Chapter

# Antibody Therapies for Multiple Myeloma

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## Abstract

Multiple Myeloma (MM) is characterized by the abberant proliferation and expansion of plasma cells in the Bone marrow. Despite the broad use of proteasome inhibitors and IMiDs, Multiple Myeloma remains an incurable disease. The introduction of Monoclonal antibodies, along with bi-specific antibodies and check point inhibitors, has significantly enhanced the armamentarium of available therapeutic options in the relapsed setting. The incorporation of the above-mentioned novel agents in triplet or quadruplet therapeutic regimens has led to significant prolongation of overall survival (OS) and progression free survival (PFS), without adding significant toxicity. Anti-CD38 monoclonal antibodies has become the cornerstone of antimyeloma therapy in both the newly diagnosed and relapsed setting.

**Keywords:** Monoclonal Antibodies, Antibody Drug Conjugates, Daratumumab, Belantamab Mafodotin

## 1. Introduction

Multiple Myeloma is characterized by the upregulation and expansion of plasma cells malignant clones in the bone marrow [1]. The introduction of novel agents such as immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) has led to significant improvement of disease prognosis and survival. However, the disease remains incurable, and all patients will relapse. Patients who are refractory to both Imids and PIs have poor survival outcomes, with a median overall survival of 9–13 months [2, 3]. The identification of novel therapeutic approaches for this group of patients represents an unmet medical need. In addition to that, patients with advanced disease characteristics and high-risk cytogenetics have a poor prognosis [4, 5]. Immune dysregulation represents a hallmark of MM pathophysiology. A better understanding of mechanisms that govern immune impairment in MM, has led to the development of several immunotherapeutic agents such as monoclonal antibodies, bispecific antibodies (BiTEs), and chimeric antigen receptor (CAR) T-cells.

## 2. Monoclonal antibodies

### 2.1 Daratumumab

#### *2.1.1 Daratumumab mechanism of action*

Daratumumab (Dara) is the first in class humanized IgG1-κ monoclonal antibody targeting CD38 through binding to a unique epitope which includes amino acids 233–246 and 267–280 [6]. Following binding to CD38, Dara exerts its action through canonical (classical) and noncanonical mechanisms [7]. Canonical mechanisms are immune-mediated, dependent on Dara binding to CD38 on the tumor cell, and include complement-mediated cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), direct cytotoxicity upon secondary cross-linking, and inhibition of CD38 enzymatic activity. Canonical mechanisms could be either Fcgamma receptor (FcgR) dependent or independent [6, 8, 9]. Whilst the canonical mechanisms explain the activity of Dara against CD38+ cells, noncanonical mechanisms are independent of Dara binding to CD38 and based on modulation of immune cells [10]. Dara targets three main categories of immunosuppressor cells that express CD38. These categories are Regulatory B cells (Bregs), which promote tumor growth and immune escape, a subset of regulatory T cells (Tregs), and Myeloid-derived suppressor cells (MDSC). After Dara binding to the CD38 in the surface of the above-mentioned cells causes depletion of their population [11]. Following the depletion of regulatory cells, there is a significant increase in the populations of CD4+ and CD8+ effector T-cells [12–15]. Effector T-cells have increased levels of granzyme-B, which results in enhanced killing capacity [12, 16].

#### *2.1.2 Daratumumab combinations in the newly diagnosed setting*

##### *2.1.2.1 Transplant-ineligible patients*

The combination of bortezomib melphalan and prednisone (VMP) is considered a standard of care regimen for patients who are not candidates for transplant. ALCYONE (NCT02195479) is a phase 3 trial in which patients with NDMM were randomized to receive bortezomib melphalan and prednisone either alone or in combination with Dara. The primary endpoint was PFS. The comparison of PFS rates at 16.5 and 40.08 months showed a sustained superiority of Dara-VMP versus VMP groups. At 16.5 and 40.08 months, PFS rates for Dara VMP and VMP groups were 71.6% (95% [CI], 65.5 to 76.8) vs. 50.2% (95% CI, 43.2 to 56.7) and 36.4 vs. 19.3 months respectively [17, 18]. At the time point of 40.08 months, the median PFS2 was not reached versus 42.3 months for the Dara-VMP and the VMP arm, respectively 32376237. The combination of Dara-VMP also demonstrated a significant reduction in the risk of death by 40% in comparison with VMP (HR 0.60 95% CI 0.46–0.80; p = 0·0003) [19]. At the time point of 42 months, the estimated overall survival rate in Dara-VMP and VMP groups was 75% vs. 62% (median not reached in either group HR: 0.60; 95% CI: 0.46 to 0.80; P = 0.0003) respectively [17, 18, 20]. The proportion of patients achieving MRD negativity was better in the Dara-VMP group (28% versus 7%) 32376237 After a median follow-up of 40.1 months, Dara-VMP increased the ORR (90.9% vs. 73.9%) and the rates of ≥VGPR (73% vs. 50%), ≥CR (46% vs. 25%), MRD-negativity (28% vs. 7%; all P < 0.0001), and ≥ CR with MRD-negativity (27% vs. 7%) vs. VMP. Time to subsequent therapy, OS, and PFS was prolonged for patients with deeper responses in both groups Alcyone 2020.

MAIA trial (NCT02252172) is a phase 3 trial in which the addition of Dara to Rd. was compared to Rd. alone. Seven hundred thirty-seven patients who were ineligible for transplant were recruited. Patients were randomly assigned to receive Rd. with or without Dara in 28-day cycles until disease progression or unacceptable toxicity. The primary end-point was progression-free survival [21]. Results from the primary analysis (median follow-up 28 months) showed that the addition of Dara to Rd. improved PFS and MRD-negativity rates. After a longer follow up period (36.4 months), patients in the DRd arm maintained deeper and durable response along with PFS benefit [22]. After a median follow-up of 47.9 months, patients in the DRd arm had better PFS in comparison with the control group (median, not reached [NR] vs. 34 mo; HR, 0.54; 95% CI, 0.43–0.67; P < 0.0001). Median PFS2 was not reached for DRd vs. 51 months in the Rd. arm. (HR, 0.65; 95% CI, 0.52–0.83; P = 0.0005). The addition of Dara to Rd. resulted in deeper responses with higher rates of CR or better and VGPR or better. The median duration of response was not reached for responders in the DRd arm vs. 44 months in the Rd. arm [23].

