to only those who can tolerate VAD then the results may be less applicable across all of the patients for whom thalidomide is the best choice. A randomized trial using VDD and thalidomide may be more feasible. Certainly, data produced from these studies will be invaluable to assist with better understanding adverse event profiles and predictors of response.

Much work is ongoing to further elucidate the mechanism of action of thalidomide. A focus on the cytokine milieu is evolving. Use of gene array technology to profile multiple myeloma and match this information to thalidomide response is also ongoing. Thalidomide represents the prototype of an emerging class of drugs, and it is imperative that its efficacy and mechanism of generating tumor response is well understood. Other immunomodulatory analogs of thalidomide like CC-5013 (Revimid) are also in clinical testing.

Symptoms and QOL is another important future direction for thalidomide research. How does thalidomide impact pain control, functional status, ability to return to work, and other QOL outcomes?

An invaluable improvement for this body of research would be a strategy of quality reporting and use of similar response criteria such as the Blade criteria. The quality of reporting was clearly limited among studies in this review. Similarly, the inconsistency of response criteria and outcomes reported limited comparisons across studies (e.g., variability in reporting and meaning of PPR). An international standard would greatly improve the accuracy and utility of future systematic reviews on myeloma treatments.

Introduction

Policy Context of the Current Technology Assessment

Section 641 of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) calls for a demonstration that would pay for drugs and biologicals that are prescribed as replacements for drugs currently covered under Medicare Part B. The demonstration project will be national in scope and will be limited to 50,000 beneficiaries or $500,000,000 in funding, whichever comes first. Forty percent of the funding for this demonstration will be reserved for oral anti-neoplastic drugs.

CMS has requested an assessment of the efficacy of selected oral cancer therapies included in the demonstration relative to drugs currently covered under Medicare Part B. This assessment will provide information that will be used to evaluate the likely effects of the demonstration on patient outcomes and may also provide underlying information to be used for cost-effectiveness analyses that will be completed by CMS.

The scope of the assessment will be limited to the following demonstration drugs and conditions:

- Imatinib for treatment of chronic myeloid leukemia;
- Imatinib for treatment of gastrointestinal stromal cancer;
- Gefitinib for treatment of non-small cell lung cancer;
- Thalidomide for treatment of multiple myeloma.

This report is responsive to the fourth item: an assessment of thalidomide for the treatment of multiple myeloma.

Clinical Context of the Current Technology Assessment

Multiple myeloma is a debilitating malignancy that is part of a spectrum of diseases ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukemia. First described in 1848, multiple myeloma is characterized by the proliferation and accumulation of cancerous plasma cells and the overabundance of monoclonal paraprotein.[2]

Plasma cells are terminally differentiated B-lymphocytes that have the ability to produce immunoglobulin (Ig, a.k.a. antibodies). The cancerous myeloma plasma cells are clonal and therefore produce an abundance of a single immunoglobulin known as a monoclonal protein (a.k.a., M-protein, myeloma paraprotein; Figure 1). Each monoclonal protein consists of two heavy polypeptide chains of the same class and subclass and two light polypeptide chains of the same type.[3] The heavy polypeptide chains are IgG, IgA, IgM, IgD and IgE while the light chain types are kappa and lambda.

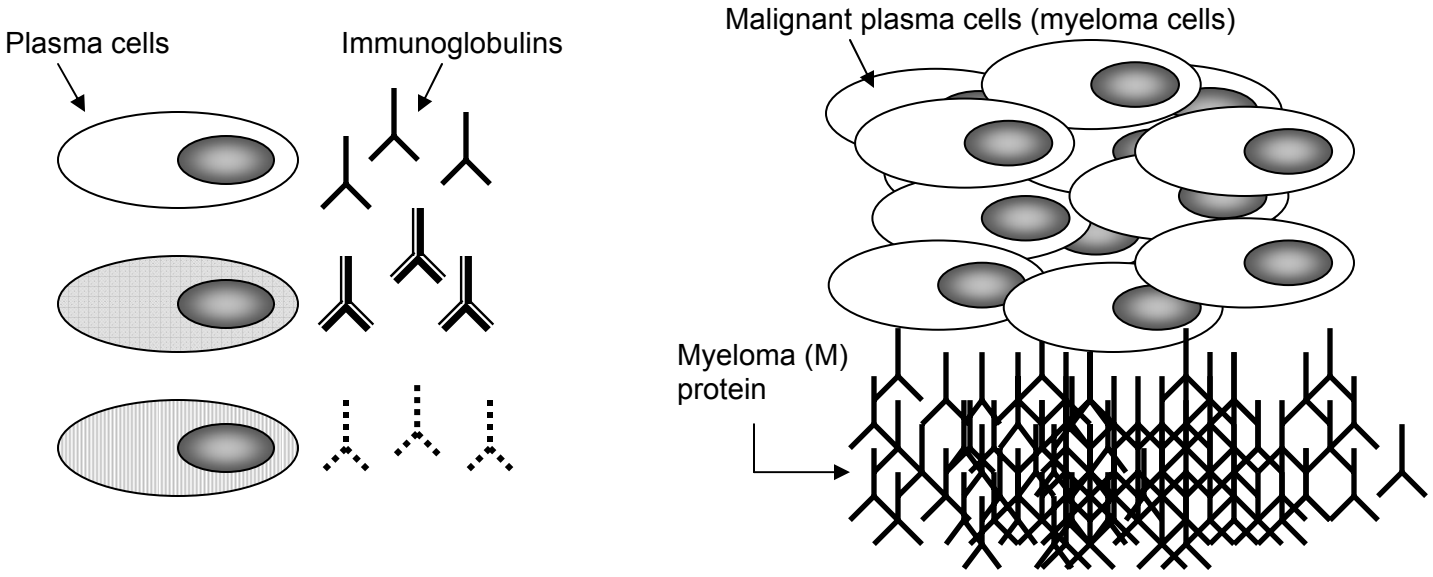
This malignant proliferation of plasma cells often results in extensive skeletal destruction; osteolytic lesions, osteopenia, and/or pathologic fractures are common. Other common clinical findings in multiple myeloma include anemia, high serum calcium levels, and kidney dysfunction. Recurrent bacterial infections and bleeding (nose, gums, easy bruising) can also occur.

Incidence & Prevalence

In the United States, multiple myeloma is uncommon, accounting for 1 percent of all cancers and 10 percent of hematologic cancers.[4] It occurs in about 4 out of 100,000 individuals each year (about 15,980 total new cases and 11,300 deaths). Multiple myeloma accounts for approximately 2 percent of all cancer deaths and close to 20 percent of the deaths caused by hematologic malignancies. Slightly more men than women develop multiple myeloma and almost twice the number of blacks as compared to whites. The predominant risk factor is age.[5] Multiple myeloma occurs most frequently in older adults; the average age at diagnosis is 65 years with less than 2 percent under age 40.

Other risk factors for the increased likelihood of multiple myeloma include genetic factors and prior diagnosis of a plasma cell proliferative process.[6] First-degree relatives with multiple myeloma related to familial clustering occurs in about 3 familial cases per 1000 patients.[5] The cause of multiple myeloma is unknown, but increased risk of myeloma has been linked to chemicals, asbestos, laxatives, and radiation.[7]

Figure 1: Production of the M-protein in multiple myeloma



Normally, plasma cells produce different immunoglobulins (antibodies), a part of the body's humoral immune system

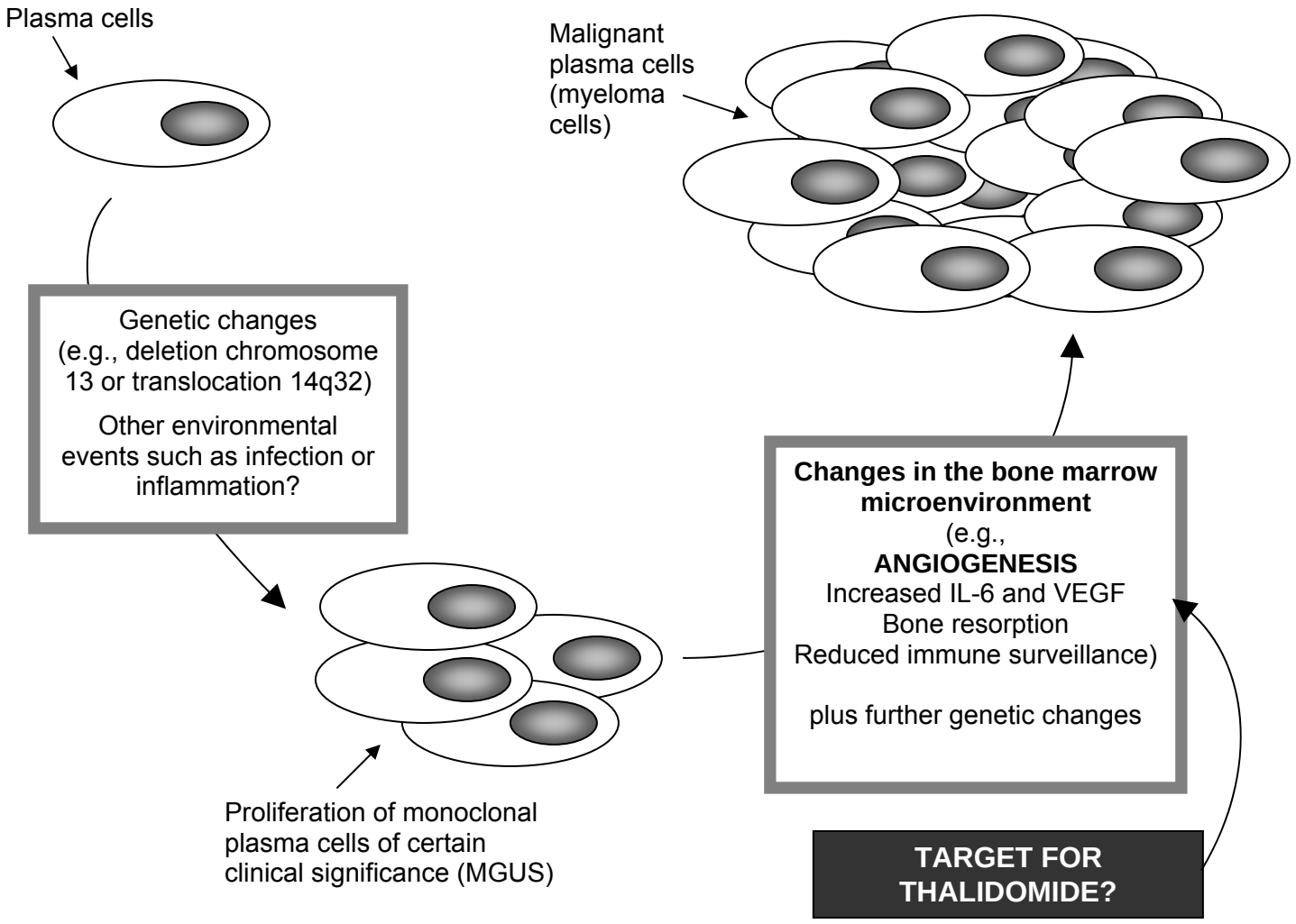
In multiple myeloma, the malignant plasma cell clones divide uncontrollably producing an abundance of the same immunoglobulin (antibody), called the M-protein or myeloma paraprotein. The rapidly growing number of myeloma cells crowd the bone marrow, destroy bone, and create mass lesions called plamacytomas. The effect of myeloma cells and substances that they produce on bone leads to weak bones and high calcium. The M-protein can clog the kidney and dilutes the function of rest of the humoral immune system leading to bacterial infections.

Pathogenesis

A series of steps leads to the development of multiple myeloma, as described by Kyle and Rajkumar in the New England Journal of Medicine in 2004 (Figure 2).[8] Not all of these are fully understood. A limited number of clonal plasma cells initially develop. Genetic translocations involving the immunoglobulin genes occur in at least half of instances. These first steps lead to the production of some monoclonal plasma cells more representative of a "monoclonal gammopathy of uncertain significance" (MGUS) rather than true multiple myeloma. Additional complex changes then occur including further genetic alterations and changes in the bone marrow microenvironment. Specifically, the bone marrow microenvironment evolves with production of new supportive blood cells (angiogenesis), suppression of cell-mediated immunity, and the development of paracrine signaling cascades involving cytokines such as interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF). This creates a supportive environment where the malignant plasma cells replicate. The disease progresses until it is a clinically

significant multiple myeloma. Interactions between the myeloma cells, bone marrow stromal cells, and microvessels contribute to expansion of the tumor and its resistance to drugs.

Figure 2: Pathogenesis of multiple myeloma
(adapted from Kyle & Kajkumar, Multiple myeloma, New England J Med, 2004, 351: 1861)



Diagnosis

The diagnosis of multiple myeloma is often suspected because of one (or more) of the following clinical presentations:[2]

- Bone pain related to lytic lesions discovered on routine skeletal films (two-thirds of cases; usually back or chest, but occasionally in arms and legs);
- An increased total serum protein concentration and/or the presence of a monoclonal protein in the urine (Bence Jones protein) or serum (M protein, usually >3 g/dL);

- Systemic signs or symptoms suggestive of malignancy, such as unexplained anemia with weakness and fatigue (two-thirds);
- Hypercalcemia (20 percent); or,
- Impaired renal function (creatinine >2.0 mg/dL; 25 percent).

The initial approach to the patient is to establish the diagnosis, which traditionally requires the detection of >10 percent plasma cells on a bone marrow examination or a plasmacytoma plus one of the following:[9, 10]

- Serum M-protein of >3 g/dL (IgG or IgA isotype most common) by immunoelectrophoresis or immunofixation (IFE). Over 80 percent of patients have serum M-protein.
- Bence Jones protein, denoting evidence of monoclonal light chain (kappa or lambda) proteins identified in a 24 hour urine collection.
- Detection of lytic bone lesions or generalized osteoporosis in skeletal x-rays. Usually a skeletal survey is conducted.

Multiple myeloma is only one disease within a category of illnesses called monoclonal gammopathies (paraproteinemias). These disorders are characterized by the monoclonal expansion of plasma cells. It can be difficult to distinguish the different gammopathies from one another, but it is important to do so as they have different prognoses and standard treatments. In response, the International Myeloma Working Group has developed the following simplified criteria for the diagnosis of MGUS, asymptomatic (smoldering) myeloma, symptomatic multiple myeloma and other gammopathies (Figure 3).[3] No specific percent of plasma cells in the bone marrow is specified for symptomatic myeloma, since 5 percent of patients may have fewer than 10 percent bone marrow plasma cells and marrow involvement may be focal, rather than diffuse. The majority do have >10 percent, however, and if flow cytometry is performed, most plasma cells (> 90 percent) will show a 'neoplastic' phenotype. Evidence of related organ or tissue impairment figures prominently in this classification system.

Approximately 5-15 percent of multiple myeloma patients meet diagnostic criteria for myeloma but are asymptomatic.[11] A confusing distinction is indolent vs. smoldering myeloma. Few resources offer a distinction between the two, and most consider them together as asymptomatic multiple myeloma. Others describe indolent myeloma as a subset of smoldering myeloma with <30 percent plasma cells in the bone marrow.[7]

Figure 3: Classification of Monoclonal Gammopathies
(International Myeloma Working Group)

Diagnosis	Criteria
Monoclonal gammopathy of undetermined significance (MGUS)	-- M-protein in serum <3 g/dL -- Bone marrow clonal plasma cells <10% and low level of plasma cell infiltration in a trephine biopsy (if done) -- No evidence of other B-cell proliferative disorders -- No related organ or tissue impairment (no end organ damage, including bone lesions)*
Asymptomatic (smoldering) myeloma	-- M-protein in serum 3 g/dL l and/or -- Bone marrow clonal plasma cells 10% -- No related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms*
Symptomatic multiple myeloma.	-- M-protein in serum and/or urine -- Bone marrow (clonal) plasma cells or plasmacytoma -- Related organ or tissue impairment (end organ damage, including bone lesions)*
Solitary plasmacytoma of bone.	-- No M-protein in serum and/or urine -- Single area of bone destruction due to clonal plasma cells -- Bone marrow not consistent with multiple myeloma -- Normal skeletal survey (and MRI of spine and pelvis if done) -- No related organ or tissue impairment (no end organ damage other than solitary bone lesion)*
Non-secretory myeloma	-- No M-protein in serum and/or urine with immunofixation -- Bone marrow clonal plasmacytosis 10% or plasmacytoma -- Related organ or tissue impairment (end organ damage, including bone lesions)*
Extramedullary plasmacytoma.	-- No M-protein in serum and/or urine* -- Extramedullary tumor of clonal plasma cells -- Normal bone marrow -- Normal skeletal survey -- No related organ or tissue impairment (end organ damage including bone lesions)*
Multiple solitary plasmacytomas (± recurrent).	-- No M-protein in serum and/or urine -- More than one localized area of bone destruction or extramedullary tumor of clonal plasma cells which may be recurrent -- Normal bone marrow -- Normal skeletal survey and MRI of spine and pelvis if done -- No related organ or tissue impairment (no end organ damage other than the localized bone lesions)
Plasma cell leukemia	Peripheral blood absolute plasma cell count of at least $2x10^9$/L and more than 20% plasma cells in the peripheral blood differential white cell count.

Figure 3: Classification of Monoclonal Gammopathies
(International Myeloma Working Group)

Diagnosis	Criteria
*Myeloma-related organ or tissue impairment (end organ damage)	-- Calcium levels increased -- Renal insufficiency -- Anemia -- Bone lesions: lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify) -- Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months) -- CRAB (calcium, renal insufficiency, anemia or bone lesions) -- Some patients may have no symptoms but have related organ or tissue impairment.

Staging:

The staging of multiple myeloma is based on the myeloma tumor cell mass (monoclonal protein, M-protein) in the serum and/or urine, along with other clinical parameters, such as the hemoglobin and serum calcium levels, and the presence of lytic bone lesions or renal failure.[12] There are two main staging systems used—the Durie/Salmon criteria and the International Myeloma Staging System (Figure 4). The Durie/Salmon system is oldest, first published in 1975.[13] Since impaired renal function worsens prognosis regardless of stage, different staging levels are subdivided into A and B based upon creatinine.

The great majority of symptomatic myeloma patients are classified as stage III by the Durie/Salmon criteria, making it difficult to identify patients with intermediate and poor prognosis.[12] Other problems with the Durie-Salmon system, such as inter-observer variability in assessment of staging, also limit its usefulness. In response, the International Myeloma Working Group derived the International Staging System,[14] and this staging system is now referred to most commonly.[12] This system was derived using multifactorial prognostic models mixed with practicality. Beta-2 microglobulin (B2M) has been shown to be a reliable marker for prognosis;[15] similarly, albumin and other clinical factors have important prognostic value in multiple myeloma. A combination of B2M and serum albumin provided the simplest, most powerful and reproducible three-stage classification when developing the model supporting the ISS. The three stages of the ISS are predictive of survival.[14] Since the ISS was only derived in the past several years and the main publication was recently released in 2005, many studies were still published with the older system.

Figure 4: Multiple Myeloma Staging Criteria

Durie/Salmon	International Myeloma Staging System
Monoclonal gammopathy of undetermined significance (MGUS) = M-protein found in blood without other diagnostic criteria for multiple	

Stage I: All of the following: • Hemoglobin >10 g/dL. • Normal serum calcium. • Normal bone structure. • Low M-protein production as shown by: o IgG <5.0 g/dL. o IgA <3.0 g/dL. o Urinary kappa (κ) or lambda (λ) light chains <4 g/24 hours. o Low myeloma cell mass (<0.6 X 10^{12}) cells/ m^2	Stage I multiple myeloma: • Beta-2-microglobulin <3.5 and • Albumin ≥3.5
Stage II: Disease neither stage I nor stage III: • Intermediate myeloma cell mass: 0.6 to 1.2 trillion (10^{12})/m^2	Stage II multiple myeloma: • beta-2-microglobulin <3.5 and albumin <3.5 or • beta-2-microglobulin 3.5 to <5.5
Stage III means 1 or more of the following: • Hemoglobin <8.5 g/dL. • Serum calcium >12.0 mg/dL. • More than 3 lytic bone lesions (>75%(. • High M-protein production as shown by: o IgG >7.0 g/dL. o IgA >5.0 g/dL. o Urinary kappa (κ) or lambda (λ) >12.0 g/24 hours. o Estimated myeloma cell mass: >1.2 trillion (10^{12})/m^2 (high burden)	Stage III multiple myeloma: • beta-2-microglobulin ≥5.5
Subclassified based upon renal function: A -- Serum creatinine <2 mg/dL B -- Serum creatinine ≥2 mg/dL	

Patients with newly diagnosed disease are staged according to these systems and then the treatment is matched to their degree of illness. This is typically described as the "newly diagnosed" or "untreated" multiple myeloma setting. Since patients with asymptomatic myeloma are often closely monitored without specific interventions as their initial treatment plan, these patients are also grouped into the "untreated" category. When the disease recurs or fails to respond to the initial therapy, the myeloma is called "refractory" or "resistant". "Advanced" myeloma can imply advanced stage disease (Stage III) or progressive disease, depending upon the author. For the purposes of this review, these categories are divided between "newly diagnosed/untreated" and "advanced/refractory/resistant". Note that some newly diagnosed advanced Stage III study participants are included in the "advanced/refractory/resistant" category based upon categorization by the study authors, although the majority of participants reported in this review in the "advanced/refractory/resistant" category have disease that has progressed after initial therapy (i.e., refractory or resistant to initial therapy).

Prognosis

Outcome for patients with multiple myeloma is highly variable.[14] The median overall survival time is 3-4 years, but ranges from less than 6 months to greater than 10 years. This is due to substantial individual variation in myeloma cell biology and clinical characteristics.

The American Cancer Society quotes 5-year survival rates for multiple myeloma, but does not designate which staging system was used to generate these data (Figure 5):[16]

Figure 5: 5-year Survival Rates for Multiple Myeloma
American Cancer Society, 2005 (www.cancer.org)

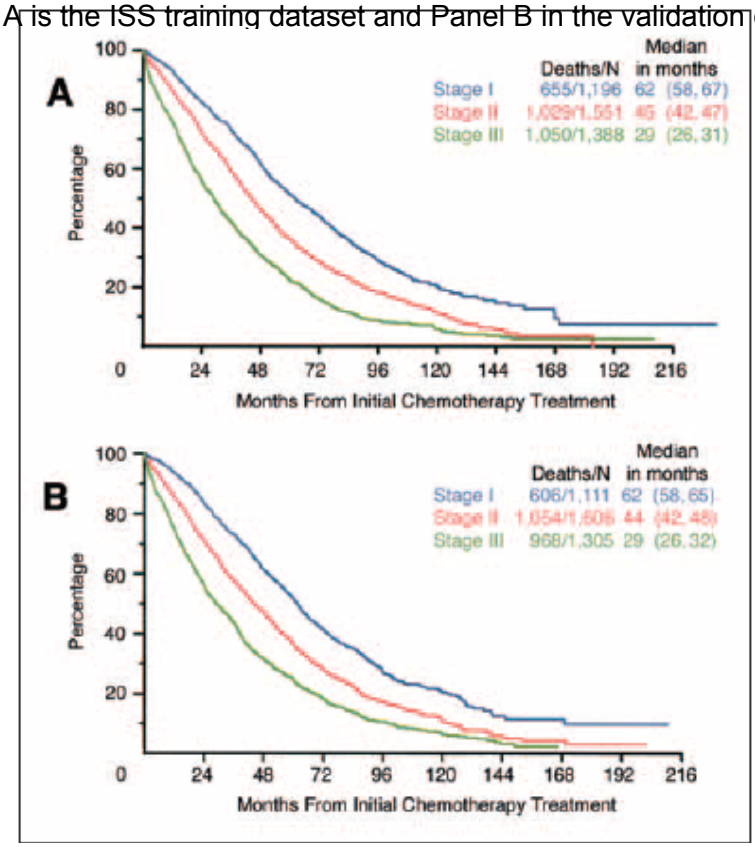
Stage	5-year Survival
Stage I	50%
Stage II	40%
Stage III	10% to 25%

Survival analyses for 10,750 patients with multiple myeloma were conducted as part of the development and validation phases for the ISS (published in 2005).[14] Clear relationships between stage and survival were identified (Figure 6 and 7). Of the total, 7,920 patients were treated with standard-dose therapy as the primary modality, whereas 2,807 patients received high dose therapy with autologous stem cell transplantation (SCT). The ISS system discriminated similarly for the two groups.

Figure 6: Multiple Myeloma Median Survival by Stage
Griepp et al., J Clin Onc 2005, 23: 3412-3420 (published May 15, 2005)

Stage	Median Survival Using the International Myeloma Staging System	Median Survival Using the Durie-Salmon System
Stage I	62 months	
IA		62 months
IB		22 months
Stage II	44 months	
IIA		58 months
IIB		34 months
Stage III	29 months	
IIIA		45 months
IIIB		24 months

Figure 7: Survival in multiple myeloma
Griepp et al, *J Clin Onc* 2005, 23: 3412-3420 (published May 15, 2005)
Panel A is the ISS training dataset and Panel B in the validation dataset



The median survival prior to the advent of any chemotherapy era was less than a year.[17]

A number of patient clinical factors and laboratory tests are indicative of poorer prognosis in multiple myeloma. In a series of 1,027 patients with multiple myeloma seen at a single

institution between 1985 and 1998, adverse prognostic risk factors affecting survival included the following:[18]

- Performance status 3 or 4 (Relative risk (RR) 1.9)
- Serum albumin <3 g/dL (RR 1.7)
- Serum creatinine 2 mg/dL (RR 1.5)
- Platelet count <150,000/microL (RR 1.5)
- Age 70 years (RR 1.5)
- Beta-2-microglobulin >4 mg/L (RR 1.5)
- Plasma cell labeling index 1 percent (RR 1.5)
- Serum calcium 11 mg/dL (RR 1.3)
- Hemoglobin <10 g/dL (RR 1.3)
- Bone marrow plasma cell percentage 50 percent (RR 1.2)

Cytogenetic findings are also associated with survival in multiple myeloma and complement established clinical prognostic factors.[8] In a study of 351 patients treated with conventional chemotherapy in an Eastern Cooperative Oncology Group (ECOG) clinical trial, the following correlation was identified:[19]

- t(4;14)(p16;q32), t(14;16)(q32;q23), and -17p13 all had poor prognosis with median survival 25 months
- -13q14 had intermediate prognosis with median survival 42 months
- All other cytogenetic abnormalities had good prognosis with median survival 50 months.

Cytogenetic abnormalities of chromosome 13 including deletion 13 occur in about one-third of patients and are associated with poorer prognosis

All of these prognostic variables were evaluated for their association with ISS stage (and therefore survival) within the ISS validation study with 10,750 myeloma patients.[14] The following factors were associated with advanced stage:

- Age >65 years ($p<0.001$)
- Beta-2-microglobulin 3.5 mg/L ($p<0.001$)
- Albumin <3.5 g/dL ($p<0.001$)
- Hemoglobin <10 g/dL ($p<0.001$)
- Creatinine 2 mg/dL ($p<0.001$)
- Platelets <130,000/microL ($p<0.001$)
- Calcium 10 mg/dL ($p<0.001$)
- >3 lytic bone lesions ($p<0.001$)
- C Reactive Protein (CRP) 0.8 mg/dL ($p<0.001$)
- Lactose dehydrogenase (LDH) above normal ($p<0.001$)
- Bone marrow plasma cells 33% ($p<0.001$)
- Performance status 2 ($p<0.001$)
- Durie-Salmon Stage III (A or B) ($p<0.001$)
- Any clonal cytogenetic abnormality ($p=0.093$)
- Complex karyotype ($p=0.162$)
- Deletion of chromosome 13 by cytogenetics ($p=0.112$)
- Deletion of chromosome 13 by fluorescence in situ hybridization (FISH; $p=0.075$)
- t(11;14) ($p=0.921$)

- t(4;14) (p=0.035)

Other predictors have been considered. Overexpression of cyclin D1 has variably predicted increased and decreased survival.[10] Measures of angiogenesis such as bone marrow microvessel density predicted survival in a study of 36 patients with multiple myeloma such that median survivals for patients with low-, intermediate-, or high-grade bone marrow angiogenesis were 77, 30, and 14 months, respectively.[20]

Treatment

Approach to treatment. The stage of the disease at presentation is a strong determinant of survival, but it has little influence on the choice of therapy since almost all patients have generalized disease except for rare patients with solitary bone tumors or extramedullary plasmacytomas.[7] Treatment selection is influenced by the age, general health of the patient, prior therapy, presence of complications of the disease (e.g., renal dysfunction), presence of complications of previous therapies (e.g., neuropathy), whether a stem cell transplantation (SCT) is planned, and patient preference.

Treatment goals and assessment. For the majority of patients with multiple myeloma, the goal of therapy is prolonging survival, relief of symptoms and disability due to the disease, and maximizing quality of life. Treatment programs are evaluated by the proportion of patients achieving an objective response, the duration of that response, survival, and adverse effects. Only a minority of patients—predominantly those with isolated plasmacytomas—have truly curable myeloma.[10] Approximately 60 percent respond to initial conventional chemotherapy; complete remissions are rare and nearly all patients relapse resulting in estimated survival rates of 25 percent at 5 years and <10 percent at 10 years.[17] For patients with progressive disease after initial therapy, response rates decrease for each subsequent treatment. Melphalan-based high-dose chemotherapy with hematopoietic stem-cell support increases the rate of complete remission and extends event-free and overall survival. However, most patients still relapse, and options for salvage therapy are limited.

Several sets of response criteria exist. It is critical that the efficacy of an intervention for myeloma be reported in the context of the response criteria used. Response criteria include the Chronic Leukemia and Myeloma Task Force criteria originally published in 1968, the Southwest Cancer Chemotherapy Study Group criteria published in 1972, MRC Myelomatosis Trials criteria published in 1992, and the EBMT/IBMTR/ABMTR criteria (also known as the Blade criteria) published in 1998.[17] The definition of complete response (CR) has been fairly consistent across the different sets of criteria (Figure 8), although some authors will report "near CR" in addition to CR. "Near CR" is persistent evidence of monoclonal protein by immunofixation (IFE) but normalization of all other parameters of the illness.[21]

Partial responses are variably reported. Most are reported in terms of the M-protein response (a.k.a. paraprotein response, PPR), since the majority of multiple myelomas have an overabundance of this monoclonal protein. There are usually corollary response cut-offs for Bence Jones proteins, although the absolute numbers for the expected response in the urine are usually higher. The Blade criteria also specify Minimal Response criteria corresponding to a

PPR of 25-49 percent. Some authors present their own response standard, starting as low as a PPR of 25 percent. As described in Figure 9, we have attempted to normalize PPR across studies starting with an objective response rate of at least 25 percent, but also reporting PPRs at the various levels to accommodate to the various ways that PPR is reported.

