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The new era of immunotherapy in multiple myeloma: daratumumab and elotuzumab

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Abstract

Objective—To review the clinical pharmacology, efficacy and safety of daratumumab and elotuzumab for the treatment of relapsed refractory multiple myeloma.

Data sources—A literature search of Medline, PubMed, the U.S. National Institutes of Health Clinicaltrials.gov, the Food and Drug administration and relevant meeting abstracts was conducted using the terms *daratumumab*, *elotuzumab*, *multiple myeloma*, *anti-CD38*, *HuMax-CD38*, *HuLuc63*, *SLAMF7* and *anti-CS1*.

Study selection/data extraction—Human and animal studies describing the pharmacology, pharmacokinetics, efficacy, and safety of daratumumab and elotuzumab for multiple myeloma were identified.

Data synthesis—Daratumumab (anti-CD38) and elotuzumab (anti-CS1) have been recently FDA approved for the treatment of relapsed refractory multiple myeloma (RRMM) after showing extraordinary efficacy in trials Elotuzumab approval based on phase III data whereas daratumumab was approved based on phase I/II trials. Daratumumab has demonstrated significant single agent activity with ORR of 36% in patients with median of 4 prior lines of therapy. On the other hand, elotuzumab has no single agent activity. But, the efficacy of both these antibodies in combination with lenalidomide and dexamethasone in RRMM showed an overall response rate (ORR) exceeding 80%. Tolerability of elotuzumab and daratumumab seems to be acceptable with the most common adverse event being infusion reactions.

Conclusion—Daratumumab and elotuzumab have shown encouraging results in RRMM that led to their FDA approval. Both are well tolerated with minimal toxicities. Phase III clinical trials will define optimal combination and place in therapy of daratumumab and elotuzumab.

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Keywords

monoclonal antibodies; immunotherapy; multiple myeloma; daratumumab; elotuzumab; treatment; refractory; relapsed

Introduction

Multiple myeloma (MM) is a plasma cell malignancy that accounts for approximately 1.6% of all new cancer cases in the United States and its incidence is estimated to be 6.3 cases per 100,000 persons per year.^{1,2} The introduction of autologous stem cell transplant (ASCT) and novel agents such as immunomodulatory drugs (IMiDs) and proteasome inhibitors has dramatically improved treatment outcomes and survival of myeloma patients.^{3–5} However, patients with disease refractory to both IMiDs and proteasome inhibitors have a median overall survival of only 9 months.⁶ Thus, despite this progress, the natural course of MM remains ultimate progression and there is still no established curative therapy available for patients diagnosed with this disease. This clearly demonstrates the need for additional agents with novel mechanisms of actions. In the past decade, extensive research has exposed many new potential therapeutic targets, including histone deacetylation, proteasome activity, signaling pathways of Akt, mammalian target of rapamycin (MTOR), MEK, and targetable surface receptors such as CS-1(SLAMF7), CD38 and CD40.⁷

Monoclonal antibodies (mAbs) are currently the most investigated therapeutic compounds in oncology and are an important new class of agents with unique mechanisms of action in the treatment of MM. Therefore in this review, we will specifically focus on daratumumab (anti-CD38) and elotuzumab (anti-CS1), which were both approved November 2015 by Food and Drug Administration (FDA) for relapsed refractory MM (RRMM) patients. We will review the mechanisms of action, clinical activity and clinically relevant adverse events of these antibodies.

Data sources

Sources were identified through searches of Medline, PubMed, and Embase databases from 2000 to January 2016 using the key terms *daratumumab*, *elotuzumab*, *multiple myeloma*, *anti-CD38*, *HuMax-CD38*, *HuLuc63*, *SLAMF7* and *anti-CS1*. Unpublished abstract information was obtained from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH). Data limits included the English language. Additional information was obtained from the U.S. National Institutes of Health Clinicaltrials.gov, product labeling, and the FDA.

Daratumumab

Mechanism of action

CD38, also known as cyclic ADP ribose hydrolase, is a transmembrane glycoprotein that is highly expressed on MM cells and at low levels on normal lymphoid and myeloid cells.^{8–10} It functions as an ectoenzyme involved in regulating intracytoplasmic concentration of calcium and the catabolism of extracellular nucleotides.¹¹ There have been many anti-CD38

monoclonal antibodies investigated, with daratumumab (IgG1-kappa; fully human) being the most promising and only FDA-approved agent. Isatuximab (SAR650984; IgG1-kappa; chimeric) and MOR202 (IgG1-lambda; fully human) are currently still being investigated.

Daratumumab destroys MM cells through multiple mechanisms (Figure 1).¹² Antibody-dependent cellular cytotoxicity (ADCC) is the cytotoxicity of an antibody-coated target cell by an effector cell via release of cytotoxic granules or by the expression of cell death-inducing molecules.¹³ Effector cells include natural killer cells, neutrophils, eosinophils, dendritic cells, monocytes and macrophages. Complement dependent cytotoxicity (CDC) occurs when the binding antibody starts the complement cascade, which results in an attack on the cell membrane causing cell lysis and death.¹³ Cell death through antibody-dependent cellular phagocytosis (ADCP) is caused by macrophages.¹⁴ There have been other proposed mechanisms including direct induction of apoptosis and inhibition of CD38 ectoenzyme activity.¹⁵ The most recent data suggested an immune modulatory role of daratumumab which included depletion of CD38 T reg, MDSC, and B regs¹⁶ and an observation of increased clonal T cells in responding patients, which suggests the possibility of an adaptive immune mechanism in response.

