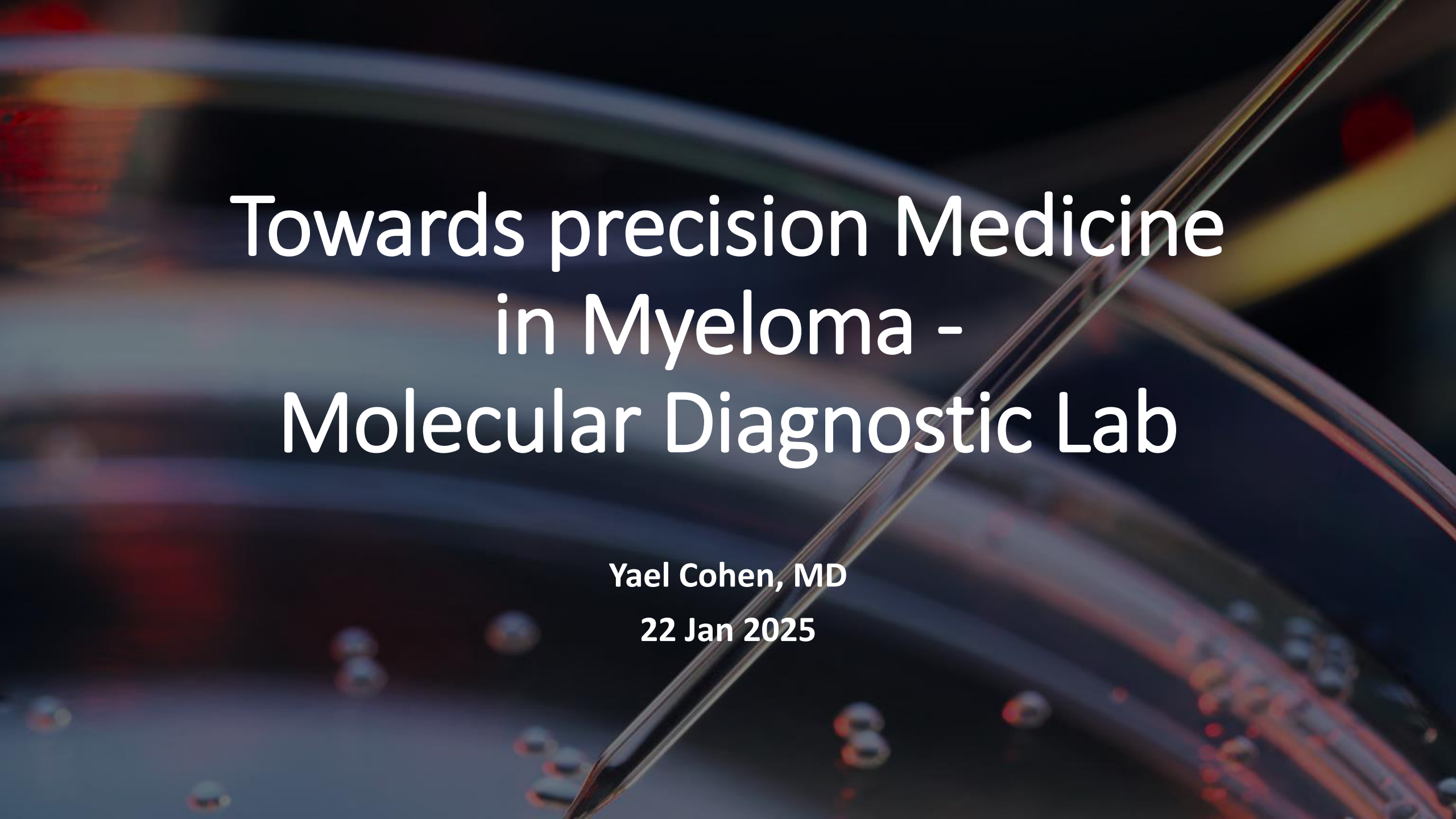
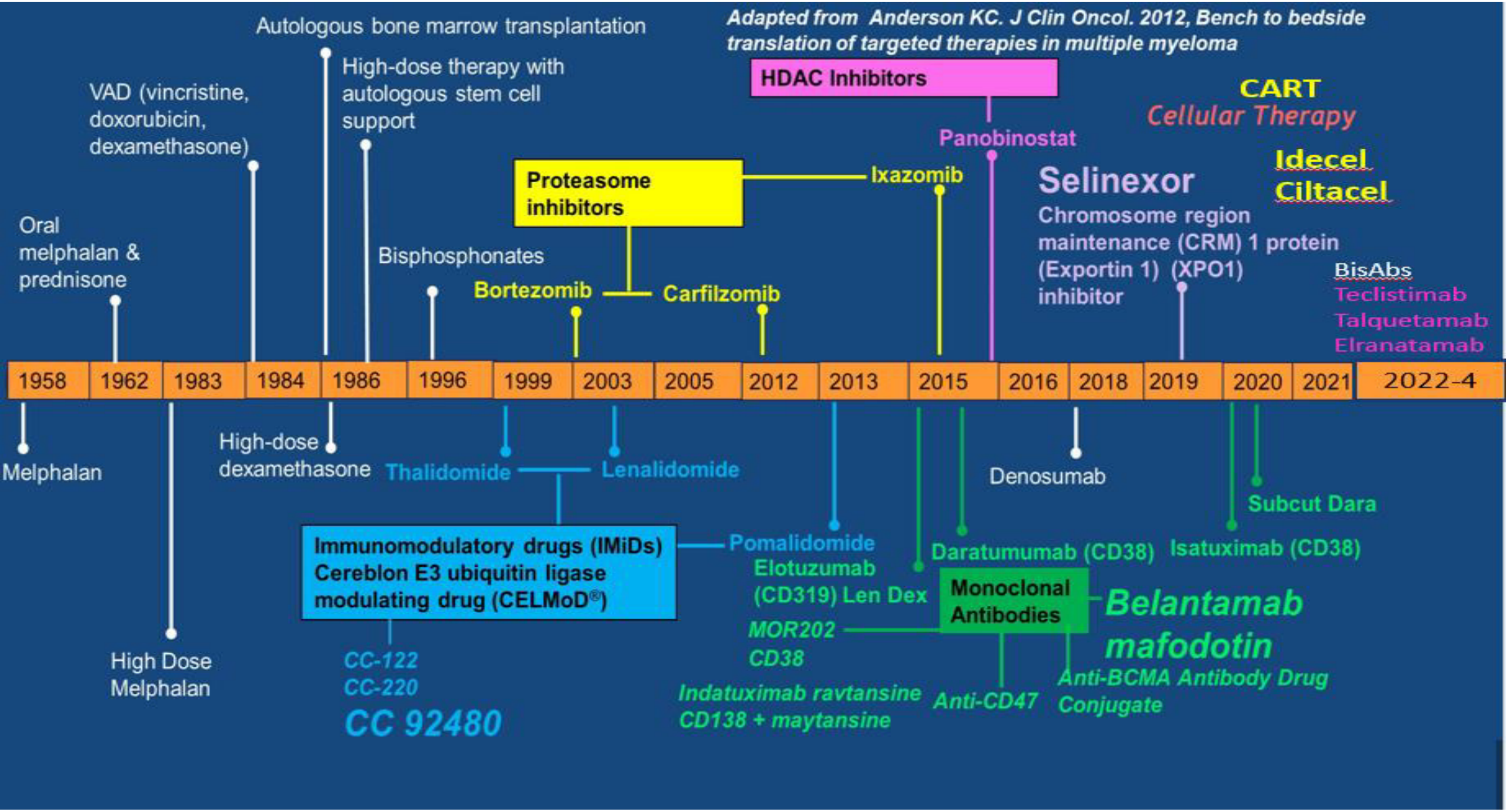


