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Elotuzumab: the first approved monoclonal antibody for multiple myeloma treatment

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***Abstract*:** Elotuzumab is a monoclonal antibody directed against the SLAMF7 receptor, expressed on normal and malignant plasma cells with a lower expression on other lymphoid cells such as natural killer (NK) cells. Elotuzumab has no significant antimyeloma activity when given as a single agent to patients with relapsed or refractory multiple myeloma (RRMM). However, when combined with other antimyeloma agents, it results in improved response and outcome. Owing to the results from the landmark ELOQUENT-2 phase III clinical trial, which compared lenalidomide and dexamethasone with or without elotuzumab in patients with RRMM, elotuzumab in combination with lenalidomide and dexamethasone was approved by the American Food and Drug Administration (FDA) in November 2015 for multiple myeloma (MM) patients who received one to three prior lines of therapy. This review will give a brief description of the signaling lymphocytic activation molecule (SLAM) family receptors, the unique SLAMF7 receptor and the mechanism of action of elotuzumab. Thereafter, we will give an overview on its antimyeloma activity in preclinical and clinical trials, including its toxicity profile and management thereof.

Keywords: combined therapy, elotuzumab, immunomodulatory drugs, multiple myeloma, proteasome inhibitors, relapse

Introduction

Multiple myeloma (MM) is a malignant plasma-cell disorder caused by an uncontrolled proliferation of monoclonal plasma cells in the bone marrow. The disease is characterized by end-organ damage, which is manifested primarily as hypercalcemia, renal failure, anemia, and bone lesions (known as the CRAB features). The malignant plasma cells nearly always secrete a monoclonal protein, which helps in the diagnosis, monitoring, and assessment of the response to treatment.

The improved response and survival in MM patients seen for over more than a decade now, is largely attributed to the introduction of two therapeutic modalities, the proteasome inhibitors (PIs) and the immunomodulatory drugs (IMiDs) [Kumar *et al.* 2008]. The PIs consist of bortezomib and the more recently introduced carfilzomib and ixazomib, while the IMiDs include thalidomide and its derivatives lenalidomide and pomalidomide. In addition, a widespread adoption of autologous stem-cell transplantation (ASCT) for fit younger patients has also contributed to improved disease control and survival, initially in the prenovel agents' era [Attal *et al.* 1996; Child *et al.* 2003; Palumbo *et al.* 2004], but also in conjunction with novel-agent-based induction [Palumbo *et al.* 2014; Gay *et al.* 2015]. Unfortunately, cure cannot be achieved in most instances and nearly all patients ultimately relapse. Remission can be regained, but the depth and duration of response to subsequent lines of therapy diminishes with each relapse. Relapses also tend to be progressively more aggressive, ultimately culminating in refractory disease to all available treatments [Dimopoulos *et al.* 2015b]. Hence, many efforts are being directed towards gaining a better understanding of the disease biology and discovering new therapeutic targets that may facilitate deeper and longer remissions and even provide a potential for cure.

During a search for therapeutic targets it was observed that most MM cells express high levels of SLAMF7 (also referred to as CS1, CD subset 2, CD319 or CRACC), a cell-surface receptor

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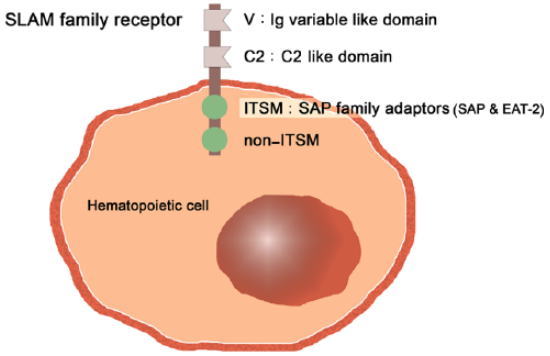

Figure 1. Model structure of SLAM receptor: an extracellular domain containing an Ig variable-like domain [V], a transmembrane C2-like domain [C2] and cytoplasmic domain of two types of immunoreceptor tyrosine-based switch motifs (ITSMs) and non-ITSMs.
Once the extracellular portion is engaged, the signal is transmitted *via* the transmembrane domain to the cytoplasmic domain. Subsequently, the ITSM undergoes phosphorylation that enables the recruitment of SLAM-associated protein (SAP) family adaptors, including SAP and EAT-2. The EAT-2 adaptor is highly expressed in natural killer (NK) cells, and is absent in plasma cells.

that belongs to the signaling-lymphocytic-activation-molecule (SLAM) family. This finding prompted the development of a humanized monoclonal antibody (mAb) against SLAMF7, named elotuzumab (trade name Empliciti, Bristol-Myers Squibb). As a single agent, this drug has no effective antimyeloma activity, but in combination with other anti-MM drugs, elotuzumab exhibits promising results in the relapsed or refractory setting. Herein, we will provide details on the development of elotuzumab from its preclinical stage to its clinical use, and its mechanism of action that triggers plasma cell killing. We will review the results of the clinical trials supporting its use in the relapsed or refractory setting and discuss the potential future incorporation of elotuzumab into the MM treatment paradigms.

