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Contributions

AP, AH, ABou, PhM designed the study; AP, CH, HM, AL, CC, AD, MM, MR, SM, FOP, LB, AB, LF, LV, CB, JRE, TG, MT, EC, RB, CM, PeM, TC, BC, LM, AC, RT, LK, DR, SH included the patients; ABou, AP, CH, PhM, AH analysed the data; AP and PhM wrote the paper; all authors interpreted the data and reviewed the manuscript.

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Novel immunotherapeutic approaches are revolutionizing the treatment of triple-class exposed patients with relapsed and refractory multiple myeloma (RRMM) (1). Teclistamab is the first bispecific antibody targeting BCMA and CD3 to be approved for the treatment of RRMM. The pivotal study for this approval was MajesTEC-1, a phase 1/2, single-arm, open-label, multicentre, multicohort study (2). Eligible patients had RRMM after at least three lines of therapy, including exposure to a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody, with an Eastern Cooperative Oncology Group Performance Status score of 0 or 1. Prior treatment with a BCMA-targeted therapy was not permitted. Among 165 patients (median, five prior lines of therapy), 78% were refractory to all three classes, and the overall response rate (ORR) (primary endpoint) was 63.0%, with 65 patients (39.4%) achieving a complete response (CR) or better. Response rates were lower in patients with extramedullary disease (EMD), stage III disease, and more than 60% marrow involvement by myeloma cells. The updated analysis indicated that the median duration of response (DOR) was 24 months, median progression-free survival (PFS) was 11.4 months, and median overall survival (OS) was 22.2 months (3). The most significant adverse event was infections, occurring in 78.8% of patients (55.2% grade 3-4) (2).

As with other registration trials, the MajesTEC-1 study had stringent eligibility criteria, making it essential to report real-world data on Teclistamab. Teclistamab became available in France in October 2022 through an early access program. Here, we report retrospective analyses on efficacy and safety among 303 consecutive patients who initiated teclistamab in 30 French centres between 14 October 2022 and 14 September 2023. The IFM 2024-09 study was submitted to the French Health Data Hub (MR004 reference, number F20240102165356). The investigators obtained the patient's non-objection to collect the data, in accordance with local ethical rules. Teclistamab was administered subcutaneously every week at 1.5 mg/kg following two step-up doses of 0.06 and 0.3 mg/kg including premedication as per EMA recommendations. The median age was 70 years (Table 1). All patients were triple-class exposed and had received a median of four previous lines of therapy; 68.6% of the patients were refractory to IMiDs, 64% of the patients were refractory to PIs, and 54.5% were refractory to anti-CD38 monoclonal antibodies. Cytogenetics was evaluated in 179 patients: 54 had del(17p) and/or *TP53* mutation. Additionally, 34 patients (11.8%) had extramedullary disease (EMD), 70 (25.5%) had paramedullary disease (PMD) and 39 (13.8%) had circulating plasma cells. At the initiation of Teclistamab, 92 patients (30.3%) had an ECOG status of 2, 3 or 4, 30 (9.9%) had severe renal impairment, and 41 (13.6%) had been previously exposed to anti-BCMA agents. Overall, 140 patients (46.2%) would not have met the inclusion criteria of MajesTEC-1 (2). At a median follow-up of 11.9 months [9.2-14.8], the ORR rate was 68.8%, including 61.4% of patients achieving a very good partial response (VGPR) or better. The median PFS was 11.3 months in the overall population (95%CI 8.9-14.9) (Figure 1a); among the 175 responding patients, the median PFS was 17 months (16.4-NA). Subgroup analyses for PFS are summarized in Supplemental table 1. Significantly, patients with EMD had a worse outcome with a median PFS of 3.7 months, as did those with circulating plasma cell disease (4.7 months) or altered *TP53* cytogenetics (Supplemental figure 1). Among 106 patients who experienced disease progression, 67 patients (63%) received at least one subsequent therapy, most commonly alkylating agents (n=28), carfilzomib (n=6), venetoclax (n=5), as well as anti-BCMA CAR T-cells (n=3) and other bispecific antibodies such as talquetamab or elranatamab (n=6). Among the 3 patients who received ide-cel, only one did respond before experiencing progression at 7 months; three of the six patients receiving talquetamab did respond (1 Minimal Response, 2 VGPR - the last 2 patients unfortunately did progress at 5 and 7 months). The median OS was 17 months (95%CI, 13.8-NA) (Figure 1b). As the cut-off date of 17 June 2024, 125 patients (41.3%) had died, primarily due to progressive disease (66.4%). No new safety signals were observed, particularly regarding the occurrence of cytokine release syndrome (CRS) or immune effector-cell associated