*2.1.2.2 Transplant-eligible patients*

The combination of Dara Bortezomib, cyclophosphamide, and dexamethasone (Dara-VCD) resulted in ORR and VGPR or better rates of 81% and 56%, respectively, in NDMM patients enrolled in the LYRA (NCT02951819) study 30828799. After 6–8 cycles of Dara-VCD induction, eligible patients underwent ASCT. All patients received Dara maintenance. The administration of Dara as maintenance therapy improved the depth of response and was associated with prolongation of both PFS and OS [24].

GRIFFIN (NCT02874742) is a phase 2 trial evaluating the addition of Dara to the induction regimen Bortezomib Lenalidomide and Dexamethasone (VRD) in NDMM transplant eligible patients. Patients were randomized to receive Dara-VRD or VRD as induction regimen, ASCT, two cycles of Dara-VRD or VRD consolidation, and Revlimid alone or in combination with Dara as maintenance for 24 cycles. The primary endpoint was the rate of s CR post-consolidation. Regarding the randomized phase of the trial, results indicated that the combination of Dara-VRD was safe and potent. Regarding the primary endpoint results favored the quadruplet regimen (D-VRD)) 42 patients (42.4%) in the D-VRD and 31 patients (32.0%) in the VRD group achieved sCR by the end of consolidation (odds ratio, 1.57; 95% [CI], 0.87–2.82 1-sided P = .068) Response improved over time. After a median follow up of 22.1 months, the sCR (62.6% vs. 45.4%; P = .0177) and MRD negativity (51.0% vs. 20.4%; P < .0001, threshold $10^{-5}$) improved in the D-VRD arm in the intent to treat population [25]. In the final analysis of the safety run-in cohort, at the end of consolidation, 9 (56.3%) patients achieved sCR, and 8 (50.0%) were MRD negative (10–5 threshold). After maintenance, 15 (93.8%) patients achieved sCR, and 13 (81.3%) were MRD ($10^{-5}$) negative. Estimated 36-month overall and progression-free survival rates were 93.8% and 78.1%, respectively. Results showed that the addition of Dara to R AND VRD resulted in durable responses and sustained MRD negativity. The depth of response improved over time [26].

CASSIOPEIA (NCT02541383) is an ongoing phase III clinical trial in newly diagnosed transplant eligible MM patients divided into two parts. Patients were randomized to receive four pre-transplant induction and two post-transplant consolidation cycles of VTd with (VTd group) or without daratumumab (D-VTd group). The primary endpoint of part 1 was the Scr rate assessed 100 days after transplantation. Part 2 (maintenance) is ongoing. After completion of induction and consolidation, the sCR rate in the D-VTd group was 28.9% vs. 20.3% in the VTd group (odds ratio 1.60, 95%CI 1.21–2.12, p = 0.0010). Additionally, the D-VTd

group had significantly prolonged PFS in comparison with VTd (HR: 0.47; 95%CI: 0.33–0.67, p < 0.0001) [27].

MASTER (NCT03224507) is an ongoing phase II clinical trial. Newly diagnosed transplant eligible MM patients received four cycles of Dara-Carfilzomib Dexamethasone (Dara-KRD) induction, followed by autologous stem cell transplantation (ASCT) and consolidation with Dara-KRD based on the MRD status. The MRD assessment method was next-generation sequencing (NGS), and the threshold was $10^{-5}$. Evaluation of MRD status was performed at specific time points. At the end of the induction, post ASCT and post cycles 4 and 8 of consolidation. Patients with two consecutive negative MRD results stopped treatment. Patients who concluded treatment underwent imaging. The administration of Dara-KRD resulted in rapid and durable responses. More than 90% of patients achieved VGPR or better response by the end of induction. The MRD negative rates at the end of induction at ASCT and at best response were 34%, 70%, and 80% (threshold $10^{-5}$) and 28%, 45%, and 65% (threshold $10^{-6}$), respectively. Until today 11 patients have concluded treatment after achieving MRD negativity without evidence of relapse. The trial is ongoing, and long term follow up results are awaited [28].

PERSEUS (NCT03710603) is a randomized, phase 3 study comparing DARA-VRd vs. VRd in transplant eligible NDMM patients, which has recently concluded its enrollment of patients. PFS is the primary endpoint, while key secondary endpoints include, ORR, MRD-negative rate and OS.

### *2.1.3 Daratumumab combinations in the R/R setting*

POLLUX (NCT02076009) is a phase III clinical trial that compared the combination of Lenalidomide Dexamethasone with or without daratumumab in MM patients who had received at least one prior line of treatment and were not refractory to Lenalidomide [15]. The addition of Dara significantly improved PFS at 12 (83.2%, 95% CI, 78.3 to 87.2 vs. 60.1%, 95% CI, 54.0 to 65.7), 25,4 (median not reached vs. 17.5 months; HR 0.41; 95% CI,0.31–0.53; P < 0.0001) and 44,3 (median 44.5 vs. 17.5 months; HR, 0.44; 95% CI, 0.35–0.55; P < 0.0001) months follow up in comparison with the control group [15, 29, 30]. The overall response rate was significantly better in the DRd group (92.9% vs. 76.4%, P < 0.001) 30237262. Post hoc analyses revealed that Dara improved PFS independently of the prior lines of treatment and high-risk cytogenetics [29]. At 25.4 months, the assessment of MRD status (threshold $10^{-5}$) revealed deeper responses in the DRd arm (26.2% vs. 6.4% P < 0.0001) [29].

CASTOR study (NCT02136134) compared the combination of Dara Vd (Dvd) versus Vd in 498 patients who had received at least one prior line of therapy (median of 2, range, 1–10; 10% three or more) and were not Bortezomib refractory. The study met its primary endpoint with a significant prolongation of PFS in the Dvd group after 7.4 months follow up (not reached in the Dvd versus 7.2 months in the Vd group), along with a significant reduction (61%) regarding the risk of disease progression or death (HR: 0.39; 95% CI, 0.28–0.53; p < 0.001). ORR was 82.9% in the Dvd vs. 63.2% in the Vd group, P < 0.001 [31]. Updated results of this trial after 40 months, reinforce the tolerability and effectiveness of Dvd. PFS was improved in all subgroups (16.7 vs. 7.1 months, [HR], 0.31; 95% [CI], 0.25–0.40; P < .0001). 32482541. The addition of Dara to Vd manage to overcome the impact of high-risk cytogenetic abnormalities (12.6 vs. 6.2 months; HR, 0.41; 95% CI, 0.21–0.83; P = 0.0106) 32819447 Patients in the Dvd group had 2.5 fold higher MRD negativity rate (10–5 threshold) [31]. Based on the results of CASTOR trial FDA and EMA approved in 2016 Dvd for RRMM patients who had received at least one prior line of treatment.