The signaling lymphocytic activation molecule family of receptors

The SLAM family receptors are a subset of cluster of differentiation 2 (CD2), a superfamily of immunoglobulins, all located on chromosome 1q23 [Liu *et al.* 2014]. The SLAM receptors are broadly expressed in hematopoietic cells and absent in nonhematopoietic cells [Veillette *et al.* 2013]. A diagrammatic model structure of the receptor is shown in Figure 1.

Most of the SLAM family receptors function as 'self-ligands', that is, they recognize the same receptor present on another cell as a ligand [Veillette, 2010; Cannons *et al.* 2011]. As a consequence, these receptors can be triggered upon interactions with either the same or different types of hematopoietic cells.

SLAMF7: a unique member of the signaling-lymphocytic activation-molecule family

The function of SLAMF7 in MM cells is not well characterized, but it appears to play a critical role in the interaction between MM cells and their adhesion to bone marrow stromal cells (BMSCs) [Tai *et al.* 2008]. In NK cells, engagement of SLAMF7 prompts cell activation as shown in Figure 2.

SLAMF7 has several distinctive features that are not found in other members of the SLAM family. SLAMF7 is uniformly expressed on normal plasma cells and MM cells. It has lower expression on NK cells, and little to no expression in normal tissue [Hsi *et al.* 2008; Tai *et al.* 2008]. This makes the receptor a compelling target for the design of immunotherapy against MM cells [Liu *et al.* 2014]. SLAMF7 is also present on plasma cells at all stages of the disease, regardless of cytogenetic abnormalities [Hsi *et al.* 2008; Van Rhee *et al.* 2009], thus creating the potential for a therapeutic agent which is risk agnostic. SLAMF7 is also found on plasma cells obtained from patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering MM and plasmacytoma, but this has limited clinical implication at this time. The function of SLAMF7 is controlled by the recruitment of Ewing's sarcoma-associated transcript 2 (EAT-2), but not by the SAP (SLAM-associated protein) adaptor. This is in contrast to the other SLAM family members that can bind both SAP and EAT-2 [Perez-Quintero *et al.* 2014].

Mechanisms of action of elotuzumab

Elotuzumab is a humanized IgG1 kappa immunostimulatory monoclonal antibody targeting and binding the extracellular domain of SLAMF7, without interacting with other members of the SLAM family. Elotuzumab binds SLAMF7 expressed both on MM and NK cells, but affects these cells differently. Elotuzumab is usually described as having a dual mechanism of action,

