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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

Abstract

Background. Survival of multiple myeloma patients has considerably improved in the last decades thanks to the introduction of many new drugs, including immunomodulatory agents, proteasome inhibitors and, more recently, monoclonal antibodies.

Methods. We analyzed the most recent literature focusing on the clinical and pharmacologic aspects of monoclonal antibody-based therapies in multiple 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. Anti-CD38 monoclonal antibodies including daratumumab, isatuximab and MOR202 have shown outstanding results in relapsed and/or refractory multiple myeloma patients. The addition of daratumumab to bortezomib-dexamethasone or lenalidomide-dexamethasone substantially improved patients' outcome in this patient population. The anti-SLAMF7 molecule elotuzumab in combination with lenalidomide-dexamethasone showed to be superior to lenalidomide-dexamethasone alone, without adding meaningful toxicity. Checkpoint blockade therapy in combination with immunomodulatory agents produced objective responses in more than 50% of treated patients. However, this combination was also associated with an increase in toxicity and a thorough safety evaluation is currently ongoing.

Conclusion. Monoclonal antibodies are reshaping the standard of care for multiple myeloma and ongoing trials will help physicians to optimize their use in order to further improve patients' outcome.

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

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 lytic bone lesions, anemia, renal impairment, and/or hypercalcemia [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]. Over the past twenty years, survival of MM patients has improved and the main reason is the increased number of available effective drugs used either as single agents 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, when 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 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 two 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. More specifically, the main mechanisms are complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) (Figure 1A) [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) form transmembrane channels disrupting phospholipid bilayer and lead to cell death [8]. The engagement of the Fc portion of antibody-tumor cell complex by Fcγ 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 ability 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 degradation by phagocytes or lysosomes when mAb is internalized in cells via Fcγ-receptor interaction [10]. The model based-pharmacokinetics analysis describing the PK profile of the majority of mAbs shows both dose-dependent elimination (with linear clearance [CL]) and non-linear 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 sizes that are precluded to the glomerular filtration, whereas currently available maximum plasma mAb concentration and target effective through concentration values are specific for each mAb class but similar and comparable among different mAbs of the same category, since these parameters are mainly based 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-hematopoetic tissues [12].

High CD38 levels have been observed in a wide number of hematologic 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 level may be obtained, which contributes 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 do not interfere with the major antigens of ABO/RhD typing, but with the minor ones. In the indirect Coombs test, mAbs bind to CD38 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, by using available protocols (Dithiothreitol [DTT] or Anti-idiotype mAb and soluble CD38) or genotyping. If a non-crossmatched emergency transfusion is required, ABO/RhD–compatible RBCs can be given, as per local blood bank practices. To avoid unnecessary delays, it is essential that the blood bank is informed that it will receive a sample from an anti-CD38 mAbs-treated patient, so that appropriate protocols can be applied. Patients have to carry a blood transfusion card indicating that they are receiving anti-CD38 mAb therapy. Indirect antiglobulin test can be positive for up to 6 months after the interruption of the 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 bronchodilatators should be considered as additional prophylaxis of IRRs in patients with a reduced FEV1. A well-performed premedication protocol including steroids and H1/H2 antihistamines is important to keep low the IRRs rate, avoid infusion delays, and allow the outpatient infusion of anti-CD38 mAbs [22–24]. Moreover, the use of the leukotriene receptor antagonist montelukast can be used to reduce the IRRs rate: in patients treated with Daratumumab, any-grade IRRs occurred in 38% vs 58.5% of patients with or without Montelukast, respectively with a first infusion median time of 6.7 vs 7.6 hours with or without Montelukast, respectively) [25].

2.1.1 Daratumumab

Daratumumab is an IgG1κ fully human mAb and is the only anti-CD38 mAb that binds two sequences of a unique CD38 epitope [26].

Population PK (PPK) analyses indicated that age, gender, renal impairment and hepatic impairment do not have clinically relevant effects on daratumumab PK, whereas its volumes of distribution and CL increase with increasing body weight, thus supporting the body-weight-based dosing regimen [27–29]. Further analysis of daratumumab monotherapy trials showed that IgG multiple myeloma patients had lower concentration of daratumumab serum due to an almost doubled CL value when compared with non-IgG patients. Moreover, 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. In non-IgG patients, no competition for FcRn occurs between mAb and IgG . However, no differences in the ORR were observed in IgG or non-IgG multiple myeloma patients.

Daratumumab monotherapy was evaluated in two trials (GEN501 and SIRIUS) enrolling relapsed/refractory MM (RRMM) patients [28,30]. Maximum tolerated dose (MTD) was not reached in the dose escalation cohort of the 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 (Cmin), 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 ≥ 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 was not associated with maximum daratumumab serum levels reached after infusion [31].

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 saturating target-mediated CL during initial dosing and maintaining saturation when doses are delayed every 2 or 4 weeks [27].

Daratumumab in combination with standard backbone MM treatments for relapsed/refractory patients, bortezomib-dexamethasone (Vd) and lenalidomide-dexamethasone (Rd), has been explored with outstanding clinical results in two large phase-III randomized trials, CASTOR and POLLUX [32,33].

The CASTOR study randomized 498 RRMM patients to daratumumab-Vd vs Vd. The daratumumab schedule was slightly different from monotherapy trials: it was given at 16 mg/kg 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%) [34].

Of interest, in both CASTOR and POLLUX studies, the addition of daratumumab to standards of care 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) [35].

