CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-430

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
ADENDUM

CLINICAL STUDIES

NDA/Serial Number:	NDA 21-430
Drug Name:	Thalomid (thalidomide capsules)
Indication(s):	Multiple myeloma
Applicant:	Celgene
Date(s):	Received: 11/23/2005
Review Priority:	Priority
Biometrics Division:	HFD-710
Statistical Reviewer:	Valeria Freidlin, Ph.D.
Concurring Reviewers:	Peiling Yang, Acting Team Leader
	Jim Hung, Ph.D., Division Director
Medical Division:	ODP/DODP
Clinical Team:	Michael Brave, MD (DODP)
	Ann Farrell, MD, Team Leader (DODP)
Project Manager:	Carl Huntley (DODP)

Keywords: Fisher's Exact test.

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Primary efficacy analysis of response rates in Study E1A100 reassessed by the FDA medical reviewer after the applicant responded to the FDA queries showed that the combination therapy was statistically significantly better than the dexamethasone only therapy relative to ECOG best response (p=0.0125). For easier comparisons with the sponsor's results, this reviewer used one-sided Fisher's exact test at the 0.025 significance level.

1.2 Brief Overview

This review presents an analysis of the reassessed response rates by the FDA medical reviewer after the applicant responded to the FDA queries.

The original NDA 21-[redacted] was a Type 6 NDA resubmission in response to the October 2004 Approvable Letter. At the FDA request, on May 13, 2005, the sponsor submitted report of a single Study E1A00. The statistical review of that submission was filed into the DFS in early November 2005. On November 23, 2005, the sponsor submitted responses to the FDA queries which resulted in the reassessment of the response rates by the medical reviewer.

1.3 Statistical Issues and Findings

The sponsor used a one-sided Fisher's exact test. For easier comparisons of the primary efficacy results this reviewer also used the one-sided test. However, this reviewer used the 0.025 significance level instead of the 0.05 significance level used by the sponsor.

Table 1shows ECOG best response rates as adjudicated by the FDA medical reviewer before and after the applicant responded to the FDA queries.

Table 1. FDA primary efficacy results for Study E1A00.
ECOG best response rates as adjudicated by the FDA medical reviewer before and after the applicant responded to the FDA queries

ECOG CR, NCR, or PR	Thal/Dex (n = 103)	Dex alone (n = 104)	*P* (one-sided Fisher Exact)
Before Applicant's responses to FDA queries	25 (24.3 %)	18 (17.3 %)	0.12
After Applicant's responses to FDA queries	53 (51.5 %)	37 (35.6 %)	0.0125

The primary efficacy analysis of Study E1A100 using the one-sided Fisher's exact test showed that the combination therapy was statistically significantly (p=0.0125) better than the dexamethasone only therapy relative to ECOG best response as reassessed by the FDA medical reviewer after applicant responded to the FDA queries.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Valeria Freidlin
1/24/2006 02:05:02 PM
BIOMETRICS

Peiling Yang
1/26/2006 04:57:06 PM
BIOMETRICS

James Hung
1/27/2006 08:41:52 AM
BIOMETRICS

Appears This Way
On Original

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 21-430
Drug Name:	Thalomid (thalidomide capsules)
Indication(s):	Multiple myeloma
Applicant:	Celgene
Date(s):	Received: 05/13/2005
Review Priority:	Priority
Biometrics Division:	HFD-710
Statistical Reviewer:	Valeria Freidlin, Ph.D.
Concurring Reviewers:	Rajeshwari Sridhara, Ph. D., Team Leader
	Kooros Mahjoob, Ph.D., Deputy Division Director
Medical Division:	ODP/DODP
Clinical Team:	Michael Brave, MD (DODP)
	Ann Farrell, MD, Team Leader (DODP)
Project Manager:	Carl Huntley (DODP)

Keywords: Fisher's Exact test, interim analysis, multiple comparisons, sequential procedure, survival analysis, Kaplan-Meier estimation procedure, missing values, exploratory analyses.