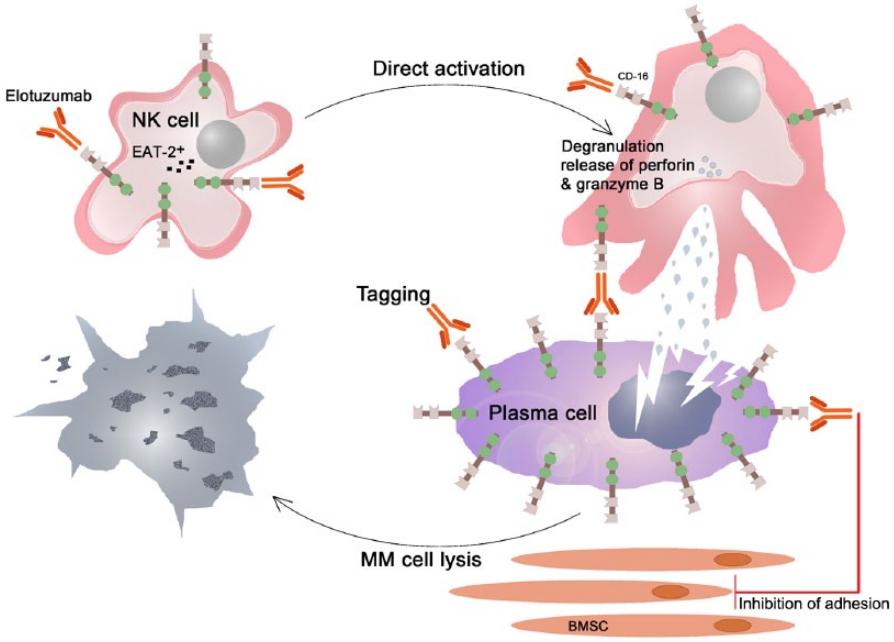

Figure 2. Dual action of elotuzumab: direct activation of NK cells and indirectly by tagging MM cells.
Through antibody-dependent cell-mediated cytotoxicity (ADCC) the tagged MM cells underwent lysis by the substances released from the degranulation of the activated NK cells.
The engagement of SLAMF7 in NK cells prompts their activation *via* phosphorylation of the ITSM domain on the SLMAF7 receptor. As a consequence of the presence of EAT-2 in NK cells, recruitment of SH2 domain containing effector molecules such as phospholipase C (PLC) and phosphatidylinositide 3-kinases (PI3Ks) occurs. This leads to hydrolysis of a subset of membrane phospholipids, activation of calcium flux and extracellular signal-regulated kinase (ERK).

direct and indirect. Elotuzumab's direct effect is *via* activation of NK cells, whereby elotuzumab's Fc portion binds to the activating Fc receptor, CD16, which is the extracellular portion of SLAMF7 on NK cells (Figure 2). This leads to phosphorylation of the two tyrosine-based motifs in the cytoplasmic domain, tyrosines 281 (Y281) and 261(Y261). The phosphorylated Y281 enables the recruitment of EAT-2, which mediates cell activation *via* interaction with the SH2 domain-containing effector molecules such as phospholipase C [PLC] and phosphatidylinositide 3-kinases [PI3Ks] [Clarkson and Brown, 2009; Collins *et al.* 2013]. These effector molecules hydrolyze a subset of the membrane phospholipids, thereby activating calcium fluxes and extracellular signal-regulated kinase [Roncagalli *et al.* 2005; Clarkson and Brown, 2009; Cruz-Munoz *et al.* 2009; Collins *et al.* 2013].

Elotuzumab's indirect effect is by binding the Fab portion of elotuzumab to the SLAMF7 receptor on myeloma cells, in a process known as cell tagging. The tagged cells are then injured and killed by the degranulation of cytotoxic granules from the activated NK cells, constituting the indirect antimyeloma effect of elotuzumab. Owing to EAT-2 absence in MM cells, elotuzumab engagement does not cause activation of MM cells.

Altogether, the simultaneous binding of elotuzumab to both NK and MM cells triggers NK cell activation and the subsequent release of cytotoxic granules. This leads to the killing of MM cells, together with the other components of antibody-dependent cellular cytotoxicity (ADCC) (Figure 2). No evidence for complement-dependent cytotoxicity (CDC) by elotuzumab was so far seen.

Importantly, the activated NK cells' cytotoxicity is directed against SLAMF7-positive MM cells but not against autologous NK cells [Kim *et al.* 2010]. Concerns were raised over elotuzumab-mediated NK cell depletion, but there is no evidence to support that. In a flow cytometry-based study on peripheral lymphocytes in three phase I clinical trials, a 75–90% reduction in the number of circulating lymphocytes was noted after the first elotuzumab infusion, with no difference

between SLAMF7-positive and SLAMF7-negative cells [Neyer *et al.* 2010]. A recovery to normal or near normal lymphocyte count was noted with subsequent elotuzumab administrations. The mechanism for this transient lymphocyte depletion is thought to be cytokine mediated, but remains elusive. No binding of elotuzumab to CD34+ hematopoietic stem cells was found, therefore elotuzumab is not assumed to be stem-cell toxic [Lee *et al.* 2004].

In addition to ADCC, additional mechanisms for killing MM cells have been proposed for elotuzumab and include among others: interfering with the adhesion of MM cells to BMSCs which may disrupt their stimulatory effects on MM cells' growth and survival [Tai *et al.* 2008]; the activation of NK cells by elotuzumab, which may release inflammatory cytokines, leading to the recruitment of other immune-cell types to augment the anti-MM effect. In a xenograft model, elotuzumab alone or in combination with lenalidomide led to recruitment of other NK cells into the tumor, presumably mediated by cytokines released from the activated NK cells [Balasa *et al.* 2015].

Preclinical experience with elotuzumab

In preclinical studies, elotuzumab was able to induce lysis of human MM cell lines that were incubated *in vitro* with peripheral blood mononuclear cells or purified NK cells [Hsi *et al.* 2008; Tai *et al.* 2008; Van Rhee *et al.* 2009]. However, killing of MM cells did not occur when elotuzumab was given alone, implying that its antimyeloma effect requires the action of immune cells. In addition, lack of activity in the absence of NK cells suggests that the antimyeloma effect of elotuzumab is, at least in part, caused by ADCC. These preclinical findings prompted phase I clinical trials of elotuzumab in patients with relapsed or refractory multiple myeloma (RRMM).

