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# Elotuzumab in multiple myeloma: a single centre experience

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**Summary.** *Background and aims of the work:* Elotuzumab is a first-in-class immunostimulatory monoclonal antibody approved in Italy in April 2017 for use in combination with lenalidomide and dexamethasone (ELd) for relapsed/refractory multiple myeloma (MM). We present our single Centre experience with ELd in patients with MM, focusing on the determinants driving the choice of the most appropriate second-line treatment. *Methods:* We performed a retrospective analysis of patients experiencing a first relapse in the Hematology and Bone Marrow Transplant Unit of the Papa Giovanni XXIII hospital in Bergamo, Italy between April and December of 2017. *Results:* We tended to administer ELd treatment to young and fit patients with non-aggressive relapsed/refractory MM. In general, ELd was well tolerated. We present details of 2 illustrative cases. *Conclusions:* The immunostimulatory effects and favorable clinical toxicity profile of elotuzumab make it an ideal drug against MM. Ongoing clinical trials will elucidate its most appropriate placement and its best combination partners to improve disease control and, therefore, the duration and quality of life.

**Key words:** multiple myeloma, treatment, elotuzumab

## Introduction

Multiple myeloma (MM) is a largely incurable tumor (1) resulting from the proliferation of monoclonal plasma cells in the bone marrow. Its incidence rate is about 8 cases per 100,000 people in Italy (2) and it has an estimated mortality rate of 2.2 cases per 100,000 people in Europe (3). Significant improvement in survival has been obtained (4), mostly due to the incorporation of autologous stem cell transplantation (ASCT) in the 1980s (5) and the availability of an increasing number of novel agents starting from 1990s. These agents, which include immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, histone deacetylase inhibitors, kinase inhibitors, heat shock protein inhibitors, signal transduction pathway inhibitors, have been used alone or in various combinations both in newly diagnosed and in relapsed/refractory MM (reviewed in 6).

Elotuzumab is a fully humanized IgGκ monoclonal antibody directed toward the extracellular region of CS1, which is a cell surface glycoprotein receptor member of the signaling lymphocytic activation molecule (SLAM) family (7). CS1 is expressed on natural killer (NK) cells, B- and T-lymphocytes, dendritic cells and monocytes, and is overexpressed in MM plasma cells (7). CS1 engagement by elotuzumab on MM plasma cells and NK cells leads to antibody-dependent cellular cytotoxicity and direct NK cell activation. CS1 has a critical role in the phagocytosis of hematopoietic tumor cells by macrophage (7), which implies another possible mechanism of action for elotuzumab. Finally, binding of elotuzumab to monocytes inhibits the production of proinflammatory cytokines (8).

Pre-clinical studies showed elotuzumab to be effective both *in vitro* against MM cells and *in vivo* in animal models of MM (9, 10). This evidence prompted clinical investigation of elotuzumab in MM patients.

Ineffective when used alone (11), elotuzumab combined with bortezomib and dexamethasone showed limited efficacy in pre-treated MM patients (12). In contrast, the randomized ELOQUENT-2 clinical trial showed that lenalidomide and dexamethasone are efficient partners of elotuzumab in relapsed/refractory MM (13, 14). Updates of the ELOQUENT-2 study in 2017 (15) and 2018 (16) confirmed that the combination of elotuzumab, lenalidomide and dexamethasone (ELd) significantly improved all clinical outcomes when compared to lenalidomide and dexamethasone alone (Ld). Finally, serum M-protein dynamic modeling predicted less tumor regrowth with ELd. Adverse events were comparable between the 2 arms, indicating that elotuzumab did not cause additional toxicity. In 2015, these data led to the approval of ELd for treatment of MM in patients with 1-3 prior therapies in the United States, and patients with ≥1 prior line of treatment in Europe. In April of 2017, the Italian Medicines Agency (AIFA) approved ELd in patients with MM who had received at least one prior therapy.

We present our single Centre experience with ELd in patients with relapsed/refractory MM. In particular, we discuss the determinants of choice of ELd as second-line treatment, its tolerability profile and the major outcomes of patients receiving ELd irrespective of their previous treatment. Two clinical cases are also presented and discussed.