Pharmacokinetics/pharmacodynamics

The maximum concentration and area under the curve (AUC) increase in proportion to dose after the first infusion and then in greater than dose-proportional manner with repeated doses.^{17,18} This may be due to the fact the daratumumab clearance is nonlinear; clearance decreases with increasing dose and with multiple doses which indicates target-mediating pharmacokinetics. The elimination half-life using a two-compartment pharmacokinetic model was 21 days. The steady state is reached approximately 5 months into the every 4-week dosing period (by about the 21st infusion).¹⁸

The volume of distribution and clearance of daratumumab increases with increasing body weight therefore dosing should be based on body weight.¹⁸ Initial studies showed that age and gender do not affect the pharmacokinetics of daratumumab. There were no pharmacokinetic or clinical differences in patients with renal impairment or mild hepatic impairment, therefore no dose adjustments are required.

Efficacy

Table 1 summarizes the clinical trials evaluating daratumumab. The first-in-human study with daratumumab was a phase I/II study, involving patients with RRMM who received at least 2 prior lines of therapy. The dose escalation portion of the study included 32 patients who were heavily pre-treated with a median of six prior lines of therapy and 75% were double refractory (to both lenalidomide and bortezomib).¹⁷ Doses ranged from 0.005 to 24 mg/kg and were given weekly over a 9-week period with 2 pre-doses and 7 full doses. It was noted that there was a dose-dependent decrease of peripheral NK cells with recovery after treatment discontinuation.¹⁹ The overall response rate (ORR) was 33% with 4 of 12 patients achieving at least a partial response (PR) when receiving doses of 4mg/kg and above. No maximum tolerated dose (MTD) was identified. In the dose expansion cohort, 30 patients (median 4 prior treatments) received 8 mg/kg and 42 patients received 16 mg/kg of

daratumumab.²⁰ The ORR was 10% in the 8 mg/kg cohort. However, 36% in the 16 mg/kg cohort had an ORR with 2 patients having a complete response (CR) and 2 having a very good partial response (VGPR) and the median progression free survival (PFS) was 5.6 months (95% CI, 4.2–8.1). The overall survival (OS) at 12 months in both cohorts was 77% (95% CI, 28–86).

The Sirius study included 106 MM patients with a median of 5 prior lines of therapy were treated with 16 mg/kg of daratumumab.²¹ The ORR was 29.2% with 3% achieving a stringent CR. Of note, 21% of the patients who are refractory to bortezomib, carfilzomib, lenalidomide and pomalidomide achieved at least a PR. The median time to progression was 3.7 months with 1-year OS of 65%. This demonstrates that daratumumab can overcome resistance from prior lines of therapy.

Studies are ongoing evaluating daratumumab in combination with other anti-myeloma agents. *Ex vivo* analyses showed enhanced lysis of MM cells in bone marrow aspirates when evaluating daratumumab in combination with lenalidomide, bortezomib and dexamethasone. Apart from lenalidomide-induced activation of effector cells, increased direct killing of MM cells was also observed.²² Bortezomib may enhance the therapeutic effect of daratumumab by sensitizing tumor cells for antibody-mediated lysis. A more than two-fold increase in MM cell lysis has been seen when bortezomib was combined with daratumumab.²³

A multicenter study phase I/II evaluating the combination of daratumumab + lenalidomide + dexamethasone in RRMM was presented at ASH 2015.²⁴ After a median follow up of 7.8 months in the expansion cohort (16 mg/kg of daratumumab), ORR was noted to be 88% (11 (34%) PRs and 17 (53%) VGPRs). The median duration of response was not reached, as 26 (93%) of 28 responders had not progressed or relapsed at the time of the analysis.

In an open label phase Ib trial the combination of pomalidomide + dexamethasone + daratumumab was evaluated in 77 patients with RRMM.²⁵ In the 53 patients that were evaluable there was an ORR of 58.5% and patients with double refractory disease had an ORR of 57.5%. It's important to note that in both trials that combined IMiDs with daratumumab, the patients who responded their responses deepened over time.

Tolerability

The most common toxicities observed with daratumumab were infusion-related reactions (IREs), seen in 43–71% of patients treated with daratumumab monotherapy with most reactions occurring with the first treatment.^{19,20} The onset of IREs was within 3–4 hours of infusion.²⁵ Reactions were mainly grade 1–2 and included rhinitis, pharyngitis, pyrexia, chills, vomiting, cough and bronchospasm. Initial trials evaluating daratumumab had no treatment discontinuations due to infusion reactions.^{19,20} Pre-medications are given prior to each infusion but if IREs occur, the infusion should be interrupted and extra corticosteroids/antihistamines should be given per physician's discretion. Inhaled beta-2 adrenergic agonists may benefit patients who develop bronchospasms. Once the reaction resolves, the infusion should be restarted at a minimum of half the rate that the infusion reaction occurred and then titrated per patient's tolerability.¹⁷ Post-infusion oral corticosteroids are also recommended for 2 days starting the day after infusion for all patients to prevent delayed IREs.