In a phase 1b study (MMY1001), the addition of Dara to Pomalidomide and Dexamethasone was tested. The study included 103 patients with a median age of 64 years and a median of four prior lines of therapy. Notably, 89% were refractory to Lenalidomide, 71% to Bortezomib, and 30% to Carfilzomib. The median OS and PFS were 17,5 and 8,8 months, respectively. The ORR was 60%. The combination of Dara Pom Dex was clearly safe and effective in this group of heavily pretreated patients [32]. Based on these results, FDA approved this triple combination for patients who had received at least two prior lines, including both a PI and Lenalidomide [32].

APOLLO trial (NCT03180736) explored the addition of Dara to Pomalidomide and dexamethasone (Pd) in 304 patients with RRMM who had received ≥one prior line of therapy, including a PI and Lenalidomide. PFS was the primary endpoint. Patients received Pomalidomide 4 mg d1–21, dexamethasone 40 mg (20 mg for patients ≥75 years of age) on 28 days cycles. Patients initially received Daratumumab iv 16 mg/kg. After protocol amendment, patients continued with Dara sc 1800 mg. Administration of Dara every week for cycles one and two, every two weeks for cycles 3–6, and every month thereafter. Prior Pomalidomide or anti-CD-38 administration was not permitted. The patient's median age was 67 (35–90) years, 35% had high-risk cytogenetics, and 63% were refractory to both Len and PI. The study met its primary endpoint. The addition of Dara to Pd led to a significant prolongation of PFS (12.4 months) versus 6.9 months in the Pd arm (HR 0.63 (95% CI, 0.47–0.85; P = 0.0018), which represents a 37% reduction in the risk of death or progression. Data regarding OS are immature, and longer follow-up is warranted. No new safety signals have emerged. Additionally, the sc formulation of Dara shortens the duration of administration. These data suggest that the D-Pd combination is safe, effective, and convenient in the RR setting [33].

CANDOR (NCT03158688) is another phase 3 trial exploring the addition of Dara to Carfilzomib and dexamethasone (Kd). Four hundred sixty-six patients were randomized to receive Dara Carfilzomib dexamethasone (DKd) vs. Kd. All patients received iv Dara at 16 mg/kg, every week for the first two cycles (the first dose was administered on days 1 and 2 of the first cycle), every two weeks for cycles 3–6, and every month thereafter, Carfilzomib, twice per week at 20 mg/m$^2$ on days 1 and 2 of cycle 1 and at 56 mg/m$^2$ thereafter and dexamethasone 40 mg every week (20 mg for patients 75 years or older). After an initial follow up of 17 months, median PFS was not reached in the DKd group versus 15.8 months in the Kd group (HR 0.63; 95% CI 0.46–0.85; two-sided p = 0.0027) [34]. Data presented in the last ASH meeting showed further improvement in PFS for patients in the KRd arm. After 28 months of follow-up, the median PFS for KRd and Kd group were 28.6 and 15.2 months, respectively (HR, 0.59, 95% CI, 0.45–0.78]. PFS benefit was consistent among subgroups, especially in Lenalidomide refractory patients. Additionally, the MRD negativity rate at 12 months was significantly better in the DKd arm at 12.5% vs. 1.3% P < 0.0001. No new safety alerts have emerged [35].

## 2.2 Isatuximab

### *2.2.1 Mechanism of action*

Isatuximab (SAR650984) is another chimeric IgG1κ monoclonal antibody, which binds on human CD38 by targeting a different epitope in comparison with Daratumumab [36]. Isatuximab and Daratumumab have several differences regarding the mechanism of action. 1/Isatuximab anti-tumor activity is mainly dependent on ADCC [37, 38] 2/Isatuximab induces direct apoptosis of CD-38 even in the absence of cross-linking agents [39] 3/Isatuximab inhibits CD-38 enzymatic activity in a dose-dependent manner [40].

### 2.2.2 Isatuximab clinical trials

In a phase I dose-escalation study, 84 patients with RRMM (median 5, range 1–13 prior lines of therapy) received Isatuximab monotherapy. Isatuximab administration showed clinical activity and a manageable safety profile. ORR was 24%, median PFS was 3.7 months. IRRs were mainly grade 1 or 2 that occurred during the first cycle [40]. These results were confirmed in a dose-finding phase II trial. Patients with RRMM who had received three or more prior lines of therapy were allocated to four different dosing schedules of isatuximab monotherapy: 3 mg/kg or 10 mg/kg every two weeks, 10 mg/kg every two weeks for one month and every month thereafter, and 20 mg/kg every week for one month and every two weeks thereafter. At doses ≥10 mg/kg 10 mg/kg OS and PFS were 18.7 and 4.6 months respectively, whereas ORR was 24.3% [41]. During the second part of the same study, patients with RRMM (median 4, range 2–10 prior lines of therapy) were randomized to receive isatuximab 20 mg/kg every week for one month, followed by 20 mg/kg every two weeks, with (n = 109) or without (n = 55) dexamethasone. Median PFS and OS were 4.9 and 18.9 and 10.2 for Isatuximab monotherapy and 10.2 and 17.3 for Isatuximab DEX group, respectively [42].

Isatuximab has also shown a synergistic effect when combined with Lenalidomide and dexamethasone. Fifty-seven patients with RRMM (median 5, range 1–12 prior lines of therapy) with 83% refractory to Lenalidomide received Isatuximab in combination with Lenalidomide and dexamethasone in this phase Ib dose-escalation study. The primary objective of the study was the determination of maximum tolerated dose (MTD) of Isatuximabwithin the combination with Lenalidomide and dexamethasone. The ORR was similar in both cohorts, 56%. Only one dose-limiting toxicity was reported (pneumonia grade II at 20 mg/kg/QW/Q2W), which resolved after discontinuation of treatment. The MTD was not reached. IRRs occurred mostly during the first infusion and were mild (grade I or II) regarding severity. These results demonstrate that the combination of Isatuximab with standard doses of Lenalidomide and Dexamethasone was active and well-tolerated in patients with RRMM [43].