neurotoxicity syndrome (ICANS). A total of 107 patients (36%) received tocilizumab (n=76, 25.6%) and/or dexamethasone (n=64, 21.5%) for CRS and/or ICANS. Among 294 patients with available data, 186 (61.4%) received immunoglobulin (Ig) supplementation, including 122 (41.8%) as primary prophylaxis. Infections led to the definitive discontinuation of teclistamab in 13% of patients; 99 patients (29.9%) were readmitted at least once for infections.

To our knowledge, our series is the largest available, demonstrating real-world results achieved with teclistamab and the longest follow-up to date. Three other studies have recently reported on the outcomes of patients treated with teclistamab as a single-agent in real-world settings, with short follow-up periods ranging from 3.5 to 5.5 months, and patient numbers ranging from 106 to 123 (Table 2) (4-6). Patients in these studies were more advanced compared to those enrolled in MajesTEC-1, exhibiting higher rates of penta-drug refractory disease, poor cytogenetics, EMD, and a significant number of cases previously exposed to BCMA agents. These trials demonstrated that teclistamab led to rapid achievement of deep hematologic responses in heavily pretreated MM, with response rates comparable to MajesTEC-1 trial and reasonable safety profiles, as seen in the pivotal trial. Nevertheless, inferior outcomes for both PFS and OS were reported, although the short follow-up times limited the reliability of these conclusions. Our analysis encompassed a very large cohort of patients treated in both university and community hospitals. Our response rate in triple-class exposed RRMM was identical to that of MajesTEC-1. Interestingly, and reassuringly, the PFS was also very similar to what was described in the pivotal study for approval, considering that approximately 47% of our patients would have been excluded from MajesTEC-1. The OS rate was also noteworthy and compared favorably to that of Majestec-1. In our real-world analysis, a high proportion of patients received Ig supplementation, which is now highly recommended in the management of such therapies in heavily pretreated patients (7-9).

Despite some limitations (retrospective design, heterogeneity in institutional practices for toxicity management, response assessment without independent review committee and minimal residual disease analyses), our study clearly confirms, on a very high number of patients treated in the real-world settings and with almost the same follow-up as MajesTEC-1, the reasonable safety and good efficacy of teclistamab in patients with RRMM.

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Table 1. Patient' characteristics in IFM2024-09 real-world study and in MajesTEC-1 (2,3).

Characteristics	**IFM 2024-09 (n=303)**	**MajesTEC-1 (n=165)**
Age (years), median [range] > 75 years, n (%)	70 [37-88] 90 (29.7%)	64 [33-84] 24 (14.4%)
Sex Male, n (%) Female, n (%)	151 (49.9%) 152 (50.1%)	96 (58.2%) 69 (41.8%)
Median prior lines of therapy [range]	4 [2-11]	5 [2-14]
Previous autologous transplant	171 (56.4%)	135 (81.8%)
IMiDs exposed IMiDs refractory	302 (99.7%) 208 (68.6%)	165 (100%) 152 (92.1%)
PIs exposed PIs refractory	303 (100%) 194 (64%)	165 (100%) 142 (86.1%)
Anti-CD38 monoclonal antibody exposed Anti-CD38 monoclonal antibody refractory	295 (97.4%) 165 (54.5%)	165 (100%) 148 (89.7%)
BCMA exposed	41 (13.6%)	0
ECOG PS > 2 at the initiation of teclistamab	26 (8.5%)	0
Severe renal failure at the initiation of teclistamab	30 (9.9%)	0
Ineligibility to MajesTEC-1	140 (46.2%)	0
High-risk cytogenetics, n (%) Del(17p) Del(17p) and/or *TP53* mutation t(4;14) t(14;16)	 34/179 (19%) 54/179 (30.2%) 27/188 (14.3%) 4/97 (4%)	 23/148 (15.5%) NA 16/148 (10.8%) 4/148 (2.7%)
Circulating plasma cells, n (%)	39 (13.8%)	NA
EMD, n (%)	34 (11.8%)	28 (17%)
PMD, n (%)	70 (25.5%)	NA
Median follow-up, months [range]	11.9 [9.2-14.8]	22 then 30.4