*Determinants of choice of ELd as second-line treatment of relapsed/refractory MM patients*

Presently in Italy, the following treatments are available in ≥ second-line: bortezomib and dexamethasone (Bd); Ld either alone or in combination with either carfilzomib (KLd) or elotuzumab (ELd); daratumumab and dexamethasone in combination with either lenalidomide or bortezomib. Although algorithms have been proposed to facilitate treatment decisions (17), the choice may still be difficult in individual patients. Indeed, both patient-related and disease-related factors must be considered to identify the treatment with the best risk-benefit ratio.

We evaluated the determinants of second-line treatment choice in a retrospective analysis of patients experiencing a first symptomatic MM progression/relapse in the Hematology and Bone Marrow Transplant Unit of the Papa Giovanni XXIII hospital in Bergamo, Italy between April and December of 2017. At that time, daratumumab combinations were not available according to AIFA regulations. Demographic and disease characteristics at MM diagnosis of the 31 patients are reported in Table 1; their first-line treatments are detailed in Table 2.

**Table 1.** Demographic and disease characteristics at MM diagnosis.

| Characteristic | |
|---|---|
| Gender, M / F | 16 / 15 |
| Age, yrs median (range) | 70 (48 - 85) |
| Isotype, n | |
| A | 6 |
| D | 2 |
| G | 17 |
| LC | 6 |
| Light chain, n | |
| κ / λ | 19 / 12 |
| Durie & Salmon stage, n | |
| I | 1 |
| II | 5 |
| III | 25 |
| A / B | 24 / 7 |
| International Staging System, n | |
| 1 | 13 |
| 2 | 6 |
| 3 | 10 |
| na | 2 |

**Table 2.** First-line treatments of 31 patients with MM.

| Treatment | Pts, n |
|---|---|
| High-Dose Therapy + Autotransplant | 13 |
| VTD | 10 |
| Ld | 1 |
| KCyD | 1 |
| VAD | 1 |
| Non-Autotransplant programs | 18 |
| VMP | 14 |
| TMP | 2 |
| Ld | 1 |
| KLd | 1 |

Median progression free survival (PFS) on first-line treatment had been 18.4 months (range 1.7-150.2 months), and the median time to next treatment (TTNT) was 22.6 months (range 2.0-271.8 months). The second-line treatments are shown in Figure 1. One patient died a few days after relapse and was excluded from analysis. Clinical and biological characteristics of the remaining 30 patients were grouped according to the type of second-line treatment (Table 3). On average, patients receiving a 2-drug combination were 10 years older and had higher frailty scores (18) (median 2 vs 1) than patients receiving a 3-drug combination. Among patients treated with a 3 drug combination, those in the ELd group had longer PFS and TTNT compared to those treated with KLd. Patients in this latter group had lower values of hemoglobin and platelets and higher LDH values. The only patient with a plasma cell leukemia relapse had received KLd. This patient did not respond to treatment and died soon after the second KLd course. At last follow-up, 21 patients (70%) were still on treatment. Overall, 9 out of 11 patients (82%) treated with ELd reached a > partial remission, and 6 patients are still on treatment. Two patients in good partial remission stopped ELd treatment after 5 and 6 courses, respectively, to undergo a second high-dose therapy with ASCT procedure. The main post-transplant complication was reactivation of cytomegalovirus, which occurred in one patient and was well-controlled with specific antiviral therapy. Thus, ELd appears to be a feasible second-line treatment for controlling MM, and may be a safe bridge to ASCT.

In conclusion, we choose a 2-drug combination (Ld or Bd) for elderly and frail patients, whereas a 3-drug combination (ELd or KLd) was reserved for younger and fitter patients. However, more than one year of experience with ELd has increased our confidence in its tolerability profile (see below), and is prompting us to consider ELd also for second-line treatment of elderly and/or frail patients. Patient preference for a completely oral regimen had a major influence on the choice of Ld over ELd. The choice between 3-drug combinations was mostly determined by the biology of each MM relapse, with ELd used in less aggressive cases. However, ELd was effective also in aggressive relapse of MM (see Clinical Case 2 below).