Other common adverse events seen include fatigue, rhinitis, diarrhea, upper respiratory tract infections and dyspnea. The most common hematological toxicity reported was neutropenia (12%).¹⁹ Grade 3 and 4 adverse events for daratumumab monotherapy were pneumonia, thrombocytopenia, neutropenia, anemia, leukopenia, and hyperglycemia. Patients should continue or be placed on antiviral prophylaxis 1 week prior to daratumumab initiation due to risk of Herpes Zoster (3%).¹⁷

Dosing and administration

The approved dose is 16 mg/kg intravenously using actual body weight.¹⁷ Dosing starts with weekly treatments for 8 weeks, then every 2 weeks from weeks 9 to 24, then every 4 weeks thereafter until disease progression. Pre-medications for daratumumab should include corticosteroid (methylprednisolone 100 mg IV or equivalent at least with first infusion then dose can be decreased in subsequent cycles), antihistamine (diphenhydramine 25–50 mg) and antipyretic (acetaminophen 650–1000 mg) given 60 minutes prior to infusion. Daratumumab should be diluted after reconstitution with 0.9% sodium chloride only. Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE) with pump tubing including an in-line filter (pore size 0.22 or 0.2 micrometer).

Due to risk of IREs, infusions should be given in a step-wise fashion where the first infusion is a larger volume (1000 ml) with slower infusion starting at 50 ml/hr, then by the second infusion the volume decreases to 500 ml, and by the third infusion the initial titration rate increases to 100 ml/hr. Therefore, the first infusion is about 6.5 hours; second infusion is about 4 hours and then subsequent infusions will be about 3.25 hours.

Elotuzumab

Mechanism of action

CS-1 (SLAMF7) is a member of the lymphocyte activating-molecule-related receptor family comprised of extracellular immunoglobulin domains and an intracellular signaling domain that has been found in several *in vitro* studies to be heavily expressed in healthy and malignant CD138 (+) plasma cells, NK cells, activated monocytes and in a soluble form in the serum of patients with multiple myeloma. Minimal expression of CS1 was demonstrated in other lymphocyte lines, organ tissues and stem cells, leading to the potential for reduced myelosuppression and end organ damage from CS1-targeted therapy. *In vivo* xenograft models additionally demonstrated that CS1 expression, although lower, is maintained in patients after relapse from standard therapy.^{26–30}

Elotuzumab, previously HuLuc63, is a recombinant humanized IgG1 antibody that combines the determining regions of the murine antibody, MuLuc63 with IgG1 heavy chain and kappa light chains. Elotuzumab induces myeloma cell death via a variety of proposed mechanisms. Although elotuzumab can directly target the CS1 glycoprotein on malignant plasma cells, it appears that the primary mechanism of action is induction of ADCC, but not CDC, via complex with CD16 and activation of EAT-2 on the surface of NK cells.^{26,31,32} While NK-mediated ADCC has been proposed as the most significant mechanism for activity,

alternative NK cell activity, such as ligation of CS1 on NK cells and interaction promotion between CS1 on both the myeloma and NK cells may enhance the antitumor effects of elotuzumab.^{27,33} When examined in cell culture, elotuzumab was able to directly inhibit, in a dose dependent fashion, the interaction and adhesion between myeloma cell lines and bone marrow stromal cells, a major cause of resistance to other standard treatment mechanisms in myeloma.²⁹ Finally, activation of core signaling pathways, ERK, STAT3 and AKT have also been proposed.³⁴

Pharmacokinetics/Pharmacodynamics

Similar to daratumumab, elotuzumab C_{max} increases in a dose dependent manner, however AUC increased to a higher degree, suggesting nonlinear clearance and target-mediated elimination. The approved dosing of 10 mg/kg achieves steady state concentrations that adequately and consistently saturate CS1.^{35,36} 97% of elotuzumab concentration is expected to be eliminated in a mean of 82.4 days. The clearance of elotuzumab increased with increasing body weight, which supports the use of weight-based dosing. No significant differences were seen in the pharmacokinetics based on age, gender, hepatic impairment and renal impairment, including patients with end stage renal disease on hemodialysis.^{35,37}

Efficacy

The first phase I in human trial evaluating the use of elotuzumab as monotherapy was an open label, dose-escalation multicenter trial of patients with RRMM. A total of 35 patients were enrolled in 6 different dosing cohorts ranging from 0.5 mg/kg up to 20 mg/kg (maximum planned dose, MPD). The median age of patients included was 64.5 years, with a median number of prior treatments of 4.5.³⁶ No MTD was observed in this trial and doses >10 mg/kg were found to consistently saturate CS1. No OR was seen during the trial, 26.5% of patients were classified as having stable disease, which was the best-observed response.

In vitro and *in vivo* cell and murine studies with elotuzumab suggested a potential augmented ADCC effect when added in combination with standard therapies such as lenalidomide and bortezomib.²⁹ When evaluating lenalidomide specifically, cell co-culture and xenograft models suggested NK cell activity of elotuzumab, which coincided with the upregulation of IL-2 and TNF-alpha resulting in enhanced tumor cell kill.³⁸ Clinical trial data for elotuzumab in combination with standard anti-myeloma therapies is listed in Table 2.

