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**Review Article**

# Elotuzumab for the Treatment of Relapsed or Refractory Multiple Myeloma, with Special Reference to its Modes of Action and SLAMF7 Signaling

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**Abstract. Elotuzumab, targeting signaling lymphocytic activation molecule family 7 (SLAMF7), has been approved in combination with lenalidomide and dexamethasone (ELd) for relapsed/refractory multiple myeloma (MM) based on the findings of the phase III randomized trial ELOQUENT-2 (NCT01239797). Four-year follow-up analyses of ELOQUENT-2 have demonstrated that progression-free survival was 21% in ELd versus 14% in Ld. Elotuzumab binds a unique epitope on the membrane IgC2 domain of SLAMF7, exhibiting a dual mechanism of action: natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and enhancement of NK cell activity. The ADCC is mediated through engagement between Fc portion of elotuzumab and FcγRIIIa/CD16 on NK cells. Enhanced NK cell cytotoxicity results from phosphorylation of the immunoreceptor tyrosine-based switch motif (ITSM) that is induced *via* elotuzumab binding and recruits the SLAM-associated adaptor protein EAT-2. The coupling of EAT-2 to the phospholipase Cγ enzymes SH2 domain leads to enhanced $Ca^{2+}$ influx and MAPK/Erk pathway activation, resulting in granule polarization and enhanced exocytosis in NK cells. Elotuzumab does not stimulate the proliferation of MM cells due to a lack of EAT-2. The inhibitory effects of elotuzumab on MM cell growth are not induced by the lack of CD45, even though SHP-2, SHP-1, SHIP-1, and Csk may be recruited to phosphorylated ITSM of SLAMF7. ELd improves PFS in patients with high-risk cytogenetics, i.e. t(4;14), del(17p), and 1q21 gain/amplification. Since the immune state is paralytic in advanced MM, the efficacy of ELd with minimal toxicity may bring forward for consideration of its use in the early stages of the disease.**

**Keywords:** Elotuzumab, Multiple myeloma, SLAMF7, SLAM-associated protein (SAP), EAT-2.

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**Introduction.** Multiple myeloma (MM) is the second most common hematological malignancy in Western countries with 62 % of patients being older than 65 years at the time of diagnosis.[1,2] According to the National Cancer Center in Japan, the number of patients with MM was 6697 in

2013, and that of deaths was 4129 in 2015; the five-year relative survival rate was 36.4% for MM patients diagnosed between 2000 to 2008.[3] Regarding morbidity in 2015 based on age and gender, the proportions of patients older than 65 years were 90.1% for females and 87.9% for males, while those of patients older than 75 years were 69.1% for females and 60.9% for males.[3] Due to its high incidence in the elderly and its incurability, there is an urgent need to develop effective and less toxic combination therapies for unfit or frail patients with MM.

The treatment outcomes of MM have significantly improved in the last decade or two due to the success of molecular targeting agents including thalidomide, lenalidomide, and bortezomib.[4-7] According to the findings of a number of clinical trials, triplet induction therapy containing proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) is the standard care for fit patients, whereas doublet induction therapy containing PIs or IMiD is administered to frail patients. In addition to the development of second- and third-generation PIs and IMiDs, monoclonal antibodies (mAb) will open a new era of MM treatments that selectively eliminate the malignant clone and reverse tumor-mediated immune paralysis.[8-12] Elotuzumab is the first therapeutic mAb targeting SLAMF7 that has been approved for relapsed or refractory (RR) MM. It induces natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and exerts stimulatory effects on immune cells, particularly NK cells, which are mediated by the engagement of elotuzumab with SLAMF7.[13,14] Clinically, the combination of elotuzumab with lenalidomide and dexamethasone (ELd) is a promising treatment for frail patients regardless of the cytogenetic risk.[8]

In this review, we will focus on the efficacy and safety of elotuzumab for the treatment of RRMM. We will also discuss the biological characteristics of SLAMF7 and SLAM-associated protein (SAP), their expression and possible functions in normal cells and hematological malignancies, as well as the modes of action of elotuzumab. We will then propose optimal use and future directions for elotuzumab in the treatment of MM.

**Elotuzumab for the Treatment of RRMM.** *Efficacy and safety of elotuzumab in combination with lenalidomide and dexamethasone*. Elotuzumab was approved in combination with lenalidomide and dexamethasone (Ld) for patients with RRMM based on the findings of the phase III, randomized, open-label, multicenter trial, ELOQUENT-2 (NCT01239797).[8] In ELOQUENT-2, the efficacy of elotuzumab combined with Ld (ELd) was evaluated for patients with RRMM who previously received one to three regimens. ELOQUENT-1 is still ongoing for patients with newly diagnosed MM (NDMM). ELOQUENT-2, in which 646 patients were randomized into ELd or Ld, demonstrated significant increase in overall response rate (ORR) and median PFS in ELd (**Table 1**).[8] Progression-free survival (PFS) has significantly improved in patients older than 75 years, particularly those with refractory disease and high-risk cytogenetic abnormalities (CA), i.e. t(4;14), del(17p), and 1q21 gain/amplification. A subanalysis of the Japanese population from ELOQUENT-2 revealed similar outcomes to the global study as well as to the Japanese phase I study; ORR were 84% in ELd vs 86% in Ld, and PFS rates at two years were 48% in ELd vs 18% in Ld.[15,16] A three-year follow-up and post-hoc analyses of ELOQUENT-2 recently confirmed that ELd provided a durable improvement in efficacy; ORR were 79% in ELd and 66% in Ld.[17] ELd reduced the risk of disease progression/death by 27% versus Ld. Interim overall survival (OS) at 3 years was 60% with ELd versus 53% with Ld. Serum M-protein dynamic modelling showed slower tumor regrowth with ELd.[17] An extended four-year follow-up of ELOQUENT-2 also demonstrated a sustained improvement in PFS in ELd versus Ld (21% vs 14%).[18] Patients with ≥ very good partial response (VGPR) had the greatest reduction (35%) in risk of progression/death. Median OS was 48% in ELd versus 40% in Ld.[18] These results further support the durable efficacy of ELd.

