Anti-CD38 and anti-SLAMF7: the future of myeloma immunotherapy

Elena Zamagni, Paola Tacchetti, Lucia Pantani & Michele Cavo

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Anti-CD38 and anti-SLAMF7: the future of myeloma immunotherapy

Elena Zamagni*, Paola Tacchetti*, Lucia Pantani and Michele Cavo

“Seràgnoli” Institute of Hematology, Bologna University School of Medicine, Bologna, Italy

ABSTRACT

Introduction: the high expression of a number of surface antigens on malignant plasma cells, the bone marrow micro-environment and immune effector T cells, makes these appealing targets for immune therapy with monoclonal antibodies (mAbs).

Areas covered: Two mAbs, anti-CD38 daratumumab (Dara) and anti-SLAMF7 elotuzumab (Elo), have achieved recent regulatory approval for relapsed or refractory MM (RRMM) and are currently being explored as possible treatment options in novel combinations and different settings. This review discusses the current landscape and possible development of anti-CD38 and anti-SLAMF7 mAbs.

Expert commentary: Three phase III trials demonstrated a significant advantage in terms of response and PFS when Dara or Elo are combined with lenalidomide-dexamethsone (Rd) or bortezomib-dexamethsone (Vd), in comparison to doublet regimens, for patients with RRMM. Treatment algorithms including Dara- or Elo-based triplets may be defined on the basis of disease and patients’ characteristics, as well as of their prior exposure to different classes of novel agents. Evaluation of these agents in new combination regimens, including second and third generation PIs and IMiDs, are under investigation. Moreover, use of mAbs in phases of the disease where the immune system is less compromised, such as newly diagnosed MM or even high-risk smoldering myeloma, appears logical.

1. Introduction

The treatment landscape for multiple myeloma (MM) has dramatically evolved in recent decades, with the increasing availability of highly active new therapies which have considerably improved patient outcomes. This has come about through a better understanding of the disease biology, leading to the discovery of novel pathways and targets. Over the past two decades, one first major change was the introduction of proteasome inhibitors (Pis) and immunomodulatory drugs (IMiDs), which resulted in doubled progression-free survival (PFS) and overall survival (OS) [1].

More recently, monoclonal antibodies (mAb) targeting MM cell surface antigens, the bone marrow microenvironment and immune effector T cells have been developed. The action mechanisms of mAbs include antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), and inducing cell death by direct effects such as alterations in cellular signaling, inhibition of function of growth factor receptor or adhesion molecules [2]. Two mAbs, anti-CD38 daratumumab (Dara) and anti-SLAMF7 elotuzumab (Elo), have achieved recent regulatory approval for relapsed or refractory MM (RRMM) patients and are currently being explored as possible treatment options in novel combinations and different settings. This review discusses the current landscape and possible development of anti-CD38 and anti-SLAMF7 mAbs.

2. CD38 and anti-CD38 mAb

CD38 is a cell surface glycoprotein with dual receptor and ectoenzyme activity [3]. CD38 has been shown to be in close contact with the B cell receptor (BCR) complex and CXCR4. It can interact with CD31 or hyaluronic acid and activate NFkB, ZAP-70, and ERK1/2 pathways. Additionally, CD38 catalyzes the synthesis and hydrolysis of cyclic ADP-ribose (cADPR) from NAD+ to ADP-ribose, essential for intracellular calcium mobilization. It is involved in the regulation of adhesion, homing, signaling, and catabolism of extracellular nucleotides [4].

CD38 is highly expressed on plasma cells (PCs), but also on normal lymphoid and myeloid cells, red blood cells, and platelets. A comparison of the mean fluorescent intensity of CD38 across these cellular populations showed that, after PCs, NK cells expressed the highest levels of CD38, followed by subpopulations of B and T cells [5]. CD38 is likewise expressed on tissues of non-hematopoietic origin, including prostatic epithelial cells, pancreatic islet cells, perikarya and dendrites of some neurons, airway striated muscle cells, renal tubules, retinal gangliar cells, and corneal cells [6-8].

Due to the high expression of CD38 on MM PCs, together with its role as a receptor and ectoenzyme, anti-CD38 mAbs represent a novel way of targeting the disease. Several anti-CD38 mAbs have been developed. Dara is a first-in-class human IgG1-k mAb with a high affinity to CD38. Dara induces cellular death through various mechanisms, including CDC,
ADCC, ADCP, and induction of apoptosis via cross-linking [9]. In addition, Dara plays a role in immunomodulation by means of depletion of CD38-positive regulatory T, regulatory B, and myeloid-derived suppressor cells, which in turn leads to an increase in T helper cells, cytotoxic T cells, T cell functional response, and T cell receptor (TCR) clonality [5]. Dara is the most advanced CD38-targeting mAb in terms of clinical development, since its recent approval by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of relapsed and refractory patients. Other anti-CD38 mAbs still at the phase of clinical study include the IgG1-k chimeric mAb isatuximab/SAR650984 targeting a completely different amino acid sequence than Dara, and the IgG1-λ human mAb MOR202 [10]. Isatuximab has CDC and ADCC actions, a strong pro-apoptotic activity independent of cross-linking, a high ability to modulate ectoenzyme function, and also immunomodulatory activities supported in preclinical experiments [10,11]. MOR202 acts mainly with ADCC and ADCP, though to a lesser extent with CDC, and induces programmed cell death via cross-linking, whereas potential immunomodulatory effects are currently unknown [10]. The functional differences between these mAbs can be explained by different epitopes targeted on the CD38 molecule along with different affinities against CD38.

2.1. Anti-CD38 mAb in relapsed/refractory MM

2.1.1. Monotherapy

Based on the results of phase I/II GEN501 [12] and phase II SIRIUS [13] studies, Dara monotherapy was approved in 2015 by the FDA and in 2016 by the EMA, for patients with RRMM whose prior therapy included a PI and an IMiD. A pooled analysis of these trials [14] (Table 1) showed the efficacy and favorable safety profile of single agent Dara, administered intravenously (iv) at the dose of 16 mg/Kg, in a heavily pretreated population. Patients received a median of 5 prior lines of therapies, 86.5% of patients were double refractory to both a PI and an IMID, 39% were refractory to the second-generation PI carfilzomib, and 55% were refractory to the third-generation IMiD pomalidomide. The overall response rate (ORR) was 31%, with 83% of patients achieving at least stable disease (SD). The median duration of response (DOR) was 7.6 months, and median PFS was 4.0 months. Notably, the median OS was 20.1 months, and the clinical benefit on OS was extended to those patients with SD or minimal response (MR). Dara showed a manageable toxicity profile in that 48% of patients experienced infusion-related reactions (IRRs), less than 3% of grade ≥3, 96% of cases occurring during the first infusion, and mainly consisting of respiratory events. Thus, these data showed no relevant safety signals except for IRRs, the achievement of at least partial response (PR) in one-third of patients, a PFS concordant with that reported in other studies for RRMM with third-generation IMiD pomalidomide or second-generation PI carfilzomib [15,16], despite the more refractory population, and an OS that appears to be extended beyond what is expected in such advanced disease. Consistently, an adjusted treatment comparison suggests that Dara monotherapy provides a substantial survival benefit compared with real-world historical controls in heavily pretreated and highly refractory MM patients [17]. Hypothesized mechanisms underlying the survival benefits and under investigation include the prolonged immune-mediated effect and possible enhanced response to subsequent treatments. Interestingly, the quality of the response to Dara has been correlated with the intensity of CD38 expression on neoplastic PCs, and with the presence of NK cells in the bone marrow microenvironment [18].

