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REVIEW

Mechanisms of Action and Clinical Development of Elotuzumab

David Ritchie^{1,*} and Marco Colonna²

INTRODUCTION

Multiple myeloma (MM) is a malignant disease of plasma cells, with a 5-year relative survival rate lower than 50%.¹ In recent years, the introduction of proteasome inhibitors (PIs) and immunomodulatory drugs has improved treatment outcomes, leading to the standard of care consisting largely of immunomodulatory drug- and PI-based regimens, or triplet therapy involving a combination of both.² Nonetheless, MM remains largely incurable and there is an unmet need for additional therapies.

Immunotherapy is a rapidly emerging area in cancer treatment. Immuno-oncology (I-O) agents (such as the anti-signaling lymphocytic activation molecule F7 (SLAMF7) monoclonal antibody elotuzumab) enhance the immune response against cancer cells, either by directly stimulating the activity of immune cells or by targeting specific cell surface tumor antigens.³

Until recently, use of immunotherapy in MM has faced two major hurdles. First, suitable targets on plasma cells have been elusive. Second, the immune system in patients with MM is significantly impaired (e.g., functional defects in T cells, B cells, natural killer (NK) cells, and dendritic cells),⁴ resulting in defective endogenous immune responses, particularly in adaptive immunity. Despite these limitations, recent clinical data suggest that immune effectors retain sufficient functionality in MM to mediate significant clinical benefit when I-O agents targeted to appropriately expressed antigens are given.⁵

In addition to elotuzumab, the anti-CD38 antibodies daratumumab, isatuximab, and MOR202, and the antikeratin cell immunoglobulin-like receptor (KIR) 2DL1/2/3 antibody lirilumab, are examples of immunostimulatory antibodies approved or in development for the treatment of MM.^{6–10} Daratumumab (in patients who have received at least three prior treatments) and elotuzumab (combined with lenalidomide and dexamethasone (Ld) in patients who have received one to three prior therapies) were approved in November 2015 by the US Food and Drug Administration (FDA) for MM treatment.^{7,8} In May 2016, this combination of elotuzumab with Ld was approved for use in Europe in adult patients with MM who had received at least one prior therapy.¹¹ Daratu-

mumab received FDA approval in November 2016, for use in combination with Ld, or with bortezomib and dexamethasone, in patients who had received at least one prior therapy. In June 2017, it was approved for use, in combination with pomalidomide and dexamethasone, in patients who had received at least two prior therapies, including lenalidomide and a PI.^{12–14}

The introduction of immunotherapies may lead to improvements in MM treatment outcomes, as agents such as elotuzumab have the potential to induce a long-term immune response coupled with a durable clinical benefit,¹⁵ which reflects a mechanism of action and response kinetics that differ from that of conventional chemotherapeutic regimens.¹⁶

This review discusses the novel dual immunotherapeutic mechanism of action of elotuzumab and its associated clinical outcomes.

PATHOPHYSIOLOGY OF MM AND RELATIONSHIP WITH SLAMF7

SLAMF7 structure and expression

SLAMF7 is a member of the SLAM family of receptors, which are involved in cytotoxicity, humoral immunity, autoimmunity, cell survival, cell adhesion, and lymphocyte development.¹⁷ SLAMF7 is a cell surface transmembrane molecule (Figure 1).^{18–20} The extracellular region consists of two immunoglobulin (Ig) superfamily domains containing several *N*-glycosylation sites. The hydrophobic transmembrane region is followed by a cytoplasmic region containing four tyrosine-based motifs, two of which recruit signaling proteins.^{18–20} Using gene expression profiling or anti-SLAMF7 antibody, SLAMF7 was found to be expressed in malignant hematopoietic cells, normal NK cells, CD8⁺ T cells, a subset of CD4⁺ T cells, plasmacytoid dendritic cells, B cells,^{18,21} activated monocytes, and mature dendritic cells.²¹ Normal nonlymphoid tissues tested negative for SLAMF7 expression.²¹

SLAMF7 is highly expressed in myeloma plasma cell samples and in plasma cells from patients with asymptomatic MM (smoldering MM and monoclonal gammopathy of undetermined significance).²¹ Expression is also maintained in patients who have received prior MM treatment—SLAMF7 gene expression was found to be comparable in previously