The safety, tolerability, and pharmacokinetics of intravenous elotuzumab have been assessed in a Phase I study of dose-escalation monotherapy at 10–20 mg/kg, demonstrating no maximum tolerated dose and modest activity with a best response of stable disease (SD).[19] The other two Phase I or Phase I/II studies also reported that the safety and tolerability of elotuzumab in combination with bortezomib or lenalidomide were acceptable.[20-22] Severe adverse events (AEs) in ELOQUENT-2 were 65% in ELd versus 57% in Ld; the most common grade 3/4 hematological

AEs in ELd vs Ld were lymphocytopenia (77% vs 49%) followed by neutropenia (34% vs 44%), thrombocytopenia (19% vs 20%), and anemia (19% vs 21%).[8] Grade 3/4 hematological AEs, except for lymphocytopenia, were less frequent with ELd than with Ld, which may be of particular benefit for frail elderly patients. Common non-hematological grade 3/4 AEs were fatigue (8% in both arms), diarrhea (5% in ELd vs 4% in Ld), and pyrexia (5% and 3% in both arms). Lymphocytopenia may develop as a result of the migration of peripheral lymphocytes including NK cells into the involved tissue sites.[19] Infusion reactions (IRs) appearing as pyrexia, chills, and hypertension were very limited when compared with daratumumab, observed in 10% of ELd versus 45.3-50% of daratumumab-containing regimens.[9-11] Premedication with antihistamines, acetaminophen, and dexamethasone have successfully prevented IRs, and now are standard of care as part of the treatment with this antibody treatment. A phase II study demonstrated that a 1-hour infusion of elotuzumab provided convenient alternative dosing.[23]

*Elotuzumab in combination with bortezomib or thalidomide.* The efficacy of elotuzumab combined with bortezomib or thalidomide was also evaluated (**Table 1**).[24,25] A randomized Phase II study of elotuzumab combined with bortezomib and dexamethasone (EBd) versus bortezomib and dexamethasone (Bd), in which 152 patients with RRMM were randomized into EBd or Bd, has demonstrated slight increase in ORR and median PFS in EBd.[24] Grade 3/4 AEs were reported in 53 patients (71%) with EBd versus 45 patients (69%) with Bd; the most common grade 3 or higher AEs of EBd vs Bd were infections (21% vs 13%) and thrombocytopenia (9% vs 17%).[24] Grade 3/4 peripheral neuropathy (9% vs 12%), paresthesia (0% vs 5%), and thrombocytopenia were slightly less frequent in EBd than in Bd.[24] Grade 1/2 IRs were observed in 5% of EBd; there were no grade 3 or higher IRs.

The efficacy of 10 mg/kg elotuzumab combined with 50-200 mg thalidomide and 40 mg dexamethasone (ETd) (with or without 50 mg cyclophosphamide), was also evaluated in a Phase II single-arm study with minimal additional toxicity.[25] IRs were observed in 15% of ETd. This clinical trial showed ORR of 38% in 40 RRMM patients with a median of three prior regimens including bortezomib (98%) and lenalidomide (73%); median PFS and OS were 3.9 months and 16.3 months, respectively.[25] These findings suggest that the combination of elotuzumab with bortezomib or thalidomide has potential as treatment option for patients with RRMM.

**Table 1.** Antibody-containing novel combination regimens for RRMM.

| Regimen | Phase | N | ≧PR (%) | ≧VGPR (%) | ≧CR (%) | Median PFS (mo.) | References (Number) |
|---|---|---|---|---|---|---|---|
| Elotuzumab+Ld vs Ld | III | 321 vs 325 | 78.5 vs 65.5 | 31 vs 29 | 4 vs 7 | 19.4 vs 14.9 | Lonial S et al., 2015 (8) |
| Elotudumab+Bd vs Bd | II | 77 vs 75 | 65 vs 63 | 37 vs 27 | 4 vs 4 | 9.7 vs 6.9 | Jakubowiak A et al., 2016 (24) |
| Elotudumab+Td | II | 40 | 38 | 18 | 8 | 3.9 | Mateos MV et al., 2016 (25) |
| Daratumumab+Bd vs Bd | III | 251 vs 247 | 82.9 vs 63.2 | 59.2 vs 29.1 | 19.2 vs 9.0 | 60.7% vs 26.9% (at 12-mo) | Palumbo A et al., 2016 (9) |
| Daratumumab+Ld vs Ld | III | 286 vs 283 | 92.9 vs 76.4 | 75.8 vs 44.2 | 43.1 vs 19.2 | 83.2% vs 60.1% (at 12-mo) | Dimopoulos MA et al., 2016 (10) |
| Daratumumab+Pd | Ib | 103 | 60 | 42 | 17 | 8.8 (at a median follow-up of 13.1 mo.) | Chari A et al., 2017 (11) |
| Pembrolizumab+Pd | II | 48 | 60 | 27 | 8 | 17.4 (at a median follow-up of 15.8 mo.) | Badros A et al., 2017 (12) |

Rd, lenalidomide and dexamethazone; Bd, bortezomib and dexamethasone; Td, thalidomide and dexamethasone; Pd, pomalidomide and dexamethasone.

## Biological Characteristics of SLAMF7 and its Adaptor Proteins.

*Biological characteristics of SLAMF receptors.* SLAMF7 is one of the nine SLAMF receptors (SLAMF1-9) belonging to the CD2 subset of the immunoglobulin superfamily. It was originally identified as CS1 (CD2 subunit 1) by a subtractive hybridization between naïve B cell cDNA and that of memory B cells and plasma cells.[13] Molecular cloning revealed that CS1 is a novel human NK cell receptor.[26] SLAMF7 may also play a growth-promoting role and be involved in the autocrine expression of cytokines in normal B cells,[27] whereas its function in normal plasma cells currently remains unknown.

SLAMF receptors are type I transmembrane glycoproteins, except a glycosylphosphatidylinositol-anchored protein SLAMF2, which is widely expressed in hematopoietic cells but not in other tissues (**Table 2**). The genes encoding SLAMF receptors are reported to be clustered within an approximately 350-kb region at 1q23.3.[28,29] Our fluorescence *in situ* hybridization (FISH) study assigned SLAMF7 to 1q21.3 using the BAC clone RP11-404F10 containing SLAMF2, SLAMF7, and SLAMF3 (Sakamoto N, Taniwaki M et al., unpublished) (**Figures 1A** and **1B)**. SLAMF7 is also included in the amplicon of chromosome 1q gain/amplification, which is a high-risk CA frequently detected in RRMM (Sakamoto N, Taniwaki M et al., unpublished) (**Figures 1C** and **1D**).

