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Debulking strategy prior to anti-BCMA/CD3 bispecific antibodies in extramedullary and/or high tumor burden RRMM: a retrospective cohort study

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Dear Editor,

Even at the era of T-cell redirecting therapies, patients with relapsed or refractory multiple myeloma (RRMM) presenting extramedullary disease (EMD) and/or high risk cytogenetic abnormalities (HRCA) constitute a particularly challenging subgroup with lower overall response rate (ORR) and poorer survival outcomes [1, 2]. A sub-analysis of the MagnetisMM-3 trial reported an ORR of 0% in patients with ISS stage III disease and HRCA or EMD, compared to ORRs of 47.4% and 71.4% in patients with ISS stages I and II with EMD or HRCA, respectively [3, 4]. Teclistamab achieved an ORR of 63% and a median progression-free survival (PFS) of 11.3 months in MajesTec-1 trial [5, 6]. In real-life setting, PFS for patients with EMD was 3.7 months vs 11.3 months for patients without EMD and ORR decreased at 37.2% [7].

Strategies to improve the efficacy and safety of BsAb therapy in high-risk patients are urgently needed. One potential approach is to implement a cytoreductive or "debulking" phase of chemotherapy prior to the initiation of BsAb therapy. Historically, conventional chemotherapy was the primary treatment for EMD in heavily pretreated patients with regimens such as PAd (bortezomib, doxorubicin, dexamethasone) or DT-PACE (thalidomide, cyclophosphamide, etoposide, dexamethasone, cisplatin, and doxorubicin) [8, 9]. Additional strategies incorporating pomalidomide or carfilzomib have also been reported [10, 11]. However, in the setting of BsAb therapy for RRMM, the role of debulking chemotherapy has not been well defined.

We conducted a retrospective, multicenter study across 14 Intergroupe Francophone du Myélome (IFM) centers to evaluate the safety, feasibility, and potential clinical benefit of cytoreductive chemotherapy administered prior to anti-BCMA BsAb therapy. Patients were included if they had received at least one full treatment dose of BsAbs and a cycle of conventional chemotherapy within the preceding month. Patients with plasma cell leukemia, amyloidosis, or those enrolled in clinical trials were excluded. Extramedullary disease was defined as a lesion confined to soft tissue without contact with bony structures. High tumor burden was determined based on medullary plasma cell infiltration (>60%), para-medullary disease, and/or elevated levels of monoclonal protein (peak >30 g/dl and/or abnormal light chain >5000 mg/L). High-risk cytogenetic abnormalities (HRCAs) were defined by the presence of del(17p), t(4;14), or t(14;16).

We included 44 patients in 14 centers in France between March 2022 and July 2024. Median age was 67 years old (min-max: 45-82) with 50% female (n = 22) (Table 1). Triple-class refractory MM represented 93% (n = 41), and median of prior lines was 4 (min-max: 2–9). EMD was found in 22 patients (50%) and PMD in 15 patients (34%). Twenty-two patients (50%) had an HRCA with 17p deletion in 41% (n = 9), 1q21 gain in 23% (n = 5), t(4;14) in 14% (n = 3) and t(14;16) in 9.1% (n = 2).

Concerning chemotherapy regimen, the most frequent class used was alkylating agent in 89% (n = 39), followed by anthracycline in 34% (n = 15), etoposide in 50% (n = 22), cisplatin in 16% (n = 7) and vincristine in 9.1% (n = 4). Combination of anthracycline and alkylating agent was used in 27% of cases (n = 12). The time between chemotherapy and anti-BCMA BsAbs was 28 days (min-max: 4–197). Teclistamab was used in 70% (n = 31) and elranatamab in 30% (n = 13). No patients received radiotherapy.

Cytokine release syndrome (CRS) rate was 64% (n = 28), with a majority of grade 1 (75%, n = 21). The immune effector cell-associated syndrome (ICANS) rate was 7% (n = 3) with two grade 1 and one grade 4. CRS and/or ICANS were managed with tocilizumab in 23% of cases (n = 10%), dexamethasone in 9.1% (n = 4) and anakinra in 2.3% (n = 1). Grade ≥3 infections were reported in 35% (n = 15) documented in 73% of cases and grade ≥3 cytopenia was reported in 33% (n = 14).

