



POST IMS 2024: BIOLOGIST VIEW

KEY ADVANCES ON THE IMMUNE SYSTEM IN MYELOMA

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# Immune changes upon MM evolution: What's new

Irene Ghobrial

Romanos SklavenitisPistofidis :

OA – 42: Single-cell RNA-sequencing of 6 million tumor and immune cells in patients with plasma cell premalignancy unveils co-regulation of disease progression by tumor biology and immune dysregulation



## The largest scRNA-seq cohort of MM & precursor conditions



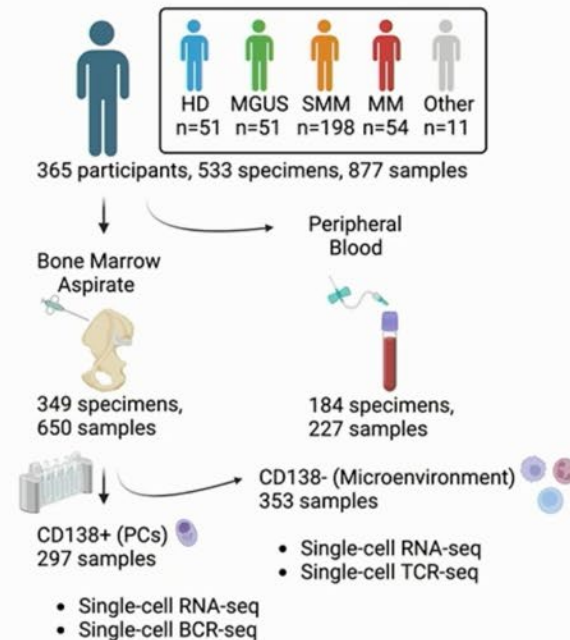
Liz Lightbody, PhD



Yoshinobu Konishi, MD, PhD



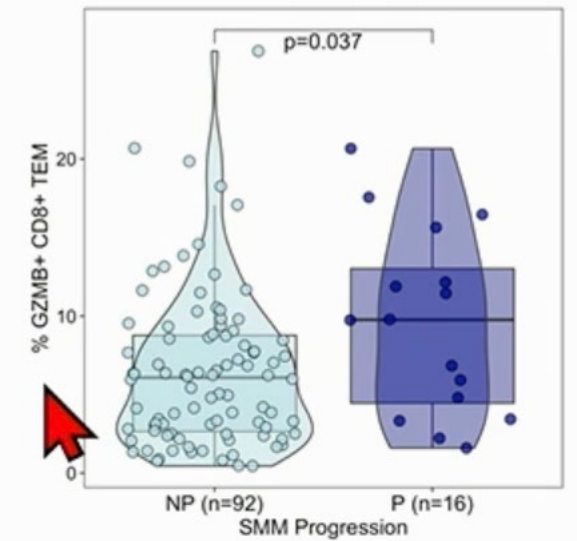
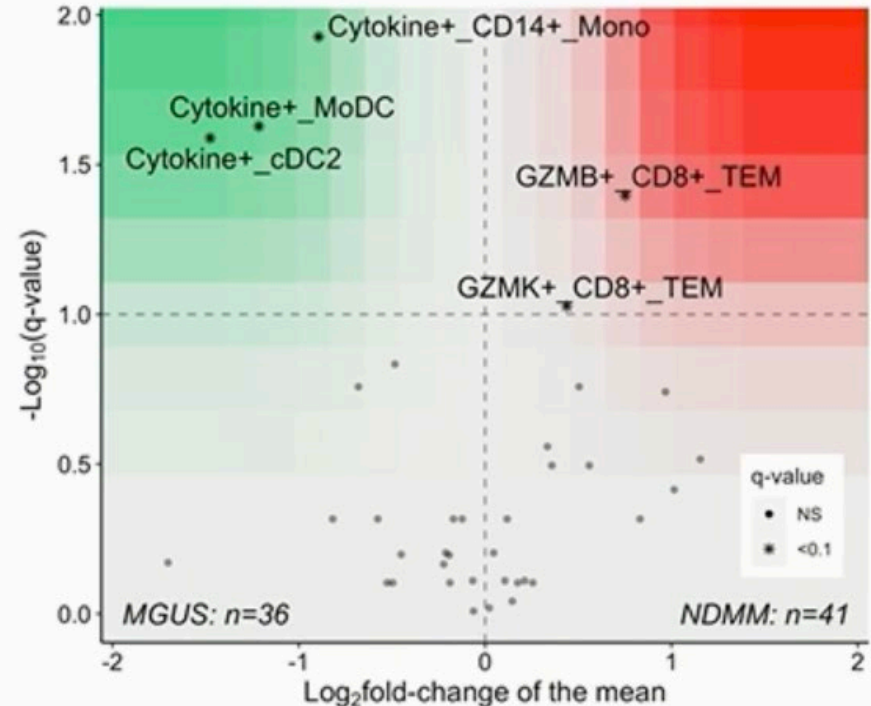
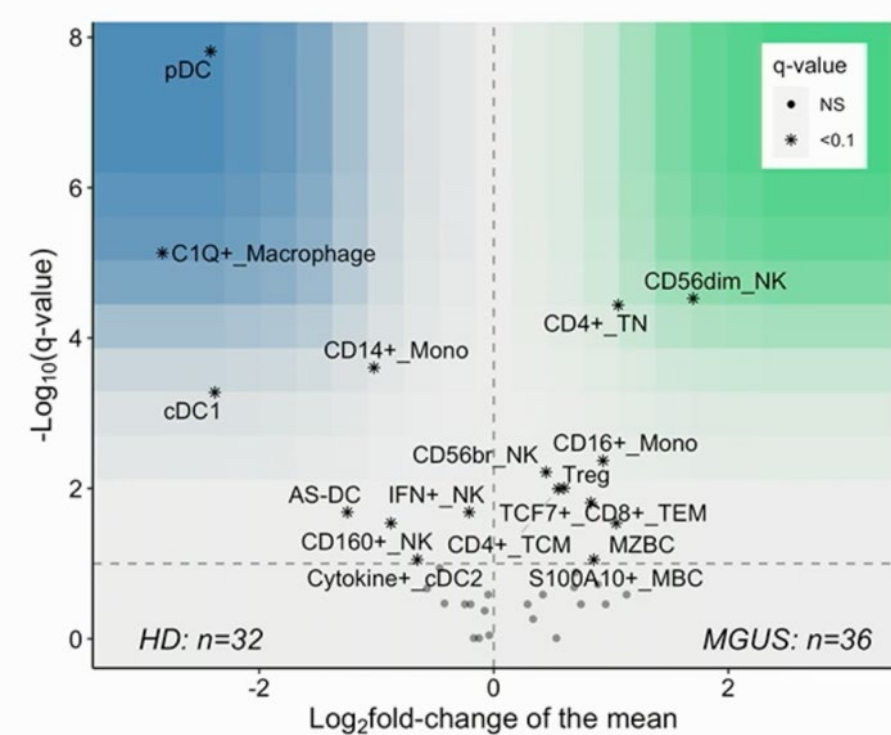
Ting Wu, MSc



~6 million tumor and immune cells

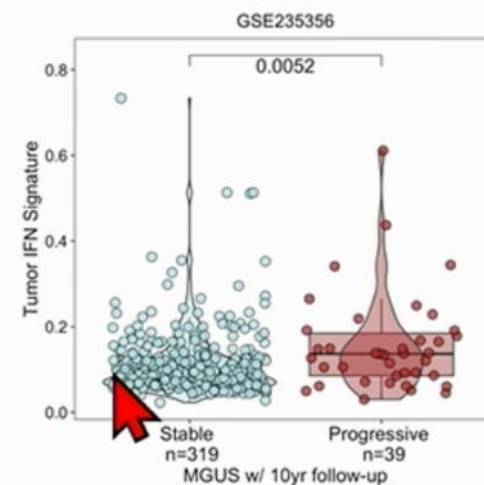
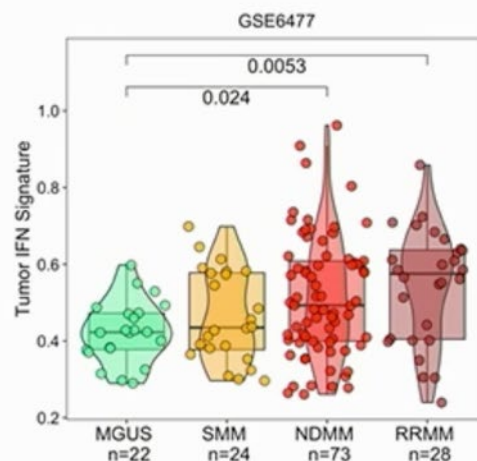
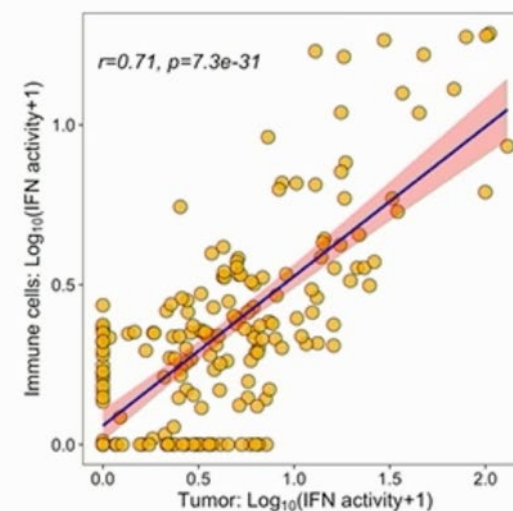
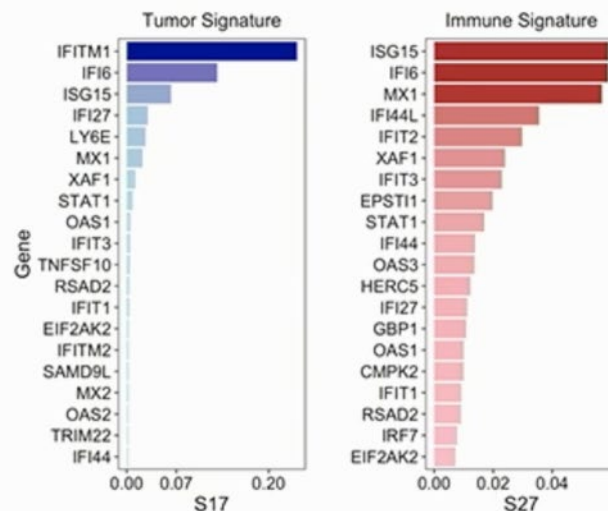
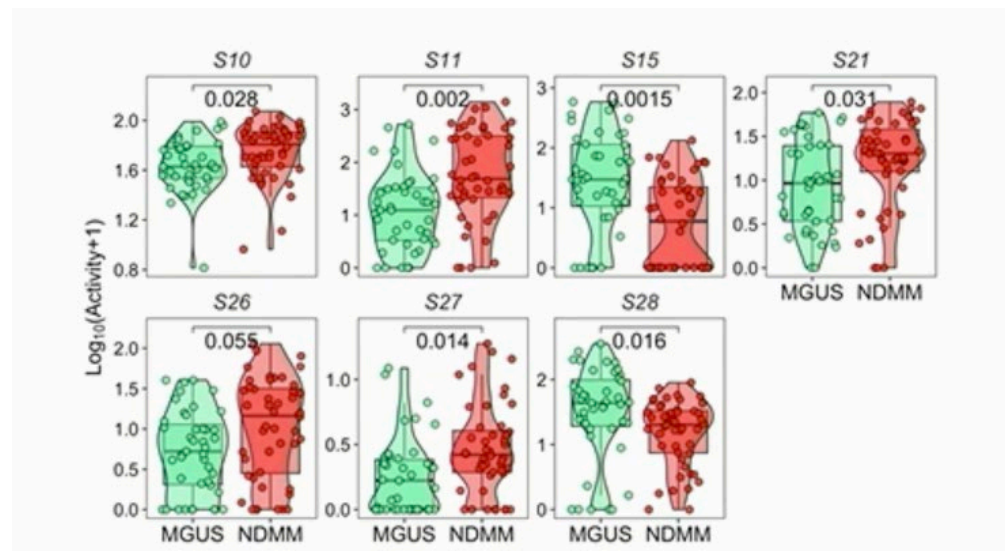
- 877 tumor and immune samples from 533 BM and PB specimens, collected from 365 participants, including MGUS (n=51), SMM (n=198), MM (n=54), and HD (n=51).
- 241 individuals had both CD138pos (tumor) and CD138neg (immune) fractions sequenced to enable integrative analyses of tumor and immune biology.
- 5' Single-cell RNA-seq & BCR-seq was performed on CD138pos cells; RNA & TCR-seq was performed on CD138neg cells.