Towards precision Medicine in Myeloma - Molecular Diagnostic Lab

Yael Cohen, MD

22 Jan 2025

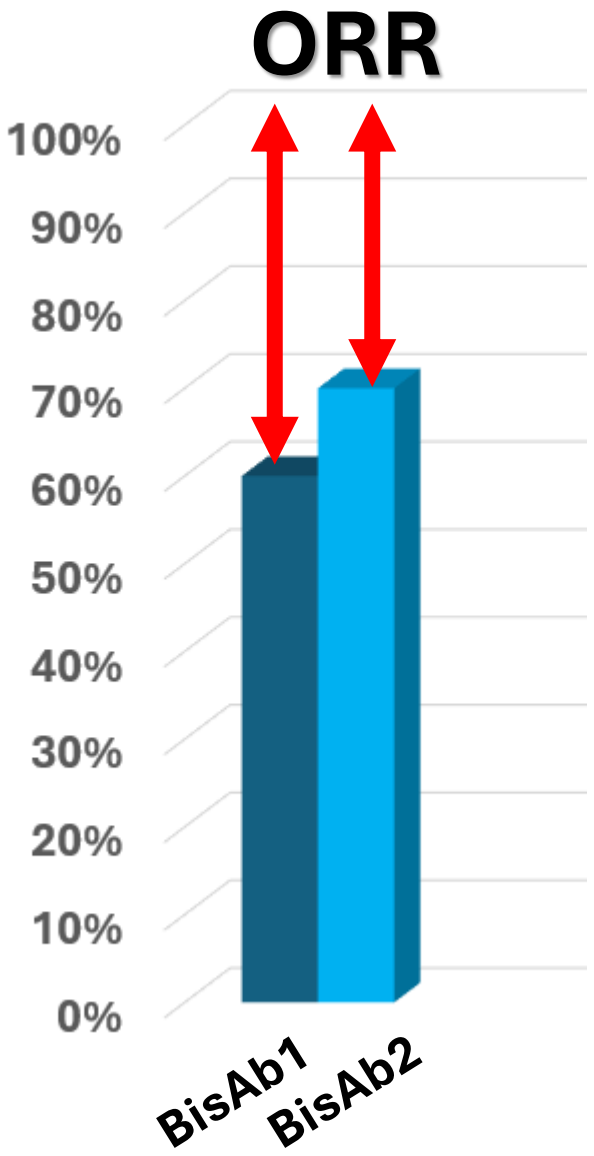

Adapted from Anderson KC. J Clin Oncol. 2012, Bench to bedside translation of targeted therapies in multiple myeloma
Autologous bone marrow transplantation
High-dose therapy with autologous stem cell support
VAD (vincristine, doxorubicin, dexamethasone)
Oral melphalan & prednisone
Bisphosphonates
Proteasome inhibitors
Bortezomib
Carfilzomib
Ixazomib
HDAC Inhibitors
Panobinostat
CART
Cellular Therapy
Idecel
Ciltacel
Selinexor
Chromosome region maintenance (CRM) 1 protein (Exportin 1) (XPO1) inhibitor
BisAbs
Teclistimab
Talquetamab
Elranatamab
1958
1962
1983
1984
1986
1996
1999
2003
2005
2012
2013
2015
2016
2018
2019
2020
2021
2022-4
Melphalan
High Dose Melphalan
High-dose dexamethasone
Thalidomide
Lenalidomide
Immunomodulatory drugs (IMiDs)
Cereblon E3 ubiquitin ligase modulating drug (CELMoD®)
CC-122
CC-220
CC 92480
Pomalidomide
Elotuzumab (CD319) Len Dex
MOR202
CD38
Indatuximab ravtansine
CD138 + maytansine
Daratumumab (CD38)
Monoclonal Antibodies
Anti-CD47
Denosumab
Isatuximab (CD38)
Subcut Dara
Belantamab mafodotin
Anti-BCMA Antibody Drug Conjugate