Another phase Ib trial (NCT02283775) evaluated the tolerability and safety of Isatuximab in combination with Pomalidomide and low-dose dexamethasone in patients with RRMM, who had received prior treatment with a PI and Lenalidomide. Forty-five patients with a median of three (range 1–10) prior lines of therapy were recruited. 91% of patients were refractory to their last line of therapy, 84% were PI refractory, and 82% Lenalidomide refractory. Patients received Isatuximab at 5, 10, or 20 mg/kg (every week for four weeks and every two weeks thereafter), Pomalidomide 4 mg (days 1–21), and dexamethasone 40 mg weekly, in 28-days cycles until progressive disease or unacceptable toxicity. The primary objective was the determination of the recommended dose of Isatuximab within this combination, along with safety. Secondary objectives included evaluation of efficacy, pharmacokinetics, and immunogenicity. Among 45 enrolled patients, 8 received Isatuximab at 5 mg/kg, 31 at 10 mg/kg and 6 at 20 mg/kg for median duration of 9.6 months. The most common adverse events included fatigue (62%), infusion reactions (42%), and upper respiratory tract infections. Infusion-related reactions, which were mainly grade I or II, occurred mostly during the first administration of the drug and were manageable with corticosteroids and antihistamines. Median PFS and median duration of response were 17.6 and 18.7 months, respectively. ORR was 62%. These results demonstrated that the combination of Isatuximab with Pomalidomide and dexamethasone was safe and effective in heavily pretreated patients with MM [44].

Based on these encouraging results, the phase III ICARIA trial (NCT02990338) compared the combination Of Isatuximab Pom Dex (IPd) versus Pom dex (Pd) in 307 patients with RRMM who had received at least two prior lines of treatment, including Lenalidomide and a proteasome inhibitor (median three range 2–4). Patients received Isatuximab 10 mg/kg every week for the first cycle and on days 1 and 15 in the subsequent cycles, plus pomalidomide 4 mg/day (day 1–21) and dexamethasone 40 mg (or 20 mg for patients >75 years) weekly on 28 days cycles. Progression-free survival was the primary endpoint. After a median follow-up of 11.6 months, median progression-free survival was 11.5 months (95% CI 8.9–13.9) in the IPd group versus 6.5 months (4.5–8.3) in the Pd group;(HR 0.596, 95% CI 0.44–0.81; p = 0·001). Responses in the IPd arm occurred faster with a significantly longer duration in comparison with the IPd arm. Additionally, patients in the IPd arm achieved a higher percentage of MRD negativity. The addition of Isatuximab to Pom dex, resulted in significant improvement of PFS [45]. The consistency of the results from the primary analysis was evaluated in patients with soft tissue plasmacytomas. Data presented at the last ASH meeting showed that PFS and ORR were improved from the addition of Isatuximab to Pd in the subgroup of patients with extramedullary disease. Median PFS was 4.57 (95% CI: 2.40, not calculable) vs. 1.56 (95% CI: 0.95, 4.47) months in the IPd and Pd arm, respectively, whereas ORR was 50% (7/14 responders) and 10% (1/10 responders) in the IPd and Pd group. ASH 2289 Based on the results of the ICARIA trial, FDA and EMA approved the combination of IPd, in patients with RRMM.

The combination of Isatuximab with Carfilzomib has been evaluated in a phase Ib clinical trial (NCT02332850) [46]. In the dose-escalation part of the study, patients with RRMM who had received at least two prior (median three range 2–8) lines of treatment were randomized to receive Isatuximab in 3 different dose levels (DL) 10/kg every two weeks, 10 mg/kg every week for a month and every two weeks thereafter and 20 mg/kg every week for a month and every two weeks thereafter, in combination with K at dose 27 mg/m $^2$. Fifteen patients received treatment in the dose-escalation and 18 in the dose-expansion cohort at DL2. The primary objective was the determination of the maximum tolerated dose (MTD). Secondary objectives included the assessment of efficacy and safety. Preliminary results showed a 66% ORR in all dose levels. Median PFS was not reached. Based on these results, the phase III IKEMA study (NCT03275285) compared the combination of IKd vs. Kd in the RR setting. Three hundred two patients with RRMM were randomized to receive IKd (n = 179) or Kd (n = 123). The administration of Isatuximab was 10 mg/kg iv weekly during the first month and every two weeks thereafter, whereas administration of Carfilzomib was 20 mg/m2 and 56 mg/m2 thereafter. The primary endpoint was PFS, and the secondary endpoints were OS and ORR [47]. Preliminary data were presented in the last ASH meeting. After a median follow-up of 20.7 months there was a statistically significant improvement of PFS in the IKd group (median PFS was not reached for IKd vs. 19.15 months for Kd; HR 0.531 (99% CI 0.318–0.889), one-sided p = 0.0007, with consistency among subgroups. ORR was 86.6% IKd vs. 82.9% for Kd, one-sided p = 0.1930. MRD negativity (10–5) in the intent to treat population (ITT) was 29.6% (53/179) vs. 13.0% (16/123) in the IKd and Kd groups, respectively descriptive p = 0.0004. Data regarding OS were immature at the time of primary analysis. The percentages of AES and SAEs were similar between the two groups. To conclude, the addition of Isatuximab to Kd lead to a significant improvement in PFS and depth of response. IKD may represent a new standard of care regimen for patients with RRMM [48].

Isatuximab is currently under investigation in the upfront setting. In transplant-ineligible patients, IMROZ trial (NCT03319667) is comparing the quadruplet combination Isatuximab-VRd with VRD, while another ongoing trial is comparing

Isatuximab-VRd to Isatuximab VCD(NCT02513186). In transplant-eligible patients, ISKIA trial is currently investigating the combination of Isatuximab-KRd vs. KRd as part of induction and consolidation regimen (NCT04483739).