*Outcome of MM patients treated with ELd*

The ELOQUENT-2 clinical trial (14-16) showed that ELd treatment improved the overall response rate (79% vs 66%, p=0.0002) and reduced the risk of pro-

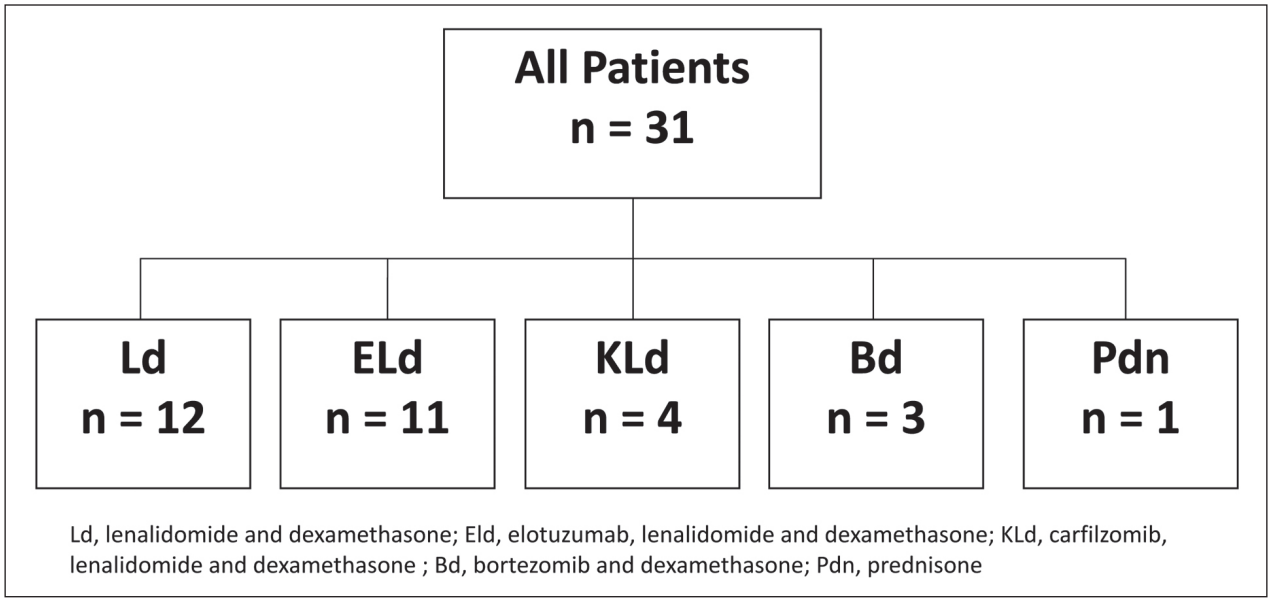


**Figure 1.** Second-line treatments received by the 31 MM patients.

**Table 3.** Patient characteristics at first symptomatic relapse according to second-line treatment selected (n = 30).

| Characteristic | Ld N = 12 | ELd N = 11 | KLd N = 4 | Bd N = 3 |
|---|---|---|---|---|
| Gender, M / F | 7 / 5 | 4 / 7 | 3 / 1 | 1 / 2 |
| Age, years | 77 (48-85) | 68 (57-78) | 64 (53-80) | 77 (67-78) |
| PFS, months | 12.3 (1.7-37.3) | 24.9 (14.4-150.2) | 18.5 (11.6-91.8) | 44.0 (15.7-64.7) |
| TTNT, months | 15.0 (2.0-38.2) | 37.0 (15.3-271.8) | 19.8 (11.8-99.1) | 44.0 (16.5-79.6) |
| ECOG | 1 (0-2) | 0 (0-2) | 0 (0-2) | 2 (1-2) |
| CIRS | 3 (0-5) | 2 (0-4) | 1 (0-7) | 2 (2-2) |
| Frailty score | 2 (0-4) | 1 (0-3) | 1 (0-2) | 2 (1-3) |
| Hemoglobin, g/dl | 11.8 (8.1-14.7) | 12.1 (8.0-15.0) | 10.9 (7.8-14.8) | 10.2 (9.5-10.9) |
| WBC, x $10^3$/ml | 6.4 (2.6-15) | 7.6 (4.3-17.3) | 6.7 (4.0-38.5) | 7 (5.6-8.4) |
| Neutrophil count, x $10^3$/ml | 4.4 (1.1-11.2) | 5.8 (2.1-15.5) | 3.3 (2.4-3.4) | 4.5 (4.0-4.9) |
| Platelet count, x $10^3$/ml | 167 (71-307) | 215 (8-291) | 63 (6-254) | 226 (91-253) |
| LDH value, U/l | 451 (308-775) | 393 (285-1062) | 659 (344-4161) | 381 (288-1229) |
| Serum creatinine, mg/dl | 0.85 (0.62-4.05) | 0.76 (0.54-2.32) | 0.86 (0.84-1.74) | 0.89 (0.65-0.99) |
| Bone marrow plasma cells, % | 35 (2-80) | 70 (5-90) | 10 (5-60) | 60 (40-80) |
| Cycles, n median (range) | 9 (1-13) | 6 (1-13) | 2 (1-9) | 8 (2-9) |
| Best outcome | | | | |
| CR | 1 | 1 | | 1 |
| VGPR | 1 | 3 | 1 | |
| GPR | 2 | 4 | | 1 |
| PR | 5 | 1 | | |
| SD | 1 | 1 | 2 | 1 |
| PD | 2 | 1 | 1 | |
| Death | 1 | 1 | 2 | 1 |