The combination of daratumumab with another IMiD, namely pomalidomide, was explored in the EQUULEUS phase 1 study [36]. 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 (Pom-Dex) standard schedule. ORR was 60% with 17% of patients achieving complete response or better. Median PFS was 8.8 vs 4 months reported with Pom-Dex alone in a similar patient population [37]. Grade ≥ 3 neutropenia rate in the daratumumab-pomalidomide-dexamethasone trial was 78%, higher than what was reported with Pom-Dex alone [37], despite a quite similar infection rate. IRRs rate was 50% (4% grade ≥ 3), similarly to other daratumumab trials in the RRMM setting [27,31–33,38].

Based on the CASTOR [32], POLLUX [33] and EQUULEUS [36] trials, daratumumab combination therapies with Vd, Rd and Pom-Dex respectively have been approved by the FDA for RRMM patients [38]. Many clinical trials combining daratumumab with other compounds and exploring its efficacy in high-risk smoldering MM (e.g. NCT02316106) and newly diagnosed MM (e.g. NCT02541383, NCT02252172) 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 ≥ 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 [39]. 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 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 [40,41].

2.1.2 Isatuximab

Isatuximab (SAR650984) is an IgG1κ 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 [42].

Few isatuximab PK data in MM patients are currently available, since phase I-II trials are ongoing and recruiting patients. Based on the currently available data, isatuximab monotherapy did not show specific PK features compared to other anti-CD38 mAbs, and PPK analyses have not been reported yet [43].

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 of 20 mg/kg) produced an ORR of 27%, similarly to daratumumab monotherapy [44,45]. In the second trial, isatuximab was given in combination with Rd in RRMM patients [46]. 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 had a similar behavior to isatuximab in monotherapy. When combined with isatuximab, lenalidomide exposure did not cause accumulation, even after repeated dosing. 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 Pom-Dex was investigated in a dose-escalation phase Ib study on RRMM patients [47]. 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% of 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 Pom-Dex vs Pom-Dex alone.

In all trials, isatuximab showed similar IRRs 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 near future.

2.1.3 MOR202

MOR202 is an IgG1λ 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 [48]. 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 Pom-Dex [49].

MTD was not reached and the maximum tested dose was 16 mg/kg weekly. No safety issues were observed. Preliminary PK results showed that, in patients treated with weekly MOR202 at 16 mg/kg, 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 [49,50].

As expected, the drug was associated with a low incidence of IRRs (6%, all grade < 3). In the MOR202-Dex cohort, ORR was 28%, while in patients treated with MOR202-Rd and MOR202-Pom-Dex ORR was 71 and 46%, respectively [49]. Of note, all patients in the MOR202-Pom-Dex cohort were lenalidomide-refratory.

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 [51]. MM cells have shown high SLAMF7 expression, providing the rationale for therapeutic targeting [52]. MAbs binding to SLAMF7 on MM cells and the induction of ADCC via NK cells Fcγ 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 [53].

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 ≥95% saturation, and this value is not affected by the addition of bortezomib or lenalidomide plus dexamethasone [54,55].

PPK analysis suggested no impact of age, sex, race, baseline LDH, albumin, β2-microglobulin, hepatic or renal dysfunction and performance status on elotuzumab CL, which nevertheless increases with increasing 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 [54].

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) [56].

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 (4 year PFS rate 21% vs 14%, HR 0.71, 95% CI 0.59-0.86, p=0.0004) and overall survival ([OS], median 48 vs 40 months, HR 0.78, 95% CI 0.63-0.96) [57,58].

Overall, the safety profile of Elotuzumab was excellent. 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 when compared to intravenous daratumumab and isatuximab; a clear respiratory pattern was not present. Moreover, the combination of Elotuzumab with other drugs did not add meaningful toxicity and the feasibility of outpatient administration was very good due to the rarity of infusion reactions and subsequent infusion delays.

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 [59]. The main immune checkpoint molecules targeted in MM are programmed cell death (PD-1) and programmed cell death ligand (PDL-1) (Figure 1B).

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.[60] 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 [61]. This process plays a major role in the maintenance of self-tolerance, and PD-1 deficient mice develop excessive and often devastating systemic inflammatory responses [62].

MM cells do express PDL-1, which, upon the engagement of PD-1, protects 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 under clinical development for MM treatment.

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 [63].

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; 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 [64].

PPK analysis revealed that nivolumab CL is affected by body weight, by ECOG status, but not by renal or hepatic impairment. Body weight and gender were associated with limited volume distribution changes, which were not clinically significant and did not require dose changes [65].

Nivolumab monotherapy was tested in a phase Ib trial in patients affected by different hematologic malignancies, including 27 patients with RRMM [66]. In MM patients, single-agent nivolumab did not show any objective response. However, considering the prolonged PD-1 receptor occupancy of nivolumab, it was hypothesized that the efficacy and safety of other drugs used immediately after nivolumab treatment could be modified [67].

Ongoing trials are evaluating nivolumab in combination with Pom-Dex 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 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 [68].

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% [69,70]. 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%). One patient died from sepsis developed in a period of neutropenia during treatment.

These data, together with the 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-Pom-Dex was compared to Pom-Dex in RRMM patients (NCT02576977). After a median follow-up of 8.1 months [71], ORR was comparable between investigational and control arm (34% vs 40%). However, grade ≥ 3 adverse events were higher in the pembrolizumab-Pd arm compared to Pd alone (83% vs 65% respectively). There were 29 deaths in the investigational arm vs 21 in the control arm. Excluding disease progression, the following causes of death were reported in the pembrolizumab-Pd arm: infections, Stevens-Johnson syndrome, cardiovascular toxicities, multiple organ dysfunction, respiratory failure and ‘unknown’.