## 2.3 Elotuzumab

### *2.3.1 Elotuzumab mechanism of action*

SLAMF7 (signaling lymphocytic activation molecule family 7) or CD319 is a cell surface glycoprotein CD2/subset 1 (CS1). SLAMF7 expression is restricted to normal and abnormal plasma cells and NK lymphocytes [49]. Activation of SLAMf7 pathway promotes cell growth and survival. It also plays a critical role in the interaction with the bone marrow microenvironment [49, 50]. Elotuzumab is humanized, first in class IgG1 monoclonal antibody targeting SLAMF7. Elotuzumab primarily activates NK cells promoting antibody-dependent cellular cytotoxicity (ADCC). Elotuzumab has shown no activity when used as a single agent in MM patients.

### *2.3.2 Elotuzumab clinical trials*

The large phase III ELOQUENT 2 trial (NCT01239797) evaluated the addition of Elotuzumab at the dose of 10 mg/kg to Lenalidomide and dexamethasone (Rd) in 646 patients with RRMM (94% lenalidomide naïve patients) who had received 1–3 prior lines of treatment. Patients received Lenalidomide 25 mg for days 1–21 and dexamethasone 40 mg on a weekly basis on 28-day cycles. Elotuzumab administration was 10 mg/kg weekly for the first two cycles, and 20 mg/kg on a monthly basis thereafter. Primary endpoints included PFS and ORR. OS was one of the key secondary endpoints. After an initial follow-up of 24.5 months, the rates of median PFS and ORR were 19.4 versus 14.9 months (HR for progression or death 0.70; 95% CI 0.57 to 0.85; P < 0.001) and 79%, versus 66% in the ELO Rd. and Rd. groups respectively. 26035255. PFS rates demonstrate sustained improvement after two (52%) and three (44%) years of follow-up (relative risk of disease progression or death by 30% and 27% respectively) 30204239. More recent data, after a 4-year follow-up, demonstrate sustained OS benefit (50 months for ELO Rd. versus 43 months for Rd. HR: 0.78; 95%CI: 0.63–0.96). 30719202 Administration of Elotuzumab was relatively safe. Most common grade 3 or 4 AEs in both arms included lymphopenia, neutropenia, pneumonia, and fatigue. Based on this trial Elotuzumab was granted approval by the FDA in December 2015 and EMA in 2016, in combination with Rd., for patients with RRMM, who had received at least one prior line of treatment [51].

Elotuzumab has also been evaluated in combination with Pomalidomide and dexamethasone (Pd). Eloquent 3 (NCT02654132) is a randomized phase II trial, comparing the combination of ELO Pd versus Pd in 117 patients who were refractory or relapsed and refractory to Lenalidomide and a proteasome inhibitor. Patients received Pomalidomide 4 mg for day 1–21 and dexamethasone 40 mg on a weekly basis on 28-day cycles. Elotuzumab administration was 10 mg/kg weekly for the first two cycles and 20 mg/kg on a monthly basis thereafter. Sixty patients were assigned to the ELO Pd group and 57 patients to the Pd group. After a follow up of 9.1 months, patients in the ELO Pd group had significantly increased PFS (10.3 vs. 4.7 months HR 0.54 CI0.34 to 0.86; P = 0.008) and ORR (53% vs. 26% odds ratio, 3.25; 95% CI, 1.49 to 7.11) in comparison with the Pd group. No significant differences were reported in the safety profiles of the two arms. Based on the results of the ELOQUENT III trial, Elotuzumab granted approval by the FDA in 2018

for RR patients who had received at least two prior lines of treatment, including Lenalidomide and a PI [52].

### 2.4 Antibody drug conjugates (ADCs)

BCMA, is a and member of the tumor necrosis factor receptors (TNFR) superfamily [53, 54]. BCMA is primarily expressed in late-stage B-lineage cells, normal and malignant plasma cells, and B-lymphocytes, with very low expression on non-hematologic cells [55]. BCMA has two main ligands: a proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF) [56–58]. Following binding of APRIL and BAFF, BCMA expression is selectively upregulated during malignant transformation of plasma cells, playing a critical role in survival, drug resistance, and tumor cell growth through activation of intracellular signal transduction pathways such as STAT3, phosphoinositide 3-kinase (PI3K), AKT, NFB and MAPK [59–63]. As demonstrated in BCMA knock-down mouse models, BCMA is not required for normal B-cell differentiation and homeostasis [64]. The shedding of BCMA from the cell surface is mediated by γ-secretase and results in a soluble form (soluble BCMA, sBCMA). Higher sBCMA levels have been associated with inferior clinical outcomes. In preclinical models, inhibition of BCMA, with specific antibodies, showed significant anti-myeloma activity. The aforementioned facts make BCMA an ideal therapeutic target for the treatment of Multiple Myeloma and provide the rationale for the development of anti-BCMA monoclonal antibodies.

GSK2857916 (Belantamab Mafodotin) is the first anti-BCMA ADC that has been investigated in clinical trials. This afucosylated, humanized, IgG1 monoclonal antibody is conjugated to monomethyl auristatin F (MMAF), an inhibitor of tubulin polymerization, through a protease-resistant maleimidocaproyl linker. Following binding to the plasma cell surface, GSK2857916 is internalized and the active cytotoxic drug (cys-mcMMAF) is released following enzymatic cleavage leading to cell death. Mechanisms of action include NK-cell mediated ADCC and ADCP [65].

DREAMM 1 (NCT02064387) is a first in human phase I, open-label study, which evaluated the administration of GSK2857916 in patients with RRMM and other hematologic malignancies expressing BCMA in terms of efficacy and safety. Dose escalation cohort (part I) included solely patients with MM who have failed previous treatment regimens, including stem cell transplant (if eligible) IMiDs, PIs, and alkylators, while the dose-expansion cohort (part2) included both patients with MM and relapsed follicular lymphoma or diffuse large B-cell lymphoma. Regarding MM patients in the expansion cohort, 57% had five or more prior lines of therapy; 89% were double (PI and IMiD) and 34% triple (PI, IMiD, and daratumumab) refractory. GSK2857916 was administered intravenously every three weeks as a 1 hr. infusion in 38 patients at different dose levels (0.03–4.6 mg/kg). Primary endpoints were safety, determination of maximum tolerated dose (MTD), and recommended phase 2 dose. Secondary objectives were the determination of pharmacodynamics and pharmacokinetics parameters, anti-drug antibodies, and clinical activity. In dose-expansion, patients received the selected recommended phase 2 dose of 3.4 mg/kg. Overall, 73 patients were recruited, thirty-eight in dose escalation and thirty-five in the dose-expansion cohort. Notably, BCMA expression was not included in the eligibility criteria of study [66].