Further developments of Dara therapy are aimed at shortening the infusion time and potentially reducing the incidence of IRRs. The subcutaneous (sc) delivery of Dara in combination with recombinant human hyaluronidase (rHuPH20) is currently under investigation. Preliminary results of the phase Ib PAVO study for patients with RRMM, have suggested that Dara administered sc, at the dose of 1800 mg over 3–5 min, achieves serum trough concentrations similar to or greater than iv delivery, with a lower rate of IRRs, and a comparable response [19,20]. A phase III clinical trial comparing sc versus iv administration of Dara for patients with RRMM is currently ongoing (NCT03277105) (Table 2).

The potent effects of targeting CD38 in MM have also been supported by the preliminary results of isatuximab and MOR202. Isatuximab at the dose of 10 and 20 mg/kg demonstrated single-agent activity in RRMM patients exposed to a median of 5 prior lines of therapy, with an ORR of 24%–29%, median PFS of 3.7 months and median OS of 18.6 months [21]. MOR202 with a dose ranging between 4 and 16 mg/kg, combined with low-dose dexamethasone, achieved an ORR of 29%, in patients with a median of 4 prior lines of therapy [22].

2.1.2. Combination therapies

Due to their peculiar action mechanism and favorable toxicity profile, CD38-targeting mAbs are attractive partners in combination regimens. Preclinical studies have initially demonstrated a synergistic effect with PIs and IMiDs, such as to increase the pro-apoptotic action and enhance NK-mediated ADCC [23], defining the rationale for clinical application.

On the basis of two phase III trials, the combinations of Dara with bortezomib-dexamethasone (DaraVd) or lenalidomide-dexamethasone (DaraRd), were approved in 2016 by the FDA and in 2017 by the EMA for patients with MM who have received at least 1 prior line of therapy. The CASTOR study (Table 1) compared eight cycles of Vd versus eight cycles of DaraVd followed by maintenance with Dara, for patients treated with at least 1 previous line of therapy and not refractory to bortezomib. The triplet regimen was associated with increased and deeper responses in comparison with the doublet regimen, reaching an ORR of 84% versus 63% (P < 0.0001), and a complete response (CR) rate of 29% versus 10% (P < 0.0001). Adding Dara to Vd translated also into extended PFS, with a median of 16.7 versus 7.1 months (HR, 0.31; 95% CI, 0.24–0.39; P < 0.0001), and this PFS benefit was confirmed in different subgroups including patients ≥65 years, those with prior bortezomib exposure and those with high-risk cytogenetics [24–26]. Overall, the benefit of DaraVd was most apparent in patients with one prior line of therapy. Similarly, the POLLUX trial (Table 1) compared continuous therapy with Rd versus DaraRd for...
Table 1. Results of selected clinical trials with daratumumab and elotuzumab in multiple myeloma.

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>N</th>
<th>Design</th>
<th>Patients</th>
<th>Key message</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daratumumab (Dara)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lokhorst et al.</td>
<td>I-II</td>
<td>104</td>
<td>Dara monotherapy</td>
<td>RRMM</td>
<td>- No MTD</td>
</tr>
<tr>
<td>NEJM 2015 [12]</td>
<td></td>
<td></td>
<td>Dose escalation</td>
<td>Prior therapies (median) = 4</td>
<td>- For the 16 mg/kg cohort:</td>
</tr>
<tr>
<td>Lonial et al.</td>
<td>II</td>
<td>106</td>
<td>Dara monotherapy</td>
<td>RRMM</td>
<td>ORR = 36% and median PFS = 5.6 months</td>
</tr>
<tr>
<td>Lancet 2016 [13]</td>
<td></td>
<td></td>
<td>16 mg/kg, weekly for 8 weeks, every 2 weeks for 16 weeks and then monthly</td>
<td>Prior therapies (median) = 5</td>
<td>At the dose of 16 mg/kg:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dual refractory = 64%</td>
<td>- ORR = 29.2%</td>
</tr>
<tr>
<td>Usmani et al.</td>
<td>I-II</td>
<td>148</td>
<td>Dara monotherapy</td>
<td>RRMM</td>
<td>- Median DOR = 7.4 months</td>
</tr>
<tr>
<td>Blood 2016 [14]</td>
<td></td>
<td></td>
<td>16 mg/kg</td>
<td>Prior therapies (median) = 5</td>
<td>- median PFS = 3.7 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dual refractory = 82%</td>
<td>- ORR 31%, ≥ VGPR 13%</td>
</tr>
<tr>
<td>Palumbo et al.</td>
<td>III</td>
<td>498</td>
<td>DaraVd versus Vd</td>
<td>RRMM</td>
<td>- Median OS = 20.1 months</td>
</tr>
<tr>
<td>NEJM 2016 [24]</td>
<td></td>
<td></td>
<td></td>
<td>Prior therapies (median) = 2</td>
<td>DaraVd resulted in:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- better ORR = 83 vs. 63%</td>
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<td></td>
<td></td>
<td>better CR rate = 19 vs. 9%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>better PFS = 16.7 vs. 7.1 months</td>
</tr>
<tr>
<td>Dimopoulos et al.</td>
<td>III</td>
<td>569</td>
<td>DraRd vs. Rd</td>
<td>RRMM</td>
<td>- Median OS = 17.5 months</td>
</tr>
<tr>
<td>NEJM 2016 [27]</td>
<td></td>
<td></td>
<td></td>
<td>Prior therapies (median) = 1</td>
<td>DaraRd resulted in:</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>- better CR rate = 55 vs. 21%</td>
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<td></td>
<td></td>
<td></td>
<td>better PFS = 58 vs. 35% @ 30-months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- ORR 60%, CR rate 16.5%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Median PFS = 8.8 months</td>
</tr>
<tr>
<td>Chari et al.</td>
<td>Ib</td>
<td>103</td>
<td>DaraPd</td>
<td>RRMM</td>
<td>- Median OS = 17.5 months</td>
</tr>
<tr>
<td>IMW 2017 [32]</td>
<td></td>
<td></td>
<td></td>
<td>Prior therapies (median) = 4</td>
<td>Dara 1800 mg sc plus rhuPH20 administered over 3–5 min showed an incidence of IRRs of only 4% with no grade 3–4</td>
</tr>
<tr>
<td>Chari et al.</td>
<td>Ib</td>
<td>78</td>
<td>Dara co-formulated with rhuPH20 by sc infusion</td>
<td>RRMM</td>
<td>- Dara shows single-agent activity in SMM</td>
</tr>
<tr>
<td>ASH 2017 [20]</td>
<td></td>
<td></td>
<td></td>
<td>Prior therapies (median) = 4</td>
<td>- Better ORR in the Long and Int than Short arm = 56 vs. 54 vs. 38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Better 12-months PFS in the Long and Int than Short arm = 95 vs. 88 vs. 81%</td>
</tr>
<tr>
<td>Hofmeister et al.</td>
<td>II</td>
<td>123</td>
<td>Dara monotherapy in 8-week cycles with 3 different schedules: - long intense (Long) - intermediate (Int) - short intense (Short)</td>
<td>SMM</td>
<td>- Better ORR = 93 vs. 76%</td>
</tr>
<tr>
<td>ASH 2017 [34]</td>
<td></td>
<td></td>
<td></td>
<td>Intermediate or high risk</td>
<td>DaraVMP resulted in:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- better CR rate = 43 vs. 24%</td>
</tr>
<tr>
<td>Mateos et al.</td>
<td>III</td>
<td>706</td>
<td>DaraVMP vs. VMP</td>
<td>NDMM</td>
<td>higher MRD negativity rate (10^−5) = 24 vs. 6%</td>
</tr>
<tr>
<td>NEJM 2017 [35]</td>
<td></td>
<td></td>
<td></td>
<td>ineligible for stem-cell transplantation</td>
<td>better PFS = 72 vs. 50% @ 18-months</td>
</tr>
<tr>
<td><strong>Elotuzumab (Elo)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zonder et al.</td>
<td>I</td>
<td>34</td>
<td>Elo monotherapy</td>
<td>RRMM</td>
<td>- No MTD</td>
</tr>
<tr>
<td>Blood 2012 [44]</td>
<td></td>
<td></td>
<td>Dose escalation</td>
<td>Prior therapies (median) = 4</td>
<td>- Only SD</td>
</tr>
<tr>
<td>Lonial et al.</td>
<td>I</td>
<td>28</td>
<td>EloRd</td>
<td>RRMM</td>
<td>- No MTD</td>
</tr>
<tr>
<td>JCO 2012 [40]</td>
<td></td>
<td></td>
<td>Dose escalation for Elo</td>
<td>Prior therapies (median) = 4</td>
<td>- ORR = 82%</td>
</tr>
<tr>
<td>Jakubowiak et al.</td>
<td>I</td>
<td>28</td>
<td>EloVd</td>
<td>RR</td>
<td>- No MTD</td>
</tr>
<tr>
<td>JCO 2012 [45]</td>
<td></td>
<td></td>
<td>Dose escalation for Elo</td>
<td>Prior therapies (median) = 3</td>
<td>- ORR = 48%</td>
</tr>
<tr>
<td>Richardson et al.</td>
<td>II R</td>
<td>73</td>
<td>EloRd</td>
<td>RRMM</td>
<td>- ORR = 84%</td>
</tr>
<tr>
<td>Lancet Haematol 2015 [47]</td>
<td></td>
<td></td>
<td>10 mg/kg vs. 20 mg/kg</td>
<td>Prior therapies (median) = 2</td>
<td>- Similar ORR in the 2 arms</td>
</tr>
<tr>
<td>Jakubowiak et al.</td>
<td>II R</td>
<td>152</td>
<td>ELOVd vs. Vd</td>
<td>RRMM</td>
<td>- Extended median PFS for EloVd vs. Vd = 9.7 vs. 6.9 months</td>
</tr>
<tr>
<td>Blood 2016 [42]</td>
<td></td>
<td></td>
<td>Dose escalation for Elo</td>
<td>Prior therapies (median) = 1</td>
<td>- better PFS = 19.4 vs. 14.9 months</td>
</tr>
<tr>
<td>Lonial et al.</td>
<td>III</td>
<td>646</td>
<td>EloRd vs. Rd</td>
<td>RRMM</td>
<td>similar toxicity (except grade 1/2 IRRs in 10% of patients)</td>
</tr>
<tr>
<td>NEJM 2015 [48]</td>
<td></td>
<td></td>
<td></td>
<td>Prior therapies (median) = 1</td>
<td>- No association between baseline %CD56dim NK cells in bone marrow and response</td>
</tr>
<tr>
<td>Richardson et al.</td>
<td>II</td>
<td>31</td>
<td>Elo monotherapy</td>
<td>SMM</td>
<td>- Elo shows single agent in SMM:</td>
</tr>
<tr>
<td>EHA 2016 [50]</td>
<td></td>
<td></td>
<td>Dose escalation for cycle 2</td>
<td>High risk</td>
<td>- ORR = 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg/kg (weekly cycles 1 and 2, twice monthly from cycle 3)</td>
<td></td>
<td>- two-year PFS = 69%</td>
</tr>
</tbody>
</table>