PFS, progression-free survival; TTNT, time to next treatment; ECOG PS, Eastern Cooperative Oncology Group performance status; CIRS, Cumulative Illness Rating Scale; CR, complete remission; VGPR. Very good partial remission; GPR, good partial remission; PR, partial remission; SD, stable disease; PD, progressive disease

gression/death by 27% (Hazard Ratio 0.73; p=0.0014) compared to Ld. Furthermore, overall survival showed a significant trend in favor of ELd (p=0.0257), with 1-, 2-, 3- and 4-year rates of 91% vs 83%, 73% vs 69%, 60% vs 53% and 50% vs 43%, respectively.

Between April 2017 and June 2018 we have treated 18 patients with ELd. Details of 11 of them have already been discussed above. Nine of the 18 patients had one or more comorbid conditions, and their frailty score was 1 or 2 in 8 cases. Although AIFA had not set a limit on the number of previous treatments above which ELd cannot be prescribed, we chose to administer it early so that elotuzumab can fully elicit its immunostimulatory effects. Indeed, more than 70% of our patients (13/18) received ELd as second-line treatment. The others received it as third-line (3), fourth-line (1) and fifth-line (1). A median of 6 cycles (range, 1-14) were administered. During treatment, we documented 2 complete remissions, 6 very good partial remissions, 4 good partial remissions, 3 partial remissions, one stable disease and one progressive disease. The overall response rate (i.e., ≥ partial remission) was 83%. As of June 2018, 12 patients were still receiving ELd treatment. Two patients discontinued treatment, one after the first cycle for an adverse event and the other after the second cycle for MM progression (see "Tolerability of ELd" below). Two patients died: one after the first ELd cycle, due to worsening general health, despite a decrease of free κ light chains from 2843 to 8.3 mg/L; the other after the second cycle, due

to MM progression. Thus, 1-year overall survival was 89%. These favorable outcomes – obtained outside of a clinical trial – closely resemble those of the ELOQUENT-2 study (14-16).

*Tolerability of ELd*

The ELOQUENT-2 clinical trial randomly assigned 321 patients to receive ELd (14-16) and established the good safety and tolerability of the ELd combination. Infusion reactions occurred mainly during the first dose and affected 10% of the patients, with only 1% Grade 3 and no Grade 4-5 reactions. Two patients (1%) discontinued elotuzumab because of infusion reactions.

Our premedication scheme before elotuzumab infusion followed the main indications from the ELOQUENT-2 study: 1. oral dexamethasone on the day before elotuzumab; 2. intravenous combination of dexamethasone, ranitidine, chlorophenamine and paracetamole before the elotuzumab infusion; 3. the first elotuzumab infusion is administered with progressively increasing infusion rate. If no reaction occurred, subsequent infusions were completed in about 60 minutes. Using this scheme, we did not observe any Grade ≥2 infusion reactions among the 18 patients treated with ELd in our Centre. Once good control of MM has been obtained, we administer dexamethasone only before elotuzumab (i.e., every 15 days), to reduce the monthly dexamethasone dose and the risk of steroid-related side effects.

Virtually all patients enrolled in the ELOQUENT-2 clinical trial experienced adverse events. Fatigue and diarrhea were the most common non-hematological events, whereas lymphocytopenia, neutropenia, anemia, and thrombocytopenia were the main hematological events. The prevalence of Grade 3-4 hematological and non-hematological adverse events was similar in the two study arms. In particular, the exposure-adjusted incidence rates per 100 patient-years for infection were 198 and 192 for ELd and Ld, respectively; for second primary malignancies, these rates were 5 and 3, respectively. Herpes zoster infections were more common in patients treated with ELd. Anti-herpetic prophylaxis is recommended for all patients treated with ELd (19).