In the second trial, pembrolizumab-Rd vs Rd alone was investigated in newly diagnosed MM patients (NCT02579863). After a median follow-up of 6.6 months [71], ORR was comparable in the experimental vs control arm (64% vs 62%), while grade ≥3 adverse events were significantly higher in the investigational arm (72% vs 50%). At the data cut-off, there were 19 deaths in the pembrolizumab-Rd arm vs 9 deaths in the Rd arm, leading to a worse overall survival in the experimental arm (HR 2.06; 95% CI 0.93-4.55). Non-disease causes of death in the experimental arm were cardiovascular toxicities, intestinal ischemia/perforation, infections and suicide.

The early results from these 2 trials raised serious concerns about CBT approach in MM. Indeed, FDA placed these phase-III randomized clinical trials on full clinical hold in July 2017.

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, although they have a similar mechanism when 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 [72].

Clinical data on PDL-1 inhibitors in MM are still not available. Phase 1 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 multiple myeloma. 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-Pom-Dex). Initial insights on the use of mAbs as 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 relied on the robust efficacy benefit at the cost of a negligible increase in adverse events. In the absence of head-to-head comparisons between treatment regimens, the choice of one combination over the other should take into account patient characteristics, disease features, and previous therapy, in order to weigh the benefit of one regimen over the other. 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. More specifically, the anti-SLAMF7 elotuzumab has an excellent safety profile and a low IRRs rate, giving practical advantages in the outpatient setting and making it an attractive choice even in patients with a high comorbidity burden. Anti-CD38 mAbs are very well tolerated even in elderly patients, but they should be used with caution in patients with reduced pulmonary function. A well-performed premedication protocol including steroids, H1/H2 antihistamines, leukotriene receptor antagonist is important to keep low the IRRs rate [22–24]. The development of effective and safe subcutaneous formulations will be pivotal for their practical clinical use in the future. Daratumumab in combination in the relapsed setting led to unprecedented results, including long-term disease control and achievement of minimal residual disease (MRD) negativity. Recent data confirm the effectiveness of both elotuzumab and daratumumab in patients with high-risk features [35,73]; mABs plus lenalidomide-dexamethasone can be preferred in patients previously treated with proteasome inhibitors and vice-versa. The optimal sequence of therapies – as to say the use of anti-CD38 before or after anti-SLAM F7 molecules – is currently unknown, due to the lack of specific data.

CBT is revolutionizing the treatment of many solid and hematologic tumors. Despite the strong biological rationale for supporting the use of these agents also in MM and in particular in combination with IMiDs, and also despite the very promising preliminary data, the toxicity reported in the 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 these combinations. 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. The discussion of other immunotherapeutic approaches such as vaccines, bispecific antibodies and adoptive cell therapy (e.g. chimeric antigen receptors-T-cells) was not the focus of this review, even though they are currently under evaluation [4]. Results of the ongoing trials will confirm whether or not these new treatments will be included in the treatment armamentarium against MM.

References

[1] Palumbo A, Anderson K. Multiple myeloma. N. Engl. J. Med. [Internet]. 2011 [cited 2017 Jun 28];364:1046–1060. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMra1011442.

[2] Pozzi S, Marcheselli L, Bari A, et al. Survival of multiple myeloma patients in the era of novel therapies confirms the improvement in patients younger than 75 years: a population-based analysis. Br. J. Haematol. [Internet]. 2013 [cited 2017 Dec 14];163:40–46. Available from: http://doi.wiley.com/10.1111/bjh.12465.

[3] Costa LJ, Brill IK, Omel J, et al. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. Blood Adv. [Internet]. 2017 [cited 2017 Dec 14];1:282–287. Available from:

http://www.bloodadvances.org/lookup/doi/10.1182/bloodadvances.2016002493.
[4] D'Agostino M, Boccadoro M, Smith EL. Novel Immunotherapies for Multiple Myeloma. Curr. Hematol. Malig. Rep. [Internet]. 2017 [cited 2017 Dec 14];12:344–357. Available from: http://link.springer.com/10.1007/s11899-017-0397-7.
[5] Romano A, Conticello C, Cavalli M, et al. Immunological dysregulation in multiple myeloma microenvironment. Biomed Res. Int. [Internet]. 2014 [cited 2017 Dec 14];2014:198539. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25013764.
[6] Gay F, D'Agostino M, Giaccone L, et al. Immuno-oncologic Approaches: CAR-T Cells and Checkpoint Inhibitors. Clin. Lymphoma. Myeloma Leuk. [Internet]. 2017 [cited 2017 Dec 14];17:471–478. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28689001.
[7] van de Donk NWCJ, Moreau P, Plesner T, et al. Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma. Blood [Internet]. 2016 [cited 2017 Dec 14];127:681–695. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26631114.
[8] Dunkelberger JR, Song W-C. Complement and its role in innate and adaptive immune responses. Cell Res. [Internet]. 2010 [cited 2017 Dec 14];20:34–50. Available from: http://www.nature.com/doifinder/10.1038/cr.2009.139.
[9] Dong JQ, Salinger DH, Endres CJ, et al. Quantitative Prediction of Human Pharmacokinetics for Monoclonal Antibodies. Clin. Pharmacokinet. [Internet]. 2011 [cited 2017 Dec 14];50:131–142. Available from: http://link.springer.com/10.2165/11537430-000000000-00000.
[10] Mould DR, Green B. Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies. BioDrugs [Internet]. 2010 [cited 2017 Dec 14];24:23–39. Available from: http://link.springer.com/10.2165/11530560-000000000-00000.
[11] Vugmeyster Y, Xu X, Theil F-P, et al. Pharmacokinetics and toxicology of therapeutic proteins: Advances and challenges. World J. Biol. Chem. [Internet]. 2012 [cited 2017 Dec 14];3:73–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22558487.
[12] Deaglio S, Mehta K, Malavasi F. Human CD38: a (r)evolutionary story of enzymes and receptors. Leuk. Res. [Internet]. 2001 [cited 2017 Dec 14];25:1–12. Available from: http://www.sciencedirect.com/science/article/pii/S014521260000093X.
[13] Lin P, Owens R, Tricot G, et al. Flow Cytometric Immunophenotypic Analysis of 306 Cases of Multiple Myeloma. Am. J. Clin. Pathol. [Internet]. 2004 [cited 2017 Dec 14];121:482–488. Available from: https://academic.oup.com/ajcp/article-lookup/doi/10.1309/74R4TB90BUWH27JX.
[14] Dianzani U, Funaro A, DiFranco D, et al. Interaction between endothelium and CD4+CD45RA+ lymphocytes. Role of the human CD38 molecule. J. Immunol. [Internet]. 1994 [cited 2017 Dec 14];153:952–959. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7913116.
[15] An G, Jiang H, Acharya C, et al. SAR 650984, a Therapeutic Anti-CD38 Monoclonal Antibody, Blocks CD38-CD31 Interaction in Multiple Myeloma. Blood [Internet]. 2014 [cited 2017 Dec 14];124:Abstract 4729. Available from: http://www.bloodjournal.org/content/124/21/4729.
[16] van de Donk NWCJ, Janmaat ML, Mutis T, et al. Monoclonal antibodies targeting CD38 in hematological malignancies and beyond. Immunol. Rev. [Internet]. 2016 [cited 2017 Dec 14];270:95–112. Available from: http://doi.wiley.com/10.1111/imr.12389.
[17] Lammerts van Bueren J, Jakobs D, Kaldenhoven N, et al. Direct in Vitro Comparison of Daratumumab with Surrogate Analogs of CD38 Antibodies MOR03087, SAR650984 and Ab79. Blood [Internet]. 2014 [cited 2017 Dec 14];124:Abstract 3474. Available from: http://www.bloodjournal.org/content/124/21/3474?sso-checked=true.
[18] Mattes MJ, Michel RB, Goldenberg DM, et al. Induction of Apoptosis by Cross-Linking Antibodies Bound to Human B-Lymphoma Cells: Expression of Annexin V Binding Sites on the Antibody Cap. Cancer Biother. Radiopharm. [Internet]. 2009 [cited 2017 Dec 14];24:185–193. Available from: http://www.liebertonline.com/doi/abs/10.1089/cbr.2008.0567.
[19] Oostendorp M, Lammerts van Bueren JJ, Doshi P, et al. When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy. Transfusion [Internet]. 2015 [cited 2017 Dec 14];55:1555–1562. Available from: http://doi.wiley.com/10.1111/trf.13150.
[20] van de Donk NWCJ, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma: back to the future. Blood [Internet]. 2018 [cited 2017 Dec 14];131:13–29. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29118010.
[21] Kotlikoff MI, Kannan MS, Solway J, et al. Methodologic advancements in the study of airway smooth muscle. J. Allergy Clin. Immunol. [Internet]. 2004 [cited 2017 Dec 14];114:S18-31. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0091674904014113.
[22] Engelhardt M, Berger DP, Mertelsmann R, et al., editors. Das Blaue Buch : Chemotherapie-Manual Hämatologie und Onkologie [Internet]. Berlin: Springer-Verlag; 2016 [cited 2018 Feb 1]. Available from: https://books.google.it/books?id=MNhCDwAAQBAJ&dq=978-3-662-51420-7&hl=it&source=gbs_navlinks_s.
[23] Scheid C, Munder M, Salwender H, et al. Infusion von Daratumumab in Kombinationstherapien: Praktische Hinweise für die sichere Durchführung im ambulanten Bereich. DMW. 2018;Awaiting publication.
[24] Köhler M, Greil C, Hudecek M, et al. Current developments in immunotherapy in the treatment of multiple myeloma. Cancer. 2018;Awaiting publication.
[25] Chari A, Mark TM, Krishnan A, et al. Use of Montelukast to Reduce Infusion Reactions in an Early Access Treatment Protocol of Daratumumab in United States Patients with Relapsed or Refractory Multiple Myeloma. Blood [Internet]. 2016 [cited 2018 Feb 1];128:Abstract 2142. Available from: http://www.bloodjournal.org/content/128/22/2142?sso-checked=true.
[26] de Weers M, Tai Y-T, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J. Immunol. [Internet]. 2011 [cited 2017 Dec 14];186:1840–1848. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21187443.
[27] Clemens PL, Yan X, Lokhorst HM, et al. Pharmacokinetics of Daratumumab Following Intravenous Infusion in Relapsed or Refractory Multiple Myeloma After Prior Proteasome Inhibitor and Immunomodulatory Drug Treatment. Clin.

