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# Clinical and Pharmacologic Features of Monoclonal Antibodies and Checkpoint Blockade Therapy in Multiple Myeloma

**Running title:** MAbs and Checkpoint Blockade Therapy in MM

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## Abstract

**Background:** Survival of MM patients has considerably improved in the last decades thanks to the various effective treatment options available today, including immunomodulatory agents, proteasome inhibitors and, more recently, monoclonal antibodies.

**Methods:** We analyzed the most recent literature and we focused on the clinical and pharmacologic aspects of monoclonal antibody-based therapies in myeloma, including monoclonal antibodies directed against plasma cell antigens, as well as checkpoint blockade therapy directed against immune inhibitory molecules, used as single agents or in combination therapy.

**Results:** Monoclonal antibodies directed against plasma cell antigens showed unprecedented results when combined with consolidated multiple myeloma backbone therapies. They can act specifically on MM cells, but also on the immune system. Multiple myeloma is characterized by a profound immune impairment, leading to the inability to identify and eliminate neoplastic cells. Monoclonal antibodies directed against plasma cell antigens that are also expressed on immune cells, and monoclonal antibodies directed against immune checkpoint molecules can boost the antitumor immunity and potentially reduce the profound immune impairment. This effect is more evident when these drugs are combined with immunomodulatory agents.

**Conclusion:** Monoclonal antibodies represent the next step in MM treatment, and future results from ongoing trials will further confirm their role.

**Keywords:** multiple myeloma (MM); monoclonal antibodies (mAbs); checkpoint blockade therapy (CBT); SLAMF7; CD38; PD-1; PDL-1

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## 1. INTRODUCTION

Multiple myeloma (MM) is a neoplastic disease characterized by uncontrolled proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein production in blood and/or urine, and organ dysfunction including bone lytic lesions, renal impairment, hypercalcemia and/or anemia [1]. MM accounts for 1% of all neoplasms and 2% of all cancer deaths. It represents approximately 13% of hematologic malignancies and accounts for 20% of deaths [2]. Survival of MM patients has improved over the past 20 years and the main reason is the increased number of available effective drugs used either as single agent or in combination [3]. A considerable change in treatment of MM has been made with the introduction of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs). Nevertheless, many steps forward can still be made, and there is a great effort to identify new targets and treatment modalities to further improve patients' outcome. A typical feature of MM biology is the clinically relevant immune dysfunction leading to a progressive functional impairment of immune cells [4]. This occurs early in the disease development, from the premalignant stages, where the immune system fails to eradicate clonal plasma cells [5]. In the past few years, several strategies that exploit the immune system to destroy MM cells have been proposed [6]. These strategies boost antitumor immunity, and they include monoclonal antibodies directed against tumor antigens – also impacting on the immune system itself - and monoclonal antibodies directed to immune cells.

In this review, we focus on the pharmacologic features and efficacy of these 2 classes of drugs, monoclonal antibodies targeting tumor-related surface molecules (mAbs), and monoclonal antibodies targeting immune inhibitory molecules (“checkpoint blockade therapy” [CBT]).

## 2. MONOCLONAL ANTIBODIES

Monoclonal antibodies label tumor cells, thus leading to a complex activation of many immune functions. Specifically, the main mechanisms are complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) [7].

CDC is prompted by the interaction of the antibody Fc domain with C1q protein, which activates the complement cascade [7]. The generation and release of opsonins, such as the chemo-attractants C3a and C5a, and the assembly of membrane attack complexes (MAC), forming transmembrane channels disrupting phospholipid bilayer, lead to cell death [8]. The engagement of the Fc portion of antibody-tumor cell complex by Fc $\gamma$  receptors of NK cells and macrophages is involved in ADCC and ADCP. Cytotoxicity in ADCC is mediated by the release of perforin, granzymes and/or tumor necrosis factor alpha by effector cells. ADCP is mediated by tumor cell internalization and intracellular destruction [7].

The activation of each of these mechanisms depends on the structure of mAbs rather than their targets. As an example, daratumumab and MOR202 are both anti-CD38 mAbs but they show a significantly different capability to induce CDC, which is high with daratumumab and absent with MOR202. These aspects may lead to clinically significant differences between molecules with the same target.

