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Letter to Editor

Teclistamab in the Treatment of Multiple Myeloma: Latest Updates from the 2023 EHA Annual Meeting

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Abstract

As a promising novel immunotherapy modality, bispecific antibodies (BsAbs) are actively being evaluated in clinical trials for patients with hematological malignancies. Teclistamab is a T-cell-directed IgG4λ BsAb that recognizes B-Cell Maturation Antigen (BCMA) on target cells and CD3ε on T cells. As one of the promising BsAbs, teclistamab was granted orphan designations for the treatment of Multiple Myeloma (MM) in both the US and EU, the breakthrough-therapy designation for the treatment of relapsed/refractory (RRMM) by the FDA, and a Priority Medicines (PRIME) designation for the treatment of adult patients with MM who previously received ≥3 prior lines of therapy by the EMA. Recent evidence suggests that teclistamab exhibits promising efficacy and low toxicity for patients with Relapsed/Refractory Multiple Myeloma (RRMM), even at late stages. As a recently approved agent by both the FDA and the EU for adult patients with RRMM who previously received ≥3 prior lines of therapy, teclistamab is being investigated as monotherapy and in combination clinical studies in patients with MM. Here we provide an overview of the latest clinical data on teclistamab in MM presented at the 2023 European Hematology Association (EHA) annual meeting.

Keywords: Bispecific antibodies; Relapsed/refractory multiple myeloma; Teclistamab; Immunotherapy

Abbreviations: BCMA: B-Cell Maturation Antigen (BCMA); BsAbs: Bispecifc Antibodies; CD38mAb: Anti-CD38 Antibody (CD38mAb); CR: Complete Response; CRS: Cytokine Release Syndrome; IMiD: Immunomodulatory Drug; IRB: Institutional Review Board; LOT: Lines of Therapy (LOT); mDOR: Median Duration of Response (mDOR); mFU: Median Follow-up; MM: Multiple Myeloma (MM); mPFS: Median Progression Free Survival; NE: Not Estimable; ORR: Overall Response Rate; PI: Proteasome Inhibitor (PI); PRIME: Priority Medicines (PRIME); RP2R: Recommended Phase 2 Regimen; RRMM: Relapsed/Refractory Multiple Myeloma; RWPC: Real World Physician's Choice

To the Editor

Teclistamab is being investigated as monotherapy and combined with other agents in Relapsed/Refractory Multiple Myeloma (RRMM). Recent evidence shows promising efficacy and low toxicity for patients with RRMM. Teclistamab was granted Orphan Drug designations for the treatment of RRMM in both the US and the EU [1,2]. Since then, more clinical studies have been done. Here we provide an overview of the latest clinical data on teclistamab in MM presented at the 2023 EHA annual meeting.

Teclistamab Monotherapy

The long-term follow-up from the MajesTEC-1 study in 165 patients with RRMM who received ≥3 prior Lines of Therapy (LOT), including a Proteasome Inhibitor (PI), an Immunomodulatory drug (IMiD) and an anti-CD38 antibody (CD38mAb), was reported [3]. After 2-year Median Follow-up (mFU), patients receiving teclistamab demonstrated deep and durable responses regardless of refractory status, with a Median Progression-Free Survival (mPFS) of 12.5 months and a Median Duration of Response (mDOR) of 24 months (not reached in patients ≥ Com-

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Table 1: Teclistamab monotherapy for relapsed/refractory multiple myeloma.

