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Commentary

Monoclonal Antibodies and Multiple Myeloma: All in All It's Just Another Brick in the Wall?

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Disclosures of potential conflicts of interest may be found at the end of this article.

In this issue of *The Oncologist*, Dr. Tzogani and coworkers, on behalf of the Committee for Medicinal Products for Human Use of European Medicines Agency, report a scientific review of the application leading to the current marketing authorization for daratumumab (Dara) in the European Union (EU) as single agent or in combination with low-dose dexamethasone and bortezomib (D-Vd) or lenalidomide (D-Rd) for relapsed/refractory multiple myeloma (RRMM) [1].

Dara is a first-in-class, fully human IgG-1k monoclonal antibody (MoAb) directed against CD38, a transmembrane protein that behaves both as a receptor and as an ecto-enzyme and is highly expressed on multiple myeloma (MM) plasma cells and, at lower levels, on other immune-competent cells [2]. The mechanisms of action of Dara on neoplastic cells are pleiotropic and include (a) immune-mediated cytotoxicities mainly through complement, monocyte and macrophages, and natural killer (NK) cells (ADCC); (b) apoptosis induced by cross linking of tumor-bound MoAb; (c) modulation of CD38 enzymatic function; and (d) inhibition of CD38+ T-reg lymphocytes and myeloid-derived suppressor cells.

Approval for Dara as single agent in RRMM was based on two phase I–II trials [3, 4], subsequently updated in a pooled analysis of 148 patients treated at the dose of 16 mg/kg [5]. Notably, although median progression-free survival (PFS; 4 months) was similar to that achievable in the same setting of heavily treated RRMM patients [6, 7], 21 months' duration of overall survival (OS) compared favorably with real-world findings reported in national databases [8] and with those of historical controls receiving salvage therapies without Dara, including next-generation proteasome inhibitors (PIs) and immunemodulatory drugs (IMIDs) [9]. With 3 years of median follow-up, single-agent Dara has recently confirmed previous data of efficacy, with no new safety signals [10]. In particular, deep and durable responses continued to be maintained in a subset (about 20%) of these heavily pretreated patients, with 36.5% of patients remaining alive 3 years after study entry.

Approval of Dara combinations in RRMM was funded on two "twin" phase III randomized trials that reported unprecedented PFS hazard ratios (HR) resulting in 61% and 63% reductions in the risk of disease progression or death with D-Vd versus bortezomib and dexamethasone alone (Vd; CASTOR) [11] or with D-Rd versus lenalidomide and dexamethasone alone (Rd; POLLUX) [12], respectively. Despite differences in patient selection and duration of treatments, these really impressive results compare favorably with all other IMIDs or PI-based randomized trials so far published in the RRMM setting, including newer agents, such as pomalidomide (MM-003), carfilzomib (FOCUS, ASPIRE, ENDEAVOR), elotuzumab (ELOQUENT-2), ixazomib (TOURMALINE-MM1), or panobinostat (PANORAMA-1) [13, 14]. Importantly, the benefits provided by Dara containing triplets were obtained in the absence of additional significant toxicities, with respect to doublets (with the exception of infusion-related reactions [IRRs]), and regardless of age, stage, and previous treatments.

Both CASTOR [15, 16] and POLLUX [17, 18] studies have recently been updated. After median follow-up, of 19.4 and 25.4 months, respectively, median PFS was still significantly prolonged in Dara-containing triplets with respect to control doublets (D-Vd 16.7 vs. Vd 7.1 months; D-Rd not reached vs. Rd 17.5 months). The benefit was most pronounced in patients receiving one prior line of therapy with D-Vd. The PFS advantage of D-Rd was maintained in patients with high cytogenetic risk and in patients who had previously received lenalidomide or were refractory to bortezomib. In both studies, significantly higher overall response rate (ORR; D-Vd 84%, D-Rd 93%) and percentages of at least very good partial response (VGPR; D-Vd 62%, D-Rd 79%) and stringent complete response/complete response (sCR/CR; D-Vd 29%, D-Rd 51%) were reached with triplets. More importantly, minimal residual disease (MRD) negative rates at three next-generation sequencing sensitivity thresholds were several times higher in Dara arms, with the 10^{-5} sensitivity threshold associated with prolonged PFS with D-Vd. Interestingly, PFS was prolonged in patients who achieved MRD-negative disease regardless of treatment group and irrespective of cytogenetic profile [19]. Progression free survival-2 (PFS2) and time to next treatment were also significantly improved in Dara-containing arms. Importantly, the safety profile remains consistent with earlier reports after longer follow-up. Of note, a significant OS benefit was observed in patients treated after a single line of therapy with D-Vd.