(Continued)
Table 2. Selected ongoing studies with antiCD38 and antiSLAMF7 monoclonal antibodies in multiple myeloma.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patients</th>
<th>Key message</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghobrial et al. I–II</td>
<td>EloRd</td>
<td>SMM</td>
<td>ORR = 82.6%</td>
</tr>
<tr>
<td>ASH 2016 [52]</td>
<td></td>
<td></td>
<td>No patients had progressed to MM at 24 months</td>
</tr>
<tr>
<td>Takezako et al. II R</td>
<td>EloRd vs. Rd</td>
<td>NDMM</td>
<td>EloRd resulted in higher ORR = 88 vs. 74%</td>
</tr>
</tbody>
</table>

N pts: number of patients; RRMM: relapsed/refractory multiple myeloma; MTD maximum tolerated dose; ORR: overall response rate; DOR: duration of response; PFS: progression-free survival; VGPR: very good partial response; OS: overall survival; DaraVd: daratumumab-bortezomib-dexamethasone; Rd: bortezomib-dexamethasone; CR: complete response; DaraRd: daratumumab-bortezomib-lenalidomide-dexamethasone; DaraPd: daratumumab-pomalidomide-dexamethasone; sc: subcutaneous; HuPH20: recombinant human hyaluronidase enzyme; IRRs: infusion-related reactions; SD: stable disease; ASCT: autologous stem cell transplantation.

Table 2. (Continued).

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patients</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT0277105</td>
<td>EloRd vs. Dara sc</td>
<td>RRMM</td>
<td>III</td>
</tr>
<tr>
<td>NCT03180736 (EMN 14)</td>
<td>DaraPd vs. Pd</td>
<td>RRMM</td>
<td>III</td>
</tr>
<tr>
<td>NCT02990338 (ICARIA-MM)</td>
<td>IsaPd vs. Pd</td>
<td>RRMM</td>
<td>III</td>
</tr>
<tr>
<td>NCT03158688 (CANDOR)</td>
<td>DaraKD vs. KD</td>
<td>RRMM</td>
<td>III</td>
</tr>
<tr>
<td>NCT03000452</td>
<td>DaraDurva</td>
<td>RRMM</td>
<td>II</td>
</tr>
<tr>
<td>NCT0321634</td>
<td>DaraPembro</td>
<td>RRMM</td>
<td>II</td>
</tr>
<tr>
<td>NCT02977494</td>
<td>DaraVd</td>
<td>RRMM with severe RI</td>
<td>II</td>
</tr>
<tr>
<td>NCT0310220</td>
<td>Dara sc vs. active monitoring</td>
<td>High-risk SMM</td>
<td>III</td>
</tr>
<tr>
<td>NCT02960555</td>
<td>Isa single-agent</td>
<td>High-risk SMM</td>
<td>III</td>
</tr>
<tr>
<td>NCT02541383 (CASSIOPEIA)</td>
<td>DaraVTD vs. VTD</td>
<td>NDMM</td>
<td>III</td>
</tr>
<tr>
<td>NCT02874742</td>
<td>DaraVRD vs. VRD</td>
<td>NDMM</td>
<td>II</td>
</tr>
<tr>
<td>NCT02955810</td>
<td>DaraCyBorD</td>
<td>NDMM</td>
<td>Ib</td>
</tr>
<tr>
<td>NCT02252172 (MAIA)</td>
<td>DaraRd vs. Rd</td>
<td>NDMM</td>
<td>III</td>
</tr>
<tr>
<td>NCT03012880</td>
<td>Dara-IxarD</td>
<td>NDMM</td>
<td>III</td>
</tr>
<tr>
<td>NCT03319667 (IMROZ)</td>
<td>IsaVRd vs. Vrd</td>
<td>NDMM</td>
<td>III</td>
</tr>
<tr>
<td>NCT03104842</td>
<td>IsaKRd (±ASCt)</td>
<td>NDMM high risk</td>
<td>II</td>
</tr>
</tbody>
</table>

AntiCD38: Daratumumab (Dara) and Isatuximab (Isa)

- NCT03277105: Dara iv vs. Dara sc
- NCT03180736 (EMN 14): DaraPd vs. Pd
- NCT02990338 (ICARIA-MM): IsaPd vs. Pd
- NCT03158688 (CANDOR): DaraKD vs. KD
- NCT03000452: DaraDurva
- NCT0321634: DaraPembro
- NCT02977494: DaraVd
- NCT0310220: Dara sc vs. active monitoring
- NCT02960555: Isa single-agent
- NCT02541383 (CASSIOPEIA): DaraVTD vs. VTD
- NCT02874742: DaraVRD vs. VRD
- NCT02955810: DaraCyBorD
- NCT02252172 (MAIA): DaraRd vs. Rd
- NCT03012880: Dara-IxarD
- NCT03319667 (IMROZ): IsaVRd vs. Vrd
- NCT03104842: IsaKRd (±ASCt)