Pharmacokinet. [Internet]. 2017 [cited 2017 Dec 14];56:915–924. Available from: http://link.springer.com/10.1007/s40262-016-0477-1.
[28] Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N. Engl. J. Med. [Internet]. 2015 [cited 2017 Oct 27];373:1207–1219. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1506348.
[29] Zirkelbach JF, Habtermariam B, Ma L, et al. 761036Orig1s000. Clinical Pharmacology and Biopharmaceutics Review(s) [Internet]. 2015 [cited 2017 Dec 14]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/761036Orig1s000ClinPharmR.pdf.
[30] Lonial S, Weiss BM, Usmani SZ, et al. Phase II study of daratumumab (DARA) monotherapy in patients with ≥ 3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius). J. Clin. Oncol. [Internet]. 2015 [cited 2017 Dec 14];33:Abstract LBA8512. Available from: http://ascopubs.org/doi/10.1200/jco.2015.33.18_suppl.lba8512.
[31] Xu X, Yan X, Puchalski T, et al. Clinical Implications of Complex Pharmacokinetics for Daratumumab Dose Regimen in Patients With Relapsed/Refractory Multiple Myeloma. Clin. Pharmacol. Ther. [Internet]. 2017 [cited 2017 Dec 14];101:721–724. Available from: http://doi.wiley.com/10.1002/cpt.577.
[32] Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N. Engl. J. Med. [Internet]. 2016 [cited 2017 Oct 26];375:754–766. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1606038.
[33] Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N. Engl. J. Med. [Internet]. 2016 [cited 2017 Oct 26];375:1319–1331. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1607751.
[34] Plesner T, Arkenau H-T, Gimsing P, et al. Phase 1/2 study of daratumumab, lenalidomide, and dexamethasone for relapsed multiple myeloma. Blood [Internet]. 2016 [cited 2017 Dec 14];128:1821–1828. Available from: http://www.bloodjournal.org/cgi/doi/10.1182/blood-2016-07-726729.
[35] Weisel KC, San Miguel J, Cook G, et al. Efficacy of daratumumab in combination with lenalidomide plus dexamethasone (DRd) or bortezomib plus dexamethasone (DVd) in relapsed or refractory multiple myeloma (RRMM) based on cytogenetic risk status. J. Clin. Oncol. 2017;35:Abstract 8006.
[36] Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood [Internet]. 2017 [cited 2017 Dec 18];130:974–981. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28637662.
[37] San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. [Internet]. 2013 [cited 2017 Dec 18];14:1055–1066. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24007748.
[38] DARZALEX ®. Daratumumab. Product Information [Internet]. JANSSEN-CILAG Pty Ltd. Macquarie Park NSW 2113--Auckland (AU--NZN); 2017 [cited 2017 Dec 15]. Available from: http://www.janssen.com/australia/sites/www_janssen_com_australia/files/prod_files/live/darzalex_pi.pdf.
[39] Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N. Engl. J. Med. [Internet]. 2017 [cited 2017 Dec 18];[Ahead of print-NEJMoa1714678]. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1714678.
[40] Chari A, Nahi H, Mateos M-V, et al. Subcutaneous Delivery of Daratumumab in Patients (pts) with Relapsed or Refractory Multiple Myeloma (RRMM): Pavo, an Open-Label, Multicenter, Dose Escalation Phase 1b Study. Blood [Internet]. 2017 [cited 2017 Dec 14];130:Abstract 838. Available from: http://www.bloodjournal.org/content/130/Suppl_1/838?sso-checked=true.
[41] Usmani SZ, Nahi H, Mateos M-V, et al. Open-Label, Multicenter, Dose Escalation Phase 1b Study to Assess the Subcutaneous Delivery of Daratumumab in Patients (pts) with Relapsed or Refractory Multiple Myeloma (PAVO). Blood [Internet]. 2016 [cited 2017 Dec 14];128:Abstract 1149. Available from: http://www.bloodjournal.org/content/128/22/1149?sso-checked=true.
[42] Deckert J, Wetzel M-C, Bartle LM, et al. SAR650984, a novel humanized CD38-targeting antibody, demonstrates potent antitumor activity in models of multiple myeloma and other CD38+ hematologic malignancies. Clin. Cancer Res. [Internet]. 2014 [cited 2017 Dec 14];20:4574–4583. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24987056.
[43] Martin T, Richter J, Vij R, et al. A Dose Finding Phase II Trial of Isatuximab (SAR650984, Anti-CD38 mAb) As a Single Agent in Relapsed/Refractory Multiple Myeloma. Blood [Internet]. 2015 [cited 2017 Dec 14];126:Abstract 509. Available from: http://www.bloodjournal.org/content/126/23/509.
[44] Martin T, Strickland S, Glenn M, et al. A Phase I trial of SAR650984, a CD38 monoclonal antibody, in relapsed or refractory multiple myeloma. Am. Soc. Clin. Oncol. [ASCO] Annu. Meet. [Internet]. Chicago: ASCO; 2014 [cited 2017 Dec 14]. p. Poster Abstract 8532. Available from: http://www.myelomabeacon.com/docs/asco2014/8532.pdf.
[45] D'Agostino M, Salvini M, Palumbo A, et al. Novel investigational drugs active as single agents in multiple myeloma. Expert Opin. Investig. Drugs [Internet]. 2017 [cited 2017 Dec 14];26:699–711. Available from: https://www.tandfonline.com/doi/full/10.1080/13543784.2017.1324571.
[46] Martin T, Baz R, Benson DM, et al. A phase 1b study of isatuximab plus lenalidomide and dexamethasone for relapsed/refractory multiple myeloma. Blood [Internet]. 2017 [cited 2017 Dec 14];129:3294–3303. Available from: http://www.bloodjournal.org/lookup/doi/10.1182/blood-2016-09-740787.
[47] Mikhael J, Richardson PG, Usmani SZ, et al. A phase Ib study of isatuximab in combination with pomalidomide (Pom) and dexamethasone (Dex) in relapsed/refractory multiple myeloma (RRMM). Am. Soc. Clin. Oncol. Annu. Meet. [Internet]. Chicago: ASCO; 2017 [cited 2017 Dec 14]. p. Abstract 144708. Available from:

https://meetinglibrary.asco.org/record/144708/abstract.
[48] Tawara T, Hasegawa K, Sugiura Y, et al. Complement activation plays a key role in antibody-induced infusion toxicity in monkeys and rats. J. Immunol. [Internet]. 2008 [cited 2018 Feb 6];180:2294–2298. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18250438.
[49] Raab M, Chatterjee M, Goldschmidt H, et al. MOR202 with low-dose dexamethasone (Dex) and in combination with pomalidomide/dex and lenalidomide/dex in relapsed or refractory multiple myeloma (RRMM): Interim analysis of a phase I/IIa dose-escalation study. J. Clin. Oncol. 2017;35:Abstract 8024.
[50] Raab MS, Goldschmidt H, Agis H, et al. A phase I/IIa study of the human anti-CD38 antibody MOR202 (MOR03087) in relapsed or refractory multiple myeloma (rrMM). Am. Soc. Clin. Oncol. [ASCO] Annu. Meet. [Internet]. 2015 [cited 2017 Dec 14]. p. Abstract 8574. Available from: http://www.myelomabeacon.com/docs/asco2015/8574.pdf.
[51] Veillette A, Guo H. CS1, a SLAM family receptor involved in immune regulation, is a therapeutic target in multiple myeloma. Crit. Rev. Oncol. Hematol. [Internet]. 2013 [cited 2017 Dec 14];88:168–177. Available from: http://www.sciencedirect.com/science/article/pii/S1040842813000838.
[52] Cruz-Munoz M-E, Dong Z, Shi X, et al. Influence of CRACC, a SLAM family receptor coupled to the adaptor EAT-2, on natural killer cell function. Nat. Immunol. [Internet]. 2009 [cited 2017 Dec 14];10:297–305. Available from: http://www.nature.com/doifinder/10.1038/ni.1693.
[53] Tai Y-T, Dillon M, Song W, et al. Anti-CS1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu. Blood [Internet]. 2008 [cited 2017 Dec 14];112:1329–1337. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17906076.
[54] Zonder JA, Mohrbacher AF, Singhal S, et al. A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. Blood [Internet]. 2012 [cited 2017 Dec 14];120:552–559. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22184404.
[55] Lonial S, Vij R, Harousseau J-L, et al. Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma. J. Clin. Oncol. [Internet]. 2012 [cited 2017 Dec 14];30:1953–1959. Available from: http://ascopubs.org/doi/10.1200/JCO.2011.37.2649.
[56] Jakubowiak A, Offidani M, Pégourie B, et al. Randomized phase 2 study: elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM. Blood [Internet]. 2016 [cited 2017 Dec 14];127:2833–2840. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27091875.
[57] Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N. Engl. J. Med. [Internet]. 2015 [cited 2017 Dec 14];373:621–631. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1505654.
[58] Dimopoulos MA, Lonial S, White D, et al. Phase 3 Eloquent-2 Study: Extended 4-Year Follow-Up of Elotuzumab Plus Lenalidomide/Dexamethasone Vs Lenalidomide/Dexamethasone in Relapsed/Refractory Multiple Myeloma. Eur. Hematol. Assoc. [Internet]. Madrid: EHA Learning Center; 2017 [cited 2018 Feb 1]. p. 181754 [Abstract S456]. Available from: https://learningcenter.ehaweb.org/eha/2017/22nd/181743/meletios.a.dimopoulos.phase.3.eloquent-2.study.extended.4-year.follow-up.of.html.
[59] Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell [Internet]. 2011 [cited 2017 Dec 14];144:646–674. Available from: http://www.sciencedirect.com/science/article/pii/S0092867411001279.
[60] Riley JL. PD-1 signaling in primary T cells. Immunol. Rev. [Internet]. 2009 [cited 2017 Dec 14];229:114–125. Available from: http://doi.wiley.com/10.1111/j.1600-065X.2009.00767.x.
[61] Day CL, Kaufmann DE, Kiepiela P, et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature [Internet]. 2006 [cited 2017 Dec 14];443:350–354. Available from: http://www.nature.com/articles/nature05115.
[62] Nishimura H, Nose M, Hiai H, et al. Development of Lupus-like Autoimmune Diseases by Disruption of the PD-1 Gene Encoding an ITIM Motif-Carrying Immunoreceptor. Immunity [Internet]. 1999 [cited 2017 Dec 14];11:141–151. Available from: http://www.sciencedirect.com/science/article/pii/S1074761300800898.
[63] Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat. Immunol. [Internet]. 2001 [cited 2017 Dec 14];2:261–268. Available from: http://www.nature.com/articles/ni0301_261.
[64] Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J. Clin. Oncol. [Internet]. 2010 [cited 2017 Dec 14];28:3167–3175. Available from: http://ascopubs.org/doi/10.1200/JCO.2009.26.7609.
[65] OPDIVO® (nivolumab) injection, for intravenous use - Full prescribing information [Internet]. 2017 [cited 2017 Dec 14]. Available from: https://packageinserts.bms.com/pi/pi_opdivo.pdf.
[66] Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. J. Clin. Oncol. [Internet]. 2016 [cited 2017 Dec 14];34:2698–2704. Available from: http://ascopubs.org/doi/10.1200/JCO.2015.65.9789.
[67] Funt SA, Page DB, Cattry D, et al. The Long PD-1 Receptor Binding Kinetics of Nivolumab May Increase Efficacy of Subsequent Therapy in Relapsed and Refractory Multiple Myeloma Patients. Blood [Internet]. 2015 [cited 2017 Dec 14];126:Abstract 3057. Available from: http://www.bloodjournal.org/content/126/23/3057?sso-checked=true.
[68] Ahamadi M, Freshwater T, Prohn M, et al. Model-Based Characterization of the Pharmacokinetics of Pembrolizumab: A Humanized Anti-PD-1 Monoclonal Antibody in Advanced Solid Tumors. CPT Pharmacometrics Syst. Pharmacol. [Internet]. 2017 [cited 2017 Dec 15];6:49–57. Available from: http://doi.wiley.com/10.1002/psp4.12139.
[69] Mateos M-V, Orlowski RZ, Siegel DSD, et al. Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM): Final efficacy and safety analysis. J. Clin. Oncol. [Internet]. 2016;34:Abstract 8010. Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.8010.
[70] Badros A, Hyjek E, Ma N, et al. Pembrolizumab, pomalidomide, and low-dose dexamethasone for relapsed/refractory