Other Dara-containing combo therapies in RRMM have been investigated. In the multiarm, phase Ib study EQUULEUS, the association of Dara plus pomalidomide and dexamethasone (D-Pd) in 103 patients showed a safety profile similar to

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that of Pd alone, excluding IRRs, and a higher incidence of neutropenia [20]. ORR was 60%, including 25% VGPR and 17% CR or better. Twenty-nine percent of patients achieved MRD negativity at a threshold of 10^{-5}. After a median follow-up of 24.7 months, 82% of patients discontinued treatment, mostly due to progressive disease. Twenty-four-month PFS and OS rates were 30% and 52%, respectively [21]. D-Pd was recently approved in the U.S. by the U.S. Food and Drug Administration (FDA) in the RRMM setting.

The combination of Dara plus carflzomib and dexamethasone (D-Kd) induced an ORR of 84% (13% sCR/CR, 47% VGPR) [22]. The 12-month PFS rate was 74% and the safety profile was consistent with that of the individual therapies. Phase III studies evaluating D-Pd versus Pd and D-Kd versus Kd in RRMM are ongoing.

Three dosing schedules of Dara as single agent have been explored in higher-risk smoldering MM (SMM; CENTAURUS phase II study) [23]. Preliminary data on 39 patients indicate a safety profile similar to that observed in RRMM, with up to 10% of drug discontinuation, no death, and an estimated 12-month PFS rate of 89%–98%. ORR ranged from 38% to 56% (at least VGPR 15%–22%), with the best results obtained in a long intense dosing schedule, which will be further evaluated in a phase III study (AQUILA) with subcutaneous administration of Dara.

The combination of bortezomib, melphalan, and prednisone (VMP) is a standard first-line therapy for MM patients not eligible for autologous transplantation (AuSCT). In the phase III, randomized trial ALCYONE, thus far the first study fully published using a MoAb in newly diagnosed MM (NDMM), VMP was compared with VMP plus Dara (D-VMP) [24] in 706 patients. At a median follow-up of 16.5 months, the median/18-month PFS rates were not reached/71.6% in the Dara group and 18.1 months/50.2% in the control group, respectively ($p < .001$). HR for disease progression or death in the D-VMP versus VMP arm was 0.50 ($p < .001$). Subgroup analyses for PFS showed that the superiority of D-VMP over VMP was consistent across all subgroups, including patients older than 75 years of age, International Staging System stage III, renal impairment, or high-risk cytogenetic profile. ORR was 90.9% in the D-VMP arm versus 73.9% in the VMP arm ($p < .001$), and the rate of CR or better was 42.6% versus 24.4% ($p < .001$). In the Dara group, 22.3% of the patients achieved MRD negativity (10^{-5}) compared with 6.2% of those in the control group ($p < .001$). Grade 3 and 4 hematologic toxicities were similar in the two groups, although the rate of grade 3 or 4 infections was higher in the D-VMP arm. Dara-associated IRRs occurred in 28% of the patients.

An ongoing, randomized trial currently compares the combination of lenalidomide, bortezomib, and dexamethasone (RVd; a standard of treatment in the U.S. for NDMM eligible for AuSCT) with RVd plus Dara (Dara-RVd) as induction, consolidation, and maintenance [25]. Available data have evidenced neither new safety signals with Dara-RVd during the induction phase (four cycles) nor detrimental effect on stem cells mobilization.

Two phase III studies comparing Dara-Rd versus Rd in NDMM not eligible for AuSCT (MAIA) and Dara-Vd + thalidomide (Dara-VTD) versus VTD as induction/consolidation and Dara maintenance in transplant-eligible NDMM patients (CASSIOPEA) are ongoing.

Finally, impressive preliminary results have recently been reported in a phase Ib study with the quadruplet Dara (2-days divided first administration), carfilzomib, lenalidomide, and dexamethasone (Dara-KRd) in NDMM, regardless of transplant eligibility [26]. ORR was 100%, including 57% sCR/CR and 33% VGPR. Twelve-month PFS and OS rates were 95% and 100%, respectively. CD34+ cell collection yields were consistent with previous KRd studies. The most clinically relevant grade 3–4 toxicity was pulmonary embolism (14%), and IRRs (all grade 1 or 2) occurred in 27% of patients.

Elotuzumab (Elo) is a first-in-class, humanized, IgG-1k chimeric, immune-stimulatory MoAb that recognizes CD319/SLAMF7, a cell surface glycoprotein that is highly expressed by 95% of MM, and across several hematopoietic cells, NK cells, but not by other normal tissue cells [27]. Elo causes MM cell death by directly activating NK cells against neoplastic plasma cells and by tagging them for recognition of ADCC.