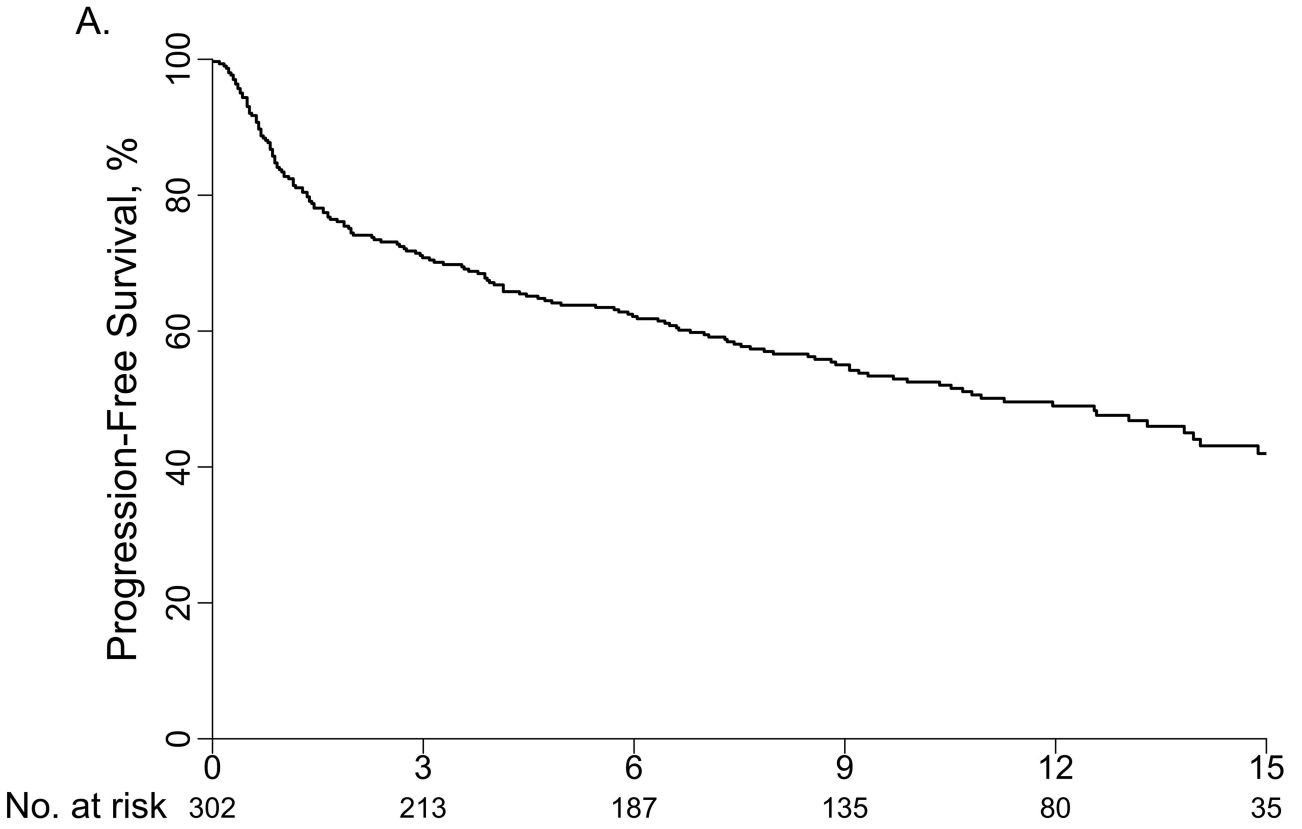
NA = not available. IMiDs = immunomodulatory drugs. PIs = proteasome inhibitors. BCMA = B-cell maturation antigen. ECOG PS = Eastern Cooperative Group Performance Status. EMD = extramedullary disease. PMD = paramedullary disease.