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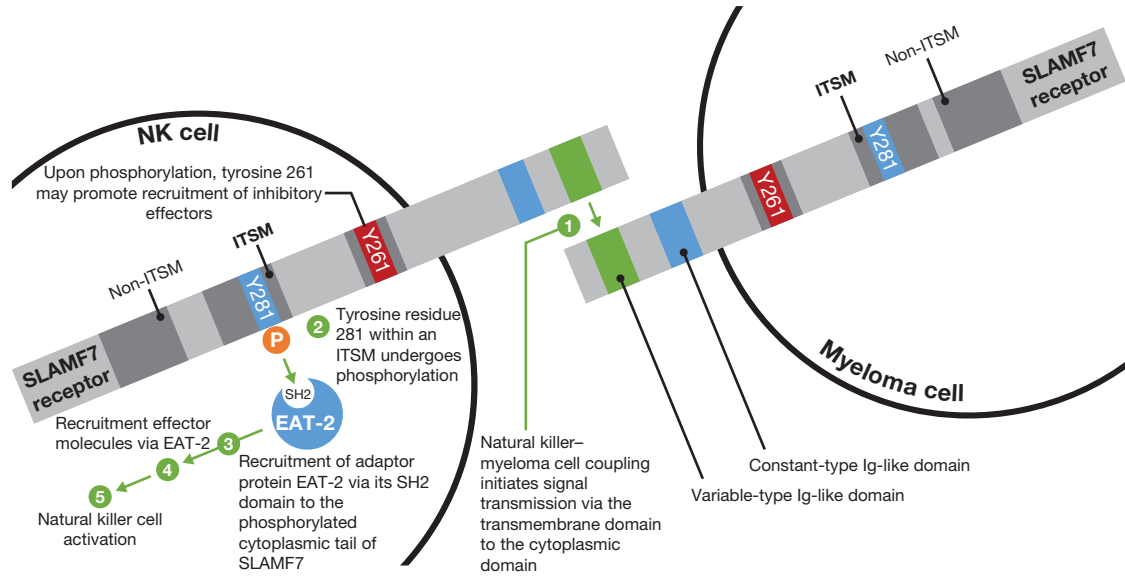


Figure 1 Signaling lymphocytic activation molecule F7 (SLAMF7) structure and signaling mechanism. SLAMF7 is a self-ligand that recognizes and binds to SLAMF7 on other cells (e.g., myeloma cells can bind to other myeloma cells via SLAMF7 coupling). Natural killer (NK) cell activation after SLAMF7 coupling is dependent on Ewing’s sarcoma-associated transcript 2 (EAT-2) signaling. Ig, immunoglobulin; ITSM, immunoreceptor tyrosine-based switch motif; SH2, Src homology 2.

untreated patients both before and after a single dose of bortezomib.²²

ELOTUZUMAB: AN I-O AGENT THAT DIRECTLY ACTIVATES NK CELLS AND INDUCES ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY

Elotuzumab is a humanized, IgG1 anti-SLAMF7 monoclonal antibody that elicits its effect via a dual mechanism of action: direct activation of NK cells and antibody-dependent cellular cytotoxicity (ADCC; **Figure 2**²³). Using a cytotoxicity assay that measures granzyme B secretion, coupling of elotuzumab to SLAMF7 on NK cells has been shown to cause granzyme B release targeted against myeloma cells,²⁴ a process that is independent from CD16-mediated ADCC.

Although NK cell activation and ADCC are the most researched mechanisms of action for elotuzumab, it is likely that elotuzumab exerts additional effects on the immune system via other SLAMF7-positive cells (e.g., CD8⁺ T cells, monocytes, and dendritic cells).^{17,18,21,25} For example, SLAMF7 expression on dendritic cells²¹ may trigger antitumor cellular immunity. Treatment with elotuzumab has been shown to reduce myeloma tumor burden in a xenograft model with defective NK cells in a CD16-dependent manner, suggesting that mechanisms other than ADCC and direct activation of NK cells may mediate the antitumor effect of elotuzumab.²⁶ Other hypotheses include the possibility that elotuzumab may inhibit plasmacytoid dendritic cells, which have been implicated in myeloma cell growth and survival.^{18,21,25} Taken together, further preclinical research is warranted to establish whether elotuzumab elicits an effect via mechanisms other than NK cell activation and ADCC.