As of June 2018, we have administered 129 ELd cycles to 18 patients. In our experience, only one patient permanently stopped elotuzumab infusions, and this was due to an adverse psychiatric event during the first cycle. The patient was switched to Ld treatment, which was also not tolerated and had to be interrupted. Thus, we attributed these psychiatric symptoms to dexamethasone, rather than elotuzumab. Two patients developed pneumonia, and required a transient interruption of ELd treatment: one of them was receiving ELd as fourth-line treatment after allogeneic bone marrow transplantation. All of our patients received acyclovir and acetylsalicylic acid prophylaxis and, so far, none has experienced reactivation of latent herpes virus or thrombotic events. Two patients are receiving monthly immunoglobulin infusions because of recurrent upper respiratory tract infections and hypogammaglobulinemia. No primary secondary cancers have occurred.

*First clinical case*

This male patient was diagnosed with IgGκ monoclonal gammopathy of undetermined significance in 1998 at the age of 38 years. Progression to symptomatic MM, Durie and Salmon (D&S) stage I-A, International Staging System (ISS) 1, was documented in 2003. In December 2004 he remained in D&S stage I-A, but his serum monoclonal component (sMC) had increased to 4.23 g/dl, proteinuria was 2.59 g/d (Bence Jones 136 mg/dl) and bone marrow aspirate showed a 60% infiltration by plasma cells. Bone involvement was absent. After discussion, the patient accepted first-line treatment consisting of induction with 3 cycles of thalidomide and dexamethasone, mobilization with cyclophosphamide 7 g/m$^2$ followed by peripheral stem cell collection, and consolidation with double ASCT following melphalan 200 mg/m$^2$. At the end of this treatment (December 2005) a very good complete remission was documented, and regular follow-up was started without maintenance therapy. In August 2009 (+45 months after the second ASCT), progression was documented as reappearance of isolated sMC that was not measurable, but positive at immunofixation. The patient was followed without treatment: in November 2011 (+72 months) sMC was 1.08 g/dl; in April 2016

(+124 months) sMC had increased to 2 g/dl. His general health was excellent: no bone pain was reported; blood cell counts, serum calcium and renal function were all normal. This situation was maintained until April 2017 (+136 months), when sMC rose to 2.61 g/dl (details in Table 4). By that time, the patient was 57 years old, still in excellent health and naïve to both bortezomib and lenalidomide. Therefore, several options could be proposed for second-line treatment according to AIFA rules:

1. Bd cycles, alone or in combination with bendamustine;
2. Ld cycles, alone or in combination with carfilzomib or elotuzumab.

Young age and favorable performance status (PS) prompted us to exclude a 2-drug combination approach. Among the 3-drug combinations, the absence of high-risk cytogenetics and the extremely slow biochemical progression favored ELd. The patient is now receiving the seventeenth ELd cycle, with a stable good partial remission characterized by the persistence of an isolated sMC of about 0.5-0.6 g/dl.

*Second clinical case*

This female patient was diagnosed with IgDλ MM, D&S III-A stage, ISS 1, in 2015 at the age of 64 years. Her first-line treatment consisted of induction with 4 cycles of bortezomib – thalidomide – dexamethasone, mobilization with cyclophosphamide 2 g/m$^2$, peripheral blood stem cell collection (2.9x10$^6$ CD34+ cells/kg body weight), and consolidation with a single ASCT following melphalan 200 mg/m$^2$. No maintenance was given. Complete remission was obtained, which lasted 16 months. Features of MM relapse are detailed in Table 5. At the time of relapse, she was hospitalized for acute coronary syndrome complicated by severe anemia requiring transfusional support. Treatment started with intravenous dexamethasone 20 mg/d for 4 consecutive days. After discharge from the cardiology unit, she started treatment with ELd. The

**Table 5.** Clinical data from case 2 at first relapse, start of ELd therapy and last visit.

| Laboratory data | Relapse | Last visit |
|---|---|---|
| Hemoglobin, g/L | 80 | 125 |
| Platelets/mm$^3$ | 8,000 | 262,000 |
| Serum IgDλ MC, g/dl | 2.02 | Negative |
| Proteinuria, g/d | 0.07 | Negative |
| Bence Jones, g/l | Positive | Negative |
| Serum free λ light chain, mg/L | 1,455 | 5.61 |
| Bone marrow plasma cells, % | >90 | nd* |
| LDH, U/L | 927 | Normal |
| Renal function & serum calcium | Normal | Normal |
| Hepatic function | Normal | Normal |