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Primary efficacy analysis of Study E1A100 showed that the combination therapy was numerically better than the dexamethasone only therapy relative to SWOG response (p=0.10), EBMT response (p=0.14), and ECOG best response (p=0.12) as adjudicated by the FDA medical reviewer. In the exploratory analysis of the revised ECOG best response adjudicated by the medical reviewer by waving missing data, the combination therapy showed a statistically significant effect (p=0.0032). For easier comparisons with the sponsor's results, this reviewer used one-sided Fisher's exact test at the 0.025 significance level. Whether the endpoint and the size of effect on this endpoint are adequate for approval is a clinical decision.

The safety analysis showed that the combination group was statistically significantly ($p<0.001$) worse than the dexamethasone only group relative to rate of thrombosis or embolism both at the interim and final analyses. By the end of all treatment cycles, there were more deaths due to cardiovascular and thrombotic problems in the combination group as compared to the dexamethasone only treatment group (7 vs. 0, $p<0.01$).

1.2 Brief Overview of Clinical Studies

This NDA is a Type 6 NDA resubmission in response to the October 2004 Approvable Letter. At the FDA request, the sponsor submitted report of a single Study E1A00.

1.3 Statistical Issues and Findings

The protocol of Study E1A100 did not address multiplicity problem which might have arisen as a result of testing five secondary endpoints listed in the study protocol. To avoid inflation of the overall Type 1 error in case the sponsor decides to include results for some secondary endpoints into the labeling or promotion, this reviewer planned to use a hierarchical testing procedure for testing the secondary endpoints in the order they are listed in the protocol.

As the sponsor used one-sided Fisher's exact test, for easier comparisons of the primary efficacy results this reviewer also used the one-sided test. However, this reviewer used the 0.025 significance level instead of the 0.05 significance level used by the sponsor.

a. The medical reviewer adjudicated the primary efficacy endpoint,and
this reviewer also performed analysis for the primary efficacy results in the table generated by the medical reviewer. Table 5 shows primary efficacy analysis using response criteria SWOG and EBMT that are standard MM response criteria.
Table 5 also shows ECOG best response rates as adjudicated by the FDA medical reviewer using strong protocol specified criteria. As an exploratory analysis, the medical reviewer also

examined the revised ECOG best response rates after waving missing paraprotein or radiographic data (Table 6).

The primary efficacy analysis of Study E1A100 using the one-sided Fisher's exact test showed that the combination therapy was numerically better than the dexamethasone only therapy relative to SWOG response (p=0.10), EBMT response (p=0.14), and ECOG best response as adjudicated by the FDA medical reviewer (p=0.12). In the exploratory analysis of the revised ECOG best response adjudicated by the medical reviewer by including all available serum or urine paraprotein data, the combination therapy showed a statistically significant effect (p=0.0032 by the one-sided Fisher's exact test).

The safety analysis showed that combination group was statistically significantly (p<0.001) worse than the dexamethasone only group relative to rate of thrombosis or embolism both at the interim and final analyses. By the end of all treatment cycles, there were more deaths due to cardiovascular and thrombotic problems in the combination arm as compared to the dexamethasone only treatment arm (7 vs. 0, p<0.01).

2. INTRODUCTION

2.1 Overview

This NDA is a resubmission in response to the October 2004 Approvable Letter. At the FDA request, the sponsor submitted report of a single Study E1A00.

2.2 Data Sources

Efficacy and safety data sets for Study E1A00 were provided by the sponsor in the EDR at: \\CDSESUB\N21430\N_000\2005-05-13.

3. STATISTICAL EVALUATION

Title of Study E1A00: A randomized Phase 3 trial of thalidomide plus dexamethasone versus dexamethasone in newly diagnosed multiple myeloma patients.

Study design

This was a multi-center study conducted by the Eastern Cooperative Oncology Group (ECOG) at 82 centers in the United States, [redacted].

Primary objective: To evaluate the response rate and toxicity of thalidomide plus dexamethasone (combination treatment) and dexamethasone alone in patients with newly diagnosed myeloma.