The Blade criteria are presented in an abbreviated format as part of Figure 8.[17]

Figure 8: Response Criteria for Multiple Myeloma
The EBMT/IBMTR/ABMTR (a.k.a. Blade) criteria

Complete response[#]	--Lack of detectable M-protein in serum or urine by immunoelectrophoresis & immunofixation, maintained for a minimum of 6 weeks --Bone marrow biopsy with <5% plasma cells --No increase in size or number of bone lesions --Disappearance of plasmacytomas (Median survival = 8 yrs)
Partial response[#]	--Reduction in serum M-protein by at least 50%, maintained for at least 6 weeks --Reduction in urine Bence Jones protein by at least 90% or <200mg, maintained for at least 6 weeks --If non-secretory, reduction in bone marrow plasma cells by at least 50%, maintained for at least 6 weeks --No increase in size or number of bone lesions (Median survival = 4 yrs)
Minimal Response[#]	--Reduction in serum M-protein by at least 25-49%, maintained for at least 6 weeks --Reduction in urine Bence Jones protein by at least 50-89%, maintained for at least 6 weeks --If non-secretory, reduction in bone marrow plasma cells by at least 25-49%, maintained for at least 6 weeks --No increase in size or number of bone lesions
Disease progression[#]	-->25% increase in M-protein, Bence Jones protein, or bone marrow plasma cells --An increase in size of bony lesions or plasmacytomas or appearance of new lesions --Hypercalcemia
Stable disease[#]	No significant changes is measurements of disease meeting criteria for at least minimal response or disease progression Bone marrow biopsy shows no change in plasma cell infiltration consistent with M protein decrease.
Overall survival[†]	The percentage of subjects in a study who have survived for a defined period of time. Usually reported as time since diagnosis or treatment. Also called the survival rate.
Time to progression[†]	A measure of time after a disease is diagnosed (or treated) until the disease starts to get worse.
Progression-free survival[†]	One type of measurement that can be used in a clinical study or trial to help determine whether a new treatment is effective. It refers to the probability that a patient will remain alive, without the disease getting worse.
Disease-free survival[12]	Length of time after treatment during which no cancer is found. Can be reported for an individual patient or for a study population.
Event-free survival*	Length of time after treatment that a participant in a clinical study remains free of pre-defined events. Events are defined by the study and can include adverse treatment effects, tumor recurrence/progression, or survival.
Survival rate[†]	The percentage of people in a study or treatment group who are alive for a given period of time after diagnosis. This is commonly expressed as 5-year survival.

Figure 8: Response Criteria for Multiple Myeloma
The EBMT/IBMTR/ABMTR (a.k.a. Blade) criteria

[#]Derived from: Blade J, Samson D, Reece D, et al.: Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 102:1115-23, 1998
[†]Quoted from the NCI's website.
*Definition derived from http://www.intelihealth.com/IH/ihtPrint/WSIHW000/8096/8241/347567.html?d=dmtContent&hide=t&k=basePrint#efsurvival.

Treatment options. Patients with asymptomatic (smoldering, indolent) multiple myeloma who have no lytic bone lesions and normal renal function may be safely observed by "watchful waiting." [22] In a randomized trial of 145 asymptomatic multiple myeloma patients comparing oral melphalan plus prednisone started at diagnosis versus at the time of disease progression, there was no difference in overall survival (OS) or myeloma paraprotein response (PPR). With a median follow up of 95 months, the median survival was 69 months. The overall response rate was 55 percent and the median duration of response was 48 months. A Cochrane Systematic Review on early versus delayed treatment for early stage multiple myeloma included 3 randomized trials and 262 participants.[23] Early treatment delayed myeloma progression (odds ratio (OR) = 0.16, 95 percent CI: 0.09-0.29), with a trend towards reduced vertebral compression (OR = 0.18, 95 percent CI: 0.02-1.59). No significant effects on mortality and response rate were seen (OR = 1.11, 95 percent CI: 0.67-1.84, and OR = 0.63, 95 percent CI: 0.33-1.23, respectively). Early treatment may have increased the risk of acute leukemia (OR = 3.20, 95 percent CI: 0.55-18.73).

For patients with symptomatic myeloma, the therapy is matched to the patient's overall physical health, ability to tolerate the interventions, prognosis, and personal preferences. Conventional oral chemotherapy, a less aggressive route, typically includes alkylating agents with prednisone (e.g., oral melphalan and prednisone (MP) or cyclophosphamide and prednisone (CP)). These oral programs improve prognosis as compared to no therapy with a median survival of 24 to 30 months and a 10-year survival of 3 percent.[4] Length of treatment is usually 1 to 2 years, continuing until the patient responds or disease stabilizes.[12]

More aggressive infusional regimens have more risk of toxicity but higher chances of response. A systematic review and meta-analysis of 27 trials comparing MP versus combination chemotherapy (CCT) was conducted in 1992 and then updated in 1998.[24] A total of 6,633 patient participants were included, for whom individual patient data were provided to reviewers for 4,930 and data were abstracted for the remaining 1,703. Among the CCT arms, chemotherapeutic intensity was standardized to the Southwest Oncology Group (SWOG) 7704/7705 regimen of vincristine, melphalan, cyclophosphamide, and prednisone (VMCP) alternating with vincristine, carmustine (BCNU), doxorubicin, and prednisone (VBAP). CCT varied and included VMCP + VBAP/VCAP (N=6 studies, VCAP=VBAP with cyclophosphamide substituted for the carmustine), regimen with another anthracycline (N=3 studies), VMP (N=2 studies, VMP=MP with vincristine added), VMCP alone (4 studies), VBCMP (N=3 studies, VBMCP = vincristine, carmustine, melphalan, cyclophosphamide, and prednisone), MOCCA (N=2 studies, MOCCA = vincristine, cyclophosphamide, lomustine, melphalan, and methylprednisolone), MCBP (N=3 studies, MCBP = melphalan, cyclophosphamide, carmustine, and prednisone), other chemotherapy (N=7 studies). The VAD

regimen (vincristine, doxorubicin, and dexamethasone) was not included in this review. The review did not specify whether patients were previously untreated or treated, however inspection of over half of the individual studies included suggests that the studies were of previously untreated patients. Overall, there was no significant difference in survival between patients allocated to CCT or MP *(*p = 0.6). The point estimate for the proportional reduction in the annual odds of death was 1.5 percent in favor of CCT but the 95 percent CIs ranged from an 8 percent benefit in favor of CCT to a 5 percent benefit in favor of MP. This range corresponded to an absolute difference in survival, at 3 years, of between 3 percent in favor of CCT or 2 percent in favor of MP. Median survival in both CCT and MP arms was 29 months and 5-year survival was 24 percent. Among all included participants age <50 years (N=526, 11 percent) the 5-year survival was 31 percent, age 50-64 (N=2,150, 44 percent) 5-year survival was 27 percent, age 65-74 (N=1,617, 33 percent) 5-year survival was 21 percent, and age 75 (N=497, 10 percent) 5-year survival was 12 percent. The main finding supporting CCT over MP was that response rates were significantly higher with CCT (60 percent vs. 53.2 percent; p < 0.00001). Response rates were not standardized across a PPR norm, but rather trials were scored according to whatever PPR was reported for that trial.

Three randomized studies of VBCMP were included in the systematic review just described.[25-28] The US Eastern Cooperative Oncology Group (ECOG) study published in 1997 included the greatest number of patients (N=479).[25] Previously untreated patients with multiple myeloma patients were randomized to VBCMP (N=235) or MP (N=230). VBCMP is given intravenously plus orally while MP is oral. Forty-two percent were Durie-Salmon Stage I-II, 58 percent were Stage III. Median age for VBCMP was 64 (range 26-85) with 27 percent age 70; median age for MP was 64 (range 21-84) with 26 percent age 70. Objective responses were defined as a M-protein PPR of 50 percent or a Bence Jones decrease by 90 percent. Objective responses were higher for VBCMP at 72 percent compared with MP at 51 percent (p<0.001). Response duration with VBCMP was longer with median 24 months vs. MP median 18 months (p=0.007). Three year response duration was 34 percent for VBCMP and 20 percent for MP. There was no significant difference in survival with median survival for VBCMP of 29 months and for MP 27 months (p=0.30). There were more early deaths with VBMCP (35 vs. 20). VBCMP early deaths were predominantly among those of advanced age 70 (57 percent) or Stage III (71 percent), with 40 percent having both advanced age and stage. At least some Grade 3 or 4 toxicity was described for 64 percent of VBMCP patients as opposed to 54 percent of MP patients (p<0.035). These toxicities for VBMCP and MP respectively were Grade 3 or 4 infection (14 percent vs. 14 percent, p=not significant), Grade 2 nausea/vomiting (31 percent vs. 10 percent, p<0.001), Grade 2 peripheral neuropathy (24 percent vs. 2 percent, p<0.001), Grade 1 alopecia (25 percent vs. 7 percent, p<0.001), Grade 3 or 4 neutropenia (46 percent vs. 37 percent, p=0.07), and Grade 3 or 4 thrombocytopenia (23 percent vs. 23 percent, p=not significant).

The traditional infusional VAD regimen was first described by Barlogie et al. in 1984.[29] Patients receive vincristine (0.4 mg) and doxorubicin (9 mg/m^2, a.k.a. Adriamycin) daily by continuous infusion for four days plus dexamethasone (dex) 40 mg orally daily on days 1 to 4, 9 to 12, and 17 to 20 of each of the monthly cycles. Results for the infusional VAD program have been reported for both previously untreated patients, as well as those with relapsed or resistant disease. In the original report of VAD, 14/20 (70 percent %) patients with relapsing or refractory myeloma resistant to alkylating agents had a PPR of 75 percent and 3/9 (33 percent) resistant to

doxorubicin had a PPR of 75 percent.[29] In the first major report of VAD for previously untreated patients published in 1990, 32 participants treated with VAD achieved an overall response of 84 percent, with 28 percent entering a complete remission (CR).[30] Response was rapid, with near-maximum response occurring after two courses of treatment. Median response duration was 18 months. Projected median survival was 44 months, with 75 percent of all patients and 83 percent of responders being alive at 2 years. In a report in which infusional VAD given as initial therapy to 75 untreated myeloma patients, the overall and complete response rates were 84 percent and 27 percent, respectively, and median survival was 36 months.[31] In the same report, 67 patients with relapsed or refractory disease treated with VAD had overall and complete response rates of 61 percent and 3 percent, respectively, and median survival was 10 months. Besides overall adverse effects related to therapy (see below) a major limitation of the infusional VAD regimen is that vincristine and doxorubicin have to be administered through a central venous catheter, with risks of sepsis and thromboembolic events. Infectious complications have been reported at 54-60 percent, depending upon whether prophylactic antibiotics are used.[32]

In 1998, Mineur et al. reported a randomized trial of VAD vs. VBCMP in 105 patients who had progressed after treatment with CP.[33] Mean age for VAD (N=50) was 62 (SD 10) and mean age for VBCMP (N=53) was 63 (SD 9). Response was defined as a PPR of 50 percent. After 4 months of therapy, response rates for VAD were 22 percent and VBCMP 13 percent. There were 5 deaths with VAD (12 percent) and 8 with VBCMP (15 percent). Median survival was 17 months and not significantly different between interventions (VAD 16 months, VBCMP 17.5 months, p=0.75). Specific toxicity rates were not described. Neutropenic infections led to four deaths (VAD 2 and VMBCP 2). Corticosteroids were responsible for major toxic effects in two cases both in the VAD arm (pancreatitis and diabetes mellitus for one case, candidal esophagitis for the other). One patient developed cardiotoxicity after three cycles of VAD and in another patient hematological toxicity after VAD required treatment modification.

The traditional VAD regimen has been modified to a rapid infusion regimen and a regimen that substitutes liposomal doxorubicin (Doxil, VDD). Both eliminate the need for an indwelling central venous catheter. Segeren et al. reported a phase II study of the rapid infusion regimen in 139 patients with untreated multiple myeloma (median age 53, range 32-65).[32] The doxorubicin was administered over 30 min daily for 4 days instead of as a continuous infusion. Patients still needed to present for treatment daily for 4 days each cycle. PPR of 50 percent was achieved in 86 percent with CR in 7 percent. Among a total of 416 cycles of rapid infusion VAD administered, toxicity of Grade 2 included nausea/vomiting 2 percent, mucositis 2 percent, liver test abnormalities 2 percent, renal insufficiency 1 percent including one patient who developed renal failure, and cardiac problems in 1 percent (arrhythmias, myocardial infarction). A total of 18 percent of patients developed neurotoxicity and 27 percent developed infections. The VDD is advantageous as it is expected to have less cardiotoxicity and does not require a central venous catheter. In 2003, Dimopoulos et al. described a randomized trial of VAD administered as intravenous bolus injection vs. VDD for patients with previously untreated myeloma.[34] Median age for bolus VAD (N=127) was 66 (37-88) and median age for VDD (N=132) was 65 (37-88). PPR of 50 percent was achieved in 61 percent with CR in 13 percent with either regimen. Median time to progression was 24 months. Median overall survival had not been reached and was expected to exceed 40 months in both arms. Toxicities in the bolus VAD and VDD arms respectively were Grade 2 neutropenia (20 percent vs. 15 percent, p=0.7), Grade 2

thrombocytopenia (10 percent vs. 5 percent, p=0.2), Grade 2 nausea/vomiting (4 percent vs. 5 percent, p=0.8), Grade 1 alopecia (55 percent vs. 37 percent, p<0.001), Grade 2 mucositis (7 percent vs. 15 percent, p=0.3), Grade 2 erythrodysesthesia (2 percent vs. 13 percent, p=0.03), and Grade 2 neurotoxicity (13 percent vs. 15 percent, p=0.9). Steroid-related side-effects occurred with equal frequency in both arms; Cushingoid features were noted in approximately one-fifth of patients, hyperglycemia in 15 percent of patients treated with bolus VAD bolus and in 12 percent treated with VDD, mood changes in <10 percent of patients in either arm and peptic ulcer disease, hiccups and proximal muscle weakness each occurred in <5 percent of patients. Infections, which required antibiotics, including neutropenic fever, were noted in 17 percent of patients treated with bolus VAD and 18 percent treated with VDD. Eleven patients (9 percent) in the bolus VAD arm and 14 (11 percent) in the VDD arm died within the first 4 months of treatment. Among the 11 patients treated with bolus VAD, three deaths were due to infections and 2 were due to heart failure and/or myocardial infarction. Of the 14 early deaths in the VDD arm, 4 were due to infections and 3 were due to heart failure and/or myocardial infarction.

Response rates with PPR 50 percent can be summarized as follows:

- Untreated multiple myeloma treated with VBCMP 72 percent
- Refractory/relapsed multiple myeloma treated with VBCMP 13 percent
- Untreated multiple myeloma treated with VAD 61-86 percent
- Refractory/relapsed multiple myeloma treated with VAD 22-70 percent

Direct comparison of VBCMP and VAD suggests that VAD is somewhat superior. While response rates are higher than traditional MP and CP chemotherapy, CCT regimens including VBCMP do not improve survival over MP and VAD does not improve survival over VBCMP. Earlier remission is an advantage in patients with hypercalcemia or renal failure, and the VAD regimen is safer in patients with renal failure, since the drugs are not excreted by the kidneys. The same regimen of dexamethasone alone has also induced a rapid remission, but the response rate was 15 percent lower than that with VAD.[8] Because of the rapid remission induced by either VAD or dexamethasone alone, usually no more than two courses are necessary to determine whether the myeloma is responding to treatment.

Further improvements in prognosis have occurred due to the introduction of newer therapies such as pulse corticosteroids, thalidomide, bortezomib, and autologous and allogeneic stem cell transplantation. For those patients who can tolerate it, high dose chemotherapy followed by single or double autologous SCT improves survival over combination chemotherapy alone.[8] In a trial of 399 participants under age 60 and of adequate performance status initially randomized to VAD treatment followed by single or double autologous SCT, the probability of surviving event-free for seven years after the diagnosis was 10 percent in the single-transplant group and 20 percent in the double-transplant group (p=0.03). The estimated overall seven-year survival rate was 21 percent for single and 42 percent for double-transplants (p=0.01).

The Technology

A large body of recent work demonstrates a major role for bone marrow angiogenesis in the biology of multiple myeloma.[8] The degree of marrow angiogenesis correlates with measures of cell proliferation, such as the plasma cell labeling index (PCLI) and the stage of the disease.[8, 20, 35] The role of angiogenesis in the progression of malignancies including myeloma provided the rationale for the use of antiangiogenic therapy for myeloma.

Thalidomide (α-*N*-[36] glutarimide, $C_{13}H_{10}N_2O_4$), a glutamic acid derivative, was initially introduced as a sedative in the late 1950s. It was subsequently withdrawn from the market because of its teratogenic effects. Clinical observations dating back to 1965 supported the potential beneficial effect of thalidomide in multiple myeloma and advanced cancers,[37] but its antiangiogenic properties were not realized until the mid-1990s. The use of thalidomide for multiple myeloma escalated rapidly after a 1999 publication by Singhal et al. documenting objective responses with thalidomide in patients with refractory myeloma.[35]

Thalidomide undergoes rapid interconversion between the *R*-enantiomer and the *S*-enantiomer and spontaneous cleavage to more than 12 metabolites in solutions at physiologic pH.[38] Study of its mechanism of action has proven difficult because its activity in most in vitro assays is moderate at best, and its effects in animal models are dependent on the species and the route of administration. Proposed mechanisms include the inhibition of tumor necrosis factor alpha (TNF-alpha), prevention of free-radical–mediated DNA damage, suppression of angiogenesis, increased in cell mediated immunity, alteration of the expression of cellular adhesion molecules, inhibition of NF-*k*B, and decreased inflammation.[8]

On July 16, 1998, the Food and Drug Administration (FDA) approved thalidomide for use in treating leprosy (Hansen's disease). Evaluation of the medication for symptoms related to AIDS, management of rheumatologic disease, and control of cancer quickly followed.

To prevent fetal exposure to thalidomide, the drug's manufacturer developed the System for Thalidomide Education and Prescribing Safety (STEPS) program. Only registered physicians may prescribe the drug to patients and those patients—both male and female—must comply with mandatory contraceptive measures, patient registration, and patient surveys. Thalidomide may be dispensed only by licensed pharmacists who are registered in the S.T.E.P.S. program and have been educated to understand the risk of severe birth defects if thalidomide is used during pregnancy. In addition, female patients' prescriptions will not be filled without a physician's written report of a negative pregnancy test that has been conducted within 24 hours of starting thalidomide therapy. Pregnancy testing is required weekly during the first month of use, then monthly thereafter in women with regular menses, or every two weeks if menses are irregular. Prescriptions are only for one month's supply. A female patient must abstain from sexual intercourse or use two highly effective methods of birth control at the same time for at least one month before receiving thalidomide and continue their use until one month after the last thalidomide dose. All patients must participate in a mandatory registry that will provide follow-up to detect any adverse effects of using thalidomide and will hopefully identify areas in which safeguards need to be improved, if problems occur.

Thalidomide itself has been off patent for decades.[39] Celgene, the U.S. producer of thalidomide, has patented the drug delivery system, S.T.E.P.S., instead. They originally started selling thalidomide capsules in the U.S. as an AIDS wasting medication. Prices have increased as the medication has started to be used for cancer. Celgene is seeking FDA approval to market thalidomide for multiple myeloma; currently, since the drug is only approved for leprosy, Celgene sales representatives aren't allowed to directly promote it for other uses. In October 2004, Celgene received a FDA approvable letter for potential accelerated approval of thalidomide in multiple myeloma; results of their final submission are outstanding.

Thalidomide is usually administered in a dosage of 200 mg per day, which is increased to 400 mg per day after two to four weeks, if tolerated. Lower doses (50 to 100 mg) are being investigated. Doses above 200 mg are generally avoided by using thalidomide in combination with corticosteroids or chemotherapy.

Scope and Key Questions

The key questions for this review were developed with experts in the field of oncology, health economics, and health policy. The key questions are as follows:

1. For patients with relapsed or refractory multiple myeloma, what is the effect of thalidomide compared to standard chemotherapy regimens (e.g., VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, and prednisone) and VAD (vincristine, doxorubicin, and dexamethasone)) on 2-year survival, disease-free survival, CR, PR (m-protein), and quality of life?

2. For patients with relapsed or refractory multiple myeloma, what is the effect of thalidomide compared to standard chemotherapy regimens (e.g., VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, and prednisone) and VAD (vincristine, doxorubicin, dexamethasone)) on adverse effects, tolerability and compliance?

3. What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy?

As there was emerging information regarding the role of thalidomide for newly diagnosed and smoldering multiple myeloma, these groups were also considered as part of this review.

Methods

Search Strategy

The search strategy was constructed by combining three concepts: (1) the intervention thalidomide; (2) the disease multiple myeloma; and (3) prospective clinical trials. To identify the intervention concept, we used the MeSH heading *thalidomide* and text word searching for the following text strings: *thalidomid* and *thalidomide$*. The disease concept was implemented using the text word and MeSH heading searching for *multiple myeloma*. A published strategy, validated for finding randomized controlled trials (RCTs), was used to identify prospective clinical trials. This strategy is designed to find all prospective clinical trials (maximize sensitivity), rather than to eliminate non-randomized trials (maximize specificity), and so is appropriate for this study's goal of finding phase II and III prospective clinical trials. Finally, the three concepts were combined (Boolean "or"). The strategy was executed in MEDLINE (1966 through September 2004, updated August, 2005) and limited to articles published in the English language. The exact text of the OVID MEDLINE versions of the search strategy is provided in Appendix A.

Supplemental searches were conducted in International Pharmaceutical Abstracts, *The Cochrane Library* (Central Register of Controlled Trials (CENTRAL) and Health Technology Assessment (HTA) database), American Society of Hematology 2004 annual meeting abstracts database, and in the American Society of Clinical Oncology 2004 and 2005 annual meeting abstracts databases. References lists of identified studies and relevant systematic reviews and meta-analyses were hand-checked. Additional articles not indexed in the major bibliographies by August 2005 were identified through ongoing searches and discussions with field experts and monitoring new sources.

Selection Criteria

Each citation identified from the search strategies was evaluated according to the following selection criteria. Evaluations were performed by the authors.

Inclusion criteria were as follows:

Patients	Patients with multiple myeloma
Interventions	Thalidomide
Comparators	Any

Study designs:

- *For **efficacy** questions*: Prospective clinical trials; may be phase II uncontrolled, or phase III randomized controlled trials.

- *For studies of **adverse effects**:* May be retrospective or prospective case series, cohort studies, or clinical trials provided the number of patients treated (at risk for adverse effects) as well as the number with adverse effects can be ascertained.

- *For studies of **predictors** of response:* May be retrospective or prospective case series, cohort studies, case-control studies, or clinical trials provided the response can be ascertained for patients with and without the predictor.

Outcomes:

- *For **efficacy** questions*: Survival, disease-free survival, tumor response, and quality of life (QOL). Tumor response was defined according to Figure 8.

- *For studies of **adverse effects**:* Adverse effects, tolerability, and compliance with treatment.

- *For studies of **predictors** of response:* Predictive value of patient or tumor characteristics that are associated with clinically important differences in treatment response that are:
  1) related to the mechanism of action of the drug (i.e., molecular target); and
  2) candidates for diagnostic testing (even if not commercially or clinically available currently (e.g., Polymerase Chain Reaction)).

Data Abstraction

The following data were abstracted from included studies: study design, population characteristics (including sex, age, and diagnosis), eligibility and exclusion criteria, interventions (dose and duration), outcomes assessed and results for each outcome.

We developed data collection forms in Excel (Microsoft; Redmond, WA) and summarized the data in evidence tables formatted like those in a 2003 report from the National Institute for Clinical Excellence (NICE) on imatinib for gastrointestinal stromal cell tumors.[40]

Quality Assessment

We assessed the quality of included studies by evaluating elements of internal validity (e.g., randomization and allocation concealment; similarity of compared groups at baseline; specification of eligibility criteria; blinding of assessors, care providers, and patients) and external validity (e.g., description of the patient population, similarity to the target population of the report, use of highly selective criteria).

We used as a framework the quality assessment criteria from NICE.[40] These are displayed in Appendix B. They provide specific criteria for the range of study designs used in this report including experimental studies, cohort studies, case-control studies, and case series.

Point scores were allocated by assigning one point for each quality category. There were a total of 6 possible categories. Quality ratings of "yes" to a quality criteria were assigned one point; no and unknown were both assigned zero points. The last category, adequate description of subseries, was not applicable to all studies. Hence, the total possible quality points were five or six depending upon the applicability of the subseries category. High quality studies were those with ≥ 4/6 points. Individual points for each article are summarized in the Appendix B table.

Abstract quality was not scored.

Data Synthesis

In addition to the data abstraction and quality analysis, a narrative description of study findings was prepared. Further quantitative analyses were considered, but the available data were not adequate to support these.

Since the various studies included in this review variably used the different response criteria or created their own, we have reported all of the paraprotein responses from the various studies using the same format according to the following cut-offs:

Figure 9: Reporting of paraprotein responses across studies

Overall Response (≥25%)* = x%
m protein reduction:
100% = x%
≥90%* = x%
≥75%* = x%
≥50%* = x%
≥25-49%* = x%

*Note: To accommodate the various ways of presenting response rates found in this literature, we have considered the Overall Response to capture responses from 25-100%. Sub-categories generally respresent 90-99%, 75-89%, 50-74%, and 25-49% - or more inclusive if the paper was presented in that manner.

Numbers were not provided for all of the categories in all of the studies. When a particular number was not available it was reported as "not stated" (NS).

When comparing response rates with the original studies for VBCMP, VAD, or other chemotherapeutic interventions for multiple myeloma, it is important to consider the definition of response used in the individual studies in order to ensure that like comparisons are made. It can be misleading to just compare the PPR50 percent rows, as some studies report PPR50 percent to mean all responses that were greater than 50 percent (i.e., 50-100 percent) and others indicate just those reflected in that response level (e.g., 50-74 percent with next response level at 75 percent).

Results

The search strategy yielded 250 articles. The selection process is described below:

Identified by search strategy
(N = 250)
|------ Excluded based on review of abstract
| (N = 115)
|
Included based on review of abstract
(N = 135)
|
|------ Unable to locate
| (N = 6)
|
|------ Excluded based on full-text review
| (N = 31)
| 16 not phase II-III for efficacy
| 3 Review article
| 3 no primary or original data (review article)
| 2 CS not selected on response
| 2 wrong drug
| 2 wrong outcome
| 1 wrong disease
| 1 CS selected on AE
| 1 No quantification of association
|
Included in full-text review and evidence tables
(N = 96)

The 96 included reports comprised 62 full reports and 34 abstract-only publications. Each report and the sections within this review in which they fell (i.e., efficacy, adverse effects, predictors) is reviewed in the Included Studies table.

There were a total of 69 studies that presented some efficacy findings. Among these, study designs included 7 phase III controlled clinical trials and 62 phase II trials. Of the phase III trials, two were published as full text articles. Neither presented unblinded results. The five remaining phase III trials were published in abstract form only.

Quality of the studies was generally poor (Appendix B and Tables 1a, 1b and 1c). Less than half of studies achieved a threshold quality score of 4/6. Quality was poor across all study types—efficacy, adverse effects, and predictors. The large volume of abstracts that could not be assessed from a quality standpoint made overall quality even more concerning.

A review of all studies included in this report, including phase, thalidomide dose, comparator, size, and quality is presented in Table 1. Efficacy studies are broken down into category

corresponding to thalidomide drug combinations and presence or absence of prior myeloma therapies (see Figure 10; Tables 2-8). Adverse effect tables are presented according to those that match studies presented in the efficacy tables (Table 9) and independent studies representing adverse effect findings (Table 10). Predictors are organized by mechanism of action (Table 11), demographic factors (Table 12) clinical predictors (Table 13), and predictors related to thalidomide dosage or response (Table 14).