AntiSLAMF7: Elotuzumab (Elo)

- NCT02654132 (ELOQUENT-3): EloPd vs. Pd
- NCT02726581 (CheckMate): NivoPd vs. Pd
- NCT03155100: Exploratory arm: EloNivoPd
- NCT03361306: EloKRd
- NCT0278833: EloPd
- NCT02252263: Elo + lirilumab or urelumab
- NCT02279394: EloRd
- NCT0133599 (ELOQUENT-1): EloRd vs. Rd
- NCT02495922: EloVRD vs. VRD
- NCT02420860: Elo + lenalidomide as maintenance post ASCT
- NCT02969837: EloVRD
- NCT02718833: EloVPd
- NCT02252263: Elo + lirilumab or urelumab
- NCT0279394: EloRd
- NCT0133599 (ELOQUENT-1): EloRd vs. Rd
- NCT03155100: Exploratory arm: EloNivoPd
- EloKd
- NCT03361306: EloKRd
- NCT0278833: EloPd
- NCT02252263: Elo + lirilumab or urelumab
- NCT02279394: EloRd
- NCT0133599 (ELOQUENT-1): EloRd vs. Rd
- NCT03104842: IsaKRd (±ASCt)
- NCT02054139: EloVRD vs. VRD
- NCT02495922: EloVRD vs. VRD
- NCT02420860: Elo + lenalidomide as maintenance post ASCT
- NCT02375555: EloVRD
- NCT01668719: EloVRD
- NCT0069837: EloKd

iv: intravenous; sc: subcutaneous; RRMM: relapsed/refractory multiple myeloma; MTD maximum tolerated dose; ORR: overall response rate; DOR: duration of response; PFS: progression-free survival; VGPR: very good partial response; OS: overall survival; DaraVd: daratumumab-bortezomib-dexamethasone; Rd: bortezomib-dexamethasone; CR: complete response; DaraRd: daratumumab-bortezomib-lenalidomide-dexamethasone; DaraPd: daratumumab-pomalidomide-dexamethasone; sc: subcutaneous; HuPH20: recombinant human hyaluronidase enzyme; IRRs: infusion-related reactions; SD: stable disease; ASCT: autologous stem cell transplantation; ELoRd: elotuzumab-lenalidomide-dexamethasone; EloVd: elotuzumab-bortezomib-dexamethasone; R: randomized.
patients treated with at least 1 previous line of therapy and not refractory to lenalidomide. Patients treated with DaraRd had higher rates of deeper response, reaching an ORR of 93% versus 76% (P < 0.0001), and a CR rate of 55% versus 21% (P < 0.0001), which translated into markedly extended PFS, with a PFS at 30 months of 58% versus 35% (HR, 0.41; 95% CI, 0.31–0.53; P < 0.0001). The PFS advantage was observed across all subgroups including patients ≥65 years, those with previous lenalidomide exposure, and those with a high-risk cytogenetic profile, although the poor risk profile conferred by cytogenetics was not completely abrogated [27–29]. The addition of Dara to either Vd or Rd likewise significantly increased the probability to achieve minimal residual disease (MRD) negativity. With a threshold of 10−5, MRD negativity was detected in 12% of patients treated with DaraVd and 27% with DaraRd, and these rates were more than fourfold higher than those were observed with the corresponding two-drug regimen [25,28]. MRD-negative status accumulated more rapidly and over time during Dara-based therapy. In high-risk patients, MRD negativity was achieved only in those treated with Dara-containing regimens [30]. Overall, it would appear that responses in the DaraRd arm of POLLUX were higher than in the DaraVd arm of CASTOR. Although the 12-month estimated PFS in POLLUX (83%) was higher than in CASTOR (60.7%), differences between these studies, including their design (such as the continuous treatment with DaraRd in the POLLUX trial versus a fixed treatment duration with DaraVd followed by maintenance with single-agent Dara in the CASTOR trial) and patients’ characteristics, hamper cross-trial comparisons (Table 3).

Results of a phase Ib study demonstrated that isatuximab too, combined with Rd, is active in patients with RRMM. Objective responses were observed in a heavily pretreated patient population: at least PR was attained in over half of the patients who were refractory to lenalidomide before entering the study [31]. Moreover, promising preliminary efficacy results have been observed with MOR202 combined with Rd in a phase I/II trial [22].

More recently, a phase Ib study demonstrated the efficacy of adding Dara to the third-generation IMiD pomalidomide and dexamethasone (DaraPd), leading in 2017 to FDA approval of this triple regimen for patients who have received at least 2 prior therapies including lenalidomide and a PI. The EQUULEUS study (Table 1) included a more heavily pretreated population than in the CASTOR and POLLUX trials, with a median of 4 prior therapies. The ORR was 60%, the CR rate was 16.5%, and median PFS and OS were 8.8 and 17.5 months, respectively [32]. A similar synergistic effect was observed when isatuximab or MOR202 were combined with Pd [22,33]. Phase III trials will further evaluate the value of adding anti-CD38 mAbs to third-generation IMiDs (NCT03180736, NCT02990338) or second-generation PIs (NCT03158688) (Table 2). Moreover, new anti-CD38 combination regimens including checkpoint blockade therapy targeting the programmed cell death protein 1 (PD1)/PD ligand 1 (PDL1) pathway are under investigation (NCT03000452, NCT03221634) (Table 2).

2.2. Anti-CD38 mAb in smoldering MM

One possible role for anti-CD38 mAbs involves the setting of smoldering MM (SMM), in the aim of delaying progression to symptomatic disease. SMM provides a virtually ideal disease setting in which to assess immunotherapy, in view of the lesser impairment of the immune system.

The phase II CENTAURUS study evaluated Dara monotherapy in patients with intermediate- or high-risk SMM (Table 1). Intermediate- or high-risk SMM was defined as ≥10% to <60% PCs in the bone marrow and ≥1 in the following: serum M-protein ≥3 g/dL; urine M-protein >500 mg/24 h; an abnormal involved/uninvolved serum-free light chain (sFLC) ratio (<0.126 or >8) with serum M-protein <3 g/dL but ≥1 g/dL; and/or involved sFLC ≥100 mg/L with an abnormal FLC ratio (<0.126 or >8), but not ≥100. Patients were randomized to three different dosing schedules of Dara 16 mg/kg iv in 8-week cycles. In the long-intense dosing schedule (Long), Dara was administered weekly in cycle 1, every other week in cycle 2–3, every 4 weeks in cycles 4–7, and every 8 weeks up to cycle 20. In the intermediate dosing schedule (Int), Dara was given weekly in cycle 1, and every 8 weeks up to cycle 20. In the short-intense dosing schedule (Short), Dara was given weekly for 1 cycle. With a median follow up of 9.6 months, preliminary results confirmed that Dara shows single-agent activity in SMM. The ORR was numerically higher in the Long and Int arms than in the Short, 56% versus 54% versus 38%, respectively. Moreover, fewer Long and Int arm patients progressed than on the Short arm, the 12-month PFS rates being

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<tr>
<td>Age, median (range) years</td>
<td>64 (30–88)</td>
<td>65 (34–89)</td>
<td>67 (37–88)</td>
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<td>High risk cytogenetic (%)</td>
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<td>31</td>
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<td>Creatinine clearance ml/min</td>
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<td>28</td>
<td>28</td>
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<tr>
<td>≥60, %</td>
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<td>71</td>
<td>70</td>
</tr>
<tr>
<td>Previous lines of therapy, median (range)</td>
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<td>1 (1–11)</td>
<td>2 (1–4)</td>
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<tr>
<td>Prior lenalidomide exposure, %</td>
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<td>5</td>
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<tr>
<td>Prior bortezomib exposure, %</td>
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<td>68</td>
</tr>
<tr>
<td>Refractory population, %</td>
<td>30</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>Refractory to bortezomib, %</td>
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<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Refractory to lenalidomide, %</td>
<td>30b</td>
<td>NA</td>
<td>NA</td>
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aImmunomodulatory drugs.
bProteasome inhibitors.