*ND, not determined

**Table 4.** Clinical data from case 1 at first relapse, start of ELd therapy and last visit.

| Laboratory data | Relapse | Start of ELd | Last visit |
|---|---|---|---|
| Hemoglobin, g/L | 154 | 152 | 117 |
| Platelets/mm$^3$ | 219,000 | 265,000 | 255,000 |
| IgGk MC, g/dl | IF+ | 2.61 | 0.6 |
| Proteinuria, g/d | 0 | 0.57 | 0.2 |
| Bence Jones, g/d | Negative | 0.4 | Negative |
| Bone marrow plasma cells, % | nd* | 60 | nd |
| FISH | Nd | 1(q21) | nd |
| LDH, U/L | Nd | Normal | Normal |
| Serum creatinine, mg/dl | 0.84 | 0.84 | 0.9 |
| Hepatic function | Normal | Normal | Normal |
| Skeletal CT | Nd | Small, diffuse osteolytic lesions | Nd |

*Not determined

choice of this treatment was based on the following issues:

1. Relapse was aggressive and occurred less than two years after the ASCT. This led us to exclude a 2-drug combination strategy;
2. Similarly, we did not consider bortezomib – dexamethasone – bendamustine because of her previous exposure to bortezomib;
3. Due to the acute coronary syndrome, a 3-drug lenalidomide and dexamethasone-based combination required the reduction of the starting dose of lenalidomide to 15 mg/d (with the usual schedule of 21 days on and 7 days off drug). We excluded the use of carfilzomib, due to its potential cardiotoxicity;
4. At the time of relapse, daratumumab was not licensed in Italy.

Hematological and general health conditions improved quickly, with thrombocytopenia normalizing after the first ELd cycle, and hemoglobin level rising above 12 g/dl after the third cycle. Complete remission was documented as the disappearance of the sMC and normalization of the serum free light chain ratio at the end of the fifth cycle; this has been maintained through the 18 cycles.

This case clearly shows that ELd can be effective for an aggressive MM relapse, suggesting that its use need not be confined to slowly progressing MM.

*Future uses of elotuzumab in MM*

In October 2016, AIFA approved Ld cycles for the first-line treatment of patients not eligible for ASCT; in June 2018, they approved lenalidomide monotherapy as maintenance in the post-ASCT setting. Thus, an increasing number of MM patients will receive lenalidomide early in the course of their disease, which implies major changes in the use of elotuzumab in the near future. Several possible scenarios can be envisioned:

1. ELd may also move to front-line treatment for MM. This is already being investigated in the phase III ELOQUENT-1 clinical trial, which is comparing ELd cycles vs Ld in newly diagnosed, non-ASCT eligible patients (20). A phase I study is currently investigating the effect of the combination of elotuzumab with bortezomib, lenalidomide and dexamethasone in newly diagnosed high-risk patients (21).
2. Elotuzumab may move to post-ASCT maintenance. In this setting a phase II study is currently investigating its effect in combination with lenalidomide (22).
3. Elotuzumab may move even further upfront and be used in smoldering MM. Indeed, clinical trials are ongoing with elotuzumab monotherapy (23) and with the ELd combination in high-risk smoldering MM (24).
4. Elotuzumab may change partners. The ELOQUENT-3 phase II clinical trial is currently recruiting patients with relapsed/refractory MM to compare elotuzumab, pomalidomide and dexamethasone with pomalidomide and dexamethasone alone. Another study is evaluating the combination of elotuzumab with thalidomide and dexamethasone in relapsed/refractory MM patients (25). Other monoclonal antibodies may be potentially interesting partners of elotuzumab. Studies combining elotuzumab with nivolumab (a PD-1 checkpoint inhibitor), lirilumab (directed against KIR2D), or urelumab (directed against CD137) are recruiting patients.

In conclusion, elotuzumab is a first-in-class monoclonal antibody approved for relapsed/refractory MM. Its CS1-mediated immunostimulatory effects and favorable toxicity profile make elotuzumab an ideal drug against MM. Ongoing clinical trials will elucidate its most appropriate placement and its ideal companions in order to improve disease control and, therefore the duration and quality of life for patients with MM.

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