Different mAbs classes share various, common pharmacokinetics (PK) properties, mostly because their great molecular size affects PK behavior. MAbs are administered by parenteral routes (intravenous [IV] is the preferred one), while oral administration is precluded due to pre-systemic metabolism. Measured volume of distribution after mAb IV administration is usually close to plasma volume, suggesting limited tissue distribution [9]. Metabolism and subsequent elimination of mAbs *in vivo* have shown aspecific mechanisms, such as proteolytic cleavage into peptides or amino acids by phagocytes or lysosomes degradation when mAb is internalized in cells via Fc $\gamma$ -receptor interaction [10]. The model based-pharmacokinetics analysis describing the PK profile of the majority of mAbs show both dose-dependent elimination (with linear clearance) and non-linear clearance (CL), depending on the mAb dose and on the level of target expression and saturation. The main cause of non-linear CL is the target mediated-elimination, a mechanism that involves the binding of Fc receptor and target molecule and the consecutive internalization and lysosomes degradation [11]. The principal PK parameters of the main mAbs used for the treatment of MM are listed in Table 1. High half-life values are consistent with the macromolecule size that are precluded to the glomerular filtration, whereas currently available maximum plasma mAb concentration and target effective through concentration values are peculiar of each mAb class but similar and comparable among different mAbs of the same category, since these parameters are based mainly on the mAb potency and binding affinity.

### 2.1 CD38 directed mAbs

CD38 is a type II transmembrane glycoprotein with both receptor and enzymatic function, it is expressed on lymphoid and myeloid cells and in some non-hematopoietic tissues [12].

High CD38 levels have been observed in a wide number of hematological malignancies. The high and uniform CD38 expression on MM cells prompted the evaluation of CD38 as a therapeutic target [13]–[16].

In addition to the typical mAb mechanisms of action (ADCC, ACDP, CDC), antiCD38 mAbs can induce direct apoptosis of MM cells and can modulate CD38 enzymatic function (ADPribose cyclase and cyclic ADPribose hydrolase). By enhancing CD38 hydrolase activity, an increased ADPribose levels may be obtained, which contribute to cell death induction [17],[18].

CD38 is weakly expressed also by red blood cells, but hemolysis is not a safety issue in patients treated with anti-CD38 mAbs. The main reason is that anti-CD38 mAbs are unable to induce CDC on red blood cells and only a small portion of red blood cells coated with mAbs are destroyed in the spleen [19]. Anti CD38 mAbs does not interfere with the major antigens of ABO/RhD typing, but with the minor ones. In the indirect Coombs test, mAbs binds to CD 38 on red blood cells, and to reagent or donor RBCs, resulting in agglutination and giving a false positive result. Blood products for transfusion can be identified for mAbs-treated patients. As an example, blood banks are able to perform compatibility tests on samples from Daratumumab-treated patients, using available protocols (Dithiothreitol [DTT] or Anti-idiotype mAb and soluble CD38) or by using genotyping. If an emergency transfusion is required, non-crossmatched, ABO/RhD-compatible RBCs can be given, per local blood bank practices. To avoid unnecessary delays, it is essential that the blood bank is informed that they will receive a sample from an anti CD38 mAbs-treated patient, so that appropriate protocols can be applied. Patients may carry a blood transfusion card indicating that they receive anti-CD38 mAb therapy. Indirect antiglobulin test can be positive for up to 6 months after the interruption of anti-CD38 mAb treatment, suggesting that a small amount of circulating drug can be detected in patients' blood for a long period of time [20].

Other CD38 expressing cells include airway muscle cells [21]. Of note, anti-CD38 mAb-associated infusion-related reactions (IRRs) have mainly a respiratory pattern (e.g. nasal congestion, allergic rhinitis, throat irritation, cough and dyspnea) [20]. Therefore, patients with severe lung disease have been excluded from clinical trials. A forced expiratory volume in 1 second (FEV1) value should be obtained in all patients with a suspected pulmonary obstructive disease and inhalatory corticosteroid and/or bronchodilators should be considered as additional prophylaxis of IRRs in patients with a reduced FEV1.