This was a multi-center, randomized (1:1), open-label, controlled, parallel-group study in patients with newly diagnosed multiple myeloma (MM). Patients who met all inclusion/ exclusion criteria were randomized to one of two treatment groups. Patients randomized to treatment Arm A (combination treatment) received thalidomide 200 mg/day for 28 days (1 treatment cycle) plus dexamethasone 40 mg/day on days 1-4, 9-12, and 17-20. Patients randomized to treatment Arm B received dexamethasone only on days 1-4, 9-12, and 17-20 of the 28-day cycle. Patients were evaluated at the end of the first treatment cycle. Patients considered as responders or with stable disease continued treatment for a total of 4 cycles (16 weeks). Patients that progressed discontinued study treatment. All patients were followed for response until progression.

Study visits were 42 days prior to randomization and then 28 days prior to each treatment cycle. Patients were also evaluated after 4 cycles and at discontinuation of study treatment.

Number of patients
Planned: 194; Randomized: 207; Analyzed by sponsor: 200 (efficacy), 204 (safety).

Duration of treatment
The duration of treatment for the first phase of the study was 4 months (4 x 28 day cycles). One treatment cycle for patients receiving combination therapy consisted of thalidomide once daily for 28 days and dexamethasone on days 1-4, 9-12, and 17-20. One treatment cycle for patients receiving dexamethasone alone consisted of dexamethasone on days 1-4, 9-12, and 17-20 during the 28-day treatment cycle.

3.1 Evaluation of Efficacy

3.1.1. Efficacy Endpoints

The Sponsor's Efficacy Endpoints
Sponsor's Primary Efficacy Endpoint was Best Overall Response during the first 4 cycles of treatment based on reduction in M-protein levels using the ECOG Myeloma Response Criteria.

Sponsor's secondary efficacy variables:

1. Best overall response to treatment during the entire treatment period
2. Time to best overall response
3. Time to first response
4. Time to disease progression
5. Overall survival.

3.1.2 Statistical Methods

Sponsor's Statistical Methods

Sample size
The sample size of 97 patients per treatment arm (194 total) was sufficient to give the study design 90% power to detect the improvement in response rate from 60% in the dexamethasone arm to 80% in the combination arm while maintaining an overall one-sided 0.05 significance level (allowing for interim analyses).

Interim Analysis

Two interim analyses were planned, but because of a quick accrual into this trial, only one interim analysis was performed. The interim analysis was performed to compare both the response rates and the toxicity rates in the two treatment arms. The interim analysis was performed when safety information was available for 192 (93%) patients and best overall response information was available for 109 (53%) patients who had completed four treatment cycles. The stopping boundaries used in the group sequential design were modified for one interim analysis. A higher response rate of at least 20% in the combination arm was considered clinically significant and would be cause for stopping the trial if the O'Brien-Fleming boundaries were exceeded. A one-sided Fisher's exact test was used to compare the response rates in treatment arms. The resulting p-value was compared to the O'Brien-Fleming upper boundary at 0.011.

Sponsor's Efficacy Analysis

The primary efficacy analyses were performed for the efficacy population that included all patients who met eligibility criteria. The primary efficacy variable was best response during the first 4 cycles of treatment based on ECOG criteria. Response rates over all cycles of treatment were also determined. Response rates in each response category comprised of complete response [CR], near complete response [NCR], and partial response [PR], and for CR+ NCR+ PR are provided together with exact 95% confidence intervals for CR+ NCR+ PR. A one-sided Fisher's exact test was used to test the null hypothesis of equal response rates in the two treatment arms versus the alternative of a better response rate in the combination arm.

Dropouts

All patients were included in the efficacy analysis if response data were available. If patients discontinued from the study prior to achieving a response, they were counted as non-responders.

Statistical Reviewer's Methods

1. The sponsor did not address multiplicity problem which might have arisen as a result of testing five secondary endpoints in the study protocol. To avoid inflation of the overall Type 1

error in case the sponsor decides to include results for some secondary endpoints into the labeling or promotion, this reviewer used a sequential testing procedure as follows. If the primary efficacy endpoint wins at the 0.05 alpha level, then the first secondary endpoint in the protocol list is tested. If the first secondary endpoint wins at the 0.05 alpha level, then the next secondary endpoint in the list is tested and so on. If a secondary endpoint does not win, then testing is stopped and no further secondary endpoints are tested.

