EUR. J. ONCOL.; Vol. 22, n. 2, pp. 65-70, 2017

Elotuzumab: the first available immunotherapeutic arrow against relapsed-refractory Multiple Myeloma

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Summary. The recent introduction of second-generation proteasome inhibitors such as carfilzomib and ixazomib and new immunomodulatory agents such as lenalidomide and pomalidomide has led to advances in the treatment of patients with relapsed/refractory Multiple Myeloma (MM). However, the discovery of several new targets on myeloma cells, has led to the use of monoclonal antibodies that have proved a promising approach in these patients. Elotuzumab, the first monoclonal antibody to be evaluated in phase 3 trial, directed against SLAMF7, induces myeloma death by direct activation of natural killer cells and via antibody-dependent cell-mediated cytotoxicity. In this paper, the main findings of the combination Elotuzumab-lenalidomide-dexamethasone in relapsed-refractory MM will be summarized.

Key words: elotuzumab, multiple myeloma, monoclonal antibodies

Despite the introduction of transplantation and several novel agents, relapse and finally refractoriness is still the rule in patients with Multiple Myeloma (MM). However, many new combinations containing carfilzomib, ixazomib (new proteasome inhibitors), pomalidomide (an analogue of lenalidomide) and panobinostat (a deacetylase inhibitors), have been recently approved for the treatment of relapsed-refractory MM, expanding the possibilities of rescuing these challenging patients (1).

Immuno-oncology (I-O), a clinical approach based on stimulation of the immune response against tumor cells by administration of monoclonal antibodies (mAbs), is increasingly important in medicine. Initially I-O showed safety and efficacy in treating some solid tumors (such as melanoma or lung cancer and advanced stage kidney disease). Over the past few years, its use in the management of different hematologic malignancies has started to spread.

Dual mechanism of action of elotuzumab

Based on the success of monoclonal antibody (mAb) therapy in the treatment of other hematologic malignancies, such as B-cell lymphoproliferative disorders, this approach is still being explored in MM by identifying specific cellular targets such as CD38 (targeted by Daratumumab and Isatuximab) and SLAMF7 (signaling lymphocytic activation molecule F7), also known as CS1 (cell-surface glycoprotein CD2 subset 1) (2). SLAMF7 is a cell-surface glycoprotein

highly expressed in normal and malignant plasma cells regardless of cytogenetic abnormalities or molecular profiles. Moreover, lower levels are expressed by natural killer (NK) cells, activated T cells and normal B cells, whereas it is absent in other normal tissues (3). Elotuzumab is a specific humanized immunoglobulin G1 kappa (IgG1k) for human SLAMF7 and does not show cross-reactivity with other SLAM family members (4). This mAb is able to bind SLAMF7 expressed both on MM and NK cells but there is a double mechanism: a direct activation of NK cells and an indirect effect by tagging MM cells (5) that, unlike NK cells, lack EAT-2 (Ewing's sarcoma-associated transcript 2), thus controlling the function of SLAMF7 (6). Therefore, the binding of Elotuzumab to both NK and MM cells induces the degranulation of cytotoxic granules from activated NK cells leading to the death of MM cells together with the other components of antibody-dependent cellular cytotoxicity (ADCC) (Fig. 1) (1). Besides these mechanisms of action, Elotuzumab is also able to inhibit myeloma cell adhesion in the bone marrow milieu (7).

Elotuzumab is the first mAb introduced in the treatment of MM, evaluated in clinical trials, to have shown antitumor activity. In a phase II study, comparing lenalidomide and dexamethasone plus Elotuzumab 20 mg/kg *vs* lenalidomide and dexamethasone plus Elotuzumab 10 mg/kg, the optimal dose of Elotuzumab was established to be 10 mg/kg (8). Elotuzumab has since been approved in combination with lenalidomide and dexamethasone (EloRd) for the treatment of patients with relapsed/refractory MM (RRMM) who have received one to three prior therapies (FDA) or ≥ 1 prior therapy (EMA).