Table 1a. Details of included studies –Thalidomide efficacy studies (corresponding to Tables 2-8)

First Author, Year	Trial Phase	Thal dose per day (mg)	Comparator	N	Quality	Comments
Thalidomide only–newly diagnosed/previously untreated multiple myeloma (TABLE 2)						
Rajkumar, 2001[41]	II	200-800		16	4/5	Asymptomatic SMM or IMM
Rajkumar, 2003[42]	II	50-800		29	3/5	Asymptomatic SMM or IMM
Total # studies in category: 2 *Total abstracts (*): 0*	*Total # Phase III: 0*			*Total N: 45*	*Total with quality 4/6: 1 of 2 (50%)*	
Thalidomide only–advanced/refractory/resistant multiple myeloma (TABLE 3)						
Barlogie, 2001[43]	II	200-800		169	4/6	
Corso, 2002[44]	II	200	CAVD chemo	21	0/5	
Hattori, 2004[45]	II	200-400		44	4/5	
Hus, 2001[46]	II	200-400	Historical control	53	3/6	Also with hypocellular BM, pancytopenia
Johnston, 2002[47]	II	50-500		12	3/5	
Juliusson, 2000[48]	II	200-800		23	1/5	
Kees, 2003[49]	II	50-400	Thal/Dex Thal/VAD	24	2/6	
*Kroeger, 2004 (ASH 1646)[50]	II	100-300		18	*	Prior to donor lymphocyte infusion
Kumar, 2003[51]	II	200-800		32	4/5	
Neben, Moehler, Egerer et al. 2001[52]	II	100-400		54	3/6	
Rajkumar, 2000[53]	II	200-800		16	3/5	
Richardson, 2004[54]	II	200-600		26	3/5	
Schey, 2003[55]	II	100-600		69	4/5	
Singhal, 1999[35]	II	200-800		84	5/5	
Tosi, 2001[56]	II	100-800		11	3/5	
Tosi, 2002 [57]	II	100-800		60	2/5	
Waage, 2004[58]	II	200-800		65	4/5	
Yakoub-Agha, 2000[59]	II	100-800		27	4/5	
Yakoub-Agha, 2002[60]	II	50-800		83	6/6	
Total # studies in category: 19 *Total abstracts (*): 1*	*Total # Phase III: 0*			*Total N: 891*	*Total with quality 4/6: 8 of 18 (44%)*	

Table 1a. Details of included studies –Thalidomide efficacy studies (corresponding to Tables 2-8)

First Author, Year	Trial Phase	Thal dose per day (mg)	Comparator	N	Quality	Comments
Thalidomide plus dexamethasone–newly diagnosed/previously untreated multiple myeloma (TABLE 4)						
*Rajkumar, 2004 (ASH 205)[61]; *Rajkumar, 2004 (ASCO 6508)[62]	III	200	Dex	198	*	RCT of Thal/Dex vs. Dex
*Ludwig, 2005 (ASCO 6537)[63]	III	200	MP	137	*	RCT of Thal/dex vs. MP for elderly pts; not completed enrollment;
Alexanian, 2003[64]	II	100-400		NS	1/6	
Rajkumar, 2002 [65]	II	50-200		50	4/5	
*Rajkumar, 2005 (ASCO 6632)[66]	II	200		24	*	
Weber, 2003[67]	II	100-600	Thal	68	3/6	Included pts that received thal alone
Total # studies in category: 6 Total abstracts (*): 4	*Total # Phase III: 2*			*Total N: 477+*	*Total with quality 4/6: 1 of 3 (33%)*	
Thalidomide plus dexamethasone–advanced/refractory/resistant multiple Myeloma (TABLE 5)						
Alexanian, 2003[64]	II	200-800		43	1/6	Mixed clinical settings
Alexanian, 2003[64]; Anagnotopoulos, 2003[68]	II	200-600		47	1/6 1/6	2 reports that combine data
Bernardeschi, 2004[69]	II	100-400		20	2/5	
Dimopoulos, 2001[70]	II	200-400		44	3/5	
Myers, 2000[71]; Myers, 2001[72]; Myers, 2002[73]	II	50-400		27	2/5	3 reports about same group of pts
Palumbo, 2001[74]	II	100		77	2/5	
Palumbo, 2004[75]	II	50-100	Historical control	120	6/6	
*Reece, 2004 (ASH 4934)[76]	II	50-400	Thal vs. Thal/dex	29	*	Thal/dex could have been thal/dex or thal/prednisone
Tosi, 2004 (ASH 4898)[77]	II	100-400		20	4/5	All with renal failure
Total # studies in category: 9 Total abstracts (*): 1	*Total # Phase III: 0*			*Total N: 427*	*Total with quality 4/6: 2 of 9 (22%)*	
Thalidomide plus other agents–newly diagnosed/previously untreated multiple myeloma (TABLE 6)						
*Facon, 2004 (ASH 206)[78]	III	400	See comment	200	*	RCT of MP vs. MP-thal, vs. high dose melphalan + VAD + SCT; not completed enrollment; age 75 yrs
*Palumbo, 2004 (ASH 207)[79]	III	100	MP	102	*	RCT of MP vs. MP-thal
*Alexanian, 2004 (ASH 210)[80]	II	100-200		25	*	Bortezomib + doxorubicin + thal + dex

Table 1a. Details of included studies –Thalidomide efficacy studies (corresponding to Tables 2-8)

First Author, Year	Trial Phase	Thal dose per day (mg)	Comparator	N	Quality	Comments
*Chanan-Khan, Miller, McCarthy, Koryzna et al., 2004 (ASH 3463)[81]	II	100-200		11	*	VAD + thal
*Dimopoulos, 2004 (ASH 1482)[82]	II	300		43	*	Melphalan + dex + thal; not completed enrollment; age 75 yrs
*Hassoun, 2004 (ASH 2409)[83]	II	200		30	*	Doxorubicin + dex followed by thal/dex
*Klueppelberg, 2004 (ASH 4932)[84]; *Klueppelberg, 2004 (ASCO 6702)[85]; *Klueppelberg, 2005 (ASCO 6697)[86]	II	100		29	*	Thal + dex + zoledronate; 14% HIV+; 3 reports of ongoing study with increasing enrollment
Schutt, 2005[87]	II	200-400		31	5/5	Thal + vincristine + epirubicin + dex
Zervas, 2004[88]	II	200		39	3/5	Thal + VAD + extra dex
Total # studies in category: 9 Total abstracts (*): 9	*Total # Phase III: 2*			*Total N: 510*	*Total with quality 4/6: 1 of 2 (50%)*	
Thalidomide plus other agents–advanced/refractory/resistant multiple myeloma (TABLE 7)						
*Badros, 2004 (ASH 2400)[89]	II	100-400		30	*	Oblimerson + dex + thal
*Bibas, 2004 (ASH 4927)[90]	II	100+		30	*	Thal + dex + zoledronate
*Chanan-Khan, Miller, McCarthy, DiMiceli et al. 2004 (ASH 2421)[91]	II	200		13	*	Bortezomib + liposomal doxorubicin + thal
Biagi, 2001[92]	II	200-800		4	1/6	Thal + interferon
Ciepluch, 2002[93]	II	200-400		13	1/5	Thal + pamidronate
Dimopoulos, 2004[94]	II	400		53	3/5	Cyclophosphamide po + thal + dex
Garcia-Sanz, 2004[95]	II	200-800		66	4/5	Cyclophosphamide po + thal + dex
*Hollmig, 2004 (ASH 2399)[96]	II	50-100		14	*	Bortezomib + doxorubicin + thal + dex
Kasper, 2004[97]	II	100-400		15	2/5	Thal + pegylated interferon
Kropff, 2003[98]	II	100-400		57	5/5	Thal + dex + iv cyclophosphamide
Mileshkin, Biagi et al. 2003[99]	II	200-1000		75	5/6	Thal +/- interferon
*Mileshkin, 2005 (ASCO 8233)[100]	II	Up to 800		66	*	Thal + celecoxib; QOL outcomes
Offidani, Corvatta, Marconi, Malerba, et al. 2004 [101]	II	100-400		59	0/6	Thal +/- melphalan
Offidani, Corvatta, Marconi, Olivieri, et al. 2004[102]	II	100-600		50	6/6	Thal +/- melphalan
*Suvannasankha, 2005 (ASCO 6591)[103]	II	200		37	*	Thal + po cyclophosphamide + prednisone
*Teoh, 2004 (ASH 4915)[104]	II	50		18	*	Thal + dex + zoledronate

Table 1a. Details of included studies –Thalidomide efficacy studies (corresponding to Tables 2-8)

First Author, Year	Trial Phase	Thal dose per day (mg)	Comparator	N	Quality	Comments
*Williams, 2004 (ASH 1499)[105, 106]	II	100-200		62	*	Thal + dex + po cyclophosphamide; includes 24% newly diagnosed pts
*Zangari, Barlogie, Hollmig, et al. 2004 (ASH 1480)[107]	II	50-200	Bortezomib	79	*	Bortezomib + thal
Total # studies in category: 18 Total abstracts (*): 9	*Total # Phase III: 0*			*Total N: 741*	*Total with quality 4/6: 4 of 9 (44%)*	
Thalidomide used as part of the pre or post stem cell transplantation regimen (TABLE 8)						
*Attal, 2004 (ASH 535)[108]	III	NS	See comments	580	*	Thal for post-SCT maintenance: randomized btwn no maintenance, pamidronate, pamidronate + thal
Barlogie, 2002[109]	III	400	No thal	231	2/6	Randomized to thal vs. no thal at beginning of Total Therapy II program; not completed enrollment; doesn't present unblinded outcomes
*Barlogie, 2004 (ASH 1483)[110]				104	*	Second report of trial; 104 of 668 randomized pts to thal vs. no thal; follow up report
Lee, 2003[21]	III	50-400	See comments	236	4/5	DTPACE x 2 then if response randomized to SCT vs. DTPACE x 4; report is for only first 2 cycles of DTPACE
Alexanian, 2002[111]; Alexanian, 2003[64]	II	100-300		21	2/5 1/6	2 reports that combine data
*Sengar, 2005 (ASCO 6731)[112]	II?	50		17	*	Randomized btwn maintenance thal or interferon after SCT; unclear if Phase II or III; no unblinded data presented
*Stewart, 2004 (ASH 335)[113]	II	200-400		67	*	Thal + prednisone for post-SCT maintenance; randomized btwn thal 200 mg and 400 mg
Total # studies in category: 6 Total abstracts (*): 4	*Total # Phase III: 3*			*Total N: 1152*	*Total with quality 4/6: 1 of 4 (25%)*	

*Presented as peer-reviewed abstract only.
Abbreviations: autoSCT = autologous stem cell transplantation; BM = bone marrow; btwn = between; CAVD = lomustine + melphalan + etoposide + dexamethasone; chemo = chemotherapy; Dex = dexamethasone; DTPACE: Dex + thal + cisplatin + doxorubicin, cyclophosphamide + etoposide; HIV = human immunodeficiency virus; IMM = indolent multiple myeloma; iv = intravenous; MP = melphalan po + prednisone; N = number; NS = not stated; po = oral; pt(s) =

patient(s); QOL = quality of life; RCT = randomized controlled trial; SCT = stem cell transplantation; SMM = smoldering multiple myeloma; Thal = thalidomide; VAD = vincristine + doxorubicin + dexamethasone; vs. = versus; yrs = years

Table 1b. Details of included studies –Articles focusing on adverse effects due to thalidomide corresponding to Table 10 (in addition to adverse events information reported in efficacy studies and presented in Table 9)

First Author, Year	Thal dose per day (mg)	Comparator	N	Quality	Adverse event
*Anaissie, 2004 (ASH 3467)[114]	NS		553	*	Avascular necrosis
Badros, 2002[115]	200-800	w/ or w/o chemo	174	2/5	Subclinical hypothyroidism
Bowcock, 2002[116]	150	Historical control	41	0/5	Thromboembolism
Fahdi, 2004[117]	200	Placebo		4/6	Bradycardia
Hall, 2003[118]	200-800	Thal and thal/dex	77	1/5	Dermatological reactions
Hattori, 2004[45]	200-400		44	4/5	Cytopenias
*Singh, 2004 (ASCO 3142)[119]	NS		257	*	Thromboembolism
*Spencer, 2004 (ASCO 6655)[120]	200		83	*	Renal function
*Tosi, 2004 (ASH 4898)[77]	200	New dx vs. pretreated	74	*	Neurotoxicity
Tosi, 2005[121]	200-400		40	4/6	Late toxicity after 1 yr of thal; Neurotoxicity
Zangari, 2001[122]	400	Thal vs. no thal	100	0/5	Thromboembolism
Zangari, Saghafifar, et al. 2002[123]	400	Thal vs. no thal	62	0/6	Thromboembolism
Zangari, Siegel, et al. 2002[124]	400	Thal + doxorubicin or no doxorubicin (DTPACE)	232	2/6	Thromboembolism
*Zangari, Barlogie, Lee, et al 2004 (ASH 4914)[125]	NS	Thal + bortezomib or no bortezomib (VDTPACE)	24	*	Thromboembolism
Zangari, 2004[126]	400	DVT prophylaxis vs. none	386	6/6	Thromboembolism prophylaxis
Total # studies in category: 15 Total abstracts (*): 5			*Total N: 45*	*Total with quality 4/6: 4 of 10 (40%)*	

*Presented as peer-reviewed abstract only.

Abbreviations: chemo = chemotherapy; Dex = dexamethasone; DTPACE: Dex + thal + cisplatin + doxorubicin, cyclophosphamide + etoposide; N = number; NS = not stated; Thal = thalidomide; V = bortezomib; vs. = versus; w/ = with; w/o = without

Table 1c. Details of included studies–Articles with information on predictors of response to thalidomide corresponding to Tables 11-14

First Author, Year	Treatment	N	Quality	Predictor
Predictors related to the potential mechanism of thalidomide action (TABLE 11)				
Singhal, 1999 {Singhal, #592}	Thal only	84	5/5	BM Microvascular Density
Mileshkin, Prince, et al., 2003[127]		75	4/6	Serum mucin-1 (sMUC-1)
Dmoszynska, 2002[128]		30	3/5	Fibroblast Growth Factor (FGF)
Neben, Moehler, Egerer et al. 2001[52]	Thal only	54	3/6	Fibroblast Growth Factor (FGF)
Neben, Moehler, Kraemer et al. 2001[129]		51	3/6	Fibroblast Growth Factor (FGF)
Tosi, 2002 [57]	Thal only	65	2/5	Fibroblast Growth Factor (FGF)
Neben, Moehler, Kraemer et al. 2001[129]		51	3/6	Hepatocyte growth factor (HGF)
Dmoszynska, 2002[128]		30	35	Interleukin-6 (IL-6)
Neben, Moehler, Kraemer et al. 2001[129]		51	3/6	Interleukin-6 (IL-6)
Thompson, 2003[130]		38	1/5	Interleukin-6 (IL-6)
Dmoszynska, 2002[128]		30	3/6	Tumor necrosis factor alpha (TNFα)
Neben, Moehler, Kraemer et al. 2001[129]		51	3/6	Tumor necrosis factor alpha (TNFα)
Thompson, 2003[130]		38	1/5	Tumor necrosis factor alpha (TNFα)
Neben, Mytilineos, et al., 2002[131]		81	3/6	TNFα polymorphisms at position -238 of the gene promoter
Neben, Mytilineos, et al., 2002[131]		81	3/6	TNFα polymorphisms at position -308 of the gene promoter
*Jaksic, 2004 (ASH 2417)[132]		16	*	t(4;14) positive multiple myeloma
Dmoszynska, 2002[128]		30	3/5	Vascular Endothelial Growth Factor (VEGF)
Neben, Moehler, Egerer et al. 2001[52]	Thal only	54	3/6	Vascular Endothelial Growth Factor (VEGF)
Neben, Moehler, Kraemer et al. 2001[129]		51	3/6	Vascular Endothelial Growth Factor (VEGF)
Tosi, 2002 [57]	Thal only	65	2/5	Vascular Endothelial Growth Factor (VEGF)
Total # studies in category: 9 *Total abstracts (*): 1*				*Total predictors in category studied: 10*
Predictors related to patient demographic factors (TABLE 12)				
Barlogie, 2002[109]	Thal + other	231	4/6	Age
Mileshkin, Biagi, et al. 2003[99]	Thal + other	75	5/6	Age
Shaughnessy, 2003[133]		231	2/6	Age
Yakoub-Agha, 2002[60]	Thal only	83	6/6	Age
Dimopoulos, 2004[94]	Thal + other	53	3/5	Gender
Dimopoulos, 2001[70]	Thal + Dex	44	3/5	Performance status (ECOG)
Dimopoulos, 2004[94]	Thal + other	53	3/5	Performance status (ECOG)
Singhal, 1999[35]	Thal only	84	5/5	% of plasma cells in BM
Garcia-Sanz, 2004[95]	Thal + other	66	4/5	Relapsed *versus* refractory disease
Yakoub-Agha, 2002[60]	Thal only	83	6/6	Time from diagnosis to onset of Thal
Total # studies in category: 8 *Total abstracts (*): 0*				*Total predictors in category studied: 6*
Predictors related to clinical diagnostic test results (TABLE 13)				

Table 1c. Details of included studies–Articles with information on predictors of response to thalidomide corresponding to Tables 11-14

Barlogie, 2001[43]	Thal only	169	4/6	Cytogenetics
Shaughnessy, 2003[133]		231	2/6	Cytogenetics
Barlogie, 2002[109]	Thal + other	231	2/5	Chromosome 13 abnormality
Mileshkin, Biagi, et al. 2003[99]	Thal + other	75	2/6	Chromosome 13 abnormality
Shaughnessy, 2003[133]		231	2/6	Chromosome 13 abnormality
Singhal, 1999[35]	Thal only	84	5/5	Chromosome 13 abnormality
*****Attal, 2004 (ASH 535)[108]	Thal + other	580	*	Chromosome 13 abnormality
Dimopoulos, 2004[94]	Thal + other	53	3/5	Albumin
Shaughnessy, 2003[133]		231	2/6	Albumin
Singhal, 1999[35]	Thal only	84	5/5	Albumin
Yakoub-Agha, 2002[60]	Thal only	83	6/6	Albumin
Garcia-Sanz, 2004[95]	Thal + other	66	4/5	Beta 2 microglobulin (B2M)
Mileshkin, Biagi, et al. 2003[99]	Thal + other	75	5/6	Beta 2 microglobulin (B2M)
Neben, Moehler, Egerer et al. 2001[52]	Thal only	54	3/6	Beta 2 microglobulin (B2M)M
Shaughnessy, 2003[133]		231	2/6	Beta 2 microglobulin (B2M)
Schutt, 2005[87]	Thal + other	31	5/5	Beta 2 microglobulin (B2M)
*****Attal, 2004 (ASH 535)[108]	Thal + other	580	*	Beta 2 microglobulin (B2M)
Dimopoulos, 2001[70]		44	3/5	Hemoglobin
Mileshkin, Biagi, et al. 2003[99]	Thal + other	75	3/6	Hemoglobin
Neben, Moehler, Egerer et al. 2001[52]		54	3/6	Hemoglobin
Garcia-Sanz, 2004[95]	Thal + other	66	4/5	Platelets
Dimopoulos, 2001[70]	Thal + Dex	44	3/5	Serum lactose dehydrogenase (LDH)
Dimopoulos, 2004[94]	Thal + other	53	3/5	Serum lactose dehydrogenase (LDH)
Mileshkin, Biagi, et al. 2003[99]	Thal + other	75	5/6	Serum lactose dehydrogenase (LDH)
Shaughnessy, 2003[133]		231	2/6	Serum lactose dehydrogenase (LDH)
Singhal, 1999[35]	Thal + other	84	5/5	Serum lactose dehydrogenase (LDH)
Shaughnessy, 2003[133]		231	2/6	C Reactive Protein
Singhal, 1999[35]	Thal + other	84	5/5	C Reactive Protein
Yakoub-Agha, 2002[60]	Thal only	83	6/6	IgA Isotype
Dimopoulos, 2001[70]	Thal + Dex	44	3/5	Light chain type
Barlogie, 2001[43]	Thal only	169	4/6	Plasma cell labeling index
Singhal, 1999[35]	Thal only	84	5/5	Plasma cell labeling index
Total # studies in category: 12 *Total abstracts (*): 1*				*Total predictors in category studied: 11*
Predictors related to Clinical Response to Thalidomide				
Neben, Moehler, et al. 2002[134]		83	4/6	Cumulative 3-mo Thal dosage
Yakoub-Agha, 2002[60]	Thal only	83	6/6	Cumulative 3-month Thal dosage
Schey, 2003[55]	Thal only	69	4/5	Change in paraprotein levels
Singhal, 1999[35]	Thal only	84	5/5	Relationship between paraprotein response and BM response
Total # studies in category: 4 *Total abstracts (*): 0*				*Total predictors in category studied: 3*

Abbreviations: B2M = beta 2 microglobulin, BM = bone marrow, Dex = dexamethasone, ECOG = Eastern Cooperative Oncology Group, FGF = Fibroblast Growth Factor, HGF = hepatocyte growth factor, IFN = interferon, PS = performance status, sMUC-1 = serum mucin-1, Thal = Thalidomide, TNF = tumor necrosis factor, VEGF = Vascular Endothelial Growth Factor

Results

Part 1. Efficacy

Efficacy is presented in Tables 2-8. The studies naturally segregated into eight groups according to the following figure:

Figure 10: Organization of Thalidomide Efficacy Tables		
	Newly diagnosed/previously untreated multiple myeloma	Advanced/refractory/ resistant multiple myeloma
Thalidomide only	Table 2	Table 3
Thalidomide plus dexamethasone	Table 4	Table 5
Thalidomide plus other agents	Table 6	Table 7
Thalidomide pre- or post-SCT	Table 8	

Table 2 presents two phase II studied of thalidomide only for asymptomatic multiple myeloma. Total number of patients represented is 35. Doses ranged widely from 50-800 mg. Thalidomide achieved CR rates of 16-25 percent and overall paraprotein responses (25 percent) of 66-81 percent, with PPR 50 percent of 34-38 percent. Length of followup was not long enough to allow meaningful comparison to historical survival controls.

Table 3 presents 19 studies with 1 in abstract form. A total of 891 patients with advanced/refractory/resistant multiple myeloma were given thalidomide, in varying doses ranging from 50-800 mg. Thalidomide achieved CR rates of 2-9 percent and overall paraprotein responses (25 percent) of 34-100 percent, with PPR 50 percent of 8-43 percent. The study by Barlogie et al. in 2001 involving 169 participants with advanced refractory myeloma had a median follow up of 22 months.[43] Estimated overall survival (OS) at 12 months was 70 percent, and event free survival (EFS) was 25 percent. The estimated 2-year OS was 48 percent +/- 6 percent with 2-year EFS at 20 percent +/- 6 percent. Responses were generally achieved quickly with PPR 50 percent of 30 percent. Of patients achieving PPR 25 percent, 70 percent achieved that response within 2 months and 90 percent within 4.5 months. Similar patterns were seen in other studies. The ideal dose was difficult to determine. Researchers tried to decrease the dose, without clear diminution in effect, however in the Barlogie et al. study higher total doses predicted superior response and survival.[43]

Table 4 presents six studies of which four are presented in abstract form; two of the abstracts are phase III. Over 447 untreated multiple myeloma patients were given thalidomide in combination with dexamethasone (thal-dex). The thalidomide dose ranged from 50-600 mg. Thalidomide achieved CR rates of 8-16 percent and overall paraprotein responses (25 percent) of 54-92 percent, with PPR 50 percent of 17-64 percent. The Rajkumar et al. study presented in abstract form in 2005 randomized 202 participants to thal-dex versus dex alone.[66] Thal-dex rendered higher response rates with 50 percent response rates of 58 percent for thal-dex and 42 percent for dex alone (p=0.0164). The Ludwig et al. study presented in abstract form in 2005[63] is a randomized controlled trial (RCT) of thal-dex versus oral melphalan and prednisone. Only 137 of a goal 350 participants have been randomized and only 93 were evaluable for this analysis. Overall, thal-dex and melphalan plus prednisone were achieving similar results except for more CRs with thal-dex (13 percent vs. 4 percent) and shorter time to best response with thal-dex (11 weeks vs. 39 weeks). In both of these studies, thalidomide was dosed at 200 mg.

Table 5 presents nine studies of which one is presented in abstract form; none are phase III. A total of 427 advanced/refractory/resistant multiple myeloma patients were given thal-dex. The thalidomide dose ranged from 50-800 mg. Thalidomide achieved CR rates of 0-13 percent and overall paraprotein

responses (25 percent) of 54-75 percent, with PPR 50 percent of 22-55 percent. Palumbo and colleagues treated patients with 50-100 mg of thalidomide and monthly pulsed dex.[75] The study included 120 patients treated with thal-dex and a group of poorly matched controls who received conventional chemotherapy. Despite its limitations this was the largest and one of the highest quality studies within this group. Patients who received thal-dex were more likely to respond to the intervention and had better overall survival (OS: conventional chemotherapy = 21 mo; thal/dex = 27 mo; p= 0.05). Across this group of studies patients routinely received smaller doses of thalidomide (50-100 mg daily) without any obvious diminution of response.

Table 6 presents nine studies of which seven are presented in abstract form; two are phase III. A total of 510 untreated multiple myeloma patients were given thalidomide with a variety of chemotherapy combinations including oral and parenteral conventional chemotherapy, bisphosphonates, and bortezomib. The thalidomide dose ranged from 100-400 mg. Efficacy results are not summarized into a single numeric range for this group of studies as the interventions are too diverse. Two phase III studies evaluating thalidomide in combination with melphalan are of particular interest. One study has not presented any data yet.[78] The study by Palumbo and colleagues identified a substantial improvement in complete response rates when thalidomide was added to standard melphalan and prednisone (CR: 26 percent vs. 4 percent) as well as improved EFS at 26 months (68 percent vs. 32 percent, $p<0.001$). [79]

Table 7 presents 18 studies of which 9 are presented in abstract form; none are phase III. A total of 741 advanced/refractory/resistant multiple myeloma patients were given thalidomide with a variety of chemotherapy combinations including oral and parenteral conventional chemotherapy, bisphosphonates, interferon, and bortezomib. The thalidomide dose ranged from 50-1000 mg. Efficacy results are not summarized into a single numeric range for this group of studies as the interventions are too diverse. The most interesting message across this group of studies was the breadth of clinical options for thalidomide with reasonable tolerability. Oral combinations like thalidomide plus corticosteroids and cyclophosphamide or melphalan looked most promising and combinations with interferon least promising.

Table 8 presents combinations of thalidomide used before or after SCT as part of the upfront therapy or maintenance program. There are six studies presented, of which three are in abstract form only; three are phase III. These data are still maturing; two studies only present blinded data. Overall, thalidomide can be used in the peri-transplant setting, but, one abstract from a randomized trial suggests that thalidomide used as part of the maintenance program after SCT may diminish options for salvage chemotherapy when it is needed in the future.[110] Lower doses of thalidomide as part of a maintenance program are likely to be better.[113]

Figure 11: Summary of Thalidomide Efficacy for CR and PPR 25%		
	Newly diagnosed/previously untreated multiple myeloma	Advanced/refractory/ resistant multiple myeloma
Thalidomide only	CR 16-25% 25% = 66-81% 50%=34-38%*	CR 2-9% 25% = 34-100% 50%=8-43%*
Thalidomide plus dexamethasone	CR 8-16% 25% = 54-92% 50%=17-64*	CR 0-13% 25% = 54-75% 50%=22-55*
Thalidomide plus other agents	Not appropriate to summarize	Not appropriate to summarize
Thalidomide pre- or post-SCT	Not appropriate to summarize	

*Reports of PPR >50% can be misleading.

Table 2. Thalidomide efficacy – Studies of thalidomide alone in newly diagnosed and/or previously untreated multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Phase II					
Rajkumar, 2001[41] Quality 4/5	200-800 mg [12 mo]	16 60 yr (38-75) 56%M 81% IgG 13% IgA 6% light chain only Previously untreated, asymptomatic SMM or IMM	16	Overall response (≥25%) = 81% m protein reduction: 100% = 16% ≥50%= 38% (95% CI, 18-63%) ≥25-49%=69% Stable = 19%	[median duration of response not reached @ median 1 yr f/u]
Rajkumar, 2003[42] Quality 3/5	50-800 mg [median f/u= NS]	29 61 (40-74) 55% M Previously untreated, asymptomatic SMM (66%) or IMM (34%) Reason for dx as "Indolent MM": Lytic lesions (n=7) Hgb < 11 g/dL (n=6) IgG 83% IgA 10%	29	Overall response (≥25%) = 66% m protein reduction: 100% = 29% ≥50% = 34% (95% CI, 18-54%) ≥25% = 66% (95% CI, 46-82%) Stable = 34% Median time to PR = 5 mo (2-9)	Median time to progression & median duration of response not reached. PFS 80% @ 1 yr 63% @ 2 yr KM estimated OS @ 2 yr = 96%

Abbreviations: CI = confidence intervals, dL= deciliter, dx= diagnosis, f/u= followup, hgb= hemoglobin, IMM= indolent multiple myeloma, KM= Kaplan-Meier, OS= overall survival, PFS= progression free survival, PR= partial response, SMM= smoldering multiple myeloma

Table 3. Thalidomide efficacy–studies of thalidomide alone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Phase II					
Barlogie, 2001[43] Quality 4/6	200-800 mg [22 mo]	169 40% >60 yr Gender not specified advanced refractory	169	Overall response (≥25%) = 83% m protein reduction: 100% = 2% ≥90% = 14% ≥50% = 30% ≥25-49% = 37%	Est. OS from KM at 12 mo = 70% Est. EFS from KM at 12 mo= 25% 2-year EFS: 20% +/- 6% 2-year OS: 48% +/- 6% Of patients achieving PPR 25%, 70% achieved that response within 2 months and 90% within 4.5 months Relationship to total dose > 42 g in 3 mo had a higher response rate 25% PPR (54% v 21%) p<0.001 and superior OS (63% v 45%) p<0.001
Corso, 2002[44] Quality 0/5	Not randomized Group 1 =11 pts treated w/Thal 200 mg duration 210 d (90-460); 4/21 also received Dex 20mg x2d q 2wks x 4 Group 2 = 10 pts treated with CAVD (≥ 4 cycles) CAVD (q4-6 wks): Lomustine 80mg/m2 d1 Melphalan 5mg/m2/d d1-5 Etoposide 60mg/m2/q12 D1-5 Dex 8mg/d D1-5 [Median f/u= NS]	21 Gender not specified Thal: 59 yr (52-67) Chemo: 61 yr (46-76)	21 Thal 11 Chemo 10	response (≥25%) = 100% m protein reduction: 100% = 9% ≥90% = NS ≥50% = 36% ≥25-49% = 55% Overall response (≥25%) = 66% m protein reduction: 100% = NS ≥90% = NS ≥50% = 66% ≥25-49% = NS	Group 1: Median time to response = 60 d (30-190) Group 2: Median duration of response = 9 mo (3-18)

Table 3. Thalidomide efficacy–studies of thalidomide alone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Hattori, 2004[45] Quality 4/5	200-400 mg [med f/u NS]	44 55.9 yr (30-70) 58% M relapsed autoSCT = 39%; stage 3 = 91% IgG = 55%, BJ protein = 23% IgA = 16% IgD = >1%	44	Overall response (≥25%) = 68% m protein reduction: 100% = 0% ≥90% = NS ≥50% = 27% ≥25-49% = 41%	
Hus, 2001[46] Quality 3/6	200-400 mg [Median f/u= NS]	53 63 yr (32-79) 51% M Relapsed, refractory w/ hypocellular BM w/ severe pancytopenia Median time since dx = 38 mo (6-144) Historical control = 35 relapsed or resistant MM pts treated in 3 participating centers during 1990-4	53 Stage II = 25% Stage III = 75% Refractory = 17% Relapsed = 83%	Overall response(≥25%) = 58.5% m protein reduction: 100% = 7.5% ≥90% = NS ≥75% = 13% ≥50% = 23% ≥25-49% =15%	Est. OS by KM w/Thal = 250 wk (vs. 210 wk in historical controls, p<0.001) PFS = 240 wk
Johnston, 2002[47] Quality 3/5	50-500 mg Median duration of Thal = 11 mo (7-15) [Median f/u= NS]	12 67.5 yr (34-85; 42% > 70 yr) 42% M Refractory or intolerant to at least 2 prior tx not including HDT IgG = 64% Plasma cell leukemia = 4 Median time since diag = 10.5 mo (3-48)	12 MM = 8 PCL= 4	Overall response (≥25%) = 59% m protein reduction: 100% = 0% ≥90% = 13 ≥75% = 13 ≥50% = 25 ≥25-49% = 0% <25% = 25%	Median dose for PR = 175 mg (100-300)

Table 3. Thalidomide efficacy–studies of thalidomide alone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Juliusson, 2000[48] Quality 1/5	200-800 mg [Med f/u= NS]	23 61.1 yr (44-78) 70% M Median 44 mo (7-137) since initial diagnosis Advanced, heavily pretreated Previous SCT = 43% IgG = 61% IgA = 22% B-J protein only = 17% Non-secretory = NS	23	Overall response (≥25%) = 65% m protein reduction: 100% = NS ≥90% = NS ≥75% = NS ≥50% = 43% partial ≥25-49% = 22% minor (% PPR not specified)	Median time to PR = 31d (28-81 d) 8/16 (50%) PRs on twice daily divided dosing and 2/7 (29%) on single daily dosing (actual doses in categories = NS)
Kees, 2003[49] Quality 2/6	50-400 mg Not randomized Thal only = 50% (n=12) Thal/Dex = 33% (n=8; Dex started if no response to thal alone at 6 months) Thal+ VAD= 17% (n=4) Med Thal dose = 100 mg/d [Median f/u= NS]	24 62 yr (45-83) 50% M Relapsed (19), resistant (5) IgG = 79% IgA = 8% Light chain only = 12% Stage III = 62%		Overall response (≥25%) = 50% m protein reduction: 100% =NS ≥90% = NS ≥75% = 12% ≥50% = 25% ≥25-49% = 13% inclusive ≥50% = 50% Thal only = 42% Thal/Dex = 63% VAD + Thal = 50%	3/24 pts d/c'd Thal due to side effects 1 pt died
*Kroeger, 2004 (ASH 1646)[50] Quality *	100-300 mg Pre donor lymphocyte infusion (DLI) [Median f/u= NS]	18 53 yr (31-64) Gender not specified Progressive or residual disease not responding to prior DLI Prior allogeneic SCT = 100%	18	Overall response (≥25%) = 67% m protein reduction: 100% = 22% ≥90% = NS ≥75% = NS ≥50% = NS ≥25-49% = 45%	2 yr estimated OS = 100% 2 yr estimated DFS = 84% Med time to response = 108 d (36-266)