# Immune changes upon MM evolution



- Patients with NDMM showed significantly higher proportion of GZMB+ CD8+ TEMs and lower proportion of Cytokine+ myeloid cells.
- These changes were independent of chronological age, which is typically higher in pts w/ NDMM.
- These changes were disease associated.

# IFN signaling associate with progression

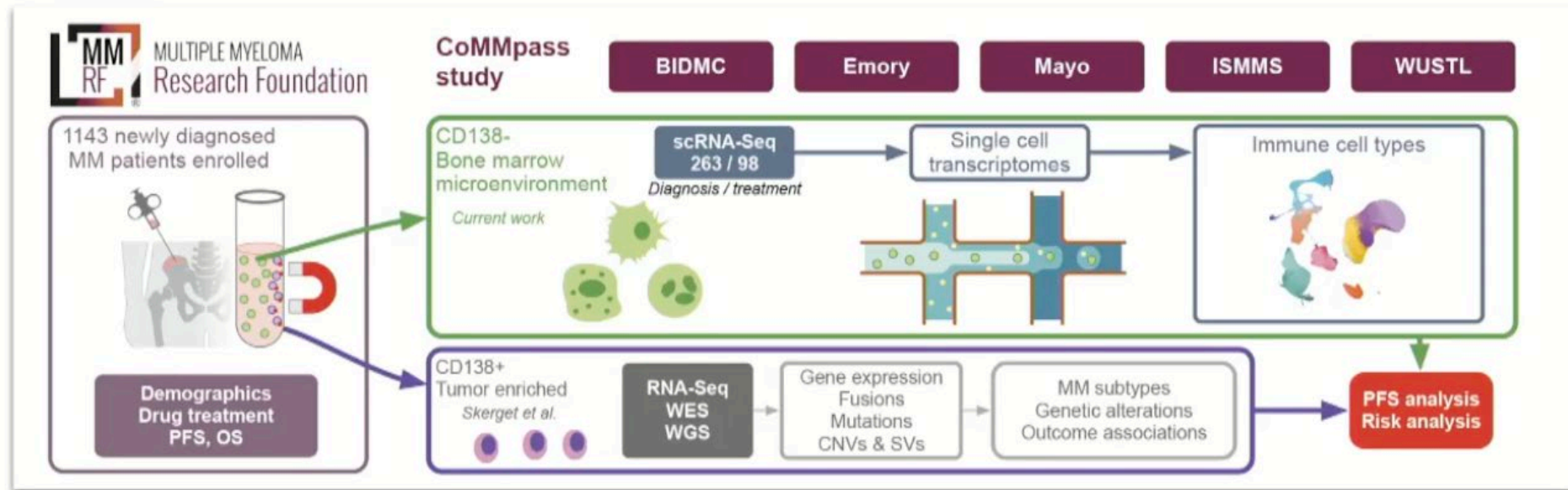


# Immune landscape of NDMM: MMRF Compass study

Chaitanya Acharya :

<https://www.biorxiv.org/content/10.1101/2024.05.15.593193v1.full.pdf>

## The Immune Atlas of NDMM from CoMMpass



**Tumor intrinsic features and host immune microenvironment and their collective influence on patient outcomes**

# Immune landscape of myeloma: MMRF Compass study

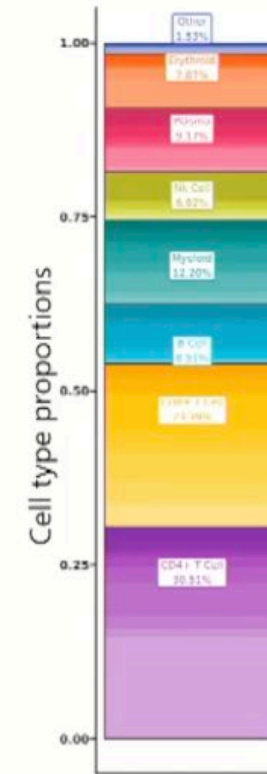
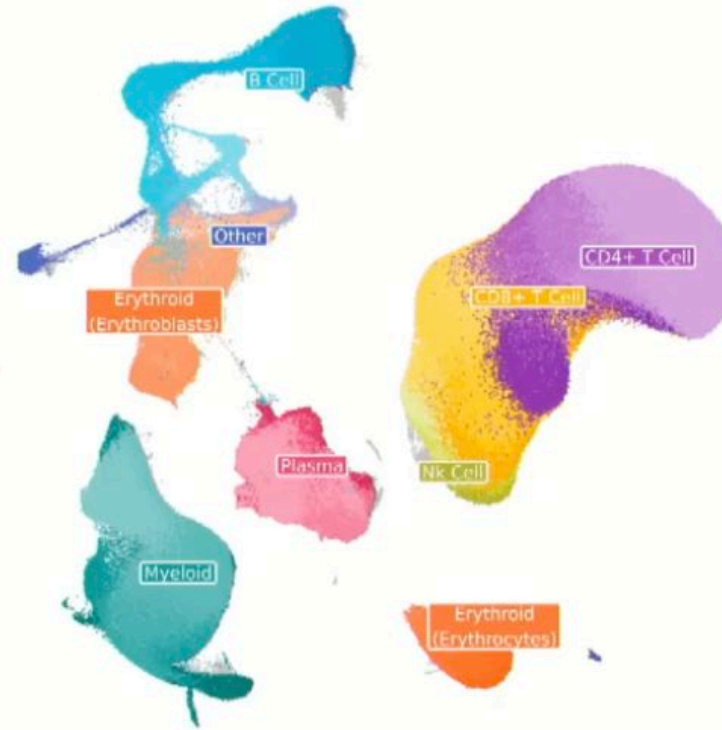
## The Immune Atlas of NDMM

263 NDMM patients at baseline

>1 million cells

>100 clusters

Several major cell compartments



Dimitra Karagouni  
BIDMC



Lijun Yao  
Washington Univ  
at St Louis



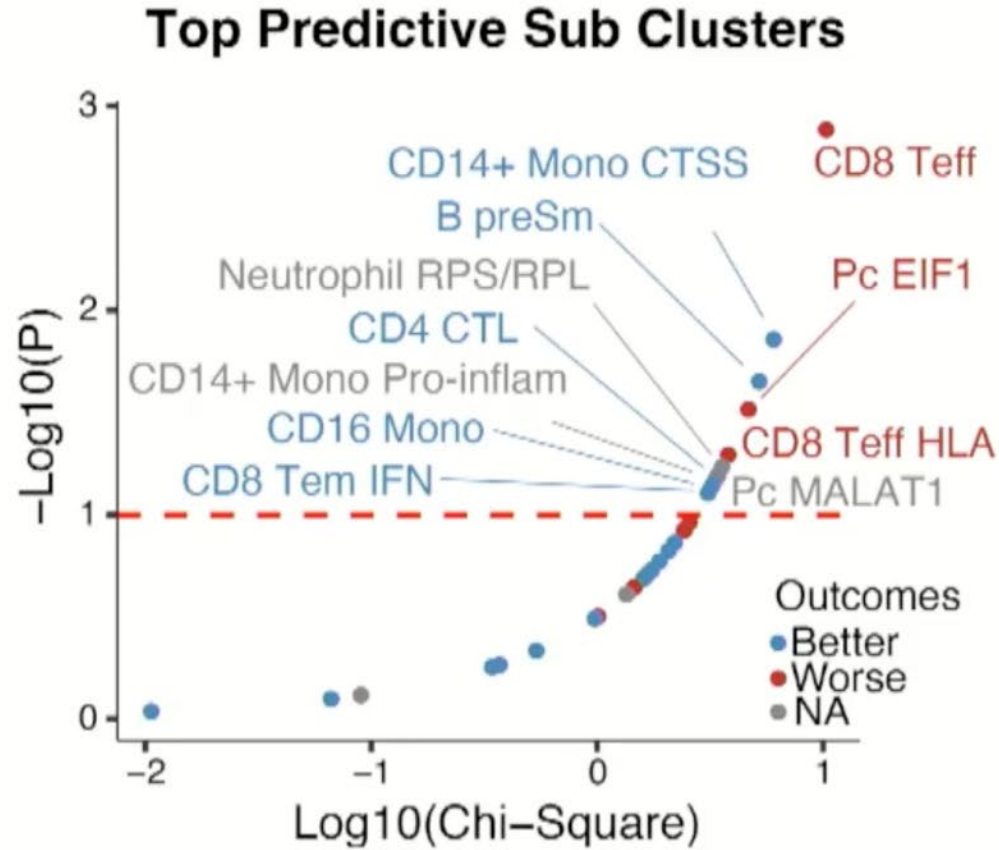
William Pilcher,  
Emory University



Edgar Gonzalez-Kozlova,  
MSSM



# Immune signature provide predictive value



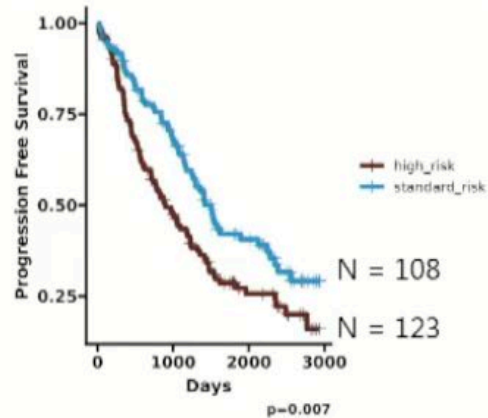
- Immune Signatures Provide Prognostic Value
- Is this independent of cytogenetics?