We have come a long way….

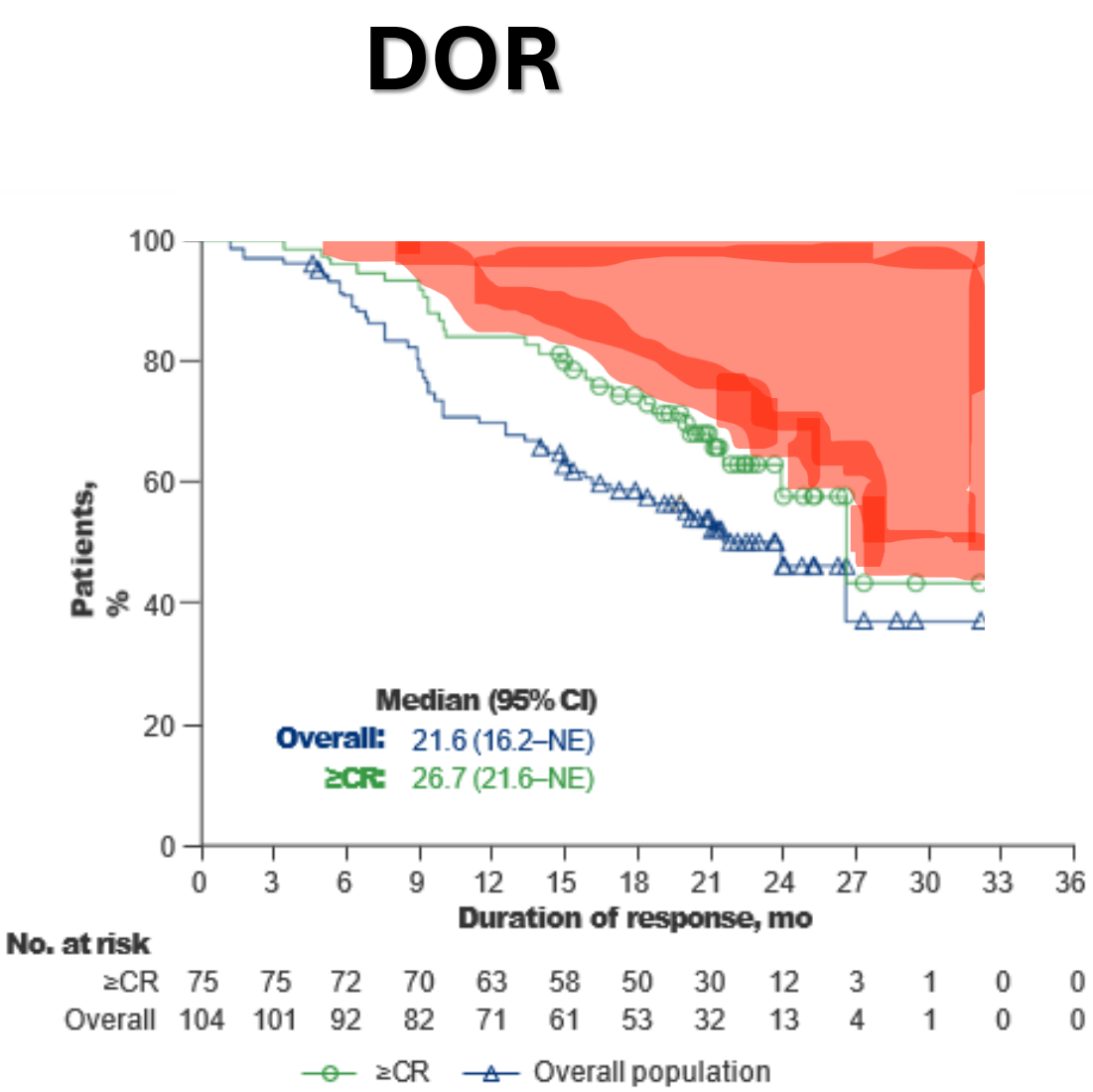
- Upfront quad therapy → anticipated over10 yrs PFS for TE, 7-8 yrs for TIE
- Heavily pre-treated MM, 6 LOT → ciltacel resulted in over 90% ORR, PFS 35 months
- Triple refractory MM with bi-specifics → ORR 60-70%, DOR up-to 2 years
- Combinations offer enhanced efficacy
- Early introduction of novel therapeutics improve outcomes even further

Some Key Challenges

- Patients fail therapy → how to select and how to sequence
- How to avoid over-treatment & excess toxicity
- Can we reach cure?



?