multiple myeloma. Blood [Internet]. 2017 [cited 2017 Dec 15];130:1189–1197. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28461396.

[71] U.S. Food & Drug Administration [FDA] - Center for Drug Evaluation and Research. FDA Alerts Healthcare Professionals and Oncology Clinical Investigators about Two Clinical Trials on Hold Evaluating KEYTRUDA® (pembrolizumab) in Patients with Multiple Myeloma [Internet]. U.S. Food & Drug Administration; 2017 [cited 2017 Dec 15]. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm574305.htm.

[72] Baverel P, Dubois V, Jin C, et al. Population pharmacokinetics of durvalumab and fixed dosing regimens in patients with advanced solid tumors. J. Clin. Oncol. [Internet]. 2017;35:Abstract 2566. Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.2566.

[73] Dimopoulos MA, Lonial S, White D, et al. Eloquent-2 Update: A Phase 3, Randomized, Open-Label Study of Elotuzumab in Combination with Lenalidomide/Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma - 3-Year Safety and Efficacy Follow-up. Blood [Internet]. 2015 [cited 2018 Feb 6];126:Abstract #28 [ASH 2015 57th Meeting]. Available from: http://www.bloodjournal.org/content/126/23/28.

[74] DARZALEX ® (daratumumab) injection, for intravenous use. Full Prescribing Information [Internet]. 2017 [cited 2017 Dec 15]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761036s005lbl.pdf.

[75] Gibiansky L, Passey C, Roy A, et al. Model-based pharmacokinetic analysis of elotuzumab in patients with relapsed/refractory multiple myeloma. J. Pharmacokinet. Pharmacodyn. [Internet]. 2016 [cited 2017 Dec 15];43:243–257. Available from: http://link.springer.com/10.1007/s10928-016-9469-x.

[76] Waddell JA, Solimando DA. Alectinib, Ceritinib, Elotuzumab, and Venetoclax. Hosp. Pharm. [Internet]. 2016 [cited 2017 Dec 15];51:524–534. Available from: http://journals.sagepub.com/doi/10.1310/hpj5107-524.

[77] Elassaiss-Schaap J, Rossenu S, Lindauer A, et al. Using Model-Based "Learn and Confirm" to Reveal the Pharmacokinetics-Pharmacodynamics Relationship of Pembrolizumab in the KEYNOTE-001 Trial. CPT Pharmacometrics Syst. Pharmacol. [Internet]. 2017 [cited 2017 Dec 15];6:21–28. Available from: http://doi.wiley.com/10.1002/psp4.12132.

[78] Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. J. Immunother. Cancer [Internet]. 2017 [cited 2017 Dec 15];5:43. Available from: http://jitc.biomedcentral.com/articles/10.1186/s40425-017-0242-5.

[79] Bajaj G, Wang X, Agrawal S, et al. Model-Based Population Pharmacokinetic Analysis of Nivolumab in Patients With Solid Tumors. CPT Pharmacometrics Syst. Pharmacol. [Internet]. 2017 [cited 2017 Dec 15];6:58–66. Available from: http://doi.wiley.com/10.1002/psp4.12143.

[80] Yamamoto N, Nokihara H, Yamada Y, et al. Phase I study of Nivolumab, an anti-PD-1 antibody, in patients with malignant solid tumors. Invest. New Drugs [Internet]. 2017 [cited 2017 Dec 15];35:207–216. Available from: http://link.springer.com/10.1007/s10637-016-0411-2.

[81] Jeanson A, Barlesi F. MEDI 4736 (durvalumab) in non-small cell lung cancer. Expert Opin. Biol. Ther. [Internet]. 2017 [cited 2017 Dec 15];17:1317–1323. Available from: https://www.tandfonline.com/doi/full/10.1080/14712598.2017.1351939.

