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Exploratory Analysis to Identify Response-Related Biomarkers in the China Cohort of the Phase 1/2 MajesTEC-1 Trial of Teclistamab for Triple-Class Exposed Relapsed/Refractory Multiple Myeloma

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Key Takeaway

Findings from the MajesTEC-1 China cohort are comparable with those observed in the pivotal RP2D population and further support the efficacy, MOA, and identification of potential biomarkers associated with response to teclistamab treatment

Conclusions

Patients in the China cohort of MajesTEC-1 demonstrated rapid, deep, and durable responses to teclistamab

PD changes, including peripheral T-cell activation and cytokine induction, were consistent with the MOA of teclistamab

Responders to teclistamab had higher baseline levels of T cells, lower baseline levels of TNF-α, IL-8, and sBCMA, and showed a trend toward greater induction of T-cell activation and cytokines vs nonresponders

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Poster

Supplementary material

https://www.congresshub.com/Oncology/EHA2024/Teclistamab/Xu

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Acknowledgments

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Disclosures

HX is employed by and may own stock in Janssen.

Introduction

- Teclistamab is the first approved B-cell maturation antigen (BCMA) × CD3 bispecific antibody (BsAb) for the treatment of triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM), with weight-based dosing and the longest study follow-up of any BsAb in multiple myeloma[1]
- In the pivotal phase 1/2 MajesTEC-1 study, rapid, deep, and durable responses were observed in patients treated with teclistamab over a median follow-up of 30.4 months[2-4]
- In the phase 2 portion of the study, the China cohort was added to evaluate the efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of teclistamab at the recommended phase 2 dose (RP2D) in Chinese patients with RRMM
- Here, we describe an exploratory analysis to identify response-related biomarkers in the China cohort of MajesTEC-1

Methods

Patients

- Patients in the China cohort had RRMM and received ≥3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody
- Patients were treated with teclistamab at the RP2D (1.5 mg/kg, subcutaneously, weekly), preceded by step-up dosing, and they could switch to teclistamab every-other-week dosing if they achieved complete response (CR) or better for ≥6 months

Endpoints and assessments

- The primary endpoint was overall response rate (ORR) per International Myeloma Working Group criteria,[5] as assessed by an independent review committee (IRC)
- Key secondary endpoints included CR rate, very good partial response (VGPR) rate, minimal residual disease (MRD) negativity rate at 10^{-5} as detected by next generation flow cytometry, duration of response (DOR), progression-free survival (PFS), overall survival (OS), PK, and PD
- Whole blood and bone marrow samples were collected to evaluate immune cell populations by flow cytometry and cytogenetics by fluorescence in situ hybridization (FISH), respectively
- Serum samples were used to analyze cytokines and soluble BCMA (sBCMA) by the Meso-Scale Discovery assay and the electrochemiluminescence immunoassay, respectively
- The following statistical tests were performed: nonparametric Wilcoxon test for responders vs nonresponders comparisons, hierarchical clustering for unsupervised clustering analysis, and Kaplan-Meier analysis with log-rank test for PFS analysis
- All patients provided informed consent

Results

Baseline characteristics

- As of the clinical cut-off (Sept 27, 2023), 26 patients had received teclistamab at the RP2D (**Table**)

Table: Baseline characteristics

Characteristic	China cohort (N=26)
Age (years), median (range)	66.0 (42–84)
Age category, n (%)	
<65 years	12 (46.2)
65 to <75 years	12 (46.2)
≥75 years	2 (7.7)
Female, n (%)	19 (73.1)
Race, n (%)	
Asian	26 (100.0)
Bone marrow plasma cells ≥60%, n (%)	4 (15.4)
≥1 extramedullary plasmacytoma, n (%)	9 (34.6)
High-risk cytogenetics, n (%)[a]	15 (57.7)
ISS stage, n (%)	
I	9 (34.6)
II	10 (38.5)
III	7 (26.9)
Time since diagnosis (years), median (range)	4.9 (1.3–11.3)
Prior lines of therapy, median (range)	5 (3–11)
Prior stem cell transplantation, n (%)	3 (11.5)
Exposure status, n (%)	
Triple-class	26 (100.0)
Penta-drug	14 (53.8)
Refractory status, n (%)	
Triple-class	16 (61.5)
Penta-drug	3 (11.5)
To last line of therapy	23 (88.5)

[a]High-risk cytogenetics: pts who are positive for any of del(17p), t(14;16), or t(4;14) by FISH.
ISS, International Staging System.