2. As the sponsor used one-sided Fisher's exact test, for easier comparisons of the primary efficacy results this reviewer also used the one-sided test. However, this reviewer used the 0.025 significance level instead of the 0.05 significance level used by the sponsor.

a. 3. The medical reviewer adjudicated the primary efficacy endpoint provided by the sponsor and

this reviewer also performed analysis for the primary efficacy results in the table generated by the medical reviewer. Table 5 shows primary efficacy analysis using response criteria SWOG and EBMT that are standard MM response criteria. Response rates for SWOG and EBMT in Study E1A100 were adjudicated by the FDA medical reviewer. For comparison, Table 5 also shows ECOG Best Response rates as adjudicated by the sponsor and by the FDA medical reviewer. In Table 5, primary efficacy analysis is based on the FDA efficacy population that includes all randomized patients (regardless of meeting eligibility criteria and receiving treatment or not).

4. This reviewer also confirmed the exploratory analysis of the FDA medical reviewer in which some patients with missing serum or urine paraprotein and radiographic data were classified as responders (Table 6).

3.1.3 Sponsor's Analysis of Study E1A00

Disposition of Patients

Data sets analyzed by the sponsor

A total of 207 patients were randomized and enrolled into the study. The safety population was defined as those patients who received at least one dose of study medication and excluded a total of three patients: two patients who were randomized but did not receive study treatment (#10016 and #10075) and one patient for whom no study data was submitted by the investigator (#10532). Of the 204 patients in the safety population, 102 (50.0%) were in the combination arm, and 102 (50.0%) were in the dexamethasone only treatment arm (Table 1).

A total of 200 patients comprised the sponsor's efficacy population, defined as all patients randomized into the study and who met all eligibility criteria. Of the 200 patients in the efficacy population, there were 99 (49.5%) in the combination arm, and 101 (50.5%) in the dexamethasone only treatment arm (Table 1). Seven patients were excluded from the efficacy population because they did not meet study eligibility criteria. Five were ineligible because

baseline laboratory values did not show measurable disease or M-protein levels, and two were ineligible because they did not have sufficient data to confirm eligibility.

One hundred twenty-seven (62.2%) of the 204 patients from the safety population completed four cycles of protocol treatment; 77/ 204 (37.7%) patients discontinued before completing the planned four cycles of therapy. The primary reason for discontinuation from the study was toxicity / side effects (19.1%; 39/ 204). The other reasons were: disease progression / relapse (5.9%; 12/ 204), death of the patient without progressive disease (3.4%; 7/ 204), patient withdrew consent, (2.9%; 6/ 204), other reason (2.9%; 6/ 204), alternative therapy (1.5%; 3/ 204), another complicating disease (1.5%; 3/ 204), or missing data (0.5%; 2/ 204). The overall frequency of discontinuations during the first four cycles of protocol treatment was similar between treatment groups. However, the frequency of discontinuations due to disease progression was higher in the dexamethasone only group (10 vs. 2 patients), while discontinuations due to toxicity was greater in the combination group (26 vs. 13 patients). Ten (83.3%) of the 12 patients who discontinued during the first four cycles of treatment due to disease progression were from the dexamethasone only treatment arm.

Table 1. Patient Disposition in Study E1A00

Disposition	**Thal +Dex**	**Dex only**	**Overall**
All randomized patients (reviewer's efficacy population)	103	104	207
Sponsor's Analysis Populations			
Safety Population	102	102	204
Efficacy Population	99	101	200
Completed four cycles of study drug	65	62	127
Did not complete four cycles of study drug	37	40	77
Extension Phase	27	13	40
Primary reason for discontinuation:			
Disease progression	2	10	12
Toxicity	26	13	39

Source: Sponsor's Table 14.1.1 (confirmed by the reviewer)

Demographic and Other Baseline Characteristics

Generally, the patient population was well balanced between treatment groups with regard to baseline demographic characteristics. In the combination group, there were approximately equal proportions of males and females. In the dexamethasone only group, the percentage of males exceeded proportion of females. Patients ranged in age from 38 to 83 years (mean, 63.9 years); a small majority of patients (51.5%; 103/ 200) were > 65 years of age and the majority of patients were white (87.0%; 174/ 200).