### 2.1.1 Daratumumab

Daratumumab is an IgG1 $\kappa$  fully human mAb and is the only anti-CD38 mAb that binds two sequences of a unique CD38 epitope [22].

Population PK (PPK) analyses indicated that age, gender, renal impairment and hepatic impairment do not have clinically relevant effects on daratumumab PK, whereas its volume of distribution and clearance (CL) increase with increasing body weight, supporting the body weight-based dosing regimen [23]–[25]. Further analysis of daratumumab monotherapy trials showed that IgG myeloma patients had lower daratumumab serum concentrations due to an almost doubled clearance value when compared with non-IgG patients, and that daratumumab CL was significantly affected by baseline IgG levels. In fact, IgG M-proteins and daratumumab are both substrates for the Brambell receptor (FcRn), a protein that binds Fc receptor and prevents molecules from elimination, and in non-IgG patients no competition for FcRn between mAb and IgG occurs. However, no differences in the ORR of IgG or non-IgG myeloma patients was reported.

Daratumumab monotherapy was evaluated in two trials (GEN501 and SIRIUS) enrolling relapsed/refractory MM (RRMM) patients [24],[26]. Maximum tolerated dose (MTD) was not reached in the dose escalation cohort of GEN 501 trial. The partial response rate (PR) ranged between 29 and 36% in patients receiving the highest dose tested (daratumumab 16 mg/kg), and responses were dose-related. The lowest daratumumab dose that at trough concentration (C<sub>min</sub>) caused the inhibition of 90% of target-mediated CL was 16 mg/kg; lower doses did not reach optimal CD38 saturation.

In the GEN501 trial, IRRs occurred in 71% of patients, they were rarely severe (grade  $\geq 3$  in 1% of the patients) and most of them occurred during the first infusion, with a very low rate of reoccurrence in subsequent infusions. Interestingly, development of IRRs is not associated with maximum daratumumab serum levels reached after infusion [27].

Based on the above positive results, the food and drug administration (FDA) recently approved daratumumab monotherapy. The optimal schedule was established according to the results of the trials mentioned above, namely 16 mg/kg weekly for 8 weeks, then every 2 weeks for the subsequent 16 weeks and every 4 weeks thereafter. This schedule is aimed at rapidly saturate target-mediated CL during initial dosing and maintain saturation when doses are delayed every 2 or 4 weeks [23].

Daratumumab in combination with standard backbone MM treatments for relapsed/refractory patients, bortezomib-dexamethasone (Vd) and lenalidomide-dexamethasone (Rd), has been explored in 2 large phase-III randomized trials (CASTOR and POLLUX respectively) with outstanding clinical results [28],[29].

The CASTOR study randomized 498 RRMM to daratumumab-Vd vs Vd. Daratumumab schedule was slightly different from monotherapy trials, and it was 16 mg/kg was given once per week during cycles 1 to 3, once every 3 weeks during cycles 4 to 8, and then once every 4 weeks. No PK data are published. A clear advantage was shown in the daratumumab-Vd arm in terms of progression-free survival (PFS) (hazard ratio [HR] 0.39,  $p < 0.001$ ) and ORR (82.9% vs 63.2%).

In the POLLUX study, 569 RRMM patients were randomized to receive daratumumab-Rd vs Rd. PK and the schedule of daratumumab administration in the daratumumab-Rd group were consistent with daratumumab monotherapy trials. Daratumumab-Rd markedly reduced the risk of progression or death (HR 0.37,  $p < 0.001$ ) and also improved ORR compared with Rd (92.9% vs 76.4%).[30]

Of interest, In both CASTOR and POLLUX studies, the addition of Dara to standard of cares improved the PFS both in patients with standard cytogenetics (HR 0.29 and 0.30 respectively) and in the patients with high risk cytogenetics (HR 0.49 and HR 0.44 respectively) [31].