Although Elo is not active as single agent in MM [28], a phase I/II extension trial reported relevant responses (ORR 92%, at least VGPR 42%, median PFS 32.9 months) with acceptable tolerability in RRMM treated with a combination of Elo, lenalidomide, and dexamethasone (Elo-Rd) [29]. These results led to the first phase III trial with a MoAb in MM (ELOQUENT-2), in which 646 RRMM patients were randomized to receive Elo (10 mg/kg) plus standard-dose lenalidomide and dexamethasone (Elo-Rd) or lenalidomide and dexamethasone (Rd) alone [30]. Patients had previously received 1–3 lines of therapy (median 2), and prior lenalidomide exposure (but not resistance) was permitted. The triplet Elo-Rd proved significantly superior to the doublet Rd, in terms of ORR (79% vs. 66%, $p < .001$) and at least VGPR (28% vs. 21%), although fewer patients in the Elo-Rd group had a CR or better (4% vs. 7%); this was probably due to a underestimation of CR response rates in the Elo-Rd group, owing to the presence of circulating Elo in serum, interfering with serum protein immunofixation assays. After a follow-up of 24.5 months, median PFS was significantly better in the Elo arm (19.4 vs. 14.9 months), translating to a 30% reduction in the risk of disease progression or death (HR, 0.70; $p < .001$). This PFS benefit was consistent across key subgroups, in particular in patients older than 65 years and in those with resistance to the most recent line of therapy, previous exposure to bortezomib or immunomodulatory drugs, or high-risk cytogenetics. Overall, toxicities of any grade were not significantly different between the two arms, the most common grade 3 or 4 with Elo being asymptomatic lymphopenia (77%). Elo-related IRRs occurred in only 10% of patients. Based on these results, Elo-Rd has been approved in the EU for the treatment of RRMM after at least one prior therapy (1–3 lines in the U.S.). In recent updates of the ELOQUENT-2 study, Elo-Rd benefits were maintained, with a PFS advantage at 3 (26% vs. 18%) and 4 years (21% vs. 14%) and a trend toward improved OS at 4 years (50% vs. 43%) compared with Rd [31, 32].

Combination of Elo with bortezomib and dexamethasone (Elo-Vd) has provided less-significant benefits in RRMM [33]. Other combinations with Elo currently under investigation in RRMM include the anti-Kir or anti-CD137 antibodies lirilumab and urelumab, association with pomalidomide and dexamethasone (Elo-Pd) ± bortezomib, and Elo-Pd plus nivolumab. Elo-Rd is also currently being investigated versus Rd in a phase II, open-label, randomized study enrolling NDMM patients

ineligible for AuSCT in Japan [34], in high-risk SMM [35] (where Elo is also explored as single agent), in phase I/II or phase III studies ± bortezomib for both transplant-eligible or non-eligible patients, and as maintenance after AuSCT.

Despite the revolutionary therapeutic success in some solid malignancies and in Hodgkin's lymphoma, the role of check-point inhibitors in MM remains controversial [36, 37]. Monotherapy with nivolumab had no relevant activity in RRMM [38]. Conversely, combination of pembrulizumab with lenalidomide or pomalidomide plus dexamethasone induced ORRs up to 77%, including a significant proportion of at least VGPR, with durable benefit even in the double-refractory (IMIDs and PIs) population [39, 40]. Notably, the rate of autoimmune disorders was significant in one study [40]. Thus, several trials were initiated to evaluate various combinations of check-point inhibitors with other agents (in particular IMIDs and MoAbs) [36, 37]. On July 3, 2017, however, the FDA placed a clinical hold on two phase III trials with pembrolizumab (KEYNOTE-183 and KEYNOTE-185) enrolling patients with RRMM and ordered the discontinuation of the lenalidomide/dexamethasone/pembrolizumab arm of another trial (KEYNOTE-023), because interim results showed that pembrolizumab was associated with an unexplained increased risk for death. On September 7, 2017, the FDA also placed a partial clinical hold on CA209602 (CheckMate-602), CA209039 (CheckMate-039), and CA204142 trials investigating nivolumab-based combinations in patients with RRMM. On December 6, 2017, however, the FDA allowed CheckMate-039 and CA204142 phase I and II trials to restart after their amendment, although the phase III study CheckMate-602 still remains on partial clinical hold. A pilot trial with pembrolizumab as single agent in higher-risk SMM patients is ongoing [41].

There are numerous new types and classes of MoAbs, directed against a variety of targets, which are under preclinical or less advanced clinical investigation in the MM setting [42, 43]. The most promising ones are next-generation anti-CD38 (Isatuximab, MOR202) and anti-B-cell activating factor (tabalumab) molecules, antibody-drug conjugates targeting B-cell maturation antigen (GSK2857916) or CD138 (Indatuximab ravtansin) and MoAbs directed against molecules involved in MM-induced bone destruction, such as RANK-L (denosumab, recently approved by the FDA for the prevention of skeletal-related events in MM) or DDKK1 (BHQ880). In this setting, interesting updates on GSK2857916 and isatuximab studies in RRMM have been presented at the ASH Meeting held in Atlanta in December 2017 [44–47].