Table 3. Thalidomide efficacy–studies of thalidomide alone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Kumar, 2003[51] Quality 4/5	200-800 mg [18.7 mo; Survivors 28.5 mo (19.3-34)]	32 67 yr (36-78) 66% M Relapsed IgG = 72% Previous SCT = 16% Median time since dx = 35.1 mo (3.1-114.9)	32	Overall Response (≥25%) = 51% m protein reduction: 100% = 0% ≥90% = NS ≥75% = NS ≥50% = 31% ≥25-49% = 22%	Median PFS-KM=15.7 mo (95% CI, 8.6-25.6 mo) Median OS-KM = 22 mo (95% CI, 10.6-35.9 mo) Median duration of response for those achieving a PR = 11.9 mo (3.7-20.3)
Neben, Moehler, Egerer et al. 2001[52] Quality 3/6	100-400 mg [15 mo, 0.3-20]	54 57 yr (34-79) 69% M Progressive MM Stage III = 87% Median prior chemo cycles = 6 (0-30) & 72% ≥ 1 HDT/PBSCT IgG 44% IgA 35%	54	Overall Response (≥25%) = 57% m protein reduction: 100% = 2% ≥90% =9% ≥75% = NS ≥50% = 26% ≥25-49% = 57%	Estimated 6 mo PFS = 73% (95% CI, 62-86%)
Rajkumar, 2000[53] Quality 3/5	200-800 mg [Median f/u= NS]	16 64 yr (48-85) 69% M Median time since dx = 32 mo Relapsed, advanced 100% Stage III 88% with 2 prior chemotherapy regimens including 25% with prior HDT/SCT	16	Overall Response (≥25%) = 57% m protein reduction: 100% = 0% ≥90% =NS ≥75% = NS ≥50% = 25% ≥25-49% = <1% Median duration of stability = 5 mo (2-9)	After Thal: Median OS = 5 mo Median PFS = 3 mo Median Survival since diagnosis =56 mo

Table 3. Thalidomide efficacy–studies of thalidomide alone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Richardson, 2004[54] Quality 3/5	200-600 mg, 200 mg maintenance for those with response or stable disease after week 12 [7 mo]	30 58 yr (39-70) 63% M Relapsed after HDC & SCT Stage III = 57% IgG = 46% IgA = 27% Light chain disease = 27% Median time since dx = 4.3 yr (10 mo- 10 yr) Median number of prior tx = 5 (2-7)	26 evaluable	Overall Response (≥25%) = 57% m protein reduction: 100% = 0% ≥90% =NS ≥75% = NS ≥50% = 33% ≥25-49% = 10%	PFS = 67% in 26 evaluable (95% CI, 48-86%) Median PFS = 6 mo Median OS not reached; 6-month OS estimate from KM = 83% Median duration of response = 6 mo
Schey, 2003[55] Quality 4/5	100-600 mg, 200 mg maintenance Median therapy duration =6 mo (3-18) Med MTD thal = 300mg [13 mo, 1-38]	69 62 yr (39-84) Gender not specified Relapsed or refractory, including light chain & relapsed after >3 mo SCT 36% had prior autoSCT Median time since dx = 31 mo (3-132)	69	Overall Response (≥25%) = 49% m protein reduction: 100% CR = 2% ≥90% =9% ≥75% = 9% ≥50% = 17% ≥25-49% = 22%	Discontinued Thal 12% neuropathy 4% constipation Median OS = 19 mo Median PFS = 14 mo
Singhal, 1999[35] Quality 5/5	200-800 mg 86% to 400 mg 68% to 600 mg 55% to 800 mg [14.5 mo (12-16)]	84 38% > 62 yr; 73% M Previously treated & progressive IgG 61% Duration of prior therapy > 5yrs = 21% Prior HDT = 90% Interval between last cycle of chemo and thal > 1 yr = 37% (med 14 mo)	84	Overall Response (≥25%) = 32% m protein reduction: 100% = 2% ≥90% =7% ≥75% = 7% ≥50%= 8% ≥25-49%= 7%	12 mo OS = 58 +/- 5% Median EFS = 3 mo At 12 mo, 22+/- 5% event free Median TTP had not been reached 12 mo rate of progression = 44 +/- 10% Median interval between start of thal and PPR by 25% = 29d (4d – 6 mo) 78% of 25% responses were evident by 2 mo Median interval between start of thal and decrease in paraprotein by 50% = 2 mo and 75% = 3 mo 23% still receiving thal 4-15 mo after starting thal (median 13 mo) Thal discontinued after med 52d (2-286)

Table 3. Thalidomide efficacy–studies of thalidomide alone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
					due to lack of response in 63% of pts and due to relapse in 14%
Tosi, 2001[56] Quality 3/5	100-800 mg [5 mo]	11 54.5 yr (42-60) 64% M stage III, Relapsing after autoSCT (7/11 with >1 autoSCT) Median time to Thal since dx = 51 mo median time between SCT & start of Thal = 16 mo	11	Overall Response (≥25%) = 72% m protein reduction: 100% = NS ≥90% = NS ≥75% = NS ≥50% = 36% ≥25-49% = 36% median response duration= 5 mo	Maximal PPR at median 2 mo after initiation of thal
Tosi, 2002[57] Quality 2/5	100-800 mg [9 mo]	65 63 yr (35-78) 71%M Relapsed/refractory (1 pt with newly diagnosed MM) Stage III = 94% Median time since dx = 44 mo (0-192) Prior autoSCT=37% IgG = 75% IgA = 15% Bence Jones = 8%	60 evaluable	Overall Response (≥25%) = 46.6% m protein reduction: 100% = NS ≥90% = NS ≥75% =8.3% ≥50% = 20% ≥25-49% = 18.3% Median response duration = 8 mo (2-16+)	At med f/u 9 mo PFS = 25% and OS = 92% (calculated from numbers in text)

Table 3. Thalidomide efficacy–studies of thalidomide alone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Waage, 2004[58] Quality 4/5	200-800 mg [2.4 yr]	65 63 yr (31-78) 59% M Refractory, relapsed Median time since dx = 4.2 yr (1-16) autoSCT = 83% Stage III = 88% IgG = 66% IgA = 15% Light chain = 14%	65	Overall Response (≥25%) = 34% m protein reduction: 100% = 6% ≥90% = NS ≥75% = NS ≥50% = 14% ≥25-49% = 14%	Median OS = 12 mo Survival landmarks: 3 mo = 74% 6 mo = 66% 12 mo = 49% 24 mo = 32% 16/22 responders with some reduction in paraprotein levels by 1 week of thal; by 3 weeks all responders with paraprotein reduction (70% had reached 25% reduction) 15% received full dose thal at 800 mg; 25% reduced dose due to side effects; 26% discontinued thal Side effects leading to Thal d/c: ileus (n=3) exanthema (n=2) neuropathy (n=2) somnolence (n=2) HRQOL (measured on QLQ C-30 at baseline (n=62), 12 wks (n=38), and 24 wks (n=20)): "HRQOL scores relatively stable throughout study", except: Pain decrease by 15 (0-100 scale) Constipation increase by 32 (0-100 scale) *20 pts completing 24 wk questionnaire were responders and had higher HRQOL at baseline
Yakoub-Agha, 2000[59] Quality 4/5	100-800 mg [105 d, 44-272]	27 62 yr (35-71) 55% M Advanced, progressed after ≥2 lines of therapy Prior autoSCT = 82% IgG = 62% IgA = 26% Light chains = 8%	27	Overall Response (≥25%) = 45% m protein reduction: 100% = NS ≥90% = NS ≥75% = 15% ≥50% = 18% ≥25-49% = 12%	Median interval between initiation of thal and 25% PPR = 30d (10-97)

Table 3. Thalidomide efficacy–studies of thalidomide alone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Yakoub-Agha, 2002[60] Quality 6/6	50-800 mg [338 d, 247-611] Median total dose of thal received in first 3 mo of therapy = 34.4g (1.6-72) Mean daily dose = 400 mg/d (27-800)	83 64 yr (40-81) 55% M Advanced, progressed after ≥2 lines of therapy IgG = 73% IgA = 18% Light chain = 6% Prior autoSCT = 70% Median time since dx = 4.2 yr (1.7-11.4)	83	Overall Response (≥25%) = 66% m protein reduction: 100% = NS ≥90% = NS ≥75% = 13%NS ≥50% = 35% ≥25-49% = 18%	Estimated OS = 391 d (95% CI , 363-577d) Median interval from initiation of thal to 25% PPR = 39d (4-123)

Abbreviations: *= abstract, autoSCT= Autologous stem cell transplant, B-J= Bence-Jones protein, BM= bone marrow, CAVD= cyclophosphamide/doxorubicin/vincristine/Dex, CI= confidence intervals, CR= Complete Response, d/c= discontinued, Dex= dexamethasone, DLI= donor lymphocyte infusion, dx = diagnosis, EFS= event free survival, f/u= followup, HDT= high dose therapy, HRQOL= health related quality of life, KM= Kaplan-Meier, LMW= low molecular weight, Med = median, NS= not stated, OS= overall survival, PBSCT= peripheral blood stem cell transplant, PCL= plasma cell leukemia, PFS= progression free survival, PPR= paraprotein reduction, pt(s)= patient(s), QLQ C-30= Quality of Life Questionnaire Cancer 30, SCT= stem cell transplant, TTP= time to progression, VAD= vincristine/doxorubicin/Dex

Table 4. Thalidomide efficacy studies – studies of thalidomide plus dexamethasone in newly diagnosed and/or previously untreated multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Phase III					
*Rajkumar, 2004 (ASH 205)[61]; *Rajkumar, 2004 (ASCO 6508)[62] Quality * 2 reports of ongoing trial = only most recent report presented here	200 mg Thal/Dex vs. Dex alone: Thal = 200 mg. + Dex 40 mg d1-4, 9-12, 17-20 Dex alone = same dose [median f/u= NS]	202 65 yr (range NS) Gender= NS Newly diagnosed, untreated, symptomatic MM Other MM characteristics =NS Enrollment appears to be complete	198 evaluable at time of report	Overall Response (≥25%) = UTD m protein reduction: 100% = NS ≥90% = NS ≥50% = Thal/Dex = 58% Dex = 42% p= 0.0164 ≥25-49% = NS	Med time to response similar in both arms = 1.1 mo Grade 3 toxicity significantly increased with Thal/dex (p<0.0001): DVT(3): Thal/Dex 18%, Dex 3% Rash(3): Thal/Dex 4%, Dex 0% Bradycardia(3): Thal/Dex 1%, Dex 0% Neuropathy(3): Thal/Dex 4%, Dex 4%
*Ludwig, 2005 (ASCO 6537)[63] Quality *	200mg Thal/Dex vs. MP (melphalan/prednisone) Thal 200 mg +Dex 40 mg d1-4, 15-18 on odd cycles & d1-4 on even cycles vs. Melphalan 2.5 mg/kg d1-4 and Prednisone 2 mg/kg d1-4 q 4-6 wks All pts got zoledronate 4 mg q mo [median f/u= NS]	137 - Enrollment ongoing (goal n = 350) 72 yr Stage III = 58% Other pt and MM characteristics NS	93 evaluable	Overall Thal/Dex Response = 63% 100% CR = 13% Near CR = 8% 90% = 10% 50% = 17% 25% = 15% Overall M/P response = 62% CR = 4% Near CR = 11% 90% = 11% 50% = 19% 25% = 18%	ITT RR = shorter time to response Thal/Dex = 8 wk MP = 10 wk p = 0.01 Shorter best response: Thal/Dex = 11 wk MP = 39 wk p= 0.0047 Pending data on PFS & OS Analysis per protocol, not ITT: Thal/Dex = 88% MP = 68% p= 0.05

Table 4. Thalidomide efficacy studies – studies of thalidomide plus dexamethasone in newly diagnosed and/or previously untreated multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Phase II					
Alexanian, 2003[64] Quality = 1/6	100-400 mg + Dex20 mg/m^2 x 4d on d1, 9 and 17 q28 days x 3 months [median f/u= NS]	Not specified Newly diagnosed	Not specified	Overall Response(≥25%) = 85% m protein reduction: 100% CR = 15% ≥75% = 70% ≥50%= NS ≥25-49%= NS	Remission onset 0.7 mo
Rajkumar, 2002[65] Quality 4/5	50-200mg + Dex 40 mg x4d on d1, 9, 17 (odd cycles) and d1 (even cycles) Dose increase to 800 mg halted after 7 pts Cycles repeated monthly [median f/u= NS]]	50 61 yr (33-78) 62% M Newly diagnosed IgG 66% IgA 20% Light chain only = 12%	50	Overall Response (≥25%) = 92% m protein reduction: 100%= NS ≥90%= NS ≥50%= 64% ≥25-49%= 28% PPR ≥50%: IgG= 62% IgA= 64% Light chain only= 60%	62% proceeded after 4 cycles of therapy to SCT
*Rajkumar, 2005 (ASCO 6632)[66] Quality *	200mg + Dex 40 mg x4d on d1, 9, 17 (odd cycles) and d1 (even cycles) Cycles repeated monthly [21 mos]	24 65.5 (36-78) 58% M Newly diagnosed Not going on to SCT Stage III = 25% Other MM characteristics = NS	24	Overall Response (≥25%) = 54% m protein reduction: 100% = 8% ≥90% = NS ≥50% = 46% ≥25-49% = NS	Med OS= 30 mo Med PFS= 19 mo Med TTP= 21 mo

Table 4. Thalidomide efficacy studies – studies of thalidomide plus dexamethasone in newly diagnosed and/or previously untreated multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Weber, 2003[67]	100-600 mg	68 Sex & Gender = NS	68	Overall Response(≥25%) = 36-88% m protein reduction:	Median time to remission: Thal alone = 4.2 mo
Quality 3/6	28 Thal alone – pts with asymptomatic MM 40 Thal/Dex @ 20mg/m2 x4d on d1, 9, 17 q month Not randomized If CR, Thal/Dex d/c'd after >4 months [25 mo, 9 mo]	Previously untreated MM	Thal alone =28 Thal/Dex =40	100% = Thal alone = 0% Thal/Dex = 16% ≥75% = Thal alone = 36% Thal/Dex = 72% ≥50% = NS ≥25-49% = NS	Thal/Dex = 0.7 mo Median time to CR: Thal/dex = 2.3 mo (1.6-2.9) Prophylactic anticoagulants also given with Thal/Dex: Coumadin n = 24 LMW heparin n = 16 >80% received thal average daily dose = 100-200mg 21/40 treated with thal/dex proceeded to autoSCT – collection was rapid and efficient

Abbreviations: *= abstract, autoSCT= Autologous stem cell transplant, B-J= Bence-Jones protein, CR= Complete Response, CS= pulse prednisone, d/c= discontinued, EFS= event free survival, f/u= followup, ITT= intention to treat, LMW= low molecular weight, NS= not stated, MP= melphalan/prednisone, OS= overall survival, PFS= progression free survival, PPR= paraprotein reduction, pt(s)= patient(s), SCT= stem cell transplant, UTD = unable to determine; TTP= time to progression

Table 5. Thalidomide efficacy studies–studies of thalidomide plus dexamethasone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Phase II					
Alexanian, 2003[64] Quality = 1/6	200-800 mg; Responders maintain Thal 100-200 mg Non-responders then added Dex 20 mg/m^2 x 4d on d1 , 9 , 17 [med f/u=NS]	45 58 yr 55% M relapsed, resistant	43	PPR 50% = 26% Non-responders (n=24) + Dex: PPR 50%= 40% Cumulative PPR 50% = 50% Overall Response (≥25%) = UTD m protein reduction: 100% = NS ≥90% = NS ≥50% = 50% ≥25-49% = NS	In responders: Median time to remission = 4 mo; Median duration of remission = about 1 yr
Alexanian, 2003[64] Quality = 1/6 Anagnotopoulos, 2003[68] Quality 1/6 Two papers with the same data	200-600 mg + Dex 20 mg/m^2 x 5d repeated every 15d; Responders maintained Thal 100-150 mg with Dex x 5d q month [med f/u= NS]	47 48 yr (31-77) Relapsed or resistant Median time from initial therapy = 36 mo Other pt and MM characteristics NS	47	Overall Response (≥25%) = 54% m protein reduction: 100% = 13% ≥90% = NS ≥75% = 47% ≥50% = NS ≥25-49% = NS	Median time to remission = 2 mo Median OS = 38 mo and “significantly longer in responsive pts”
Bernardeschi, 2004[69] Quality 2/5	50-400 mg +Dex 40 mg x4d q mo	20 65.8 yr (50-83) 55% M Refractory to prior chemo Other MM characteristics NS		Overall Response (≥25%) = 55% m protein reduction: 100% = NS ≥90% = NS ≥50% = 55% ≥25-49% = NS Recalculated % based on table	Median OS = 37 mo
Dimopoulos, 2001[70] Quality 3/5	200-400 mg + Dex 20 mg/m^2 x4d on d1, 9 and 17 then qmo x 4d [med f/u= NS]	44 67 yr (38-87) 73% M Refractory, resistant Median time since initial tx = 23.3 mo (2.7-134.4)	44	Overall Response (≥25%) = 57% m protein reduction: 100% = NS ≥90% = NS ≥75% = 30% ≥50% = 25% ≥25-49% = 2%	Med OS= 12.6 mo Med interval between start of Thal and PPR by >50% = 1.3 mo (0.75-3.6)

Table 5. Thalidomide efficacy studies–studies of thalidomide plus dexamethasone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Myers, 2000[71] Myers, 2001[72] Myers, 2002[73] Quality 2/5 2 letters of Thal and Thal/dex and 1 follow up letter of combined group	50-400 mg Group 1 (n= 9) Thal only @ 200-600 mg[71] Group 2 (n=26, n=17 added to Group 1 (10 Thal only and 7 with 4 mg Dex slow taper added for inadequate response)[73] Group 3 (n=27, addition of 1 to Group 3 not specified) – in this report a total of 17 had received Dex (dose unspecified)[73] [16 mo]	27 72 yr (51-90) 67% M Relapsed after prior chemo	27 Thal = 10 Thal/Dex=17 Dex added if no response to Thal alone	ORR both groups (≥50%) = 63% Thal only: ORR = 37% 100% = NS >75% = 15% >50% = 22% ≥25-49% = NS Thal + Dex: ORR = 100% = NS >75% = 0 >50% = 26% ≥25-49% = NS	Median duration of response: Thal = 16 mo (3-22) Thal/Dex= 7.5 mo (3-12)
Palumbo, 2001[74] Quality 2/5	100 mg + Dex 40 mg/d x4d q mo [8 mo]	77 65 yr Gender not specified Refractory or relapsed Median time since dx = 46 mo Stage III = 43% IgG = 60% IgA=27%	77	Overall Response (≥25%) = 69% m protein reduction: 100% = 3% ≥90% = NS ≥75% =18% ≥50% = 23% ≥25-49% =25%	Thal ↓100 to 50 mg = 4% Median time to response = 4.2 mo (0.6-10.2) Med TTP = 12 mo OS not reached and 91% of pts still alive

Table 5. Thalidomide efficacy studies–studies of thalidomide plus dexamethasone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Palumbo, 2004[75] Quality 6/6	50-100 mg +Dex 40 mg d1-4 qmo Historical controls not well matched Duration of Thal tx = 4-36 mo	120 62 yr (range = NS) Relapsed/refractory Not randomized Compared with matched controls β2M & Durie-Salmon stage treated with conventional chemo = CC Median duration since dx: With one prior chemo line: Thal/Dex= 23 mo CC = 18 mo With ≥2 chemo lines: Thal/Dex = 60 mo CC = 55 mo	120 with 1 chemo line Thal/Dex=62 CC = 82 after ≥2 chemo lines Thal/Dex=58 CC = 38	After 1 line of prior chemo Thal/Dex vs. CC ORR (≥25%) = 56% vs. 43% m protein reduction: 100% = NS ≥90% = NS ≥75% = 27% vs. 19% ≥50% = 29% vs. 27% ≥25-49% = NS After >2 chemo lines Thal/Dex vs. CC ORR (≥25%) = 46% vs. 42% m protein reduction: 100% = NS ≥90% = NS ≥75% = 21% vs. 17% ≥50% = 25% vs. 25% ≥25-49% = NS	Median time to maximal response to Thal/Dex = 4 mo (0.5-21) Maximal response to Thal/Dex occurred: Within 2 mo = 33% After 3 mo= 17% After 4 mo= 14% After 6 mo= 26% After 9 mo= 11% PFS: CC = 11 mo Thal/Dex = 12 mo (p = not sig) OS: CC = 21 mo Thal/Dex = 27 mo (p= 0.05) Med f/u @ 18 mo:
*Reece, 2004 (ASH 4934)[76] Quality *	50-400 mg Med Thal dose = 150mg Thal +/- CS = Pulse Prednisone 50-100 mg q2d (N=15) or Dexamethasone (N=14) [Median duration of therapy= 7 mo (1.5-19+)]	33 73 yr (70-88) 4 = Thal alone 29 = Thal + CS Newly diagnosed = 6% Stage III = 76% IgG = 61% IgA = 30% B-J protein = 3%	29	Overall Response (≥25%) = 57% m protein reduction: 100% = NS ≥90% = NS ≥75% = NS ≥50% = 42% ≥25-49% =15%	OS @ 1 yr = 80% OS @ 2 yr = 55% PFS @ 1 yr = 42% PFS @ 1 yr = 20%
Tosi, 2004[135] Quality 4/5	100-400 mg Thal only = 8 pt Thal + Dex 40mg/d x 4d q month = 12 pt [13 mo]	20 65.8 yr (54-76) 75% M Stage III relapsed/refractory and renal failure (creat >130 mmol/L and creat clearance <60 ml/min) Hemodialysis = 15% Med time from dx to Thal = 34 mo (2-120)	20	Overall Response (≥25%) = 75% m protein reduction: 100% = NS ≥90% = NS ≥75% = NS ≥50% = 45% ≥25-49% = 30% Median response duration = 7 mo (2-24)	80% of responders (12/15) recovered renal function creat <130 mmol/L Mean OS =7 mo At 13mo f/u 8/15 responders with disease progression

Table 5. Thalidomide efficacy studies–studies of thalidomide plus dexamethasone in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
		Previous autoSCT = 45%			

Abbreviations: *= abstract, autoSCT= Autologous stem cell transplant, B-J= Bence-Jones protein, CI= Confidence Intervals, CR= Complete Response, creat= creatinine, CS= pulse prednisone, EFS= event free survival, f/u= followup, NS= not stated, OS= overall survival, PFS= progression free survival, PPR= paraprotein reduction, pt(s)= patient(s), SCT= stem cell transplant, TTP= time to progression; UTD = unable to determine

Table 6. Thalidomide efficacy studies–studies of thalidomide plus other agents in newly diagnosed and/or previously untreated multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Phase III					
*Facon, 2004 (ASH 206)[78] Quality *	Up to 400 mg MP vs. MPT vs. MEL100: Arm A =Standard MP (*assumed – exact MP regimen not stated:* melphalan 4mg/m^2 po d1-7; prednisone 40 mg/m^2 d1-7 q6 wk x 12), Arm B =MPT = same MP + Thal up to 400 mg Arm C = MEL100 = VAD x 2 + melphalan 100 mg/m^2 iv x 2 (w/ cyclophosphamide 3g/m^2 for stem cell collection) [12 mos]	200 - Enrollment ongoing (goal N = 500) Inclusion = age 65-75 yr Actual age & gender of enrolled pts = NS	200	Not reported	Planned interim analysis at N = 200 for safety Shows no clear advantage or disadvantage of either MP-Thal or MEL100 over MP.
*Palumbo, 2004 (ASH 207)[79] Quality *	100 mg MPT vs. MP: melphalan 4 mg/m^2 po + prednisone 40 mg/m^2 d1-7 q mo +/-Thalidomide 100 mg Not randomized enoxaparin prophylaxis added after trial started [15 mo]	200 – Enrollment appears complete 72 yr (56-85) Gender not specified Newly diagnosed MM MM characteristics = NS	102 evaluable at time of report	Overall Response (≥25%) = UTD m protein reduction: 100% = UTD ≥90% = NS ≥75% =18% ≥50% = UTD ≥25-49% =UTD After MPT: CR = 25.9% Near CR = 5.5% PR = 48.2% After MP: CR = 4.2% Near CR = 0% PR = 43.6%	EFS @ 26 mos: EFS w/MPT = 67.8 % EFS w/MP = 32.4% p<0.001 OS not reached Treatment related mortality: MPT = 5% MP = 2% Adverse events: DVT: MPT 19%, MP 2% Infections (Grade 3/4): MPT 13%, MP 2% Neurotoxicity (Grade 1/2) : MPT 36%, MP 5% Hem. toxicity (Grade 3/4) : MPT 23%, MP 28%

Table 6. Thalidomide efficacy studies–studies of thalidomide plus other agents in newly diagnosed and/or previously untreated multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Phase II					
*Alexanian, 2004 (ASH 210)[80] Quality *	100-200 mg VTD: Velcade (Bortezomib) 1.0-1.9 mg/m^2 d1, 4, 8 & 11 Thal 100-200 mg Dex 20 mg/ m^2 q4d d1, 9, 17 Repeat VTD q4 wk [6 mo (2-14)]	25 63 yr (39-81) Gender not specified Previously untreated MM characteristics = NS		Overall Response (≥25%) = UTD m protein reduction: 100% = UTD ≥90% = NS ≥75% =76% ≥50% = 84% ≥25-49% = NS	Median time to remission = 0.6 mo (0.3-1.8) Autologous blood stem cells easily collected in 12 pts who were intensified for a median 3.6 mo after initial therapy
*Chanan-Khan, Miller, McCarthy, Koryzna et al., 2004 (ASH 3463)[81] Quality *	100-200 mg VAD d1-4 qmo + Thal 100-200 mg Repeat q 4wk x 4 cycles Coumadin 1-2 mg for DVT prophylaxis [Med f/u= NS]	16 58 yr (46-77) 50% M >Stage 1 No prior therapy Stage III = 69%	11 evaluable	Overall Response (≥25%) = 91% m protein reduction: 100% = 3% ≥90% = NS ≥75% =64% ≥50% = NS ≥25-49% = NS	
*Dimopoulos, 2004 (ASH 1482)[82] Quality *	300 mg MDT: Melphalan 8 mg/ m^2 d-4, Dexamethasone 12 mg/ m^2 d1-4, 14-18 Thal 300 mg. d1-4, 14-18 Repeated q5wk x 10 cycles [15 mo]	43 – Enrollment ongoing (goal N = NS) 78 yr (75-85) No prior therapy Inclusion = Symptomatic MM with age ≥ 75 yr Stage III = 58% Other MM characteristics = NS	43	Overall Response (≥25%) = 72% m protein reduction: 100% = 10% ≥90% = NS ≥75% = NS ≥50% = 62% ≥25-49% = NS	Median time to PR = 2 mo (0-5-5.5) OS @ 15 mo median f/u = 88%
*Hassoun, 2004 (ASH 2409)[83]	AD/TD = Doxorubicin/Dex followed by Thal/Dex	38 – Enrollment ongoing (goal N = NS) 59 yr (35-82)	30	Overall Response (≥25%) = 86.6% m protein reduction: 100% = 20%	

Table 6. Thalidomide efficacy studies–studies of thalidomide plus other agents in newly diagnosed and/or previously untreated multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Quality *	Doxorubicin = 9 mg/m^2 d1-4, Dex = 40 mg/d, d1-4, 9-12, 17-20; Thal = 200 mg Dex as above	58% M Stage II & III symptomatic MM MM characteristics = NS		≥90% = 26.6% ≥75% = NS ≥50% = 40% ≥25-49% =25%	
*Klueppelberg, 2004 (ASH 4932)[84]; *Klueppelberg, 2004 (ASCO 6702)[85]; *Klueppelberg, 2005 (ASCO 6697)[86] Quality * 3 reports of ongoing study with increasing enrollment; most data presented here from most recent report with highest n	100 mg TDZ: Thal 100 mg + Dex 10-40 mg d1-4, 9-12, 17-20 for 6 mo then d1-4 qmo +zoledronate 4mg qmo [Mean time on TDZ = 12 mo; 13 pts followed for 12-24 mo]	33 61 yr (43-82) 73% F Newly diagnosed MM HIV+ = 14% Stage III = 69% Other MM characteristics=NS	29 evaluable	Overall Response (≥25%) = 90% m protein reduction: 100% = NS ≥90% = 28% ≥75% =% ≥50% = 34% ≥25-49% =28% Cumulative probability of ≥25% PPR = 73% (+/- 20.6%) within 10 mo	Responses were unaffected to HIV status or antiviral treatment Median time to response = 5.9 mo Age-adjusted 1-year OS = 74$
Schutt, 2005[87] Quality 5/5	200-400 mg Thal-VED: Thal starting at 200 mg and increasing to 400 mg/d + vincristine 1.5 mg d1 + epirubicin 30mg/m^2/d d1-2 + Dex 20 mg/m^2/d d1-5 Repeated q3wk Mean # cycles = 4 (1-8) [Med f/u= NS]	31 57 yr (32-77) 68% M Untreated MM Stage III = 91% IgG = 58% IgA = 19% B-J protein = 16% Non-secretory = 7%	31	Overall Response (≥25%) = 80% m protein reduction: 100% = 19% ≥90% = NS ≥75% = NS ≥50% = 61% ≥25-49% = NS	EFS @ 36mo =26% OS @ 36 mo = 62% Med EFS = 36 mo Med OS not reached at 40 mo Max response to treatment achieved by median 2.8 mo (1.4-7.2 mo) 20 were candidates for SCT and PBSC were collected In all

Table 6. Thalidomide efficacy studies–studies of thalidomide plus other agents in newly diagnosed and/or previously untreated multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Zervas, 2004[88] Quality 3/5	200 mg + VAD + Dex 40 mg/m^2 x 4d on d15 of cycle 1 only VAD: VCR 2mg Liposomal doxorubicin 40 mg/m^2 Dex 40 mg/m^2 qdx4 [10 mo, 2-22]	39 68 yr (43-75) 51% M Newly diagnosed with symptomatic MM, Stage III = 64% IgG = 56.5% IgA = 28% Light chain = 13%	39	Overall Response (≥25%) = 82% m protein reduction: 100% = 10% ≥90% = NS ≥75% = NS ≥50% = 64% ≥25-49% = 8%	EFS @ 22 mo = 55% OS @ 22 mo = 74% 6 Early deaths: 4 = disease progression 2 = neutropenic infection 38% proceeded to SCT (47% of responders)

Abbreviations: *= abstract, AD/TD= Doxorubicin/Dex + Thal/Dex, alloBMT= allogeneic bone marrow transplant, B-J= Bence Jones protein, CR= Complete Response, Dex= Dexamethasone, DVT= Deep venous thrombosis, EFS= event free survival, f/u= followup, Hem= hematologic, HIV+= Human Immunodeficiency Virus Positive, IFN= Interferon, MP= melphalan/prednisone, MPT= MP + Thal, Near CR= positive IFE only, NS= not stated, OS= overall survival, PFS= progression free survival, PPR= Paraprotein reduction, PR= partial response, pt(s) = patient(s), SCT= stem cell transplant, T= Thalidomide, TDZ = Thal/Dex/ Zoledronate, UTD= unable to determine, VAD= standard chemotherapy including Vincristine/Doxorubicin/Dexamethasone, V= Velcade (Bortezomib), VCR= Vincristine, VED= combination chemotherapy including Vincristine/Etoposide/Dex, VTD= Velcade/Thal/Dex

