Abstract: S186

Title: ACQUIRED RESISTANCE TO BISPECIFIC ANTIBODIES BY GENETIC OR EPIGENETIC INACTIVATION OF THE TARGET IN MULTIPLE MYELOMA

Abstract Type: Oral Presentation

Session Title: MM biology & translational

Background:

Bispecific antibodies (BsAb) are monoclonal antibodies that redirect T cells by targeting both the T cell co-receptor CD3 and markers expressed on the surface of tumor cells. BsAb targeting BCMA (teclistamab) or GPRC5D (talquetamab) demonstrated promising efficacy in relapsed or refractory multiple myeloma (RRMM) in recent phase 1-2 studies. However, ~30% of patients did not respond, and half of the responders experienced disease progression within 12 months. Thus, it is crucial to understand the mechanisms of innate and acquired resistance to BsAb.

Aims:

Here, we explore the mechanisms of acquired BsAb resistance in two RRMM patients enrolled in phase 1 talquetamab trials.

Methods:

We conducted a multi-omic characterization of myeloma cells, before talquetamab treatment (t1) and after relapse (t2), by whole genome sequencing (WGS) and single-cell Multiome allowing simultaneous profiling of gene expression (RNA-seq) and open chromatin (ATAC-seq) from the same cells.

Results:

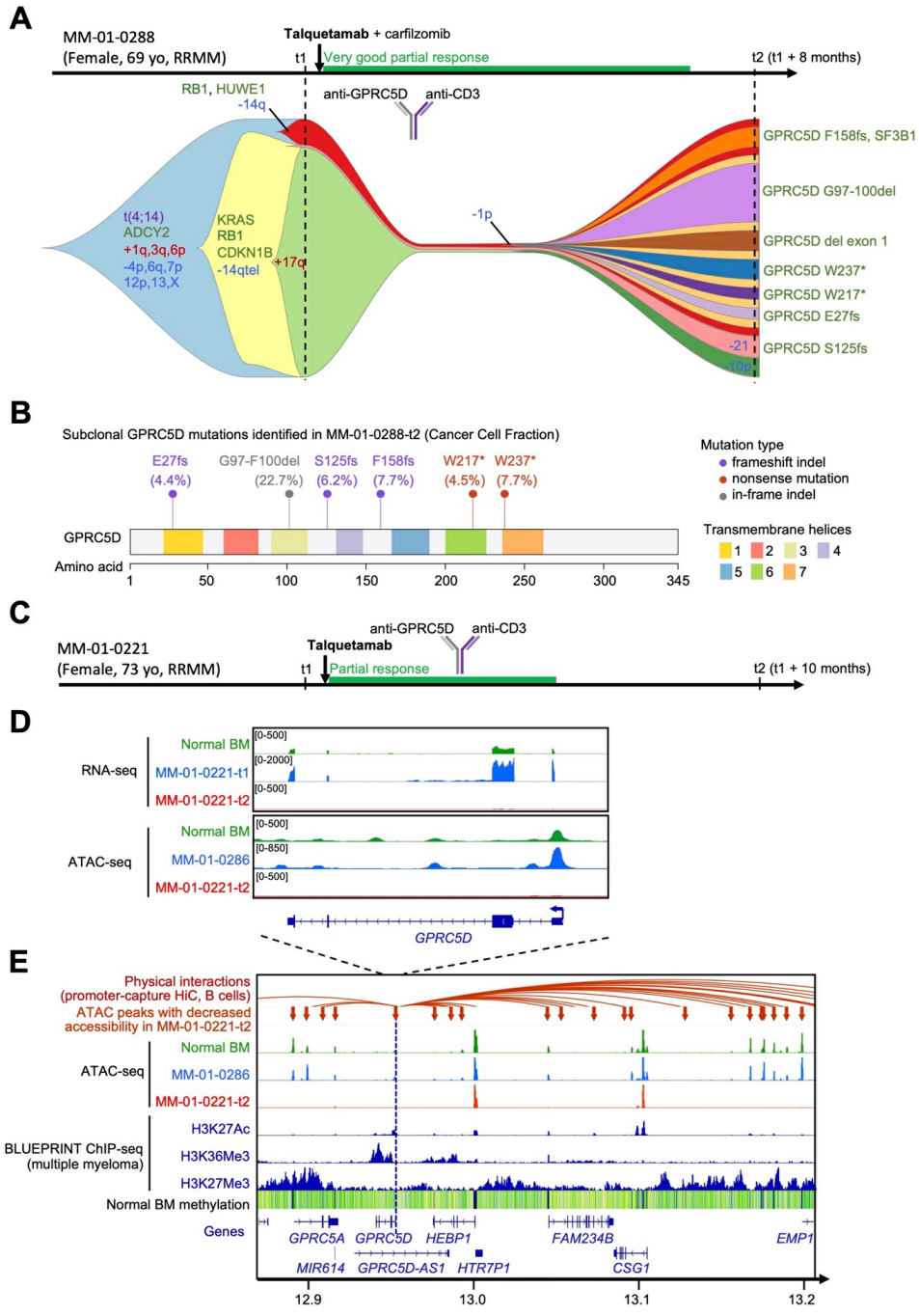
MM-01-0288 was a female patient diagnosed with immunoglobulin G (IgG) myeloma at 64 yo. After 4 previous therapy lines, she received talquetamab in combination with carfilzomib, and achieved very good partial reponse for 6 months before relapse. WGS at t1 revealed clonal t(4;14), 1q gain, 13q loss and a focal deletion at 12p encompassing *GPRC5D* locus, so that a single copy of the BsAb target remained in tumor cells. Other driver alterations included *KRAS* G12R mutation and bi-allelic *RB1* and *CDKN1B* inactivation (**Fig. 1A**). Substantial genetic evolution was observed at t2, including the emergence of 7 resistant subclones harboring damaging *GPRC5D* alterations: 3 frameshift indels (E27fs, S125fs, F158fs), 2 nonsense mutations (W217*, W237*), an in-frame deletion of 4 amino acids (G97-F100), and a 10 kb deletion encompassing the transcription start site (**Fig. 1B**). Thus, talquetamab resistance in this patient with a pre-existing 12p deletion involved the independent acquisition of second hits in *GPRC5D* by several subclones, leading to the bi-allelic inactivation of the target.