EHA 2023 Abstract#	Phase	Setting	NCT	Number	Median number of prior LOT (range)	Number of treatment cycles	mFU (month)	CR%	ORR% or mORR	mDOR, month (range)	mPFS, month	CRS% (grade >3,%)
P879	I/II	≥3 prior LOT including a PI, an IMiD, and an anti-CD38 mAb.	NCT03145181, NCT04557098	165	5 (2–14):	switch to Q2W if ≥PR after ≥4 cycles of therapy in phase 1 or ≥CR for ≥6 months in phase 2	22	43%	mORR 21.9 mo (95% CI, 16.0–NE)	24 (95% CI, 16.2–NE)	12.5 (95% CI, 8.8–17.2)	72% (0.6%)
P881	I/II	≥3 prior LOT including a PI, an IMiD, and an anti-CD38 mAb.	NCT03145181, NCT04557098	165 (60 to Q2W)	4	switch to Q2W if ≥PR after ≥4 cycles of therapy in phase 1 or ≥CR for ≥6 months in phase 2	11.1	49% (82% in 60 pts to Q2W)	66% (100% in 60 pts to Q2W)	20.5 (1–23)	NA	29% (0.0%)
P911	I/II	≥3 prior LOT including a PI, an IMiD, and an anti-CD38 mAb.	NCT03145181, NCT04557098	14	4 (2–7)	subcutaneous tec (following 2 step-up doses) in a prospective exploratory cohort at the RP2D or in a fixed-dose cohort	1.2 mo (range 0.2–4.6).	NA	57% (4/7)	NA	NA	29% (0.0%)
P940	IIT	≥3 prior LOT and 3 pts prior BCMA CAR-T.	NA	9	≥3	Step-up doses were given on days 1, 3 and 8 at outpatient setting	NA	NA	NA	NA	NA	33.3% (0.0%)
P962	IRB approved trial	≥3 prior LOT including a PI, an IMiD, and an anti-CD38 mAb.	NA	26	8.5 (4-13)	Commercial Tec with standard step-up doses were given	2.1	NA	67% (12/18 pts)	NA	NA	44% (0.0%)

CD38mAb: Anti-CD38 Antibody; CR: Complete Response; CRS: Cytokine Release Syndrome; IRB: Institutional Review Board; IMiD: Immunomodulatory Drug; LOT: Lines of Therapy; mDOR: Median Duration of Response; mPFS: Median Progression Free Survival; NA: Not Available; NE: Not Estimable; ORR: Overall Response Rate; PI: Proteasome Inhibitor; Q2W: Bi-weekly; RP2D: Recommended Phase 2 Dose; Tec: Teclistamab

plete Response (CR). These data support teclistamab as a safe and effective off-the-shelf BCMA bispecific therapy for RRMM (Table 1). The DOR with biweekly dosing of teclistamab in 165 patients in the pivotal cohort who had received teclistamab at the recommended phase 2 dose showed that, 60/104 patients switched to Q2W dosing. At the time of switch, 49 (82%) patients achieved ≥CR, and 11 (18%) had a very good partial response. The median time to switch from QW to Q2W dosing was 11.1 months [4]. Prophylactic tocilizumab can reduce Cytokine Release Syndrome (CRS) risk in RRMM patients during teclistamab step-up dosing [5]. An outpatient model was reported as safe and feasible in RRMM patients with ≥3 lines or with prior BCMA CAR-T pre-treatment who received teclistamab step-up dosing on days 1, 3 and 8, with 6 hours' observation in the clinic after each step-up dose administration [6]. Another study of teclistamab treatment in 12 RRMM patients with prior anti-BCMA therapy revealed that teclistamab remains effective in RRMM despite prior exposure to anti-BCMA therapies, though exposure to multiple prior anti-BCMA therapies may be predictive of diminished efficacy [7]. Teclistamab had significantly improved patient-reported outcomes over the real world physician's choice of therapy in patients with triple-class exposed RRMM, with a positive impact on health-related quality of life in addition to significant efficacy benefits in RRMM patients [8]. In addition, teclistamab can reduce the levels of polyclonal immunoglobulins and impair the humoral immune response following vaccination. Intravenous immunoglobulin supplementation in patients with polyclonal IgG levels <4g/L should be used to prevent infections [9].

Teclistamab in Combination

Promising efficacy results from the phase 1B multicohort MajesTEC-2 study were reported. With teclistamab in combination with lenalidomide in previously treated MM patients who received ≥2 prior LOTs (median 4 prior LOT, range, 2–9) including a PI, IMiD, and CD38mAb, the results showed that among 31 patients who received teclistamab plus lenalidomide with a mFU of 9.9 months, the ORR was 74.2% (≥CR 35.5%) (Table 2) [10]. Furthermore, the results of teclistamab plus nirogacestat in RRMM who received ≥3 prior LOT or double refractory to PI and IMiD and triple exposed to PI, IMiD and CD38mAb, with progressive disease within 12 months of last LOT. The combination yielded response rates of 57–92% across the three dose levels assessed. This provides evidence on the combination of BCMA-directed therapies with a gamma secretase inhibitor [11].