# Immune landscape of myeloma:

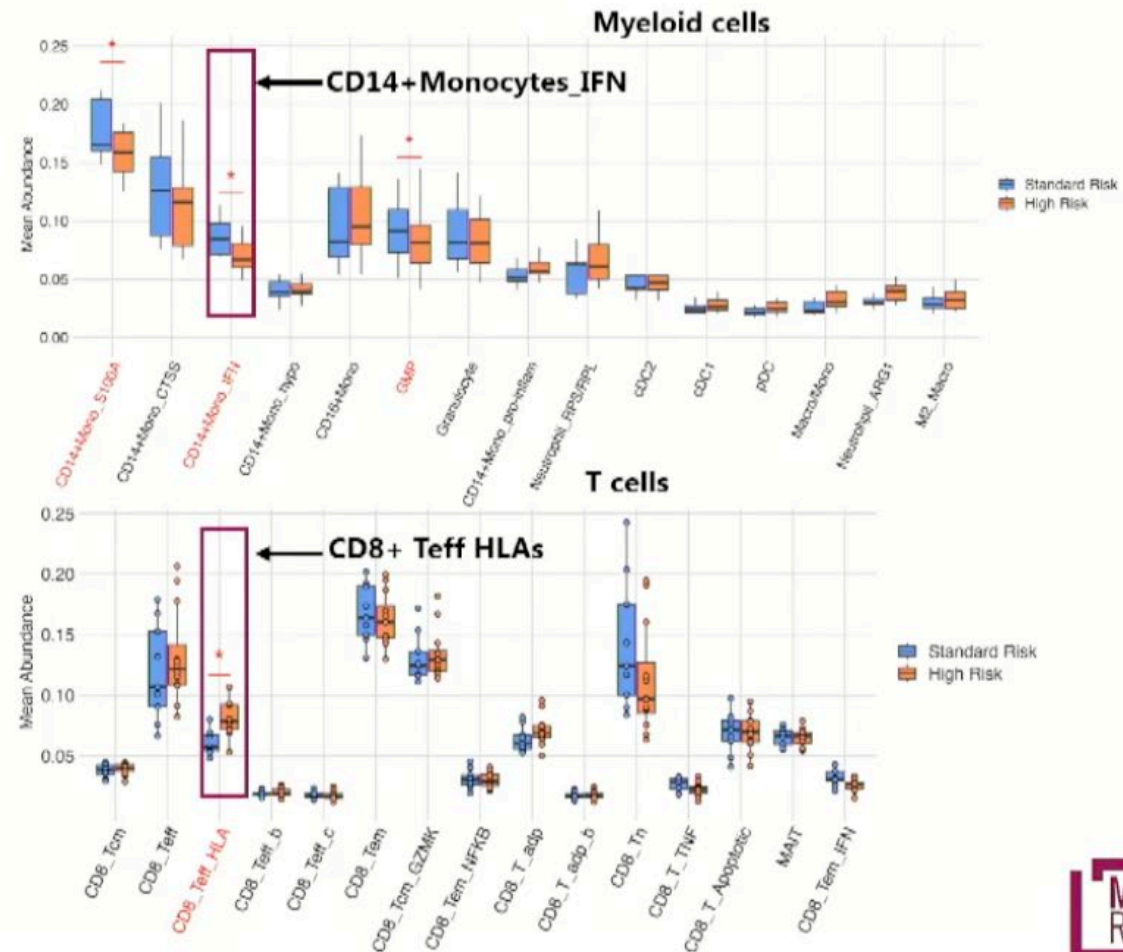
## Cytogenetic Risk and Immune Microenvironment

### HRMM (modified Skerget et al)

- del17p13
- t(8;14)[MAFA]
- t(14;20)[MAFB]
- t(4;14)[WHSC1/MMSET/NSD2]
- t(14;16)[MAF]
- **1q gain**



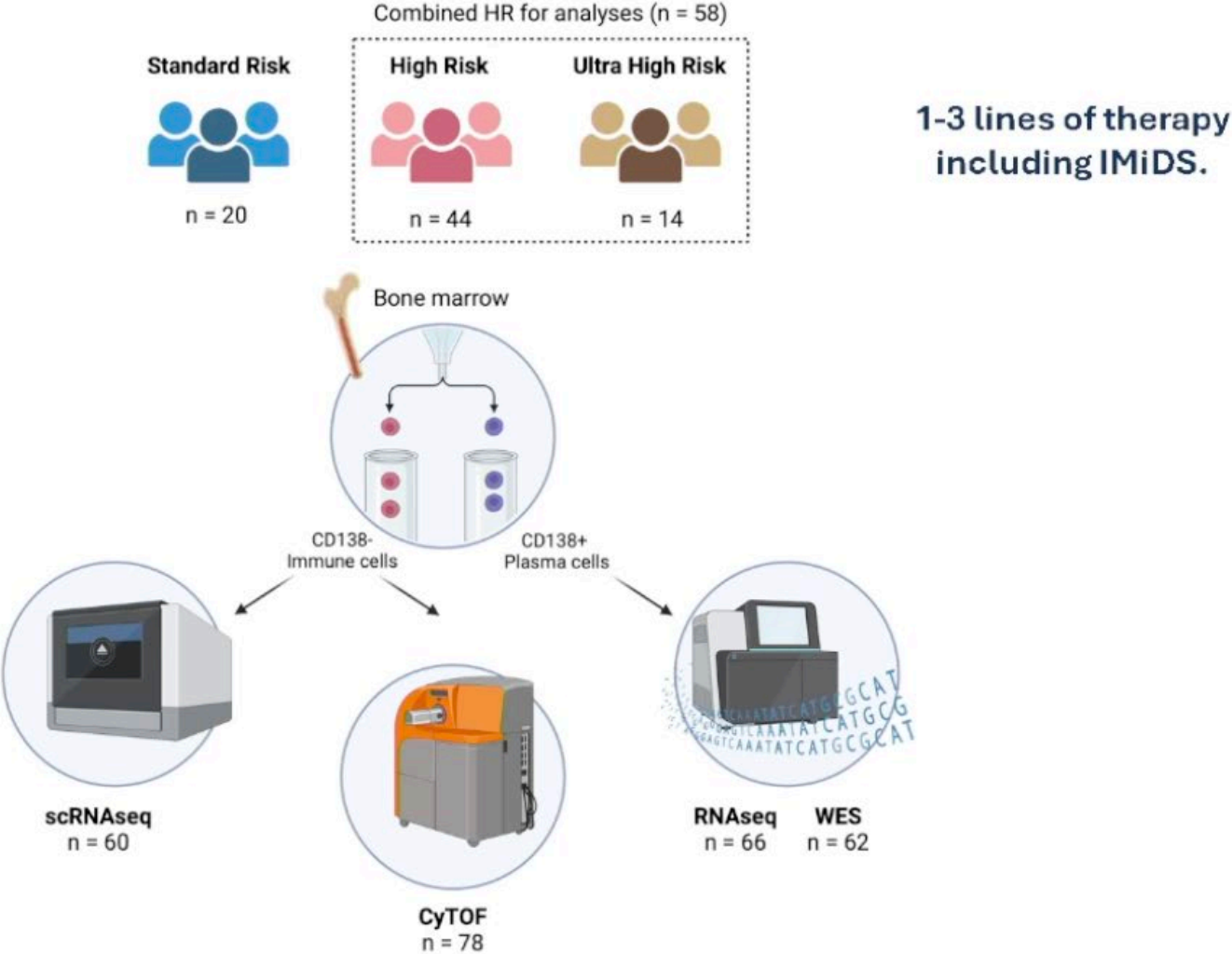
Yered Pita Juarez,  
BIDMC





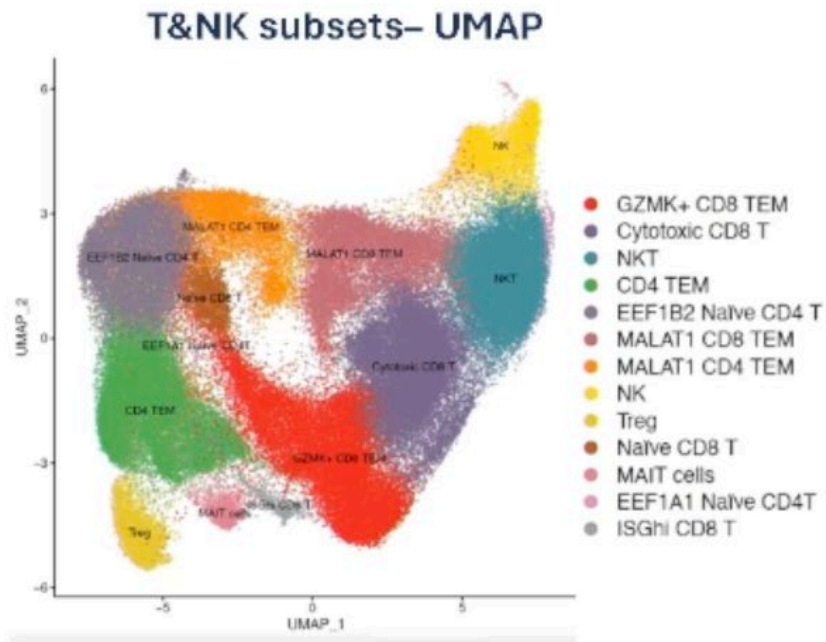
# High-Risk and Standard-Risk Multiple Myeloma Patients : Selma Bekri

## Study design

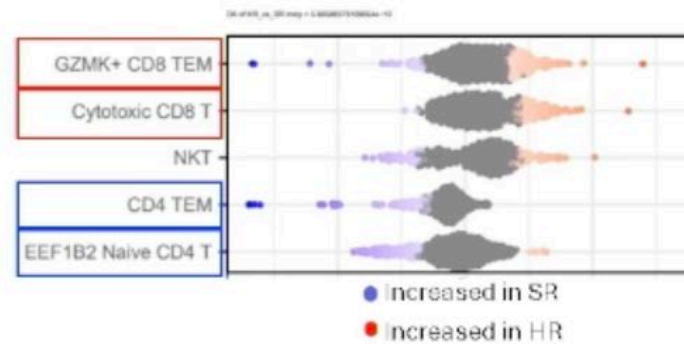


# High-Risk and Standard-Risk Multiple Myeloma Patients : Selma Bekri

## Senescence and exhaustion markers dominate the T cell profile in HR patients

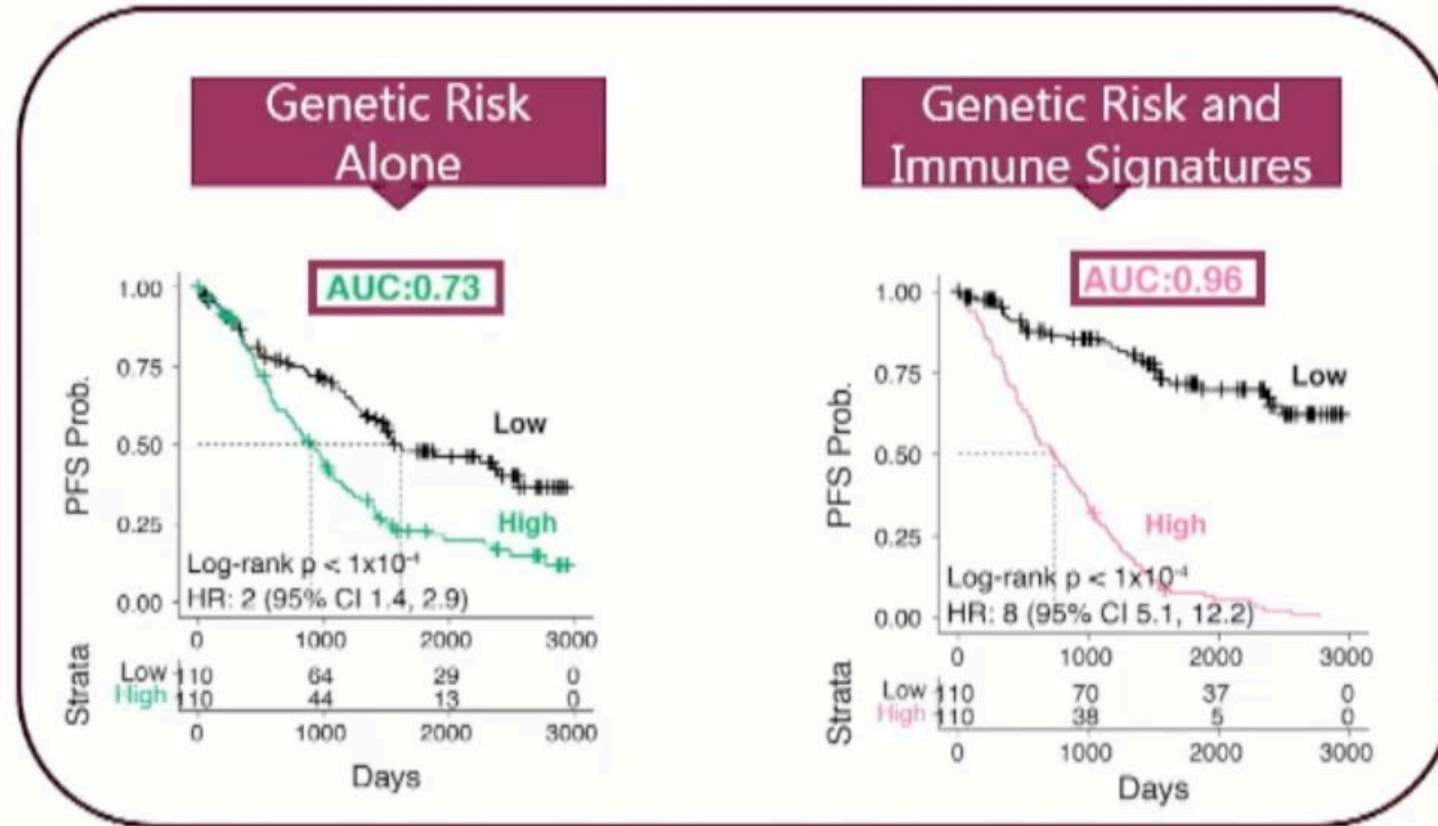


### T&NK subsets – Milo Results – HR > SR



- Increased abundance in HR: **GZMK+ CD8 T cells**, CTLs and NKT
- Increased abundance in SR: naïve and Effector memory CD4T Cells