SLAMF receptors are structurally characterized by distal Ig variable-like (IgV) and proximal C2-like (IgC2) domains within an extracellular portion and one or more immunoreceptor tyrosine-based switch motifs (ITSMs) within the cytoplasmic portion. The exception is that SLAMF3 has duplicated IgV-IgC2 sequences, and SLAMF8 and SLAMF9 lack tyrosine motifs.[28,30,31] SLAMF receptors 1, 3, 5 to 7, and 9, are "self-ligands" that recognize the same receptor molecule on another cell as a ligand; SLAMF2 and SLAMF4 are "co-ligands" that recognize each other.[27,28,32] Interactions between SLAMF receptors occur at their IgV domains between identical or different types of hematopoietic cells. The engagement of SLAMF receptors mediates regulatory effects on immune cells in the presence of the SLAM-associated protein (SAP) family of adaptors.[26,33,34] Two SAP family adaptors have been identified in humans: SAP (SH2D1A) and EWS-Fli1-activated transcript-2 (EAT-2, SH2D1B), which are intracellular proteins containing the Src homology2 (SH2) domain devoid of enzymatic

**Table 2.** Cytogenetic abnormalities valuable to predict prognosis of MM with candidate genes.

| Cytogenetic findings | Frequency (%) | Band | Candidate genes | | Prognosis |
|---|---|---|---|---|---|
| **Primary changes** | | | | | |
| *IGH* translocation | 45-55 | | | | |
| t(11;14) | 15-20 | 11q13 | *CCND1* | *MYEOV* | Good |
| t(4;14) | 15 | 4p16 | *FGFR3* | *MMSET* | Poor |
| t(14;16) | 5-10 | 16q23 | *MAF* | *WWOX* | Poor |
| t(14;20) | 1-2 | 20q11 | *MAFB* | | Poor |
| t(8;14), t(8;22) | 1 | 8q24 | *MYC* | *PVT1* | Poor |
| Hyperdiploidy | 45-55 | | | | Good |
| **Secondary changes** | | | | | |
| 8q24 translocation | 13-22 | 8q24 | *MYC* | *PVT1* | Poor |
| 8q24.1 gain | 15 | 8q24.1 | *MYC* | *PVT1* | Unknown |
| del(13q)/-13 | 50 | 13q14 | *RB* | | Poor by metaphase cytogenetics |
| | | 13q13 | *NBEA (BCL8B)* | | |
| del(17p) | 10-15 | 17p13 | *TP53* | | Poor |
| 1q21 gain/amplification | 30-40 | 1q21-23 | *PDZK1, CKS1B, BCL9, MUC1, RAB25, FCRL4 (IRTA1), FCRL5 (IRTA2), SLAMF7* | | Poor |

*MYEOV*, Myeloma-overexpressed; *MMSET*, multiple myeloma SET domain; *WWOX*, WW domain containing oxidoreductase; *PVT1*, plasmacytoma variant translocation 1; *NBEA*, neurobeachin; *PDZK1*, PDZ domain containing 1; *CKS1B*, cyclin-dependent kinases regulatory subunit 1; *MUC1*, mucin 1, cell surface associated; *RAB25*, RAB25, member RAS oncogene family; *FCRL*, Fc receptor-like protein gene; *IRTA*, immune receptor translocation-associated protein; *SLAMF7*, signaling lymphocyte activation molecule family 7.

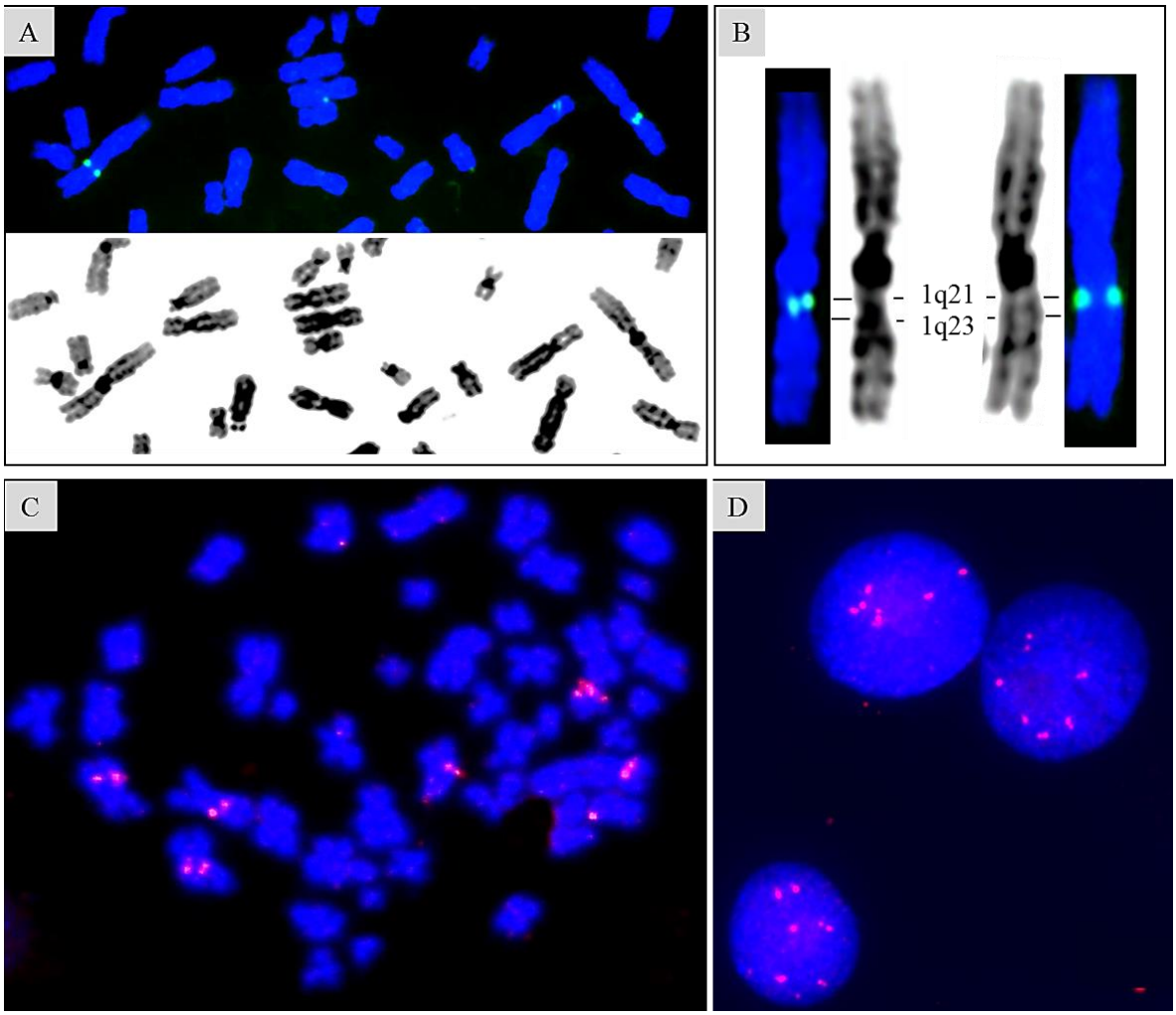


**Figure 1**. **Fluorescence in situ hybridization mapping of *SLAMF7* gene on normal metaphase and MM cells** (Sakamoto N, Taniwaki M et al., unpublished). FISH is performed as described as previously.[98] (A) Representative mapping finding of *SLAMF7* gene on a partial metaphase cell using BAC clone RP11-404F10 containing *SLAMF2*, *SLAMF7*, and *SLAMF3*. (**B**) An enlarged view of chromosomes 1 shown in (**A**). *SLAMF7* gene is assigned to 1q21.3 in our FISH study, although reportedly to be at the chromosomal band 1q23.3. (**C**) (**D**) Amplification of *SLAMF7* gene in a metaphase spread and interphase nuclei obtained from a MM patient harboring pseudodiploid karyotype with 1q gain.

