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Risk of Infections Associated with the Use of Monoclonal Antibodies in Multiple Myeloma (MM)

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Abstract: Patients with Multiple Myeloma have an increased susceptibility to severe infections due to several various factors, especially the high tumor burden. The use of the anti-CD38 monoclonal antibodies-based therapies has changed the frequency and epidemiology of infections. We report herein the safety profile of the pivotal clinical trials conducted with anti-CD38 mAbs (daratumumab and isatuximab) and anti-SLAMF7 mAbs (elotuzumab) that led to the approval of regimens employed today in NDMM and RRMM patients.

Keywords: infectious diseases, Multiple Myeloma, monoclonal antibody based-strategies

1. Introduction

Patients with newly diagnosed Multiple Myeloma (NDMM) have an increased susceptibility to severe infections due to several various factors, especially the high tumor burden [1]. Approximately 10% of patients with NDMM die prematurely as a result of infection before induction therapy [2,3]. The infectious risk is more evident in patients with refractory/relapsed Multiple Myeloma (RRMM), particularly due to cumulative immunosuppression developing from several previous treatments, myeloablative regimens, continuous therapy.

The anti-CD38 monoclonal antibodies (mAbs)-based therapies are approved for NDMM and RRMM and their use has changed the frequency and epidemiology of infections. The Food and Drug Administration's Adverse Events Reporting System (FAERS), a pharmacovigilance monitoring database, recently reported the characteristics and incidence of infections in patients with MM treated by daratumumab [4]. The FAERS showed that 2.7% of 7152 adverse events (AEs), in the period 2015-2021, were opportunistic infections from Herpes Zoster (25.1%), CMV (22.0%) and Hepatitis B Virus reactivation (6.7%), Pneumocystis Jirovecii Pneumonia (17.4%), bronchopulmonary Aspergillosis (8.2%) and tuberculosis (2.5%) [4,5].

We report herein the safety profile of the pivotal clinical trials conducted with anti-CD38 mAbs (daratumumab and isatuximab) and anti-SLAMF7 mAbs (elotuzumab) that led to the approval of regimens employed today in NDMM and RRMM patients. We also report herein also some other potentially employable schemes.

2.1. Transplant-eligible newly diagnosed MM

The randomized phase 3 **CASSIOPEIA** trial (NCT02541383) (daratumumab, bortezomib, thalidomide and dexamethasone, D-VTd vs VTd) was the first study to demonstrate a significant superiority of daratumumab + VTd (D-VTd) before and after autologous stem cell transplantation (ASCT) in transplant-eligible patients with NDMM [6]. Recently, Moreau et al. [7] and Sonneveld at al. [8] performed a MAIC (matching-adjusted indirect treatment comparison) analysis of the CASSIOPEIA vs IFM2009 and CASSIOPEIA vs GMMG-MM5 phase 3 trials, respectively, and demonstrated that the D-VTd + ASCT from CASSIOPEIA performed significantly better than VRd + ASCT (IFM200) and VCd + ASCT + lenalidomide consolidation/maintenance (GMMG-MM5) in terms of both PFS and OS. As regards clinical infections, infections of any grade were more common in the D-VTd subgroup vs the VTd subgroup (65% vs 57%), but the numbers of grade ≥3 infections were similar (22% vs 20%), including pneumonia (4% vs 2%) [6]. Infections led to discontinuation of

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daratumumab-based treatment in only 1% of patients [6]. The most common grade ≥3 haematological AEs were neutropenia (28% in the D-VTd group and 15% in the VTd group) and lymphopenia (17% in the D-VTd group and 10% in the VTd group) [6].

The randomized phase 2 **GRIFFIN** trial (NCT02874742) (daratumumab, bortezomib, lenalidomide, and dexamethasone, D-VRd vs VRd) investigated the superiority and safety of another quadruplet in transplant-eligible patients with NDMM [9, 10]. Infections of any grade were more common in the D-RVd group compared with the RVd group (90.9% vs 61.8%), largely due to more grade 1 or 2 upper respiratory tract infections. The incidence of grade 3 or 4 infections (23.2% vs 21.6%) and pneumonia (8.1% vs 10.8%) was similar between groups, as was the percentage of infections leading to discontinuation (2.0% vs 2.9%). Grade 3 or 4 neutropenia (41.4% vs 21.6%), and lymphopenia (23.2% vs 21.6%) were more common with D-RVd [9].