# Immune landscape of myeloma: combine genetic and immune risk

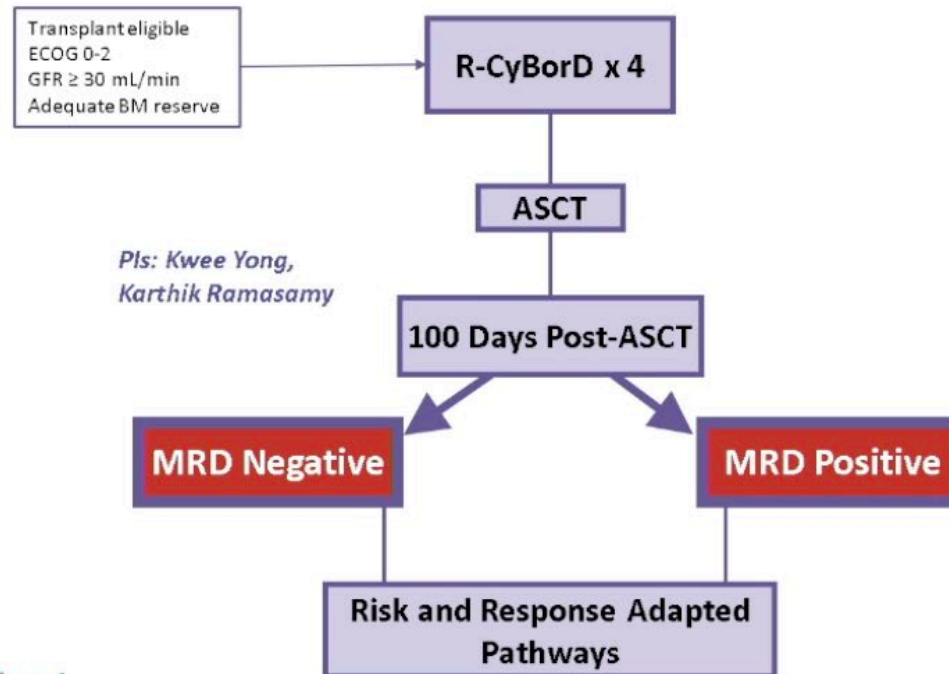


## UKMRA RADAR Trial



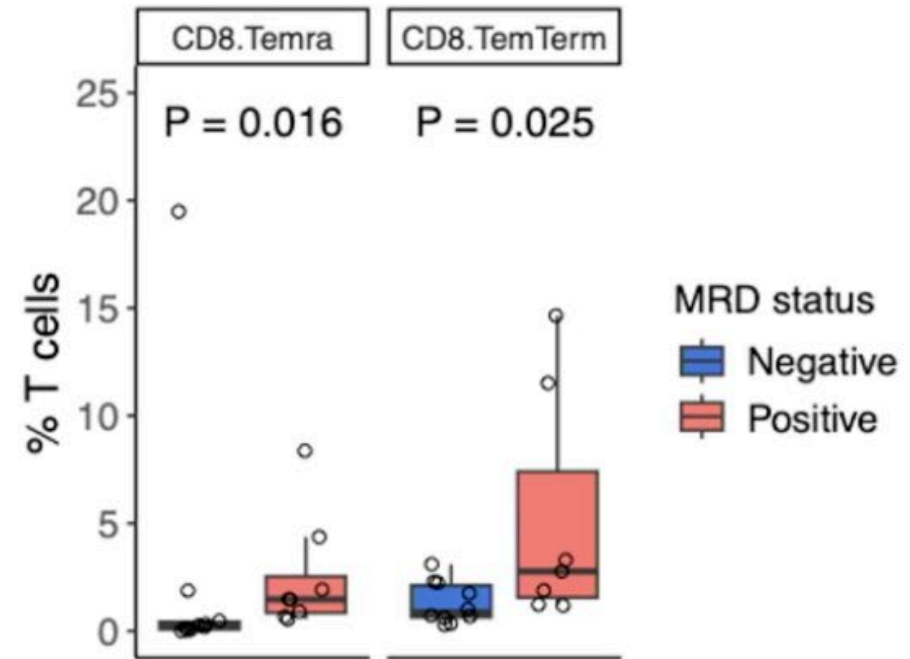
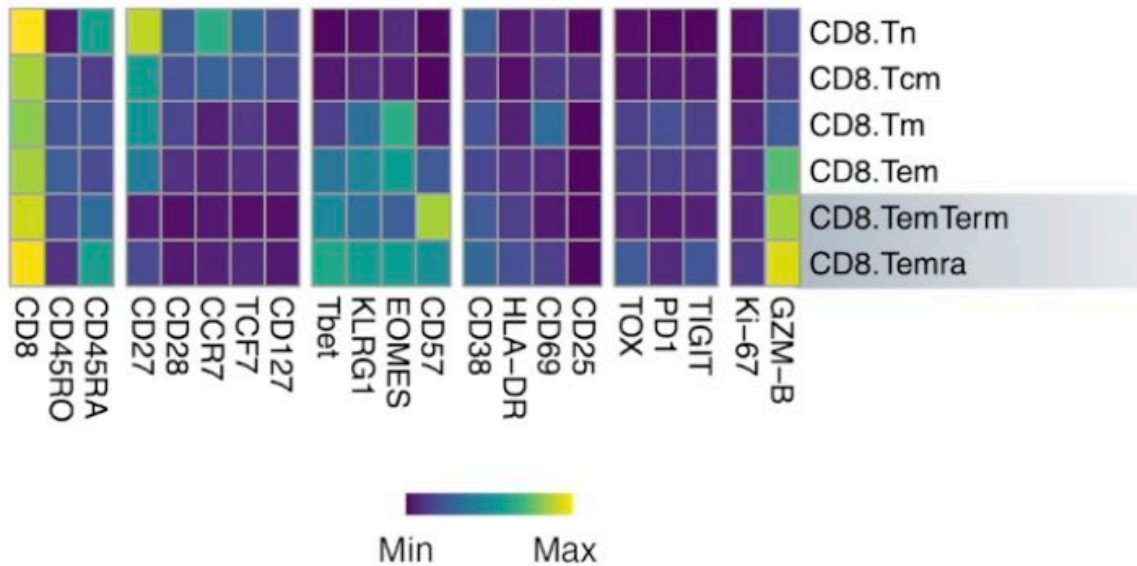
**RADAR**  
UK-MRA Myeloma XV

Risk-Adapted therapy Directed According to Response comparing treatment escalation and de-escalation strategies in newly diagnosed patients with multiple myeloma suitable for stem cell transplant

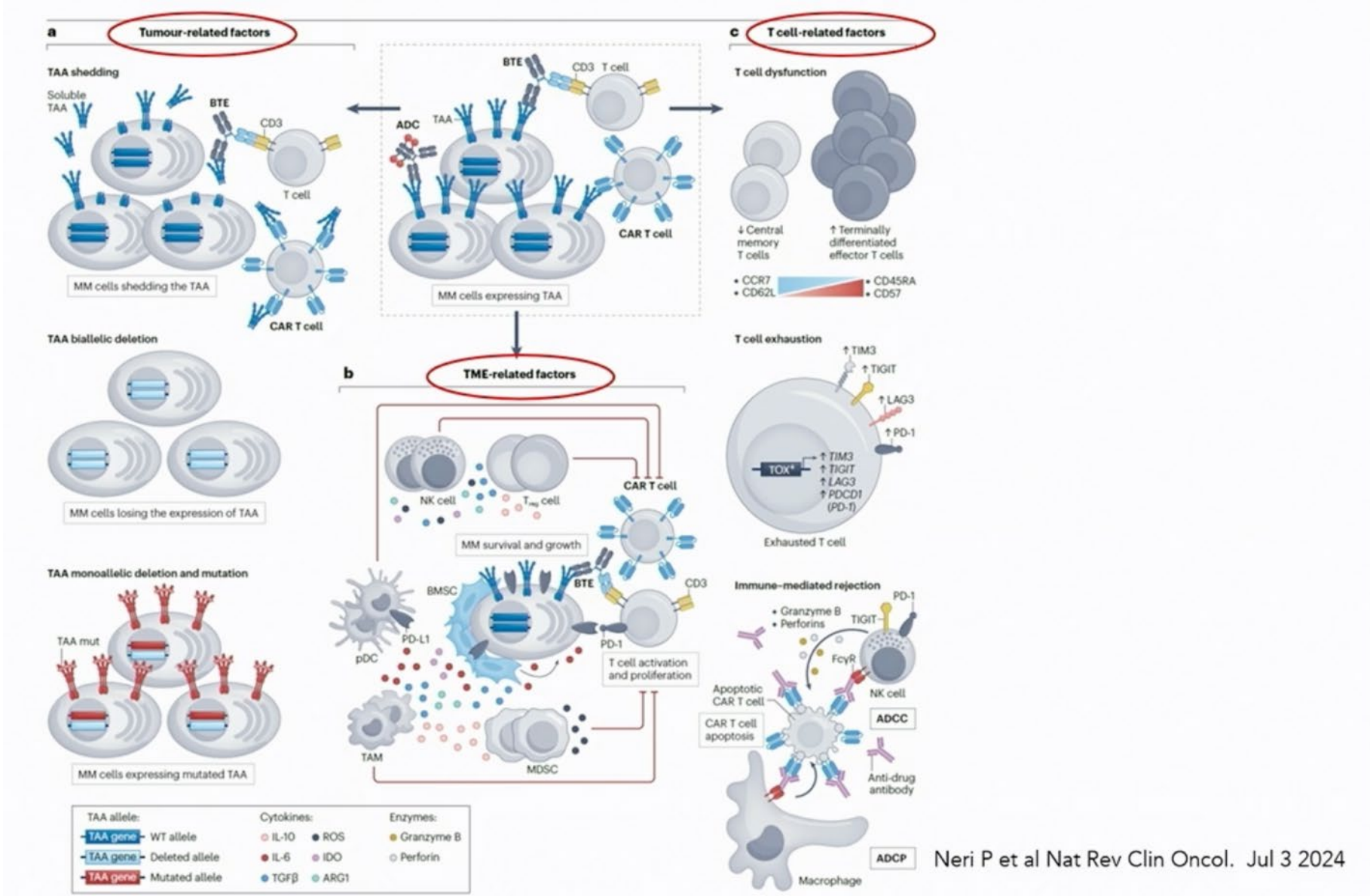


## Terminally differentiated CD8+ T-cells enriched in MRD+ patients

CD8+T<sub>EM</sub> terminal, CD8+T<sub>EMRA</sub>  
Late differentiated (GZM-B+CD57+, CD45RA+/-)