activity.[28,31,35] Although most SLAMF receptors bind SAP and EAT-2, SLAMF7 is reported to be functionally controlled by EAT-2 only.[33,36] However, RNA interference experiments have demonstrated that SLAMF7 may interact with SAP when the concentration of SAP is significantly higher than that of EAT-2 in cells.[37] Hence, the selective binding of SLAMF7 to EAT-2 is due to its greater affinity to EAT-2 than SAP by nearly two orders of magnitude.[37] Moreover, a recent study reported that SLAMF7 interacted with integrin Mac-1 instead of SAP adaptors utilizing signals involving immunoreceptor tyrosine-based activation motifs (ITAMs), which induced the promotion of phagocytosis.[38] Further studies are needed in order to elucidate the exact role of SLAMF7 in myeloma cell pathophysiology.

*SLAM-associated adaptor proteins and downstream signal transduction*. SLAMF functions as an either inhibitory or activating receptor depending on the availability of the SAP-related adaptor proteins, SAP and EAT-2. SAP is expressed in T, NK, NKT, and germinal center B cells. SAP expression has been reported in some Epstein-Barr virus (EBV)-transformed B cells, Hodgkin's lymphoma, and angioimmunoblastic T-cell lymphoma.[39-41] EAT-2 is expressed in NK cells and a range of antigen-presenting cells including monocytes.[42,43] When the SLAMF receptor is engaged, tyrosine (Y) 281 located in ITSMs is phosphorylated, recruiting SAP or EAT-2.[28,32] Through the SH2 domain, SAP or EAT-2 binds SLAMF at the phosphorylated ITSMs with overlapping specificities for activating and inhibitory binding partners. SAP contains an

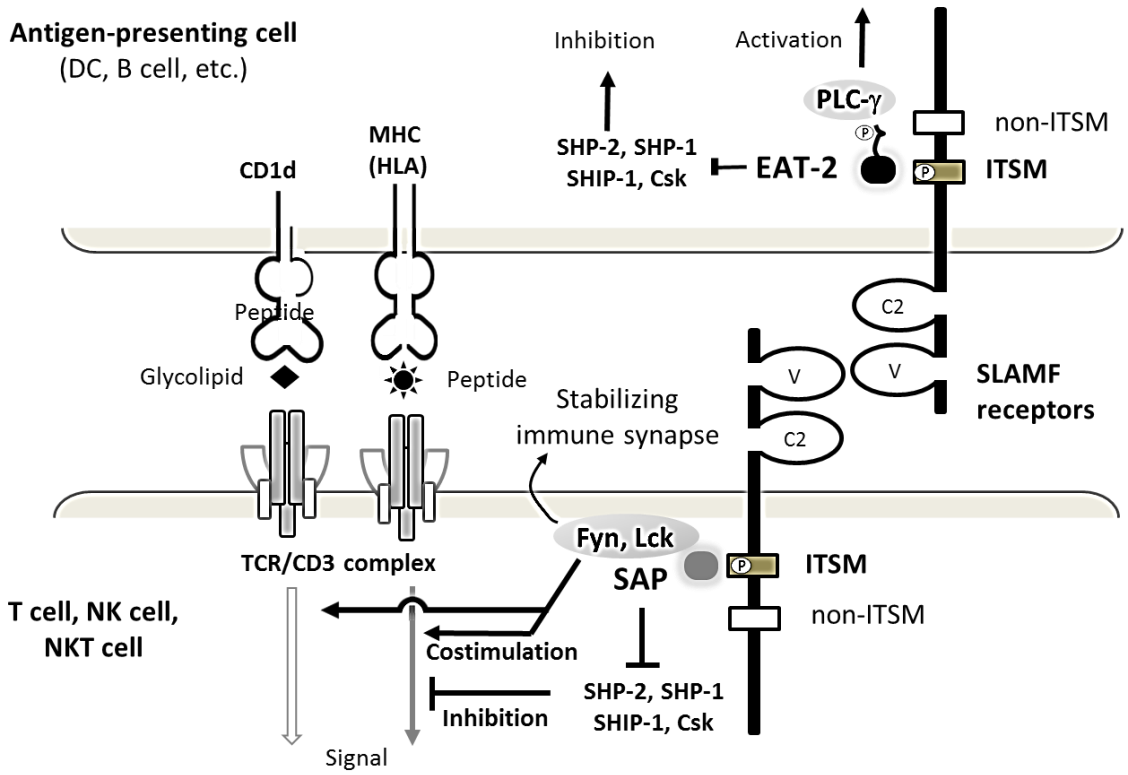


**Figure 2. Structure and function of SLAMF receptor in an immune synapse.** The SLAMF receptors are structurally characterized by IgV and IgC2 domains within an extracellular portion and one or more ITSMs, depicted as a closed rectangle, within the cytoplasmic portion. The mostly homophilic interactions between SLAMF receptors result in their costimulatory effects on TCR/CD3 complex signaling pathway. When the SLAMF receptor is engaged by its ligand, cytoplasmic domain ITSMs with tyrosine-based motifs undergo phosphorylation, recruiting adaptors proteins, SAP or EAT-2. SAP can then recruit the Src family protein tyrosine kinase Fyn or Lck, which is important for activation via SLAM family receptors. The coupling of EAT-2 carboxyl-terminal tail to the PLC-γ SH2 domains leads to an additional activation pathway. ITSM-like motif (non-ITSM) depicted as an unfilled rectangle does not bind SAP or EAT-2. SAP is mostly expressed in T cells, while EAT-2 is primarily expressed in antigen-presenting cells.