Currently**,** new studies are currently being conducted to validate the importance of minimal residual disease (MRD) as a key prognostic marker and guide to treatment decision making. In fact, in the **PERSEUS** trial (NCT03710603) (daratumumab, bortezomib, lenalidomide, and dexamethasone, D-VRd vs VRd), a phase 3 study of a similar design, 709 transplant-eligible patients with NDMM received bortezomib, lenalidomide plus dexamethasone with or without daratumumab [11, 12] and the incorporation of daratumumab in the treatment regimen significantly improved the overall response rate (≥CR 87.9% vs 70.1%; p<0.0001) and also showed a higher rate of MRD negativity (75.2% vs 47.3%; p<0.0001). At a median follow-up of approximately 4 years, the percentage of patients with progression-free survival at 4 years was 84.3% in the D-VRd group and 67.7% in the VRd group [12]. The most common hematologic AE of grade 3 or 4 in the daratumumab group was neutropenia (62.1% vs 51.0%), and the most common non-hematologic AEs of any grade in the daratumumab group were tract respiratory infections (CoV-19 infections [35.0% vs 23.9%], upper respiratory tract infections [31.6% vs 25.1%], and pneumonia [18.2% vs 11.0%]) [11, 12]. The phase 3 **IsKia** trial (NCT04483739) (isatuximab, carfilzomib, lenalidomide and dexamethasone, Isa-KRd vs KRd) assessed the efficacy and safety of one other anti-CD38 mAb, isatuximab + KRd as pre-ASCT induction and post-ASCT consolidation vs KRd [13]. The incorporation of isatuximumab in the treatment regimen was responsible for a higher rate of minimal residual disease negativity (77.0% vs 67.0%; p<0.049). The most common grade 3 or 4 non-hematologic AEs in the Isa-KRd group compared with the KRd group were infections (excluding COV-19) (16% vs 12%). Treatment discontinuation (TD) for toxicity was 6% in IsaKRd vs 5% in KRd arms; there were 4 with IsaKRd (2 COVID, 1 pneumonia, 1 pulmonary embolism) and 1 with KRd (septic shock). The most common grade 3 or 4 hematologic AE in Isa-KRd vs KRd was neutropenia (37% vs 22%; p=0.008).

2.2. Transplant-ineligible newly diagnosed MM

The randomized phase 3 **ALCYONE** (NCT02195479) (daratumumab, bortezomib, melphalan, and dexamethasone, D-VMP versus VMP) and **MAIA** (NCT02252172) (daratumumab, lenalidomide and dexamethasone, D-Rd versus Rd) trials demonstrated a significant superiority of daratumumab + Rd and daratumumab + VMP in transplant-ineligible patients with NDMM in terms of ORR, OS, PFS and MRD negativity rates [14-17]. In D-VMP, during the quadruplet treatment (9 cycles), although grade 3 or 4 neutropenia did not differ substantially between the two groups (39.9 vs 38.7), the incidence of grade ≥3 infections was higher in the D-VMP group than the VMP group (23.1% vs 14.7%), while pneumonia was the most common grade ≥3 infection disease (11.3% vs 4.0%) [14]. Fortunately, most infections, including pneumonia, resolved (87.9% in the D-VMP group vs 86.5% the VMP group) and rates of TD and death due to infections did not differ substantially between the two groups (0.9% vs 1.4% and 1.4% vs 1.1%, respectively) [14]. In the MAIA trial, the D-Rd group had higher rates of grade 3 or 4 neutropenia (50.0% vs 35.3%) and infections (32.1% vs 23.3%) including pneumonia (13.7% vs 7.9%) than the Rd control group. TD due to infection was 0.5% in the D-Rd arm and 1.4% in the Rd arm, while the rates of death due to pneumonia did not differ substantially between the two groups (0.5% vs 0.8%) [15]. After a median follow-up of 28.0 months, a primary interim analysis confirmed that the D-Rd group had higher rates of grade ≥3 neutropenia (54.0% vs 37.0%), infections (41.0 vs 29.0) and pneumonia (19.0% vs 11.0%) than the control group; despite this,