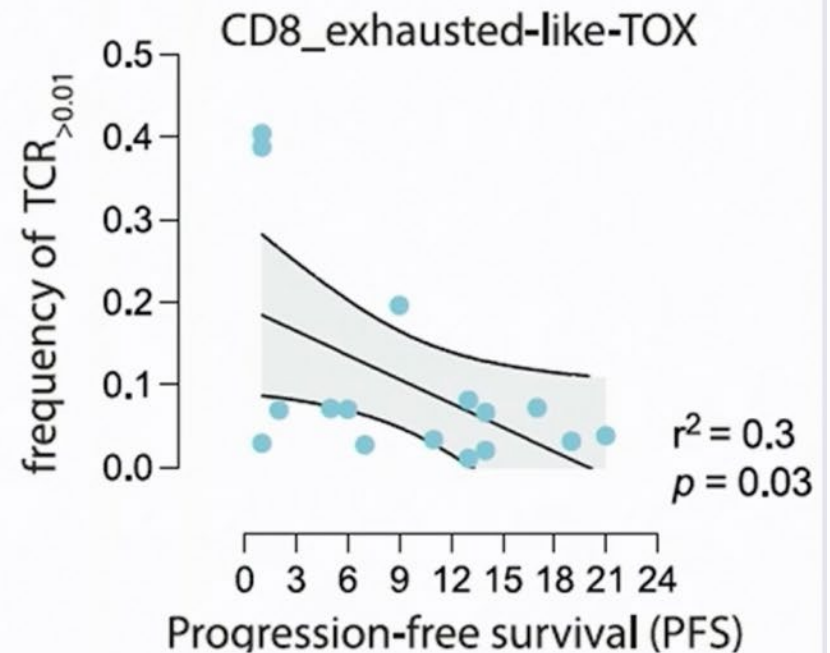
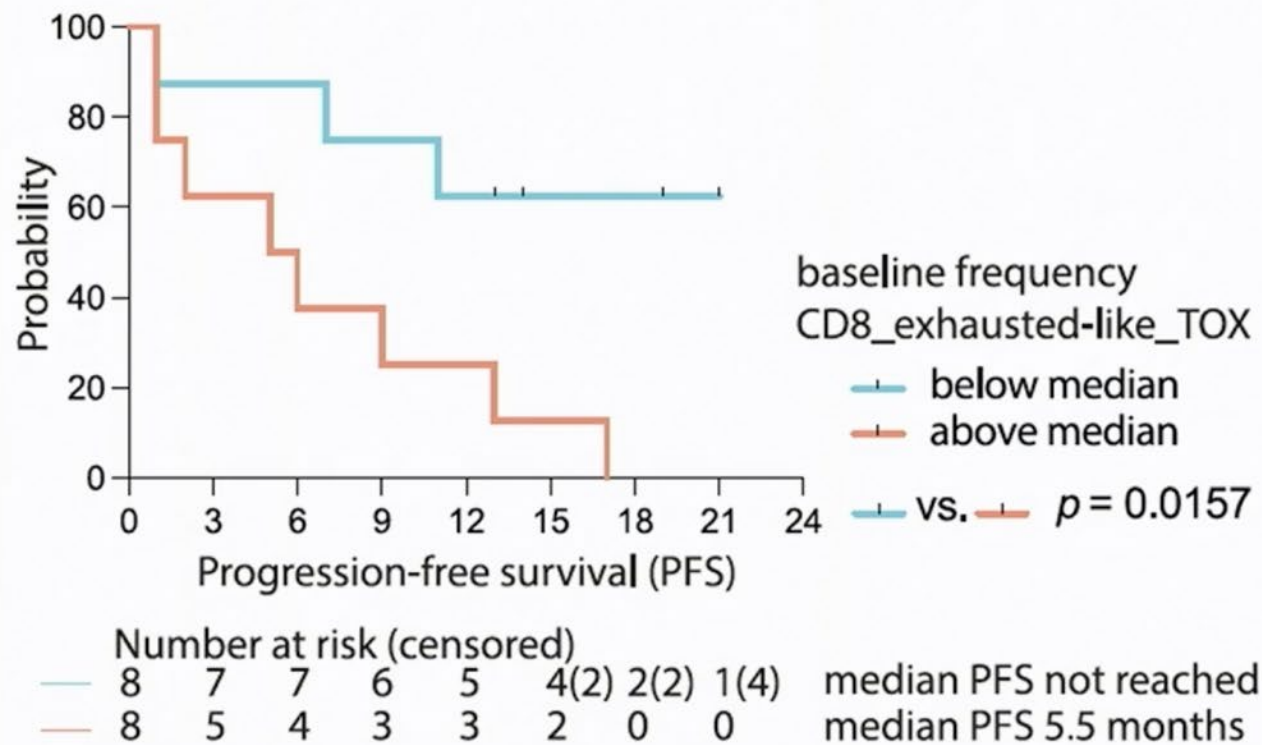


# Mechanisms of resistance to CAR-T and BsAbs : P.Neri and N.Bahlis



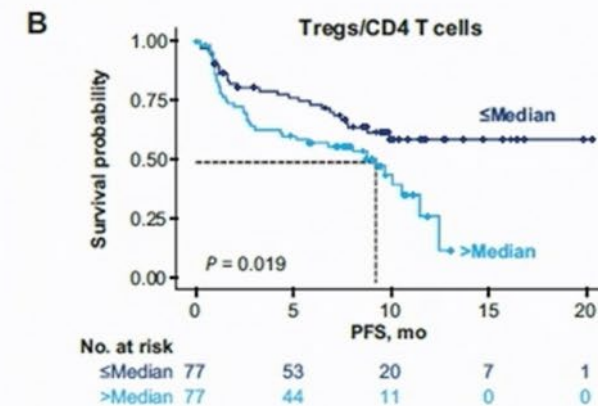
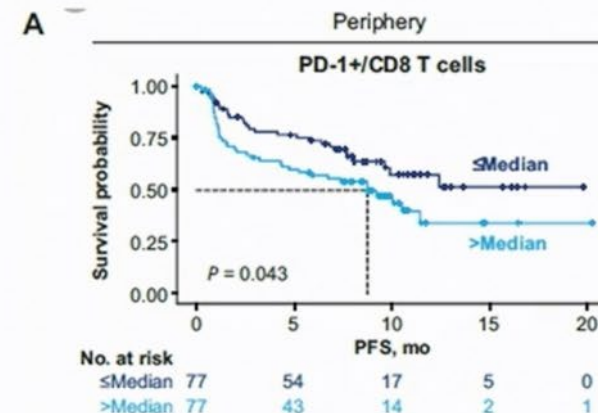
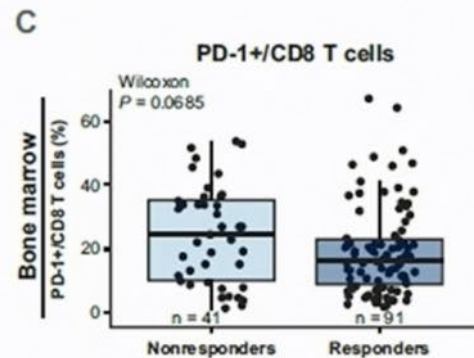
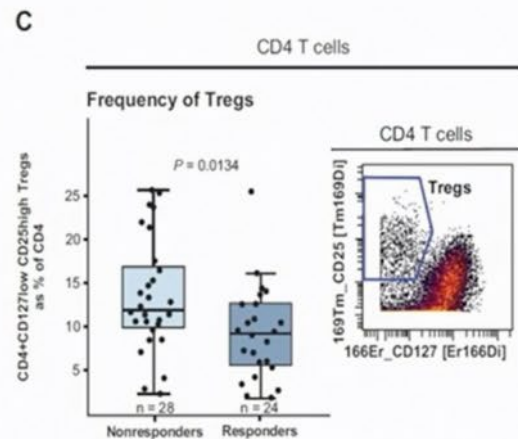
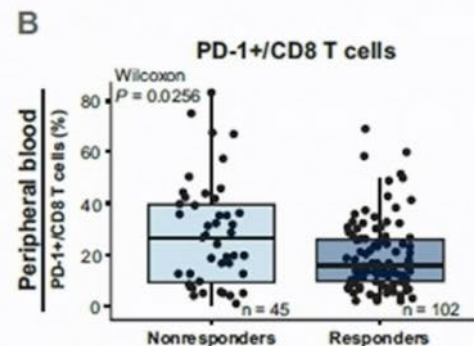
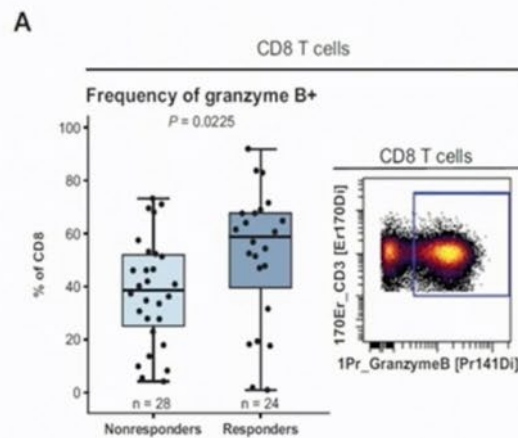
# Exhausted T cells correlate with poor Elranatamab efficacy

Proportion of pre-existing exhausted CD8+ clonotypes pre-therapy is significantly increased in BCMAxCD3 TCE non-responder patients



# Immune Fitness correlates with Teclistamab PFS in Majestic 1

## Correlation of immune fitness with response to Teclistamab

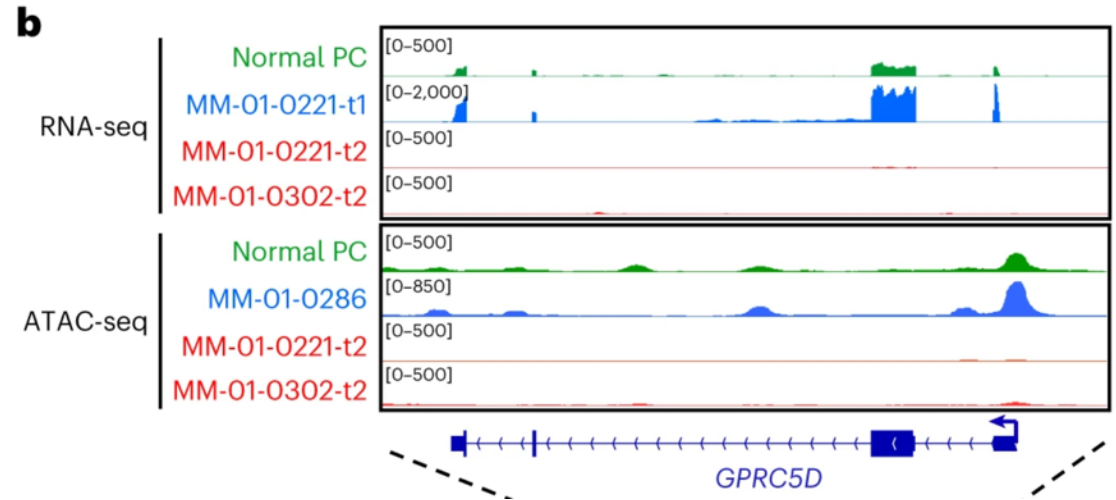
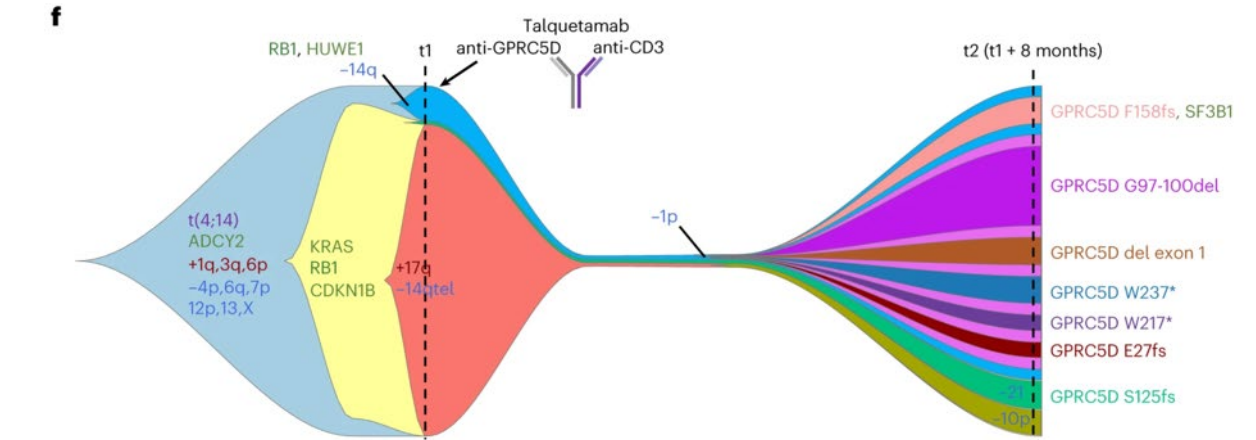
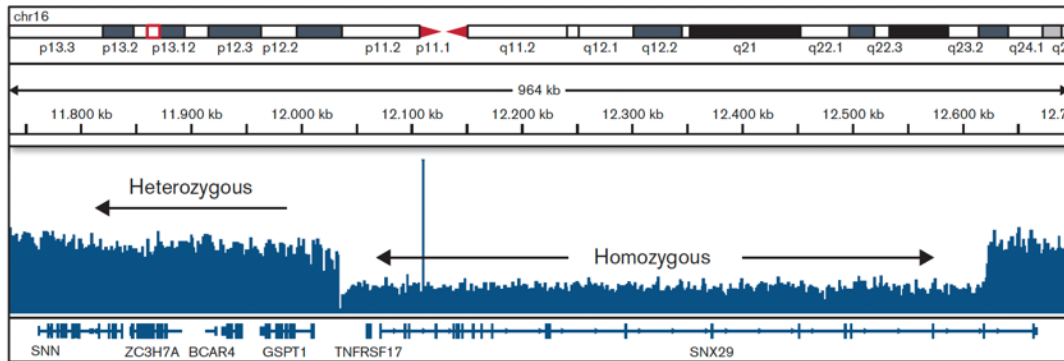
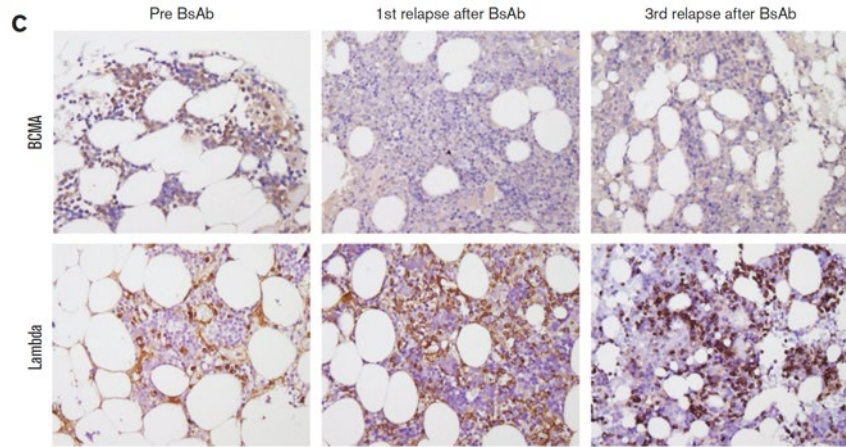