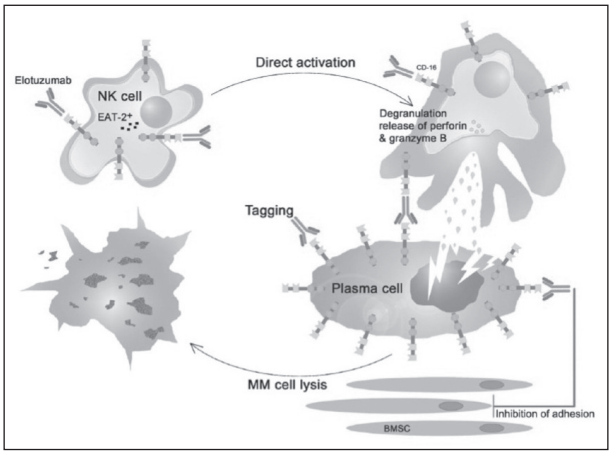

Figure 1. Dual action of elotuzumab: direct activation of NK cells and indirectly by tagging MM cells (from Ref. 5, pag. 189,© 2017 reprinted by permission of SAGE Publications, Ltd.).

The ELOQUENT-2 trial results

The authorization was based on the results from the ELOQUENT-2 study (9), an open-label, multicenter phase III trial, in which 646 patients with RRMM, who had received 1-3 prior lines of therapy were randomized to receive EloRd or Rd in 28-day cycles until disease progression or unacceptable toxicity. Primary endpoints of the study were PFS and ORR with OS being a secondary endpoint (Fig. 2). Baseline characteristics were well balanced between the two arms; particularly, median age of patients receiving Elotuzumab was 67 years (37-88), 32% had the del(17p) and 9% the t(4;14). Furthermore, 19% of patients were classified at high risk according to the presence of ISS stage II or III and del(17p) or t(4;14) abnormalities. Finally, approximately one third of the patients (35%) were resistant to their most recent line of therapy.

After a median follow-up of 24.5 months, patients receiving a triplet combination achieved a significantly higher ORR (79% *vs* 66% in the control group, p<0.001) with 33% of patients obtaining at least a VGPR *vs* 28% in the Rd group. No relevant increase of adverse events was observed with Elotuzumab and infusion reactions, the main criticism of immunotherapy, occurred in 10% of patients (none higher than grade 3), mainly during the administration of the first dose of mAb, but only 2 patients (1%) discontinued the study due to an infusion reaction (9). Of note, a recent phase 2 study reported the safety of a faster infusion of Elotuzumab, in combination with lenalidomide and dexamethasone, administered over about one hour by the third dose (10). A shorter infusion should eliminate any doubt regarding the use of mAb and may be beneficial in clinical practice.

The addition of Elotuzumab to Rd resulted in a significant improvement in PFS (median 19.4 *vs* 14.9 months) with a 30% reduction in the risk of disease