After the debulking chemotherapy-based regimen, ORR was 32% (n = 37) with 16% of ≥VGPR (Fig. 1A). ORR after cycle 1 of BsAb was 64% (n = 39) with 33% of CR and 46% VGPR or better. After cycle 3 (n = 34), the ORR was 73% and 87% at cycle 6 (n = 21). At one year, in the 10 patients evaluated, ORR was 80% with 30% of CR. Only few patients did have a PET-CT after C1 (n = 4), C3 (n = 7) and C6 (n = 7). Best response rate to BsAb for all patient was CR in 39%, VGPR in 18% with an ORR at 68%. Conversion of response rate was reported on Fig. 1B.

Among patients in CR or VGPR after debulking (n = 3, both), 100% responded to BsAb (≥PR or better). For patients with disease progression after chemotherapy (n = 8), 50% had a response to BsAb. Among patients with EMD, ORR after C1 and C3 was 53% (n = 9/17 and n = 8/15), at C6 ORR was 77.8% (n = 7/9) and 50% at C12 (2/4). Concerning patient with HRCA, ORR after C1 was 64% (n = 12/19), 73% after C3 (n = 12/15), 82% (n = 9/11) and 83% (n = 5/6) after C6 and C12, respectively.

The median follow-up of the study was 12 months (range: 1–31). In the overall population, median PFS was 10.2 months (95%CI: 6.87–18.6) (Fig. 1C). Regarding EMD, patients without EMD had a median PFS at 14.1 months (95%CI: 6.47-NR) vs 9.3 months (95%CI: 3.7-NR) for patients with EMD (p = 0.05) (Fig. 1D). Patients with HRCA had a median PFS at 10.2 months (95%CI: 5.02-NR) versus 7.6 (95%CI: 5.0-NR) for patients without HRCA (p = 0.9).

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Table 1. Patient/treatment characteristics and safety outcomes.

n(%)	N = 44 patients
Median age, years-old	66 (min-max: 45–82)
Female, n(%)	22 (50)
Median of prior lines	4 (min-max : 2–9)
Triple class refractory, n(%)	41 (93)
ISS score III, n(%)	20 (48)
Cytogenetic abnormalities, n(%)	22 (50)
17p deletion	9 (20)
1q21 gain	5 (11)
t(4; 14)	3 (7)
t(14; 16)	2 (4)
Del1p32	2 (4)
1q21 amplification	1 (2)
Extramedullary disease, n(%)	22 (50)
Number of involved sites, n(%)	
1	4 (9)
2	5 (11)
≥3	10 (23)
Type of localization, n(%)	
Cerebral	2 (4)
Lung	4 (9)
Liver	3 (7)
Kidney	3 (7)
Digestive	7 (16)
Cutaneous	8 (18)
Muscle	5 (11)
ORL	1 (2)
High plasma cell infiltration, n(%)	12 (28)
Acute kidney failure, n(%)	14 (32)
Hypercalcemia, n(%)	10 (23)
Number of cycles of chemotherapy, n(%)	
1	30 (68)
2	7 (16)
≥3	7 (16)
Alkylating agent, n(%)	39 (89)
Cyclosphosphamide	37 (84)
Bendamustine	5 (11)
Belustine	1 (2.3)
Anthracycline agent, n(%)	15 (34)
Etoposide	22 (50)
Vincristine	4 (9.1)
Cisplatin	7 (16)
Other	9 (20)
Anti-BCMA bispecific, n(%)	
Teclistamab	31 (70)
Elranatamab	13 (30)
Delay between chemotherapy and bispecific, median days (min-max)	28 (4–197)
CRS rate, n(%)	28 (64)
Grade 1	21 (75)
Grade 2	6 (21)
Grade 3	1 (3.6)
ICANS rate, n(%)	3 (7)
Grade 1	2 (67)
Grade 2-3	0
Grade 4	1 (33)
Tocilizumab use, n(%)	10 (23)
Dexamethasone use, n(%)	4 (9.1)
Infection, n(%)	
Grade 3 infection	12 (80)
Ig supplementation therapy	35 (80)
Antipneumocystisis agent	38 (89)
Antibioprophylaxis	24 (55)
Antiviral agent	43 (98)
Grade 3 cytopenias, n(%)	14 (33)

Median OS was 20.1 months (95%CI: 13.8-NR) for all patients (Fig. 1E). For patients with EMD, median OS was 13.7 months (95% CI: 6.5-NR), not reached for patients without EMD (95%CI: 13.8-NR) ($p = 0.1$) (Fig. 1F). In patients with HRCA, median OS was 19.3 (95% CI: 13.8-NR) vs 13.8 (95%CI: 7.45-NR) for patient without HRCA ($p = 0.8$). Death occurred in 19 patients (43%), 14 due to disease progression, 3 to infection and 2 others causes.