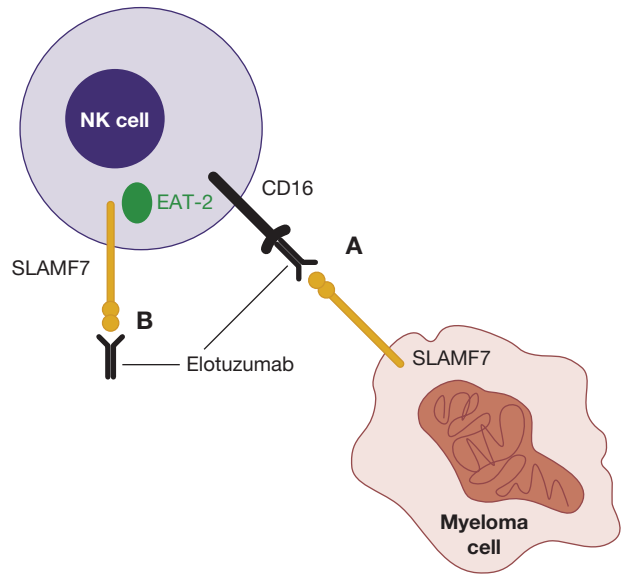


Figure 2 Elotuzumab mechanism of action. Elotuzumab primarily acts by activating natural killer (NK) cell-mediated killing of myeloma cells via antibody-dependent cellular cytotoxicity (A). Elotuzumab also directly activates NK cells to kill myeloma cells (B). EAT-2, Ewing’s sarcoma-associated transcript 2; SLAMF7, signaling lymphocytic activation molecule F7. Figure from Lonial, S. *et al. Expert Opin. Biol. Ther.* **16**, 1291–1301 (2016). Reprinted with permission from Taylor & Francis © 2016.

ELOTUZUMAB MECHANISM OF ACTION DOWNSTREAM OF SLAMF7 SIGNALING

SLAMF7 is a homotypic receptor that recognizes and binds to SLAMF7 on other cells, thus allowing myeloma cells to adhere to other myeloma cells or to conjugate with NK cells.

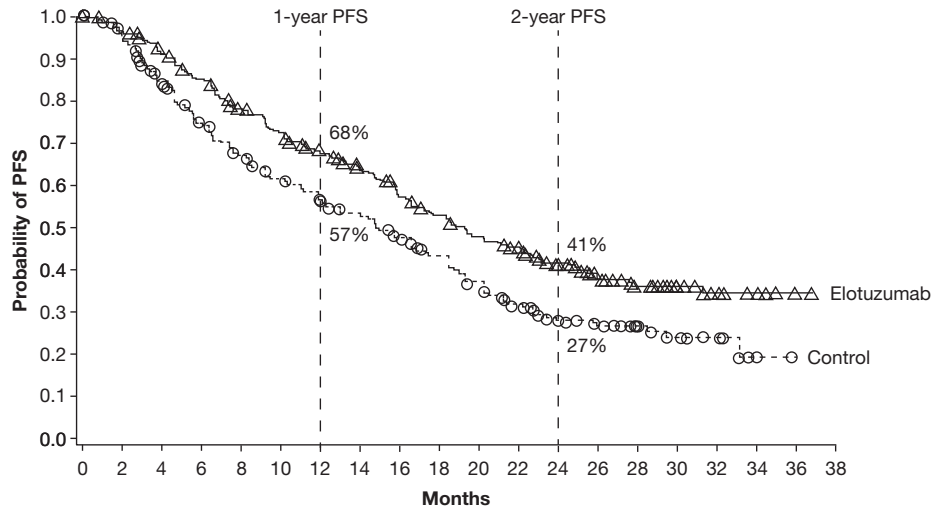


Figure 3 Kaplan–Meier curves showing progression-free survival (PFS) in patients with relapsed or refractory multiple myeloma receiving elotuzumab plus lenalidomide and dexamethasone (“Elotuzumab”) or lenalidomide and dexamethasone (“Control”). Figure from Lonial, S. *et al.* Elotuzumab therapy for relapsed or refractory multiple myeloma. *N. Engl. J. Med.* **373**, 621–631. ©2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

NK cells are involved in the immune defense against transformed cells,²⁷ such as myeloma cells. This process is regulated by their expression of inhibitory or activating receptors. However, in patients with MM, changes in NK cell receptors may enable myeloma cells to evade immunosurveillance.^{28–30}