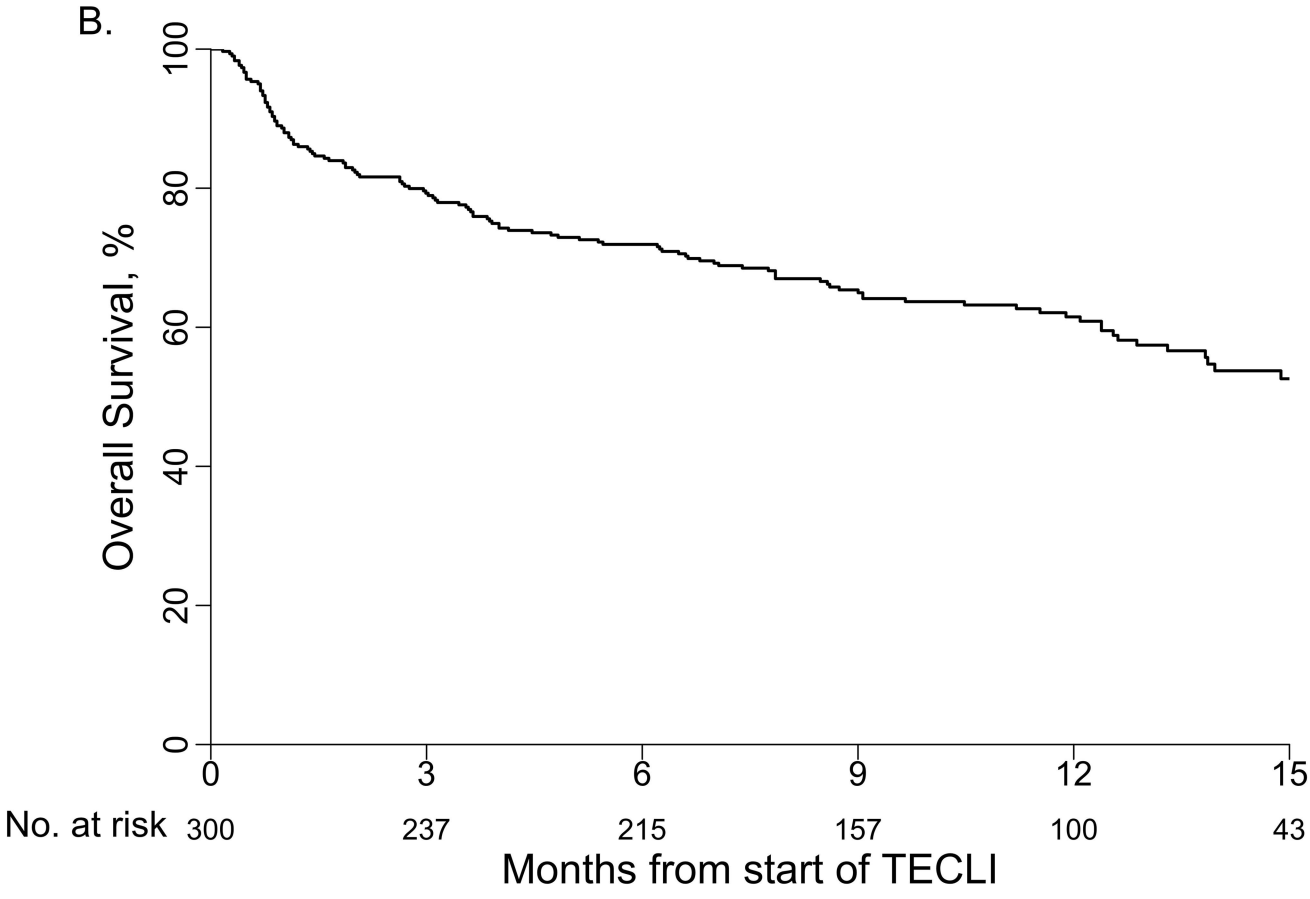
Table 2. Real-world studies of teclistamab for relapsed refractory multiple myeloma patients.

