

Submitted by:
Awny Farajallah, MD, FACP
Vice President, Head US Medical Oncology
Bristol-Myers Squibb Company
777 Scudders Mill Road
Plainsboro, NJ 08536
609-897-3945; awny.farajallah@bms.com
November 30, 2015

NCCN Guidelines® Panel: Multiple Myeloma

Dear Panel Members,

On behalf of Bristol-Myers Squibb Company, I respectfully request the Panel to consider recommending elotuzumab in combination with lenalidomide and dexamethasone in the NCCN Multiple Myeloma Guidelines as a Category 1 preferred regimen for previously treated multiple myeloma.^{1,2}

Additionally, please consider elotuzumab in combination with bortezomib and dexamethasone as a treatment option for previously treated multiple myeloma.³

These data are being submitted in response to a standing request from NCCN for new clinical data.

Specific Changes: In section MYEL-D, I respectfully request that elotuzumab in combination with lenalidomide and dexamethasone be added as a NCCN Category 1 preferred regimen for previously treated multiple myeloma.

FDA Clearance:

On November 30, 2015 the FDA approved EMPLICITI® (elotuzumab) in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.¹

Rationale for Proposed Change:

Phase 3 study: Elotuzumab in combination with lenalidomide and dexamethasone (ELd) versus lenalidomide and dexamethasone (Ld) for previously treated multiple myeloma

In support of this request, FDA approval was based on an open-label, phase 3 study, which randomized patients 1:1 to receive elotuzumab in combination with lenalidomide and dexamethasone or lenalidomide and dexamethasone alone, until disease progression or unacceptable toxicity. The planned interim analysis for co-primary endpoints of progression free survival (PFS) as assessed by hazard ratio (HR) and objective response rate (ORR) included a total of 646 patients, of which 321 were treated with ELd and 325 patients treated with Ld.²

Efficacy findings, highlights²

- After a median follow-up of 24.5 months, results of an interim analysis demonstrated a 30% reduction in risk of disease progression or death for patients in the ELd arm compared to patients in the Ld arm (HR 0.70; 95% CI, 0.57–0.85); $P < .001$), which is statistically significant. Median PFS was 19.4 (95% CI, 16.6–22.2) months and 14.9 (95% CI, 12.1–17.2) months for the ELd-treated and Ld-treated patients, respectively. Additionally, statistical significance was achieved for overall response rate which was 79% (95% CI, 74–83) and 66% (95% CI, 60–71) for ELd and Ld arms, respectively. The odds ratio for the ELd arm versus the Ld arm was 1.9; 95% CI, 1.4–2.8; $P < 0.001$)

Safety findings, highlights²

- Common grade 3-4 adverse events (AEs) reported in $\geq 25\%$ in ELd (n= 318) versus Ld (n=317), respectively included: lymphocytopenia (77% vs. 49%), neutropenia (34% vs. 44%), anemia (19% vs. 21%), and thrombocytopenia (19% vs. 20%).
- Serious AEs were reported in 65% and 57% of patients treated with ELd and Ld, respectively.
- Discontinuation of therapy at the time of data cut-off occurred in 65% of patients receiving ELd and 79% of those receiving Ld.
- Infusion reactions occurred in 10% of patients treated with ELd, but no patient had a grade 4 or 5 reaction.

- There were fewer deaths in the ELd arm (94 patients out of 318 patients) compared to the Ld arm (116 patients out of 317 patients).

Phase 2 study: Elotuzumab plus bortezomib and dexamethasone (EBd) versus bortezomib (Bd) and dexamethasone for previously treated multiple myeloma

The open-label, phase 2 study randomized patients 1:1 to receive either elotuzumab in combination with bortezomib and dexamethasone or bortezomib and dexamethasone alone, until disease progression or unacceptable toxicity. The trial that was sized using a 2-sided 0.30 level test with 80% power to detect an HR of 0.69, and had a 80% power to detect a PFS effect with a small sample size (N=152, 77 patients treated with EBd and 75 patients treated with Bd alone).

Efficacy findings, highlights³

- Results of the interim analysis, demonstrated a 28% reduction in risk of disease progression or death for patients in the EBd arm compared to patients in the Bd arm (HR, 0.72; 70% CI, 0.59-0.88), which is statistically significant. Median PFS was 9.7 months vs. 6.9 months in the EBd and Bd treatment arms, respectively.

Safety findings, highlights³

- AE's of any grade were reported in 100% in the EBd arm (n=75) and 96% in the Bd arm (n=75).
- Common grade 3-4 AEs reported in $\geq 5\%$ of patients treated with EBd versus Bd, respectively included: infections and infestations (17% vs. 13%), diarrhea (8% vs. 4%), anemia (7% in both arms), peripheral neuropathy (8% vs. 9%), paresthesia (0% vs. 5%), and thrombocytopenia (9% vs. 17%).
- Serious AEs were reported in 47% of patients treated with EBd and 41% of patients treated with Bd.
- Grade 1-2 infusion reactions occurred in 5 patients in the EBd arm.

The following resources are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications/presentations.

1. EMPLICITI Prescribing Information
2. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa1505654.
3. Jakubowiak A, Offidani M, Pegourie B, et al. A randomized, open-label, Phase 2 study of bortezomib and dexamethasone with or without elotuzumab in patients with relapsed/refractory multiple myeloma. Oral presentation at: The 20th Congress of the European Hematology Association (EHA) Annual Meeting; June 11-14, 2015; Vienna, Austria

Thank you for your consideration of this request.

Sincerely,



Awny Farajallah, MD, FACP
Vice President, Head US Medical Oncology
Bristol-Myers Squibb Company