The study with teclistamab plus talquetamab in RRMM or patients intolerant to the last LOT also revealed promising results. As a BCMA- and GPRC5D-bispecific-targeted strategy, teclistamab plus talquetamab at the Recommended Phase 2 Regimen (RP2R) has a manageable safety profile consistent with each of the monotherapies. A 92% ORR was observed in patients with advanced RRMM at the RP2R, and an ORR of 83% was achieved in high-risk patients with extramedullary disease, supporting further evaluation of the combination [12].

In conclusion, promising clinical trial interim results have demonstrated teclistamab as an effective novel immunotherapy for treating RRMM with a manageable safety profile, which supports the further investigation of teclistamab monotherapy

Table 2: Teclistamab combination for relapsed/refractory multiple myeloma.

EHA 2023 Abstract#	Phase	Setting	Combination Regimen (grouping)	Number	Median number of prior LOT (range)	Number of treatment cycles	mFU (month)	CR% or ≥VGPR (≥CR)	ORR% or mORR
P865	IB	≥2 prior LOT including a PI, IMiD, and CD38mAb.	Tec+ Len (0.72 mg/kg + 25 mg, n=12)	31	4 (2–9)	Until PD or unacceptable toxicity	9.9 (1.1–15.4)	35.50%	ORR 74.2%
			Tec+ Len (0.72 mg/kg + 25 mg, n=19)						
S190	IB	RR or intolerant to the last LOT; were exposed to a PI, IMiD, and CD38mAb; and had measurable disease.	Tec+Tal evaluation for safety and to identify a RP2R for the combination.	63	5 (1–11)	Until PD or unacceptable toxicity	14.4 (0.5–21.9).	34% (≥CR 31%)	84% (52/62)
S194	IB	≥3 prior LOT or were double refractory to PI and IMiD and triple exposed to PI, IMiD, and CD38mAb, with progressive disease within 12 months of last LOT.	Tec+Niro evaluation for safety and to identify a RP2R for the combination.	28	≥3 (NA)	9.4 mo (0.03–19.7) for tec and 4.7 mo (0.16–13.0) for niro	Total: 11.96 (0.5-19.7) Group 1: 19.3 (0.5-19.7)	Total VGPR: 77.8% (51.9%)	Total: 77.8% (21/28)
			Group 1: tec 720 µg/kg QW + concurrent niro (100 mg BID starting with first dose of tec; n=8);				Group 2: 15.3 (1.6-16.6)	Group 1: 71.4% (42.9%)	Group 1: 71.4% (5/8)
			Group 2: tec 720 µg/kg QW + QD delayed LD niro (100 mg QD starting after tec step-up dosing; n=7);				Group 3: 11.3 (4.3-14.2)	Group 2: 57.1% (57.1%)	Group 2: 57.1% (4/7)
			Group 3: tec 1500 µg/kg QW + QD delayed LD niro (n=13).					Group 3: 92.3% (53.8%)	Group 3: 92.3% (12/13)

BID: Twice Daily; CD38mAb: Anti-CD38 Antibody; CR: Complete Response; CRS: Cytokine Release Syndrome; IMiD: Immunomodulatory Drug; LD: Low-Dose; Len: Lenalidomide; LOT: Lines of Therapy; mDOR: Median Duration of Response; mPFS: Median Progression free Survival; n: number; NA: Not Available; Niro: Nirogacestat; ORR: Overall Response Rate; PI: Proteasome Inhibitor; QD: Once Daily; QW: Weekly; RP2R: Recommended Phase 2 Regimen; Tal: Talquetamab; Tec: Teclistamab; VGPR: Very Good Partial Response.

in earlier lines of treatment and in combination with other agents like lenalidomide and nirogacestat. More randomized, controlled, large-scale clinical trials are needed to further validate the efficacy.

Author Statements

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Author Contributions

JY designed the study. HS, XL and LH drafted the manuscript and prepared the tables. ZJ and YS provided resources. All authors participated in the process of drafting and revising the manuscript. All authors read and approved the final manuscript.

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Availability of Data and Material

The material supporting the conclusion of this study has been included within the article.

Competing Interests

All authors declare no conflict of interest.

Ethics Approval and Consent to Participate

This is not applicable for this summary.

Consent for Publication

This is not applicable for this summary.

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