In the Phase I study of elotuzumab in combination with lenalidomide and dexamethasone, 29 patients (1 patient lenalidomide refractory) were enrolled in a dose-escalation scheme of elotuzumab (5, 10 or 20 mg/kg) along with lenalidomide and dexamethasone.³⁹ Patients had received a median of 3 prior regimens before study enrollment, with 10% of patients having high-risk cytogenetics. The ORR was 82% with nine patients achieving at least a VGPR. Response rate was preserved despite the number of prior regimens (88% if < 3 prior regimens vs. 75% if 4 or more prior regimens). Time to progression (TTP) was not reached at a median follow up of 16.4 months. These results were confirmed in a phase Ib-2 in which patients with RRMM were randomized to either 10 mg/kg or 20 mg/kg of elotuzumab in

combination with lenalidomide and low dose dexamethasone (OR 84%, 42% VGPR, median PFS 10 mg/kg 26.9 mo).⁴⁰

The ELOQUENT-2 study was an open label, randomized phase III trial comparing the combination of elotuzumab, lenalidomide and low dose dexamethasone (ELd) vs. lenalidomide and low dose dexamethasone (Ld) in patients with RRMM (median prior therapies 2, lenalidomide sensitive, 32% with 17p deletion, 9% with t(14;4)).⁴¹ 646 patients were randomly assigned in a 1:1 ratio either ELd or Ld in 28 day cycles. Elotuzumab therapy significantly prolonged PFS (1 year: 68 vs. 57%; 2-year: 41 vs. 27%, Median 19.4 vs. 14.9 mo, HR 0.70, 95% CI 0.57–0.85, $p<0.001$). ORR was higher in the patients receiving ELd (79 vs. 66%, OR 1.9, 95% CI 1.4–2.8, $p<0.001$), however there were fewer CR's in the elotuzumab arm. Benefit in favor of ELd was also seen across several high-risk subgroups. The ongoing ELOQUENT-1 study will evaluate the use of ELd vs. Ld in untreated patients ineligible for stem cell transplantation.⁴²

Additional data has been published supporting the combination of elotuzumab with bortezomib. In preclinical data, pretreatment of myeloma cell lines with bortezomib enhanced the anti-myeloma effects of elotuzumab.⁴³ A phase I trial evaluating the combination of bortezomib and elotuzumab in patients with RRMM revealed good tolerability and encouraging activity. The ORR was 48%, and 63% of patients achieved at least a minor response, including response in two of three patients with bortezomib refractory disease.⁴⁴ The Phase II open label analysis comparing bortezomib, dexamethasone +/- elotuzumab (EBd, Bd) in RRMM, in which 50% of patients had received prior bortezomib therapy was presented at ASH in 2015. 152 patients were randomized to receive either EBd or Bd until disease progression or toxicity. When PFS was adjusted for prognostic factors, there was a significant improvement in the EBd arm (HR 0.60, 70% CI 0.48–0.74, $p=0.0116$, median 9.9 vs. 6.8 months). ORR was similar in the two treatment arms.⁴⁵

Tolerability

In the initial phase 1 data with elotuzumab, 88.2% of patients experienced a treatment related adverse drug event, most common including chills, fatigue, pyrexia, anemia, nausea and back pain.³⁶ IRE's were frequent (58.8%), therefore requiring an amendment to the protocol to include standard pre-medications to mitigate this adverse effect. In the phase 3 trial, 10% of patients experienced an IRE, 70% of which occurred with the first dose of drug, and were mostly grade 1 and 2 in nature.⁴¹ 5% of patients required infusion interruption and all but 2 patients were able to resume therapy.

Secondary to the transient decrease in lymphocyte counts seen in patients in the phase I data with elotuzumab, there is increased risk of infection in these patients. Decreases in lymphocyte counts appear to be related to lymphocyte trafficking from the periphery upon disruption of the bone marrow microenvironment and levels appear to normalize within 7 days. In the phase I trial of elotuzumab monotherapy, 29.4% of patients, experienced an infection during therapy, however no fungal or viral opportunistic infections were seen.³⁶ Phase 3 data demonstrated an infection rate of 81 vs. 74% in ELd and Ld arms, respectively.⁴¹ After adjustment for exposure, the rates of infection were similar in the 2

arms (197 events per 100 patient years). Rates of herpes zoster were also higher in the elotuzumab arm. Grade 3/4 cytopenias were also observed in the phase 3 trial, however, they did not differ significantly from the control group suggesting a correlation with earlier data demonstrating low CS1 expression on other cell lines. Additional adverse effects observed in low rates in the phase 3 trial include possibility of secondary malignancies (7% vs. 4%) and elevation of hepatic enzymes (2.5% of ELd treated patients).

Dosing and administration

Elotuzumab is dosed as 10 mg/kg every week for the first two cycles, followed by dosing every 2 weeks in combination with lenalidomide 25 mg PO daily on days 1–21, and regimen-specified dexamethasone dosing on 28 day cycles until disease progression or unacceptable toxicity.³⁵ Early studies with elotuzumab required protocol modification to incorporate pre-medications to prevent the occurrence of infusion related reactions associated with therapy. Pre-medications consist of both an H1- and H2-receptor antagonist, acetaminophen and dexamethasone. On days of elotuzumab therapy, patients must receive 28 mg of dexamethasone 3 to 24 hours prior to the dose and an additional 8 mg intravenously 45 to 90 minutes prior to administration. After completion of the first 2 cycles, dexamethasone can be administered as 40 mg standard dose in weeks where elotuzumab is not administered (days 8 and 22).

No physical or biochemical compatibility studies have been performed with elotuzumab, therefore it should be further diluted after reconstitution with 0.9% sodium chloride or 5% dextrose solution only. Infusion bag must be made of PVC or polyolefin and be infused with an infusion set containing an in-line filter (pore size of 0.2–1.2 micrometer).