Cortes-Selva D et al, Blood. 2024 Aug 8;144(6):615-628

Higher frequency Tregs and PD1+ CD8 T cells in non-responders to Teclistamab



# Tumor intrinsic : Loss of BCMA or GPRC5D target



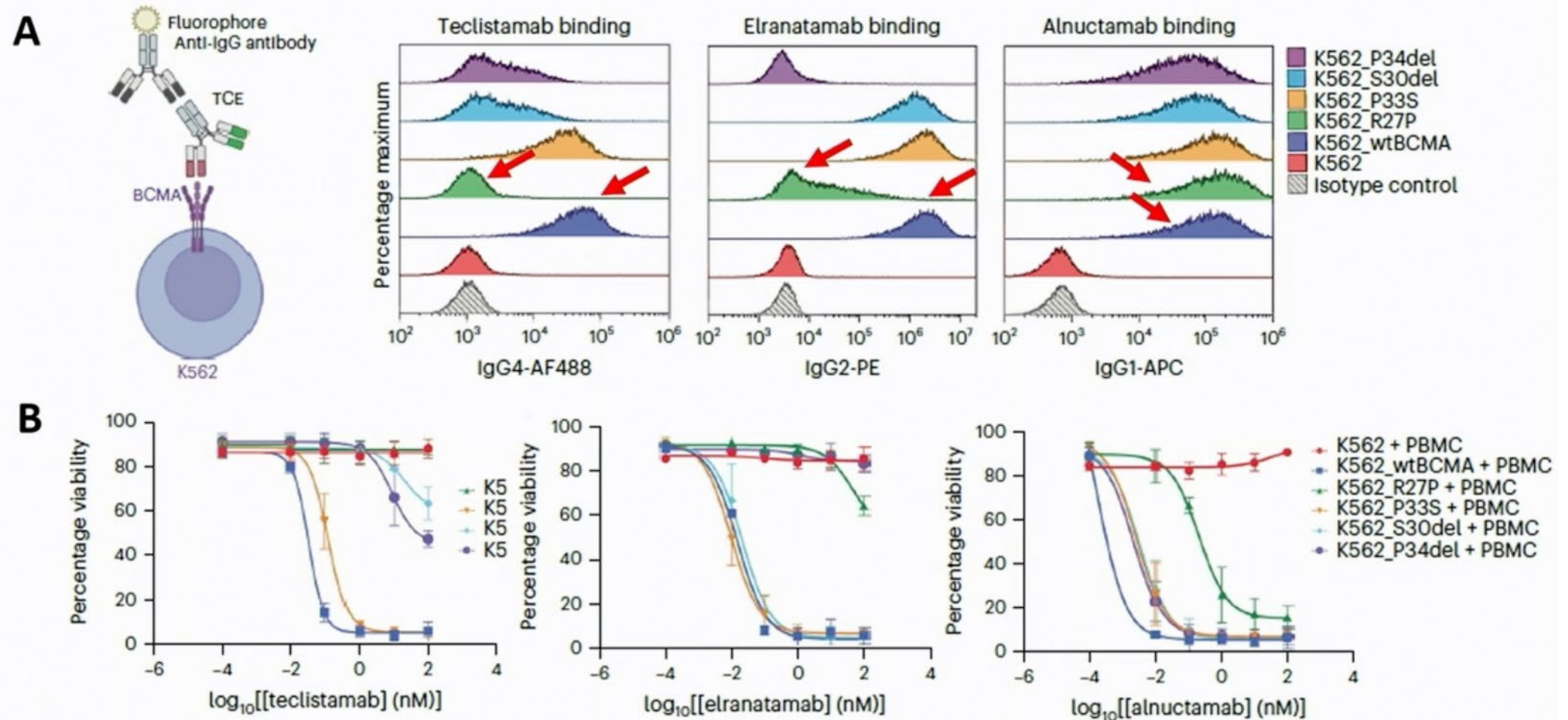
Truger MS, et al. Single- and double-hit events in genes encoding immune targets before and after T cell-engaging antibody therapy in MM. *Blood Adv* . 2021 Oct 12;5(19):3794-8.

Samur MK, et al. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma. *Nature Communications* volume 12:868 (2021)

Derrien J, et al. Acquired resistance to a GPRC5D-directed T-cell engager in multiple myeloma is mediated by genetic or epigenetic target inactivation. *Nature cancer* 2023.

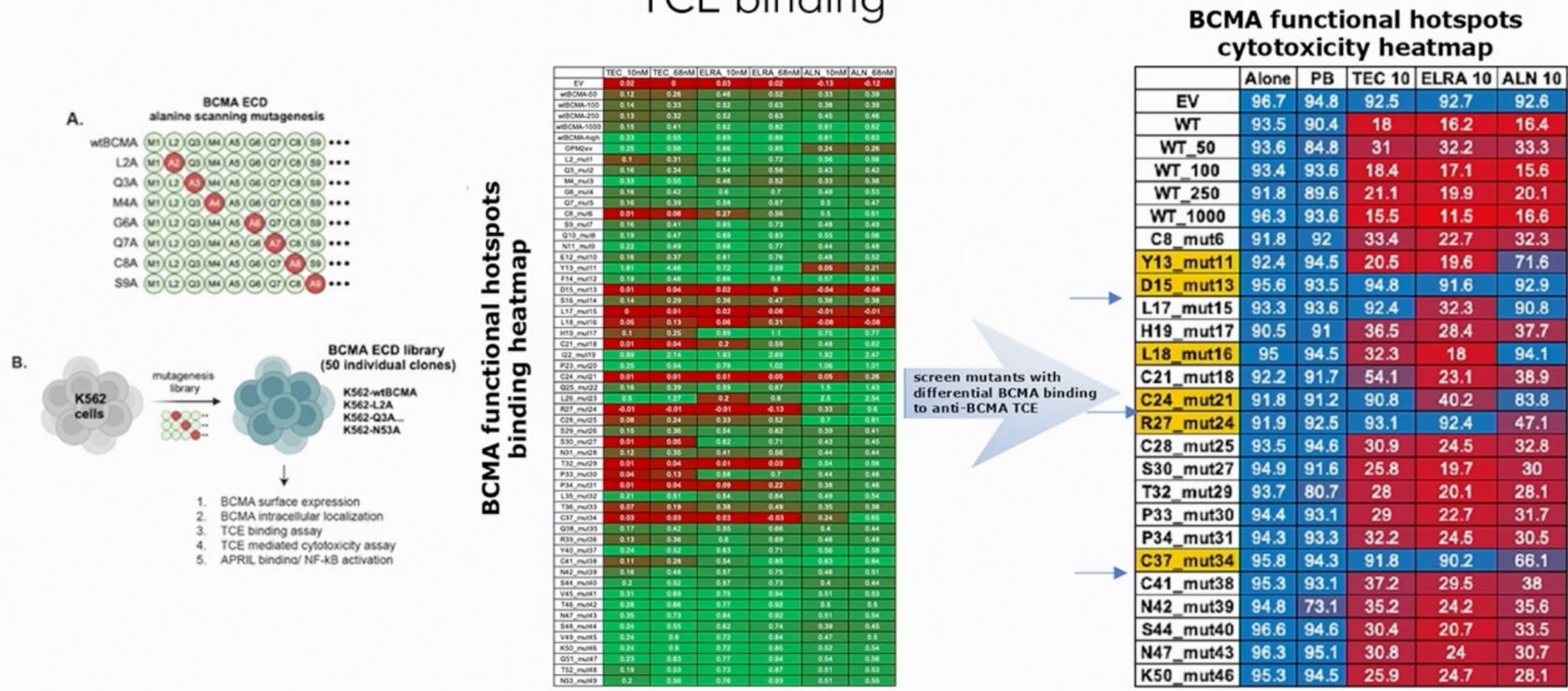
# Tumor intrinsic : BCMA epitope mutations limits BsAb binding

Differential sensitivity of BCMA mutant clones to BCMA xCD3 T-cell engaging BsAb



# Tumor intrinsic : Map BCMA epitope mutations and BsAb activity

BCMA extracellular domain "functional" hotspots required for anti-BCMA TCE binding