This multicenter retrospective study is the first to evaluate the efficacy and tolerability of conventional debulking chemotherapy prior to initiating anti-BCMA bispecific antibody therapy in patients with RRMM and either EMD or high tumor burden. Our findings suggest that this sequential approach is both effective and tolerable. Herein, the choice of chemotherapy was largely based on alkylating agents, especially cyclophosphamide (84%). Cyclophosphamide not only induces cytotoxicity but also modulates the immune microenvironment, reduces T-cell exhaustion, and enhances T-cell activation —all potentially boosting BsAb efficacy [12]. These immunomodulatory effects, combined with tumor debulking, may help improve the effector-to-target cell ratio, which plays a key role in the success of BsAb therapies. There is also a theoretical rationale that chemotherapy-induced cell death may promote neoantigen release and immune priming, further amplifying BsAb effectiveness [12].

At a median follow-up of 12 months in our study, median PFS was 10.2 months. These outcomes align with prior BsAb trial data, such as teclistamab (11.3 months) and elranatamab (17.6 months) [3, 5]. In the IFM 2024-09 real-world study, the median PFS for patients with EMD was 3.7 months vs 11.3 months for patients without EMD treated by Teclistamab [7]. In contrast, our results suggest improved disease control in this subgroup, although long-term benefit remains limited.

The safety profile of this approach was acceptable given the heavily pretreated patient population [13]. Despite prior chemotherapy, the incidence of CRS and ICANS remained low—7% for ICANS and no apparent increase in grade ≥3 infection frequency [13, 14]. This observation suggests that prior chemotherapy does not significantly increase the risk or severity of CRS associated with bispecific antibodies, countering some theoretical concerns.

The retrospective nature and modest size of our study introduce limitations. The heterogeneity of chemotherapy regimens and the lack of a comparator group make it difficult to draw definitive conclusions about the superiority of the