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the TD rate due to infections (including pneumonia) (1% vs 2%) or death was similar between the two groups [19]. Both daratumumab trials presented a frailty subanalysis (simplified frailty score with age, CCI, and ECOG) [20, 21]. Like in the overall population, in frailty subgroup analysis of ALCYONE, grade leading ≥3 neutropenia, pneumonia (14.4% vs 5.3%) and clinical infections (30.0% vs 17.9%) were more frequent in patients who received D-VMP vs VMP. In the D-VMP cohort, the most commonly reported infection to TD or death (1.3% vs 0.0%) was pneumonia [20]. In the frailty subgroup analysis of MAIA, the frail subgroup had an increased incidence of hematologic and non-hematologic grade 3/4 treatment-related AEs (TEAEs), serious TEAEs, and deaths in both treatment cohorts vs the total–non-frail subgroup. It is very interesting to observed that the incidence of pneumonia and death was higher with Rd versus D-Rd (Rd 1,8% vs D-Rd 1,2%). This was not related to the dose intensity of daratumumab (similar across frailty subgroups [total-non-frail 98.2% vs frail 98.0%]), but, probably, to an inferior lenalidomide dosage [21].

2.3. Refractory/Relapsed MM

The prospective pivotal randomized phase 3 **CASTOR** trial (NCT02136134) (daratumumab, bortezomib and desamethasone, D-Vd vs Vd) and **POLLUX** trial (NCT02076009) (daratumumab, lenalidomide and dexamethasone, D-Rd vs Rd), designed specifically for RRMM patients, investigated the efficacy and tolerability of daratumumab + Vd and daratumumab + Rd [22, 24]. In the D-Vd, regarding the safety profile, the results of the trial documented a higher incidence of upper respiratory tract infections and pneumonia of any grade (24.7% and 11.9%, respectively) in the D-Vd group than in the Vd group (18.1% and 11.8%, respectively) [22]. The incidence of grade 3-4 upper respiratory tract infections and pneumonia was of 1.6% and 8.2%, respectively, in the D-Vd group, while 0.8% and 9.7%, respectively, in the Vd group [22]. No clear signs of increased toxicity were observed in patients aged ≥75 years in the D-Vd group. After median follow-up of three years, despite a higher incidence of upper respiratory tract infections (any grade) in the D-Vd subgroup, the rate of pneumonia (any grade) was similar in the two groups [23]. In the POLLUX trial, despite higher rates of grade ≥3 neutropenia in the D-Rd group (51.9% vs 37.0%), the incidence of grade ≥3 infections was slightly higher in the D-Rd group than in the Rd group control (28.3% vs 22.8%), while the rate of grade ≥3 pneumonia was similar in the two groups (7.8% vs 8.2%) [24]. Neutropenia was the most common grade 3–4 TEAE in patients aged 65–74 years, as well as in those aged 75 years, and no increased toxicities were observed in patients aged ≥75 years; this may be due to a lower lenalidomide dose in older patients (≥75 years) than in patients aged 65 to 74 years [25]. The most common AEs that led to the DT included pneumonia (1.1% of patients in D-Rd group and 0.7% in the control group) [24]. After a long follow-up of 44.3 months, no new safety concerns were reported in either treatment group [26].

Daratumumab was investigated in combination with pomalidomide in previously treated MM in the **APOLLO** (NCT03180736) [27] and **MM014** (NCT01946477) [28] (daratumumab, pomalidomide and dexamethasone, D-Pd vs Pd) trials. The randomized phase 3 APOLLO study demonstrated the superiority of daratumumab, pomalidomide and dexamethasone vs pomalidomide and dexamethasone after both short (16.9 months) and long follow-up (39.6 months). The most common grade 3-4 AEs were neutropenia (68% in the D-Pd group vs 51% in the Pd group). Infections of any grade occurred in 70% of patients in the D-Pd group vs 55% of patients in the Pd group; grade 3-4 infections occurred in 28% of patients in the D-Pd group vs 23% of patients in the Pd group. Serious TEAEs occurred in 27% of patients in the D-Pd group vs 10% of patients in the Pd group, and the most common serious TEAEs were pneumonia (9% vs 1%), lower respiratory tract infection (3% vs 1%), and febrile neutropenia (3% vs 1%) [27]. The same combination D-Pd was investigated in a phase 2 MM-014 trial [28]. Infections (79.5%) and neutropenia (67.0%) of any grade were the most common TEAEs. Grade 3-4 infections were noted in 36.6% of patients, including 16.1% with grade 3-4 pneumonia [28].