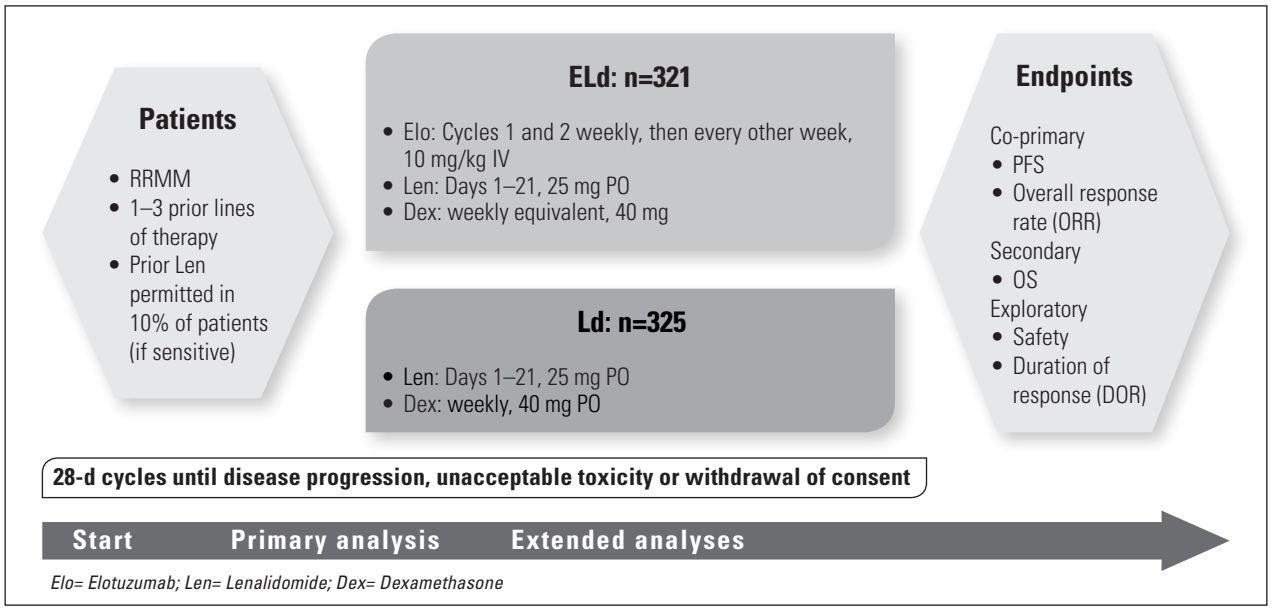

Figure 2. Eloquent-2 trial design (from Ref. 12 mod)

progression or death (HR 0.70; p<0.001) (9). At 1, and 2 years, PFS rates in patients receiving Elotuzumab were 68% and 41% respectively, compared to 57% and 27% in patients treated with Rd (9). Recently, the extended 3-years follow-up results have been published (11). In the triplet combination Elotuzumab showed to maintain reduction in the risk of progression or death of 27% (HR 0.73; p=0.0014) with a relative improvement of 44% in PFS rate *vs* Rd (26% *vs* 18%) (Fig. 3) (11). Importantly, PFS curves showed an early separation that was maintained over time.

Moreover, the benefit in terms of PFS was consistent across the different subgroups of patients, including those older than 75 years, those with the del(17p) or t(4;14), those refractory to the most recent treatment or who had received 2 or 3 prior lines of therapy (Fig. 4) (11). However, the best results in terms of PFS were obtained in patients with a history