Activation of NK cells following SLAMF7 coupling is dependent on the SLAM-associated protein Ewing’s sarcoma-associated transcript 2 (EAT-2), which binds to the cytoplasmic domain of SLAMF7 (Figure 1).^{18–20} EAT-2 expression is high in NK cells freshly isolated from blood or cultured in interleukin-2, and in NK cell lines,²⁰ but it is not expressed by CD4⁺ T cells, B cells, dendritic cells, or myeloma cells; hence, these cells are not activated by SLAMF7–SLAMF7 coupling.^{19,20}

The importance of SLAMF7 in mouse NK cell activation has been demonstrated.³¹ In SLAMF7-deficient mice, NK cells lacked all cell surface expression of SLAMF7 (confirmed by immunoblot analysis), whereas other SLAM family receptors and SLAM-associated protein-related adaptors were unchanged.³¹ These mice failed to show cytotoxicity towards target cells expressing SLAMF7. EAT-2 involvement was established by examining the effects of the absence of EAT-2 on the NK cell-activating function of SLAMF7. Function was impaired in NK cells isolated from mice with inactivating mutations in EAT-2.³¹ Taken together in the presence of EAT-2, SLAMF7 coupling activates NK cells, but in its absence this activation is lost and NK cell function is inhibited.³¹

In ADCC, the Fab portion of elotuzumab binds to SLAMF7 on myeloma cells and the Fc portion binds to the Fc receptor CD16 (FcγRIII) on NK cells,^{31,32} tagging myeloma cells for ADCC and myeloma cell death via the release of cytotoxic granules.²⁴ ADCC occurs in a dose-dependent manner against SLAMF7-expressing cell lines, and in patients with newly diagnosed MM as well as in patients resistant to conventional therapies.³³ Blocking the Fc recep-

tor on NK cells with an anti-CD16 antibody inhibits this action.²¹

ELOTUZUMAB CLINICAL OUTCOMES

Efficacy

In addition to the preclinical studies on elotuzumab and SLAMF7 described above, the efficacy of elotuzumab in combination with approved agents has been assessed in a number of clinical trials: in combination with Ld (ELd) in the ELOQUENT-2 study (NCT01239797) and in combination with bortezomib and dexamethasone (EBd) in study 009 (NCT01478048).^{5,15,34,35} Other ongoing elotuzumab clinical trials are using alternative combinations, such as pomalidomide and dexamethasone (EPd),^{36,37} and there are immunotherapies currently in development—for example, elotuzumab in combination with the anti-KIR antibody lirilumab.⁶

The phase III ELOQUENT-2 study assessed ELd vs. Ld alone in patients with relapsed or refractory multiple myeloma (RRMM).⁵ In the primary analysis, ELd reduced the risk of disease progression or death by 30% vs. Ld (hazard ratio (HR) 0.70; 95% confidence interval (CI) 0.57, 0.85; $P < 0.001$), with an early separation between the Kaplan–Meier progression-free survival (PFS) curves that was maintained over time (Figure 3).⁵ The observed early curve separation may be attributed to the conventional therapy backbone (Figure 4).³⁸ Median PFS was 19.4 months with ELd vs. 14.9 months with Ld; PFS at 1 year was 68% in the ELd arm vs. 57% in the Ld arm; at 2 years, it was 41% vs. 27%, respectively.⁵ The overall response rate (ORR) was 79% in the ELd arm vs. 66% in the Ld arm ($P < 0.001$).⁵

I-O agents exhibit response kinetics defined by the building of a cellular immune response, followed by tumor regression. This is associated with durable clinical benefit that may persist after the therapy is discontinued,^{16,39–41} leading to long-term survival benefits. Thus, an immunotherapy-