Primary Resistance

Secondary Resistance

Potential Clinical Dilemmas

- **CASE 1**:
  Triple class exposed & BELA resistant.
  BCMA-CART? Talq? BCMA-TCE?
  ? BCMA deletion or Mutation; GPRC5D status

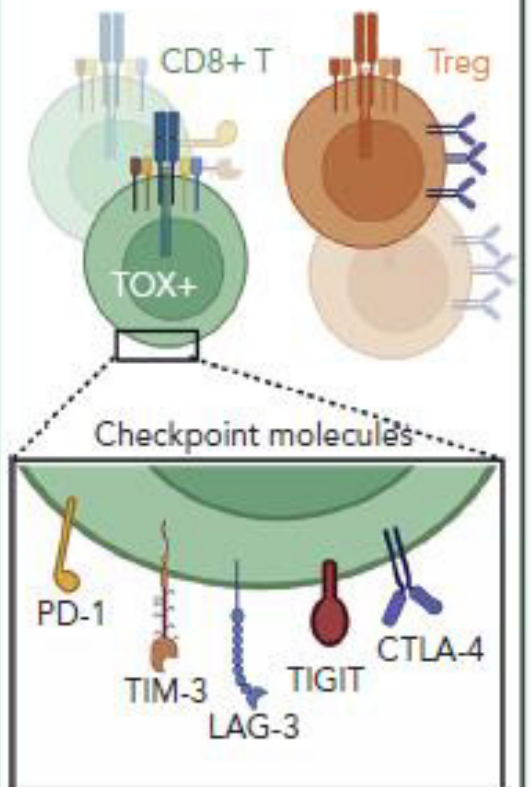
- **CASE 2:**
  RRMM 4LOT, progressing on Elranatamab in last line.
  BCMA-CART? Talq? TEC?
  ? BCMA deletion or Mutation; TME status

- **CASE 3:**
  Older RRMM Pt, advanced, progressing on TAL.
  Tec? Elra? Bela?
  ? BCMA deletion or Mutation; TME status

Mechanisms of Resistance to TCE

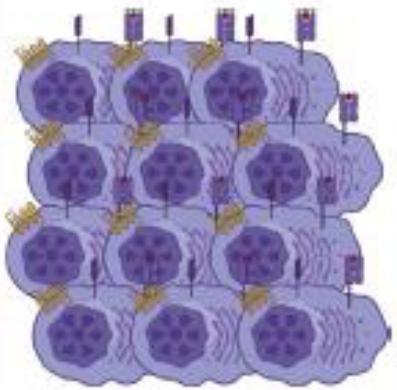
T cell dysfunction

T cell exhaustion
↑ CD8+ Tex
↓ CD8+ Teff
Checkpoint receptor expression
Lack of clonotypic expansion
CD4+ regulatory T cells (Treg)

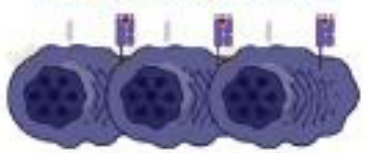


Tumor intrintsic

Tumor Biology
BMPC >50-60%
R-ISS stage III
Extramedullary disease



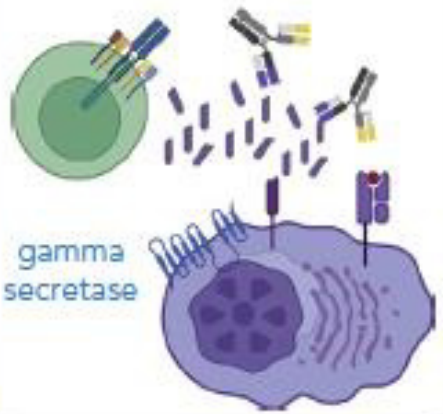
Target antigen loss



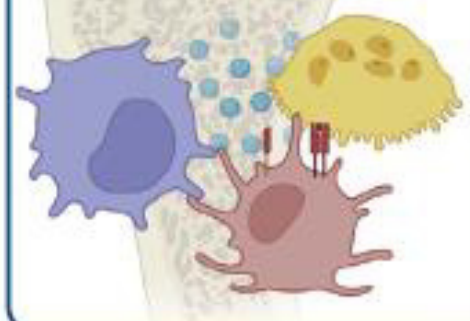
MHC downregulation

Tumor microenvironment

Soluble BCMA sink



Immunosuppressive cells & cytokines
Osteoclasts, tumor associated macrophages, plasmacytoid DC, myeloid-derived suppressor cells
IL-6, IL-10, TGF-β, IDO