Efficacy[6]

- ORR was 76.9% (≥CR, 57.7%) (**Supplemental Figure 1**)
- Median DOR and PFS were not reached (**Supplemental Figure 2A, 2B**)
- Median time to first response was 1.4 months (range, 1.1–5.5)
- The probability of remaining in response at 12 months was 78.5%
- 12-month PFS and OS rates were 68.0% and 83.5%, respectively
- 90% of patients with MRD samples available (18/20) were MRD negative

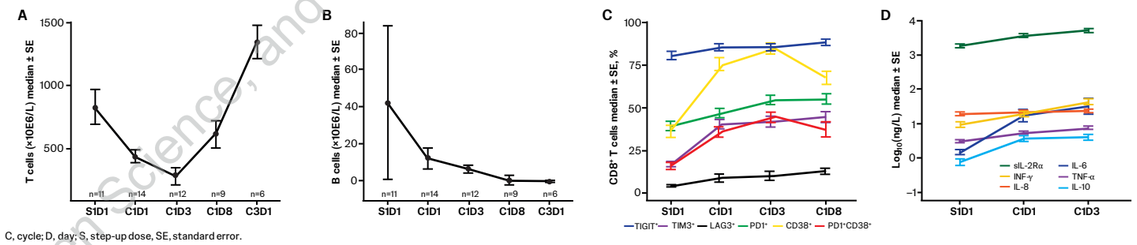
Pharmacodynamics

- PD changes in the periphery, including T-cell redistribution (**Figure 1A**), B-cell reduction (**Figure 1B**), T-cell activation (**Figure 1C**), and cytokine induction (**Figure 1D**), were observed during the first treatment cycles, consistent with the known MOA of teclistamab

Biomarkers: Baseline prediction of response

- Responders had higher baseline levels of CD4+ T cells (584.0 vs 259.0 × 10^6/L; P=0.003) than nonresponders (**Figure 2A**) but a lower trend of baseline CD45RA- regulatory T cells than nonresponders (P=0.075)

Figure 1: PD changes in the periphery observed during early treatment cycles, consistent with known MOA of teclistamab: (A) T-cell redistribution; (B) B-cell reduction; (C) T-cell activation; (D) cytokine induction



C, cycle; D, day; S, step-up dose, SE, standard error.

Biomarkers: Baseline prediction of response (continued)

- Clustering of baseline serum cytokine profiles suggested response was associated with lower cytokine levels (**Supplemental Figure 3**), specifically lower tumor necrosis factor-alpha (TNF-α) (2.79 vs 5.28 ng/L; P=0.007) (**Figure 2B**) and IL-8 (17.2 vs 32.6 ng/L; P=0.019) (**Figure 2C**)
- Baseline serum sBCMA was higher in nonresponders vs responders (median [min, max]: 321 [79.6, 1050.0] µg/L vs 75.8 [4.9, 358.0]; P=0.013) (**Supplemental Figure 4A**), and baseline sBCMA was higher in patients with more advanced disease and greater tumor burden (**Supplemental Figure 4B**, **4C**)

Longitudinal association

- Responders showed a trend toward greater induction of T-cell activation markers (eg, CD38, PD-1; **Figure 3**)
- Induction of cytokines was higher in responders vs nonresponders for soluble IL-2Rα (sIL-2R α) (1.74 vs 0.61 $\log_2$ max fold change over baseline, P=0.023; **Figure 4A**) and IL-10 (2.38 vs 1.17 $\log_2$ max fold change over baseline, P=0.023; **Figure 4B**)
- Similarly, longer PFS was also associated with greater induction of sIL-2Rα (P=0.021; **Figure 4C**) and IL-10 (P=0.00052; **Figure 4D**) using the median as the cut-off