The randomized phase 3 **ICARIA** study (NCT02990338) (isatuximab, pomalidomide, and dexamethasone, Isa-Pd vs Pd) evaluated the addition of the anti-CD38 mAb isatuximab to pomalidomide and dexamethasone in heavily pretreated MM patients [29]. All grade respiratory

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infections were more frequent in the Isa-Pd group vs Pd group control (upper respiratory tract infection 28% vs 17%; bronchitis 24% vs 9%; pneumonia 20% vs 17%). The incidence of grade 3-4 pneumonia was slightly higher in the Isa-Pd group vs the Pd control group (16% vs 14%). Neutropenia of grade 4 was more frequent in patients who received Isa-Pd (61.0% vs 31.0%). At 24 months after the primary analysis, neutropenia of grade >3 was more frequent in patients who received Isa-Pd (50.0% vs 35.0%), while pneumonia was comparable in both standard and experimental arms, with a slightly higher incidence in the Isa-Pd group (23% vs 21%) [30]. Death owing to an infectious disease was similar between the two groups (1% vs 1%) [29]. Schjesvold F et al. [31] presented a frailty subanalysis (simplified frailty score). As in the overall population, in the frailty subgroup analysis, grade ≥3 neutropenia (50% vs 46.4%), and clinical infections (46.5% vs 35.7%) were more frequent in patients who received Isa-Pd vs Pd.

Combinations of carfilzomib plus an anti-CD38 mAb have been evaluated in two phase 3 studies. In the randomized phase 3 **IKEMA** study (NCT03275285) (isatuximab, carfilzomib and dexamethasone, Isa-Kd, vs Kd) the combination of isatuximab plus carfilzomib and dexamethasone was prospectively compared with carfilzomib plus dexamethasone in patients with RRMM who had received one to three previous lines of therapy [32]. The grade >3 neutropenia was more frequent in patients who received Isa-Kd vs Kd (19.0% vs 7.0%). Upper respiratory tract infections (36.0% vs 24%), pneumonia (29.0% vs 23.0%), and bronchitis (23.0% vs 12.0%) were all more common in the Isa-Kd group than the control group [30]. In long-term follow-up study, Moreau et al. [33] confirmed similar data on safety: the incidence of upper respiratory tract infections (37.0% vs 27%), pneumonia (27.0% vs 21.0%), and neutropenia (57.0 vs 45.0) was higher in the Isa-Kd group than the control arm. A subgroup analysis of the IKEMA study analyzed efficacy and safety in patients aged <70 and >70 years, showing that respiratory infections (upper respiratory tract infection 39.2% vs 23.5%; bronchitis 31.4% vs 5.9%) were slightly higher in patients aged ≥70 years [34]. The randomized phase 3 **CANDOR** study (NCT03158688) (daratumumab, carfilzomib and dexamethasone, D-Kd, vs Kd) prospectively compared the combination of daratumumab plus carfilzomib and dexamethasone with carfilzomib plus dexamethasone in patients with RRMM who had received one to three previous lines of therapy [35]. All grade upper respiratory tract infections occurred with a ≥5% higher incidence in the D-Kd group than the Kd group (29% vs 23%). Grade >3 pneumonia (13.0% vs 9.0%) occurred with a ≥2% higher incidence in the D-Kd group than the Kd group. Five deaths were reported as treatment-related, all in the D-Kd group (pneumonia; sepsis with the development of Clostridium difficile enterocolitis; septic shock in the setting of pneumocystis pneumonia; acinetobacter infection; and cardiorespiratory arrest [n=1 each]).

Aside from anti-CD38 mAbs, one other mAb that targets SLAMF7 has been approved in treatment combinations for patients with RRMM on the basis of the results of two randomized trials. Both **ELOQUENT-2** (NCT01239797) (elotuzumab, lenalidomide and dexamethasone, E-Rd, vs Rd) and **ELOQUENT-3** (NCT02654132) (elotuzumab, pomalidomide and dexamethasone, E-Pd, vs Pd) showed a consistent PFS and OS benefit with the addition of elotuzumab to either lenalidomide and dexamethasone or pomalidomide and dexamethasone [36-38]. In the pivotal phase 2 **ELOQUENT-3** study, the incidence of respiratory infections of any grade in the Elo-Pd group was similar to that observed with Pd (65% vs 65%) (nasopharyngitis 17% vs 15%; upper respiratory tract infection 12% vs 15%: lower respiratory tract infection 17% vs 9%; bronchitis 10% vs 9%; pneumonia 7% vs 11%; Herpes zoster infection 5% vs 2%). Conversely, grade 3-4 infections occurred in 13% of the patients in the Elo-Pd group and in 22% in the control group. The addition of elotuzumab did not result in a higher rate of treatment related neutropenia (18% in the Elo-Pd group and 20% in the control group) [37, 38].