Given the high risk of IREs associated with elotuzumab therapy, infusion of drug must be performed in a step-wise fashion with a starting rate of 0.5 mL/min up to a maximum infusion rate of 2 mL/min. The infusion rate may be increased to 5 mL/min in patients who have successfully completed 4 cycles of therapy. In patients that experience an infusion reaction grade >2, the infusion should be stopped until resolution and then restarted at a rate of 0.5 mL/min and gradually increased back to rate where reaction occurred with close monitoring of vital signs during and up to 2 hours following the infusion. If recurrence of reaction occurs on re-challenge, elotuzumab treatment on that day should be held. Permanent discontinuation of elotuzumab therapy is indicated in patients who experience a severe infusion-related reaction.

Drug-drug and drug-lab interactions for elotuzumab and daratumumab

No formal drug-drug interaction studies have been conducted with daratumumab and elotuzumab. Therefore, no drug interactions are known at this time.^{17,35} However, caution should be taken as elotuzumab is only used in combination, and standard agents used in combination may have significant drug-drug interactions (lenalidomide, bortezomib, and dexamethasone).

Interference of therapeutic antibodies with laboratory tests is being increasingly recognized. Daratumumab can be detected as an individual monoclonal band in serum protein

electrophoresis (SPEP) and serum immunofixation (IFE).^{20,47} Similarly, elotuzumab is produced by complexing the murine signaling region from MuLuc63 with an IgG1 heavy chain region and kappa light chain regions; therefore it may be detected on SPEP and IFE assays.⁴⁸ Comigration of daratumumab or elotuzumab with the patient's M-protein may lead to a small absolute overestimation of the M-spike. This can lead to a false positive SPEP and IFE assay results for patient with IgG kappa MM impacting assessment of response via International Myeloma Working Group (IMWG) criteria. In addition, the appearance of a new IgG kappa band may represent daratumumab and not disease progression/recurrence or secondary MGUS. Therefore, determining if patient is in CR or progressing may be more difficult especially in patients with IgG kappa MM and bone marrow biopsy may be indicated to confirm results. This may be the reasoning for decreased CR rates seen in the Phase III ELOQUENT-2 study. Soluble levels of SLAMF7 may be an indicator of disease burden in multiple myeloma and potentially useful for determining response to elotuzumab therapy.⁴⁹

Daratumumab binds to CD38 on red blood cells and interferes with routine pre-transfusion compatibility testing including antibody screening and cross matching.^{50–53} This includes positive antibody screens and pan-reactive plasma in erythrocyte panel testing (positive indirect antiglobulin test – Coombs test). Reactions remain positive for 2–6 months after last daratumumab dose.⁴⁹ Importantly, no major transfusion-related events were seen in daratumumab-treated patients receiving blood transfusions. This interference can be negated by neutralizing daratumumab in plasma samples with an anti-idiotypic antibody (anti-daratumumab mouse antibody) or by using the reducing agent dithiothreitol (DTT) for denaturation of CD38 receptors from reagent red blood cells.⁵¹ However, there are disadvantages to both approaches.

Resistance to antibody therapy

Monoclonal antibodies have been shown to have promising efficacy in MM but there is marked heterogeneity in the responses seen. Also, the majority of the patients who do respond eventually develop resistance.⁵⁴ Response to daratumumab has been associated with CD38 expression on tumor cells.⁵⁵ This may explain why patients with higher CD38 expression have better response. However, the relationship between CD38 expression and response is still under investigation. Another theory proposed has been the downregulation of the target antigen which may contribute to resistance during therapy.⁵⁶

Antibodies against mAbs may develop and reduce their biological activity. Antidrug antibodies developed in 39% of patients with single agent elotuzumab and in 15% of patients in the phase III trial in combination with lenalidomide and dexamethasone.³⁶ No anti-daratumumab antibodies have been detected to date.

Place in therapy

Even though there is no established curative therapy for patients with MM, the introduction of daratumumab and elotuzumab has the potential to dramatically transform the treatment of MM. Despite the fact that daratumumab and elotuzumab are FDA approved in the relapsed

and relapsed refractory setting, there are several trials evaluating their incorporation in different treatment regimens for RRMM, newly diagnosed MM patients, high-risk smoldering MM and maintenance (Table 3).

Conclusion

Monoclonal antibodies represent a new and promising group of agents with a distinctive mechanism of action for MM. Daratumumab and elotuzumab have clinically significant activity as a single agent and/or in combination with other anti-MM therapies in heavily pre-treated MM patients. The additive toxicity seems to be limited when combining and incorporating these mAbs with standard anti-multiple myeloma treatment options. This new class of agents has shown tremendous promise in further improving patient outcomes in MM. Trials have proven their place in therapy in RRMM and data evaluating their role in newly diagnosed patients is eagerly awaited.

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Figure 1.

Mechanisms of action of daratumumab. Daratumumab can directly induce multiple myeloma cell apoptosis when cross-linked with anti-human immunoglobulin.¹² It can also induce tumor cell killing via Fc-dependent effector mechanisms including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADPC) and complement-dependent cytotoxicity (CDC). ADCC is achieved through activation of Fc receptors on myeloid and NK effector cells by tumor cell-attached immunoglobulins. ADPC is mediated by macrophages. CDC is dependent on interaction of the antibody Fc domains with the classic complement-activating protein C1q leading to activation of downstream complement proteins which results in assembly of membrane attack complex (MAC) which creates holes in tumor cell membrane.