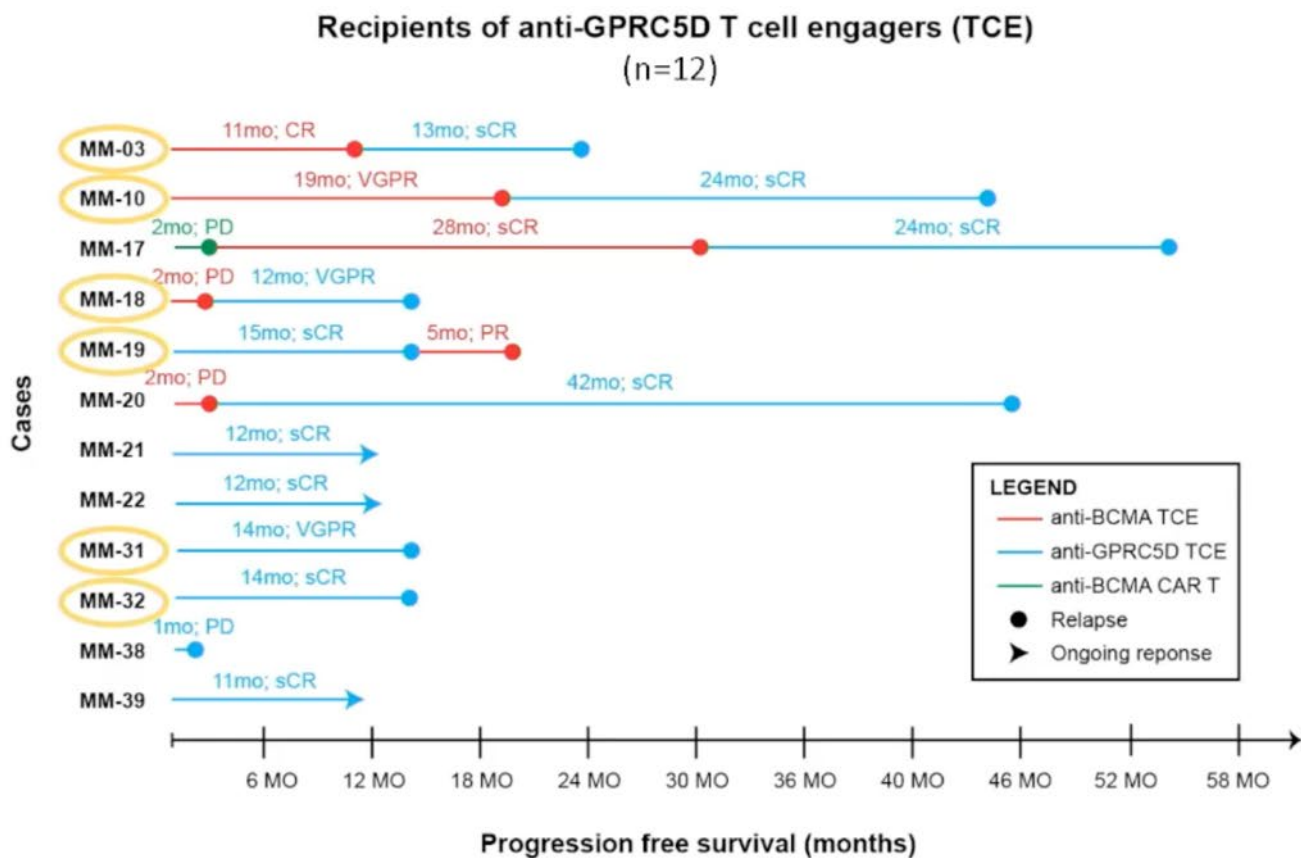


These results indicate the BCMA ECD residues required for anti-BCMA TCE binding, provide a valuable tool for rational design and selection of anti-BCMA TCEs.

Holly Lee, manuscript in preparation

# Impaired membrane trafficking of GPRC5D mediates resistance to anti-GPRC5D TCE : Holly Lee

## High incidence of GPRC5D mutations (CNV/ SNV) at relapse post talquetamab



Median PFS = 12 months

9/12 = progressive disease

7/9 with genomic data available

6/7 with *GPRC5D* CNV/ SNV

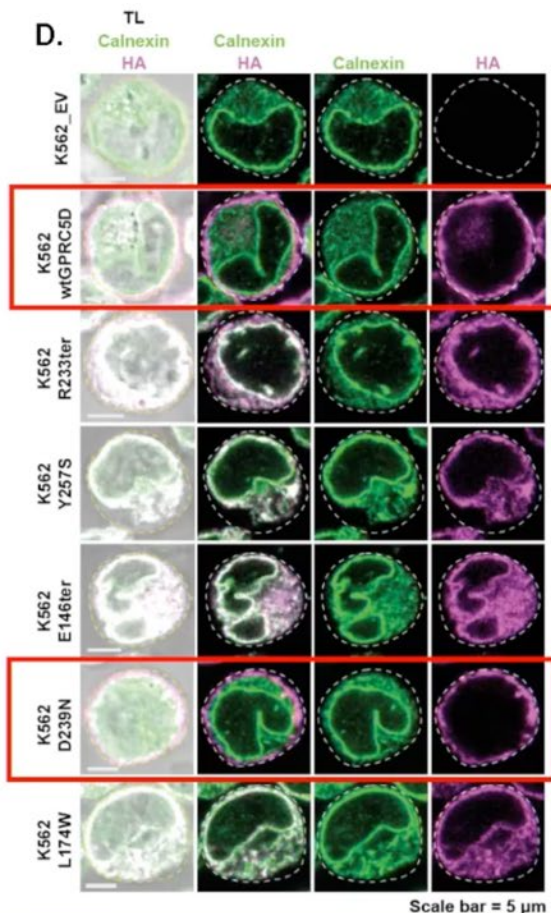
Biallelic *GPRC5D* deletion

- MM-10
- MM-19

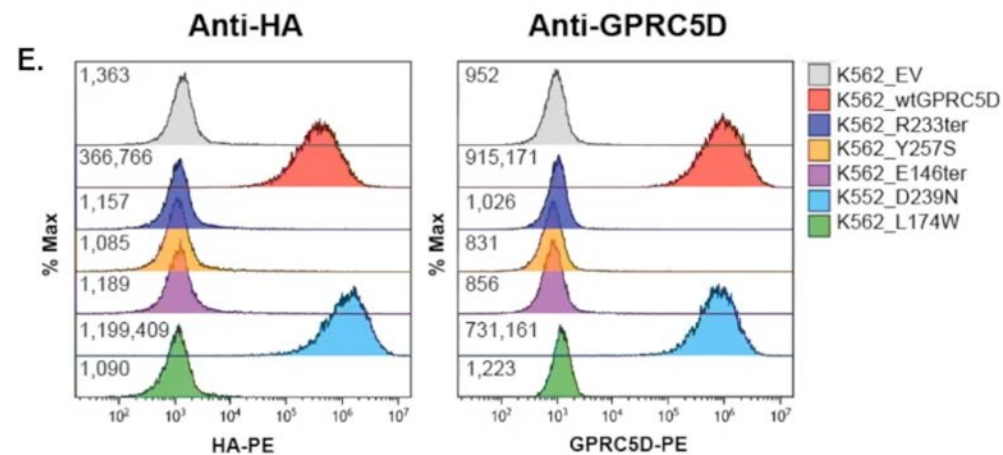
Monoallelic deletion + SNVs

- MM-03
- MM-18
- MM-31
- MM-32

# Impaired membrane trafficking of GPRC5D mediates resistance to anti-GPRC5D TCE : Holly Lee



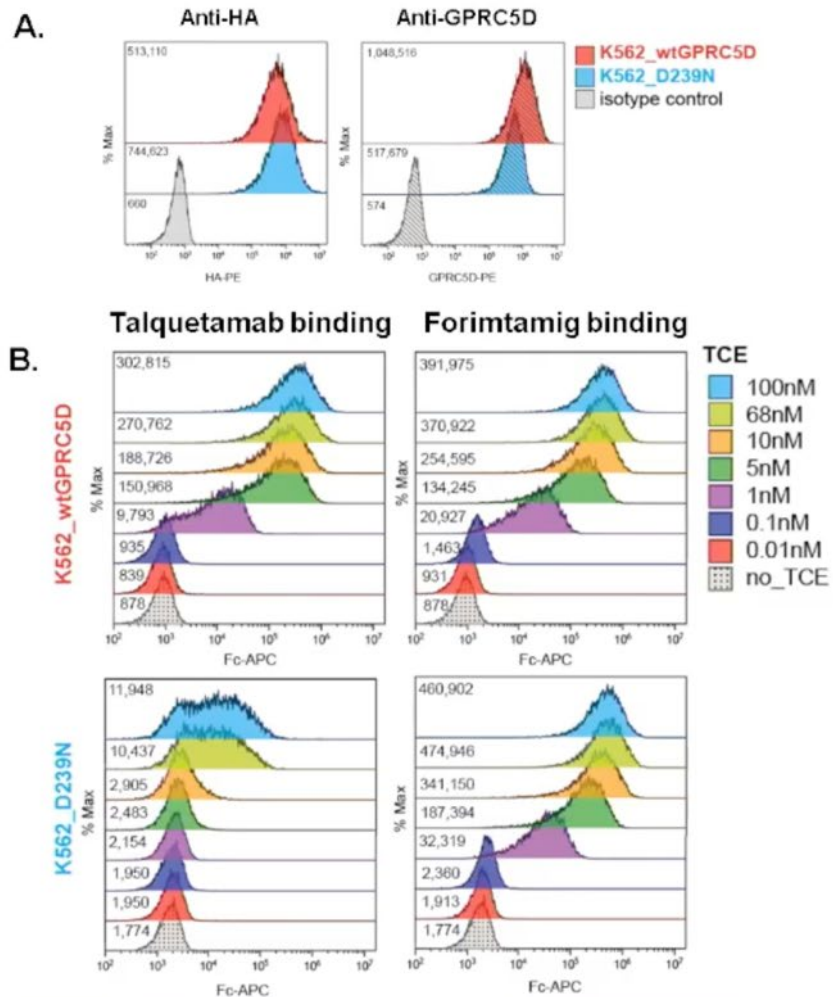
Most *GPRC5D* mutations result in ER trapping and loss of membrane trafficking



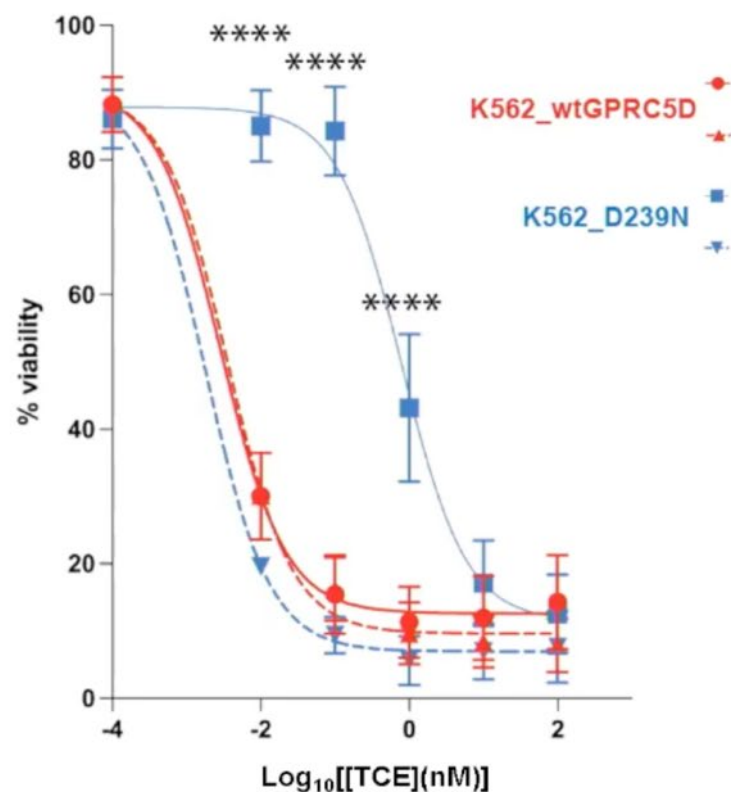
Calnexin = Endoplasmic reticulum  
HA tag = GPRC5D