arginine-based motif in the SH domain, which mediates binding to the Src family protein Fyn, thereby stabilizing immune synapses (**Figure 2**).[44] SAP also enhances adhesion between NK and target cells. On the other hand, EAT-2 controls NK cell function through the phospholipase Cγ enzymes (PLC-γ), $Ca^{2+}$ fluxes, and the MAPK/Erk pathway, leading to granule polarization and the exocytosis of cytotoxic granules toward target cells (**Figure 3**).[45] SAP and EAT-2 both prevent SLAMF receptors from interacting with inhibitory effectors such as SH2-domain-containing tyrosine phosphatase (SHP)-2, SHP-1, SH2 domain-containing 5' inositol phosphatase (SHIP)-1, or C-terminal Src kinase (Csk).[36,41] Hence, SLAMF receptors become inhibitory in the absence of SAP-related adaptors, suppressing the function of activating NK-cell receptors such as CD16, natural-killer group-2 member-D (NKG2D), and DNAX accessory molecule-1 (DNAM-1).[32]

The SAP gene located at Xq25 was identified as the causative gene altered in X-linked lymphoproliferative syndrome (XLP).[46,47] Germline mutations or deletions in SAP have been implicated in XLP, resulting in aberrant functions of SLAMF1.[48,49] Aberrant functions of SLAMF1, 2, and 6 caused by SAP mutations result in extreme sensitivity to EBV infection in patients with XLP. EBV-specific cytotoxic CD8+ T cells in XLP exhibit defects in the cytolysis of EBV-infected B cells. They escape an apoptotic death, which results in the uncontrolled proliferation of B cells and T cells, thereby causing fulminant infectious mononucleosis (60%), lymphomas (30%), and dysgammaglobulinemia (30%).[48,50]

## Expression of SLAMF7 in Normal Cells, MM, and other Hematological Malignancies.

*Expression of SLAMF7 in normal cells and MM cells:* SLAMF7 is expressed on NK cells, NKT cells, a subset of cytotoxic T-lymphocytes (CTLs) including CD8+ and CD4+ cells, mature dendritic cells (DCs), and activated B cells, regulating T- and B-cell functions. (**Table 2**).[27,31-33,51,52] Normal plasma cells also highly express SLAMF7 at the mRNA and protein levels.[13,14] SLAMF7 is not

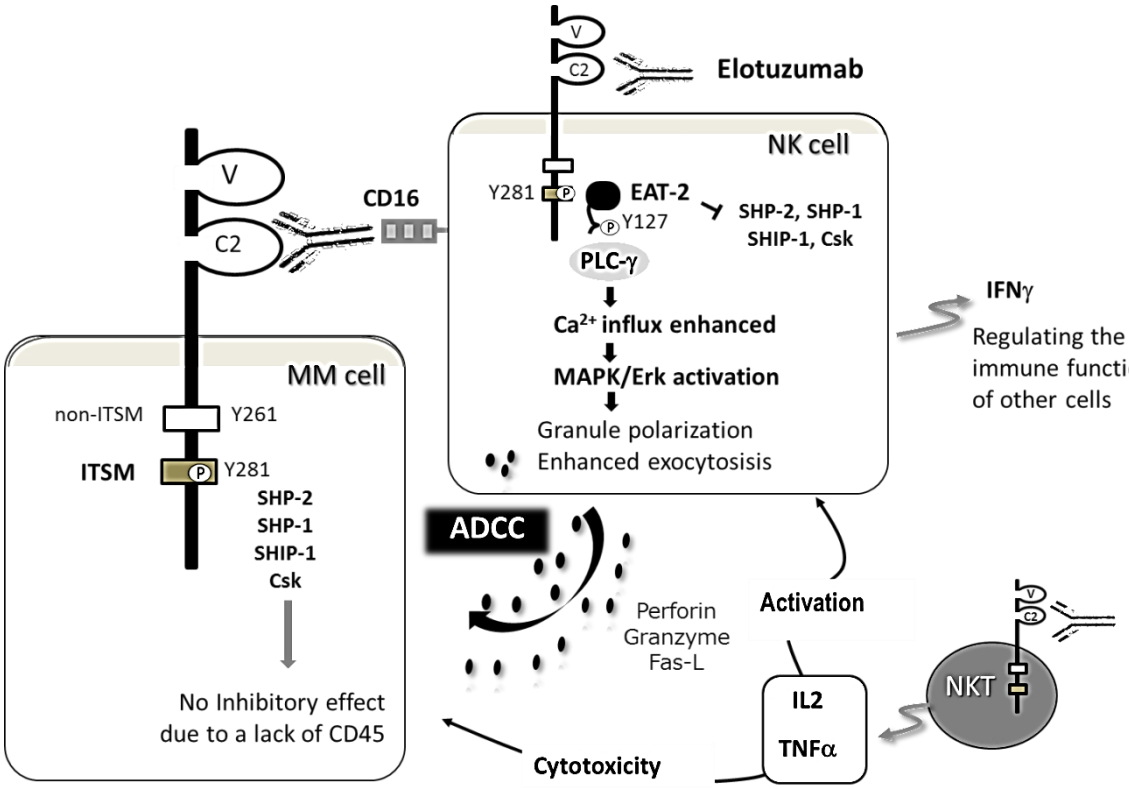


**Figure 3. Effect of elotuzumab to NK, NKT, and MM cells.** The primary mechanism of action of elotuzumab is NK cell-mediated ADCC against MM cells. Elotuzumab also directly activates NK and NKT cells, but not MM cells, by its engagement with SLAMF7. This effect results in phosphorylation of tyrosine 281 (Y281) located in ITSMs, thereby recruiting a SLAM-associated adaptor EAT-2. EAT-2 binds to the SH2 domains of PLC-γ, and leads to enhanced $Ca^{2+}$ influx and MAPK/Erk pathway activation, finally resulting in granule polarization and enhanced exocytosis in NK cells. Tyrosine 261 (Y261), needed for the inhibitory function of mouse SLAMF7, is conserved in human SLAMF7.[31] NKT cells are also activated *via* elotuzumab binding, resulting in the accelerated secretion of IL2 and TNFα, which induces the cytotoxicity of NK cells against MM cells.[64] Elotuzumab binds to the proximal IgC2 domain of SLAMF 7.

expressed in resting B cells, monocytes, granulocytes, or hematopoietic stem cells.[13,14,36] On the other hand, SLAMF7 is highly expressed in neoplastic plasma cells from more than 95% of patients with MM, plasmacytoma,[13,14] and plasma cell leukemia (PCL). It is also expressed in CD138 purified plasma cells from patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM).[14] There have been no studies describing the higher expression of SLAMF7 in MM than in normal plasma cells. Soluble SLAMF7 (sSLMF7) lacking transmembrane and cytoplasmic domains was detected in patients with MM, particularly at advanced stages, but not in those with MGUS or healthy individuals.[14] The role of sSLMF7 in myeloma cell pathophysiology remains to be elucidated.

