An Actionability Score for BCMA-, GPRC5D-, and CD38-targeted therapy selection in multiple myeloma

BostonGene

Abstract MM-442

Konstantin Chernyshov, Stanislav Kurpe, Maria Kuzmicheva, Kseniia Fede, Sargis Margaryan, Daria Goncharova, Anastasiya Evdokimova, Dmitrii Grachev, Oleg Baranov, Polina Turova, Alexander Nesmelov, Andrey Kravets, Eduardo Shugaev-Mendosa, Nikita Kotlov

BostonGene Corporation, Waltham, MA

Introduction / Background

In multiple myeloma (MM), the absence of predictive biomarkers forces clinical teams to select CAR-T and T-cell engager (TCE) therapies based solely on prior lines of treatment. This lack of precision leaves clinical development vulnerable to diluted efficacy, unoptimized trial cohorts, and critical guesswork in selecting both target (e.g., BCMA vs. GPRC5D) and therapeutic modality (e.g., CAR-T vs. TCE). To solve this bottleneck, we developed an NGS-based Actionability Score (AS) framework that integrates malignant plasma cell dynamics and tumor microenvironment (TME) features.

Methods

Thorough literature review and analysis of publicly accessible MM cohorts, including bulk RNA-seq (n = 715, n = 290) and scRNA-seq (n = 6, n = 5) cases, were used to develop the AS framework for anti-BCMA CAR-T and TCE, anti-GPRC5D TCE, and anti-CD38 monoclonal antibodies (mAb). The AS represents a normalized (0 to 1), weighted score integrating the expression of related target genes (TNFRSF17, GPRC5D, CD38), resistance factors (STAT3, γ-secretase), immune modulators (CD274 / PD-L1, CD55, CD59, ICAM1) and relevant TME signatures (e.g., T-cell exhaustion, T-reg fraction). (**Fig. 1**).

MM — multiple myeloma,
TCE — T-cell engager,
AS — Actionability Score.

References

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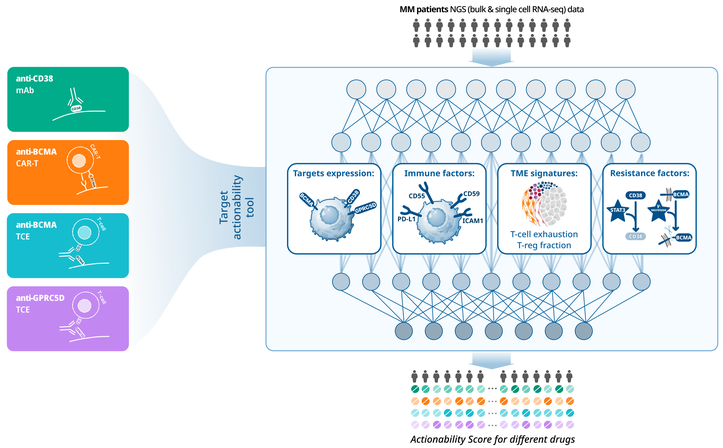
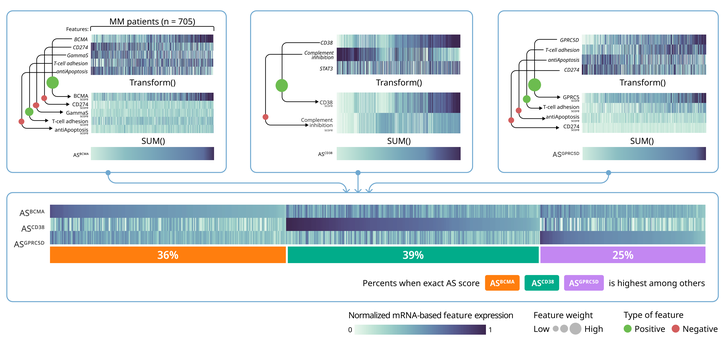
Results

Figure 1. Workflow of Actionability Score prediction for MM patients



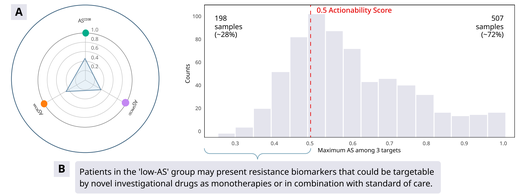
The "Actionability Score" predicts the suitability of selecting specific therapy drugs for MM patients using NGS data, considering factors like target expression, immune factors, tumor microenvironment (TME) signatures, and resistance factors.