Figure 2: Responders had higher baseline levels of (A) CD4+ T cells and also showed lower cytokine levels of (B) TNF-α and (C) IL-8 than nonresponders

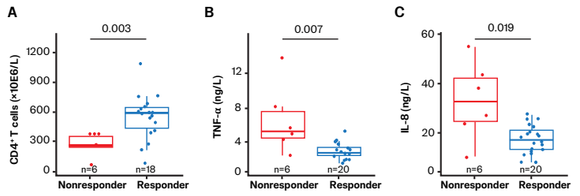


Figure 3: A trend for greater induction of key T-activation markers was observed in responders vs nonresponders

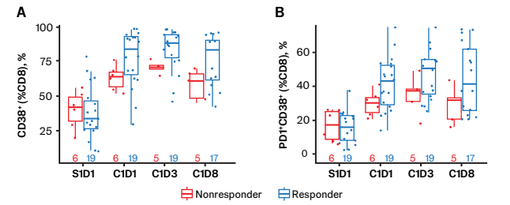
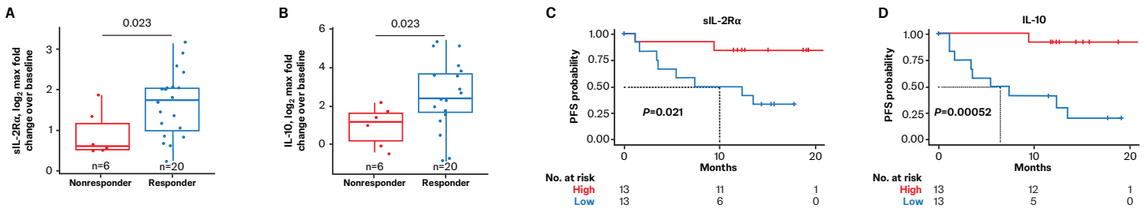


Figure 4: Greater induction of (A) sIL-2Rα and (B) IL-10 were observed for responders; longer PFS was associated with higher induction of (C) sIL-2Rα and (D) IL-10