Updated results of this study, after an extended median follow-up of 12.5 months, demonstrate that was effective in this heavily pretreated group of patients [67]. Achievement of response occurred early during the study after the first or second infusion. Interestingly, dose reduction did not affect the depth and duration of response. 21/65 patients in the dose-expansion part achieve partial or better response, including 2PRs, 14VGPRs, 3CRs, and two sCRs. 18/32 (56.3%)

patients who were double refractory (IMiDs and PIs) achieved response to treatment. For double refractory patients (IMiDs and PIs), with prior Daratumumab exposure, OR was 38.5%. The median PFS and DOR were 12 and 14.3 months, respectively. Among double refractory patients, the median PFS was 7.9 months. For patients with and without prior Daratumumab exposure, median PFS was 6.8 and 15.7 months, respectively. For double refractory patients with prior Daratumumab exposure, median PFS was 6.2 months [67].

The most frequent AEs were fatigue, nausea, chills, anemia, pyrexia, hypercalcemia, thrombocytopenia, and dry eye, while the most common grade 3 or 4 toxicities included neutropenia, anemia, and thrombocytopenia. Infusion-related reactions (IRRs) (Grade 1 or 2) were reported in 7 patients across all dose levels, and all of them occurred during the first dose. Of note, there were no dose-limiting toxicities (DLT) and no MTD identified in the dose-escalation phase. Ocular toxicity, including blurred vision, foreign body sensation, and photophobia, were common presented in 53% of patients in part 1 and in 63% in part 2. Most common findings during eye examination under a slim lamp included keratitis and corneal microcystic changes. All AEs were reversible. The median time to onset was 23 days (range 1–84). Management included dose reductions and/or delays, artificial tears, and steroid eye drops. The median time to resolution was 30 days (range 5–224). Even though the exact pathophysiologic mechanism of keratopathy is unknown, it may be attributed to the uptake of the payload (MMAF) in the basal epithelial layer of the cornea 2938270. Ocular toxicity resulted in two treatment discontinuations in part 1 and no discontinuations in part 2 of the study. The main reasons for treatment discontinuation were disease progression (n = 15) and AEs (n = 2). Based on these promising results, FDA granted GSK2857916 a breakthrough therapy designation for the treatment of RRMM patients who had receive three prior lines of treatment, including an anti-CD38 antibody, and were refractory to both an IMiD and a PI [68].

Following the encouraging results of DREAMM-1 study, the subsequent DREAMM-2 trial (NCT03525678) further explored the safety and activity of Belantamab mafodotin (GSK2857916) in the RR setting. Patients were refractory to PI, IMiD and an anti-CD38 mAb alone or in combination and randomized 1:1 to receive 2.5 mg/kg (n = 97) or 3.4 mg/kg (n = 99) Belantamab Mafodotin iv, every three weeks until disease progression or unacceptable toxicity. Regarding refractoriness to previous lines of treatment, 76% and 75% were refractory to bortezomib, 65% and 58% to Carfilzomib, 90% and 89% to Lenalidomide, 87% and 78% to Pomalidomide and 100% and 92% to Daratumumab in the 2.5 and 3.4 mg/kg dose arms, respectively. Patients had receive a median of 6 (range 3–21) and 7(range 3–21) prior lines of treatment, respectively [69].

Overall response rate (ORR) was the primary objective of the study. After a median follow up of 6.5 months (6.3 in the 2.5 mg cohort and 6.9 in the 3.4 mg cohort), median PFS was 2.9(95% CI: 2.1–3.7) and 4.9(95% CI: 2.3–6.2) months in the two groups while the ORR was 31% (30/97 97.5% CI 20.8–42.6) and 34% (34/99CI 23.9–46) respectively 31859245. At this time point, OS data were not mature. Updated analysis of this trial, with a median, follow up of 9 months, demonstrated a median PFS of 2.8 and 3.9 months in the two cohorts with one year OS probability of 53% 21/48 and similar ORR among the group of patients with 3–6 (34%) and seven or more (30%) prior lines of therapy [69]. Two post hoc analyses demonstrate the efficacy of Belantamab mafodotin in the subgroups of patients with high-risk cytogenetics and impaired renal function (EGFR 30 ml/min) [70, 71].

Regarding AEs, this study confirmed the frequent occurrence of corneal events. 72% of patients developed keratopathy of any grade, while 31% developed

keratopathy grade 3–4. Keratopathy was attributed to the MMAF payload and was reversible after temporary discontinuation of the drug. Other frequent adverse events grade 3–4 were anemia (21%) and thrombocytopenia (22%). Infusion-related reactions (IRRs) were reported in 21% and 16% in the two treatment arms and were mostly grade 1 or 2. Serious AEs occurred in 40% and 47% in the 2.5 mg/kg and 3.4 mg/kg cohorts respectively. Two reported cases lead to death, potentially connected to study drug. One case of sepsis in the 2.5 mg/kg and one of haemophagocytic lymphohistiocytosis in the 3.4 mg/kg cohort.

Currently, the role of Belantamab Mafodotin (GSK2857916) is being evaluated in the RRMM setting.

DREAMM-6 (NCT03544281) is an ongoing Phase I/II, a two-part study of GSK2857916 in combination with lenalidomide/dexamethasone (Arm A) or BorDex (Arm B) in patients with RRMM who had received ≥one prior therapy. Refractory to Bortezomib patients were not excluded. Preliminary results from Arm B, presented in the last ASH meeting, have shown a high ORR of 78% (95% CI 52.4–93.6). No new safety signals have emerged.

Three-phase III studies are currently ongoing, evaluating the safety and efficacy of belantamab mafodotin in combination with Pomalidomide (NCT04162210; DREAMM-3) daratumumab plus bortezomib (NCT04246047; DREAMM-7) or Pomalidomide plus Bortezomib (NCT04484623: DREAMM-8). The results are eagerly awaited.