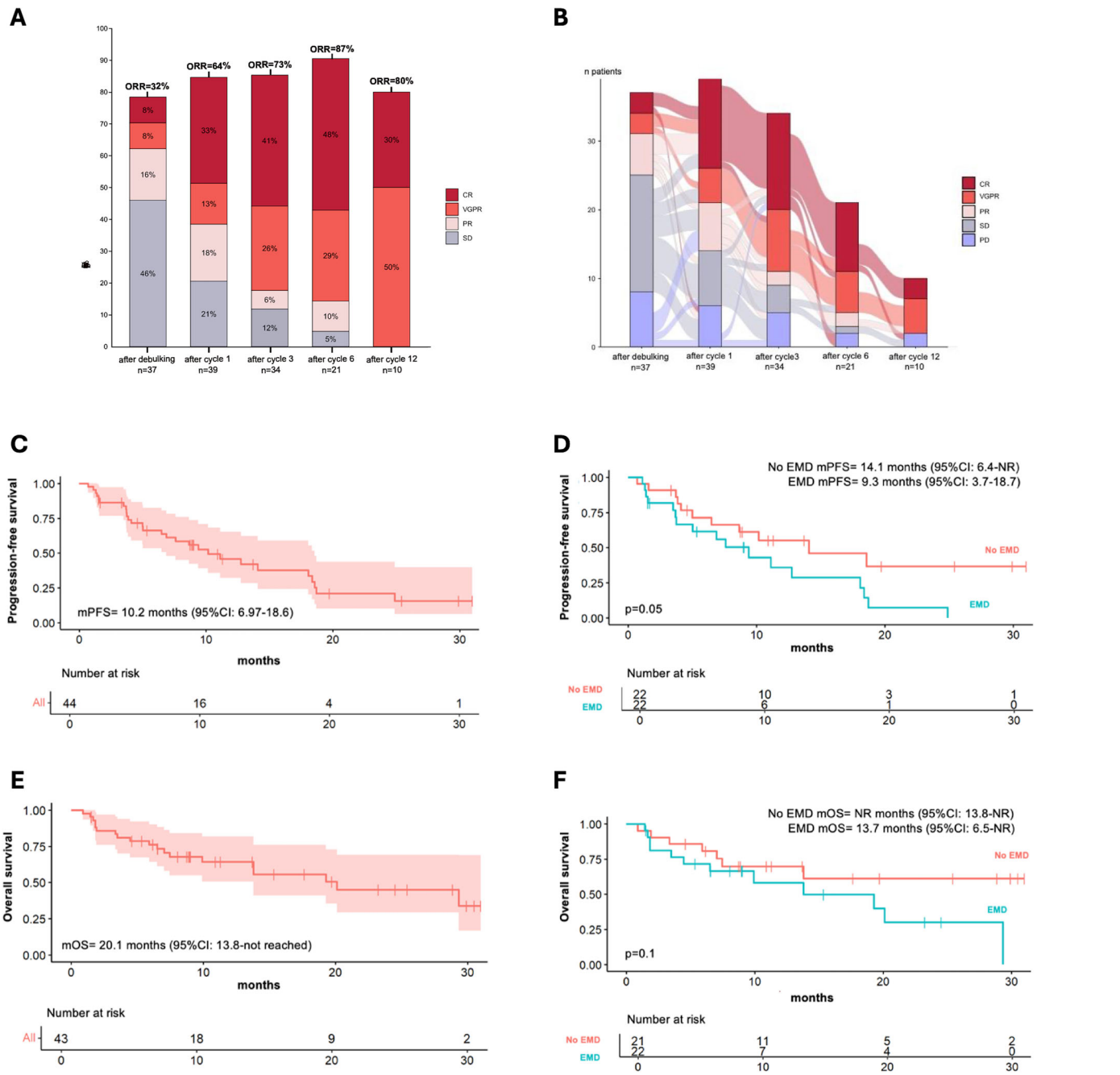

Fig. 1 Response rate, response conversion over cycles, progression free survival and overall survival. A Overall Response Rate (ORR) across cycles. **B** Conversion rate across cycles. **C** Progression-free survival (PFS) among all patients and **D** according EMD. **E** Overall survival (OS) in entire population and **F** according EMD.

sequential approach over BsAb monotherapy. Infrequent PET-CT assessments also limited our ability to fully evaluate depth of response, especially in patients with EMD. Prospective trials are needed to refine these aspects and to validate our findings. Additionally, translational studies evaluating immune markers, T-cell subsets, and changes in the tumor microenvironment before and after chemotherapy could help elucidate mechanisms of synergy and resistance.

Moreover, emerging combinations of BsAb with immunomodulators, proteasome inhibitors, or even other BsAb have been explored in clinical trials with promising results [15]. Whether debulking chemotherapy can be integrated into such regimens to improve outcomes in patients with high tumor burden or EMD remains an open question.

Our study suggests that chemotherapy-based tumor debulking before anti-BCMA BsAb therapy is a feasible and promising strategy for patients with RRMM and high tumor burden or EMD. It appears to enhance early responses while maintaining a manageable safety profile. These preliminary findings warrant confirmation in larger, prospective trials, along with deeper investigation into the biological underpinnings of this potentially synergistic treatment sequence.

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DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

TCh, HD, AP, CS, CJ, ZDW, AR, MR, GL, VM, LV, VS, TCa and AB followed study patients. TCh, EC, XL and SM interpreted the results; EC performed statistical analysis; TCh wrote the manuscript; XL and SM supervised the project; XL, EC, and SM revised the manuscript. All authors approved the manuscript.

COMPETING INTERESTS

TC: Consultant/Advisory Boards: BMS, Takeda, Janssen, GSK, Griffols, Amgen, Sanofi, Pfizer, Stemline. XL has received consultancy, honoraria and travel fees from Sanofi, Janssen-Cilag, Kite/Gilead, Amgen, Novartis, Takeda, Pfizer, Oncopeptide, AbbVie, GSK and Bristol Myers Squibb. AB received consultancy and honoraria from Sanofi, Janssen-Cilag. The other authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All centers obtained institutional review board approval, which granted a waiver of patient consent, and the study was conducted in accordance with the Declaration of Helsinki. This study was approved by the local Ethics Committees, in compliance with applicable ethical standards (n° 2024 053 and CNIL n° 18355189).

ADDITIONAL INFORMATION

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