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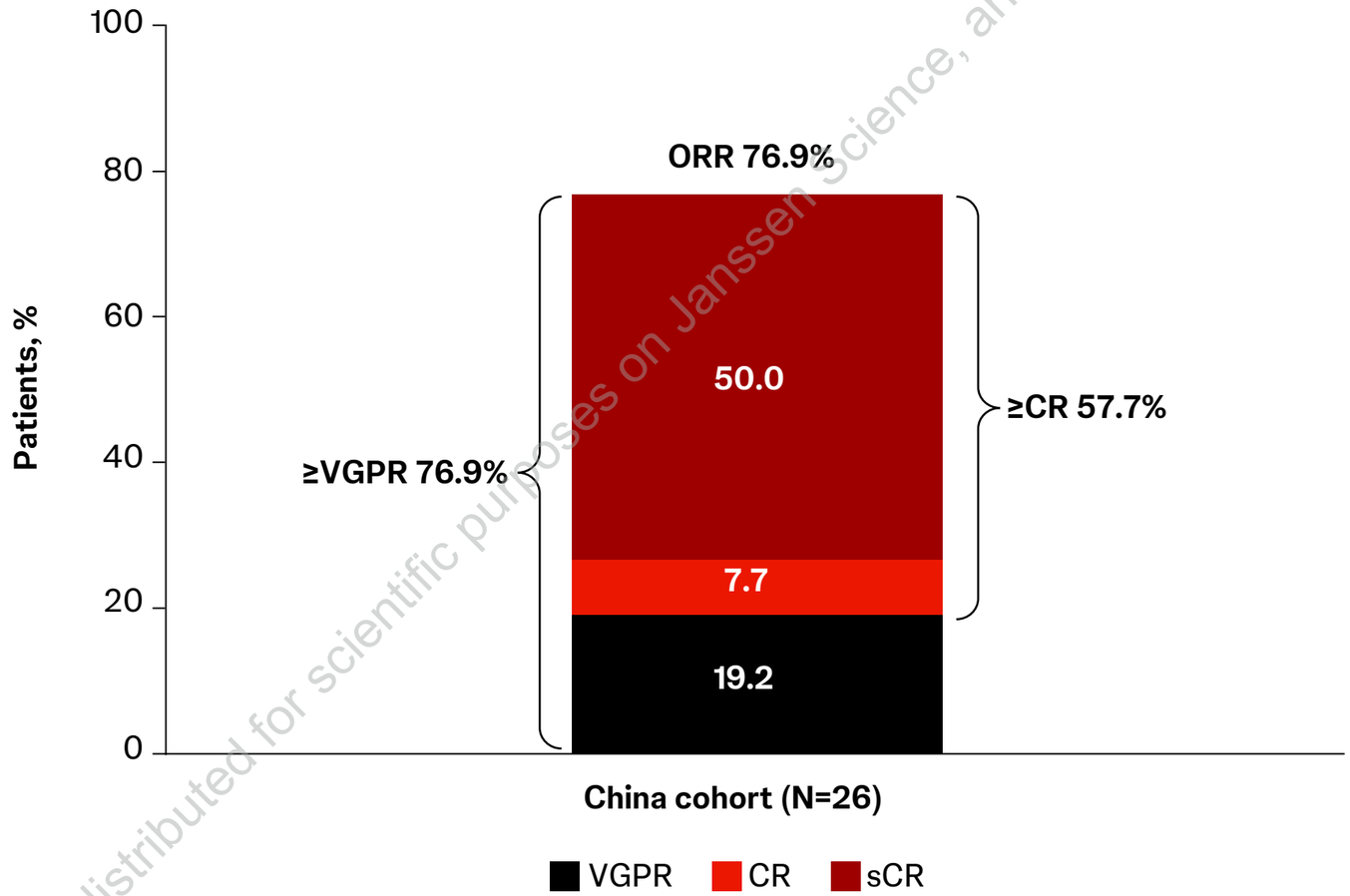
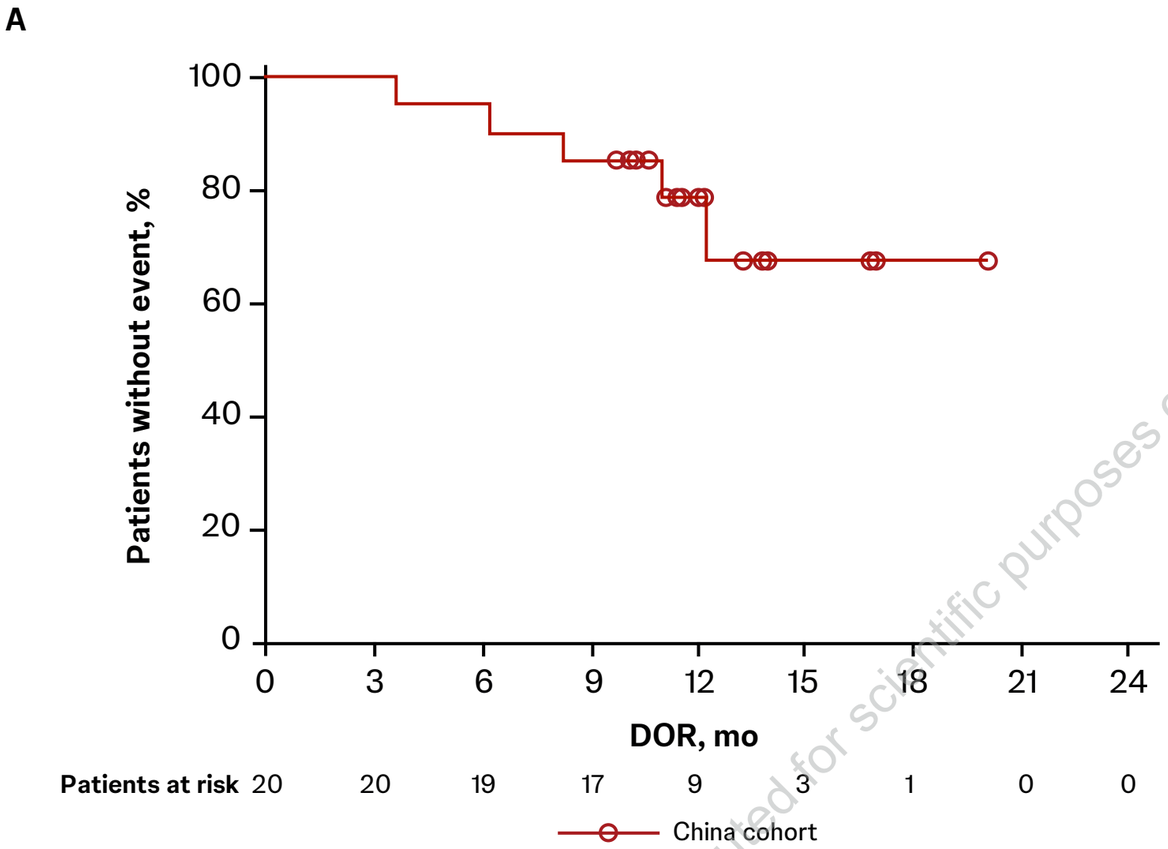
Multiple Myeloma