Table 7. Thalidomide efficacy studies–studies of Thalidomide plus other agents in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of follow-up]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Phase II					
*Badros, 2004 (ASH 2400)[89] Quality *	100-400 mg Oblimerson 5-7 mg/kg/d x 7d q21d. D= Dex 40 mg x 4d Thal 100-400 mg [12 mo (1.5-16.6)]	33 60 yr (28-76) 67% M Relapsed MM Median 3 prior regimens (2-4) Other MM characteristics= NS	30 evaluable	Overall Response (≥25%) = 80% m protein reduction: 100% = 7% Near CR = 13% ≥75% = NS ≥50% = 40% ≥25-49% = 20%	Estimated PFS = 12 mo Estimated OS = 17.4 mo Median response duration = 13 mo
Biagi, 2001[92] Quality 1/6 (While called "phase II" by authors, reported more as a case series of 4 patients selected on response to Thal)	200-800 mg IFNα added @ 12 wk	4 44.8 yr (40-50) 75%M 75% extramedullary (EM) relapse after alloBMT	4	All 3 with EM MM had complete resolution of EM disease (but not necessarily other systemic response)	"Extramedullary myeloma is particularly sensitive to Thalidomide"
*Bibas, 2004 (ASH 4927)[90] Quality *	100+ mg Low dose Thal 100mg up to max tol dose + Dex 40 mg+ zoledronate 4 mg [2-21 mo]	30 (53-81 yr) 73% F refractory, relapsed IgG = 80% IgA = 17% B-J protein = 3%	30	Overall Response (≥25%) = 63% m protein reduction: 100% = 13% ≥75% = NS ≥50% = 50% ≥25-49% = NS	Responders with neuropathy were decreased to Thal for only 10 days/mo

Table 7. Thalidomide efficacy studies–studies of Thalidomide plus other agents in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of follow-up]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
*Chanan-Khan, Miller, McCarthy, DiMiceli et al. 2004 (ASH 2421)[91] Quality *	200 mg VDT: Bortezomib (V), liposomal doxorubicin(D), & low-dose Thal V= 1.3 mg/m^2 (d1,4, 15, 18); D = 20 mg/m^2 (d1, 15); Thal 200 mg. Repeated q 4 wks for 4-6 cycles	18 56 yr. (44-80) 61% F Refractory/relapsed Prior SCT = 46% 16 MM & 2 Waldenström's Macroglobulinemia; all stage III, pretreated median 2 (1-7) other prior regimens 46% SCT	13 evaluable	Overall Response (≥25%) = 100% m protein reduction: 100% = NS ≥75% = 38% ≥50% = 62% ≥25-49% = NS	
Ciepluch, 2002[93] Quality 1/5	200-400 mg + Pamidronate 90 mg q28d mean treatment duration 12.4 wk (3-36 wk) [med f/u= NS]	13 61.5 yr (35-87) 62% M resistant w/ osteolytic lesions	13	Overall Response (≥25%) = 76% m protein reduction: 100% = 23% "good clinical response" inclusive ≥25-99% = 53% ≥75% = NS ≥50% = NS ≥25-49% = NS	85% of responders responded in first 4-8 wk of treatment Osteodynia: Partial improvement = 31% Marked improvement = 23% (measurement of osteodynia and definitions of improvement not stated)
Dimopoulos, 2004[94] Quality 3/5	400 mg CTD: Cyclophosphamide 150mg/ m^2 q12h d1-5 + Thal 400 mg/d d1-5 & 14-18 + Dex 20mg/ m^2 d1-5 & 14-18 Repeated q 4 wks x 3 [med f/u= NS]	53 64 yr (36-86) 49% M Treatment resistant = 87% 3 prior chemo regimens = 55% Prior tx with Thal = 19% Med time from initial dx to enrollment = 26 mo (3-141) IgG = 55% IgA = 25% B-J protein = 18% Non-secretory = 2%	53	Overall Response (≥25%) = 94% m protein reduction: 100% = 5% ≥75% = 34 ≥50% = 55% ≥25-49% = NS	Med time to response = 1.5 mo (0.46-4.82) Pts with prior treatment with Thal less likely to respond (PPR 50%, prior Thal vs. no prior Thal = 30% vs. 67%, p=0.03) Med TTP = 8.9 mo Med TTP if achieved a PPR50%= 12 mo Med OS = 17.5 mo

Table 7. Thalidomide efficacy studies–studies of Thalidomide plus other agents in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of follow-up]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Garcia-Sanz, 2004[95] Quality 4/5	200-800 mg ThaCyDex: Thal 200-800 mg +cyclophosphamide 50 mg qd + pulsed Dex 40mg/d x 4 days q3 weeks Med dose thal = 600mg [med f/u= 1.5 yr]	71 65% >65 yr 52% M Refractory/relapsed Stage III= 42% IgG= 60% IgA= 20% B-J protein = 20%	66 evaluable	Overall Response (≥25%) = 89% m protein reduction: 100% = 2%, CR increased to 10% @ 6 mo ≥75% = ≥50% = 55% ≥25-49% = 26%	@ 2 years, EFS = 57% & OS = 66%
*Hollmig, 2004 (ASH 2399)[96] Quality *	50-100 mg VATD: Bortezomib 1.0 or 1.3mg/m^2 d1,4, 9,11); Doxorubicin 2.5-10 mg/m^2 d1-4 & d9-12 cont infusion; Thal 50-100 mg d 1-12; Dex 20-40 mg. d1-4, & 9-12 [Med f/u= NS]	20 Pt and MM characteristics NS	14 evaluable	Overall Response (≥25%) = 50% m protein reduction: 100% = 0% ≥75% = 50% ≥50% = NS ≥25-49% = NS	
Kasper, 2004[97] Quality 2/5	Thal 100-400 mg + PegIFNα 20-50 µg	15 60 yr (56-79) 53% F Heavily pretreated 73% with 1 cycle of HDCT (SCT not stated) 80% Stage III Myeloma sub-types not stated	15	Overall Response (≥25%) = 40% m protein reduction: 100% = NS ≥75% = NS ≥50% = 7% ≥25-49% = 33%	PFS 14 mo (3-14) PegIFNα had to be stopped in 46% due to adverse effects

Table 7. Thalidomide efficacy studies–studies of Thalidomide plus other agents in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of follow-up]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Kropff, 2003[98] Quality 5/5	100-400 mg + Dex 20mg/ m^2 x4d on d1, 9, 17 during cycle 1 then option to reduce to q28d + hyperfractionated cyclophosphamide 300 mg/ m^2 iv q12hrs x6 doses (median 4 cycles) [med f/u=NS]	60 43% >60 yr 67% M Refractory or relapsed IgG = 69% IgA = 16% Light chain only = 9%	57 evaluable	Overall Response (≥25%) = 84% m protein reduction: 100% = 4% ≥75% = NS ≥50% = 68% ≥25-49% = 12%	Median EFS = 11 mo Median OS = 19 mo 67% grade IV neut w/ ≥1 cycle (median duration 3 d) Infections: grade 3 = 17% Grade 4 = 9% Neutropenic infection = 2 deaths Thal d/c 'd for thromboembolic event = 1 Cerebrovascular event = 3 Pt choice = 1 Not documented = 3
Mileshkin, Biagi, et al., 2003[99] Quality 5/6	200-1000 mg +/- IFNα @ week 12 [18 mo (6-26)] Not randomized	75 56 Thal alone 19 Thal + IFN 64 yr (36-83, 48% >65) 61% M Relapsed or resistant (must have had systemic combination chemotherapy, Dex alone was not acceptable) Prior chemo regimens median = 3 cycles (1-7) 27% prior HD chemo	All: 75	Overall Response (≥25%) = 29% m protein reduction: 100% = 1% ≥75% = NS ≥50% = 28% ≥25-49% = NS 38% for those ≤ 65 yr responded 17% for those > 65 yr responded (p=0.043)	Median time to response = 12.4 wk (4-114) Median PFS by KM =5.5 mo (CI, 3.6-6.8 mo) Median OS by KM = 14.6 mo (CI, 9.7 to >26.3 mo) KM Estimated for 1-year: PFS 23 % (CI, 14-34%) OS 56% (CI, 44-67%) Median survival: ≤ 65 yr = 6.7 mo > 65 yr = 4.1 mo p=0.045

Table 7. Thalidomide efficacy studies–studies of Thalidomide plus other agents in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of follow-up]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
*Mileshkin, 2005 (ASCO 8233)[100] Quality * *May include pts presented below*	Up to 800 mg Thal + celecoxib 400mg bid EORTC QLQ-C30 QOL questionnaires administered at baseline, monthly and after therapy [20 mo]	66 No pt or MM characteristics reported	66	Overall Response (≥25%) = 42% m protein reduction: 100% = NS ≥75% = NS ≥50% = NS ≥25-49% = NS	PFS @ 20 mo = 6.8 mo OS @ 20 mo = 21.4 mo Med baseline global health score GHS = 58 (range 8-100; higher is better) GHS decreased in 80% between baseline and 1st score For CR+PR pts (n=28): GHS declined = 54% GHS improved = 29% GHS same = 14% PR+CR pts vs. non-responders more likely to show improvement in best on-treatment GHS: 61% vs. 27%, p=0.024
Offidani, Corvatta, Marconi, Malerba, et al. 2004 [101] Quality 0/6 *May include pts presented below*	100-400 mg +/- melphalan 0.20mg/kg/d x 4d q 28d Thal mean daily dose = 158mg (SEM +/- 12.6) [med f/u not stated] Not randomized	59 69 yr Advanced MM 4 = stable 55 = active progressive 4 = new diagnosis	59 32 Thal alone 27 Thal + Melphalan	Overall Response (≥25%) = 64% m protein reduction: 100% = NS ≥75% = 10% ≥50% = 34% ≥25-49% = 20% PPR ≥50% (inclusive) = 44% TM = 63% T alone = 37% p = 0.015	Mean duration/pt= 320 days Mean Thal dosage /pt= 52g 100 mg = 15% 200 mg = 46% 300 mg = 10% 400 mg = 29% Thal d/c'd for AE = 27% but not dose dependent 2 yr OS = 58% Peripheral neuropathy 39%: median time to PN = 16 mo PN risk factors = median dose>150 mg (p=0.038) disease history > 3yr (p=0.099) and prior tx w/ VCR (p=0.104);

Table 7. Thalidomide efficacy studies–studies of Thalidomide plus other agents in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of follow-up]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Offidani, Corvatta, Marconi, Olivieri, et al. 2004[102] Quality 6/6 *May include pts presented above*	100-600 mg +/- melphalan 0.20mg/kg/d x4d q 28d (Thal-M) [13 mo]	50 74 yr (46-84) 40% M 27 pts recruited on study and 23 pts met same eligibility criteria and included in analysis but not consented into the study >2 previous chemo tx = 54% IgG = 82% Disease hx > 60 mo = 34% Other MM characteristics NS	50 Thal-M = 23 Thal = 23	Thal-Melphalan: Overall Response (≥25%) = 81 % m protein reduction: 100% = 13% ≥75% = 2% ≥50% = 44% ≥25-49% = 22% Thal: Overall Response (≥25%) = % m protein reduction: 100% = NS ≥75% = 4% ≥50% = 22% ≥25-49% = 17% TM response superior to T p=0.009	2 yr PFS = 57% 2-yr OS = 59% PFS: Thal-Melphalan = med not reached 2yr PFS = 61% Thal = 13.1 mo 2yr PFS = 45% p=0.0356 No difference between Thal-M and Thal for OS
*Suvannasankha, 2005 (ASCO 6591)[103] Quality *	200 mg CTP: Thal 200 mg+ Cyclophosphamide 50 mg bid x21d q 28d + Prednisone 50 mg qod [18.37 mo, 95% CI 15.18-21.52]	37 65 yr (49-87) Gender NS Prior HDSCT = 43% Other MM characteristics NS	35	Overall Response (≥25%) = 69% m protein reduction: 100% = 22% Near CR = 6% ≥75% = NS ≥50% = 41% ≥25-49% = NS	Median TTP = 13.24 mo (95% CI 9.40-20.99) Median OS = 20.4+ mo Median # treatment cycles = 7 (1-12)
*Teoh, 2004 (ASH 4915)[104] Quality *	50mg DTZ: Thal 50 mg daily + Dex 20 mg d1-4qmo +zoledronate 4mg qmo Pts treated for 3 mo [med f/u= NS]	18 Previously treated with symptomatic MM and unable to tolerate “conventional doses of Dex and/or Thal and/or chemo		Overall Response (≥25%) = UTD m protein reduction: 100% = 22% “Good responses” (undefined) = 61% ≥75% = NS ≥50% = NS ≥25-49% = NS	Median time to remission = 8.2 mo

Table 7. Thalidomide efficacy studies–studies of Thalidomide plus other agents in advanced/refractory/resistant multiple myeloma

Study ID	Thalidomide Dose Daily [Median length of follow-up]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
*Williams, 2004 (ASH 1499)[105] Quality *	100-200 mg CTD: Cyclophosphamide 500 mg. orally d1,8 &15 Thal 100-200 Dex 40 mg d1-4, 15-18 Repeated q4 wks for 2-6 cycles [19 mo]	62 55 yr (31-73) Gender not specified Newly diagnosed = 24% Refractory to VAD = 47% Relapsed MM = 27% IgG = 61% IgA = 27% B-J protein = 10% Non-secretory = 2%	62 New dx = 15 VAD refractory = 29 Relapsed = 17	Newly diagnosed Overall Response (≥25%) =100% m protein reduction: 100% = 20% ≥75% = NS ≥50% = 80% ≥25-49% = NS VAD refractory Overall Response (≥25%) = 83% m protein reduction: 100% = NS ≥75% = NS ≥50% = NS ≥25-49% = 83% Relapsed: Overall Response (≥25%) = 71% m protein reduction: 100% = NS ≥75% = NS ≥50% = 71% ≥25-49% = NS	
*Zangari, Barlogie, Hollmig, et al. 2004 (ASH 1480)[107] Quality *	50-200 mg V+Thal: Bortezomib (V) 1.0-1.3 mg/ m^2 d1,4, 8, 11) + Thal (T) 50-200 mg at increasing doses per cohort Repeated q 21 days [med f/u= NS]	79 Age >65 = 28% Gender NS Advanced refractory MM IgA = 18% Other MM characteristics NS	79	V alone: Overall Response (≥25%) = 25% m protein reduction: 100% = NS Near CR = 10% ≥75% = NS ≥50% = 15% ≥25-49% = NS V+Thal: Overall Response (≥25%) = 70% m protein reduction: 100% = NS Near CR = 10% ≥75% = NS ≥50% = 20% ≥25-49% = 40%	EFS = 7 mo Median OS = 21 mo

Abbreviations: * = abstract, alloBMT= allogeneic bone marrow transplant, B-J= Bence Jones protein, CI= Confidence Intervals, CR= Complete Response, CT= consolidation therapy, CTD= cyclophosphamide/Thalidomide/Dex, d/c= discontinued, Dex= Dexamethasone, DTPACE= combination chemotherapy including Dex/Thal/Cisplatin/Doxorubicin/Cyclophosphamide/Etoposide, DTZ= Dex/Thal/zoledronate, EFS= event free survival, EORTC QLQ-C30= European Organization for Research & Treatment of Cancer Quality of Life Questionnaire Core-30, EM= extramedullary, f/u= followup, GHS= global health status, HDSCT= high dose stem cell transplant, HDT= high dose therapy, IFN= Interferon, KM= Kaplan-Meier, Near CR= positive IFE only, med= median,

neut= neutropenic, NS= not stated, OS= overall survival, PegIFNα= pegylated interferon alpha, PFS= progression free survival, PN= peripheral neuropathy, PR= partial response, pt(s)= patient(s), QOL= quality of life, SCT= stem cell transplant, T= Thalidomide, TTP= time to progression, tx= treatment/therapy, UTD= unable to determine, VAD= standard chemotherapy including Vincristine/Doxorubicin/Dexamethasone, V= Velcade (Bortezomib), VCR= Vincristine

Table 8. Thalidomide efficacy–thalidomide used as part of the pre or post stem cell transplantation regimen

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Phase III					
*Attal, 2004 (ASH 535)[108]	Thal dose NS HDT w/VAD then auto SCT w/ melphalan 200 mg/m^2 If no progression at 2 mo after second ASCT, randomized to 3 arms. A = no maintenance B = pamidronate C = Thal + pamidronate [26 mo (6-50)]	580 Inclusion <65 yr "At diagnosis" Other pt and MM characteristics NS	580 Arm A = 195 Arm B= 190 Arm C = 195		Probability of PFS @ 40 mo: Arm A = 53% (95% CI = 37-65) Arm B = 52% (95% CI = 36-68) Arm C = 70% (95% CI = 42-80) p=0.007 Thal also improves EFS; p<0.01 60% enrolled in Arms A and B received Thal at relapse; OS survival similar in all 3 groups
Barlogie, 2002[109] Quality 2/6 Thalidomide as initial phase of Total Therapy program	400 mg 50% randomized to Thal then Intensive Induction w/ VAD (Thal group) or CAD/DCEP (no Thal group) then MEL & transplant; consolidation with DECP (Thal group) or DCEP/CAD (no Thal group); maintenance IFN [27 mo]	231 20% >65 yr old gender not specified (This is a report on the first 231 randomized of a total 450; patients were randomized to Thal 400 vs. no Thal at the beginning of the Total Therapy II program – these data do not present unblinded outcomes)	231	BLINDED DATA – DO NOT KNOW WHICH PATIENTS RECEIVED THAL Overall Response (≥25%) =UTD m protein reduction: @ end of induction CR + near CR = 30% after second HDT cycle CR + near CR = 66% 100% CR = 46% Near CR = 20% ≥90% = NS ≥50% = %	BLINDED DATA – DO NOT KNOW WHICH PATIENTS RECEIVED THAL Overall 3 year estimated Followup EFS = 71% OS = 77%
*Barlogie, 2004 (ASH 1483)[110] Quality * Thalidomide as initial phase of Total Therapy program	Updated report from Barlogie, 2004 (ASH 1483) [Evaluated at time of treatment failure = med 23 mo from enrollment]	As of 8/4/04, 104 of 668 pts enrolled have been randomized Thal = 61 No Thal = 43			Thal salvage response rate = 26% No Thal salvage response rate= 51% p=0.028 Survival from time of relapse on Total Therapy II was better for those who did not receive Thal maintenance (med 29 vs. 8 mo, p = 0.0001) Hazard ratio for OS post-relapse when Thal maintenance used = 2.6 p=0.0006

Table 8. Thalidomide efficacy–thalidomide used as part of the pre or post stem cell transplantation regimen

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
Lee, 2003[21] Quality 4/5	50-400 mg within DTPACE regimen DTPACE x 2 cycles then if >50% response randomized to tandem SCT with high-dose melphalan or 4 more cycles of DTPACE or if <50% SCT; maintenance with Thal 50-200mg and Dex 20mg/dx4d q 4 wks – 10% required a 50% dose reduction of Thalidomide by 2nd cycle of DTPACE Dex 40qd x 4d Thal 400 qhs Cisplatin 10mg/m2/d x 4d Doxorubicin 10mg/m2/d x 4d Cyclophosphamide 400 mg/m^2/d x 4d Etoposide 40mg/m^2/d x 4d	236 60 yr (31-84) 64% M Previously treated 63% progressive disease after chemo IgG = 56% IgA = 19% Light chain = 2%	DTPACE cycle #1: 229 DTPACE cycle #2: 229	Overall Response (≥25%) = 73% m protein reduction: 100% = 3% Near CR = 5% ≥90% = NS ≥75% = 9% ≥50% = 53 Overall Response (≥25%) = 86% m protein reduction: 100% = 7% Near Cr = 9% ≥90% = NS ≥75% = 16% ≥50% = 54%	Extensive toxicity data – cannot determine what is due to thalidomide
Phase II					
Alexanian, 2002[111] Quality 2/5 Alexanian, 2003[64] Quality = 1/6 Two papers with the same data	100-300 mg + Dex20 mg/m^2 x 4d on d1, 9 and 17 q28 days – started 7 mo (4-20) after intensive therapy Responders maintain Thal 100-150 mg [treatment > 3 mo; med f/u not stated]	21 54 yr (37-61) 71% M stable, partial responders after intensive CT and SCT (consolidation therapy after SCT)	21	Overall Response (≥25%) = 81% m protein reduction: 100% = 19% ≥90% = 38% ≥75% = 19% ≥50% = 5%	

Table 8. Thalidomide efficacy–thalidomide used as part of the pre or post stem cell transplantation regimen

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Paraprotein response	Survival/other
*Sengar, 2005 (ASCO 6731)[112] Quality *	50 mg After high dose melphalan+ SCT: Randomized to maintenance Thal vs. IFN randomized (unclear if phase II or phase III)	70 – Unclear if enrollment continuing or goal n 52 yr (26-65) 74%M Stage III = 70% Other MM characteristics NS	17 randomized		UNBLINDED DATA NOT PRESENTED PFS = 55% OS = 60% Median duration of maintenance = 14 mo
*Stewart, 2004 (ASH 335)[113]	200-400 mg Thalidomide/Prednisone maintenance after ASCT with Melphalan 200 mg/ m^2: Prednisone 50 mg qod + Thal 200 vs.400 mg Randomized Phase II [36.8 mo]	67 Pt and MM characteristics NS Numbers randomized to each arm NS	67	Overall Response (≥25%) =UTD m protein reduction: post-tx CR or near CR = 15% @ 1 yr CR + near CR = 38% ≥90% = NS ≥50% = NS	PFS post-ASCT = 32.3 mo OS @ 1 yr = 91% Primary endpoint = incidence of dose reduction or dropout: Thal 200 arm = 31% Thal 400 arm = 64% Allowing for dose reductions, # on each arm at 18 mo after registration: Thal 200 arm = 76% Thal 400 arm = 41% Because of excessive treatment toxicity enrollment in the 400mg dose arm was closed after completing the first phase of the planned enrollment

Abbreviations: *= abstract, ASCT= Autologous stem cell transplant, CI= Confidence Intervals, CR= Complete Response, CT= consolidation therapy, DTPACE= combination chemotherapy including Dex/Thal/Cisplatin/Doxorubicin/Cyclophosphamide/Etoposide, EFS= event free survival, HDT= high dose therapy, IFN= Interferon, Near CR= +IFE only, NS= not stated, OS= overall survival, pt(s)= patient(s), SCT= stem cell transplant, UTD= unable to determine, VAD= standard chemotherapy including Vincristine/Doxorubicin/Dexamethasone

Part 2. Adverse Effects

Adverse effects are summarized on Tables 9 and 10. Table 9 includes studies presented in the previous efficacy analysis that also included adverse events information. Table 10 represents studies that were presented as reports of adverse events only.

Review of Table 9 highlights six main themes:

1. Using data from studies of thalidomide only, thalidomide side effects include constipation (3-11 percent grade 3 and 4), neurotoxicity predominantly evident as peripheral neuropathy (1-7 percent grade 3 or 4) and sedation (3-13 percent grade 3 or 4), cardiac insufficiency due to bradycardia (2-6 percent grade 3 or 4), leukopenia (2-31 percent grade 3 and 4), and blood clots (2-10 percent grade 3 or 4).
2. In many instances, patients with more advanced multiple myeloma have more side effects, as would be expected, but not overwhelmingly more.
3. The profile of side effects shifts when dex is combined with thal. There is less peripheral neuropathy (2 percent grade 3 or 4). There are two columns for the Weber study.[67] Patients represented in the column with N=28 received thal only while those in the N=40 column received thal-dex. Sixty-eight percent of patients who received thal developed some peripheral neuropathy, as opposed to 50 percent of those who did not receive dex. A similar pattern was seen in the Weber study for decreased constipation with thal-dex (68 percent vs. 55 percent). However, with dex there was more weakness/fatigue/lethargy and edema. Thromboembolic events and skin reactions appear to increase when dex is included as well.
4. Combining thalidomide with other agents increases side effects further.
5. Side effects increase as multiple myeloma advances or the patient has been exposed to other treatments.
6. Outside of the addition of dex, adding other chemotherapeutic agents generally increases the side effect profile.

Table 10 demonstrates the growing insight around thalidomide and its side effects that is rapidly accumulating in the literature. Fahdi and colleagues demonstrated that the incidence of bradycardia was 53 percent in their population of patients receiving thalidomide.[117] Thalidomide does not increase the incidence of avascular necrosis when it is combined with steroids.[114] Work by Badros et al. suggests that subclinical hypothyroidism with TSH >5 is about 13 percent more common with thalidomide than with conventional chemotherapy.[115] Hall et al. reviewed skin reactions associated with thal and thal-dex, documenting the risk of severe exfoliative reactions like toxic epidermal necrolysis.[118] Hattori et al. verified the cytopenias seen with thalidomide and documented that the neutropenia can be ameliorated with GCSF.[45] Tosi documented that the neurotoxicity rate with thalidomide was nearly the same for newly diagnosed myeloma patients and those with refractory or resistant disease.[77] Tosi and colleagues also documented that the peripheral neuropathy associated with thalidomide accumulates and worsens over time.[121] And finally, a growing body of work from Zangari and colleagues carefully documents that the incidence of DVT is approximately 24-36 percent higher when patients receive thalidomide, that DVTs occur approximately 6 weeks after initiation of thalidomide, they may be associated with chromosome 11 abnormalities, and they do not alter the efficacy of thalidomide.[126,125,124,123,122] Zangari and colleagues also document that low dose warfarin does not mitigate the DVT risk with thalidomide, but low dose enoxaparin does decrease the risk to baseline levels.

Table 9: Adverse effects reported in efficacy studies

Toxicities	Thalidomide only/untreated		Thalidomide only, refractory, relapsed, progressive (part 1)											
Study	Rajkumar [41], 2001 untreated SMM or IMM n=16		Barlogie [42], 2001 heavily pretreated, progressive MM n= 169	Hus [43], 2001 relapsed, refractory whypocellular BM & severe pancytopenia n = 53					Neben [52],2001 progressive MM 87% Stage III n = 54		Richardson [54], 2004 Relapsed, refractory n = 30		Schey [55] 2003 Relapsed, refractory n = 69	
grade	grade 1-2	gr 3	>grade 2	total # patients	WHO I	WHO II	WHO III		gd 3	gd 4	grade 1-2	grade 3	grade 1-2	grade 3
drug	Thalidomide		Thalidomide	Thalidomide					Thalidomide		Thalidomide		Thalidomide	
dosage	200-800 mg		200-800	200-400 mg				200-800 mg	100-400mg		200-800 mg		100-800 mg	
constipation	94%		18%	31				6%			43%	3%	6%	4%
nausea/vomiting														
mouth dryness/xerostomia														
mucositis														
liver AST/ALT								3%						
fever/chilliness				5	4	1								
neurotoxicity	81%		9%											
impotence												6%		
weakness or fatigue or lethargy				38	35	3		3%			37%			
somnolence/sedation	94%	6%	58% CNS (sedation, somnolence, confusion, depression, tremor)	42	42			13%				3%	15%	
dizziness														
tingling or numbness/peripheral neuropathy				12	10	2			6%		30%	7%	14%	1%
headache														
poor coordination/muscle cramps								6%						
tremors														
altered hearing or vision									1%					
confusion														
Mood changes/anxiety/depression	13%													
vertigo								3%						
cerebrovascular event								3%						
cardiac function/tachycardia									2%	1%				
syncope	6%								2%					
heart insufficiency/bradycardia				3	2	1		6%						
thrombocytopenia														
leukopenia/neutropenia				14	9	2	3	31%	2%					12%
infections (grade 3)														
febrile neutropenia								6%						
neutropenic infections									5%	2%				
DVT/thrombolytic event			<2%					3%	4%					10%
renal toxicity														
edema	13%													
PPE palmar-plantar erythrodysesthesia														
rash	44%			4	3	1		3%			33%	3%		
dry skin/ skin reaction														
hypothyroidism														
dyspnea/pneumonia								3%						
none														

Toxicities	Thalidomide only, refractory, relapsed, progressive (part 2)											Thal/Dex untreated			
Study	Singhal [35], 1999 Previously treated & progressive n = 84				Tosi [57], 2002 relapsed/refractory 94% Stage III n = 65		Weage [58], 2004 Relapsed, refractory n = 85		Yakoub-Agha [59] 2002 Advanced progressive after ≥ 2 lines of therapy n = 83		Yakoub-Agha [60] 2000 progressive advanced MM n = 27	Rajkumar [55], 2002 Newly diagnosed n = 50		Weber [57] 2003 Previously untreated n = 68	
grade	incidence of grade 1 or 2 adverse events				grade > 2 toxicity		gd3	gd4	# of events		% observed side effects	grade 1-2	grade 3	percent with side effects	
drug	Thalidomide				Thalidomide		Thalidomide		Thalidomide		Thalidomide	Thalidomide / dexamethasone		Thalidomide / dexamethasone	
dosage	200mg	400mg	600mg	800mg	100-800 mg		100-400 mg		<400	≥400	100-800 mg	50-800 mg		200-600 mg	
constipation	35%	44%	44%	59%	52.3%	4.6%	11%	2%	14	31	28%	72%	8%	68%	55%
nausea/vomiting	12%	15%	23%	11%					1	7	18%				
mouth dryness/xerostomia							2%		3	6	7%				
mucositis															
liver AST/ALT												22%			
fever/chilliness											11%				
neurotoxicity					13.8%	3%									
impotence					4.6%				3	16					
weakness or fatigue or lethargy	29%	31%	39%	48%	33.8%							50%		39%	55%
somnolence/sedation	34%	43%	40%	43%					16	40	66%	46%	2%		
dizziness	17%	25%	23%	28%							4%				
tingling or numbness/peripheral neuropathy	12%	14%	19%	28%			3%		1	9	7%	58%	2%	68%	50%
headache	12%	10%	14%	11%			3%								
poor coordination/muscle cramps	16%	17%	14%	22%			2%							43%	13%
tremors	10%	13%	19%	22%							11%	30%		38%	30%
altered hearing or vision							3%				4%				
confusion															
Mood changes/anxiety/depression											7%		2%		
vertigo															
cerebrovascular event															
cardiac function/tachycardia											4%		2%		
syncope													2%		
heart insufficiency/bradycardia							3%	2%							
thrombocytopenia															
leukopenia/neutropenia					3%	1.5%					10%				
infections (grade 3)														14%	13%
febrile neutropenia															
neutropenic infections															
DVT/thrombolytic event					1.5%	1.5%	3%						12%	4%	15%
renal toxicity					4.6%										
edema	8%	10%	12%	22%	3%				2	13	4%	28%	2%	25%	35%
PPE palmar-plantar erythrodysesthesia															
rash	16%	18%	21%	28%	10.7%	4.6%	3%					38%	6%	61%	55%
dry skin/ skin reaction															
hypothyroidism															
dyspnea/pneumonia													4%		
none					3%										