DaraVd: Daratumumab-bortezomib-dexamethasone; DaraRd: Daratumumab-lenalidomide-dexamethasone; EloRd: Elotuzumab-lenalidomide-dexamethasone; NA: not applicable.
estimated at 95%, 88%, and 81%, respectively. Dara was well tolerated with a safety profile similar to that in relapsed or refractory MM [34]. A phase III study is ongoing to evaluate long intense dosing with sc administration of Dara versus active monitoring for high-risk SMM (NCT03301220). Moreover, a phase II study is currently evaluating single-agent isatuximab in a similar setting (NCT02960555) (Table 2).

2.3. Anti-CD38 mAb in newly diagnosed MM

Given the proven efficacy of combination regimens including anti-CD38 targeting mAbs for RRMM, ongoing randomized clinical trials have been designed to explore the incorporation of these agents in first-line therapy.

In the phase III ALCYONE trial (Table 1), 706 patients with newly diagnosed MM (NDMM) ineligible for stem-cell transplantation were randomized to receive nine 42-day cycles of standard bortezomib, melphalan, and prednison (VMP) either alone or with Dara (DaraVMP). In the experimental group, Dara 16 mg/kg iv was administered once weekly in cycle 1, every 3 weeks in cycles 2 through 9, and every 4 weeks thereafter until disease progression or unacceptable toxic effects. The primary end point was PFS. At a median follow up of 16.5 months, in a prespecified interim analysis, the addition of Dara to VMP reduced the risk of progression or death by 50%, the 18-month PFS rate being 71.6% versus 50.2% (HR 0.50; 95% CI, 0.38 to 0.65; \( P < 0.001 \)). DaraVMP also correlated with significantly deeper responses than with VMP, including an ORR of 90.9% versus 73.9% (\( P < 0.001 \)), a CR rate of 42.6% versus 24.4% (\( P < 0.001 \)), and a more than three times higher MRD-negative rate, 24.4% versus 6.2% with a threshold of \( 10^{-5} \) (\( P < 0.001 \)). No new safety signals were observed except for higher infection events (23.1% vs. 14.7% grade 3–4) which resolved. Dara-associated IRRs occurred in 27.7% of the patients [35].

Several additional frontline phase II and III clinical trials with anti-CD38 mAbs are currently ongoing or will start very soon (Table 2). In the setting of transplant eligible patients, the randomized CASSIOPEIA trial is exploring the four-drug regimen Dara-bortezomib-thalidomide-dexamethasone (DaraVTD) versus the standard triplet regimen VTD (NCT02541383), as induction and consolidation therapy before and after high-dose melphalan, followed by maintenance treatment with single-agent Dara or observation. In the setting of transplant ineligible patients, ongoing clinical studies are exploring either Rd or bortezomib-lenalidomide-dexamethasone (VRd) as the backbone of newer therapies incorporating anti-CD38 mAbs. In particular, the combination of DaraRd versus Rd is currently under investigation in the phase III MAIA trial (NCT02252172), whereas the phase III IMROZ trial (NCT03319667) is aimed at exploring the combination of isatuximab-VRd (IsaVRd) versus VRd.

3. SLAM F7 and anti-SLAM F7 mAb elotuzumab

SLAMF7 (also referred to as CS1, CD2 subset-1, CRACC, and CD319) is a glycosylated cell surface protein and a member of the signaling lymphocyte activation molecule (SLAM) family, which is mainly expressed on NK cells, CD8 + T cells, activated B cells, and mature dendritic cells, while it is not expressed on hematopoietic stem cells or other normal tissues [36,37]. More than 95% of patients with MM express SLAMF7 regardless of their cytogenetic-molecular profile. Several studies have demonstrated that once SLAMF7 is stimulated by an antibody or a natural ligand, it activates NK cells and other immune cells [37,38]. The role of SLAMF7 in myeloma cells is not entirely clear, but some data suggest that this protein plays an important role in the interaction between myeloma cells and bone marrow stromal cells, enhancing the survival of PCs [36].

Elo is a humanized IgG1-k mAb that binds to the cell surface receptor SLAMF7 and exerts its antitumor effects through several mechanisms. First, Elo has proved to mediate ADCC against PCs [39–41]. At the same time, Elo activates NK cells via binding of the Fc portion of Elo to the Fc receptor (CD16), in association with its adaptor protein EAT-2, which is present on NK cells, but absent on MM cells [39–41]. In a recent phase II study, different polymorphisms of CD16 on NK cells were demonstrated, showing that patients homozygous for the high-affinity allele seem to have the greatest benefit from Elo when compared with patients with a low-affinity allele [42]. As the SLAMF7 protein is virtually unexpressed on normal cells, Elo can selectively kill myeloma cells with minimal effects on healthy tissues. Thus, Elo as monotherapy does not bind to CD34+ hematopoietic stem cells and has no apparent effect on total lymphocyte T and B cell counts when blood samples from healthy individuals have been cultured with different concentrations of anti-SLAMF7 [43].

3.1. Elotuzumab in relapsed/refractory MM

Elo was first tested in several phase I studies in RRMM, either as a single agent or in combination with PIs or IMiDs, to evaluate safety and determine the safe dose; in these trials, despite the favorable preclinical data, it was demonstrated that this agent is not effective as monotherapy [44–46]. In combination with bortezomib, at the standard dose of 1.3 mg/m² twice weekly, Elo was tested in 28 patients with RRMM on days 1 and 11, with a 3 + 3 dose-escalation design in 21-day cycles, at the dosages of 2.5, 5.0, 10, or 20 mg/kg [45]. At least a minor response was achieved in two-thirds of the patients and the median time to progression (TTP) was 9.46 months. In a subsequent randomized phase II study, the combination of Elo (10 mg/kg/week during cycles 1 and 2, on days 1 and 11 during cycles 3–8 and on days 1 and 15 thereafter)-bortezomib-dexamethasone (EloVd) was compared to the standard iv or sc Vd (bi-weekly cycles 1–8 and days 1, 8, and 15 thereafter) in 152 patients with RRMM (1–3 prior therapies) [42]. Despite a similar ORR between the two cohorts (66% versus 63%), the median PFS had a trend in favor of the Elo arm, 9.7 months versus 6.9 months (HR 0.72; 70% CI 0.59, 0.88; \( p = 0.09 \)), respectively [42]. Subgroup analysis of PFS was impaired by the limited number of patients. The 2-year OS rate was 73% in the EloVd arm versus 66% in the control arm. Preclinical evidence also showed that lenalidomide enhances the antitumor activity of Elo, via triggering of the effector cells of ADCC, which formed the rationale for clinical evaluation of this combination [36]. In a phase I/II study, two different doses of Elo (10 mg/kg or 20 mg/kg) in combination...
with oral lenalidomide and dexamethasone at standard doses were evaluated in 73 patients with RRMM. Elo was administered on days 1, 8, 15, and 22 during cycles 1 and 2, and on days 1 and 15 for subsequent cycles [47]. The ORR was 84% with 14% stringent CR (sCR) or CR and 42% VGPR. The efficacy appeared better in the 10 mg/kg cohort than in the 20 mg/kg cohort, with a PFS of 32 and 25 months (median 32 months), respectively, but this was not statistically significant. These data, in combination with preclinical data, identified a dose of 10 mg/kg for further studies.