Lee et al Blood 2024

Tumor intrinsic resistance

nature medicine

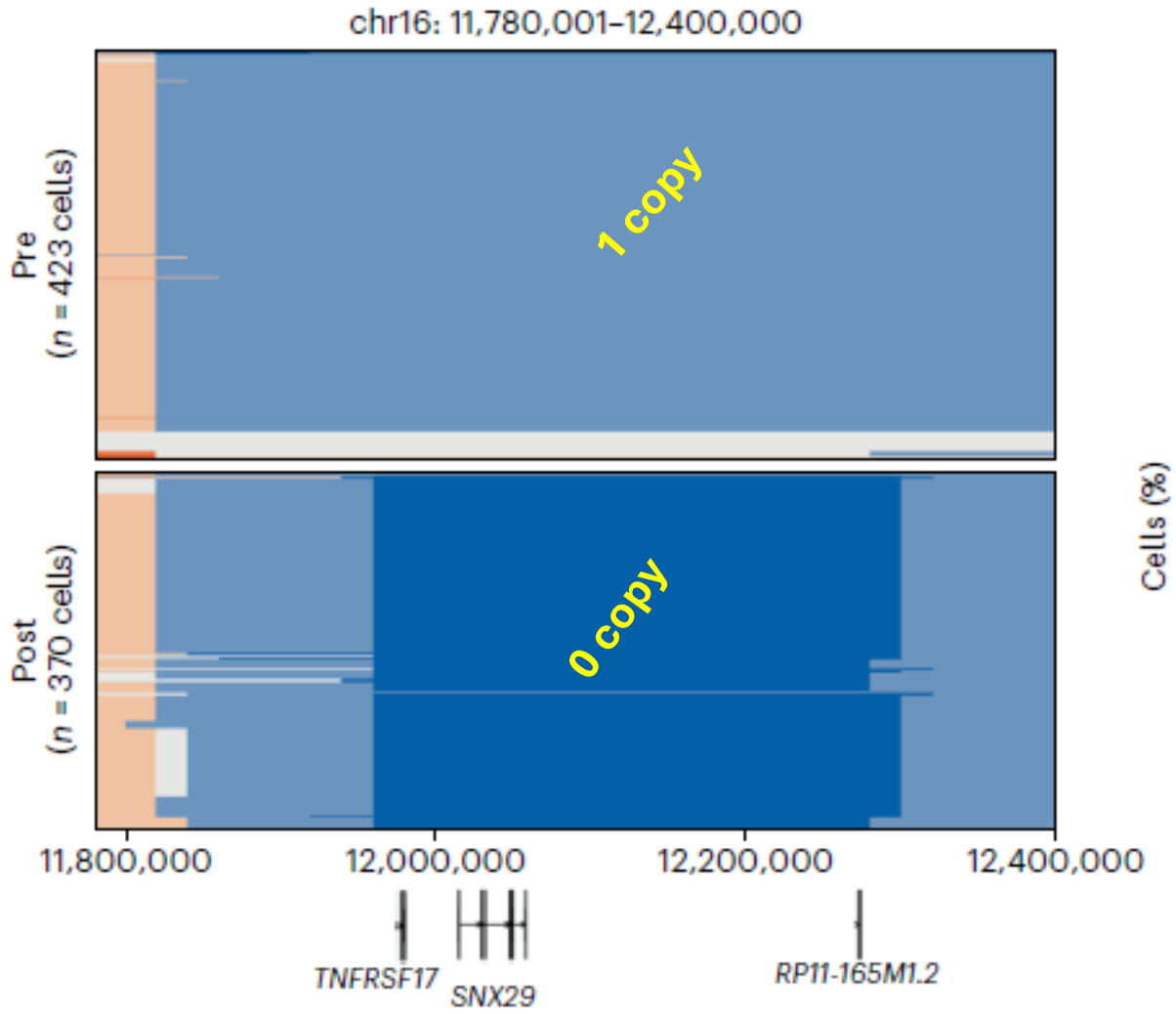
Article

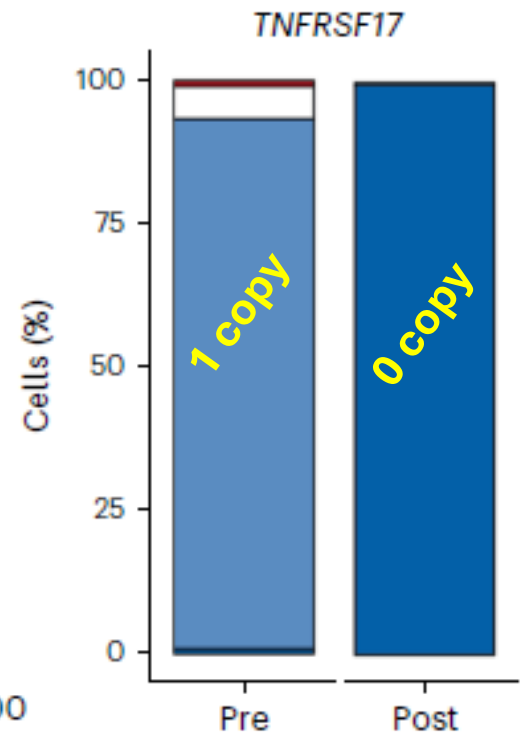
https://doi.org/10.1038/s41591-023-02491-5

Mechanisms of antigen escape from BCMA- or GPRC5D-targeted immunotherapies in multiple myeloma

Holly Lee[1], Sungwoo Ahn[1], Ranjan Maity[1], Noemie Leblay[1], Bachisio Ziccheddu[2], Marietta Truger[3], Monika Chojnacka[2], Anthony Cirrincione[2], Michael Durante[2], Remi Tilmont[1], Elie Barakat[1], Mansour Poorebrahim[1], Sarthak Sinha[4], John McIntyre[5], Angela M.Y. Chan[5], Holly Wilson[5], Shari Kyman[6], Amrita Krishnan[7], Ola Landgren[2], Wencke Walter[3], Manja Meggendorfer[3], Claudia Haferlach[3], Torsten Haferlach[3], Hermann Einsele[8], Martin K. Kortüm[8], Stefan Knop[8,9], Jean Baptiste Alberge[10], Andreas Rosenwald[11], Jonathan J. Keats[6,7,13], Leo Rasche[8,12,13] ✉, Francesco Maura[2,13] ✉, Paola Neri[1,13] & Nizar J. Bahlis[1,13] ✉