Sponsor's Efficacy Results

Sponsor's Primary Efficacy Endpoint

Table 2 shows sponsor's primary efficacy results for the overall best response based on ECOG criteria as adjudicated by the sponsor. Sponsor's adjudicated ECOG response showed that treatment with combination therapy had a statistically significantly higher best overall response rate as compared with dexamethasone alone, 61.6% versus 39.6% (p= 0.001 by one-sided Fisher's Exact Test).

(Note that the FDA medical reviewer's adjudication of ECOG best response does not agree with the sponsor's adjudication as shown in Table 5 in the Section 3.1.4).

Table 2. Sponsor's Primary Efficacy Analysis
(Best response rate in first 4 cycles, Efficacy Population, N=200)

	Thal+Dex N=99	Dex only N=101	p-value
ECOG criteria			
Number of Responders (CR+NCR+PR)	61 (62%)	40 (40%)	0.001*
Complete Response (CR)	5 (5%)	0	
Near Complete Response (NCR)	0	1 (1%)	
Partial Response (PR)	56 (57%)	39 (39%)	
No Change (NC)	21 (21%)	38 (38%)	
Progressive Disease (PD)	2 (2%)	3 (3%)	
Not Evaluable (NE)	15 (15%)	20 (20%)	

Source: Sponsor's Table 14.2.1. Analysis is confirmed by the reviewer.
**One-sided Fisher's exact test*

Sponsor's adjudicated overall best response (First Four Cycles and Extension Phase)

Patients with a response to treatment or without disease progression during the four cycles of protocol therapy were allowed to stay on treatment in an extension phase. Table 3 shows the overall best response rate adjudicated by the sponsor for all cycles of treatment (including the first four cycles). The difference between groups was significant in favor of the combination arm (p< 0.001; one-sided Fisher's Exact Test).

Table 3. Sponsor's adjudication of best response rate in all cycles, Efficacy Population, N=200

	Thal+Dex N=99	Dex only N=101	p-value
ECOG criteria			
Number of Responders (CR+NCR+PR)	63 (64%)	40 (40%)	<0.001*
Complete Response (CR)	6 (6%)	1 (1%)	
Near Complete Response (NCR)	0	1 (1%)	
Partial Response (PR)	57 (58%)	38 (39%)	
No Change (NC)	21 (21%)	39 (39%)	
Progressive Disease (PD)	2 (2%)	3 (3%)	
Not Evaluable (NE)	13 (13%)	19 (19%)	

* *One-sided Fisher's exact test*

Source: Sponsor's Table 14.2.2 (Analysis confirmed by the reviewer)

Secondary Efficacy Endpoints

Sponsor's Time to Response

In Study E1A100, "time to response" secondary variables had missing values for the patients who did not achieve response. Therefore, time to censoring was not available for these variables and no Kaplan-Meier estimation was possible to perform. The sponsor just compared median and mean time to response and ignored the censoring time.

Table 4. Time to Best Response and First Response (First 4 Cycles) Efficacy Population (N=200)

	Thal +Dex, N=99	Dex only, N=101
ECOG criteria		
Number of Responders (CR+ NCR+ PR); n (%)	61 (62%)	40 (40%)
Time to Best Response (weeks)		
Median (95% CI)	4.9 (4.6, 7.3)	5.1 (4.6, 7.9)
Mean (SD)	7.2 (4.2)	6.6 (2.9)
Range	3.3, 18.1	3.1, 12.7

Source: Sponsor's Tables 14.2.4 and 14.2.5 (Results confirmed by the reviewer).

Based on the sponsor's adjudication of ECOG criteria, there was no statistically significant difference between the two treatment groups relative to time to the best myeloma response during the first four cycles of treatment. As this secondary endpoint did not win, according to the sequential testing procedure no testing of other secondary endpoints should be performed in order to maintain the overall Type 1 error.