MEDI2228 is another antibody-drug conjugate (ADC) composed of fully human monoclonal antibody, conjugated to a dimeric cross-linking pyrrolobenzodiazepine (PBD) dimer (tesirine) via a protease-cleavable dipeptide (valine-alanine) linker8/42 MEDI2228 has shown potent antitumor activity in preclinical models, including cell lines resistant to Lenalidomide. Based on these reports, a phase I open-label, dose-escalation, and expansion first in-human study (NCT03489525) evaluated safety, clinical activity, and pharmacokinetics of MEDI2228 in patients with RRMM. All patients had progressive disease after treatment with an IMiD, a PI, and a monoclonal antibody. In the dose-escalation part of the study, MEDI2228 was administered iv every three weeks in five sequentially ascending dose levels (0.0125, 0.025, 0.05, 0.1, and 0.2 mg/kg). DLTS lead to dose de-escalation from 0.2 mg/kg to 0.14 mg/kg. Primary endpoints included safety and tolerability. 0.14 mg/kg Q3W was determined as the maximum tolerated dose (MTD). In the 0.14 mg/kg cohort 53.7% experienced photophobia and 19.5% eye dryness. There were no incidents of visual acuity loss or keratopathy in the 0.14 mg/kg cohort. Other treatment-related AEs included thrombocytopenia (31.7%) rash (29.3%), increased gamma-glutamyltransferase (24.4%) and pleural effusion (19.5%). In the 0.14 mg/kg cohort, ORR was 61.0% (95% [CI]: 44.5%, 75.8%), including 10 (24.4%) VGPRs and 15 (36.6%) PR. These data suggest that MEDI2228 is clinically efficient in this heavily pretreated group of patients [72].

### 2.5 Bispecific antibodies

Bispecific T-cell engagers (BiTEs) are monoclonal antibodies with two separate antigen recognition domains. One with a high affinity to an antigen in the surface of tumor cell and another targeting CD-3 in the surface of T-cells. Binding to those two distinct epitopes leads to the formation of an immunologic synapse. Binding to the CD3e epitope augments the t-cell recruitment and activation, leading to cell death. In MM, the majority of BiTEs targeting BCMA in the surface of plasma cells.

AMG-420, formerly known as BI 836909, is the first BiTE demonstrating clinical activity. It is comprised of two single-chain variable fragments (scFvs), one targeting BCMA and one targeting CD3. AMG-420 is the compound with the

most available data to date. In a first in human dose-escalation study, AMG420 was administered in 42 patients with RRMM (NCT02514239). Eligible patients had progressed after a minimum of 2 prior lines of treatment, including a PI and an IMiD 31895611. The median number of prior lines of therapy was 4 (range 2–13). 31% of patients were double refractory to IMiDs and PIs, and 21% were daratumumab refractory. AMG420 was administered at different dose levels, 0.2-800 μg/d, through a continuous iv infusion for four weeks in 6-week cycles due to its low molecular weight and short half-life. Patients received treatment for up to 10 cycles Monitoring of toxicities required hospitalization at the beginning of cycles one (4 days) and two (1 day) [73].

There were two deaths reported from adverse events: One patient in the 50 μg/d cohort died after the first cycle due to respiratory distress syndrome caused by concurrent influenza and aspergillosis, and one from hepatic failure from adenovirus. None of these incidents were considered related to treatment. There were no grade 3 or greater CNS toxicities reported. At the 800 μg/d dose level, two-thirds of the patients experienced DLTs. One patient had gr 3 CRS and one gr 3 peripheral polyneuropathy, which included progressive dysfunction of the peripheral motor and sensory nerves. Following the interruption of the study drug, both toxicities resolved. No DLTs were observed up to the level of 400 μg/d. In the most recent follow-up of the study, 40 patients discontinued treatment. Twenty-five due to disease progression, seven due to AEs, four died, three completed treatment (10 cycles), and 1 withdraw consent [73]. ORR was 31% (13/42patients). At the MTD of 400 μg/d, the response rate was 70% (7/10). In the 400 μg/d group, five patients achieved MRD negativity, one achieved PR, and one VGPR.

As mentioned, because of its low molecular weight and short half-life, AMG420 was administered through a continuous iv infusion for four weeks in 6-week cycles due to its low molecular weight and short half-life. AMG 701, a BiTE with an extended half-life allowing once-weekly subcutaneous administration, was developed and is currently under investigation (NCT03287908).

PF-06863135 (PF-3135) is a humanized Ig-like Bispecific antibody targeting both BCMA and CD3. PF-06863135 has been administered intravenously at 0.1–50 μg/kg weekly in patients with RRMM. Preliminary results demonstrate antimyeloma activity. The maximum tolerated dose was not reached [74]. In order to reduce the maximum concentration (Cmax) of the drug, which was possibly associated with inflammatory response and cytokine release syndrome (CRS), subcutaneous administration of the drug was tested. Preliminary results were reported in the last ASH meeting [75]. 2 6/8(75%) patients achieved a response at the two highest dose levels evaluated. The sc administration modulates Cmax. This could allow the administration of higher doses without increased incidence of CRS. The trial is ongoing.

## 3. Immune checkpoint inhibitors

The programmed death-1 (PD-1) receptor is a type-1 transmembrane glycoprotein, expressed on antigen-activated B-cells, T-cells, and NK-cells. The binding of PD-1 ligands (PD-L1 and PD-L2) on PD-1 receptor results in downregulation of immune functions mediated by T-cells such as cytokine production, t-cell proliferation, and cytotoxicity [76]. The overexpression of PD-L1 and PD-L2 is a well recognizable mechanism of immune evasion. Preclinical data from MM patients have shown an increased expression of PD-L1 and PD-1 on malignant plasma cells and T and NK cells respectively [77, 78]. The deciphering of this particular mechanism of action has lead to the development of immune checkpoint inhibitors that