	Mohan M *et al*. (4)	Dima D et al. (5)	Riedhammer C *et al.* (6)
Country	USA	USA	Germany
Number of patients	110	106	123
Median age (years) [range] > 75 years	68 [37-89] 28 (25%)	66.5 [35-87]	67.0 [35-87]
ECOG PS > 1	NA	35 (33%)	NA
Cytogenetics del(17p)	23 (20.9%)	24 (25%)	NA
Extramedullary disease (EMD)	48 (44%)	45 (42%)	43/119 (36.1%)
Priori lines of therapy	6 [3-13]	6 [4-17]	6 [3-14]
Prior autologous transplant	86 (87%)	61 (58%)	NA
Refractory status PIs IMiDs Anti-CD38 antibodies Triple-class	 NA NA NA 95 (86%)	 102 (96%) 102 (96%) 106 (100%)	 NA NA NA 113 (92.6%)
Exposure to BCMA therapy	38 (35%)	56 (53%)	45 (36.6%)
Ineligibility to MajesTEC-1	NA	88 (83%)	39%
Median follow-up, months	3.5	3.8	5.5
ORR rate, %	62%	66%	59.3%
Median PFS, months	NR	5.4 (95% CI, 3.4-NR)	8.7
Median OS, months	NR	NR	NR

ECOG PS = Eastern Cooperative Group Performance Status. NA = not available. EMD = extramedullary disease. PIs = proteasome inhibitors. IMiDs = immunomodulatory drugs. BCMA = B-cell maturation antigen. ORR = overall response rate. PFS = progression-free survival. NR = not reached. OS = overall survival.

Figure 1: Outcomes of relapsed refractory multiple myeloma patients treated with teclistamab as part of early access in France. a. Progression-Free Survival, b. Overall Survival.


A.
Progression-Free Survival, %
0
20
40
60
80
100
0
3
6
9
12
15
No. at risk
302
213
187
135
80
35


B.
Overall Survival, %
0
20
40
60
80
100
0
3
6
9
12
15
No. at risk
300
237
215
157
100
43
Months from start of TECLI

Supplemental table 1: Subgroups analysis of progression-free survival in IFM 2024-09 study.
(NA= not achieved)

Subgroups	**Median PFS (95% CI)**	
Age < 75	9.1 months (6.3-13)	p = 0.007
Age 75 or more	16.4 months (10.7-NR)	
EXTRA MEDULLARY DISEASE	3.7 months (2-NR)	
No EXTRA MEDULLARY DISEASE	11.3 months (8.8-16.2)	p = 0.057
PARAMEDULLAR DISEASE	16.2 months (9.3-NR)	
No PARAMEDULLAR DISEASE	9.2 months (7.3-13.3)	p = 0.103
CIRCULATING PLASMACYTOSIS	4.7 months (1.7-10.5)	
No CIRCULATING PLASMACYTOSIS	12.6 months (9.7-16.4)	p = 0.001
del(17p) or TP53 mutation	5.2 months (2.9-9.1)	
No del(17p), no mutation TP53	16.4 months (4.1-NR)	p = 0.009
INELIGIBILITY TO MAJESTEC-1	6.6 months (3.15-10.9)	
ELIGIBILITY TO MAJESTEC-1	16.5 months (13.9-NR)	p < 0.001
SEVERE RENAL IMPAIRMENT	3.5 months (1.3-10.3)	
NO SEVERE RENAL IMPAIRMENT	13 months (9.3-16.5)	p = 0.001
ANTI-BCMA AGENTS in previous lines	7.1 months (3.5-NA)	
No ANTI-BCMA AGENTS in previous lines	12.6 months (9.3-16.4)	p = 0.09
No AUTOLOGOUS TRANSPLANT in previous	12.5 months (9.7-NR)	
AUTOLOGOUS TRANSPLANT in previous lines	9.1 months (6.3-16.2)	p = 0.357

Supplemental Figure 1: Progression-free survival according the extramedullary disease status.