Figure 2. Distribution of high "Actionability Score" for target-specific therapies in MM patient cohort



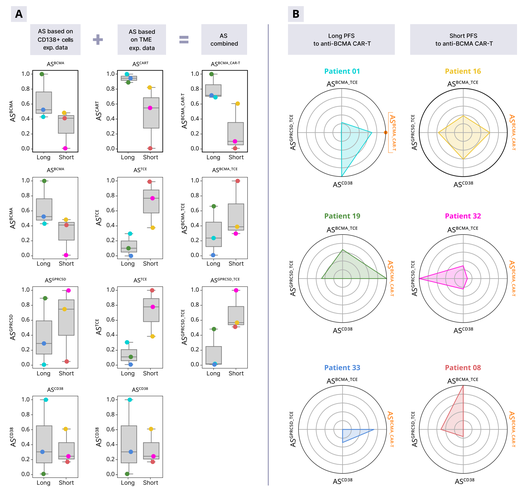
This framework was demonstrated using MM CoMMpass gene expression data from 705 patients. For each drug, related mRNA expression based features were selected, transformed based on their supposed contribution to drug efficacy, and summed to create a normalized Actionability Score. Feature weight is shown by the number of circles, and the input's sign (positive/negative) by the colors (green/red). The top plots show patients sorted by AS for anti-BCMA, anti-CD38, and anti-GPRC5D, while the bottom section shows patients sorted by percentage of maximum AS among those 3 targets.

Figure 3. Identifying actionable pathways linked to resistance for 'low-AS' group



A. Distribution of the "Maximum Actionability Score among 3 targets", denoting each patient's highest score among the 3 therapies, shows that some patients did not achieve a AS greater than 0.5 for any drug. **B.** Potential solutions are presented for patients whose AS is below 0.5 across all drugs.

Figure 4. Actionability Score prediction accurately stratified anti-BCMA CAR-T treated patients with long / short PFS



A. Boxplots comparing scores for 'long' and 'short' PFS patients treated with anti-BCMA CAR-T therapy. For each of anti-BCMA CAR-T and TCE, anti-GPRC5D TCE, and anti-CD38 therapy, components of the final combined Actionability Score are shown; these consist of the addition of AS score derived from CD138+ sorted cells (pure tumor cells) and the score derived from unsorted cells (mostly TME). Together, combined AS better stratifies patients, considering both tumor and TME features. **B.** Spyderplots show calculated Actionability Score per patient, indicating the predicted most preferable therapy.

Results

We observed heterogeneous profiles in MM (CoMMpass), reflecting potential treatment benefit (**Fig. 2**):

- 36% of patients (pts) had high $AS^{BCMA\text{-}CAR\text{-}T/TCE}$
- 39% had high $AS^{CD38\text{-}mAb}$
- 25% had high $AS^{GPRC5D\text{-}TCE}$

Notably, 28% of pts had a low AS (< 0.5) for all tested immunotherapies (**Fig. 3A**).

Within this 'low-AS' group, our approach identified other actionable pathways potentially linked to treatment resistance (e.g., 2% high γ-secretase, 3% high STAT3), highlighting alternative intervention opportunities (**Fig. 3B**).

To illustrate the predictive utility our approach, we applied it to anti-BCMA CAR-T-treated pts (GSE210079) (**Fig. 4**). All three pts with high $AS^{BCMA\text{-}CAR\text{-}T}$ (> 0.6) had long PFS (> 6 months). For pts with short PFS (< 6 months) on CAR-T treatment, AS highlighted the possibility for alternative therapies:

- pt 8 ($AS^{BCMA\text{-}TCE}$ = 1.0)
- pt 32 ($AS^{GPRC5D\text{-}TCE}$ = 1.0)
- pt 16 ($AS^{CD38\text{-}mAb}$ = 0.61)

These data suggest that higher baseline $AS^{BCMA\text{-}CAR\text{-}T}$ may be associated with prolonged PFS in pts receiving anti-BCMA CAR-T.

Conclusions

By mapping tumor target expression and TME resistance factors, the AS enables precise, biomarker-driven patient selection in MM. Beyond basic stratification, it proactively pre-identifies likely CAR-T and TCE responders, predicts durable PFS, and flag high-risk non-responders requiring alternative combination regimens. This framework equips biopharma and clinical teams to de-risk development pipelines, optimize trial enrichment, and confidently guide target-modality selection and therapeutic sequencing to maximize clinical efficacy.

Contact: Alexander Bagaev
aleksander.bagaev@bostongene.com