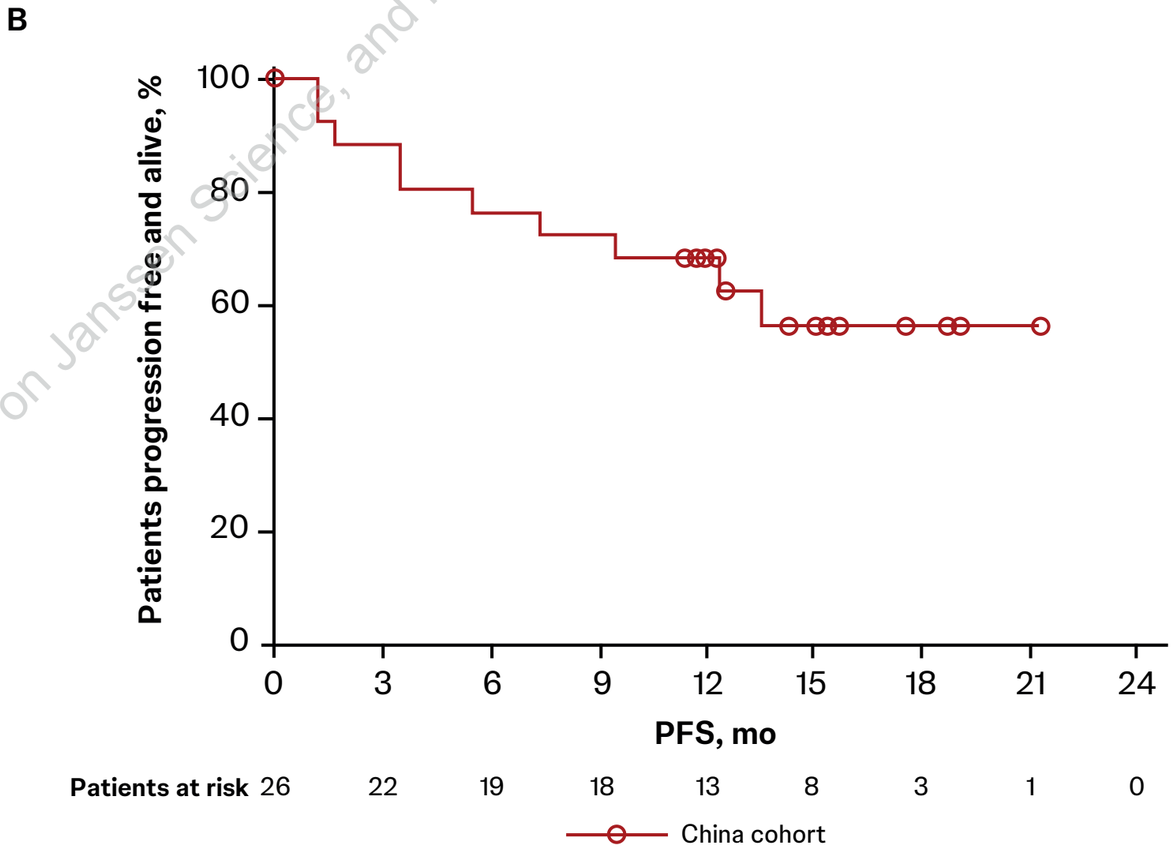
Supplemental Figure 1: Overall Response Rate Based on IRC Assessment; All Treated Analysis Set