Clinical experience with elotuzumab

Phase I clinical trials

In the first-in-human study of elotuzumab, 35 patients with RRMM were treated with elotuzumab in a dose-escalation plan [Zonder *et al.* 2012]. However, no meaningful response was achieved and most patients had a progressive disease while on treatment. This study also suggested that drug clearance is target mediated, and can reach a plateau once all targets are saturated. Therefore, while the plasma level of elotuzumab increases with dose escalation, its clearance decreases. The lack of response despite target saturation on plasma cells and the encouraging preclinical data led to a transition towards trials in which elotuzumab was combined with other antimyeloma drugs.

In a phase I study, elotuzumab was given in escalating doses (2.5–20 mg/kg, days 1 and 11) in combination with bortezomib [1.3 mg/m^2 intravenously (IV), days 1, 4, 8 and 11] in a 21-day cycle [Jakubowiak *et al.* 2012]. Patients (n = 28) with RRMM (median of two prior therapies) were enrolled; 68% of patients were treated with elotuzumab at the maximum dose. The maximum tolerated dose (MTD) was not reached in this trial. The overall response rate (ORR, i.e. partial response or better) was seen in 48% of patients, including in patients refractory to bortezomib. Patients with high-risk cytogenetics demonstrated an ORR of 70% including one patient with a complete response (CR). The median time to progression (TTP) in this trial was 9.5 months.

Elotuzumab was also investigated in combination with lenalidomide and low-dose dexamethasone (Rd) in 29 RRMM patients (median of three prior therapies) [Lonial *et al.* 2012], including six patients with prior lenalidomide exposure (which required a washout period of at least 6 weeks). Elotuzumab was given weekly in three dose cohorts (5, 10, or 20 mg/kg intravenously) in a 28-day cycle in the first two cycles, and biweekly in each subsequent cycle; lenalidomide was given 25 mg (days 1–21); and dexamethasone was given 40 mg weekly. The ORR was 82%. The response rate among lenalidomide-exposed patients was 33%, including the lenalidomide-refractory patient. This suggests that elotuzumab, lenalidomide and dexamethasone combination therapy may also be effective in patients previously exposed to lenalidomide. Responses were durable, with a median TTP in the 20 mg/kg cohort not reached after a median of 16 months of follow up. No dose-limiting toxicities were found with the above doses. Elotuzumab, therefore, appeared synergistic with lenalidomide and dexamethasone in RRMM and this combination was elected for further clinical investigation.

Phase II clinical trials

Elotuzumab, in combination with bortezomib. A phase II trial randomized 152 RRMM patients

to either elotuzumab in combination with bortezomib and dexamethasone (EBd arm, $n = 77$), or bortezomib and dexamethasone (Bd arm, $n = 75$). Elotuzumab (10 mg/kg IV) was administered weekly in cycles one and two, on days 1 and 11 in cycles three to eight, and then biweekly. Bortezomib (1.3 mg/m^2 IV/subcutaneously) was administered on days 1, 4, 8 and 11. Half of the patients had prior bortezomib exposure. The ORR was 65% in the EBd arm *versus* 63% in the Bd arm. The median progression-free survival (PFS) in the EBd arm was 10 months *versus* 7 months in the Bd arm ($p = 0.08$). In this trial, polymorphism in the FCYRIIIa receptor on NK cells (to which the Fc portion of elotuzumab binds) might had an impact on elotuzumab efficacy. Patients with a high-affinity allele treated with EBd had a median PFS of 22.3 months compared with 9.8 months in patients with low-affinity allele treated with EBd, with little power to demonstrate statistical significance. Therefore, the role of FCYRIIIa receptor polymorphism in elotuzumab efficacy should be further investigated in trials incorporating elotuzumab into the treatment scheme.