Table 1

Published trials and abstracts of daratumumab 19,20,21,24,25

Combination	Phase	# of pts	Patient population	Schedule	Outcomes	Toxicities
Monotherapy – GEN501 (Plesner 2012, Lokhorst 2015) ^{17,20}	I/II	32-dose escalation 72-dose expansion	RRMM (median 2 prior regimens)	Dose escalation: IV weekly × 9 weeks Dose (mg/kg): 0.005–24 mg/kg Dose expansion: IV weekly × 8 weeks then every 2 weeks × 16 weeks then monthly until disease progression Dose (mg/kg): 8 mg/kg & 16 mg/kg	No MTD reached up to 24 mg/kg Dose expansion: ORR 10% for 8 mg/kg and 36% for 16 mg/kg Median PFS 5.6 months (95% CI 4.2–8.1) OS at 12 months 77% (95% CI 52–90)	Fatigue, allergic rhinitis, pyrexia, diarrhea, upper respiratory tract infection, dyspnea Gr 3/4 pneumonia, thrombocytopenia, neutropenia, leukopenia, anemia, hyperglycemia
Monotherapy – Sirius (Lonial 2015) ²¹	II	106	RRMM (median 5 prior regimen)	IV weekly × 8 weeks then every 2 weeks then monthly until disease progression Dose: 8 mg/kg or 16 mg/kg, 16 mg/kg established as recommended dose	With 16 mg/kg dosing: PR: 29% VGPR: 9% CR: 3% Median PFS: 3.7 months OS at 12 months: 65%	Fatigue, anemia, nausea, thrombocytopenia, back pain, cough Infusion related reactions 43% only included 5% that were Gr 3/4
Daratumumab + Lenalidomide + Dexamehasone (Plesner 2015) ²⁴	I/II	32 – dose expansion	RRMM (median 2 prior regimens)	Daratumumab IV weekly × 8 weeks then every 2 weeks × 16 weeks then monthly until disease progression Lenalidomide PO 25 mg daily day 1–21 Dexamethasone PO 40 mg weekly	ORR 88% (34% PR, 28% VGPR, 25% CR) OS at 12 months: 65%	Neutropenia, muscle spasms, cough, diarrhea, fatigue, hypertension Infusion related reactions 56% which only included 6% that were Gr 3/4
Daratumumab + Pomalidomide + Dexamehasone (Chari 2015) ²⁵	Ib	77	RRMM (median 3.5 prior regimens)	Daratumumab IV weekly × 8 weeks then every 2 weeks × 16 weeks then monthly until disease progression Pomalidomide PO 4 mg daily day 1–21 Dexamethasone PO 40 mg weekly	PR: 28% VGPR: 23% CR: 8%	Neutropenia, anemia, fatigue, dyspnea, cough, nausea, diarrhea Infusion related reactions 61% (little added toxicity when pomalidomide is added to daratumumab)

RRMM: relapsed/refractory multiple myeloma; MTD: maximum tolerated dose; PFS: progression free survival; ORR: objective response rate; PR: partial response; VGPR: very good partial response; CR: complete remission; IV: intravenously; PO: orally

Table 2

Published trials and abstracts of elotuzumab^{36,39-41,44-46}

Combination	Phase	# of pts	Patient population	Schedule	Outcomes	Toxicities
Monotherapy (Zonder 2012) ³⁶	I	35	RRMM	IV every 14 days for 8 weeks Dose levels (mg/kg): 0.5, 1, 2.5, 5, 10, 20	No MTD reached, CSI reliably saturated with doses of 10–20 mg/kg, no objective response seen	Chills, fatigue, pyrexia, cough, headache, anemia, nausea, back pain Infection in 29.4% of patients Infusion reaction in 58.8% of patients
Elotuzumab + Lenalidomide + Dexamethasone (Lonial 2012) ³⁹	I	29	RRMM (1 prior regimen)	IV on days 1, 8, 15, 22 × 2 cycles, then day 1, 15 Dose levels (mg/kg): 5, 10, 20 Lenalidomide 25 mg days 1–21 Dexamethasone 40 mg PO weekly Cycle length: 28-day	No MTD reached, objective response in 82%, VGPR in 32%, median TTP not reached at 16.4 mo follow up	Gr 3/4 neutropenia (36%), Gr 3/4 thrombocytopenia (21%) Infusion reaction in 89% of patients
Elotuzumab + Lenalidomide + Dexamethasone (Richardson 2015) ⁴⁰	Ib-II	73	RRMM (1–3 prior regimens)	IV on days 1, 8, 15, 22 × 2 cycles, then day 1, 15 Dose levels (mg/kg): 10, 20 Lenalidomide 25 mg days 1–21 Dexamethasone 40 mg PO weekly Cycle length: 28-day	Objective response in 84%, VGPR in 42%, PR in 27%	Diarrhea, muscle spasm, fatigue, gr 3/4 lymphopenia (21%), gr 3/4 neutropenia (19%) Infusion reaction in 12% of patients
Elotuzumab + Lenalidomide + Dexamethasone (ELOQUENT-2, Lonial 2015) ⁴¹	III	646 (321 ELD, 325 Ld)	RRMM (1–3 prior regimens)	IV on days 1, 8, 15, 22 × 2 cycles, then day 1, 15 Dose levels (mg/kg): 10 Lenalidomide 25 mg days 1–21 Dexamethasone 40 mg PO weekly, or 8 mg + 28 mg on elotuzumab days Cycle length: 28-day Mandatory premedication: H1/H2 antagonist, APAP	1 yr PFS: 68 vs. 57% 2 yr PFS: 41 vs. 27% Median PFS: 19.4 vs. 14.9 mo (HR 0.70, 95% CI 0.57–0.85, p<0.001) ORR: 79 vs. 66% (odds ratio 1.9, 95% CI 1.4–2.8, p<0.001) **Responses sustained even in high risk populations	Grade 3/4 toxicities: lymphocytopenia, neutropenia, fatigue, pneumonia Infusion reaction in 10% of patients
Elotuzumab + Bortezomib (Jakubowiak 2012) ⁴⁴	I	28	RRMM (1–3 prior regimens)	IV on days 1, 11 within 30 min of bortezomib Dose levels (mg/kg): 2.5, 5, 10, 20 Bortezomib 1.3 mg/m ² on days 1, 4, 8, 11 Cycle length: 21-day Mandatory premedication: H2 antagonist, APAP, methylprednisolone	No MTD reached, median TTP 9.46 mo, ORR 48%, MR or better in 63%	Grade 3/4 toxicities: Lymphopenia (25%), fatigue (14%) 71% of patients with peri-infusion adverse event
Elotuzumab + Bortezomib + Dexamethasone (Palumbo 2015) ⁴⁵	II	152 (77 EBd, 75 Bd)	R/RR MM (1–3 prior tx regimens)	IV weekly (cycles 1–2), days 1, 11 (cycles 3–8), then days 1, 15 Dose levels (mg/kg): 10 Bortezomib 1.3 mg/m ² on days 1, 4, 8, 11 (cycles 1–8), then days 1, 8, 15 Dexamethasone 20 mg on non-elotuzumab days, and 8 mg + 8 mg on elotuzumab days Cycle length: 21-day (cycles 1–8), then 28-day	2 yr PFS: 18 vs. 10% (HR 0.60, 70% CI 0.48–0.74, p=0.0116) Median PFS: 9.9 vs. 6.8 mo ORR: 65 vs. 63%	Grade 3/4 toxicities: Thrombocytopenia (9%), infections (23%) Infusion reaction in 5% of patients