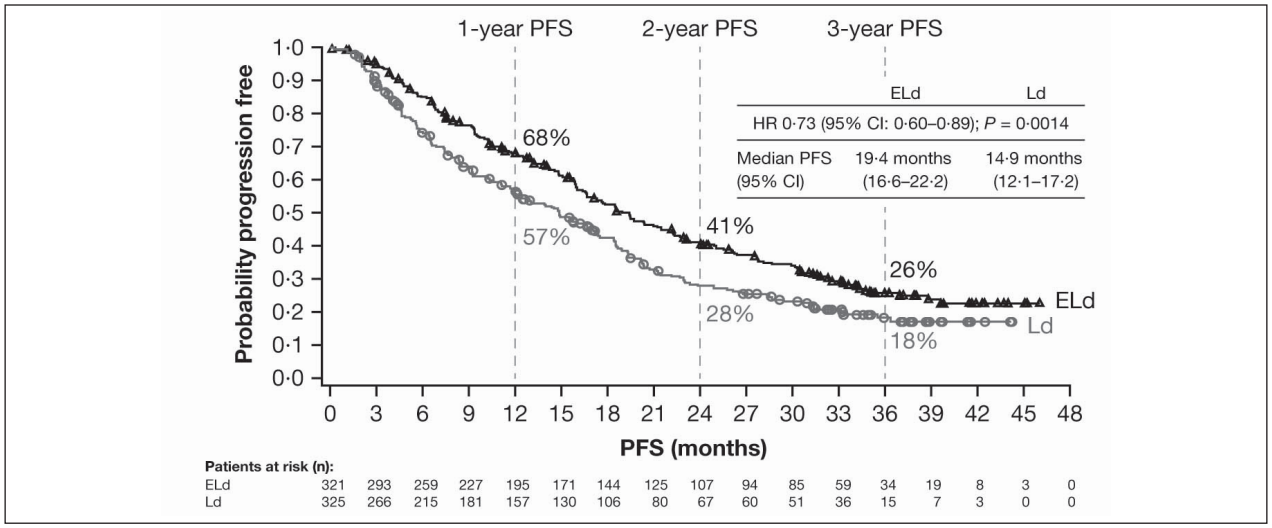

Figure 3. Kaplan–Meier curves of PFS (primary definition) (11) . CI, confidence interval; ELd, elotuzumab + lenalidomide/dexamethasone; HR, hazard ratio; Ld, lenalidomide/dexamethasone; PFS, progression-free survival. (From Ref. 11, pag. 900,© 2017 reprinted by permission of John Wiley and Sons, Ltd.).