Elotuzumab in combination with lenalidomide. Patients ($n = 73$) with RRMM previously treated with one to three prior therapies were randomized to elotuzumab 10 or 20 mg/kg IV (weekly in cycles one and two and biweekly in cycle three onwards) plus lenalidomide 25 mg (days 1–21) and dexamethasone 40 mg weekly [Richardson *et al.* 2015]. Treatment was given until progression, unacceptable toxicity or death. The ORR was 84%, higher in the 10 mg/kg cohort compared with the 20 mg/kg cohort (92% *versus* 76%, respectively). The response difference between dose cohorts might represent an underpowered study to detect differences between groups or a more favorable response at the 10 mg/kg dose, especially as saturation of SLAMF7 on bone marrow-derived myeloma cells was similar between 10 mg/kg and 20 mg/kg doses [Zonder *et al.* 2012]. With a median follow up of 18 months, the response advantage in the 10 mg/kg cohort was translated into longer PFS as compared with the higher-dose cohort (median 27 months *versus* 18.6 months, respectively). The number of prior lines of therapy did not impact the likelihood of response [ORR for patients with 1 ($n = 33$) or at least two prior therapies ($n = 40$) was 91% and 78%, respectively] with a similar PFS (median 25 and 21 months, respectively). Based on these encouraging results, two phase III trials (ELOQUENT-1 and ELOQUENT-2) were launched, comparing the efficacy and the safety of lenalidomide and low-dose dexamethasone (Rd) with or without elotuzumab in patients with newly diagnosed myeloma and RRMM patients, respectively.

Phase III clinical trials with elotuzumab

ELOQUENT-2 is a randomized, multicenter, phase III trial which compared the efficacy and safety of Rd with or without elotuzumab in RRMM patients after one to three prior lines of therapy [Lonial *et al.* 2015]. Prior lenalidomide exposure was seen in 10% of study population (as permitted by the study protocol), but for enrollment these patients had not to be lenalidomide-refractory. A total of 646 patients were randomized to receive 28-day cycles of lenalidomide 25 mg (days 1–21) and dexamethasone 40 mg weekly with or without elotuzumab (10 mg/kg IV on days 1, 8, 15 and 22 in the first two cycles and on days 1 and 15 from cycle three). A total of 321 patients were randomized to the Rd-elotuzumab (elotuzumab arm) and 325 to the Rd (control arm). The ORR in the elotuzumab arm was 79% compared with 66% in the control arm ($p < 0.0001$). With a median follow up of nearly 25 months, the median PFS was 19.4 months in the elotuzumab arm compared with 14.9 months in the control arm [hazard ratio (HR) 0.7; 95% confidence interval (CI) 0.57–0.85; $p < 0.0001$]. The PFS advantage was noted also at 3 years (HR 0.73; 95% CI 0.6–0.89) [Dimopoulos *et al.* 2015a]. The advantage of the elotuzumab arm was seen across different subgroups, including patients with adverse cytogenetics, patients with renal impairment and those with prior lenalidomide treatment (although this must be taken with caution, as only small number of patients had prior lenalidomide exposure). The last updated analysis presented in late 2015 also points to overall-survival advantage for the elotuzumab arm (median 43.7 months compared with 39.6 months in the control arm; $p = 0.0257$) [Dimopoulos *et al.* 2015a], but longer follow up is needed to reconfirm that. Both arms were well tolerated in terms of toxicity, with comparable toxicity profile between arms. Based on the ELOQUENT-2 trial, elotuzumab was granted FDA approval in November 2015, for the treatment of multiple myeloma in combination with lenalidomide and dexamethasone for patients who have received one to three prior therapies.

ELOQUENT-1, with a similar design to ELOQUENT-2, but performed in the newly

diagnosed setting, and randomized 750 patients ineligible for stem-cell transplantation to Rd in combination with elotuzumab, or to Rd alone. Results of this trial have not been published yet and are expected in 2016.

Elotuzumab in renal dysfunction

A phase Ib study was performed to investigate the effect of various degrees of renal function on elotuzumab pharmacokinetics and tolerability [Berdeja *et al.* 2015]. In this study, elotuzumab was given in combination with lenalidomide and dexamethasone. Maximum elotuzumab concentration in the serum, and serum concentration over time did not differ significantly between patients with normal kidney function ($n = 8$), those with severe renal dysfunction not requiring dialysis ($n = 9$) and those with end-stage renal disease requiring dialysis ($n = 9$). Toxicity was also comparable. Although the study was too small to assess efficacy, no significant difference in response rate was observed across the various renal function subgroups.

Adverse events

In the ELOQUENT-2 trial, serious adverse events (AEs) were reported in 65% and 57% in the elotuzumab and control groups, respectively. The most common grade 3 or 4 hematological AEs observed in the elotuzumab arm, were lymphocytopenia (77% *versus* 49% in the control) and neutropenia (34% *versus* 44% in the control), while fatigue (8% in both arms) represented the most common nonhematological grade 3 or 4 AE, followed by diarrhea and pyrexia (5% and 3% in each arm, respectively). This lymphocytopenia may be a result of changes in lymphocyte trafficking, including in NK cells, as discussed above. However, there was no clinical evidence of immune dysregulation associated with the use of elotuzumab.