MoAbs currently available for real-life clinical use [48–50] represent a new and heterogeneous class of effective drugs for MM that significantly differ from other treatments due to their capacity in stimulating immune-competent cells to kill neoplastic plasma cells. They have specific, but manageable, safety profiles and may be combined with other agents without adding significant toxicities and inducing synergistic antineoplastic activities that ensure enhancement of both depth (including MRD negativity) and duration of responses. Hopefully, this could translate to a cure of the disease, at least in a proportion of patients. Thus, we are probably at the beginning of a new era in which, as occurred for other hematological malignancies, MoAbs would seem to be almost ready to represent, in the near future, the backbone for various types of treatments that could really change first-line and salvage therapy paradigms of both younger and elderly patients with NDMM and RRMM [51, 52].

From a practical point of view, IRRs (occurring mostly during the first infusion in about 50% and 10% of patients receiving Dara or Elo, respectively), interference of Dara with blood type characterization and that of both Dara and Elo in assessment and monitoring of deepest responses to treatment, represent unique and well-known challenges, which are manageable with appropriate measures and techniques [2, 27]. To shorten the long and tedious first infusions of Dara, accelerated infusion rates [53] or a split dose over 2 days, for cycle one, day 1 [26, 54], have been suggested. More interestingly, s.c. administration of Dara over only 3–5 minutes at the flat dose of 1,800 mg, showing comparable efficacy to intravenous ones, similar serum through concentrations, and lower-than-expected rates of IRRs, is close to being introduced in the clinical practice [55].

Other issues, however, remain to be better elucidated. For example, MM patients show inherent and therapy-related immune suppression. The impact of MoAbs on the remaining innate immunity, particularly against infections, is unknown. A retrospective study of 170 RRMM patients who received Dara as single agent or in various combinations recently showed a high rate of infectious complications (36.5%), most often viral, which were significantly associated with lower nadir of neutrophils and lymphocytes and represented a major cause of death of patients who survived less than 3 months [56]. Increased awareness of Dara-associated risk of infection is therefore important to permit clinical recognition and appropriate anti-infective measures.

The relative contribution of mechanisms to kill MM cells differs among the CD38 MoAbs mostly investigated in the clinical setting, probably because of targeting of different epitopes on the CD38 molecule [2, 50]. It is still not clear whether these functional differences affect their therapeutic utility. Interestingly, recent in vitro data indicate that Dara reacts with CD38 expressed on monocytes, and its binding inhibits osteoclastogenesis and bone resorption in the bone marrow niche of MM patients, targeting early osteoclast progenitors [57]. These observations provide a rationale for the use of an anti-CD38 antibody-based approach as a potential treatment for MM-induced bone disease.

The choice of the most appropriate MoAb, optimal partners and duration of the treatment, identification of translational biomarkers to correlate with response, the possibility of resistance or re-treatment, whether MoAbs are able to target MM stem cells, and their role in allogeneic transplant, SMM, and ultra-high-risk MM variants (i.e., primary plasma cell leukemia) all represent important questions that remain to be answered. Of note, the possible use of MoAbs as maintenance therapy, in order to exert an immunological control of the disease once tumor size has been significantly reduced, seems to be a particularly interesting issue to pursue, but it requires hazard ratio relative risk analysis at different time points, rather than "median" evaluations, that do not provide a true reflection of the survival time that may be expected from the patients who are alive after the median OS is reached.

The true impact of MoAbs in real life must be carefully addressed, as preliminary data seems to indicate that ORR and PFS could be lower than those reported in clinical trials,

especially in heavily treated patients [58]. Furthermore, although available data appear to be quite reassuring, due to profound interaction with the immune system, long-term safety of different MoAbs, in terms of possible increased risk of autoimmune disorders and secondary malignancies, also remains to be better clarified. In this setting, waiting for the final and long-term results of current ongoing clinical trials, caution, above all about the use of some types of combinations (as the history of checkpoint inhibitors in MM teaches!), is still needed.

Finally, MoAbs should soon be integrated and positioned within the context of an emerging scenario in which, along with "novel-novel agents," adoptive immunotherapy with chimeric antigen receptor T cells targeting B-cell antigens [37, 59] and newer examples of precision medicine (i.e., the Bcl-2 inhibitor venetoclax in MM patients carrying t(4;11) [60, 61] or the first-in-class selective inhibitor of nuclear export compound Selixenor [62]) could play a relevant therapeutic role for MM patients in the near future.

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Editor's Note:

See the related article, "EMA Review of Daratumumab for the Treatment of Adult Patients with Multiple Myeloma," by Kyriaki Tzogani et al. on page 594 of this issue.