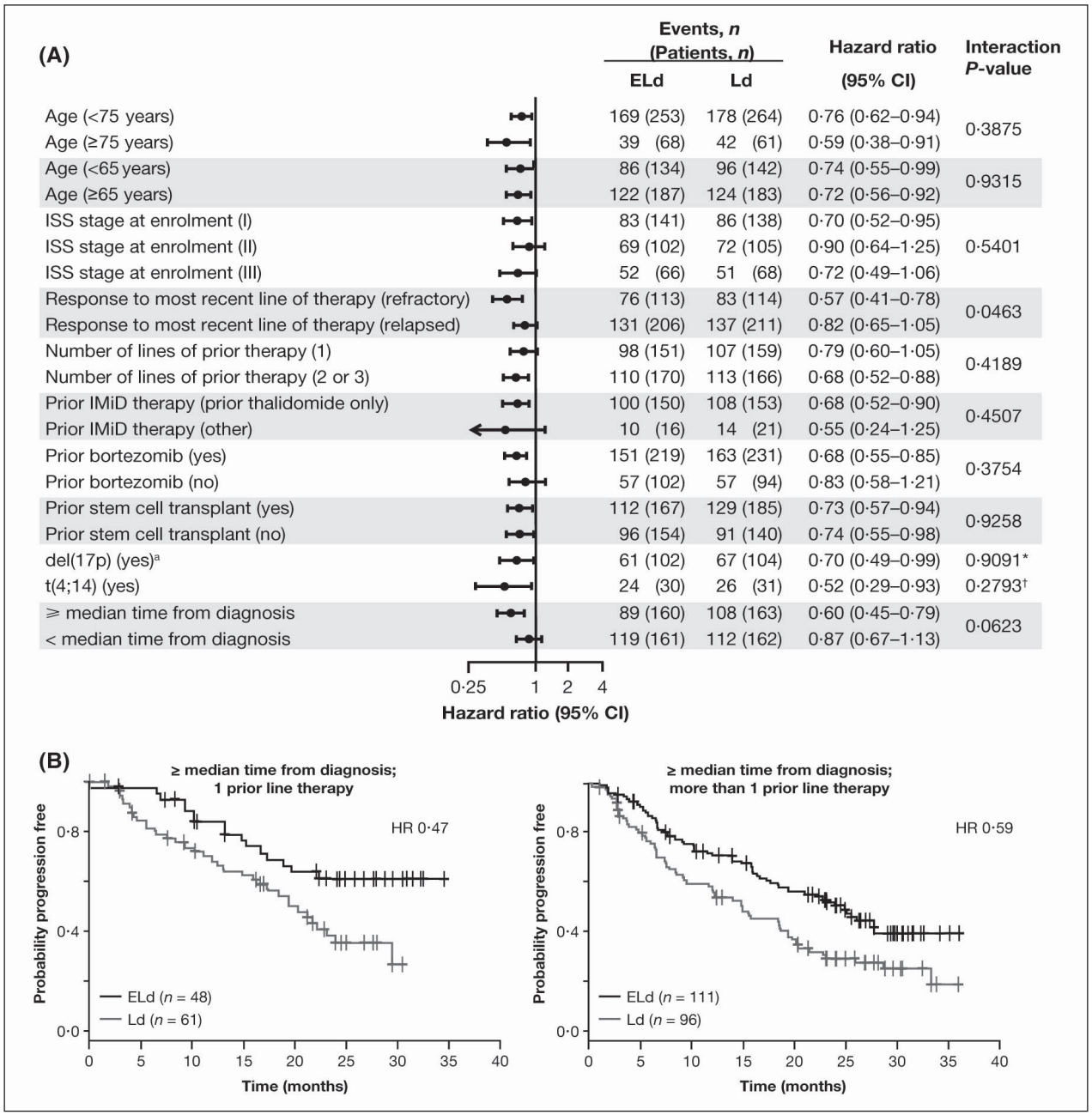

Figure 4. (A) PFS by predefined subgroups and (B) Kaplan–Meier curves of PFS (primary definition), stratified by median time from diagnosis and number of prior lines of therapy. [a]Patients were considered del(17p) positive if any cell was positive (11). *Interaction P-value corresponds to del(17p) (yes) versus del(17p) (no); †Interaction P-value corresponds to t(4:14) (yes) versus t(4:14) (no). CI, confidence interval; ELd, elotuzumab + lenalidomide/dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; ISS, International Staging System; Ld, lenalidomide/dexamethasone; PFS, progression-free survival. (From Ref. 11, pag. 901,© 2017 reprinted by permission of John Wiley and Sons, Ltd.).

of disease longer than 3.5 years and treated in first relapse (HR=0.47) (Fig. 4B) (11).

Interim analysis of 3-year OS, a secondary endpoint of the trial, demonstrated a trend in favour of patients receiving EloRd vs Rd (60% vs 53%, respectively), with an HR for OS of 0.77 (p=0.0257) (Fig. 5) (11). Moreover, survival curves showed an early separation that was maintained over time, supporting