The combination of daratumumab with another IMiD, namely pomalidomide, has been explored in the EQUULEUS phase 1 study. 103 RRMM patients who received at least 2 prior lines of therapy, including lenalidomide and bortezomib, were enrolled. Daratumumab was administered at the approved monotherapy schedule of 16 mg/kg in addition to pomalidomide-dexamethasone standard schedule. ORR was 60% with 17% of patients achieving complete response or better. Median PFS was 8.8 vs 4 months reported with pomalidomide-dexamethasone alone in a similar patient population. Grade  $\geq 3$  neutropenia rate (78%) was higher than what was reported with pomalidomide-dexamethasone alone, despite a quite similar infection rate. IRRs rate was consistent with other daratumumab trials [32],[33].

Based on these aforementioned trials, daratumumab combination therapies with Vd, Rd and pomalidomide-dexamethasone have been approved by the FDA in RRMM patients [34]. Many clinical trials combining daratumumab with other compounds and exploring its efficacy in High-Risk Smoldering MM and newly diagnosed MM are ongoing.

Preliminary data of the first trial evaluating the addition of daratumumab to one of the standards of care in elderly newly diagnosed MM patients (bortezomib-melphalan-dexamethasone, VMP) have been recently presented. The addition of daratumumab to VMP followed by daratumumab maintenance compared to VMP alone significantly reduced the risk of progression/death (HR 0.50,  $p < 0.001$ ). Grade  $\geq 3$  infections were higher in the daratumumab arm (23.1% vs 14.7%), but treatment discontinuation due to infections was low in both arms (0.9% and 1.4% respectively). The rate of IRRs (27.7%) was lower compared to trials using daratumumab in RRMM patients [35]. Moreover, some of the recent trials are evaluating the subcutaneous administration of daratumumab that could potentially reduce the hospital length of stay and thus improve patients' compliance. First data about a phase 1b study exploring subcutaneous delivery of daratumumab with recombinant hyaluronidase enzyme (rHuPH2) in RRMM were presented. RHuPH2 is an enzyme that by breaking the hyaluronic acid in the subcutaneous soft tissue, creates a pouch under the skin of the patient that is filled with the drug delivered. In particular, in the second part of the study a pre-mixed vial containing daratumumab (1800 mg in 15 mL) and rHuPH20 (30000 U) was administered by manual subcutaneous injection in 3-5 minutes with the same schedule of approved intravenous single-agent daratumumab. Preliminary results with the pre-mixed formulation were very appealing, with low IRRs (<5%), a low rate of local adverse events at the injection site (reversible erythema in 20% of patients) and an ORR of 42%. The low rate of IRRs and the encouraging ORR compare favorably with the results from the studies performed with the intravenous formulation [36],[37].

### 2.1.2 Isatuximab

Isatuximab (SAR650984) is an IgG1 $\kappa$  chimeric mAb that binds a discontinuous epitope, which involves amino acids located opposite to CD38 catalytic site. Isatuximab showed a potent direct proapoptotic activity, and, differently from daratumumab, it does not require CD38 cross-linking [38].

Few isatuximab PK data in MM patients are currently available, since phase I-II trials are still ongoing and recruiting participants. Based on the currently available data, isatuximab monotherapy did not show peculiar PK features compared to other anti-CD38 mAbs, and PPK analyses have not been reported yet [39].

So far, preliminary results of three phase I/II dose-escalation trials in RRMM patients are available.

In the first trial, isatuximab monotherapy given at increasing doses (MTD not reached, maximum tested dose 20 mg/kg) produced an ORR of 27%, similarly to daratumumab monotherapy [40],[41]. In the second trial, isatuximab was given in combination with Rd in RRMM patients [42]. The MTD was not reached and again the maximum tested dose was 20 mg/kg weekly in the first cycle and biweekly thereafter. PK data revealed that isatuximab in combination with Rd has a similar behavior to isatuximab in monotherapy. When combined with isatuximab, lenalidomide exposure did not cause accumulation after repeated dosing either. The ORR was 56% in a heavily pretreated patient population (median of 6 prior therapeutic lines in the 20 mg/kg cohort).