Although SLAMF7 expression level in MM cells were independent of the cytogenetic subtypes of MM, one of the highest expression levels was found in t(4;14)-positive MM.[13] A recent study demonstrated that the knockdown of SLAMF7 induced cell cycle G1 arrest or apoptosis, and also reduced colony formation in t(4;14) MM cells.[53] Overexpressed SLAMF7 in t(4;14)-positive MM cell lines was down-regulated by MMSET shRNAs.[53] These findings suggest a direct effect on the transcription of SLAMF7 by the MMSET protein. Although the mechanisms underlying the upregulation in plasma cells and MM cells currently remain unclear, a recent study demonstrated that SLAMF7 transcription was positively regulated by Blimp-1 (B lymphocyte-induced maturation protein-1) in NK cells and B cells.[54] Blimp-1 is a known transcriptional repressor in macrophages, NK cells, B cells, T cells, and skin epithelial cells. Plasma cell function is controlled by Blimp-1 through the regulation of immunoglobulin secretion and the unfolded protein response.[55]

*Expression of SLAMF7 in other hematological malignancies.* Most of B-cell lymphomas including various histological subtypes and Hodgkin lymphoma do not express SLAMF7, as

assessed by immunohistochemistry (IHC). Neither acute myeloid leukemias nor lymphoblastic leukemias express SLAMF7.[13] The SLAMF7 protein was detected in 25% of peripheral T-cell lymphomas (PTCL) at a modest level using IHC. PTCL is a heterogeneous disease, but generally shows the CD4-positive phenotype. Using IHC, we identified various CD4+ Th subsets (Th1, Th2, Th17, and Treg) as possible normal counterparts of PTCL based on the expression of master regulators such as T-bet, GATA3, BCL6, RORγt, and FOXP3.[56] These findings suggest that some functional subsets of CD4+ T cells expressing SLAMF7 exist. Recent studies demonstrated the clonal expansion of CD4+ CTLs expressing SLAMF7, granzyme A, IL-1β, and TGF-β1, at inflamed tissue sites of IgG4-related disease.[52] Although CD4+ CTLs may develop from naïve T (Th0) and various Th subsets, Th1 cells regulated by T-bet represent the majority of CD4+ CTLs secreting IFN-γ.[57] CD4+ CTLs have been detected among peripheral blood lymphocytes under conditions of chronic viral infections and during antitumor responses.[58,59]

**Dual Immunotherapeutic Mechanism of Elotuzumab.**

*Elotuzumab induces NK cell-mediated ADCC.* Elotuzumab is a humanized immunoglobulin G1 kappa (IgG1κ) monoclonal antibody, that binds a unique epitope on the IgC2 domain of SLAMF7.[13,14] Human IgG1 elicits ADCC and complement-dependent cytotoxicity (CDC) activities. However, elotuzumab and the novel anti-SLAMF7 mAb PDL241 did not mediate CDC.[60,61] Elotuzumab-induced ADCC is mediated through the engagement of its Fc portion with FcγRIIIa/CD16 on NK cells.[14,61] On the other hand, elotuzumab is unable to directly suppress the growth of MM cells. In MM cells lacking EAT-2, inhibitory molecules including SHP-2, SHP-1, SHIP-1, and Csk are recruited to the phosphorylated ITSMs of SLAMF7.[62] However, inhibitory effects are not induced in MM cells, partly due to a lack of CD45. Elotuzumab also does not induce the proliferation of myeloma cells (**Figure 3**).[45,62]

Preclinical studies demonstrated that elotuzumab strongly induced cytotoxicity in established MM cell lines and primary samples including bortezomib-resistant MM cells when incubated with peripheral blood mononuclear cells (PBMCs) or purified NK cells.[63] This anti-myeloma effect of elotuzumab was prevented when CD16 was inhibited.[64] Elotuzumab alone does not affect the viability of MM cells without PBMCs or purified NK cells *in vitro*. SLAMF7 may also potentiate interactions between NK and target MM cells through its homotypic engagement recognizing the distal epitope IgV.[65] NK cells activated by elotuzumab do not show cytotoxicity against autologous NK cells.[14] In mice, the interaction between NK cells by the SLAMF7 engagement may enhance their function.[36]

*Elotuzumab directly stimulates NK cells.* Elotuzumab directly enhances the cytotoxic activity of NK cells in addition to primarily inducing ADCC against MM cells, giving rise to a dual immunotherapeutic mechanism of action.[13,14,63] NK cell activation is mediated by the SLAMF adaptor proteins EAT-2 and SAP, the cooperated expression of which promotes the cytotoxic activity of NK cells. NK cell cytotoxicity is also dependent on PLCγ1 and PLCγ2.[66] SAP promotes and stabilizes adhesion between NK cells and target cells in a dual manner: one is by the coupling of SLAMF receptors to the protein tyrosine kinase Fyn, and the other is by preventing SLAMF receptors from coupling inhibitory signals involving SHIP and SHP-1.[67,68] On the other hand, EAT-2 does not enhance adhesion between NK and target cells, but controls NK cell function through PLCγ, $Ca^{2+}$ fluxes, and the MAPK/Erk pathway, leading to granule polarization and the exocytosis of cytotoxic granules toward target cells (**Figure 3**).[45] NKT cells are also activated *via* elotuzumab binding, resulting in the accelerated secretion of IL2 and TNFα, which induces the cytotoxicity of NK cells against MM cells (**Figure 3**).[64] While most SLAMF receptors bind SAP and EAT-2,[35] SLAMF7 is functionally controlled by EAT-2, not SAP.[34,35]

A previous study showed that lenalidomide augmented elotuzumab-induced ADCC against MM cells *in vitro*.[14,64] The enhanced NK cell function was associated with the up-regulation of IL-2Rα expression, IL-2 production by CD3+CD56+ lymphocytes including NKT cells, and TNFα production.[64] Augmentations in NK-cell cytotoxic activity were also demonstrated with pomalidomide.[69,70] Low-dose bortezomib[71] and

carfilzomib[72] also augmented NK-cell cytotoxic activity against MM cells. This effect was associated with the enhanced expression of the activating or co-activating molecules of NK cells including MHC class I polypeptide-related sequence A (MICA), NKG2D, and DNAM-1 ligands (PVR and Nectin-2). These findings may provide the rationale for combining these agents with elotuzumab. However, further studies are needed in order to delineate which and how immune cells other than NK cells are modulated in their function by elotuzumab.