Response and progression were assessed by IRC, based on IMWG consensus criteria (2016).
CR, complete response; IMWG, International Myeloma Working Group; IRC, independent review committee; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

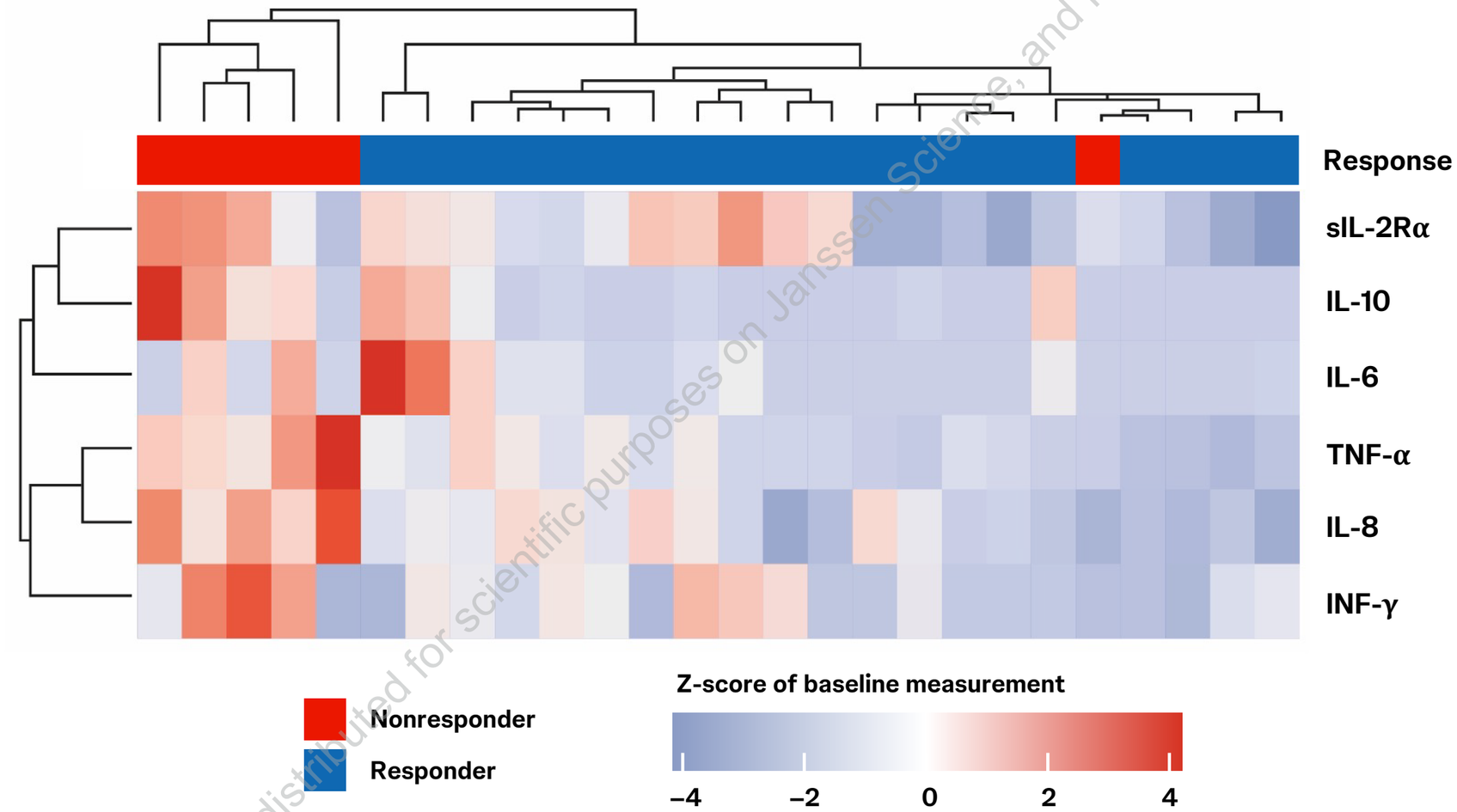
Supplemental Figure 2: Kaplan-Meier Plot for (A) DOR and (B) PFS Based on IRC Assessment; All Treated Analysis Set