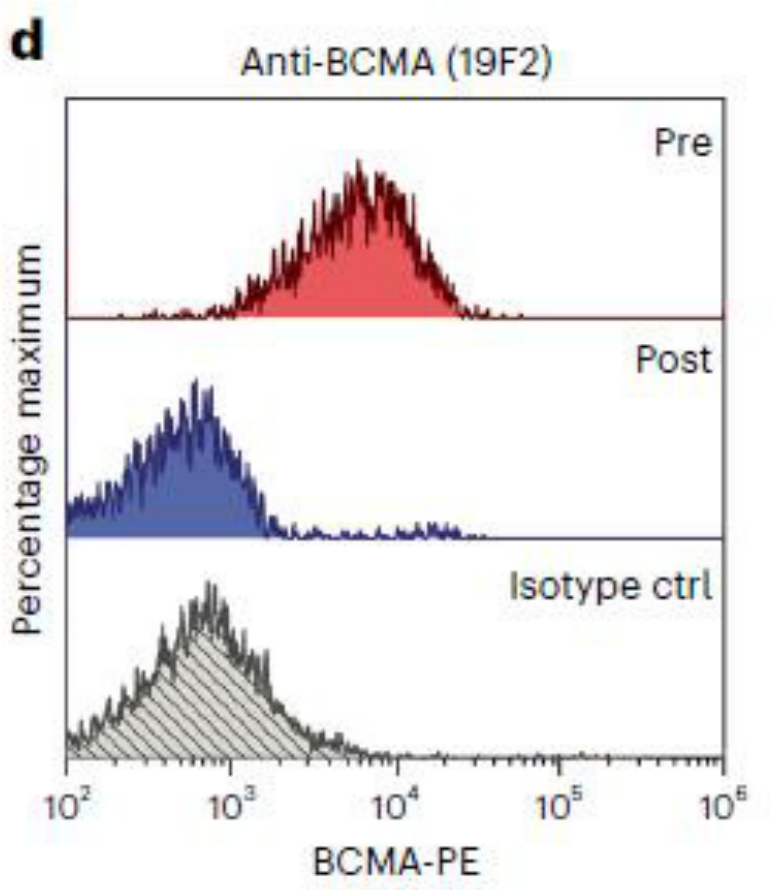
Focal biallelic loss of *TNFRSF17* → *relapse*