Toxicities	Thal/Dex - advanced/refractory		Thal/Other untreated			Thal/Other - Advanced/refractory						
Study	Dimopoulos [79] 2001 refractory, resistant n = 44	Palumbo [74], 2001 Refractory, relapsed n = 77	Zervas [69] 2009 untreated Thal/VAD-Doxil n = 39		Schutt [67], 2006 untreated n = 91	Offidani [101], 2004 Mixed phases; 85% relapsed, n = 59	Offidani [102], 2004 relapsed/resistant not eligible for transplant n = 50 (thal =23; thal + melphalan = 27)		Dimopoulos [84], 2004 previously treated n = 53			Cleplusch [85], 2002 resistant w/ osteolytic lesions n = 21
grade	% common side effects	grade 1	% Gd ≤ 2	% Gd 3-4	% frequency of adverse events	> grade 2	% patients with side effects		grade 1	grade 2	grade 3 +4	% common side effects
drug	Thalidomide related side effects	Thalidomide / dexamethasone	Thalidomide		Thalidomide + VEC	Thal vs Thal/Melphalan	Thalidomide	Thalidomide + Melphalan	Thalidomide/Dexamethasone + pulsed cyclophosphamide			thalidomide + pamidronate
dosage	200-400 mg	100 mg	200 mg		200-400 mg	100-400mg	100-600 mg		400 mg			200-400 mg
constipation	75%	12%	67%	10%	65%	71%	61%	82%	36%	4%	0%	38%
nausea/vomiting												
mouth dryness/xerostomia									17%	0%	0%	
mucositis			18%	5%								
liver AST/ALT												
fever/chilliness												
neurotoxicity												
impotence												
weakness or fatigue or lethargy		8%				20%	28%	22%	30%	0%	0%	
somnolence/sedation	57% (and/or fatigue)	6%	54%		45%	35%	35%	41%				30%
dizziness		3%	41%			7%	9%	0%				30%
tingling or numbness/peripheral neuropathy	23%	17%	46%	2.50%	64%	30%	30%	56%	4%	0%	0%	15%
headache	21%					5%	4%	7%	8%	0%	0%	
poor coordination/muscle cramps												
tremors	34%	3%	33%						10%	0%	0%	7%
altered hearing or vision												
confusion						5%						7%
Mood changes/anxiety/depression							9%	3%				
vertigo												
cerebrovascular event												
cardiac function/tachycardia												
syncope												
heart insufficiency/bradycardia						5%	4%	7%				32.3%
thrombocytopenia			10%	15%	3.2%				6%	4%	2%	23%
leukopenia/neutropenia			13%	15%	32%	10%	28%	46%	8%	8%	26%	23%
infections (grade 3)			10%	8%			0%	0%				
febrile neutropenia												
neutropenic infections				13%	grade 3 = 23% grade 4 = 0.7%							
DVT/thrombolytic event	7%			10%	26%	7%	4%	11%	2%	0%	0%	
renal toxicity		3%										
edema	17%		23%						8%	0%	0%	
PPE palmar-plantar erythrodysesthesia			10%									
rash	21%	1 pt erysipela 3%	13%	5%								
dry skin/ skin reaction									4%	0%	0%	7%
hypothyroidism		3%				3%	0%	3%				
dyspnea/pneumonia												
none					pneumonia = 13%				alopecia = 2%	0%	0%	

Table 10. Adverse effects of thalidomide–Studies of specific adverse effects

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Adverse Effects	Other
*Anaissie, 2004 (ASH 3467)[114] Quality *	Thal dose not specified, randomization to receive thal or not after Dex-containing chemo ASCT, consolidation and IFN [33 mo, 5-114]	553	553	9% Avascular necrosis (AVN) of femoral head Among thal treated pts, prevalence similar to control group (8% vs. 10%; p=0.58)	Median time to onset of AVN of femoral head 12 mo (2-41) Risk factors: Cumulative Dex dose (p=0.0006; OR 1.028; 95% CI 1.012-1.044) per Dex 40 mg Male gender (p=0.009; OR 0.390; 95%CI 0.192-0.790) Younger age (p-0.0122; OR 0.961, 95% CI 0.934-0.991/year) FDG-PET failed to detect abnormal uptake
Badros, 2002[115] Quality 2/5	200-800 mg +/- chemo [med f/u NS]	343 174 =MM treated in prior clinical trial 169 = relapsed MM Age & gender not specified	174 92 chemo +Thal; 82 chemo 169 Thal relapsed MM	Chemo + Thal =92 20% TSH > 5 7% TSH >10 Chemo only =82 7% TSH >5 0% TSH >10 Thal = 169 22% TSH >5 14% TSH >10	Conclusion = subclinical hypothyroidism occurred more frequently with Thal
Bowcock, 2001[116] Quality 0/5	Mean dose 150 mg [5 mo]	23 65.6 yr = avg age for thromboembolism (TE) pts Gender not specified relapsed, resistant Historical control group = 18 pts with relapsed, resistant MM who had not received thal (age, gender not specified)	23 18	5 DVT 2 Cerebral TE (1 = TIAs) 1 Cerebral TE (TIAs)	Conclusion = TE more common on thal

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Adverse Effects	Other
Fahdi, 2004[117] Quality 4/6	Combo chemo VAD/PAC then randomized to placebo vs. Thal Induction = 400 mg Maintenance = 200 mg q other day x 1 yr then 100 mg/d [med f/u NS]	200 50 yr +/- 3 yr Gender not stated newly diagnosed	200 Placebo = 104 Thal = 96	Bradycardia: Baseline = 9.1% 4-12 weeks = 8.3% Baseline = 9.4% 4-12 weeks = 38.8% Thal: Overall 53% developed bradycardia; (4.8% required pacemaker)	Bradycardia defined as 30-60 beats/min. TSH, cardiac history, diabetes, & renal function were equivalent between groups
Hall, 2003[118] Quality 1/5	200-800 mg Group 1 (Indolent) & group 2 (refractory)	40 Age & gender not specified (Thal only: Group 1 Indolent = 19 & Group 2 refractory = 31)	Group 1 = 19 Group 2 = 31	Minor = 14 Moderate = 8 Severe (exfoliative) = 1	Minor derm toxicity = rash that didn't require change in thal schedule; Mod = altered in schedule or dose; Severe = discontinued drug due to rash
	200-400 mg + Dex 40 mgx4d on D1, 9, 17 on odd-numbered cycles and D1 on even-numbered cycles [med f/u NS]	Thal/Dex 37 Age & gender not specified Newly diagnosed	37	Minor = 5 Moderate = 8 Severe =3 Toxic necrolysis =1 Erythema multiforme = 1 Exfoliative = 1	Onset of skin reactions from 1st mo until after 4 mo after Thal begun 3 pts ↓ Thal until rash resolved 5 pts interrupted Thal due to adverse reactions; resumed at lower doses 3 stopped Thal
Hattori, 2004[45] Quality 4/5	200-400 mg Dose reductions + G-CSF for neutropenia [med f/u NS]	44 55.9 yr (30-70) 58% M relapsed refractory	44		11% d/c Thal due to grade 4 cytopenia 25% had ≥ 50% drop in neutrophils (w/ lower hgb, platelets, & BM plasma cells than in nonneut. pts) 11% = concomitant thrombocytopenia; Nadir = 3-8 wk "Dose reduction and exogenous GCSF usually ameliorated neutropenia"

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Adverse Effects	Other
*Singh, 2004 (ASCO 3142)[119] Quality *	Thal dose NS [med f/u NS]	257 235 cases reviewed from FDA representing reports from clinical practice and compared to clinical trials reports in the medical literature (n=22) Includes information about completeness of age, gender, dose, etc. in study but not reported in abstract	166 Clinical practice reports Clinical trial reports N=69		Case Report Information: In comparison with reports from clinical practice settings (n=166), clinical trial reports (n = 69) had higher rates of inclusion of information on: thalidomide administration dates (77% vs. 32%), DVT/PE onset date (62% vs. 23%), no of days from thal administration to DVT/PE (52% vs. 17%), and DVT/PE treatment (76% vs. 42%) [p < .0001 for each comparison]
*Spencer, 2004 (ASCO 6655)[120] Quality *	Thal 200 mg + Zoledronic acid (ZA) 4 mg IV q 28d +Prednisolone 50 mg qod As post – SCT maintenance [med f/u NS]	83 Age & gender well-matched but specifics not included 12 mo post-ASCT non-progressive MM Randomized to zoledronic acid +/- Thal	83 enrolled 40 ZA/Thal 43 ZA alone	Higher creatinine levels (i.e. renal dysfunction) associated with: Male gender + pre-ASCT B2M >4 mg/L (p<0.001) But not cumulative ZA dose – NS Or presence of thal - NS	No evidence of PK interaction Thal to ZA.
*Tosi, 2004 (ASH 4898)[77] Quality * Likely includes pts presented in report below	n = 34 on Thal 200 + Dex 40 d1-4 even cycles & d1-4, 9-12, 17-20 odd cycles Followed by cyclophosphamide 7 g/m^2 + G-CSF; then auto PBSCT. n = 40 on Thal 200 mg + Dex 40 mg d1-4 q mo [med f/u NS]	74 >8 mo Thal/Dex treatment 34 = newly diagnosed symptomatic MM 55 yr 52% M 40 = pretreated (14 relapsed or 26 progressive) 61 yr 68% M	74	Neurotoxicity Newly diagnosed = 74% Grade I = 57% Grade III = 0% Pretreated = 75% Grade II = 32.5% Grade III = 27.5%	Not related to sex, M protein isotype or daily Thal dose Grades II + III correlated to longer disease duration (“significant”)

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Adverse Effects	Other
Tosi, 2005[121] Quality 4/6 Likely second report of the pretreated pts presented in report above	100-400 mg Some (N NS) received dex 40mg/d x4d q4 wks Eligibility criteria = on thal for > 1 year	40 61.5 yr (34-78) 68% M Stage III = 90% Previous SCT = 55% Previous conventional chemo = 38% IgG = 68% IgA = 17% B-J protein = 12% Non-secretory = NS	40	Goal = evaluation of toxicity I pts exposed to long-term thal Median tx duration = 15 mo (12-44) Sub-clinical hypothyroidism = 3% Sinus bradycardia = 6% Peripheral neuropathy = 75% Grade 1: 6 months = 35% 12 months = 15% Grade 2: 6 months = 18% 12 months = 33% Grade 3: 6 months = 0% 12 months = 28% Med time to onset of sx = 11 mo (5-13) Electrophysiologic evaluation tested in all with Grade >1 neurotoxicity revealed sensory axonal polyneuropathy = 100%	Pts with longer time from diagnosis to onset of thal with higher risk of toxicity (p=0.01) but this was not related to the prior therapies used
Zangari, 2001[122] Quality 0/5	400 mg (see Total Therapy II program Barlogie, 2002[109]) Pts randomized to thal or not within Total Therapy II [med f/u not stated]	100 randomized 56 (32-71) 67% M 6 with previous DVT o/w equal distribution of risk factors (doesn't state which groups 6 previous DVT were in) DVT confirmed by Doppler ultrasound or venography	Thal = 50 No thal = 50		DVT = 14/50 (28%) DVT = 2/50 (4%) P=0.002 Median time from start of thal to diagnosis of DVT = 42.5d (7-93d)

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Adverse Effects	Other
Zangari, Saghafifar, et al. 2002[123] Quality 0/6	400 mg (see Total Therapy II program Barlogie, 2002[109]) Pts randomized to thal or not within Total Therapy II [med f/u not stated]	62 randomized 61 (33-76) 58% M 3 with previous DVT o/w equal distribution of risk factors (doesn't state which groups 6 previous DVT were in) Incidence of APC resistance in absence of Factor V Leiden mutation 23%, 8/30 thal pts and 6/32 no thal pts DVT confirmed by Doppler ultrasound or venography	Thal = 30 No thal = 32		DVT = 11/30 (37%) DVT = 1/32 (1%) P=0.002 Median time from start of thal to diagnosis of DVT = 42.5d (7-93d) Pts with APC resistance on thal with highest likelihood of developing DVT (50%) and developing early DVTs (p=0.04)
Zangari, Siegel, et al. 2002[124] Quality2/6	400 mg Pts enrolled in 2 different Phase III studies – Total Therapy II using DT-PACE (see Total Therapy II program Barlogie, 2002[109]) and study with relapsed patients after autoSCT that used DCEP-T which is the same combination of agents minus doxorubicin [med f/u NS]	232 DT-PACE: Med age = 60 Gender not stated Serum M protein = 1.7 g/dL DCEP-T: Med age = 58 Gender not stated Serum M protein = 0.01 g/dL DVT confirmed by Doppler ultrasound or venography	DT-PACE Thal including doxorubicin = 192 DCEP-T (Thal) = 40		DVT = 1/40 (2.5%) DVT = 31/192 (16%) P=0.02 DT-PACE with shorter time to develop DVT (p=0.04) Pts with chromosome 11 abnormalities developed DVT more frequently than those without them (23% vs. 11%, p=0.04) In addition to doxorubicin, risk factors (RF) determined to be age >60 and chromosome 11 abnormalities Cumulative incidence of DVT on thal: No doxo, No RF 3% Doxo, No RF 12% Doxo, 1 RF 23% Doxo 2 RF 46%

Study ID	Thalidomide Dose Daily [Median length of followup]	No. of patients, age, sex, additional MM characteristics	N	Adverse Effects	Other
*Zangari, Barlogie, Lee, et al. 2004 (ASH 4914)[125] Quality *	Thal dose NS DVT in Thal regimens where bortezomib (V) is added or not added to Dex & Doxorubicin without anticoagulation (VDT-PACE vs. DT-PACE) [med f/u NS]	24 Age & gender not specified	24 pts Received 98 cycles DTPACE 69 cycles VDTPACE	10% DVTs in these pts 0% thromboembolic events reported in these pts Historical reports of DVT in Thal/Dex = 12-16%	
Zangari, 2004[126] Quality 6/6	400 mg (see Total Therapy II program Barlogie, 2002[109]) Pts randomized to thal or not within Total Therapy II Cohort 1 = 221 pts – no anticoagulation with n=87 randomized to thal Cohort 2 = 35 pts all on thal and received low dose warfarin Cohort 3 = 130 with pts randomized to thal (n=68) receiving enoxaparin 40mg sc daily [22 mos]	386 Age 65 yr = 18% 62% M Prior chemotherapy = 15% IgG = NS IgA = 21% B-J protein = NS Non-secretory = NS Known risk factors for DVT similar across groups Cohorts similar except Cohort 3 with significantly more pts with high LDH >190 IU/l, >50% plasma cells in BM, and platelet count <150 x 10^9/l	386 Cohort 1 = 221 Thal = 87 No thal = 134 Cohort 2 = 35 (all thal) Cohort 3 = 130 Thal = 68 No thal = 62	Cohort 1 DVT incidence: Thal = 30% No thal = 4% p = 0.0001 OR DVT = 4.3 (CI 2.09-8.65) Cohort 2: Incidence of DVT similar with and without warfarin 1 mg/d (p = 0.07) Cohort 3 DVT incidence: Thal + enoxaparin = 15% No thal = 15% p = 0.81	All DVTs occurred within 15 months of starting thal No relationship between DVT and paraprotein response

Part 3. Predictors

The predictors tables have been divided into four sections: Table 11 reviews reports of predictors related to the presumed mechanism(s) of action of thalidomide, Table 12 reviews reports related to patient demographic factors, Table 13 reviews reports related to known clinical diagnostic tests, and Table 14 reviews reports that are related to thalidomide dosage and response factors. Each detailed table is preceded by a summary table.

Bone marrow angiogenesis has a role in the biology of multiple myeloma,[8] and the anti-angiogenic properties of thalidomide provided the initial rationale for using this drug for this disease.[35] Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are the most potent and specific factors to be known to be involved in angiogenesis. Measurement of these appears to relate to angiogenic activity and increased microvessel density. Growth of multiple myeloma is also regulated by another pro-angiogenic cytokine network where TNF-alpha and IL-6 play a key role.[128] Thalidomide has strong immunomodulatory and anti-inflammatory activity and modulates T-cell subset function and cytokine production in addition to angiogenesis.[128]

In Table 11, the most notable finding among the predictors potentially related to the mechanism of action of thalidomide listed is the lack of consistency among any of the positive findings. None of these are consistent predictors of thalidomide response or survival with thalidomide. The heterogeneity across this group of studies is supportive of what is known—and needs to be known—in order to better elucidate the mechanism of action of thalidomide in multiple myeloma. Of note, hepatocyte growth factor (HGF) levels are reflective of tumor burden and not an indicator of specific effect of thalidomide. It is expected to decrease with tumor response and was used as a control condition for one of the studies.[129]

Review of the summary tables for Tables 12 and 13 suggests that the long known prognostic factors hold up with thalidomide, including age, performance status, cytogenetic abnormalities, albumin, beta-2 microglobulin, and others.

Table 14 confirms that paraprotein response with thalidomide corresponds to multiple myeloma tumor response including bone marrow response and early response predicting later response. Also, two studies suggested that higher doses of thalidomide predicted survival.[60, 134]

Table 11. Predictors of disease response or survival–Tumor characteristics related to the potential mechanism of thalidomide action: Summary

Prognostic factor	Number of studies indicating significant correlation with tumor response / total number of studies indicating factor	Number of studies indicating significant correlation with survival / total number of studies indicating factor
BM Microvascular Density	Equivocal 1/1 (Singhal, 1999[35])	
Serum mucin-1 (sMUC-1)	No correlation = 1/1 (Mileshkin, Prince, et al., 2003[127])	No correlation = 1/1 (Mileshkin, Prince, et al., 2003[127])
Fibroblast Growth Factor (FGF)	*Some* correlation with response = 2/4 (Dmoszynska, 2002[128]; [52]) No correlation = 2/4 (Neben, Moehler, Kraemer et al. 2001[129]; Tosi, 2002 [57])	
Hepatocyte growth factor (HGF)	Correlation with response = 1/1 (Neben, Moehler, Kraemer et al. 2001[129])	
Interleukin-6 (IL-6)	Some correlation with response = 2/3 (Dmoszynska, 2002[128]; Thompson, 2003[130]) No correlation = 1/3 (Neben, Moehler, Kraemer et al. 2001[129])	
Tumor necrosis factor alpha (TNFα)	Some correlation with response = 2/3 (Dmoszynska, 2002[128]; Thompson, 2003[130]) No correlation = 1/3 (Neben, Moehler, Kraemer et al. 2001[129])	
TNFα polymorphisms at position -238 of the gene promoter	Correlation with response = 1/1 (Neben, Mytilineos, et al., 2002[131])	Correlation with survival = 1/1 (Neben, Mytilineos, et al., 2002[131])
TNFα polymorphisms at position -308 of the gene promoter	No correlation = 1/1 (Neben, Mytilineos, et al., 2002[131])	No correlation = 1/1 (Neben, Mytilineos, et al., 2002[131])
t(4;14) positive multiple myeloma	Correlation with poor response to alkylating agents = 1/1 17)[132])	
Vascular Endothelial Growth Factor (VEGF)	Some correlation with response = 2/4 (Dmoszynska, 2002[128]; Tosi, 2002 [57]) No correlation = 2/4 (Neben, Moehler, Egerer et al. 2001[52]; Neben, Moehler, Kraemer et al. 2001[129])	

Table 11. Predictors of disease response or survival–Tumor characteristics related to the potential mechanism of thalidomide action: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
BM Microvascular Density	Singhal, 1999[35] 84 pts with 14.5 mo med f/u Thal only Relapse/refractory [Quality 5/5]	Microvascular density and BM % of plasma cells correlated (p0.01) Although the microvascular density decreased markedly in some pts with a CR or near CR, estimates of the slope of change were not significantly different from zero among those with a response (p=0.39) or without a response (p=0.22)	
Serum mucin-1 (sMUC-1)	Mileshkin, Prince, et al., 2003[127] 75 pts w/ med f/u 18 mo Relapsed/refractory Some pts received IFN [Quality 4/6]	At 18 mo follow up, sMUC-1 is not predictive for PFS: Normal sMUC-1 = 6.1 mo Elevated sMUC-1 = 5 mo (p=0.31)	At 18 mo follow up, sMUC-1 is not predictive for OS Normal sMUC-1 = 15 mo Elevated sMUC-1 = 16 mo (p=0.31)
Fibroblast Growth Factor (FGF)	Dmoszynska, 2002[128] 30 pts with med f/u not stated Thal alone 200-500mg Advanced, resistant [Quality 3/5]	All Pre-treatment FGF 52.9 +/- 9.6 After 8 weeks FGF 49.0 +/- 8.7 (p<0.05 compared to pretreatment) Responders = 60% Pre-treatment FGF 53.6 +/- 10.5 After 8 weeks FGF 47.0 +/- 9.0 (p<0.05 compared to pretreatment) Non-responders = 40% Pre-treatment FGF 51.9 +/- 8.6 After 8 weeks FGF 52.0 +/- 7.7 Major; 50% = 33% FGF 56.0 at pre-treatment Minor; 25% = 27% FGF 52.4 at pre-treatment (Greatest responses in those with highest VEGF and FGF pre-treatment)	

Table 11. Predictors of disease response or survival–Tumor characteristics related to the potential mechanism of thalidomide action: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
	Neben, Moehler, Egerer et al. 2001[52] 54 pts w/ 15 mo med f/u Progressive 72% with prior HDCT/SCT Tx'd with Thal 100-400 mg [Quality 3/6]	Relationship to response to Thal: Effect 50-100 pg/ml (peripheral blood) OR 3.33 (1.33-8.33) Relationship to PFS: Effect 50-100 pg/ml HR 0.87 (0.59-1.27)	
	Neben, Moehler, Kraemer et al. 2001[129] 51 pts with 6 mo f/u Progressive 69% with prior HDCT/SCT Tx'd with Thal 100-400 mg [Quality 3/6]	By two-sided Page test, no difference in FGF 6-mo trends between MM pts with response to Thal vs. those who did not	
	Tosi, 2002 [57] 65 pts (60 evaluable) w/ 9 mo med f/u (VEGF evaluated in 24 pts) Advanced relapse/refractory 36% with prior HDCT/SCT Tx'd with Thal 100-800mg [Quality 2/5]	FGF secretion by BM plasma cells: Thal response = (N = NS) No Thal response = (N = NS) (p = not significant)	
Hepatocyte growth factor (HGF)	Neben, Moehler, Kraemer et al. 2001[129] 51 pts with 6 mo f/u Progressive 69% with prior HDCT/SCT Tx'd with Thal 100-400 mg [Quality 3/6]	By two-sided Page test, significant difference in HGF 6-mo trends between MM pts with response to Thal vs. those who did not (p=0.02) (HGF –HGF levels are reflective of tumor burden and not an indicator of specific effect of Thal on cytokine levels)	

Table 11. Predictors of disease response or survival–Tumor characteristics related to the potential mechanism of thalidomide action: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
Interleukin-6 (IL-6)	Dmoszynska, 2002[128] 30pts with med f/u not stated Thal alone 200-500 mg Advanced, resistant [Quality 3/5]	All Pre-treatment IL-6 2.97 +/- 0.47 After 8 weeks IL-6 2.74 +/- 1.06 (p<0.05 compared to pretreatment) Responders = 60% Pre-treatment IL-6a 3.00 +/- 0.53 After 8 weeks IL-6 1.95 +/- 0.28 (p<0.001 compared to pretreatment) (p<0.001 compared to nonresponders) Non-responders = 40% Pre-treatment IL-6 2.92 +/- 0.38 After 8 weeks IL-6 3.92 +/- 0.57	
	Neben, Moehler, Kraemer et al. 2001[129] 51 pts with 6 mo f/u Progressive 69% with prior HDCT/SCT Tx'd with Thal 100-400 mg [Quality 3/6]	By two-sided Page test, no difference in IL6 6-mo trends between MM pts with response to Thal vs. those who did not	
	Thompson, 2003[130] 38 pts w/ unstated f/u Newly diagnosed (N=20) or SMM (N=18) Thal dose/duration not stated Newly diagnosed pts also received Dex at unstated dose [Quality 1/5]	Before Thal values= 3 pg/mL (0.5-24) After Thal values= 4 pg/mL (0.5-33) (p = not significant) IL-6 > 2 pg/ml (high) = poorer PFS 24% vs. 70% @ 2 year, p = 0.01	

Table 11. Predictors of disease response or survival–Tumor characteristics related to the potential mechanism of thalidomide action: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
Tumor necrosis factor alpha (TNFα)	Dmoszynska, 2002[128] 30pts with median f/u = NS Thal alone 200-500mg Advanced, resistant [Quality 3/5]	All Pre-treatment TNF-alpha 6.2 +/- 0.14 After 8 weeks TNF-alpha 6.16 +/- 0.18 Responders = 60% Pre-treatment TNF-alpha 6.2 +/- 0.16 After 8 weeks TNF-alpha 6.05 +/- 0.12 (p<0.001 compared to pretreatment) (p<0.001 compared to nonresponders) Non-responders = 40% Pre-treatment TNF-alpha 6.19 +/- 0.12 After 8 weeks TNF-alpha 6.33 +/- 0.11	
	Neben, Moehler, Kraemer et al. 2001[129] 51 pts with 6 mo f/u Progressive 69% with prior HDCT/SCT Tx'd with Thal 100-400 mg [Quality 3/6]	By two-sided Page test, no difference in TNF-alpha 6-mo trends between MM pts with response to Thal vs. those who did not	
	Thompson, 2003[130] 38 pts w/ f/u = NS Newly diagnosed (N=20) or SMM (N=18) Thal dose/duration = NS Newly Dex at unstated dose [Quality 1/5]	Before Thal values 11 pg/mL (10-32) After Thal values 11 pg/mL (9-19) (p = not significant) TNFα > 11 pg/ml (high) = poorer PFS 48% vs. 74% @ 2 year (p = 0.01)	
TNFα polymorphisms at position -238 of the gene promoter	Neben, Mytilineos, et al., 2002[131] 81 pts w/ 15 mo median f/u (presumed from previous study to which this design is referred[52], but that study had 54 pts and this one has 81) Progressive Tx'd with Thal 100-400 mg [Quality 3/6] (presumed from [52])	Peripheral blood TNFα levels : TNF -238A allele 9.7 pg/ml TNF -238G allele 5.2 pg/mL (p=0.047) PFS: TNF -238A allele 86% TNF -238G allele 44% (p=0.003) >25% reduction in M protein: TNF -238A allele 75% TNF -238G allele 38% (p=0.05)	OS: TNF -238A allele 100% TNF -238G allele 84% (p=0.07)

Table 11. Predictors of disease response or survival–Tumor characteristics related to the potential mechanism of thalidomide action: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
TNFα polymorphisms at position -308 of the gene promoter	Neben, Mytilineos, et al., 2002[131] 81 pts w/ 15 mo median f/u (presumed from previous study to which this design is referred[52], but that study had 54 pts and this one has 81) Progressive Tx'd with Thal 100-400 mg [Quality 3/6] (presumed from [52])	PFS by KM: TNF -308A allele vs. TNF -308G allele (p=0.31)	OS by KM: TNF -308A allele vs. TNF -308G allele (p=0.31)
t(4;14) positive multiple myeloma	*Jaksic, 2004 (ASH 2417)[132] 16 pts with t(4;14) 14 received salvage Thal or Dex after relapse with alkylating agents Thal dose NS [Quality *]	Report that 64% PPR 25% with Thal and/or Dex whereas significantly shorter than expected OS with high dose alkylating agents with or without SCT – conclude that should use Thal and/or Dex based regimens for these patients	
Vascular Endothelial Growth Factor (VEGF)	Dmoszynska, 2002[128] 30pts with med f/u not stated Thal alone 200-500 mg Advanced, resistant [Quality 3/5]	All Pre-treatment VEGF 153.2 +/- 32.9 After 8 weeks VEGF 118.2 +/- 34.9 (p<0.001 compared to pretreatment) Responders = 60% Pre-treatment VEGF 154.8 +/- 36.6 After 8 weeks VEGF 106.8 +/- 29.5 (p<0.001 compared to pretreatment) (p<0.05 compared to non-responders) Non-responders = 40% Pre-treatment VEGF 150.9 +/- 27.9 After 8 weeks VEGF 135.4 +/- 36.4 Major; 50% = 33% VEGF 177.9 at pre-treatment Minor; 25% = 27% VEGF 140.9 at pre-treatment (Greatest responses in those with highest VEGF and bFGF pre-treatment)	

Table 11. Predictors of disease response or survival–Tumor characteristics related to the potential mechanism of thalidomide action: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
	Neben, Moehler, Egerer et al. 2001[52] 54 pts w/ 15 mo median f/u Progressive 72% with prior HDCT/SCT Tx'd with Thal 100-400 mg [Quality 3/6]	Relationship to response to Thal: Effect 100-300 pg/ml (peripheral blood) OR 0.56 (0.22-1.41) Relationship to PFS: Effect 100-300 pg/ml HR 0.83 (0.47-1.46)	
	Neben, Moehler, Kraemer et al. 2001[129] 51 pts with 6 mo f/u Progressive 69% with prior HDCT/SCT Tx'd with Thal 100-400 mg [Quality 3/6]	By two-sided Page test, no difference in VEGF 6-mo trends between MM pts with response to Thal vs. those who did not	
	Tosi, 2002 [57] 65 pts (60 evaluable) w/ 9 mo med f/u (VEGF evaluated in 24 pts) Advanced relapse/refractory 36% with prior HDCT/SCT Tx'd with Thal 100-800mg [Quality 2/5]	VEGF secretion by BM plasma cells: Thal response = 126.5 +/- 165 pg/ml No Thal response = 227.1 +/- 70 pg/ml (p = 0.04)	

THE FOLLOWING STUDIES PRESENTED SOME NEGATIVE DATA RELEVANT TO THESE PREDICTORS (OFTEN PRESENTED IN TEXT FORM ONLY):

- Richardson, 2004[54] did not find a significant association between change in IL2, IFN, sICAM-1, IL6, VEGF, or TNF-a and tumor response in a study with N=30 receiving Thal for relapse/refract MM after HDCT/SCT (results of statistical tests not reported)
- Thompson, 2003[130] did not find a significant relationship between VEGF, bFGF or IL8 levels and Thal therapy, nor were any of these related to PFS (these data are in addition to IL6 and TNF findings above)
- Schutt, 2005[87] also investigated IL-2R and thymidine kinase which were all significant for EFS in univariate models but not in the multivariate model (only B2M significant as on table 13); study included 31 pts with untreated MM administered Thal + vincristine + epirubicin + Dex

Abbreviations: BM = bone marrow, CR = complete response, d = day, Dex = dexamethasone, FGF = Fibroblast Growth Factor, f/u = followup, HDCT = high dose chemotherapy, HGF = Hepatocyte growth factor, HR = Hazard ratio, IFN = interferon, IL = interleukin, KM = Kaplan-Meier, med = median, mg = milligram, ml = milliliter, mo = month, NS = not stated, OR = overall response, OS = overall survival, PFS = progression free survival, pg = picogram , pt(s) = patient(s), SCT = stem cell transplant, SMM = smoldering multiple myeloma, sMUC = serum mucin, Thal = Thalidomide, TNF = tumor necrosis factor, tx'd = treated, VEGF = Vascular Endothelial Growth Factor , vs. = versus, w/= with