| Description | Phase | NCT number | Population |
|---|---|---|---|
| DARATUMUMAB | | | |
| A Study of Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Treatment in Participants With Newly Diagnosed Multiple Myeloma Who Are Minimal Residual Disease Positive After Frontline Autologous Stem Cell Transplant (AURIGA) | 3 | NCT03901963 | NDMM |
| Study of Melphalan Flufenamide (Melflufen) in Combination With Daratumumab in Relapsed Refractory Multiple Myeloma (LIGHTHOUSE) | 3 | NCT04649060 | RRMM |
| Daratumumab, VELCADE (Bortezomib), Lenalidomide and Dexamethasone Compared to VELCADE, Lenalidomide and Dexamethasone in Subjects With Previously Untreated Multiple Myeloma (PERSEUS) | 3 | NCT03710603 | NDMM |
| ISATUXIMAB | | | |
| Isatuximab Bortezomib, Lenalidomide and Dexamethasone Combination in NDMM Patients Not Eligible for Transplant (IMROZ) | 3 | NCT03319667 | NDMM |
| Isa-KRd vs. KRd in Newly Diagnosed Multiple Myeloma Patients Eligible for Autologous Stem Cell Transplantation (IsKia) | 3 | NCT04483739 | NDMM |
| ANTIBODY-DRUG CONJUGATES | | | |
| Study of Single Agent Belantamab Mafodotin Versus Pomalidomide Plus Low-dose Dexamethasone (Pom/Dex) in Participants With Relapsed/Refractory Multiple Myeloma (DREAMM-3) | 3 | NCT04162210 | RRMM |
| Study Evaluating Safety, Tolerability and Clinical Activity of GSK2857916 in Combination With Pembrolizumab in Subjects With Relapsed/Refractory Multiple Myeloma (DREAMM-4) | 1/2 | NCT03848845 | RRMM |
| Platform Study of Belantamab Mafodotin as Monotherapy and in Combination With Anti-cancer Treatments in Participants With Relapsed/Refractory Multiple Myeloma (RRMM) (DREAMM 5) | 1/2 | NCT04126200 | RRMM |
| To Evaluate Safety, Tolerability, and Clinical Activity of the Antibody-drug Conjugate, GSK2857916 Administered in Combination With Lenalidomide Plus Dexamethasone (Arm A), or in Combination With Bortezomib Plus Dexamethasone (Arm B) in Participants With Relapsed/Refractory Multiple Myeloma (DREAMM-6) | 1/2 | NCT03544281 | RRMM |
| Evaluation of Efficacy and Safety of Belantamab Mafodotin, Bortezomib and Dexamethasone Versus Daratumumab, Bortezomib and Dexamethasone in Participants With Relapsed/Refractory Multiple Myeloma (DREAMM-7) | 3 | NCT04246047 | RRMM |
| Belantamab Mafodotin Plus Pomalidomide and Dexamethasone (Pd) Versus Bortezomib Plus Pd in Relapsed/Refractory Multiple Myeloma (DREAMM-8) | 3 | NCT04484623 | RRMM |
| Study of Belantamab Mafodotin Plus Standard of Care (SoC) in Newly Diagnosed Multiple Myeloma (DREAMM-9) | 1 | NCT04091126 | NDMM |

| Description | Phase | NCT number | Population |
|---|---|---|---|
| A Study of Belantamab Mafodotin (GSK2857916) in Multiple Myeloma Participants With Normal and Varying Degree of Impaired Renal Function (DREAMM-12) | 1 | NCT04398745 | RRMM |
| A Study of Belantamab Mafodotin (GSK2857916) in Multiple Myeloma Participants With Normal and Impaired Hepatic Function (DREAMM-13) | 1 | NCT04398680 | RRMM |
| BISPECIFIC ANTIBODIES | | | |
| PF-06863135 As Single Agent And In Combination With Immunomodulatory Agents In Relapse/ Refractory Multiple Myeloma | 1 | NCT03269136 | RRMM |
| MagnetisMM-3: Study Of Elranatamab (PF-06863135) Monotherapy in Participants With Multiple Myeloma Who Are Refractory to at Least One PI, One IMiD and One Anti-CD38 mAb | 2 | NCT04649359 | RRMM |
| First in Human (FIH) Study of REGN5458 in Patients With Relapsed or Refractory Multiple Myeloma | 1/2 | NCT03761108 | RRMM |
| A Study of Teclistamab, in Participants With Relapsed or Refractory Multiple Myeloma | 2 | NCT04557098 | RRMM |
| A Study of Talquetamab in Participants With Relapsed or Refractory Multiple Myeloma | 2 | NCT04634552 | RRMM |

**Table 1.**
*Ongoing clinical trials.*

block receptors (PD-1) and ligands (PD-L1 and PD-L2), resulting in the recovery of immune response.

Pembrolizumab is a humanized IgG4 monoclonal antibody with high specificity against PD-1 receptors. Pembrolizumab was evaluated in combination with Lenalidomide and low dose dexamethasone in a phase I dose-escalation study (KEYNOTE-023 trial NCT02036502). Sixty-six patients with RRMM were recruited. Pembrolizumab was treatment-related AEs. Grade 3 AEs (mainly cytopenias fatigue and diarrhea) occurred in 37 (59,7%) patients. ORR OS and median PFS were 44%, not reached, and 7.2 months respectively [79, 80]. Pembrolizumab has also been evaluated in combination with Pomalidomide and dexamethasone in another phase II study (NCT02289222). Forty-eight patients with RRMM were recruited. Patients had received 2–5 (median 3) prior lines of treatment. 73% were refractory to both IMIDs and PIs. ORR was 60%. The percentage of SCR and CR, VGPR, and PR were 8%, 19%, and 33%, respectively. After a median follow-up of 15.6 months, OS and PFS were not reached and 17.4 months, respectively. (40%) [81].

Based on these results, two-phase three trials were designed to evaluate the combination of Pembrolizumab dexamethasone with Lenalidomide (KEYNOTE-185 NCT02579863) or Pomalidomide (KEYNOTE-183 NCT02576977) in ND and RR setting respectively. Interim analysis of both studies showed excessive administered for a median of 7 cycles (range 1–67). Overall, 95% of patients experienced unanticipated deaths attributed to the combination of Pembrolizumab Dexamethasone with Lenalidomide or Pomalidomide. These results showed that the risk profile of these novel combinations was unfavorable, and both trials were terminated early [82, 83].

Nivolumab is a fully human IgG4 Moab targeting PD-1 receptors. Investigation of Nivolumab with IMiDS has been placed on clinical hold after reviewing data

regarding Pembrolizumab. Nivolumab is currently under investigation in combination with daratumumab (NCT03184194), Elotuzumab (NCT02612779), Pomalidomide (NCT02726581), and Carfilzomib (NCT03605719) in phase 2 trials.

In **Table 1**, we present selected clinical trials conducted with monoclonal antibodies in the newly diagnosed and relapsed refractory setting.

## 4. Conclusion

Despite therapeutic improvements Multiple Myeloma remain an incurable disease. The treatment of patients with RR remains a challenging issue. Antibody therapy has significantly enhanced the armamentarium of therapeutic options. Further research should focus on tailoring the combination regimens based on disease and patient characteristics in order to optimize the efficacy and safety.

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