The positive results of the phase II trial provided further support in justification of the first and only hitherto completed phase III study (ELOQUENT-2) of Elo in relapsed myeloma, which led to the approval of the drug by the FDA in December 2015 and by the EMA in 2016 for RRMM patients who have received at least 1 line of prior therapy, in combination with Rd [48]. In total, 646 patients with RRMM, who had received a median of 2 prior therapies (1–4), were randomized to receive Elo (10 mg/kg weekly for 2 cycles then biweekly until progression or unacceptable toxicity) in combination with lenalidomide (25 mg on days 1–21) plus oral dexamethasone (40 mg/week orally, or 28 mg/week orally and 8 mg intravenously on Elo dosing days) or Rd alone. By the study design, patients could have been exposed to lenalidomide before (<10%) but could not be refractory to the agent [48]. The ORR was 79% in the Elo arm versus 66% in the control arm (odds ratio 1.9, 95% CI 1.4, 2.8; p = 0.001); the median PFS was 19.4 versus 14.9 months, respectively (HR 0.73, 95% CI 0.60–0.89, p = 0.0014). The PFS benefit was consistent across all subgroups, including patients >65 years, those with del(17p) and t(4;14) abnormalities, or with renal failure (creatinine clearance between 30 and 60 ml per minute) [48]. The interim OS analysis demonstrated a strong trend in favor of the Elo arm (HR = 0.77), with a median of 43.7 months versus 39.6 months in the control arm (p = 0.0257), although the follow up was not yet mature [48]. At a longer follow up, 4-year estimates of PFS and OS for patients treated with EloRd were 21% and 50%, respectively, versus 14% and 43% for patients in the control group [49]. Notably, the greatest PFS benefit with EloRd was seen in patients with non-aggressive relapse (as reflected, by a median time of more than 3.5 years since diagnosis) (HR = 0.56) and more than 1 prior line of treatment. Moreover, EloRd-treated patients had a median delay of 1 year in the time to next treatment (TTNT) versus Rd-treated patients (HR 0.62; 95% CI, 0.50–0.77). Safety data were consistent with prior findings and relatively similar between the two arms of the trial [49].

Table 1 summarizes the principal clinical trials of Elo conducted as a single agent and in combination.

Other Elo-based trials in RRMM are currently in progress (Table 2). Two phase II trials (NCT02654132, NCT026112779) are aimed at investigating Elo in combination with Pd, while the four-drug regimen Elo plus nivolumab (PD-1 inhibitor)-pomalidomide-dexamethasone is explored in a phase III study (CheckMate 602; NCT02726581). Moreover, phase II trials will evaluate the value of adding Elo to the second-generation PI carfilzomib (NCT03155100, NCT033613060).

3.2. Elotuzumab in smoldering MM

Elo has also been tested in different settings, like SMM. A first phase II study investigated Elo as a single agent in high-risk SMM, defined as the presence of an M component of more than 3 g/dl and/or abnormal sFLC ratio and/or urine M protein >200 mg/24 h (Table 1). The initial results of the trial were reported on 31 patients, 15 treated at the dose of 20 mg/kg (days 1 and 8 cycle 1, monthly from cycle 2), and 16 at 10 mg/kg (weekly cycles 1 and 2, twice monthly from cycle 3) [50]. Treatment was continued until progression, according to the modified IMWG criteria [51]. The primary end point was the association between baseline % CD56dim NK cells in bone marrow and maximal change in serum M protein; however, this association was not established in the first analysis. On the contrary, Elo monotherapy proved active in patients with SMM, of whom 10% achieved PR, 19% MR and 71% SD. One- and two-year PFS were 80% and 69%, respectively, meaning that Elo may delay progression from SMM to MM. The safety profile of the drug was consistent with that reported in prior Elo studies [50].

Another phase II/II trial is determining whether adding Elo to Rd improves PFS in patients with newly diagnosed high-risk SMM [52]. Patient eligibility was determined upon recently defined criteria for high-risk SMM. Patients were planned to receive weekly Elo (10 mg/kg) on days 1, 8, 15, and 22 for the first two 28-day cycles; lenalidomide 25 mg on days 1–21; and dexamethasone 40 mg on days 1, 8, and 15. Patients were then allowed to continue on maintenance therapy with Elo 20 mg/kg monthly and lenalidomide 25 mg days 1–21 for 16 cycles. A total of 51 patients were enrolled in this study and the first results were presented 1 year ago [52]. The ORR was 82.6%, including 2 CR, 6 VGPR, and 11 PR. The clinical benefit rate was 100%. At the time of the analysis, no patients had progressed to MM at 24 months (primary end point: 2-year PFS). The safety profile was again similar to expected. The researchers concluded that the combination of EloRd is very well tolerated among patients with high-risk SMM and manages to delay progression to active disease [52] (Table 1).

3.3. Elotuzumab in newly diagnosed MM

Several phase II and III clinical trials are currently proceeding for patients with NDMM. A phase III trial (ELOQUENT-1) is comparing the combination of EloRd versus Rd in patients with non-transplant eligible NDMM. The primary and secondary outcomes are PFS and ORR/OS, respectively [53]. A similar randomized phase II study on 82 NDMM nontransplant eligible patients (Table 1) was presented at the ASH meeting in 2017 and showed that the combination of EloRd leads to an ORR rate higher than Rd alone (88% vs. 74%). In this study, a faster infusion rate of Elo, up to 5 mL/min, was tested, without additional IRRs [54]. Another phase III trial (NCT02495922) is currently recruiting patients to evaluate the effect of Elo in combination with VRD during induction and consolidation and with lenalidomide as maintenance treatment in patients with transplant eligible NDMM. Elo is also being investigated...
in a phase II study of where the initial treatment is combined with carfilzomib, lenalidomide and dexamethasone (KRd) in NDMM (NCT02969837), while it is associated with VRD in another phase II trial (NCT02375555) (Table 2).

4. Specific management of mAb

Practical aspects for anti-CD38 and anti-SLAMF7 mAbs include the management of IRRs – which are the commonest side effect of these agents – and the management of possible interference with laboratory tests by the therapeutic mAbs.

4.1. Safety profile of anti-CD38 mAb and infusion reactions

Although CD38 is expressed on various different cells and tissues, these mAbs have a very favorable toxicity profile. In the pooled analysis of phase I/II trials on Dara monotherapy for RRMM patients with advanced disease [14], the commonest treatment-emerging adverse events (≥20%) – excluding IRRs – were fatigue, nausea, anemia, back pain, cough, upper respiratory tract infection, thrombocytopenia, and neutropenia. Similarly, data on Dara-combination regimens showed clinically manageable adverse events consistent with the known toxic effects of single agents [24,27,35]. Higher rates of grade 3–4 thrombocytopenia (45.3% vs. 32.9%) and neutropenia (12.8% vs. 4.2%) were observed for DaraVd than for Vd [24], and a higher rate of grade 3–4 neutropenia (51.9% vs. 37%) was observed for DaraRd versus Rd [27] in RRMM. In the NDMM setting, a higher rate of grade 3–4 infection events (23.1% vs. 14.7%) was observed for DaraVMP versus VMP [35]. No increase in the rate of discontinuation of trial treatments due to adverse events was observed in the Dara groups versus the control groups [24,27,35].