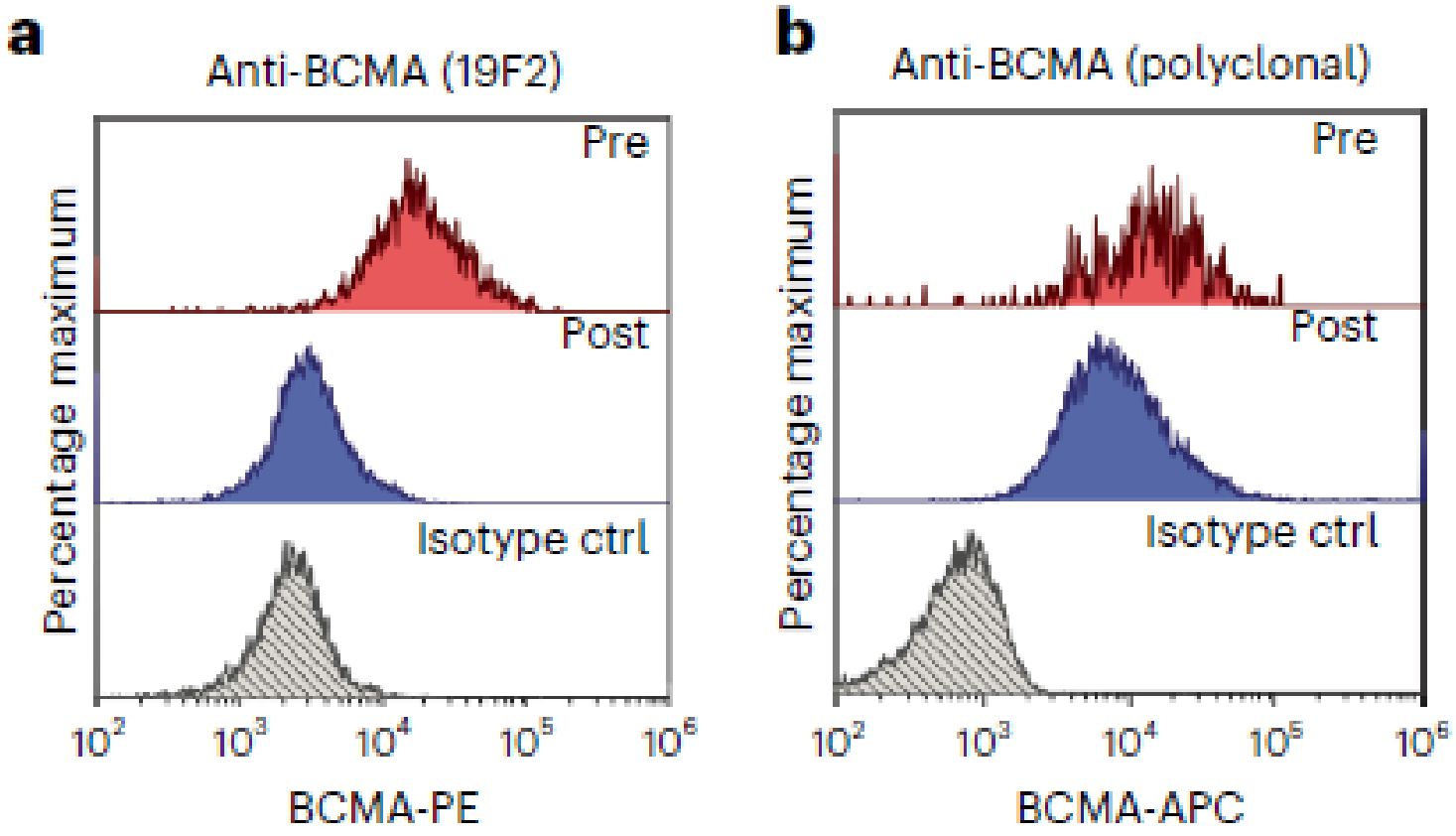


CNV	Pre-therapy (%)	Post-therapy (%)
4	1.1	0
3	0	0
2	5.7	0
1	92.4	0.5
0	0.8	99.5

Loss of BCMA expression



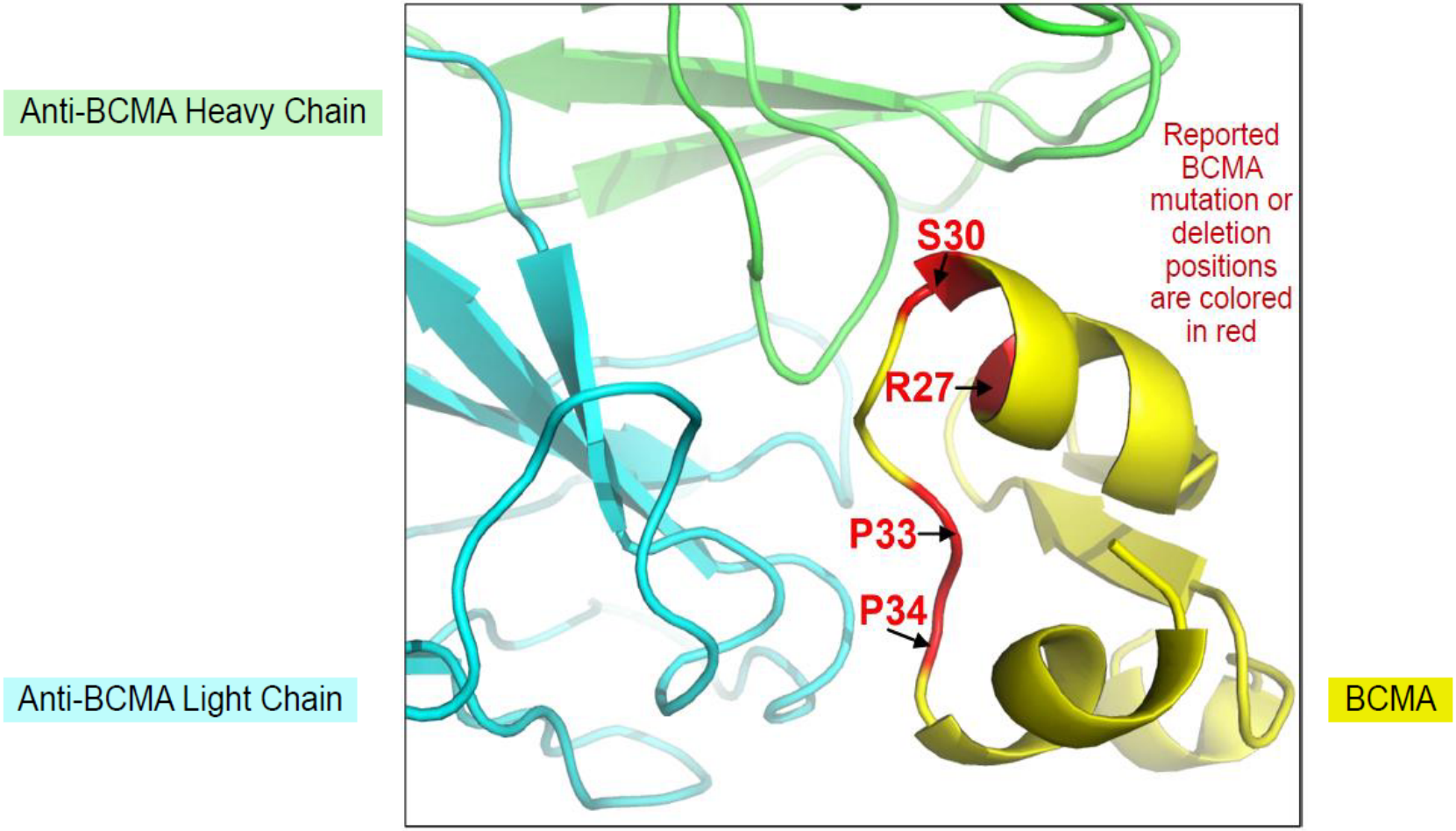
Monoallelic *TNFRSF17* deletion coupled with p.Arg27Pro mutation in the extracellular domain of BCMA mediates MM relapse after anti-BCMA TCE therapy