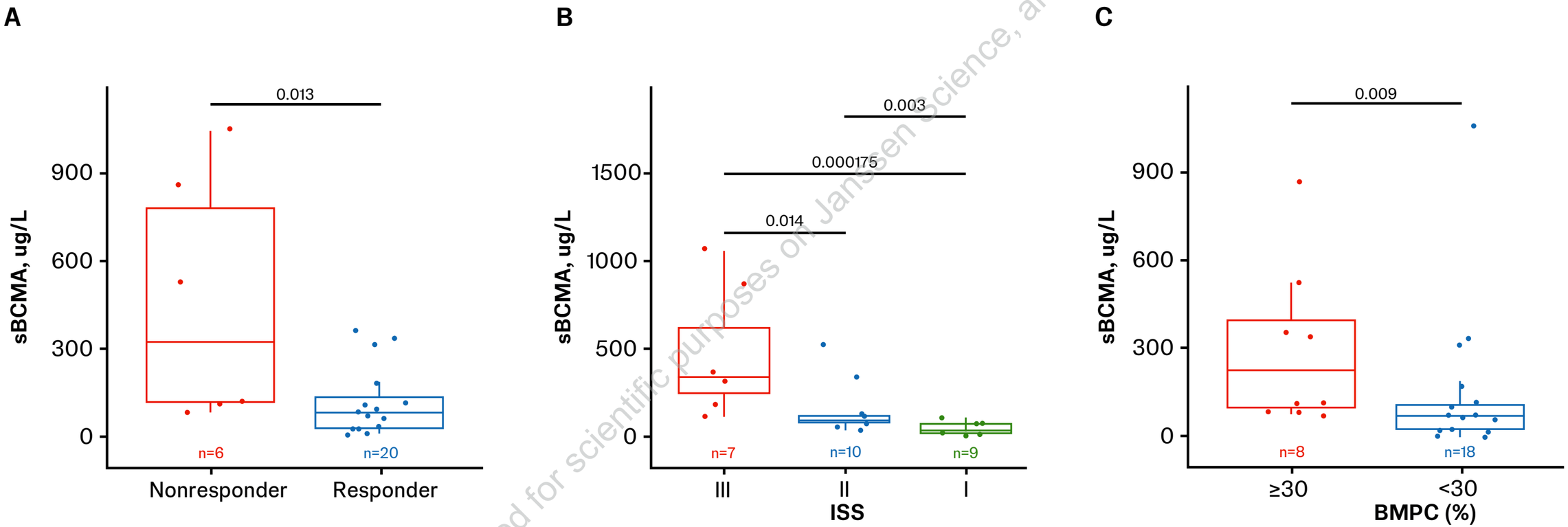
Response and progression were assessed by IRC, based on IMWG consensus criteria (2016).
DOR, duration of response; IMWG, International Myeloma Working Group; IRC, independent review committee; PFS, progression-free survival.

Supplemental Figure 3: Unsupervised Hierarchical Clustering of Baseline Serum Cytokine Profile



Response and progression were assessed by IRC, based on IMWG consensus criteria (2016).
IFN, interferon; IL, interleukin; IMWG, international Myeloma Working Group; IRC, independent review committee; TNF, tumor necrosis factor.

Supplemental Figure 4: Baseline Serum sBCMA by (A) Clinical Response per IRC Assessment, (B) ISS Stage, and (C) BMPC



Response and progression were assessed by IRC, based on IMWG consensus criteria (2016).
BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cell; IMWG, international Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; sBCMA, soluble BCMA.