IRRs are reported after Dara iv infusion in around 28%–50% of patients [14,24,27,35]. Due to the CD38 expression on airway smooth muscle cells, IRRs consist mainly of respiratory conditions with nasal congestion, throat irritation, laryngeal edema, cough, dyspnea, and less frequently chills and vomiting. They are predominantly grade 1 or 2 and ≤5% of patients experience grade 3–4 IRRs. More than 90% of IRRs occur during the first infusion whereas the incidence falls to 7% during subsequent administrations [14,24,27,35]. Similarly, isatuximab-induced IRRs occur in 55% of patients with characteristics comparable to those mediated by Dara [21,33]. Conversely, a lower incidence of IRRs, around 10%, has been reported for MOR202 treatment, probably explainable by the low CDC activity [22]. Moreover, it should be noted that a significant reduction in IRRs after Dara administration has been reported with the use of sc delivery in combination with rHuPH20 in the PAVO phase Ib trial [19,20]. The pharmacokinetic for Dara 1800 mg sc was similar to that of a 16 mg/kg iv dose. Adverse events for Dara sc were similar to Dara iv with no new safety signals and with a lower IRR incidence and intensity [19]. The coformulation of Dara 1800 mg sc plus rHuPH20 administered over only 3–5 min showed an incidence of IRRs of only 4% with no grade 3–4 [20].

MM patients treated with anti-CD38 mAbs should receive pre-medications 30–60 min before administration of the therapeutic mAb, with corticosteroid, antipyretic, and antihistamine [2]. Moreover, a multicenter, open-label, early access treatment protocol conducted in RRMM showed that the IRR rate during the first Dara infusion was one-third lower (38.0% vs. 58.5%) in patients for whom pre-infusion medications included 10 mg of montelukast >30 min prior to the first Dara administration [55]. Oral methylprednisolone or equivalent may be administered on the 2 days after Dara infusions [13]. If an IRR develops, the infusion should be temporarily interrupted, and treatment with extra corticosteroids, antihistamines, iv fluids or inhaled β2 adrenergic receptor agonists may be given. When the symptoms of the IRR have resolved, the infusion can be restarted at a lower infusion rate than the infusion rate prior to the reaction. Infusion must be discontinued permanently if life-threatening IRRs occur [2].

Last, currently available data suggest that renal impairment (RI) does not affect the pharmacokinetics of mAbs [56]. Moreover, phase III trials showed no safety alert for Dara in patients with mild or moderate RI, including patients with a creatinine clearance more than 20 ml per minute in the CASTOR trial, and more than 30 ml per minute in the POLLUX trial [24,27]. A phase II clinical trial is currently ongoing to evaluate Dara for patients with severely reduced renal function (NCT02977494) (Table 2).

4.2. Safety profile of elotuzumab and infusion reactions

Safety data regarding Elo mainly come from the ELOQUENT-2 trial, where the good tolerability and feasibility of the drug was clearly demonstrated. The rate of any grade adverse events was identical in the two arms of the trial, with a slightly higher final incidence of grade 3–4 in the Elo arm, as compared to the control arm (77% vs. 68%, respectively) [49]. No patient had a grade 4 or 5 reaction. The main reason for treatment discontinuation was disease progression in both the arms of the study (65% in the Elo group and 79% in the control group) [48]. The commonest adverse events (>10%) in the Elo arm, with a clinically significant difference (5% greater) from the control arm, included fatigue (47% vs. 39%), diarrhea (47% vs. 36%), pyrexia (37% vs. 25%), constipation (36% vs. 27%), cough (31% vs. 18%), nasopharyngitis (25% vs. 19%), upper respiratory tract infection (23% vs. 17%), and pneumonia (20% vs. 14%) [48]. Grade 3–4 lymphocytopenia was higher in the Elo group than the Rd arm (77% vs. 44%, respectively), and was probably responsible for a slightly higher incidence of herpes zoster infection in patients receiving Elo. However, the rate of exposure-adjusted infections was similar in the two arms of the trial [49]. The rate of neutropenia was similar in the two groups.

IRRs occurred in 33 patients (10%) in the Elo group, mainly at the first dose (70%), and were grade 1 or 2 in the majority of them (1% grade 3, no grade 4–5) [48]. The reaction consisted in pyrexia in one-third of cases, chills and hypertension in the remaining patients. In the early trials, acute infusion reactions were common and appeared to correlate with increases in the levels of pro-inflammatory cytokines [57]. In subsequent and current trials, patients on the Elo arms are receiving premedication with dexamethasone, diphenhydramine or its equivalent, ranitidine or its
equivalent and acetaminophen 30–90 min before drug infusion [48,58]. Correct management of IRRs is important to allow patients to receive the recommended dose intensity of the drug. The infusion should be interrupted immediately for grade 2 or higher reactions and permanently discontinued for severe ones; the patient should then be treated as clinically indicated with one or more of the same class of medications as those used for premedication. Once the Elo IRR has resolved or improved to grade ≤1, the infusion can be restarted at 0.5 mL/minute and the rate gradually increased by 0.5 mL/minute every 30 min as tolerated.

Elo displays nonlinear pharmacokinetics, suggesting target-mediated clearance. Analysis according to renal impairment (from mild to end-stage renal disease) did not show any clinically relevant variations in its pharmacokinetic properties [46]. These results suggest that Elo might be administered without dose adjustment for renal function. As is the case with other mAb, no drug interaction has been described. Further follow up is needed to evaluate long-term overall safety.

### 4.3. Evaluation of response during elotuzumab and daratumumab therapy

Dara and Elo are humanized IgG1-k mAbs that can be detected on serum protein electrophoresis (SPEP) and immunofixation (IFE). This interference may confuse the response assessment in patients with IgG-k MM, mainly as concerns determination of sCR/CR/VGPR and early relapse from CR [59]. Apparently, 18.5% of the patients enrolled in different Elo trials proved positive for antidrug antibodies and this might have justified an underestimation of the response category [57]. Similarly, Dara is detected in SPEP and IFE, but this interference can be mitigated by using a mouse-anti-Dara antibody, which binds Dara and shifts the migration of Dara away from the M-protein on IFE [60]. Strategies are being developed to moderate this interference for patients treated with Elo, based on shifting the therapeutic antibody band.

### 4.4. Interference of daratumumab with blood typing

CD38 is weakly expressed on human red blood cells, explaining why Dara-treated patients have pan-reactive indirect antiglobulin tests. Hence, Dara may interfere with indirect antiglobulin tests by binding to endogenous CD38 present on the surface of red blood cells, leading to false positive results at an indirect Coombs test. Importantly, Dara does not interfere with the major antigens of ABO/RhD typing, but with the minor ones. Several options have been suggested to mitigate this interference, including prevention of Dara binding to red blood cells by denaturation of red blood cell CD38 epitopes with dithiothreitol (DTT), or neutralizing interference by adding an anti-idiotypic antibody or soluble CD38 to patient serum samples [61,62]. Moreover, identifying compatible blood products by phenotyping or genotyping patients before treatment with Dara is initiated could be implemented [63]. Interference with routine laboratory tests used in blood transfusion medicine is common for other CD38 mAbs as well, and similar mitigation strategies can be used as clinically indicated [64].

Notably, no red blood cell transfusion-related adverse events, including hemolysis, were observed in the CASTOR, POLLUX and SIRIUS, trials [24,27,65].

### 5. Expert commentary

The treatment landscape in MM is constantly evolving. New insights into the biology of the disease have prompted intense research focused on the development of novel agents targeting specific molecules and pathways. The high expression of a number of surface antigens on malignant PCs, the bone marrow microenvironment and immune effector T cells, makes these appealing targets for immune therapy with mAbs. PC surface targets of mAbs that are in the most advanced phase of development and approval include CD38 and SLAMF7. Another mAb recently developed is targeting the B cell maturation antigen (BCMA), a receptor able to promote cell survival by transduction of signals from two known ligands, B cell activating factor from the tumor necrosis factor (TNF) family (BAFF/BLyS), and APRIL, a proliferation-inducing ligand [66]. Antibodies that increase the host immune response through immune checkpoint inhibitors targeting PD-1 and PD-L1 are also in development [67].