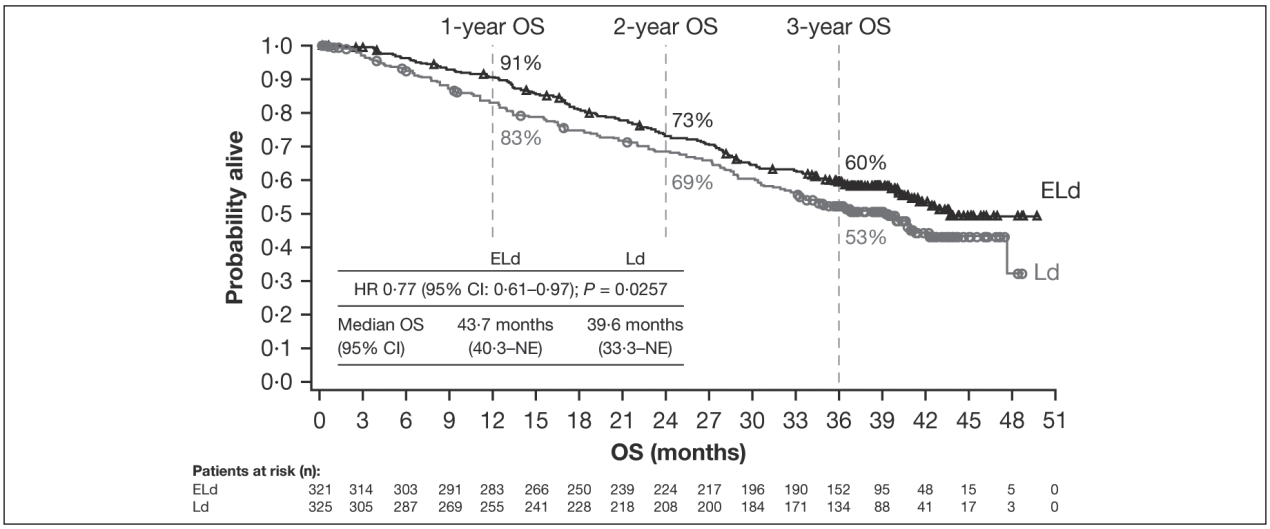

Figure 5. Kaplan–Meier curves of OS (11). CI, confidence interval; ELd, elotuzumab + lenalidomide/dexamethasone; HR, hazard ratio; Ld, lenalidomide/dexamethasone; NE, not evaluable, OS, overall survival. (From Ref. 11, pag. 902,© 2017 reprinted by permission of John Wiley and Sons, Ltd.).

a trend of an OS benefit in favor of EloRd (11).

The durable benefit of EloRd in terms of PFS and OS may be due to different response kinetics of immuno-oncology (I-O) agents such as Elotuzumab, that, in a serum M protein dynamic modeling, demonstrated to slow down tumor regrowth more than Rd (14). These data also explain the difference between EloRd and Rd in terms of Time to Next Treatment (TTNT): EloRd-treated patients had a 38% reduction in the risk of starting subsequent therapy with a median delay of 1 year in the TTNT *vs* patients receiving Rd, supporting the long-term immunologic disease control exerted by Elotuzumab (11).

Safety data in terms of grade 3-4 adverse events and infusion reactions did not significantly change compared with those previously reported (9). Particularly the exposure-adjusted incidence rates per 100 patient-years for infections and second primary malignances were similar.

New data presented at ASCO and EHA 2017

At American Society of Clinical Oncology (ASCO) congress held in Chicago and at the 22nd Congress of European Hematology Association (EHA) held in Madrid, 4-years follow-up data were presented (12, 13). EloRd continued to show benefit in PFS with a 29% reduction in risk of progression/death *vs* Rd (HR=0.71). PFS was 21% *vs* 14% in EloRd and in Rd respectively, namely a 50% relative PFS improvement. The greatest reduction in the risk of progression or death (35%) was observed in patients achieving at least a VGPR (12, 13).

Median OS was 48 month in EloRd treated patients compared to 40 month in those receiving Rd (HR= 0.78) (13).

Conclusions

The treatment of RRMM is becoming a real challenge in MM with the increasing number of approved therapies in recent years. The efficacy of triplet combinations (lenalidomide- or bortezomib-based) has proved to be superior to doublet regimens (14) and EloRd is the first approved regimen containing immuno-oncology agents with the longest follow-up of a mAb in MM. EloRd showed to significantly reduce the risk of progression and death with no excess toxicity and it was able to offer control of long-term disease in different subgroups, including older pa-

tients, those with high-risk cytogenetics or patients who had received more than one prior line of therapy. Based on the efficacy and safety profile of Elotuzumab, the ideal patients for this treatment could be those with a long history of non-aggressive disease, either young with cardiovascular disease (or other comorbidities) or fit/unfit elderly patients, including those aged over 75 years, particularly in first relapse.

In conclusion, the introduction of Elotuzumab in the therapeutic armamentarium of MM represents a major milestone and allows a long-term, hopefully chronic, control of this still incurable disease. However, the clinical benefit of I-O therapies, such as Elotuzumab, follow response kinetics that differ from conventional therapies and are associated on the one hand with durable responses and long-term survival, on the other with stimulation of effective cellular immune responses that lead to tumor regression. Understanding the overall benefits of I-O agents therefore, requires long-term follow-up and time-point analyses for endpoints such as PFS and OS.

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Received: 1 July 2017
Accepted: 10 September 2017
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