Combination	Phase	# of pts	Patient population	Schedule	Outcomes	Toxicities
Elotuzumab + Lenalidomide+ Bortezomib+	I	8	Newly diagnosed, symptomatic multiple myeloma	<i>Induction phase (8 cycles)</i> IV days 1, 8, 15 (cycles 1–2), then days 1, 11 (cycles 3–8)	All 6 patients completed 8 cycles of induction, 4 pts completed at least 4 maintenance cycles	Most common adverse effects: fatigue, peripheral neuropathy, edema, lymphopenia, leukopenia
Dexamethasone (SWOG 1211, Usmani 2015) ⁴⁶				Dose levels (mg/kg): 10 Lenalidomide 25 mg PO days 1–14 Bortezomib 1.3 mg/m ² SQ days 1, 4, 8, 11 Dexamethasone 20 mg days 1, 2, 4, 5, 8, 9, 11, 12 Cycle length: 21-day <i>Maintenance phase</i> IV days 1, 15 Dose levels (mg/kg): 10 Lenalidomide 15 mg on days 1–21 Bortezomib 1 mg/m ² SQ days 1, 8, 15 Dexamethasone 12 mg PO days 1, 8, 15 Cycle length: 28-day		

RRMM: relapsed/refractory multiple myeloma; MTD: maximum tolerated dose; H1/H2: Histamine 1/2 receptors; APAP: acetaminophen; PFS: progression free survival; ORR: objective response rate;
VGPR: very good partial response; TTP: time to progression; MR: minor response