*Quantity and quality of NK cells in MM.* The quantity and quality of effector cells including NK cells are essential for ADCC activity. Peripheral blood (PB) NK cell counts from MM patients increased or showed no changes in the earlier stages and decreased in the advanced stages.[73-75] Patients with MGUS also showed no changes in PB NK cell counts form those of the controls.[74,76,77] On the other hand, NK cell counts in bone marrow (BM) from MM patients were reported to increase.[73,78] However, the functions of NK cells differ among their subsets. $CD56^{bright}CD16^{-/dim}$ NK cells are mainly responsible for the production of cytokines, while $CD56^{dim}CD16^{+}$ NK cells are mainly responsible for cytotoxic activities.[75] $CD16^{+}$ subsets were decreased in MM patients.[79]

Regarding the quality of NK cells in MM patients, previous studies suggested that they were dysfunctional and showed decreased or no cytotoxicity in advanced MM, while they remained functional in MGUS.[79-83] NK cell dysfunction is often associated with the down-regulated expression of activating molecules including natural cytotoxicity receptors, NKG2D, and SLAMF4 (2B4) in BM NK-cells.[84] Other studies also demonstrated the down-regulated expression of SLAMF4 and DNAM-1 in NK cells, and this was associated with a reduction in NK cell cytotoxicity against MM.[83,85] MM cells escape NK cell cytotoxicity due to the lack of a HLA Class I loss, the shedding of surface MICA, and circulating MICA, which result in the down-regulation of NKG2D. NK cells from MM patients also express programmed death protein 1 (PD-1), which results in escape from immune surveillance.[86,87] In mouse tumor models, an anti-PD-1 antibody enhances elotuzumab efficacy due to the production of tumor-infiltrating NK and $CD8^{+}$ T cell activity.[88] These findings may provide the rationale for combination therapy of elotuzumab and PD-1 blockade.

*Response to elotuzumab and the polymorphism of FcγRIIIa/CD16.* The FcγRIIIa/CD16 genotype may provide some guidance for the administration of elotuzumab to patients who are expected to have a favorable response. Since the allelic variation affects the affinity of FcγRIIIa for IgG1 antibodies, differential responses to mAb have been reported to correlate with specific polymorphisms.[89,90] The presence of a valine (V) at position 158 of FcγRIIIa is associated with high-affinity to the Fc portion of IgG1 mAb, in contrast to phenylalanine (F) with low affinity. The high-affinity "VV" genotype of FcγRIIIa has been associated with enhanced ADCC in rituximab treatments for patients with follicular lymphoma.[91,92]

In a randomized phase II study of EBd versus Bd for RRMM, patients homozygous for the high-affinity FcγRIIIa V allele (VV) showed longer survival than those who were homozygous for the low-affinity FcγRIIIa F allele (FF).[24] A subanalysis of PFS by the CD16a genotype showed no significant difference between VV and FF in ELOQUENT-2. A difference was noted between VV/VF and FF in the study of elotuzumab monotherapy, although the interpretation of this finding is limited by the small number of patients with each genotype.[93] The incidence of the high-affinity VV allele is 59% in the Japanese population versus 17% in the populations of Western countries.[24,94] In Japanese patients, the genetic FcγRIIIa-V158F polymorphism may have a significant impact on myeloma cell killing by ADCC.

**Optimal use of ELd for the Treatment of RRMM.** Three factors need to be considered in order to achieve better outcomes using ELd: risk of the disease, frailty of the patients, and the quantity and quality of effector cells. Prior to introducing elotuzumab, many patients were treated with lenalidomide-based regimens until disease progression as first-line therapy, and were lenalidomide refractory at the time of first relapse. Since elotuzumab is approved in combination with Ld for the treatment of RRMM, there are two possible conditions under which to administer elotuzumab: starting ELd as second-line later

treatment or adding elotuzumab to Ld ongoing as first-line or later treatment. In the case of second-line or later treatment, patients with PR, VGPR, or CR using Ld may be the ideal candidates for the addition of elotuzumab. This is because PFS by tumor responses between the ELd and Ld groups was significantly better in patients who achieved PR or better than in patients with a minor response or SD in ELOQUENT-2.[8]

According to the ELOQUENT-2 study, elotuzumab is beneficial for patients with high-risk CA including del(17p), 1q21 gain/amplification, and particularly t(4;14). A direct effect on SLAMF7 transcription by the MMSET protein has provided the rationale to use elotuzumab for t(4;14)-positive MM patients.[53] Secondary CA may impact adversely on treatment outcomes and survival in both NDMM and RRMM regardless of the primary high-risk CA (**Table 3**). For example, t(11;14) is not necessarily associated with a good, but with a poor prognosis when identified concomitantly with a high-risk secondary CA, such as 1q21 gain/amplification and del(17p) (**Figure 4**).[95] In the novel agent era, chromosomal rearrangements at 8q24 is also high-risk CA.[96,97] We previously detected 8q24 rearrangements involving *MYC* or *PVT1* (plasmacytoma variant translocation 1) loci in 24% of patients with MM.[98]

Taking the modes of action of elotuzumab into consideration, the counts and functions of immune cells, particularly NK cells are crucial as already mentioned. In this regard, the findings of Phase II and III trails in patients with SMM have been encouraging. Elotuzumab monotherapy may delay progression to MM in patients with SMM, resulting in favorable PFS, because most patients achieved the best overall response of SD or MR, with ≥MR in 29% including PR in 10%.[99] Early treatments with Ld in patients with high-risk SMM provided a significant benefit over observations in terms of time to progression.[100] Since elotuzumab is well tolerated with minimal toxicity, elderly or frail patients who are ineligible for PI/MiD-based triplet therapy or transplantation are suitable candidates for ELd treatment. Moreover, the addition of elotuzumab to bortezomib, lenalidomide, and dexamethasone (LBd) is feasible without major additive AEs beyond what is already known about LBd, as