In the third trial, isatuximab in combination with pomalidomide-dexamethasone was investigated in a dose-escalation phase Ib study on RRMM patients [43]. In this trial, PK parameters of isatuximab were not affected by co-administration with Pom/Dex. Isatuximab doses of 5, 10, or 20 mg/kg (4 weekly doses, then every 2 weeks) have been explored. ORR was 62% in a population of patients including 77% patients refractory to prior immunomodulatory drugs. Response rate in the 10 and 20 mg/Kg dose were similar. A randomized phase III trial is currently ongoing (NCT02990338), and compares isatuximab (10 mg/Kg) plus pome-dex vs pom-dex.

In all trials, isatuximab showed similar IRR rate and characteristics compared with daratumumab treatment. At present, isatuximab is being evaluated in many combination trials, even in the upfront setting, and results will be available in the next future.

### 2.1.3 MOR202

MOR202 is an IgG1 $\lambda$  fully human anti-CD38 mAb. Unlike other anti-CD38 mAbs, MOR202 is not able to induce CDC and this mechanism is suspected to be the main contributor to IRRs.[44] MOR202 is currently being investigated in a phase I/II dose

escalation trial in RRMM as monotherapy, in combination with dexamethasone, with lenalidomide-dexamethasone, and with pomalidomide-dexamethasone [45].

MTD was not reached and the maximum tested dose was 16 mg/kg weekly. No safety issues have been observed. Preliminary PK results showed that in patients treated with 16 mg/kg weekly full-target occupancy was reached, thus an equal dose was used when combined with pomalidomide or lenalidomide and dexamethasone. At present, no PPK data are available [45],[46].

As expected, the drug was associated with a low incidence of IRRs (7% all grade). In the MOR202-dexamethasone cohort ORR was 29%, while in patients treated with MOR202-immunomodulatory drugs-dexamethasone ORR was 73%.

## 2.2 SLAMF7 directed mAbs

Signaling Lymphocyte Activation Molecule Family 7 (SLAMF7 or CS1) is a glycoprotein highly expressed on NK cells, activated T-cells and B-cells [47]. MM cells have shown high SLAMF7 expression, providing the rationale for therapeutic targeting [48]. MAbs binding to SLAMF7 on MM cells and the induction of ADCC via NK cells Fc $\gamma$  receptor are the main mechanisms mediating anti-MM activity. Anti-SLAMF7 mAbs bind also to SLAMF7 expressed by NK cells, causing cytokine release and degranulation, thus enhancing their activity. Another peculiar mechanism of this class of drugs is the inhibition of MM adhesion to bone marrow stromal cells to avoid growth and survival signals [49].

### 2.2.1 Elotuzumab

Elotuzumab is an IgG1 fully human mAb targeting SLAMF7. PK analysis data of elotuzumab in monotherapy and in combination regimens showed that SLAMF7 saturation increased with higher elotuzumab doses. In particular, doses of 10-20 mg/kg every 2 weeks of elotuzumab caused  $\geq 95\%$  saturation, and this value is not affected by the addition of bortezomib or lenalidomide plus dexamethasone [50],[51].

PPK analysis suggested no impact of age, sex, race, baseline LDH, albumin,  $\beta 2$ -microglobulin, hepatic or renal dysfunction and performance status on elotuzumab CL. Elotuzumab CL increases with body weight. Differently from target saturation, Elotuzumab CL was significantly lower when administered with Rd or Vd, mostly because of dexamethasone co-administration.

Elotuzumab monotherapy in RRMM was well tolerated, MTD was not reached and the maximum tested dose was 20 mg/Kg every 15 days. However, no objective responses were observed [50].

In a phase II randomized trial, elotuzumab-Vd was compared to Vd. Elotuzumab was administered at 10 mg/kg weekly in 21-day cycles during cycles 1 and 2, on days 1 and 11 for cycles 3 to 8, and then on days 1 and 15 thereafter, together with standard Vd treatment. PR rate was comparable between the two arms, but a slightly longer PFS in patients in the elotuzumab-Vd group was observed (9.7 vs 6.9 months, HR 0.72,  $p=0.09$ ) [52].