Table 12. Predictors of disease response or survival–Patient demographic factors that predict response to thalidomide*:* Summary

Prognostic factor	Number of studies indicating significant correlation with tumor response / total number of studies indicating factor	Number of studies indicating significant correlation with survival / total number of studies indicating factor
Age	Correlation with response = 2/3 (Barlogie, 2002[109];Yakoub-Agha, 2002[60]) No correlation = 1/3 (Shaughnessy, 2003[133])	Correlation with survival = 3/3 (Mileshkin, Biagi, et al. 2003[99]; Shaughnessy, 2003[133]; Yakoub-Agha, 2002[60])
Gender		Correlation with survival = 1/1 (Dimopoulos, 2004[94])
Performance status (PS measured on the ECOG PS scale)	Correlation with response = 1/1 (Dimopoulos, 2001[70])	Correlation with survival = 2/2 (Dimopoulos, 2001[70]; Dimopoulos, 2004[94])
% of plasma cells in the BM		Correlation with survival = 1/1 (Singhal, 1999[35])
Relapsed vs. refractory disease	Correlation with response = 1/1 (Garcia-Sanz, 2004[95])	
Time from diagnosis to onset of Thal	Correlation with response = 1/1 (Yakoub-Agha, 2002[60])	

Table 12. Predictors of disease response or survival–Patient demographic factors that predict response to thalidomide: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
Age	Barlogie, 2002[109] 231 pts w/ median f/u 27 mo Newly diagnosed Thal part of Total Therapy II regimen At time of analysis, still blinded as to whether or not pts received Thal [Quality 4/6]	<65yr: CR or near CR = 70% >65 yr: CR or near CR = 53% (p=0.001)	
	Mileshkin, Biagi, et al. 2003[99] 75 pts w/ med f/u 18 mo Relapsed/refractory Some pts received IFN [Quality 5/6]		<65yr: Estimated med survival = 6.7 mo >65 yr: Estimated med survival = 4.1 mo (p=0.045) HR = 1.66 (1.00-2.74)
	Shaughnessy, 2003[133] 231 pts w/ median f/u 27 mo Thal within Total Therapy II regimen At time of analysis, still blinded as to whether or not pts received Thal [Quality 2/6]	EFS with age 65 yrs: HR not significant	OS with age 65 yrs: HR 2.0 (p=0.015)
	Yakoub-Agha, 2002[60] 83 pts w/med f/u 338 d Thal alone Relapsed/refractory Quality 6/6	EFS with age > 60 yrs: RR 4.08 (1.52-10.97) (p=0.005)	OS with age > 60 yrs: RR 3.46 (1.28-9.32) (p=0.014)
Gender	Dimopoulos, 2004[94] 53 pts with med f/u NS CTD regimen = cyclophosphamide + Thal + dex Relapsed/refractory Quality 3/5		In multivariate analysis, gender associated with OS: Female: OS = 10.9 mo Male: OS not reached Univariate p=0.008 Multivariate p =0.009
Performance status (PS measured on the ECOG PS scale)	Dimopoulos, 2001[70] Thal + Dex; resistant/refractory 44 pts w/ med f/u = NS [Quality 3/5]	PS= 0: Response to Thal = 83% PS >0: Response to Thal = 37% (p=0.002)	PS 0: Med survival = 13.0 mo PS >0: Med survival = 6.6 mo (p=0.002)

Table 12. Predictors of disease response or survival–Patient demographic factors that predict response to thalidomide: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
	Dimopoulos, 2004[94] 53 pts with med f/u NS CTD regimen = cyclophosphamide + Thal + dex Relapsed/refractory [Quality 3/5]		In multivariate analysis, PS associated with OS: PS 0: OS not reached PS 1: OS = 11.4 mo Univariate p=0.0001 Multivariate p <0.0001
% of plasma cells in the BM	Singhal, 1999[35] 84 pts with median f/u 14.5 mo Thal only Relapse/refractory [Quality 5/5]		High number of plasma cells in BM related to "short OS" (p=0.05)
Relapsed *versus* refractory disease	Garcia-Sanz, 2004[95] 66 pt with med f/u 15 mo Thal combined with oral cyclophosphamide + dex [Quality 4/5]	Relationship between disease status before therapy and response at 6 mo: Relapse = 81% responding Refractory = 50% responding Multivariate p = 0.02	
Time from diagnosis to onset of Thal	Yakoub-Agha, 2002[60] 83 pts w/med f/u 338 d Thal alone Relapsed/refractory [Quality 6/6]	EFS with time <4.2 yrs: RR 3.62 (1.38-9.45) (p=0.008)	

THE FOLLOWING STUDIES PRESENTED SOME NEGATIVE DATA RELEVANT TO THESE PREDICTORS (OFTEN PRESENTED IN TEXT FORM ONLY):

- Also reported in Mileshkin, Biagi et al. 2003[99] but not significant = CRP, creatinine, calcium, plasma cells in BM, response to prior CT
- Yakoub-Agha 2002 [60] also investigated RBC transfusion requirement, platelet count at onset of Thal, prior autoSCT, performance status, and relapse/refractory disease status as potential predictors of response to Thal – all of these not significant

Abbreviations: CR = complete response, CTD = cyclophosphamide + Thalidomide + Dexamethasone, d = day, Dex = Dexamethasone, ECOG = Eastern Cooperative Oncology Group, EFS = event free survival, f/u = followup, g = grams, HR = hazard ratio , IFN = interferon, med = median, mo = month, NS = not stated, OS = overall survival, PS = performance status, pt(s) = patient(s), RR = relative risk , SCT = stem cell transplant, Thal = Thalidomide, w/ = with, yr = year

Table 13. Predictors of disease response or survival–Clinical diagnostic tests that predict response to thalidomide: Summary

Prognostic factor	Number of studies indicating significant correlation with tumor response / total number of studies indicating factor	Number of studies indicating significant correlation w survival / total number of studies indicating factor
Cytogenetics	Correlation with response = 2/2 (Barlogie, 2001[43]; Shaughnessy, 2003[133])	Correlation with survival = 1/1 (Shaughnessy, 2003[133])
Chromosome 13 abnormality	Correlation with response = 2/3 (Barlogie, 2002[109]; Shaughnessy, 2003[133]) No correlation = 1/3 (*Attal, 2004 (ASH 535)[108])	Correlation with survival = 4/4 (Barlogie, 2002[109]; Mileshkin, Biagi, et al. 2003[99]; Shaughnessy, 2003[133]; Singhal, 1999[35])
Albumin	*Some* correlation with response = 2/3 (Dimopoulos, 2004[94]; Yakoub-Agha, 2002[60]) No correlation = 1/3 (Shaughnessy, 2003[133])	Correlation with survival = 3/3 (Shaughnessy, 2003[133]; Singhal, 1999[35]; Yakoub-Agha, 2002[60])
Beta 2 microglobulin (B2M)	*Some* correlation with response = 4/5 (Garcia-Sanz, 2004[95]; Shaughnessy, 2003[133]; Schutt, 2005[87]; *Attal, 2004 (ASH 535)[108]) No correlation = 1/5 (Neben, Moehler, Egerer et al. 2001[52])	Correlation with survival = 3/3 (Mileshkin, Biagi, et al. 2003[99]; Shaughnessy, 2003[133]; Schutt, 2005[87])
Hemoglobin	No correlation = 1/1 (Neben, Moehler, Egerer et al. 2001[52])	No correlation = 2/2 (Dimopoulos, 2001[70]; Mileshkin, Biagi, et al. 2003[99])
Platelets	Correlation with response = 1/1 (Garcia-Sanz, 2004[95])	
Serum lactose dehydrogenase (LDH)	Correlation with response = 3/3 (Dimopoulos, 2004[94]; Shaughnessy, 2003[133]; Singhal, 1999[35])	Correlation with survival = 4/4 (Dimopoulos, 2001[70]; Dimopoulos, 2004[94]; Mileshkin, Biagi, et al. 2003[99]; Shaughnessy, 2003[133])
C Reactive Protein (CRP)	Correlation with response = 2/2 (Shaughnessy, 2003[133]; Singhal, 1999[35])	Correlation with survival = 1/1 (Shaughnessy, 2003[133])
IgA isotype	Correlation with response = 1/1 (Yakoub-Agha, 2002[60])	Correlation with survival = 1/1 (Yakoub-Agha, 2002[60])
Light chain type	Correlation with response = 1/1 (Dimopoulos, 2001[70])	Correlation with survival = 1/1 (Dimopoulos, 2001[70])
Plasma cell labeling index (PCLI)	Correlation with response = 2/2 (Barlogie, 2001[43]; Singhal, 1999[35])	

Table 13. Predictors of disease response or survival–
Clinical diagnostic tests that predict response to thalidomide: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
Cytogenetics	Barlogie, 2001[43] 169 pts w/ median f/u 22 mo [Quality 4/6]	PPRs more frequent with normal cytogenetics (52% vs. 28%) (p=0.003) EFS HR: 2.15 (p<0.001) OS HR: 2.53 (p=0.002)	
	Shaughnessy, 2003[133] 231 pts w/ median f/u 27 mo Thal within Total Therapy II regimen At time of analysis, still blinded as to whether or not pts received Thal [Quality 2/6]	EFS with abnormal cytogenetic findings other than chromosome 13: HR 2.1 (p=0.05) 3yr estimate of EFS: No cytogenetic abnormalities 80% Non-chromosome 13 abnormalities 66% Chromosome 13 abnormalities 39% (p<0.001)	OS with abnormal cytogenetic findings other than chromosome 13: HR not significant 3yr estimate of OS: No cytogenetic abnormalities 83% Non-chromosome 13 abnormalities 65% Chromosome 13 abnormalities 57% (p<0.001)
Chromosome 13 abnormality	Barlogie, 2002[109] 231 pts w/ median f/u 27 mo Newly diagnosed Thal part of Total Therapy II regimen At time of analysis, still blinded as to whether or not pts received Thal [Quality 2/5]	No deletion: 3-yr EFS = 79% Deletion: 3-yr EFS = 32% (p<0.0001)	No deletion: 3-yr OS = 83% Deletion: 3-yr OS = 49% (p<0.0001)
	Mileshkin, Biagi, et al. 2003[99] 75 pts w/ med f/u 18 mo Relapsed/refractory Some pts received IFN [Quality 2/6]		No: HR = 1.00 Yes: HR = 3.40 (1.40-8.38)

Table 13. Predictors of disease response or survival–
Clinical diagnostic tests that predict response to thalidomide: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
	Shaughnessy, 2003[133] 231 pts w/ median f/u 27 mo Thal within Total Therapy II regimen At time of analysis, still blinded as to whether or not pts received Thal [Quality 2/6]	EFS with chromosome 13 abnormality detected by cytogenetic analysis: HR 3.5 (p<0.001) EFS with chromosome 13 abnormality detected by FISH analysis: HR 3.9 (p<0.0001) 3yr estimate of EFS: No FISH chromosome 13 abnormalities 80% FISH Chromosome 13 abnormalities 62% (p=0.009) More rapid relapse for chromosome 13 abnormality: 61% vs. 38% @ 3 yr (p = 0.02)	OS with chromosome 13 abnormality detected by cytogenetic analysis: HR 3.4 (p<0.001) OS with chromosome 13 abnormality detected by FISH analysis: HR 3.4 (p=0.011) 3yr estimate of OS: No FISH chromosome 13 abnormalities 90% FISH Chromosome 13 abnormalities 65% (p=0.002) More rapid death in the setting of chromosome 13 abnormality: 43% vs. 35% @ 3 yr (p = 0.1)
	Singhal, 1999[35] 84 pts with median f/u 14.5 mo Thal only Relapse/refractory [Quality 5/5]		Chromosome 13 abnormality related to "short OS" (p=0.004)
	*****Attal, 2004 (ASH 535)[108] 580 pts with med f/u 26 mo Thal as post-SCT maintenance (RCT of no maintenance pamidronate, pamidronate +Thal) [Quality *****]	Deletion of chromosome 13 not associated with EFS	
Albumin	Dimopoulos, 2004[94] 53 pts with med f/u NS CTD regimen = cyclophosphamide + Thal + Dex Relapsed/refractory [Quality 3/5]	"Low albumin" significantly associated with shorter TTP Details not provided	

Table 13. Predictors of disease response or survival–
Clinical diagnostic tests that predict response to thalidomide: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
	Shaughnessy, 2003[133] 231 pts w/ median f/u 27 mo Thal within Total Therapy II regimen At time of analysis, still blinded as to whether or not pts received Thal [Quality 2/6]	EFS with albumin <35 g/dL: HR not significant	OS with albumin <35 g/dL: HR 1.9 (p=0.037)
	Singhal, 1999[35] 84 pts w/ median f/u 14.5 mo Thal only Relapse/refractory [Quality 5/5]		Low albumin related to "short OS" (p<0.001)
	Yakoub-Agha, 2002[60] 83 pts w/med f/u 338 d Thal alone Relapsed/refractory [Quality 6/6]	EFS with albumin <30 g/l: RR 2.55 (1.05-6.17) (p=0.037)	OS with albumin <30 g/l: RR 2.85 (1.16-6.99) (p=0.022)
Beta 2 microglobulin (B2M)	Garcia-Sanz, 2004[95] 66 pt with med f/u 15 mo Thal combined with oral cyclophosphamide + Dex [Quality 4/5]	Relationship between B2M and response at 6 mo: B2M 4 mg/l = 90% responding B2M >4 mg/l = 44% responding Multivariate p = 0.004	
	Mileshkin, Biagi, et al. 2003[99] 75 pts w/ med f/u 18 mo Relapsed/refractory Some pts received IFN [Quality 5/6]		3 mg/L: HR = 1.00 3-6 mg/L: HR = 2.77 (1.35-5.71) 6 mg/L: HR = 2.54 (1.23-5.23)
	Neben, Moehler, Egerer et al. 2001[52] 54 pts w/ median f/u 15 mo Progressive 72% with prior HDCT/SCT Tx'd with Thal 100-400 mg [Quality 3/6]	Relationship to response to Thal: Effect 2.5-5.0 mg/l OR 2.16 (0.67-6.94) Relationship to PFS: Effect 2.5-5.0 mg/l HR 1.35 (0.82-2.11)	

Table 13. Predictors of disease response or survival–
Clinical diagnostic tests that predict response to thalidomide: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
	Shaughnessy, 2003[133] 231 pts w/ median f/u 27 mo Thal within Total Therapy II regimen At time of analysis, still blinded as to whether or not pts received Thal [Quality 2/6]	EFS with B2M 4mg/l: HR 2.0 (p=0.034)	OS with B2M 4mg/l: HR 2.3 (p=0.001)
	Schutt, 2005[87] 31 pts with med f/u NS Thal combined with vincristine + epirubicin + Dex [Quality 5/5]	Pretreatment B2M <6 ml/L predictive of improved EFS univariate p<0.0001 multivariate p= significant but otherwise = NS	Pretreatment B2M <6 ml/L predictive of improved EFS univariate p<0.0001 multivariate p= significant but otherwise = NS
	*Attal, 2004 (ASH 535)[108] 580 pts with med f/u 26 mo Thal as post-SCT maintenance (RCT of no maintenance pamidronate, pamidronate + Thal) [Quality *]	Longer EFS associated with lower B2M at dx (p<0.01)	
Hemoglobin	Dimopoulos, 2001[70] Thal + Dex; resistant/refractory 44 pts w/ med f/u = NS [Quality 3/5]		8.5 g/dL: Med survival = 13.0 mo <8.5 g/dL: Med survival = 4.8 mo (p=0.0004)
	Mileshkin, Biagi, et al. 2003[99] 75 pts w/ med f/u 18 mo Relapsed/refractory Some pts received IFN [Quality 3/6]		11 g/dL: HR = 1.00 <11 g/dL: HR = 2.15 (0.70-1.89)
	Neben, Moehler, Egerer et al. 2001[52] 54 pts w/ median f/u 15 mo Progressive 72% with prior HDCT/SCT Tx'd with Thal 100-400 mg [Quality 3/6]	Relationship to response to Thal: Effect 9-12 g/dL OR 0.44 (0.10-1.93) Relationship to PFS: Effect 9-12 g/dL HR 1.19 (0.53-2.69)	

Table 13. Predictors of disease response or survival–
Clinical diagnostic tests that predict response to thalidomide: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
Platelets	Garcia-Sanz, 2004[95] 66 pt with med f/u 15 mo Thal combined with oral cyclophosphamide + Dex [Quality 4/5]	Relationship between platelet count and response at 6 mo: Platelet count >80 x 10^9/lL= 78% responding Platelet count 80 x 10^9/L = 25% responding Multivariate p = 0.004	
Serum lactose dehydrogenase (LDH)	Dimopoulos, 2001[70] Thal + Dex; resistant/refractory 44 pts w/ med f/u = NS [Quality 3/5]		220 IU/L: Med survival = 13.0 mo >220 IU/L: Med survival = 6.6 mo (p=0.009)
	Dimopoulos, 2004[94] 53 pts with med f/u= NS CTD regimen = cyclophosphamide + Thal + Dex Relapsed/refractory [Quality 3/5]	"High levels of LDH" associated with shorter TTP High LDH: TTP = 3.7 mo Not high LDH = 11.7 mo	In multivariate analysis, LDH associated with OS: 220 IU/L: OS not reached >220 IU/L: OS = 6.6 mo Univariate p=0.003 Multivariate p <0.0001
	Mileshkin, Biagi, et al. 2003[99] 75 pts w/ med f/u 18 mo Relapsed/refractory Some pts received IFN [Quality 5/6]		ULN: HR = 1.00 >ULN: HR = 2.34 (1.32-4.17)
	Shaughnessy, 2003[133] 231 pts w/ median f/u 27 mo Thal within Total Therapy II regimen At time of analysis, still blinded as to whether or not pts received Thal [Quality 2/6]	EFS with LDH 190 IU/l: HR 3.1 (p<0.001)	OS with LDH 190 IU/L: HR 1.9 (p=0.018)
	Singhal, 1999[35] 84 pts with median f/u 14.5 mo Thal only Relapse/refractory [Quality 5/5]	Elevated LDH related to "brief EFS" (p=0.001)	

Table 13. Predictors of disease response or survival–
Clinical diagnostic tests that predict response to thalidomide: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
C Reactive Protein (CRP)	Shaughnessy, 2003[133] 231 pts w/ median f/u 27 mo Thal within Total Therapy II regimen At time of analysis, still blinded as to whether or not pts received Thal [Quality 2/6]	EFS with CRP 4.0 mg/L: HR 2.0 (p-0.041)	OS with CRP 4.0 mg/L: HR 1.8 (p=0.034)
	Singhal, 1999[35] 84 pts with median f/u 14.5 mo Thal only Relapse/refractory [Quality 5/5]	Elevated CRP related to "brief EFS" (p=0.007)	
IgA isotype	Yakoub-Agha, 2002[60] 83 pts w/med f/u 338 d Thal alone Relapsed/refractory [Quality 6/6]	EFS with IgA isotype: RR 3.03 (1.36-6.75) (p=0.006)	OS with IgA isotype: RR 2.2 (1.05-5.01) (p=0.039)
Light chain type	Dimopoulos, 2001[70] Thal + Dex; resistant/refractory 44 pts w/ med f/u = NS [Quality 3/5]	Kappa: Response to Thal = 73% Lambda: Response to Thal = 25% (p=0.004)	Kappa: Med survival = 13.0 mo Lambda: Med survival = 6.6 mo (p=0.004)
Plasma cell labeling index (PCLI)	Barlogie, 2001[43] 169 pts w/ median f/u 22 mo [Quality 4/6]	PPRs more frequent with high PCLI >0.05% (44% vs. 10%) (p<0.001) EFS HR: 1.86 (p=0.002) OS HR: 1.82 (p=0.009)	
	Singhal, 1999[35] 84 pts with median f/u 14.5 mo Thal only Relapse/refractory [Quality 5/5]	Low PCLI (assessed a continuous variable): Associated with response among group with 25% PPR (p=0.01) Associated with response among group with 50% PPR (p=0.01) Reduction in paraprotein by 25%: PCLI <0.2%: 46% PCLI >0.2%: 9% (p<0.05) Elevated PCLI related to "brief EFS" (p=0.006)	

THE FOLLOWING STUDIES PRESENTED SOME NEGATIVE DATA RELEVANT TO THESE PREDICTORS (OFTEN PRESENTED IN TEXT FORM ONLY):

- Also reported in Mileshkin, Biagi et al. 2003[99] but not significant = CRP, creatinine, calcium, plasma cells in BM, response to prior CT
- Also reported in Neben, Moehler et al. 2001[52] but not significant = CRP, albumin
- According to Weber 2003[67], no clinical or lab features including B2M and paraprotein level correlated with response to Thal
- Yakoub-Agha 2002 [60] also investigated RBC transfusion requirement, platelet count at onset of Thal, prior autoSCT, performance status, and relapse/refractory disease status as potential predictors of response to Thal – all of these not significant
- Dimopoulos, 2004[94] also investigated hemoglobin, platelet count, albumin, CRP, and BM plasma cell which were all significant for OS in univariate models but not in the multivariate model (only LDH, gender and performance status significant for predicting OS as on table, with LDH and albumin significant for predicting TTP as on table); study included 53 pts with refractory/resistant MM treated with cyclophosphamide + Thal + Dex
- Schutt, 2005[87] also investigated CRP, IL-2R and thymidine kinase which were all significant for EFS in univariate models but not in the multivariate model (only B2M significant as on table); study included 31 pts with untreated MM administered Thal + vincristine + epirubicin + Dex
- Garcia-Sanz, 2004[95] also investigated hemoglobin, MM isotype, and presence of extramedullary myelomatous lesions which were all significant for predicting tumor response in univariate models but not in the multivariate model (only B2M, platelets and relapse/refractory disease status significant as on table); study included 66 pts with previously treated MM administered Thal + cyclophosphamide + Dex

Abbreviations: * = abstract, BM = bone marrow, B2M = beta-2 microglobulin, FGF = Fibroblast Growth Factor , CRP = C-reactive protein, CT = chemotherapy, CTD = cyclophosphamide + Thalidomide + Dexamethasone, d = day, Dex = Dexamethasone, dL = deciliter, EFS = event free survival, FISH = fluorescence in situ hybridization , f/u = followup, g = grams, HDCT = high dose chemotherapy, HR = hazard ratio , IFN = interferon, IU = international units, L = liter, LDH = ?, med = median, mo = month, ml = milliliter, NS = not stated, OS = overall survival, PCLI = plasma cell labeling index , PPR = paraprotein reduction, pt(s) = patient(s), RCT = randomized controlled trial, RR = relative risk , SCT = stem cell transplant, Thal = Thalidomide, tx'd = treated, ULN = upper limit of normal , VEGF = Vascular endothelial growth factor, vs. = versus, w/ = with, yr = year

Table 14. Predictors of disease response or survival–Thalidomide dosage and response factors that correlate with overall response to thalidomide: Summary

Prognostic factor	Number of studies indicating significant correlation with tumor response / total number of studies indicating factor	Number of studies indicating significant correlation with survival / total number of studies indicating factor
Cumulative 3-mo Thal dosage	*Some* correlation with response = 1/2 (Yakoub-Agha, 2002[60]) No correlation = 1/2 (Neben, Moehler, et al. 2002[134])	Correlation with survival = 2/2 (Neben, Moehler, et al. 2002[134]; Yakoub-Agha, 2002[60])
Change in paraprotein levels	Correlation with response = 1/1 (Schey, 2003[55])	
Relationship between paraprotein response and BM response	Correlation with response = 1/1 (Singhal, 1999[35])	

Table 14. Predictors of disease response or survival–Thalidomide dosage and response factors that correlate with overall response to thalidomide: Detailed review of studies

Prognostic factor	Studies indicating an association and quality	Strength of association with tumor response	Strength of association with survival
Cumulative 3-mo Thal dosage	Neben, Moehler, et al. 2002[134] 83 pts w/ median f/u 17 mo Relapsed/refractory 72% with prior HDCT/SCT Tx'd with thal 100-400 mg Retrospective review [Quality 4/6]	82% escalated to full 400 mg dose but 84% required dose reductions Thal dosage @ 400 mg @ 3 mo = 54% @ 6 mo = 33% @ 9 mo = 24% @12 mo = 17% PFS: HR for Thal total dose (interval analyzed 19.8–31.8)= 0.62 (CI 0.25-1.53)	≥ 31.8 g Thal (400 mg qd x 3 mo) = 15-20% higher predicted OS than ≤19.8 g(↓from 400 to 200 mg @1 mo) (p = 0.001) But not related to body size/weight OS: HR for Thal total dose (interval analyzed 19.8–31.8)= 0.07 (CI 0.01-0.37)
	Yakoub-Agha, 2002[60] 83 pts w/median f/u 338 d Thal alone Relapsed/refractory [Quality 6/6]	Relationship between total dose and EFS: >34.4 g: EFS = 391 d 34.4 g: EFS = 350 d (p=0.083) Relationship between total dose and time to response: >34.4 g: TTR = 49 d 34.4 g: TTR = 88 d (p=0.009)	Relationship between total dose and OS: >34.4 g: EFS = 404 d ≤34.4 g: EFS = 363 d (p= 0.036)
Change in paraprotein levels	Schey, 2003[55] 69 pt with median f/u 13 mo Relapsed/refractory Tx'd with Thal 50-600 [Quality 4/5]	Fall in M protein 14-28 days is correlated with M protein response at 3 mo (p<0.001) >25% fall in M protein 14-28 d after starting Thal = 25% with "improved response" at 3 mo	
Relationship between paraprotein response and BM response	Singhal, 1999[35] 84 pts with 14.5 mo median f/u (48 had BM assessments) Thal only Relapse/refractory [Quality 5/5]	Paraprotein response associated with BM response in 81%: 27/84 with paraprotein response 17/21 of those with paraprotein response on BM assessment with BM response	

Abbreviations: BM = bone marrow, d = day, EFS = event free survival, f/u = followup, g = gram, HDCT = high dose chemotherapy, HR = hazard ratio , mg = milligram, mo = month, OS = overall survival, pt(s) = patient(s), RR = relative response , SCT = stem cell transplant, Thal = Thalidomide, TTR = time to response, tx'd = treated, w/= with

Discussion

In this section we summarize the findings of the review in terms of answering the key questions initially posed, and then discuss the clinical and research implications of these data.

Multiple myeloma is a progressive, debilitating malignancy characterized by the proliferation and accumulation of cancerous plasma cells and the overabundance of monoclonal paraprotein. Extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures is common, as well as anemia, hypercalcemia, and kidney dysfunction. Although treatable, multiple myeloma is considered incurable[1] and accounts for approximately 2 percent of all cancer deaths.[1] Historically, intermittent oral melphalan and prednisone (MP) was standard therapy for untreated symptomatic multiple myeloma.[24] In more recent years, newer combination chemotherapy regimens have been used both as initial first-line chemotherapy and as salvage regimens, with better response rates but little effect on overall survival.[1, 24, 33] Example combination chemotherapy programs include VBCMP (vincristine, carmustine, cyclophosphamide, melphalan, and prednisone) and VAD (vincristine, doxorubicin, and dexamethasone). There is a survival benefit when patients responding to chemotherapy such as VAD are treated with high dose chemotherapy plus single or double autologous stem cell transplantation. Nonetheless, over 80 percent of patients still relapse within 7 years.[136] Treatment programs that include transplantation have limited applicability due to toxicity and associated age, performance status, and organ function requirements. Nearly all patients with multiple myeloma will eventually relapse and become resistant to further treatment. Median survival remains approximately 4 years.[1]

Bone marrow angiogenesis plays a substantial role in the development of multiple myeloma.[8] Thalidomide's anti-angiogenic properties were appreciated in the 1990's and the first publication documenting objective responses with thalidomide in patients with refractory myeloma was published in 1999.[35] Mechanism of action for thalidomide in multiple myeloma has been speculated to include inhibition of tumor necrosis factor *alpha* (TNF-alpha), prevention of free-radical–mediated DNA damage, suppression of angiogenesis, increased cell mediated immunity, alteration of the expression of cellular adhesion molecules, inhibition of NF-*k*B, and decreased inflammation.[8] Since 1999 there has been a rapid proliferation of published and abstract reports on the use of thalidomide in multiple myeloma including its efficacy, adverse effects, and potential predictors of response. Ninety-six reports are included in this review.

On July 16, 1998, the Food and Drug Administration (FDA) approved thalidomide for use in treating leprosy (Hansen's disease). It is not currently FDA-approved for multiple myeloma. Thalidomide has been off patent for decades.[39] Thalidomide can only be prescribed under the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program, patented by Celgene Corporation. Fifty mg, 100 mg, and 200 mg capsules are available.

1. *For patients with relapsed or refractory multiple myeloma, what is the effect of thalidomide compared to standard chemotherapy regimens (e.g., VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, and prednisone) and VAD (vincristine, doxorubicin, and dexamethasone)) on 2-year survival, disease-free survival, CR, PR (m-protein), and quality of life (QOL)?*

While the original question was about relapsed or refractory multiple myeloma, we expanded our review of the topic to include untreated myeloma because many of the newer studies of thalidomide focused on this setting. Also, we included some studies of asymptomatic myeloma as presented in Table 2 although the current standard is not to treat this group but rather adopt an approach of "watchful waiting." The breadth of studies, myeloma treatment settings (first-line, relapsed, asymptomatic, peri-transplantation), and drug combinations highlights the many ways that thalidomide is quickly becoming incorporated into myeloma treatment regimens. Key clinical issues include the mechanism of this prototype drug, managing toxicity, and finding the most effective dose, schedule and medication combinations. Nonetheless, thalidomide's most critical contribution to the array of anti-myeloma treatments is as a oral medication with a tolerable side effect profile that has efficacy in the relapsed or refractory setting and can be administered to the elderly and/or debilitated patients typical of the multiple myeloma population.

VBCMP and VAD are the comparators. No studies have randomized patients to thalidomide versus these interventions. As such, historical rates and survival estimates from previous trials including these agents must be used as the comparison group (Figure 12). Two-year survival rates were rarely reported except in the Samson et al. study of VAD for untreated patients where 83 percent of responders were alive at 2 years.[30] In the Mineur et al. trial of bolus VAD vs. VDD for untreated myeloma,[33] median time to progression was 24 months. Median overall survival had not been reached and was expected to exceed 40 months with both arms.

Tables 2-5 are summarized in Figure 12. Importantly, it is difficult to directly compare numbers between categories as response criteria for the various studies vary widely and very few of the thalidomide data presented are from randomized studies (only thalidomide-dexamethasone vs. dexamethasone or MP in untreated myeloma). Our use of PPR 25 percent as the summary response criteria for thalidomide is supported in another recent literature review for multiple myeloma.[137] This is notably different than the PPR 50 percent criteria described for most of the older trials. It can be misleading to compare the PPR 50 percent rows, as some studies report PPR 50 percent to mean all responses that were greater than 50 percent (i.e., 50-100 percent) and others indicate just those reflected in that response level (e.g., 50-74 percent with next response level at 75 percent). Response ranges for thalidomide are broad reflecting heterogeneity among studies and study populations, including the volume and intensity of previous myeloma treatments, study quality, and study size. Also, participant populations may be represented multiple times in the different published analyses of these studies; it is difficult to determine.