**Table 3.** SLAM family receptors: their expression and interaction with adaptor proteins.

| SLAMF Receptors | Ligands | Expression | | Interaction with | | Effectors |
|---|---|---|---|---|---|---|
| | | Normal | MM | SAP | EAT-2 | |
| SLAMF1 | SLAMF1<br>measles virus | T, B, DCs, Mφ, Platelets | + | + | + | Fyn, Lck, SHIP1, Dok1, PKCθ, Akt |
| SLAMF2 | SLAMF4<br>CD2 | Lymphocytes, Immune cells, DCs, Endothelial cells | ++ | − | − | Fyn, Lck |
| SLAMF3 | SLAMF3 | T, B, NK, DCs, Mφ | +++ | + | + | Fyn, Lck, ERK, AP2, Grb2 |
| SLAMF4 | SLAMF2 | NK, NKT, D8+ T, DCs, Mφ, Eosinophils | + | + | + | Fyn, Lck, LAT, PI3K, Vav1, SHIP1, cCbl, ERK, p38, SHP1, SHP2 |
| SLAMF5 | SLAMF5 | T, B, NK, DCs, Mφ, Granulocytes, Platelets, Mast cells, Eosinophils | + | + | + | Fyn, Lck |
| SLAMF6 | SLAMF6 | T, B, NK, DCs, Neutrophils | ++ | + | + | Fyn, Lck, PLC-γ, PI3K, SHP1, cCbl, Vav1 |
| SLAMF7 | SLAMF7 | NK, NKT, T, Plasma cells, B, DCs, Mφ | +++ | − | + | Fyn, Lck, PLC-γ, Vav1, PI3K |
| SLAMF8 | SLAMF8 | Granulocytes, Mφ, Monocytes, DCs | unknown | − | − | unknown |
| SLAMF9 | unknown | Immune cells | unknown | − | − | unknown |

SAP, SLAM-associated protein; EAT-2, EWS-Fli1-activated transcript-2; T, T cells; B, B cells; NKT, natural killer-T cells; NK, natural killer cells; DCs, dendritic cells; Mφ, macrophages

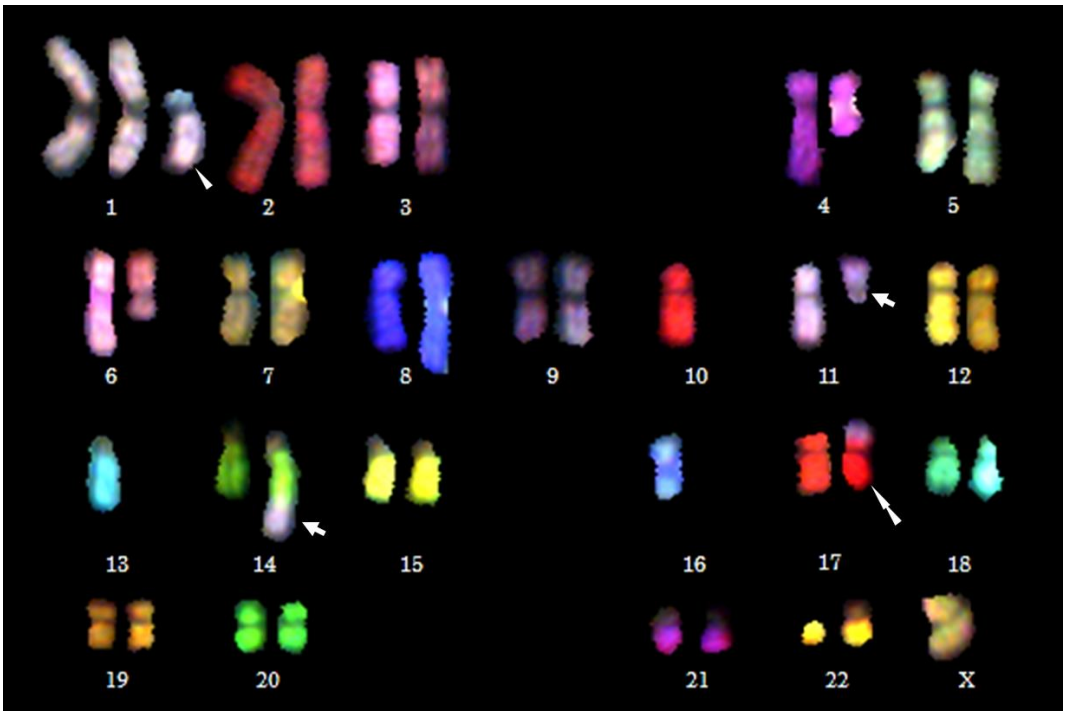


**Figure 4. Chromosomal abnormalities in a patient with t(11;14)-positive primary refractory PCL detected by multicolor spectral karyotyping (SKY)** (Goto M, Taniwaki M, et al. unpublished). SKY is performed as described as previously.[98] Arrows indicate a balanced translocation t(11;14)(q13;q32). Three secondary CA are detected in this patient: der(1)t(1;16)(q10;p10) indicated by an arrowhead, monsomy 13 (-13), and der(17)t(4;17)(?;p13) indicated by a double arrowhead. Unbalanced translocations, der(1)t(1;16)(q10;p10) and der(17)t(4;17)(?;p13), result in 1q gain and 17p deletion, respectively, which are high-risk secondary CA in MM (Goto M, Taniwaki M, et al. unpublished).

demonstrated in SWOGS1211 trial.[101] However, the efficacy of elotuzumab in combination with LBd needs to be studied.

**Conclusions.** A number of molecular targeting agents are currently available for MM; therefore, risk stratification and frailty assessments are critical for their optimal combination. Secondary CA are effective biomarkers, and more than 50% of patients are unfit because they are older than 75 years. However, even with the use of novel agents, MM remains incurable with recurrence and refractoriness to treatment, and frequently develops extramedullary disease and secondary plasma cell leukemia (sPCL) at the end stages of the disease. Although a number of clinical trials have attempted to achieve high tumor responses in RRMM using novel triplet therapy with second- and third-generation PIs and IMiDs, difficulties are associated with successfully treating extramedullary lesions and sPCL. Therefore, it is important not only to develop treatments with high tumor responses, but also to have early therapeutic interventions for MM. Moreover, 30-50% of MM patients are transplant-ineligible or unable to receive PI/IMiDs based triplets therapy.[102,103] Hence, elotuzumab is promising and beneficial for the treatment of frail patients with MM.

The mechanisms of action of elotuzumab and the functional role of SLAMF7 in relation to pathophysiology of MM remain unclear. For example, what the signal transduction pathway of engaged SLAMF7 in MM cells is involved in is unknown, and which or how immune cells other than NK cells are implicated in killing MM cells has yet to be elucidated by elotuzumab. It will be beneficial for patients with RRMM to clarify whether elotuzumab has a marked impact on the recovery of immune paralysis in combination with other novel molecular targeting agents such as carfilzomib and pomalidomide. In order to address these questions, basic research is conducted to investigate the molecular mechanisms involving SLAMF receptors and SAP-related adaptors with their downstream molecules in the signal transduction pathway.

The efficacy of ELd with minimal toxicity and the paralytic immune state in advanced MM may bring forward for consideration of early therapeutic intervention in patients with SMM. However, studies are needed in order to clarify whether ELd is effective for patients with SMM.

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