3.1.4 Reviewer's Efficacy results

As the sponsor used one-sided Fisher's exact test for the primary efficacy analysis, for easier comparison this reviewer also used the one-sided test. However, this reviewer used the 0.025 significance level instead of the 0.05 significance level used by the sponsor.

a. The medical reviewer adjudicated the primary efficacy endpoint reported by the sponsor and

this reviewer also performed analysis for the primary efficacy results in the table of responses adjudicated by the medical reviewer. Table 5 shows primary efficacy analysis using response criteria SWOG and EBMT that are standard MM response criteria. Response rates for SWOG and EBMT in Study E1A100 were adjudicated by the FDA medical reviewer. For comparison, Table 5 also shows ECOG Best Response rates as adjudicated by the FDA medical reviewer and by the sponsor. In Table 5, primary efficacy analysis is based on the FDA efficacy population that includes all randomized patients (regardless of meeting eligibility criteria or not).

Table 5. FDA Primary Efficacy Analysis.
Response rates during 4 cycles as adjudicated by the FDA medical reviewer (FDA efficacy population)

Response	**Thal/Dex N=103**	**Dex alone N=104**	**P-value (Fisher's exact one-sided test)**
SWOG OR + Improvement	21 (20.4 %)	14 (13.5 %)	0.10
EBMT CR + PR	21 (20.4 %)	15 (14.4%)	0.14
ECOG CR + NCR + PR, adjudicated by:			
FDA Medical Reviewer	25 (24.3%)	18 (17.3 %)	0.12
Sponsor (shown for comparison)	*62 (60 %)*	*40 (38 %)*	*0.001*

As the primary efficacy endpoint did not win using the FDA adjudication, no testing of the secondary endpoints should be performed.

As an exploratory analysis, the medical reviewer examined the ECOG response rates after including as responders some patients for whom one or more urine or serum paraprotein or radiographic measurements were missing. Table 6 shows that in the exploratory analysis for the ECOG best response as adjudicated by the FDA medical reviewer including all available serum or urine paraprotein data, the combination therapy had a statistically significant effect (p=0.0032 by the one-sided Fisher's exact test).

Table 6. Exploratory analysis of ECOG best response in first 4 cycles as adjudicated by the FDA medical reviewer by waving missing data.

ECOG CR, NCR or PR	Thal/Dex N=103	Dex alone N=104	P-value (one-sided Fisher's exact test)
By the strict protocol-defined criteria	25 (24.3 %)	18 (17.3 %)	0.12
Waving missing paraprotein or radiographic data	48 (46.6 %)	29 (27.9 %)	0.0032

3.2 Evaluation of Safety

Duration of treatment

The mean duration of treatment was balanced between the two treatment groups: 13.7 ± 4.8 weeks (range 2 to 22 weeks) for combination treated patients and 12.7 ± 4.1 weeks (range 2 to 18 weeks) for dexamethasone only treated patients in the first four cycles of treatment. The average daily dexamethasone dose was similar between the groups. More patients on combination arm experienced at least one thalidomide dose reduction as compared to those on dexamethasone alone (34 versus 18 in the first 4 cycles and 38 versus 20 overall).

Interim Analysis of Adverse Events

The rates for the adverse events of deep vein thrombosis, rash, neuropathy, or bradycardia of NCI CTC Grade 3 or higher were monitored by the study DMC at the interim analysis. At the time of the interim analysis, the rate of toxicity for monitored events was 41.0% for the combination treatment arm and 16.0% for the dexamethasone treatment arm ($p<0.001$). This difference between treatment arms was due primarily to the increased rate of thrombosis observed in the combination treatment arm at the time of the interim analysis.

As the enrollment was rapid and all patients were accrued to the trial and had completed a minimum of four cycles of therapy, and as the response rate in the combination treatment arm was significantly higher than in the dexamethasone alone arm (79% vs. 49%; $p=0.0030$) the DMC considered that the benefit of combination therapy outweighed the associated risks and in collaboration with the NCI (CTEP) allowed the study to continue. A letter was sent to all study participants (both investigators and patients) informing them of the findings of the DMC.