The most notable findings in the comparison presented in Figure 12 are the following:

- Thalidomide has activity in both the untreated and resistant/refractory settings.
- Generally, survival and responses are better when dexamethasone has been added.
- Response rates and survival estimates do not appear to be substantially different from that seen with VBCMP or VAD.

Figure 12: Comparison of efficacy		
	Newly diagnosed/previously untreated multiple myeloma	**Advanced/refractory/ resistant multiple myeloma**
VBCMP		
Median survival	29 months[24 25]	17 months[33]
PPR 50%	72%	13%
VAD		
Median survival	36-44 months[30, 31]	10-17 months[31 33]
PPR 50%	61-86%	22-70%
Thalidomide only		
Median survival	Estimated 2-year overall survival = 96%[42] Median overall survival not stated	Estimated 2-year overall survival = 48% ± 6%[43] Median overall survival = 5-58 months[46, 51, 53 55, 58, 60]
Complete response	16-25%	2-9%
PPR 25%	66-81%	34-100%
PPR 50%	34-38%*	8-43%*
Thalidomide plus dexamethasone		
Median survival	Median overall survival = 30 months[66]	Estimated 2-year overall survival = 55%[76] Median OS = 7-38 mo[64, 69, 70 135]
Complete response	8-16%	0-13%
PPR 25%	54-92%	54-75%
PPR 50%	17-64%*	22-55%*

Thalidomide's place in the multiple myeloma therapeutic armamentarium is clarified as these similar response rates are considered in terms of the comparative adverse events, ease of administration, and ability to be combined with other treatments.

- First, thalidomide (or thalidomide plus dexamethasone) has a different toxicity profile than the combination chemotherapy regimens. Until head to head studies are done it will be difficult to be certain; however, thalidomide appears to have less intense toxicity with fewer treatment-related deaths. Deaths such as those related to neutropenic fever from VBCMP and VAD and cardiotoxicity with VAD are not reported for thalidomide. The unexpected thromboembolic risk of thalidomide can be mitigated by adding enoxaparin. Thalidomide's peripheral neuropathy is cumulative and will need further consideration. Sedation can be minimized by slowly escalating the dose.
- Second, thalidomide is oral and can be managed in the outpatient setting. It does not require venous access or central venous catheters. This is balanced by the increased burden of the S.T.E.P.S. program, an important reminder and safeguard for the known teratogenicity of thalidomide.
- Third, thalidomide can be administered in elderly, immunocompromised patients and those with renal or cardiac dysfunction. It is unlikely that the true magnitude of this advantage is represented across the efficacy studies, as such ill patients are often excluded from the study populations.
- Fourth, it has activity even when patients have been heavily pretreated with VAD, VBCMP or high dose chemotherapy plus autologous stem cell transplant. Hence, thalidomide can be added to the list of appropriate options for treatment of multiple myeloma and the timing of its use is considered based upon the needs of the individual.

- Fifth, evidence of maximal response is seen early so thalidomide does not need to be continued for long periods if it is not effective. In the 2001 Barlogie et al. study of thalidomide only in refractory/relapsed myeloma, 70 percent of patients achieving a PPR >25 percent did so within 2 months and 90 percent within 4.5 months.
- Sixth, it can be combined with other agents with additive effect. In particular, lack of severe myelosuppression with thalidomide makes this possible. Thalidomide plus MP appears to be superior to MP alone[79] and there are many promising combinations presented in Table 6 and 7.
- Seventh, thalidomide can be used in the pre- and post-transplantation settings (Table 8) although some recent data suggest that it may be better not to use thalidomide for post-transplant maintenance but rather save the intervention for future relapse states.[110]

Should thalidomide always be combined with dexamethasone? Pre-clinical data suggests synergistic effects when thalidomide is combined with dexamethasone.[138] Dexamethasone is the main active agent in VAD.[8] Weber et al. reported that thalidomide restored the sensitivity of myeloma cells to dexamethasone-induced apoptosis.[67] Generally, survival and responses are better when dexamethasone has been added, with fewer side effects. Thalidomide doses are generally lower when dexamethasone is added. Dexamethasone dosing is variable across studies. Unless a patient has a contraindication to high dose dexamethasone (e.g., severe labile diabetes, history of steroid psychosis), the addition of dexamethasone is quickly becoming standard when thalidomide is used.

The ideal dose of thalidomide is unclear. The 2001 Barlogie et al. study demonstrated that patients who received >42 g of thalidomide in the first 3 months had significantly better response rates and survival.[43] Similar findings were noted in both of the predictors study on the topic presented in Table 14.[60, 134] Recent studies have looked to decreasing the thalidomide dose though, predominantly in an effort to decrease adverse effects. This is most noticeable across the range of thalidomide plus dexamethasone studies, some of which start at 50 mg and many of which fix the thalidomide dose at 200 mg.

The role of thalidomide in soft tissue plasmacytomas is also unclear. Some authors report poorer responses in this setting.[48, 57, 135] More data are needed.

Only one study specifically evaluated QOL outcomes. In an abstract presented at the American Society of Clinical Oncology meeting in May 2005, Mileshkin and colleagues investigated the effect of thalidomide plus celecoxib in 66 patients with relapsed multiple myeloma.[100] The EORTC QLQ-C30 was used to measure QOL. Overall response to thalidomide (PPR 25 percent) was 42 percent. Global health on the QLQ-C30 decreased (lower is worse) for 80 percent of participants over the first month of thalidomide treatment. Among responders, QOL on this sub-scale increased for 29 percent of individuals. Responders were more likely to have improvement in QOL than non-responders (61 percent vs. 27 percent, p=0.024). Health-related QOL was also reported in a study of 65 patients with refractory/relapsed myeloma treated with thalidomide only. The QLQ-C30 was again used as the measurement instrument. Pain improved and constipation worsened with thalidomide, but otherwise it was difficult to determine the impact of thalidomide on QOL from this report.

2. *For patients with relapsed or refractory multiple myeloma, what is the effect of thalidomide compared to standard chemotherapy regimens (e.g., VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, and prednisone) and VAD (vincristine, doxorubicin, dexamethasone)) on adverse effects, tolerability and compliance?*

Tables 9 and 10 review the adverse effects identified for thalidomide. Randomized trials are necessary to be able to quantify the exact differences in the frequency of adverse between the comparator chemotherapy programs and the various thalidomide regimens. Such trials are forthcoming. The two most notable adverse effects with thalidomide are peripheral neuropathy and thromboembolism. Bradycardias, skin toxicity, constipation, and neutropenia are also well described. Using data from studies of thalidomide only, thalidomide side effects include constipation (3-11 percent grade 3 and 4), neurotoxicity predominantly evident as peripheral neuropathy (1-7 percent grade 3 or 4) and sedation (3-13 percent grade 3 or 4), cardiac insufficiency due to bradycardia (2-6 percent grade 3 or 4), leukopenia (2-31 percent grade 3 and 4), and blood clots (2-10 percent grade 3 or 4). Side effects are dose dependent as evidenced in studies by Singhal et al., Hus et al., and Rajkumar et al. that escalated thalidomide up to 800 mg with exaggeration of side effects including somnolence, neuropathy, and constipation.[35, 46, 53]

In the 1998 Mineur et al. randomized trial of VAD vs. VBCMP, toxicities described included neutropenic infections that led to four deaths (VAD 2 and VMBCP 2), corticosteroid effects in two cases both in the VAD arm (pancreatitis and diabetes mellitus for one case, candidal esophagitis for the other), cardiotoxicity after three cycles of VAD, and hematological toxicity after VAD requiring treatment modification.[33] In the 2003 Dimopoulos et al. randomized trial of VAD administered as intravenous bolus injection vs. VDD for patients with previously untreated myeloma, toxicities in the bolus VAD and VDD arms respectively were grade 2 neutropenia (20 percent vs. 15 percent, p=0.7), grade 2 thrombocytopenia (10 percent vs. 5 percent, p=0.2), grade 2 nausea/vomiting (4 percent vs. 5 percent, p=0.8), grade 1 alopecia (55 percent vs. 37 percent, p<0.001), grade 2 mucositis (7 percent vs. 15 percent, p=0.3), grade 2 erythrodysesthesia (2 percent vs. 13 percent, p=0.03), and grade 2 neurotoxicity (13 percent vs. 15 percent, p=0.9).[34] Steroid-related side-effects occurred with equal frequency in both arms; Cushingoid features were noted in approximately one-fifth of patients, hyperglycemia in 15 percent of patients treated with bolus VAD bolus and in 12 percent treated with VDD, mood changes in <10 percent of patients in either arm and peptic ulcer disease, hiccups and proximal muscle weakness each occurred in <5 percent of patients. Infections, which required antibiotics, including neutropenic fever, were noted in 17 percent of patients treated with bolus VAD and 18 percent treated with VDD. Eleven patients (9 percent) in the bolus VAD and 14 (11 percent) in the VDD arm died within the first 4 months of treatment. Among the 11 patients treated with bolus VAD, 3 deaths were due to infections and 2 were due to heart failure and/or myocardial infarction. Of the 14 early deaths in the VDD arm, 4 were due to infections and 3 were due to heart failure and/or myocardial infarction.

There are no prospective comparative studies between thalidomide and VAD/VBCMP to specifically answer this question. However, Cavo et al. recently presented a retrospective review that compared the experience of 200 patients receiving thalidomide plus dexamethasone or VAD as preparative regimens for SCT.[139, 140] Patients were matched on age, disease stage, and B_2 microglobulin. Grade 3/4 toxicity was presented. Among patients receiving thalidomide plus

dexamethasone, 15 percent developed DVT, 0 percent granulocytopenia, 9 percent constipation, 4 percent infections, 4 percent neuropathy, and 6 percent deaths during treatment. Among patients receiving VAD, 2 percent developed DVT, 12 percent granulocytopenia, 3 percent constipation, 5 percent infections, 7 percent neuropathy, and 6 percent deaths during treatment.

A more complete review of the differences in administration and tolerability is provided in the previous section. Compliance data were not identified during this review.

3. *What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy?*

Thus far, despite myriad studies reporting predictors of response, little consistent data support the use of any specific tests related to the mechanism of the disease. TNFα polymorphisms at position -238 of the gene promoter were correlated with response and survival in the one study of the topic,[131] but, as was seen across this group of studies, often a single study was positive but subsequent confirmations were negative. Two studies of TNFα as a predictor suggested that TNFα correlated with survival,[128, 130] but one did not.[129] The same studies reported similar findings for IL6. Studies of Vascular Endothelial Growth Factor (VEGF), Vascular Endothelial Growth Factor (VEGF), and other substances had very few consistent positive findings. Taken together, these studies suggest that we have a lot to learn about the mechanism of action of thalidomide, that predictors related to angiogenesis are likely to be less helpful, and that cytokine like TNFα and IL-6 play may be more predictive after future study.

Tables 12-14 present a variety of other clinical and demographic factors that predict response including age and beta-2 microglobulin. These findings do not substantially add to current care, as the findings were fairly consistent with the previously known predictors for myeloma.

Once large randomized trials are available, predictor analyses should be repeated to see if any new patterns or predictors emerge.

Current State of Clinical Use

The National Cancer Institute (NCI) guidelines at lists thalidomide as a treatment option within the array of current options, without specifying where in the treatment order it should fall.[12] The guidelines argue that the choice of first-line and subsequent therapies should be individualized based upon patient age, general health, and patient preference. A dose of thalidomide is not recommended and the guideline argues that more data are needed until clear recommendations about the role of dexamethasone and enoxaparin can be provided. The NCCN does not have a guideline for multiple myeloma.

Implications for Future Research

As has been highlighted throughout this review, there is much work to be done on both the clinical and basic science levels. Clinically, randomized data are needed. The final results of the ongoing phase III trials are anxiously awaited. These will guide subsequent directions for therapy. It is unclear whether a randomized study of VAD versus thalidomide (or thal-dex) will be possible, as the older patient profile ideal for thalidomide may be able to tolerate the standard chemotherapy arm. If the study is limited to only those who can tolerate VAD then the results may be less applicable across all of the patients for whom thalidomide is the best choice. A randomized trial using VDD and thalidomide may be more feasible. Certainly, data produced from these studies will be invaluable to assist with better understanding adverse event profiles and predictors of response.

Much work is ongoing to further elucidate the mechanism of action of thalidomide. A focus on the cytokine milieu is evolving. Use of gene array technology to profile multiple myeloma and match this information to thalidomide response is also ongoing. Thalidomide represents the prototype of an emerging class of drugs, and it is imperative that its efficacy and mechanism of generating tumor response is well understood. Other immunomodulatory analogs of thalidomide like CC-5013 (Revimid) are also in clinical testing.[141]

Symptoms and QOL is another important future direction for thalidomide research. How does thalidomide impact pain control, functional status, ability to return to work, and other QOL outcomes?

An invaluable improvement for this body of research would be a strategy of quality reporting and use of similar response criteria such as the Blade criteria. The quality of reporting was clearly limited among studies in this review. Similarly, the inconsistency of response criteria and outcomes reported limited comparisons across studies (e.g., variability in reporting and meaning of PPR). An international standard would greatly improve the accuracy and utility of future systematic reviews on myeloma treatments.

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Included Articles
and the Tables on which they are Reported

(numbers refer to the list of articles presented in the Reference List)

First Author, Year	Quality Table	Efficacy Table	Adverse Effects Table	Predictors Table
FULL TEXT ARTICLES				
1. Alexanian, 2002[111]	x	x		
2. Alexanian, 2003[64]	x	x		
3. Anagnostopoulos, 2003[68]	x	x		
4. Badros, 2002[115]	x		xx	
5. Barlogie, 2001[43]	x	x	x	
6. Barlogie, 2002[109]	x	x		x
7. Bernardeschi, 2004[69]	x	x		
8. Biagi, 2001[92]	x	x		
9. Bowcock, 2002[116]	x		xx	
10. Ciepluch, 2002[93]	x	x	x	
11. Corso, 2002[44]	x	x		
12. Dimopoulos, 2001[70]	x	x	x	x
13. Dimopoulos, 2004[94]	x	x	x	x
14. Dmoszynska, 2002[128]	x			x
15. Fahdi, 2004[117]	x		xx	
16. Garcia-Sanz, 2004[95]	x	x		x
17. Hall, 2003[118]	x		xx	
18. Hattori, 2004[45]	x	x	xx	
19. Hus, 2001[46]	x	x	x	
20. Johnston, 2002[47]	x	x		
21. Juliusson, 2000[48]	x	x		
22. Kasper, 2004[97]	x	x		
23. Kees, 2003[49]	x	x		
24. Kropff, 2003[98]	x	x		
25. Kumar, 2003[51]	x	x	x	
26. Lee, 2003[21]	x	x		
27. Mileshkin, Biagi et al. 2003[99]	x	x		x
28. Mileshkin, Prince et al. 2003[127]	x			x
29. Myers, 2000[71]	x	x		
30. Myers, 2001[72]	x	x		
31. Myers, 2002[73]	x	x		
32. Neben, Moehler, Kraemer et al. 2001[129]	x			x
33. Neben, Moehler, Egerer et al. 2001[52]	x	x	x	x
34. Neben, Moehler et al. 2002[134]	x			x
35. Neben, Mytilineos, et al., 2002[131]	x			x
36. Offidani, Corvatta, Marconi, Malerba, et al. 2004 [101]	x	x	x	
37. Offidani, Corvatta, Marconi, Olivieri, et al. 2004[102]	x	x	x	
38. Palumbo, 2001[74]	x	x	x	
39. Palumbo, 2004[75]	x	x		
40. Rajkumar, 2000 [53]	x	x		
41. Rajkumar, 2001 [41]	x	x	x	
42. Rajkumar, 2002 [65]	x	x	x	
43. Rajkumar, 2003 [42]	x	x		
44. Richardson, 2004 [54]	x	x	x	x
45. Schey, 2003[55]	x	x	x	x
46. Schutt, 2005[87]	x	x	x	x

47. Shaughnessy, 2003[133]	x			x
48. Singhal, 1999[35]	x	x	x	x
49. Thompson, 2003[130]	x			x
50. Tosi, 2001[56]	x	x		
51. Tosi, 2002 [57]	x	x	x	x
52. Tosi, 2004 [135]	x	x		
53. Tosi, 2005[121]	x		xx	
54. Waage, 2004[58]	x	x	x	
55. Weber, 2003[67]	x	x	x	x
56. Yakoub-Agha, 2000 [59]	x	x	x	
57. Yakoub-Agha, 2002[60]	x	x	x	x
58. Zangari, 2001[122]	x		xx	
59. Zangari, Saghafifar, et al. 2002[123]	x		xx	
60. Zangari, Siegel, et al. 2002[124]	x		xx	
61. Zangari, 2004[126]	x		xx	
62. Zervas, 2004[88]	x	x	x	
ABSTRACT ONLY PUBLICATIONS				
63. Alexanian, 2004 (ASH 210)[80]	*	x		
64. Anaissie, 2004 (ASH 3467)[114]	*		xx	
65. Attal, 2004 (ASH 535)[108]	*	x		x
66. Badros, 2004 (ASH 2400)[89]	*	x		
67. Barlogie, 2004 (ASH 1483)[110]	*	x		
68. Bibas, 2004 (ASH 4927)[90]	*	x		
69. Chanan-Khan, Miller, McCarthy, DiMiceli et al 2004 (ASH 2421)[91]	*	x		
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71. Dimopoulos, 2004 (ASH 1482)[82]	*	x		
72. Facon, 2004 (ASH 206)[78]	*	x		
73. Hassoun, 2004 (ASH 2409)[83]	*	x		
74. Hollmig, 2004 (ASH 2399)[96]	*	x		
75. Jaksic, 2004 (ASH 2417)[132]	*			x
76. Klueppelberg, 2004 (ASH 4932)[84]	*	x		
77. Klueppelberg, 2004 (ASCO 6702)[85]	*	x		
78. Klueppelberg, 2005 (ASCO 6697)[86]	*	x		
79. Kroeger, 2004 (ASH 1646)[50]	*	x		
80. Ludwig, 2005 (ASCO 6537)[63]	*	x		
81. Mileshkin, 2005 (ASCO 8233)[100]	*	x		
82. Palumbo, 2004 (ASH 207)[79]	*	x		
83. Rajkumar, 2004 (ASH 205)[61]	*	x		
84. Rajkumar, 2004 (ASCO 6508)[62]	*	x		
85. Rajkumar, 2005 (ASCO 6632)[66]	*	x		
86. Reece, 2004 (ASH 4934)[76]	*	x		
87. Sengar, 2005 (ASCO 6731)[112]	*	x		
88. Singh, 2004 (ASCO 3142)[119]	*		xx	
89. Spencer, 2004 (ASCO 6655)[120]	*		xx	
90. Stewart, 2004 (ASH 335)[113]	*	x		
91. Suvannasankha, 2005 (ASCO 6591)[103]	*	x		
92. Teoh, 2004 (ASH 4915)[104]	*	x		
93. Tosi, 2004 (ASH 4898)[77]	*		xx	
94. Williams, 2004 (ASH 1499)[105]	*	x		
95. Zangari, Barlogie, Hollmig, et al. 2004 (ASH 1480)[107]	*	x		
96. Zangari, Barlogie, Lee, et al. 2004 (ASH 4914)[125]	*		xx	

* = abstract only, no quality score; ASH = American Society of Hematology Annual Meeting; ASCO = American Society of Clinical Oncology Annual Meeting; x = on main table; xx=on supplementary table (adverse effects only)

Included Articles

Alexanian R, Wang LM, Weber DM, et al. VTD (Velcade, Thalidomide, Dexamethasone) as primary therapy for newly-diagnosed multiple myeloma. Blood 2004;104(11):Abstract #210.

Alexanian R, Weber D, Anagnostopoulos A, et al. Thalidomide with or without dexamethasone for refractory or relapsing multiple myeloma. Seminars in Hematology 2003;40(4 Suppl 4):3-7.

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Appendix A:
MEDLINE Search Strategy

Database: Ovid MEDLINE(R) <1966 to September Week 3 2004>
Search Strategy:
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1 (gefitinib or erlotinib or iressa or tarceva or lapatinib or ekb-569 or ci-1033 or zd1839 or osi-774).mp. (817)
2 exp lung neoplasms/ or carcinoma, non-small-cell lung/ (96461)
3 1 and 2 (339)
4 randomized controlled trial.pt. (194192)
5 controlled clinical trial.pt. (67292)
6 Randomized Controlled Trials/ (34359)
7 Random Allocation/ (51911)
8 Double-Blind Method/ (79820)
9 Single-Blind Method/ (8433)
10 or/4-9 (329367)
11 Animal/ not Human/ (2838957)
12 10 not 11 (311915)
13 clinical trial.pt. (392148)
14 exp Clinical Trials/ (159166)
15 (clinic$ adj25 trial$).tw. (103424)
16 ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (76365)
17 Placebos/ (23320)
18 placebo$.tw. (86217)
19 random$.tw. (294378)
20 Research Design/ (38965)
21 (latin adj square).tw. (2126)
22 or/13-21 (693867)
23 22 not 11 (643785)
24 23 not 12 (342333)
25 Comparative Study/ (1152523)
26 exp Evaluation Studies/ (499768)
27 Follow-Up Studies/ (288858)
28 Prospective Studies/ (178265)
29 (control$ or prospectiv$ or volunteer$).tw. (1483791)
30 Cross-Over Studies/ (15073)
31 or/25-30 (2964552)
32 31 not 11 (2271429)
33 32 not (12 or 24) (1817997)
34 12 or 24 or 33 (2472245)
35 3 and 34 (241)
36 limit 35 to english language (216)
37 from 36 keep 1-216 (216)
38 (imatinib or gleevec or glivec or STI571).mp. (1613)
39 exp leukemia, myeloid, chronic/ (9737)

40 38 and 39 (718)
41 40 and 34 (286)
42 limit 41 to english language (250)
43 from 42 keep 1-250 (250)
44 (gist or (gastro$ adj2 stromal adj (tumo$ or cancer$))).mp. (1111)
45 38 and 44 (236)
46 45 and 34 (98)
47 limit 46 to english language (88)
48 from 47 keep 1-88 (88)
49 exp multiple myeloma/ (18390)
50 thalidomide/ or thalidomid$.mp. or thalomid.mp. (3142)
51 49 and 50 (352)
52 51 and 34 (172)
53 limit 52 to english language (151)
54 from 53 keep 1-151 (151)

Appendix B:
Quality Criteria

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups random?
   Adequate approaches to sequence generation
   - Computer-generated random numbers
   - Random numbers tables

   Inadequate approaches to sequence generation
   - Use of alternation, case record numbers, birth dates or weekdays
2. Was the treatment allocation concealed?
   Adequate approaches to concealment of randomization
   - Centralized or pharmacy-controlled randomization
   - Serially-numbered identical containers
   - On-site computer based system with a randomization sequence that is not readable until allocation
   - Other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients

   Inadequate approaches to concealment of randomization
   - Use of alternation, case record numbers, birth dates or weekdays
   - Open random numbers lists
   - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
3. Were the groups similar at baseline in terms of important prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were the point estimates and measure of variability presented for the primary outcome measure?
9. Did the analyses include an intention to treat analysis?

Quality criteria for assessment of observational studies

From the York CRD handbook (http://www.york.ac.uk/inst/crd/crd4_ph5.pdf)

Cohort studies

Is there a sufficient description of the groups and the distribution of prognostic factor?
Are the groups assembled at a similar point in their disease progression?
Is the intervention/treatment reliably ascertained?
Were the groups comparable on all-important confounding factors?
Was there adequate adjustment for the effects of these confounding variables?
Was a dose-response relationship between intervention and outcome demonstrated?
Was outcome assessment blind to exposure status?
Was follow-up long enough for the outcomes to occur?
What proportion of the cohort was followed-up?
Were dropout rates and reasons for dropout similar across intervention and unexposed groups?

Case-control studies

Is the case definition explicit?
Had the disease state of the cases been reliably assessed and validated?
Were the controls randomly selected from the source of population of the cases?
How comparable are the cases and controls with respect to potential confounding factors?
Were interventions and other exposures assessed in the same way for cases and controls?
How was the response rate defined?
Were the non-response rates and reasons for non-response the same in both groups?
Is it possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
Was an appropriate statistical analysis used (matched or unmatched)?

Case series

Is the study based on a representative sample selected from a relevant population?
Are the criteria for inclusion explicit?
Did all individuals enter the survey at a similar point in their disease progression?
Was follow-up long enough for important events to occur?
Were outcomes assessed using objective criteria or was blinding used?
If comparisons of sub-series are being made, was there a sufficient description of the series and the distribution of prognostic factors?

Appendix B Table. Quality of included studies

Quality Question 1. Is the study based on a representative sample from a relevant population?
Quality Question 2. Are the criteria for inclusion explicit?
Quality Question 3. Did all individuals enter the survey at a similar point in disease progression?
Quality Question 4. Was follow up long enough for important events to occur?
Quality Question 5. Were outcomes assessed using objective criteria or was blinding used?
Quality Question 6. If comparisons of sub-series, was there a sufficient description of the series and distribution of prognostic factors?

	First Author, Year	Quality 1:	Quality 2:	Quality 3:	Quality 4:	Quality 5:	Quality 6:	Total score
1.	Alexanian, 2002[111]	N	Y	N	Unk	Y	N/A	2/5
2.	Alexanian, 2003[64]	Unk	N	Unk	Unk	Y	N	1/6
3.	Anagnostopoulos, 2003[68]	Unk	N	Unk	Unk	Y	N	1/6
4.	Badros, 2002[115]	Y	N	Unk	Unk	Y	N/A	2/5
5.	Barlogie, 2001[43]	Y	Y	N	Y	Y	N	4/6
6.	Barlogie, 2002[109]	Unk	N	Unk	Y	Y	N	2/6
7.	Bernardeschi, 2004[69]	Unk	N	N	Y	Y	N/A	2/5
8.	Biagi, 2001[92]	N	Y	N	N	Y	N	1/6
9.	Bowcock, 2002[116]	Unk	N	Unk	Unk	No	N/A	0/5
10.	Ciepluch, 2002[93]	N	Y	N	Unk	N	N/A	1/5
11.	Corso, 2002[44]	N	N	Unk	Unk	Unk	N/A	0/5
12.	Dimopoulos, 2001[70]	Y	Y	N	N	Y	N/A	3/5
13.	Dimopoulos, 2004[94]	Y	Y	N	Unk	Y	N/A	3/5
14.	Dmoszynska, 2002[128]	Y	N	N	Y	Y	N/A	3/5
15.	Fahdi, 2004[117]	Y	Y	Unk	Y	Y	N	4/6
16.	Garcia-Sanz, 2004[95]	Y	Y	N	Y	Y	N/A	4/5
17.	Hall, 2003[118]	Unk	N	Unk	Unk	Yes	N/A	1/5
18.	Hattori, 2004[45]	Y	Y	Y	Unk	Y	N/A	4/5
19.	Hus, 2001[46]	Y	Y	N	Unk	Y	N	3/6
20.	Johnston, 2002[47]	N	Y	N	Y	Y	N/A	3/5
21.	Juliusson, 2000[48]	N	N	N	Unk	Y	N/A	1/5
22.	Kasper, 2004[97]	N	N	N	Y	Y	N/A	2/5
23.	Kees, 2003[49]	N	N	N	Y	Y	N	2/6
24.	Kropff, 2003[98]	Y	Y	Y	Y	Y	N/A	5/5
25.	Kumar, 2003[51]	Y	Y	N	Y	Y	N/A	4/5
26.	Lee, 2003[21]	Y	Y	Y	Y	N	N/A	4/5
27.	Mileshkin, Biagi et al. 2003[99]	Y	Y	N	Y	Y	Y	5/6
28.	Mileshkin, Prince et al. 2003[127]	Y	Y	N	Y	Y	N	4/6
29. 30. 31.	Myers, 2000, 2001, and 2002[71-73]	Unk	N	Unk	Y	Y	N/A	2/5
32.	Neben, Moehler, Kraemer et al. 2001[129]	Y	N	N	Y	Y	N	3/6
33.	Neben, Moehler, Egerer et al. 2001[52]	Y	N	N	Y	Y	N	3/6
34.	Neben, Moehler et al. 2002[134]	Y	Y	Unk	Y	Y	N	4/6
35.	Neben, Mytilineos, et al., 2002[131]	Y	N	N	Y	Y	N	3/6 (presumed from [52])
36.	Offidani, Corvatta, Marconi, Malerba, et al. 2004 [101]	Unk	N	N	Unk	N	N	0/6
37.	Offidani, Corvatta, Marconi, Olivieri, et al. 2004[102]	Y	Y	Y	Y	Y	Y	6/6
38.	Palumbo, 2001[74]	Unk	N	Unk	Y	Y	N/A	2/5

	First Author, Year	Quality 1:	Quality 2:	Quality 3:	Quality 4:	Quality 5:	Quality 6:	Total score
39.	Palumbo, 2004[75]	Y	Y	Y	Y	Y	Y	6/6
40.	Rajkumar, 2000 [53]	Y	Y	N	Unk	Y	N/A	3/5
41.	Rajkumar, 2001 [41]	Y	Y	Y	N	Y	N/A	4/5
42.	Rajkumar, 2002 [65]	Y	Y	Y	Unk	Y	N/A	4/5
43.	Rajkumar, 2003 [42]	Y	Y	N	N	Y	N/A	3/5
44.	Richardson, 2004 [54]	Y	Y	Unk	N	Y	N/A	3/5
45.	Schey, 2003[55]	Y	Y	Unk	Y	Y	N/A	4/5
46.	Schutt, 2005[87]	Y	Y	Y	Y	Y	N/A	5/5
47.	Shaughnessy, 2003[133]	Unk	N	Unk	Y	Y	N	2/6
48.	Singhal, 1999[35]	Y	Y	Y	Y	Y	N/A	5/5
49.	Thompson, 2003[130]	Unk	N	Unk	Unk	Y	N	1/6
50.	Tosi, 2001[56]	Y	Y	N	N	Y	N/A	3/5
51.	Tosi, 2002 [57]	Y	N	N	N	Y	N/A	2/5
52.	Tosi, 2004 [135]	Y	Y	N	Y	Y	N/A	4/5
53.	Tosi, 2005[121]	Y	Y	N	Y	Y	N	4/6
54.	Waage, 2004[58]	Y	Y	Unk	Y	Y	N/A	4/5
55.	Weber, 2003[67]	Y	N	Unk	Y	Y	N	3/6
56.	Yakoub-Agha, 2000 [59]	Y	Y	Y	N	Y	N/A	4/5
57.	Yakoub-Agha, 2002[60]	Y	Y	Y	Y	Y	Y	6/6
58.	Zangari, 2001[122]	Unk	N	Unk	Unk	N	N/A	0/5
59.	Zangari, Saghafifar, et al. 2002[123]	Unk	N	Unk	Unk	N	N	0/6
60.	Zangari, Siegel, et al. 2002[124]	Unk	N	N	Y	Y	N	2/6
61.	Zangari, 2004[126]	Y	Y	Y	Y	Y	Y	6/6
62.	Zervas, 2004[88]	Y	Y	N	N	Y	N/A	3/5

Abbreviations: N = No; Y = Yes; N/A = not applicable; Unk = unknown