3. Discussions

Randomized trials, meta-analyses and MAICs indicate that the addition of mAbs to standard treatments such as Rd, VMP, VTd, Kd and Pd has radically changed the scenario for both transplant-eligible and transplant-ineligible patients. Unfortunately, from an extended clinical review of the pivotal randomized phase 3 clinical trials examining the current use of anti-CD38 mAbs in MM, the

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addition of anti-CD38 mAbs resulted in a higher rate of AEs in the overall population, particularly in terms of infections (including pneumonia) and neutropenia plus lymphocytopenia. In fact, as regards infectious diseases, the FAERS suggests a significant association between daratumumab-based regimens and multiple opportunistic infections [4] and pivotal randomized phase 3 clinical trials documented that the rates of infectious complications, in particular respiratory tract infections including viral complications, are higher in the anti-CD38 mAbs combination with IMiDs or PIs plus dexamethasone group than IMiDs or PIs and dexamethasone alone. In the same line, a recent metanalysis of clinical trials [39], pooling five randomized phase 3 studies (ALCYONE, MAIA, CASSIOPEIA, CASTOR and POLLUX), confirmed that the incidence of TD due to infection/pneumonia was slightly higher with daratumumab than in the control group (0.95% vs 0.73%); conversely, the rates of TD due to treatment-emergent adverse events (TEAEs) (6.77% vs 10.08%) and treatment-related deaths (3.61% vs 4.34%) were significantly lower in the daratumumab group than in the control arm. In contrast to anti-CD38 mAbs, the addition of elotuzumab with IMiDs did not result in a higher incidence of treatment-related neutropenia and pneumonia [36-38].

Despite these clinical observations, to analyze the severity and outcomes of infectious disease with daratumumab vs comparators, some questions need to be asked. Firstly, it is very interesting to observe that, although grade ≥3 infections (25.7% vs 19.0%) and pneumonia (9.3% s 5.7%) [5] were reported more frequently in the anti-CD38 mAbs group than in the control group, the incidence of serious AEs and the incidence of infections leading to death were similar compared with control arms [39]. The safety profile of quadruplet regimens is similar to those of triplet regimens and there is no evidence of additional significant toxicities [6, 9-13]. Secondly, van de Donk et al. [40], using pooled data from patients treated in the ALCYONE and MAIA trials, showed a progressive decrease of the infectious risk after 6 months of treatment (10% vs 20%), and a lower grade ≥3 infection risk in the daratumumab group compared with the standard-of-care arm after 2 years of treatment. In an inter analysis of the ALCYONE trial [18], after a long median follow-up of 40.1 months, Mateos et al. confirmed that, during maintenance daratumumab monotherapy, the most common AEs observed were respiratory infections of grade 1-2 (up to 19%), suggesting that after more than 3 years of follow-up, the D-VMP group continued to show significant improvements in progression-free survival with no increasing susceptibility to infections. Thirdly, the frailty analyses of ALCYONE [20] and MAIA [21] trials, an Italian retrospective clinical study [41] and a multicenter real-world retrospective experience of patients with RRMM enrolled in compassionate early access programs (EAPs) for Isa-Pd in France [42] support the clinical benefit of anti-CD38 mAbs-based treatment also in frail patients. In accordance with frailty subanalyses, in the POLLUX trial [24] no increased toxicity was observed in patients aged ≥75 years; this was probably related to a lower median dose intensity of lenalidomide and dexamethasone than daratumumab with D-Rd vs Rd in all frailty subgroups, suggesting that clinicians were more likely to modify the dose of lenalidomide and/or dexamethasone due to AEs. In fact, the median dose intensity of daratumumab was similar across frailty subgroups (total-non-frail 98.2% vs frail 98.0%). Fourthly, in Isa-Pd arm of the ICARIA trial [30], the incidence of pneumonia was lower in elderly patients, and this may be due to the higher percentage of older patients receiving prophylactic strategies revealing the efficacy of this approach. In fact, granulocyte-colony stimulating factor was used in 69% of patients in the Isa-Pd group, and 53% in the Pd control arm [30].