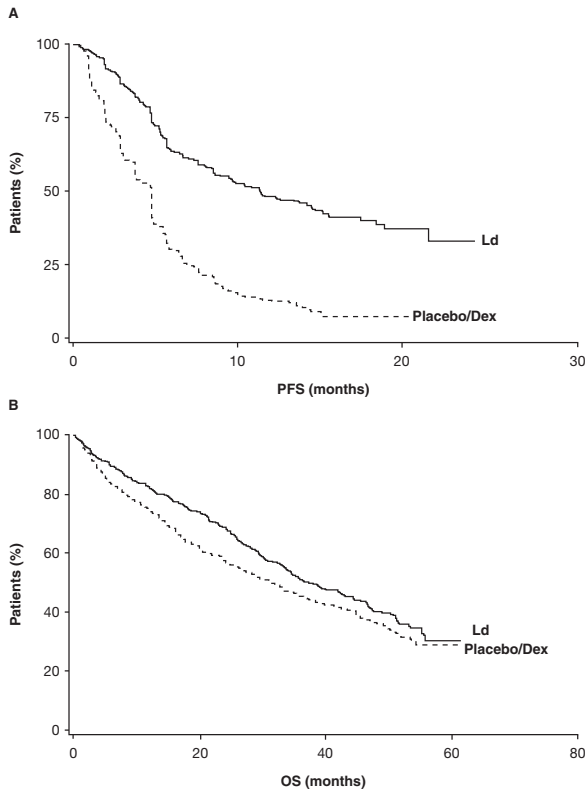


Figure 4 Kaplan–Meier curves showing **(A)** progression-free survival (PFS) and **(B)** overall survival (OS) in patients with relapsed or refractory multiple myeloma receiving lenalidomide (L) and/or dexamethasone (d/Dex). Reprinted with permission from Macmillan Publishers: Dimopoulos, M.A. *et al. Leukemia* **23**, 2147–2152 (2009), ©2009.

specific approach with end points that reflect the increased durability of response is required for assessment of I-O therapy outcomes. Such end points may include long-term follow-up, timepoint analyses of survival, and HRs over the study duration.¹⁶

Extended 3-year follow-up of ELOQUENT-2 demonstrated that ELd reduced the risk of disease progression or death by 27% (HR 0.73; 95% CI 0.60, 0.89; $P = 0.0014$).¹⁵ The separation between the Kaplan–Meier curves for PFS in the primary analysis was maintained in the 3-year follow-up, showing long-term durability of response with ELd vs. Ld alone.^{5,15} The 3-year PFS was 26% and 18% in the ELd vs. Ld arm, respectively, indicating a relative improvement in PFS of 44% at 3 years, while ORR was 79% with ELd and 66% with Ld ($P = 0.0002$).¹⁵ An interim overall survival (OS) analysis demonstrated a strong trend in favor of ELd (HR 0.77; 95% CI 0.61, 0.97; $P = 0.0257$), in which there was a clear separation in the tail end of the Kaplan–Meier curves (**Figure 5**).¹⁵ Median (95% CI) OS was 43.7 months (40.3, not estimable (NE)) in the ELd arm and 39.6 months (33.3, NE) in the Ld arm.¹⁵ The 4-year PFS data support a sustained durable PFS benefit with ELd in comparison with Ld, showing a relative improvement in PFS of 50% (PFS rates of 21% vs. 14%) and a reduction in the risk of progression or death of 29% (HR 0.71; 95% CI 0.59, 0.86) consistent with prior follow-up analysis.⁴² The OS trend in favor of ELd was also sustained at the 4-year follow-up (HR 0.78; 95% CI 0.63, 0.96; non-prespecified OS analysis), with a median (95% CI) OS of 48 months (40.3, 54.4) and 40 months (33.3, 45.4) for ELd and Ld, respectively.⁴² Long-term survival follow-up is still ongoing.

The extended 3-year follow-up of ELOQUENT-2 also demonstrated that ELd reduces the risk of starting a subsequent line of therapy during follow-up by 38% (HR 0.62; 95% CI 0.50, 0.77).¹⁵ Median (95% CI) time to next treatment (TTNT) was 33 months (26.2, 40.2) with ELd vs. 21 months (18.1, 23.2) with Ld, revealing that ELd-treated patients had a median delay of 1 year in TTNT vs. Ld-treated patients,¹⁵ which may be indicative of extended PFS and longer OS.

Study 009, a proof-of-concept, open-label, phase II study, assessed Ebd or bortezomib and dexamethasone (Bd) alone in patients with RRMM.³⁵ In the primary analysis, the study met the primary end point of PFS: the HR was 0.72 (70% CI 0.59, 0.88; stratified log-rank $P = 0.09$), representing a 28%