Better results were reported with elotuzumab plus Rd, probably because of lenalidomide synergistic effect on immune cells. Patients in the experimental group received elotuzumab 10 mg/kg weekly for 8 weeks and once every 2 weeks thereafter. In a large phase III randomized trial, elotuzumab-Rd compared with Rd produced a better PR rate (79% vs 66%) and significantly prolonged PFS (19.4 vs 14.9 months, HR 0.70,  $p<0.0001$ ) [53].

Overall, the safety profile of Elotuzumab was good. Similarly to anti-CD38 mAbs, IRRs were mostly mild and they occurred mainly during the first infusion. Rate of IRRs ranged from 5 to 10% and consisted mainly of fever and chills, much lower compared to intravenous daratumumab and isatuximab; a clear respiratory pattern was not present.

## 3 CHECKPOINT BLOCKADE THERAPY

Immune checkpoint molecules are expressed by immune cells and they work as breaks to shut off immune responses in order to avoid excessive tissue destruction and autoimmune reactions once the target of immune cells is destroyed. Malignant plasma cells aberrantly express these molecules avoiding the control of the immune system [54]. The main immune checkpoint molecules targeted in MM are programmed cell death (PD-1) and programmed cell death ligand (PDL-1).

The transmembrane PD-1 receptor is a negative regulator of T-cell response, which is expressed on T cells, B cells, NK cells and monocytes.[55] Immune cells activated by various stimuli express PD-1 that binds to its ligand PDL-1 on antigen presenting cells and shuts off the immune response [56]. This process play a major role in the maintenance of self-tolerance and PD-1 deficient mice develop excessive and often devastating systemic inflammatory responses [57].

MM cells do express PDL-1, which, upon the engagement of PD-1, protect them from immune-mediated killing.

Differently from mAbs targeting tumor-related surface molecules, mAbs used as CBT inhibit the interaction between checkpoint molecules, allowing immune cells to recognize and kill neoplastic cells. Molecules targeting both PD-1 and PDL-1 are in clinical development in MM.

### 3.1 Nivolumab

Nivolumab is a human IgG4 mAb that binds to the PD-1 receptor on activated immune cells and blocks its interaction with PD-L1 and PD-L2 [58].



PK data on single agent nivolumab are reported in phase I trials on patients with solid tumors. The most striking characteristic of nivolumab is its very high binding affinity to PD-1. Indeed, about 80% of saturation is reached in less than one day following a single nivolumab infusion at the dose of 3 mg/kg and PD-1 occupancy is maintained above 70% for almost 60 days. Detectable levels of PD-1 receptor occupancy were observed more than 3 months after nivolumab infusion [59].

PPK analysis revealed that nivolumab CL is affected by body weight, ECOG status but not by renal or hepatic impairment. Body weight and gender were associated with limited volume distribution changes, that were not clinically significant and did not require dose changes [60].

Nivolumab monotherapy was tested in a phase Ib trial in patients affected by different hematologic malignancies, including 27 patients with RRMM [61]. In MM patients, single-agent nivolumab did not show any objective response. However, building on nivolumab prolonged PD-1 receptor occupancy, it was hypothesized that the efficacy and safety of other drugs used immediately after nivolumab treatment could be modified [62].

Ongoing trials are evaluating nivolumab in combination with pomalidomide-dexamethasone and other mAbs such as daratumumab (NCT01592370) and Elotuzumab (NCT02726581). Combination with another CBT targeting CTLA4 after autologous (NCT02681302) and allogeneic (NCT01822509) stem cell transplantation is under evaluation as well.

### 3.2 Pembrolizumab

Pembrolizumab is an IgG4k humanized anti-PD-1 mAb. This molecule has been widely investigated in several solid tumors and it is approved in many indications, such as non-small cell lung cancer, head and neck cancer, classical Hodgkin lymphoma and urothelial carcinoma. PK data came from several early clinical trials evaluating pembrolizumab on solid tumors at the dose of 2 mg/kg every 3 weeks. Pembrolizumab PK is not affected by age, sex, race, renal/hepatic impairment and ECOG status, thus dose adjustment is not necessary. Moreover, in the model-based characterization of pembrolizumab PK, both fixed dosing (200 mg every 3 weeks) and body weight-based dosing (2 mg/kg every 3 weeks) perform similarly [63].