Currently, the FDA and EMA approved mAbs for treatment of MM are Dara and Elo. Dara, targeting CD38, has multiple action mechanisms, including CDC, ADCC, ADCP, direct induction of apoptosis, and modulation of the immunosuppressive bone marrow micro-environment. Elo, targeting SLAMF7, exerts antitumor effects by ADCC and enhancing NK cell cytotoxicity.

Dara shows remarkable single-agent activity in heavily pretreated RRMM. On the contrary, Elo is not effective as mono-therapy. This difference may be explained by the distinct effector mechanisms. Indeed, Dara acts by a dual pro-apoptotic and immune-mediated action, whereas Elo has principally an immuno-oncologic mechanism and requires additional stimuli for effective immune activation to kill myeloma cells, particularly in a setting with compromised NK cell function. The peculiar action mechanism of mAbs and their low toxicity makes these agents ideal components of combination regimens. The rationale of using combination therapy in MM relies upon the heterogeneity of the disease, given the coexistence of multiple clones with variable drug sensitivity. In comparison with doublet regimens, Dara-Rd and Dara-Vd enhanced the rate and depth of response in patients with RRMM after at least 1 prior line of therapy, ultimately prolonging their PFS. Similarly, Elo-Rd yielded superior response rates and PFS when compared with Rd, in a similar RRMM setting. Treatment algorithms including Dara- or Elo-based triplets may be defined on the basis of disease and patients’ characteristics, as well as of their prior exposure to different classes of novel agents. Although cross-trial comparison is limited by multiple factors (Table 3), it would appear that Dara triplet regimens correlate with deeper response and higher survival advantages than are achieved with EloRd. However, multiple factors, including differences in the number of median prior therapies and percentage of patients with high-risk cytogenetic features, hamper...
cross-trial comparison. The benefits of triplet regimens containing Dara or Elo have been confirmed in different subgroups, including elderly patients, refractory populations and high-risk cytogenetics (Table 4), whereas the poor risk profile conferred by cytogenetics has not been completely abrogated. In EloRd, greater benefit has been observed in patients with a longer median time from diagnosis, which might suggest a higher efficacy from immunomodulation in a non-aggressive setting.

Moreover, it should be noted that the novel action mechanism of mAbs may suggest a need to use novel trial end points. Indeed, the more pronounced benefit in terms of OS than PFS reported for single-agent Dara, as well as that of TTNT over PFS observed for EloRd, could be due to a prolonged immune-mediated effect. Thus, the definition of clinical benefit, may have to include response (including MRD) and PFS, as well as long-term survival outcomes like TTNT and OS. Likewise, in the setting of SMM, the appropriate measure of efficacy should be the evolution to active disease, also exploring the long-term biologic implications of early treatment. Last, new strategies to evaluate the high-quality responses and blood typing (for Dara) should always be taken into account when treating patients with mAbs.

In conclusion, the recent development of Dara and Elo has proven transformative in MM and demonstrated high efficacy in RRM, Evaluation of these agents in new combination regimens, including second- and third-generation PIs and IMiDs, are under investigation. Other anti-CD38 mAbs displaying preliminary signs of efficacy, such as isatuximab and MOR202, are being studied.

6. Five-year view

MAbs targeting CD38 and SLAMF7 have been established as a new treatment paradigm for RRMM due to their multiple modes of action, including immunomodulation. Use of mAbs in phases of the disease where the immune system is less compromised, such as in patients with NDMM or even high-risk SMM, appears logical. Phase III trials exploring the role of mAbs in combination with the current standards of care for NDMM patients who are either eligible or not to receive ASCT, are currently ongoing or ready to start. The results of these studies will definitely clarify if 3 or 4 drug regimens including mAbs plus IMiDs and/or PIs will be the game changers over the next few years. If a higher proportion of MRD negativity, obtained by the addition of Dara or Elo, as well as extended PFS and OS are clearly demonstrated, these mAbs could become the backbone of MM treatment in combination with standard therapies, much like what is happening with non-Hodgkin B cell lymphomas. Moreover, we will have the results of using mAbs as early therapy for patients with high-risk SMM. Furthermore, a better knowledge of resistance mechanisms to these mAbs, as well as the possible presence of biomarkers of response, will allow us to determine the best clinical situation for their use. Changes in frequency and activity of effector cells may affect the efficacy of anti-CD38 or anti-SLAMF7 targeting mAbs [68,69]. The presence of anti-drug antibodies has also been described [70]. Moreover, potential resistance mechanisms toward anti-CD38 mAbs include increased expression of the complement inhibitors CD55 and CD59 on MM cells or the outgrowth of subpopulations with high expression of complement inhibitors, and CD38 reduction on non-depleted tumor cells [71]. Conversely, the density of CD38 surface expression correlates with response to Dara [18], whereas patients homozygous for the high-affinity FcγRIIIa V allele seem to have the greatest benefit from Elo when compared with patients with a low-affinity allele [42]. The better understanding of these complex biological interactions, and the combination of mAbs with new novel agents as well with each other, might help to overcome some escape mechanisms.
Finally, more than 20 novel mAbs, with different targets, are being studied in MM and some are in advanced stages of clinical development. Likewise, another kind of immunotherapy that acts directly on the tumor is represented by the chimeric antigen receptor (CAR) T cells. A variety of antigen targets are being studied at this time and include CD38, SLAMF7, BCMA, CD138, kappa light chain, NKGa2D and CD44v6, demonstrating preclinical anti-MM activity. Ongoing clinical trials will define the role CAR T-cell approaches, particularly with the use of targets that are more specific to the myeloma cell, such as BCMA and SLAMF7 [72,73]. Incorporation of immunotherapy in MM treatment is enriching the current scenario.

Key issues
- Dara is a humanized IgG1-k mAb directed against CD38; it exerts its anti-tumor activity inducing ADCC, CDC and ADCP on PCs and via immunomodulation, reducing Treg cells and activating T helper and cytotoxic cells
- Dara has demonstrated both single-agent activity and synergism with different drugs, with different action mechanisms
- Elo is a humanized IgG1-k mAb, targeting SLAMF7; it exerts its anti-tumor effects by inducing ADCC in PCs and by NK cell activation
- Elo has no single-agent activity, but acts synergistically in combination therapy, due to its distinct action mechanism
- Three randomized phase III trials have demonstrated a significant advantage in terms of response, PFS and (one of them) OS from the combination of Dara or Elo with Rd or Vd, in comparison to doublet regimens alone
- The PFS advantage has been confirmed in various different subgroups, including elderly patients, refractory populations and high-risk cytogenetics
- Dara and Elo have a very favorable toxicity profile, and the addition of these mAbs to standard regimens did not translate into any significant increase in toxicity
- Adequate pre- and post-medications and timely management of infusion reactions are recommended; the use of sc administration of Dara may significantly reduce this event.
- Dara and Elo are proving to require specific strategies for the evaluation of high quality responses and, in Dara’s case, for blood-typing, while new trial end-points to evaluate the long-term immune effect seem to be called for.
- On-going trials are evaluating the role of Dara and Elo in other clinical settings (SMM, NDMM, maintenance)
- Other mAbs, in different phases of clinical development, will enrich the therapeutic scenario in the near future

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References
Papers of special note have been highlighted as either of interest (+) or of considerable interest (++), or of considerable interest to readers.


**Prospective study demonstrating the superiority of DraVd triple regimen over standard doublet regimen Vd for the treatment of RRMM.**


**Prospective study demonstrating the superiority of DraRd triple regimen over standard doublet regimen Rd, for the treatment of RRMM.**


**First prospective study demonstrating the benefit of adding Dara in the first-line therapy for NDMM.**


**Prospective study demonstrating the superiority of EloRd triple regimen over standard Rd doublet regimen, for the treatment of RRMM.**