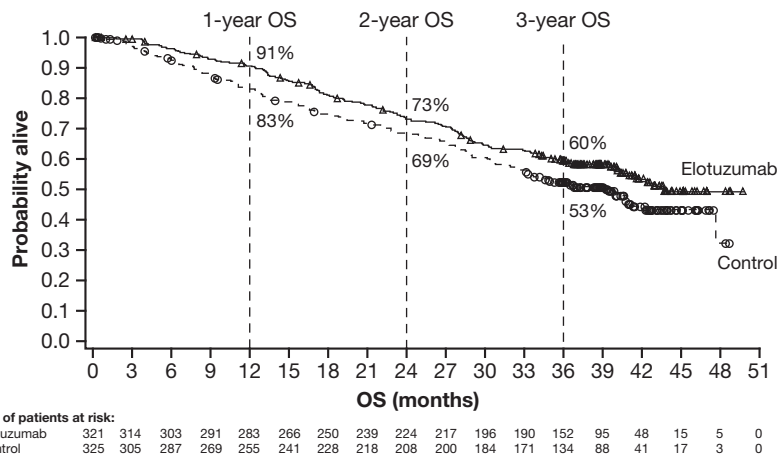


Figure 5 Kaplan–Meier curves showing overall survival (OS) in patients with relapsed or refractory multiple myeloma receiving elotuzumab plus lenalidomide and dexamethasone (“Elotuzumab”) or lenalidomide and dexamethasone (“Control”). Figure from Dimopoulos, M.A. *et al. Br. J. Haematol.* **178**, 896–905 (2017). Reprinted with permission from John Wiley & Sons ©2017.

reduction in the risk of disease progression or death.³⁵ In an updated analysis performed 1 year after the primary analysis, ORR (95% CI) was 66% (55%, 77%) in the EBd arm and 63% (51%, 74%) in the Bd arm.³⁵ Early OS results favored EBd, revealing an HR of 0.61 (70% CI 0.43, 0.85).³⁵ Although these data suggest a survival benefit with EBd over Bd, with a tail-end separation in the Kaplan–Meier curves³⁵ as seen in ELOQUENT-2,¹⁵ it is too early to draw firm conclusions and longer-term follow-up is ongoing.

Safety and tolerability

The safety and tolerability of elotuzumab has been shown to be consistent across clinical studies, which demonstrated minimal incremental toxicity with the addition of elotuzumab to established regimens. This may be due to the lack of SLAMF7 expression in normal tissue,²¹ limiting the toxicity associated with SLAMF7-targeted therapy with elotuzumab.

The most common adverse events (AEs) of any grade in the ELOQUENT-2 study were lymphocytopenia (ELd, 99%; Ld, 98%), anemia (ELd, 96%; Ld, 95%), and thrombocytopenia (ELd, 84%; Ld, 78%).⁵ Infusion reactions (IRs), which are commonly associated with antibody therapy and included pyrexia, chills, and hypertension, were reported in 10% of patients receiving ELd, most of which were Grade 1 or 2 in severity.⁵ Importantly, safety and tolerability data from the 3- and 4-year extended follow-up of ELOQUENT-2 are consistent with the primary analysis.^{15,42} In the 009 study, infection (67%), diarrhea (44%), and constipation (40%) were the most common AEs of any grade in the EBd arms, compared with infection (53%), peripheral neuropathy (36%), and diarrhea (33%) in the Bd arm. The rate of IRs in the 009 study was low; only 5% of patients experienced IRs, all of which occurred in the EBd arm and were Grade 1 or 2 in severity.³⁵

Initial data from study 142 (NCT02612779), an ongoing, phase II, multicenter, single-arm study of EPd in patients with RRMM, indicated that the combination is well tolerated, with a safety profile consistent with ELd.³⁷ Efficacy data from this study will inform therapeutic decisions regarding EPd for patients who experience relapse after, or are refractory to, lenalidomide.

SUMMARY

The data described herein indicate that the I-O agent elotuzumab, when combined with Ld or Bd, provides a durable and clinically meaningful benefit for patients with RRMM. The clinical efficacy data presented could result from elotuzumab inducing long-term effects in the immune system, as has been shown with other immunotherapies. Measurable antitumor activity may take longer to appear with immunotherapies, as responses to such therapies may occur after apparent disease progression, and discontinuation of therapy may not always be appropriate.⁴³ Taking these points into consideration, since a clinical response can take longer to become apparent with immunotherapies than with conventional regimens, caution should be exercised when deciding to terminate therapy with an I-O agent. In the future, it will be important to establish how prior treatment regimens, which may affect immune system function, impact further treatment decisions (i.e., elotuzumab plus anti-KIR agents

or programmed death-1 inhibitor combination therapies). It is evident that additional analyses such as TTNT should be considered when measuring response to treatment with I-O agents, as current standards may not take into consideration delayed clinical benefits or the durability of response vs. the fast/deep responses seen with some regimens; these durable responses have been demonstrated with I-O agents, including elotuzumab.

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