MM-01-0221 was a female patient diagnosed with light chain myeloma at 67 yo. After 5 therapy lines in 6.5 years, she received talquetamab and achieved partial response for 5 months before relapse (**Fig. 1C**). WGS revealed a clonal t(11;14) and bi-allelic *TP53* inactivation, but no alteration of *GPRC5D* locus in the relapse. By contrast, RNA-seq revealed a sharp decrease of *GPRC5D* expression between t1 (210 transcripts per million, tpm) and t2 (1.3 tpm, fold-change=0.0062, **Fig. 1D**). In absence of genetic insult, we examined the chromatin landscape at *GPRC5D* locus. We identified the loss of 70 chromatin accessibility peaks in an extended 1.3 Mb region, including *GPRC5D* promoter, 4 referenced enhancers and 21 other peaks found to interact with *GPRC5D* promoter in conformational Hi-C data (**Fig. 1E**). Thus, acquired talquetamab resistance in this patient involved long-range epigenetic silencing of *GPRC5D* locus, with coordinated chromatin silencing of its promoter and enhancer regions.

Summary/Conclusion:

In conclusion, we report two mechanisms of acquired talquetamab resistance resulting from genetic or epigenetic inactivation of the target. Pre-existing chromosome 12p deletion may favor the emergence of resistant subclones

with inactivation of the second *GPRC5D* allele, mirroring previous results on BCMA CAR-T resistance. We anticipate that a thorough monitoring of the genetic and epigenetic status of the targets will help guiding the choice of BsAb and early detection of resistance in MM.



Keywords: Drug resistance, Genomics, Multiple myeloma, Immunotherapy