Table 1: Key monoclonal antibodies pharmacokinetic parameters

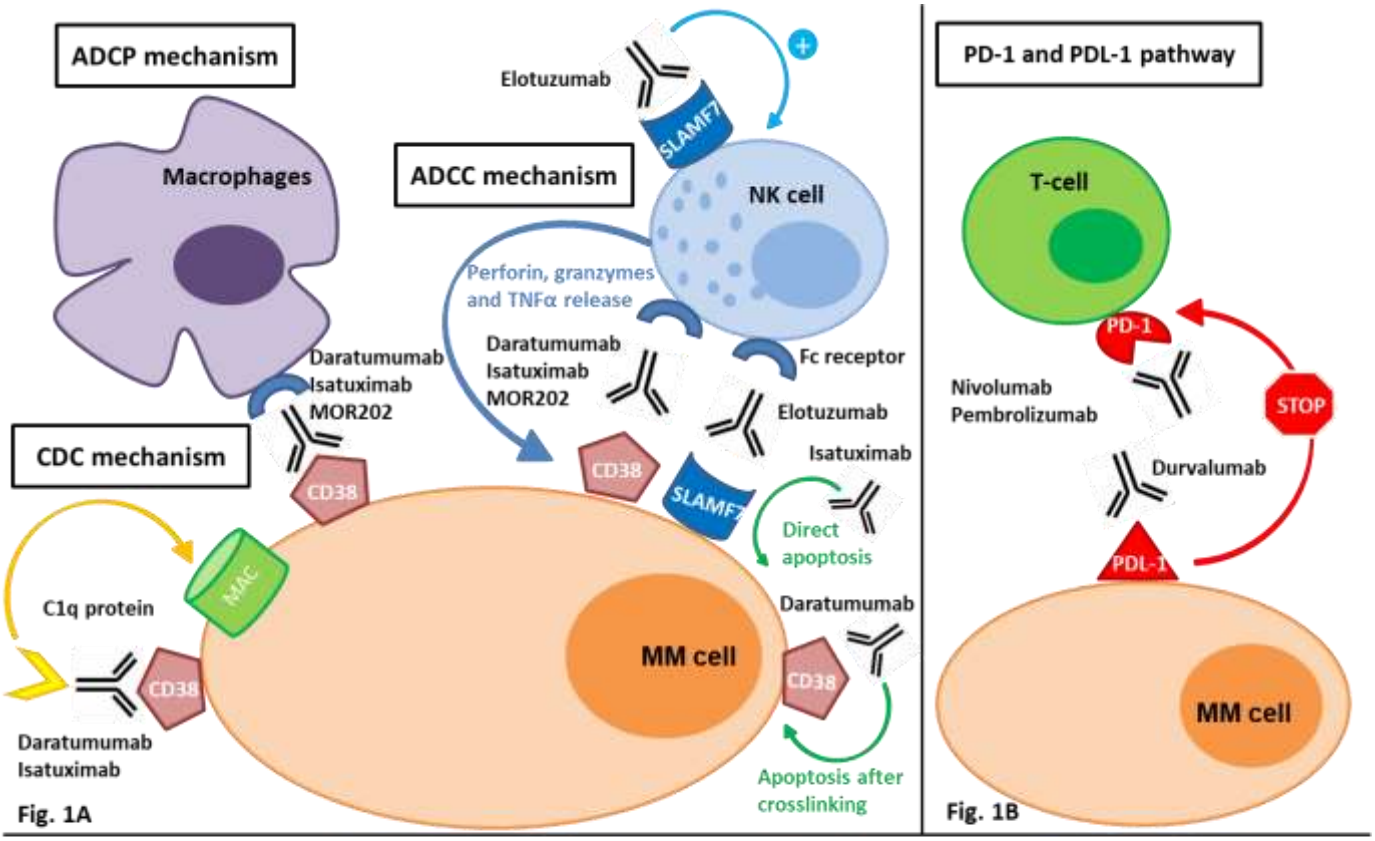
Target	mAb	Trial	Dose schedule	Cmax after first infusion	Mean linear clearance	Volume of distribution of central compartment	Target effective trough concentration	Target saturation at the effective trough concentration	Terminal half-life at steady-state
CD38	**Daratumumab**	Phase I GEN501 and SIRIUS [27,31,38]	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 [34,38,74]	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 [44,46]	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
SLAMF7	**Elotuzumab**	Pooled analysis of ELOQUENT-2 and CA204-007 trials [53,54,75,76]	Elotuzumab 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. [68,77,78]	Pembrolizumab 2 mg/kg Q3W in monotherapy	66.3 µg/mL $^{\Delta}$	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. [64,79,80]	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 CD-ON-MEDI 4736-1108 [72,81]	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; Cmax: 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; $^{\Delta}$ Cmax value measured at steady state.

Figure: title and legends

Figure 1: monoclonal antibodies' mechanism of action
Panel A: CDC, ADCP and ADCC mechanisms are based on the interaction between mAb and its target receptor expressed by MM cells. MAb Fc portion binds to Fc receptor of effector cells leading to MM cell death by cell lysis (involving NK cells in ADCC), by phagocytosis (involving macrophages in ADCP) and by membrane phospholipid bilayer disruption (involving C1q protein, complement cascade and MAC generation in CDC). Daratumumab and Isatuximab have also a direct proapoptotic activity, the latter one independently from Fcγ receptor-mediated CD38 molecules cross-linking [20].
Panel B: PD-1 expressed by T cells down-regulates anti-MM immune response engaging PDL-1 aberrantly expressed by MM cells. Both anti PD-1 and ant-PDL1 mAbs prevent this interaction.



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Abbreviations: CDC: complement-dependent toxicity, ADCP: antibody-dependent cellular phagocytosis, ADCC: antibody-dependent cellular cytotoxicity, MAC: membrane attack complexes, TNFα: tumor necrosis factor α, SLAMF7: signaling lymphocyte activation molecule family 7, MM: multiple myeloma, NK cell: natural killer cell, PD-1: programmed-cell death 1, PDL-1: programmed-cell death ligand 1.

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