Adverse events analysis at the end of study

All patients experienced at least one adverse event. The rate of thrombosis was significantly higher ($p<0.001$) in the combination treatment group (22.5%) as compared to patients treated with dexamethasone only (4.9%). For most of adverse events, the combination arm had numerically higher rates than the dexamethasone only treatment arm.

Mortality

There were 3 deaths in the study within 30 days of the last dose: two in the combination arm and one in the dexamethasone only treatment arm. Overall during the study protocol, there were 11 deaths in the combination arm and nine deaths in the dexamethasone only treatment arm. Mean survival time was similar in the two treatment groups: 70.1 (± 27.7) weeks in the combination arm and 68.1 (± 28.7) in the dexamethasone only treatment arm. There were more deaths due to cardiovascular and thrombotic problems in the combination arm as compared to the dexamethasone only treatment arm (7 vs. 0).

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

Statistical and analytical issues

1. The sponsor did not address multiplicity problem which may arise as a result of testing five secondary endpoints in the study Protocol. To avoid inflation of the overall Type 1 error in case the sponsor decides to include results for some secondary endpoints into the labeling or promotion, this reviewer planned to use a hierarchical testing procedure of testing the secondary endpoints in the order they are listed in the protocol.

2. The sponsor used for the primary efficacy analysis one-sided Fisher's exact test. For easier comparisons, this reviewer also used the one-sided test. However, instead of the 0.05 significance level used by the sponsor, this reviewer used the 0.025 significance level. This approach is preferable in regulatory settings because it promotes consistency with two-sided confidence intervals that are generally appropriate for estimating the possible sample size of the difference between two treatments.

b. 3. The medical reviewer adjudicated the primary efficacy endpoint reported by the sponsor and

this reviewer also performed analysis for the primary efficacy results in the table generated by the medical reviewer. Table 5 shows primary efficacy analysis using response criteria SWOG and EBMT that are standard MM response criteria.

For comparison, Table 5 also shows ECOG best response rates as adjudicated by the FDA medical reviewer using strong protocol specified criteria. As an exploratory analysis, the medical reviewer also examined the revised ECOG best response rates after including as responders some patients for whom one or more missing urine or serum paraprotein or radiographic measurements were missing (Table 6).

The primary efficacy analysis of Study E1A100 using the one-sided Fisher's exact test showed that the combination therapy was numerically better than the dexamethasone only therapy

relative to SWOG response (p=0.10), EBMT response (p=0.14), and ECOG best response as adjudicated by the FDA medical reviewer (p=0.12). In the exploratory analysis of the revised ECOG best response adjudicated by the medical reviewer by waving missing data, the combination therapy had a statistically significant effect (p=0.0032 by the one-sided Fisher's exact test).

The safety analysis showed that the combination group was statistically significantly (p<0.001) worse than the dexamethasone only group relative to rate of thrombosis or embolism both at the interim and final analyses. By the end of all treatment cycles, there were more deaths due to cardiovascular and thrombotic problems in the combination arm as compared to the dexamethasone only treatment arm (7 vs. 0, p<0.0 1).

4.2 Conclusions and Recommendations

The primary efficacy analysis of Study E1A100 using the one-sided Fisher's exact test showed that the combination therapy was numerically better than the dexamethasone only therapy relative to SWOG response (p=0.10), EBMT response (p=0.14), and ECOG best response as adjudicated by the FDA medical reviewer (p=0.12). In the exploratory analysis of the revised ECOG best response adjudicated by the medical reviewer by including all available serum or urine paraprotein data, the combination therapy had a statistically significant effect (p=0.0032 by the one-sided Fisher's exact test). Whether the endpoint and the size of effect on this endpoint are adequate for approval is a clinical decision.

The safety analysis shows that combination group was statistically significantly (p<0.001) worse than the dexamethasone only group relative to rate of thrombosis or embolism both at the interim and final analyses. By the end of all treatment cycles, there were more deaths due to cardiovascular and thrombotic problems in the combination arm as compared to the dexamethasone only treatment arm (7 vs. 0, p<0.01).