There are no data on pembrolizumab monotherapy in MM. In a phase I study enrolling RRMM patients, pembrolizumab has been tested in combination with Rd. The MTD of pembrolizumab was 200 mg every 21 days and the PR rate was 50%. In a phase II trial, pembrolizumab was combined with another immunomodulatory drug, pomalidomide, and dexamethasone. Pembrolizumab was given at a dose of 200 mg every 2 weeks, and led to an ORR rate of 60% [64],[65]. Immune mediated adverse events, a well-known risk associated with CBT, were observed in 33% of patients (grade>3 in 10%) and were represented by pneumonitis (13%), hypothyroidism (10%), adrenal insufficiency (4%), hepatitis (4%) and vitiligo (2%)

These encouraging data, together with the strong biologic rationale of combining an immunomodulatory drug boosting immune responses with CBT to release the breaks induced by tumour on immune cells, prompted the evaluation of pembrolizumab in 2 randomized phase-III trials. In the first trial, pembrolizumab-pomalidomide-dexamethasone was compared to pomalidomide-dexamethasone in RRMM patients (NCT02576977). In the second trial pembrolizumab-Rd vs Rd alone was investigated in newly diagnosed MM patients (NCT02579863).

Although safety is not the main focus of this paper, these 2 trials raised serious concerns about CBT approach in MM. Indeed, after an early interim analysis, FDA placed these phase-III randomized clinical trials on full clinical hold in July 2017. This decision was made upon a decreased survival noted in the investigational arms, where pembrolizumab was combined with immunomodulatory drugs. This survival difference was due mainly to drug-related toxic deaths. For safety issues, studies evaluating other PD-1/PDL-1 inhibitors in combination with immunomodulatory drugs are actually on partial clinical hold until updated safety data will be available [66].

### 3.3 Durvalumab

Durvalumab is a human IgG1k antibody targeting PDL-1. Little is known on the differences between PD-1 and PDL-1 targeting, however they have a similar mechanism compared with CBT. As in PD-1 directed therapy, PK data of durvalumab were defined in phase I and II trials on patients affected by solid tumors. Weight-based durvalumab dose (10 mg/kg Q2W) and fixed durvalumab dose (1500 mg Q4W or 750 mg Q2W) demonstrated similar PK features. Patient and disease characteristics did not affect drug bioavailability, supporting the concept that no dose adjustments are needed [67].

Clinical data on PDL-1 inhibitors in MM are still not available. Phase I studies investigating durvalumab in combination with immunomodulatory drugs are currently on clinical hold for the reasons explained in the previous paragraph.

## 4 CONCLUSION

In the first decade of 2000s, the availability of PIs and IMiDs led to unprecedented outcomes in MM patients. Nowadays, PI- and IMiD-based combinations represent the standard of care and the backbone therapy for newly diagnosed and relapsed and/or refractory disease. Second-generation PIs and IMiDs have recently increased the treatment armamentarium for MM patients,

together with mAbs, a different class of drugs directed against plasma cell antigens. The association of PIs and IMiDs plus mAbs led to the development of new standards in relapsed and/or refractory disease (Elotuzumab-Rd, Daratumumab-Vd, Daratumumab-Rd, Daratumumab-Pomalidomide-dexamethasone). Initial insights on the use of mAbs in first-line treatment are very promising as well (Daratumumab-VMP), and trials exploring other potential novel standards in the upfront setting are ongoing (Elotuzumab-Rd, Daratumumab-Rd, Daratumumab-VTD, Daratumumab-VRD). In all the trials performed so far, the main advantage of this drug class relies in the robust efficacy benefit at the cost of a negligible increase in adverse events. IRRs are a class-specific type of adverse event that tends to disappear after the first infusion and proved to be manageable in the great majority of cases. The development of effective and safe subcutaneous formulations will be pivotal for their practical clinical use. The other class of drugs in an earlier phase of evaluation in MM is CBT which is revolutionizing the treatment of many solid and hematologic tumors and there is a strong rationale for its use in MM as well. After very promising preliminary data, the toxicity reported in two recent randomized phase III trials of pembrolizumab in combination with lenalidomide and pomalidomide led the FDA to place a clinical hold on trials exploring anti-PD1 therapy in combination with IMiDs in MM: the related safety concerns are consistent with the mechanism of action of both drug classes, modifying the behavior of immune cells. The analysis of mature safety data, together with the deep understanding of the biologic mechanisms behind this clinical observation, will be essential in order to use CBT in a safe way in MM. At present, trials exploring CBT in combination with other drugs are ongoing, with no safety issues raised so far. Results of all these trials could confirm whether CBT is going to become another option in the treatment of MM patients.