Rates for grade 3 or 4 anemia, thrombocytopenia, neutropenia, cardiac disorders, and renal disorders were similar between both groups in the ELOQUENT-2 trial. There was also no difference in rates of infections after adjustment for drug exposure (197 events per 100 patient-years in both arms), although an increased rate of herpes zoster infection (4.1 *versus* 2.2 per 100 patient-years) observed in the elotuzumab group. Importantly, there was no change in pain or health-related quality of life among patients who received elotuzumab, supporting the tolerability of this agent.

Infusion-related reactions, manifesting as pyrexia, chills and hypertension were the most notable of grade 1 or 2 toxicity, seen in 10% of elotuzumab-treated patients (grade 1 or 2 in 29 patients, grade 3 in four patients and no grade 4 or 5). Most of these reactions (70%) occurred during the first infusion, and resolved in all but two patients (1%), who both discontinued treatment because of the infusion reaction. These reactions may be mediated by direct effects of elotuzumab on immune-effector cells, and were found to correlate with an early increase in proinflammatory cytokines [Collins *et al.* 2013]. The majority of these infusion reactions have been mitigated with premedication that included steroids, antihistamines and acetaminophen given 30–60 min before infusion. An emphasis must be placed on prevention of these AEs to avoid drug discontinuation that may in turn adversely affect treatment efficacy.

In the ELOQUENT-2 trial, death from AEs was observed in five patients (2%) in the elotuzumab group [infection ($n = 2$), pulmonary embolism ($n = 1$), gastrointestinal cancer ($n = 1$) and myelodysplastic syndrome ($n = 1$)], compared with six patients (2%) in the Rd group [infection ($n = 5$) and pulmonary embolism ($n = 1$)).

A similar profile of grade 3 or 4 AEs was observed in the phase I trial of elotuzumab in combination with bortezomib and dexamethasone and the major toxicity was attributed to infusion reactions. However, AEs were more frequent in the EBd arm when compared with the Bd arm (grade 3 or 4 AEs in 71% of patients in the EBd arm compared with 60% of patients in the Bd arm).

In summary, the addition of elotuzumab to lenalidomide was not associated with excess toxicity, apart from preventable infusion-related reactions, while its addition to bortezomib seems less synergistic and associated with increased AEs.

Miscellaneous

Interference with immunofixation and serum protein electrophoresis (SPEP) assays has been reported in patients treated with elotuzumab, as the drug-monoclonality property may be detected on SPEP in the early gamma region. Thus, elotuzumab-driven persistence of an IgG-kappa band

may lead to underestimation of CR in patients with IgG-kappa monoclonal band, or to suspicion of new clonal emergence in patients with non-IgG kappa myeloma. Two approaches can help in solving this diagnostically challenging phenomenon. First, the elotuzumab band may have a different migration pattern in the gamma region than the myeloma monoclonal protein. Second, commercialized antielotuzumab antibodies may specify the presence of elotuzumab in the gamma region of the SPEP, but none are currently commercially available.

Antibodies to elotuzumab were found in 39% of the patients treated with elotuzumab alone [Zonder *et al.* 2012], and in 15% of the patients in the ELOQUENT-2 trial [Lonial *et al.* 2015]. This phenomenon may lead to a reduced response to elotuzumab. Similarly, the density of SLAMF7 on the surface of MM and NK cells may also play a role in the response to elotuzumab, as may the availability of NK cells. These assumptions have to be checked, but currently there are no data to support or refute this hypothesis.

Unlike daratumumab, the second approved monoclonal antibody in MM that targets the CD38 (expressed on plasma cells but on red blood cells as well), elotuzumab does not interfere with blood-bank compatibility tests, as SLAMF7 is not expressed on red blood cells.

Conclusion

A therapeutic approach utilizing multidrug combinations has been increasingly used in MM, both in newly diagnosed patients and in RRMM. This approach has proved to be more effective than single agent or doublets. As a single agent, elotuzumab did not produce any significant activity in the early clinical trials, while the integration of elotuzumab into different combination regimens represents the elotuzumab-treatment paradigm. The optimal elotuzumab-containing regimen has not been determined yet, but the most promising results so far come from the incorporation of elotuzumab into the Rd backbone with no excessive toxicity.