# Impaired membrane trafficking of GPRC5D mediates resistance to anti-GPRC5D TCE : Holly Lee

## p.Asp239Asn GPRC5D mutants are resistant to talquetamab

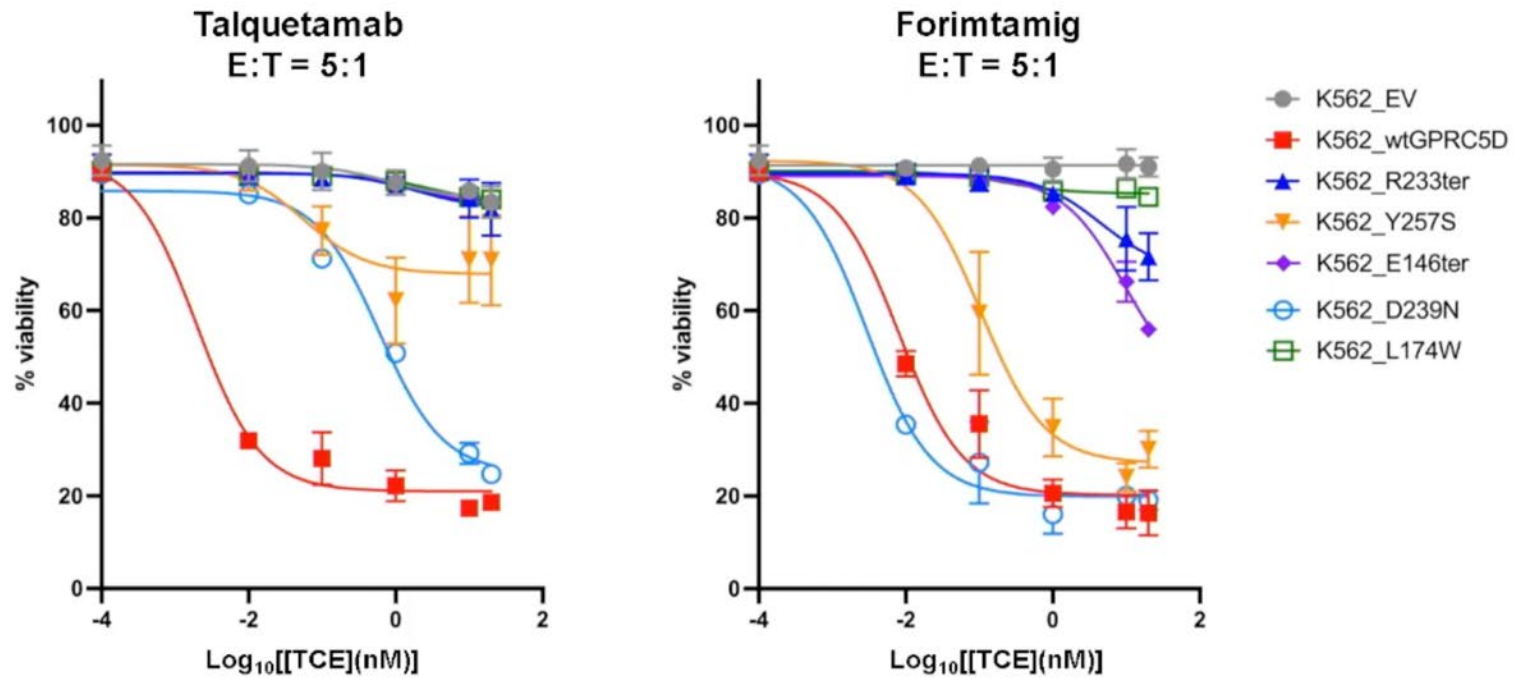


**C.**      Dose response cytotoxicity assay  
48 hour co-culture  
effector : target = 10:1



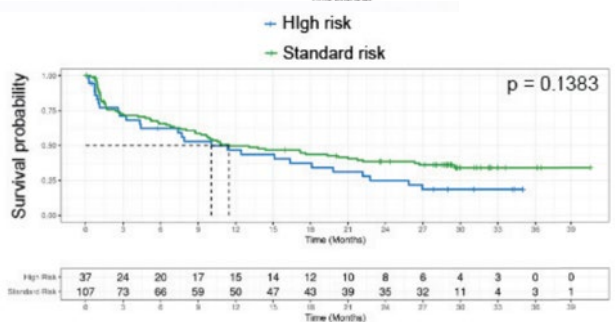
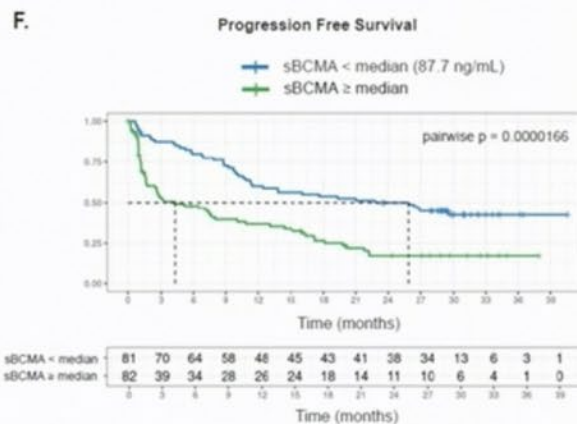
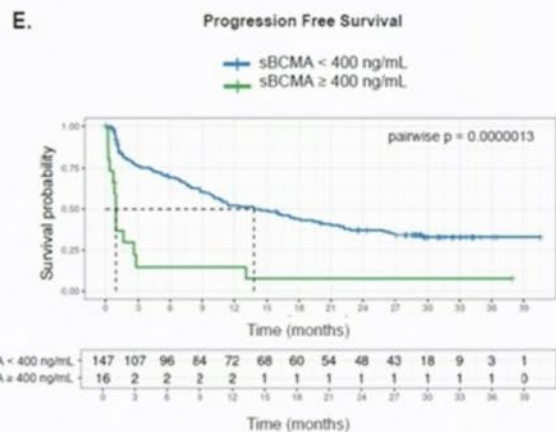
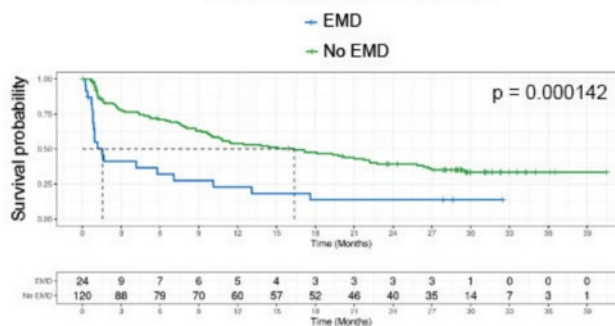
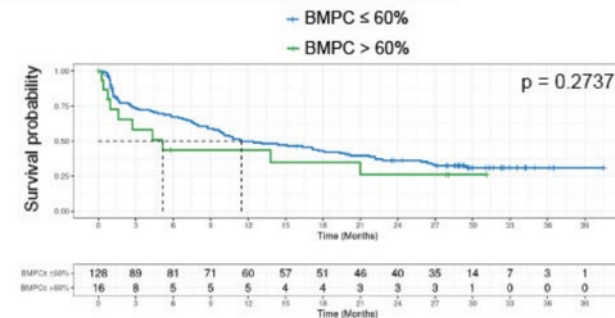
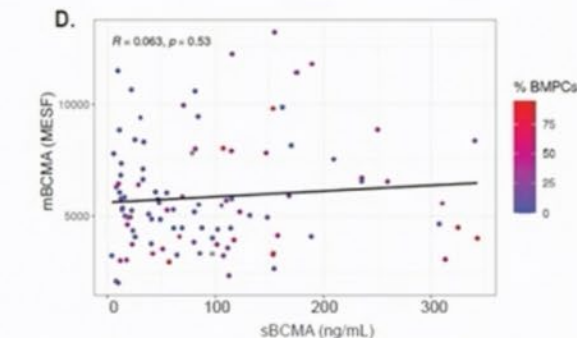
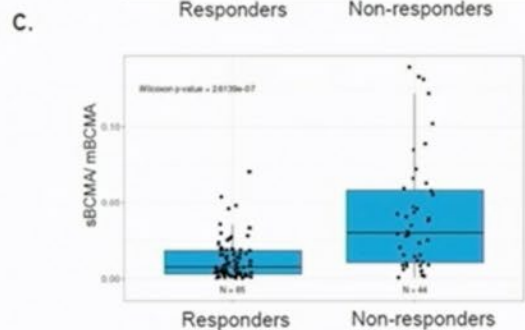
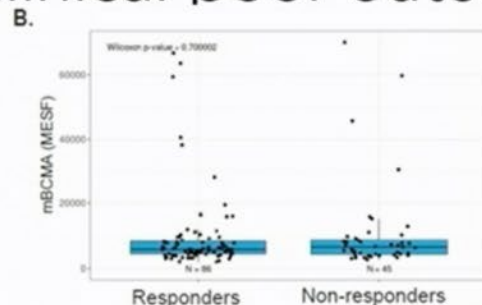
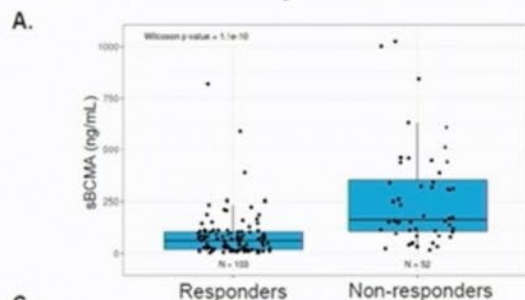
# Resistance to anti-GPRC5D TCE : Holly Lee

## Differential sensitivity of GPRC5D mutants to anti-GPRC5D TCE



# High sBCMA correlates with poor BsAbs outcome

High baseline sBCMA predicts clinical poor outcome of anti-BCMA TCE





# Determinant of BsAbs efficiency

## Context of Research

Approximately 30% of patients with relapsed/refractory multiple myeloma (RR MM) fail to respond to anti-BCMA T Cell Engagers (TCE)

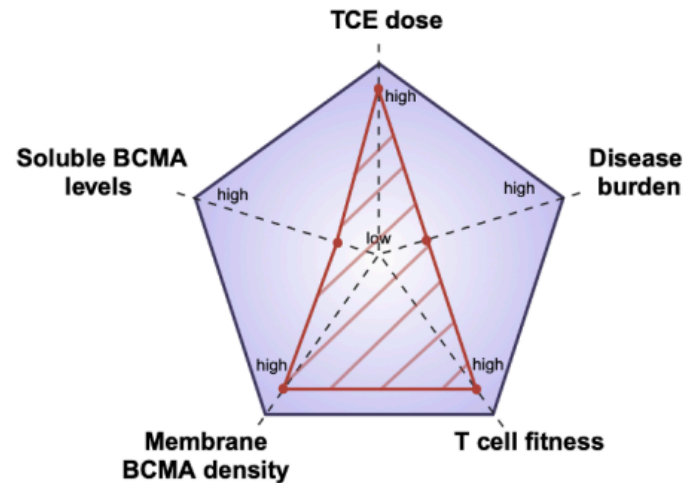
## Aim of This Study

In this work, we employed whole genome sequencing and *in vitro* assays to identify the mediators of primary refractoriness to anti-BCMA TCE in MM

## Findings

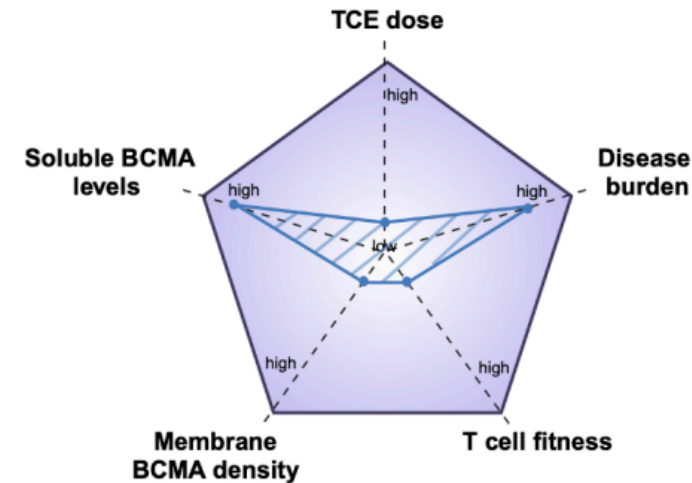
Radar plots showing the results of *in vitro* modeling of the variables involved in the response to anti-BCMA TCE

### Responding patients:



- Therapeutic TCE dosing
- Normal T cell absolute count/ fitness
- Low disease burden
- Low soluble BCMA (<400 ng/mL)
- High membrane bound BCMA

### Non-responding patients:



- Sub-therapeutic TCE dosing
- Low T cell absolute count/ fitness
- High disease burden
- High soluble BCMA (>400 ng/mL)
- Low membrane bound BCMA

**Merci pour votre attention**