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**Table 1:** Key monoclonal antibodies pharmacokinetic parameters

Target	mAb	Trial	Dose schedule	C <sub>max</sub> after first infusion	Mean linear clearance	Volume of distribution of central compartment	Target effective trough concentration	Target saturation at the effective trough concentration	Terminal half-life at steady-state
CD38	Daratumumab	Phase I GEN501 and SIRIUS [23],[27],[34]	Daratumumab 16 mg/kg QW for 8 weeks, Q2W for 16 weeks and Q4W thereafter	263 µg/mL	0.17 L/day	4.7 L	236 µg/mL	99%	18 days
		Phase I/II GEN503 [30],[34],[68]	Daratumumab 16 mg/kg QW for 8 weeks, Q2W for 16 weeks and Q4W thereafter plus lenalidomide (25 mg days 1-21) and dex (40 mg QW)	265 µg/mL	NA	4.4 L	NA	NA	23 days
	Isatuximab	Phase I/II TED10893 and phase IB TCD11863 [40],[42]	Isatuximab 10 mg/kg QW or Q2W in monotherapy or plus lenalidomide (25 mg days 1-21) and dex (40 mg QW)	122 µg/mL for isatuximab 10 mg/kg QW. 212 µg/mL for isatuximab 10 mg/kg Q2W.	NA	NA	NA	80% of CD38 occupancy reached with isatuximab at 10 mg/kg QW, rising to 90% of saturation with isatuximab 10 mg/kg Q2W	NA
SLAM F7	Elotzumab	Pooled analysis of ELOQUENT-2 and CA204-007 trials [49],[50],[69],[70]	Elotzumab 10 mg/kg QW in monotherapy or combined with lenalidomide (25 mg days 1-21) and dex (40 mg QW)	337 µg/mL	0.09 L/day	4.04 L	70 µg/mL	≥95%	NA
PD-1	Pembrolizumab*	Pooled analysis of KEYNOTE-001, 002 and 006. [63],[71],[72]	Pembrolizumab 2 mg/kg Q3W in monotherapy	66.3 µg/mL <sup>Δ</sup>	0.22 L/day	3.48 L	NA	95% of PD-1 occupancy with pembrolizumab doses ≥ 0.8 mg/kg Q3W.	27 days
	Nivolumab*	Pooled analysis of phase I and II clinical trials of nivolumab. [59],[73],[74]	Nivolumab 3 mg/kg Q2W in monotherapy	68.8 µg/mL	0.22 L/day	3.63 L	NA	>70% PD-1 occupancy at undetectable serum levels (< 1.2 µg/mL)	25 days
PDL-1	Durvalumab*	Phase I/II dose-finding CDON-MEDI 4736-1108 [67],[75]	Durvalumab 10 mg/kg Q2W in monotherapy	NA	0.24 L/day	3.6 L	50 µg/mL	>99% PDL-1 occupancy at doses ≥40 µg/mL	23 days

**Abbreviations.** mAb: monoclonal antibody; C<sub>max</sub>: maximum observed concentration; QW: weekly; Q2W: every 2 weeks; Q3W: every 3 weeks; Q4W: every 4 weeks; dex: dexamethasone.

\* PK data derived from melanoma and NSLC patients; <sup>Δ</sup> C<sub>max</sub> value measured at steady state.