Treatment options in RRMM have greatly increased in the past decade, with numerous combination options available. However, until further data appear, the use of elotuzumab outside a clinical trial setting should be in combination with lenalidomide–dexamethasone (also known as ERd). Since responses to ERd were lower in patients exposed or refractory to lenalidomide, this combination is better utilized in patients not previously exposed to lenalidomide. Whether to combine elotuzumab with Rd or to recommend Rd alone is a matter of elotuzumab availability and patient preferences. However, patients with high-risk MM should be strongly considered for the triplet combination to allow for a better chance of long-term disease control, although data are limited to reinforce that recommendation. Choice of the ERd triplet over other available triplets (such as ixazomib and Rd) should be guided by prior responses, drug availability and patient preferences.

New elotuzumab-containing combinations of special interest include: the addition of elotuzumab to lenalidomide-bortezomib-dexamethasone in newly diagnosed patients [ClinicalTrials.gov identifier: NCT02375555]; elotuzumab in combination with lenalidomide as maintenance treatment following ASCT [ClinicalTrials.gov identifier: NCT02420860]; and elotuzumab in combination with Rd in high-risk smoldering MM [ClinicalTrials.gov identifier: NCT02279394]. Elotuzumab is also being evaluated in combination with other monoclonal antibodies, such as an ongoing phase I study of elotuzumab in combination with either Lirilumab [ClinicalTrials.gov identifier: NCT02252263] or Urelumab [ClinicalTrials.gov identifier: NCT02252263]. Also, a randomized controlled trial with pomalidomide and dexamethasone with or without nivolumab (an anti-PD-1 monoclonal antibody). This study is designed to include an exploratory arm in which patients treated with pomalidomide and dexamethasone, and progressed on this regimen, will be allowed to crossover to the exploratory arm, in which the treatment will consist of elotuzumab, nivolumab, pomalidomide and dexamethasone (EN-Pd) [ClinicalTrials.gov identifier: NCT02726581]. These studies are an important step towards optimizing elotuzumab integration into MM therapy.

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Conflict of interest statement

The authors report no conflict of interests.

References

Attal, M., Harousseau, J., Stoppa, A., Sotto, J., Fuzibet, J., Rossi, J. *et al.* (1996) A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. *N Engl J Med* 335: 91–97.

Balasa, B., Yun, R., Belmar, N., Fox, M., Chao, D., Robbins, M. *et al.* (2015) Elotuzumab enhances natural killer cell activation and myeloma cell killing through interleukin-2 and TNF-α pathways. *Cancer Immunol Immunother* 64: 61–73.

Berdeja, J., Jagannath, S., Zonder, J., Badros, A., Kaufman, J., Manges, R. *et al.* (2015) Pharmacokinetics and safety of elotuzumab combined with lenalidomide and dexamethasone in patients with multiple myeloma and various levels of renal impairment: results of a phase Ib study. *Clin Lymphoma Myeloma Leuk* 16: 129–138.

Cannons, J., Tangye, S. and Schwartzberg, P. (2011) SLAM family receptors and SAP adaptors in immunity. *Annu Rev Immunol* 29: 665–705.

Child, J., Morgan, G., Davies, F., Owen, R., Bell, S., Hawkins, K. *et al.* (2003) High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 348: 1875–1883.

Clarkson, N. and Brown, M. (2009) Inhibition and activation by CD244 depends on CD2 and phospholipase C-gamma1. *J Biol Chem* 284: 24725–24734.

Collins, S., Bakan, C., Swartzel, G., Hofmeister, C., Efebera, Y., Kwon, H. *et al.* (2013) Elotuzumab directly enhances NK cell cytotoxicity against myeloma *via* CS1 ligation: evidence for augmented NK cell function complementing ADCC. *Cancer Immunol Immunother* 62: 1841–1849.

Cruz-Munoz, M., Dong, Z., Shi, X., Zhang, S. and Veillette, A. (2009) Influence of CRACC, a SLAM family receptor coupled to the adaptor EAT-2, on natural killer cell function. *Nat Immunol* 10: 297–305.

Dimopoulos, M., Lonial, S., White, D., Moreau, P., Palumbo, A., San Miguel, J. *et al.* (2015a) ELOQUENT-2 update: a phase III, randomized, open-label study of elotuzumab in combination with lenalidomide/dexamethasone in patients with relapsed/refractory multiple myeloma – 3 year safety and efficacy follow-up. *Blood* 126: 28.

Dimopoulos, M., Richardson, P., Moreau, P. and Anderson, K. (2015b) Current treatment landscape for relapsed and/or refractory multiple myeloma. *Nat Rev Clin Oncol* 12: 42–54.

Gay, F., Oliva, S., Petrucci, M., Conticello, C., Catalano, L., Corradini, P. *et al.* (2015) Chemotherapy plus lenalidomide *versus* autologous transplantation, followed by lenalidomide plus prednisone *versus* lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase III trial. *Lancet Oncol* 16: 1617–1629.