Therefore, based on these data, the increasing susceptibility to infections in patients with anti-CD38 mAbs-treated MM is documented to be multifactorial. In addition to the intrinsic anti-CD38 mAbs effects on the immune system (defects in T-cell function responsible for cytomegalovirus and varicella-zoster reactivation, Pneumocystis Jirovecii Pneumonia; B-cell dysfunction with secondary low immunoglobulin levels causes the emergence of major pathogens including pneumococci, Haemophilus influenza), several other factors are related to the increased infectious risk such as the higher incidence of secondary neutropenia, many prior lines of therapy, the complex schedules and the disease characteristics (disease burden, advanced ISS disease stage, aggressiveness, refractory/relapsed disease). In our recent analysis [43], in accordance with recent literature data [44], we emphasized the hypothesis that the disease burden appears to reduce the immunity acquired

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from vaccinations rather than the treatment type and timing of vaccinations and plays a very important role in the infectious risk.

To prevent infections the three main potential strategies are antimicrobial prophylaxis, vaccinations, and, in patients with significant hypogammaglobulinemia, immunoglobulin substitution therapy. Recommendations for antibiotic prophylaxis are less clear, but a recent randomized study from the UK showed a significant reduction in the rate of infections or death (27% vs 19%) with the addition of prophylactic levofloxacin to active myeloma treatment particularly in transplantation-ineligible patients (HR 0.51) within the first 3 months [45]. Consensus reports from European experts recommend prophylactic antibiotic treatment in patients at high risk of infectious complications such as elderly patients, those with active, poorly controlled disease, comorbidities, those with a history of an increased incidence of infections and those receiving highly myelotoxic therapy [46]. Conversely, anti-bacterial prophylaxis may be considered in all other cases. Commonly used antibiotics are co-trimoxazol, amoxicillin/clavulate or levofloxacin. Recent international guidelines recommend fluconazole prophylaxis in cases of a history of fungal infection, prolonged neutropenia or steroid administration [46]. Recent guidelines also recommend in all patients appropriate vaccinations against pneumococci, influenza, COV-19, Herpes zoster and those bacteria and viruses (haemophilus influenzae, meningococci, and hepatitis) that frequently may pose a significant risk to patients with MM [46, 47].

Further optimization of myeloma treatment approaches could be, in particular, dexamethasone-free strategies, that can allow patients to remain on treatment longer, maintaining disease control over time and reducing the rates of clinical infections [48, 49]. Data on a phase 3 trial reported that, in patients receiving Rd, reducing the lenalidomide dose and discontinuing dexamethasone after the first 9 cycles did not affect the efficacy but limited toxicities as compared to full-dose Rd [48]. Data have been recently reported from the multicenter randomized phase 3 IFM 2017-03 trial evaluating the dexamethasone-sparing regimen of Dara+Lena compared with Lena+Dexa in patients aged ≥65 years with NDMM, classified as frail according to age, comorbidities and ECOG PS ≥2 [49]. The dexamethasone-sparing regimen of Dara+Lena was associated with higher response rates (ORR 96% vs 85%), and rates of MRD negativity at 10^{-5} (10% vs 3%), and a favorable safety profile compared with Lena+Dexa (no increased risk of infection or pneumonia [p 0.29], and similar TD rates between arms [p 0.65]) [49]. The dexamethasone-sparing regimen of Dara+Lena resulted in better tolerability compared with Rd, particularly in terms of non-hematologic toxicities [49].

In conclusion, some important clinical scenarious should be considered when using anti-CD38 mAbs to treat myeloma patients. Firstly, all data provided by randomized trials, meta-analyses and MAICs have demonstrated that anti-CD38 mAbs-based regimens remain an extraordinary therapeutic approach in NDMM and also in RRMM. The addition of daratumumab enhances the efficacy of standard first-line therapy for transplantation-eligible patients with NDMM and the safety profile of this quadruplet therapy is similar to those of triplet regimens and does not impede proceeding to transplantation. Secondly, the TEAEs did not result in higher treatment interruption rates or fatal AEs, revealing that these hematologic and non-hematologic TEAEs were manageable. Thirdly, based on recent literature data [40, 18], and according to Dryson et al. [45], antibacterial prophylaxis might be appropriate and justified during the first months of therapy in particular in frail patients, patients with a high-risk of infections and when the disease burden is high. Fourthly, a dexamethasone-sparing approach can be considered if an infection risk limits treatment tolerability, since there is emerging evidence of similarly effective steroid-sparing regimens [48, 49].

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