Table 3

Selected ongoing clinical trials with daratumumab and elotuzumab^{41,57–66}

Combination	Phase	# of pts (estimated)	Patient population	Schedule	Outcomes planned
Daratumumab combined with VD, VTD, VMP, Pom/Dex (NCT01998971) ⁵⁷	Ib	190	Transplant eligibility and ineligible patients for VD and VTD and transplant ineligible patients for VMP, RMM for Pom/Dex.	VD and VTD arms: daratumumab IV weekly × 2 cycles then every 3 weeks × 16 cycles (3 week cycles) VMP arm: daratumumab IV weekly × 1 cycle then every 3 weeks × 8 cycles (6 week cycles) Pom/Dex arm: daratumumab IV weekly × 2 cycles then every 2 weeks × 4 cycles then every 4 weeks until progression (4 week cycles) **Other chemotherapy dosing is not specified	Primary: Safety and DLTs Secondary: ORR, duration of response
Daratumumab monotherapy maintenance (NCT02316106) ⁵⁸	II	120	Intermediate- or high-risk smoldering multiple myeloma <5 yrs	Arm A: Daratumumab IV 16 mg/kg every week cycle 1 then every other week cycle 2–3 then every 4 weeks cycle 4–7 then every 8 weeks cycle 8–20 (8 week cycles) Arm B: Daratumumab IV 16 mg/kg every week cycle 1 then every 8 weeks cycle 2–20 (8 week cycles) Arm C: Daratumumab IV 16 mg/kg every week cycle 1	Primary: CR Secondary: MRD, TNT, PFS, OS
Daratumumab + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone (NCT02252172) ⁵⁹	III	730	Newly diagnosed non-transplant eligible patients	Daratumumab IV weekly × 8 weeks then every 2 weeks × 16 weeks then monthly until disease progression Lenalidomide 25 mg PO daily day 1–21 Dexamethasone 40 mg PO weekly	Primary: PFS Secondary: TTP, ORR, MRD, duration of response, OS, quality of life
Daratumumab + bortezomib + dexamethasone vs. bortezomib + dexamethasone (NCT02136134) ⁶⁰	III	480	Relapsed (to at least 1 prior line of therapy) multiple myeloma	Velcade 1.3 mg/m ² subcutaneously Days 1, 4, 8 and 11 of 21 day cycle Daratumumab IV 16 mg/kg weekly × 3 cycles, on Day 1 of cycle 4–9, then every 3 weeks thereafter Dexamethasone PO 20 mg Days 1, 2, 4, 5, 8, 9, 11 and 12	Primary: PFS Secondary: TTP, ORR, duration of response, time to response, MRD, OS
Daratumumab + VMP vs. VMP alone (NCT02195479) ⁶¹	III	700	Newly diagnosed non-transplant eligible patients	Daratumumab IV weekly × 6 weeks cycle 1 then every 3 weeks cycle 2–9 then monthly until disease progression Bortezomib 1.3 mg/m ² subcutaneous twice weekly weeks 1, 2, 4 and 5 cycle 1 then once weekly weeks 1, 2, 4 and 5 cycle 2–9 Melphalan 9 mg/m ² PO days 1–4 cycle 1–9 Prednisone 60 mg/m ² PO days 1–4 cycle 1–9	Primary: PFS Secondary: TTP, ORR, MRD, duration of response, OS, quality of life
VTD then ASCT followed by VTD consolidation or VTD + daratumumab consolidation followed by observation or daratumumab maintenance (NCT02541383) ⁶²	III	1080	Newly diagnosed transplant eligible patients	Maintenance daratumumab: 16 mg/kg every 8 weeks for 2 years ** Other chemotherapy dosing is no specified	Primary: sCR, PFS Secondary: TTP, OS, MRD
Elotuzumab + Lenalidomide (Maintenance, NCT02420860) ⁶³	II	48	Newly diagnosed MM s/p autologous transplant	IV on days 1, 8, 15, 22 (cycles 1–2), days 1, 15 (cycles 3–6), then day 1 Dose levels (mg/kg): 10, 20 (after cycle 6) Lenalidomide 10 mg PO daily (may be escalated to 15 mg) Cycle length: 28-day Pre-medication: dexamethasone 28 mg + 8 mg, H1/H2 antagonist	Primary: PFS Secondary: Safety

Combination	Phase	# of pts (estimated)	Patient population	Schedule	Outcomes planned
Elotuzumab + Lenalidomide + Dexamethasone (ELOQUENT-1) ⁴²	III	750	Previously untreated multiple myeloma AND not a candidate for high-dose therapy with stem cell transplant	IV on days 1, 8, 15, 22 × 2 cycles, then day 1, 15 (cycles 3–18), then day 1 Dose levels (mg/kg): 10, 20 (cycle 19+) Lenalidomide 25 mg days 1–21 Dexamethasone 40 mg PO weekly, or 8 mg + 28 mg on elotuzumab days Cycle length: 28-day	Primary: TTP, change in CS1 expression (sub-study) Secondary: change in serum CS1 levels (sub-study)
Elotuzumab + Thalidomide + Dexamethasone (NCT01632150) ⁶⁴	II	40	RRMM (5 prior regimens)	IV weekly (cycles 1–2), then every 2 weeks Dose levels (mg/kg): 10 Thalidomide 50 mg (cycle 1, days 1–14), 100 mg (cycle 1, days 15–28), 200 mg (cycle 2 +) Dexamethasone 28 mg days 1, 8, 15, 22 (cycle 1–2), days 1, 15 (cycle 3 +), 40 mg on non-elotuzumab days Cycle length: 28-day	Primary: Safety/feasibility
Elotuzumab + Lenalidomide + Dexamethasone vs. Elotuzumab + Lenalidomide (NCT02279394) ⁶⁵	II	82	High-risk smoldering multiple myeloma	IV on days 1, 8, 15, 22 × 2 cycles, then day 1, 15 Dose levels (mg/kg): 10 Lenalidomide 25 mg days 1–21 Dexamethasone 40 mg PO 1, 8, 15, 22 (cycles 1–2), days 1, 8, 15 (cycles 3+) Cycle length: 28-day Mandatory premedication: H1/H2 antagonist, APAP	Primary: 2-yr PFS Secondary: ORR, safety, TTP, OS
Elotuzumab + Pomalidomide + Dexamethasone (NCT02612779) ⁶⁶	II	60	RRMM (1–2 prior regimens, including lenalidomide)	IV on days 1, 8, 15, 22 × 2 cycles, then day 1, 15 (cycles 3–6) Dose levels (mg/kg): 10, 20 (cycle 7+) Pomalidomide 4 mg PO days 1–21 Dexamethasone 28 mg + 8 mg days 1, 8, 15, 22 (40 mg on non-elotuzumab days), 8 mg + 8mg in pts >75 yo Cycle length: 28-day	Primary: PFS Secondary: ORR, OS

VD: bortezomib/dexamethasone; VTD: bortezomib/thalidomide/dexamethasone; VMP: bortezomib/melphalan/prednisone; Pom/dex: pomalidomide/dexamethasone; RRRMM: relapsed/refractory multiple myeloma; IV: intravenously; DLT: dose limiting toxicity; ORR: overall response rates; PFS: progression free survival; TTP: time to progression; MRD: minimal residual disease; OS: overall survival; PO: orally; sCR: stringent complete response; TNT: time to next treatment