Hsi, E., Steinle, R., Balasa, B., Szmania, S., Draksharapu, A., Shum, B. *et al.* (2008) CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. *Clin Cancer Res* 14: 2775–2784.

Jakubowiak, A., Benson, D., Bensinger, W., Siegel, D., Zimmerman, T., Mohrbacher, A. *et al.* (2012) Phase I trial of anti-CS1 monoclonal antibody elotuzumab in combination with bortezomib in the treatment of relapsed/refractory multiple myeloma. *J Clin Oncol* 30: 1960–1965.

Kim, J., Mathew, S., Patel, R., Pertusi, R. and Mathew, P. (2010) Altered expression of signalling lymphocyte activation molecule (SLAM) family receptors CS1 (CD319) and 2B4 (CD244) in patients with systemic lupus erythematosus. *Clin Exp Immunol* 160: 348–358.

Kumar, S., Rajkumar, S., Dispenzieri, A., Lacy, M., Hayman, S., Buadi, F. *et al.* (2008) Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 111: 2516–2520.

Lee, J., Boles, K. and Mathew, P. (2004) Molecular and functional characterization of a CS1 (CRACC) splice variant expressed in human NK cells that does not contain immunoreceptor tyrosine-based switch motifs. *Eur J Immunol* 34: 2791–2799.

Liu, Y., Szmania, S. and Van Rhee, F. (2014) Profile of elotuzumab and its potential in the treatment of multiple myeloma. *Blood Lymphat Cancer* 2014: 15–27.

Lonial, S., Dimopoulos, M., Palumbo, A., White, D., Grosicki, S., Spicka, I. *et al.* (2015) Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med* 373: 621–631.

Lonial, S., Vij, R., Harousseau, J., Facon, T., Moreau, P., Mazumder, A. *et al.* (2012) Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma. *J Clin Oncol* 30: 1953–1959.

Neyer, L., Ding, H., Chen, D., Sheridan, J., Rice, A., Balasa, B. *et al.* (2010) Effect of elotuzumab on circulating lymphocytes, chemokines, and cytokines in multiple myeloma patients. *Blood* 116: 4070.

Palumbo, A., Bringhen, S., Bertola, A., Cavallo, F., Falco, P., Massaia, M. *et al.* (2004) Multiple myeloma: comparison of two dose-intensive melphalan regimens [100 *versus* 200 mg/m(2)]. *Leukemia* 18: 133–138.

Palumbo, A., Cavallo, F., Gay, F., Di Raimondo, F., Ben Yehuda, D., Petrucci, M. *et al.* (2014) Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med* 371: 895–905.

Perez-Quintero, L., Roncagalli, R., Guo, H., Latour, S., Davidson, D. and Veillette, A. (2014) EAT-2, a SAP-like adaptor, controls NK cell activation through phospholipase Cγ, Ca++, and Erk, leading to granule polarization. *J Exp Med* 211: 727–742.

Richardson, P., Jagannath, S., Moreau, P., Jakubowiak, A., Raab, M., Facon, T. *et al.* (2015) Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: final phase II results from the randomised, open-label, phase Ib-2 dose-escalation study. *Lancet Haematol* 2: e516–527.

Roncagalli, R., Taylor, J., Zhang, S., Shi, X., Chen, R., Cruz-Munoz, M. *et al.* (2005) Negative regulation of natural killer cell function by EAT-2, a SAP-related adaptor. *Nat Immunol* 6: 1002–1010.

Tai, Y., Dillon, M., Song, W., Leiba, M., Li, X., Burger, P. *et al.* (2008) Anti-CS1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu. *Blood* 112: 1329–1337.

Van Rhee, F., Szmania, S., Dillon, M., van Abbema, A., Li, X., Stone, M. *et al.* (2009) Combinatorial efficacy of anti-CS1 monoclonal antibody elotuzumab (HuLuc63) and bortezomib against multiple myeloma. *Mol Cancer Ther* 8: 2616–2624.

Veillette, A. (2010) SLAM-family receptors: immune regulators with or without SAP-family adaptors. *Cold Spring Harb Perspect Biol* 2: a002469.

Veillette, A. and Guo, H. (2013) CS1, a SLAM family receptor involved in immune regulation, is a therapeutic target in multiple myeloma. *Crit Rev Oncol Hematol* 88: 168–177.

Zonder, J., Mohrbacher, A., Singhal, S., Van Rhee, F., Bensinger, W., Ding, H. *et al.* (2012) A phase I, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. *Blood* 120: 552–559.