Monoclonal Anti-BCMA

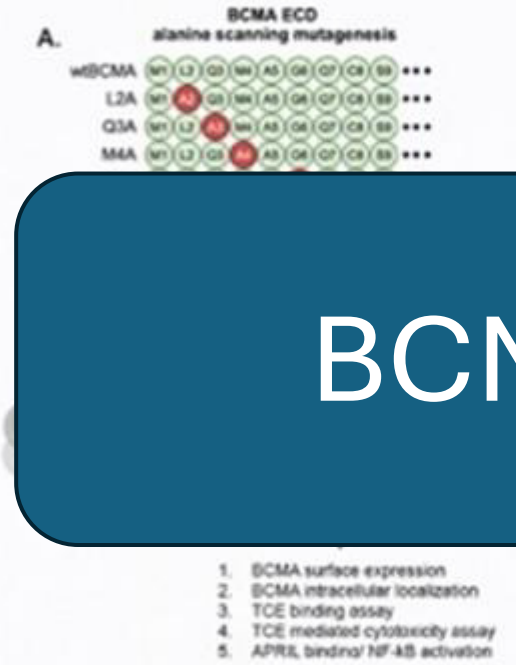
Polyclonal Anti-BCMA

Figure: Mapping the Reported BCMA Mutations on the Co-Structure of BCMA in Complex With the Parental Fab of Elranatamab[a]



Josic M et al. Poster presentation at ASCO 2024 (Abstract 7546).
Josic M et al. ePoster presentation at EHA 2024 (Abstract P1941).

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



BCMA functional hotspots cytotoxicity heatmap

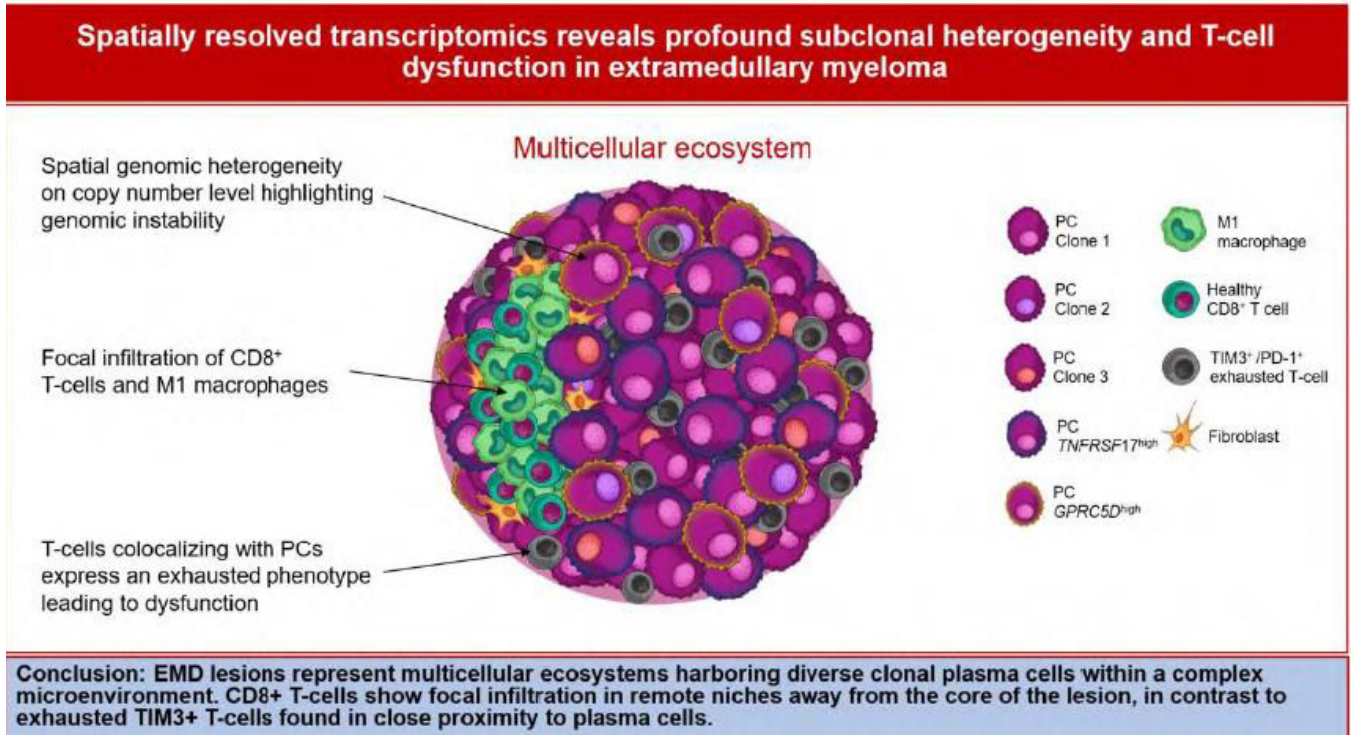
	Alone	PB	TEC 10	ELRA 10	ALN 10
EV	96.7	94.8	92.5	92.7	92.6
WT	93.5	90.4	18	16.2	16.4
WT_50	93.6	84.8	31	32.2	33.3
WT_100	93.4	93.6	18.4	17.1	15.6
WT_250	91.8	89.6	21.1	19.9	20.1
					16.6
					32.3
					71.6
					92.9
					90.8
					37.7
					94.1
					38.9
					83.8
					47.1
					32.8
					30
T32_mut29	93.7	80.7	28	20.1	28.1
P33_mut30	94.4	93.1	29	22.7	31.7
P34_mut31	94.3	93.3	32.2	24.5	30.5
C37_mut34	95.8	94.3	91.8	90.2	66.1
C41_mut38	95.3	93.1	37.2	29.5	38
N42_mut39	94.8	73.1	35.2	24.2	35.6
S44_mut40	96.6	94.6	30.4	20.7	33.5
N47_mut43	96.3	95.1	30.8	24	30.7
K50_mut46	95.3	94.5	25.9	24.7	28.1

Holly Lee, manuscript in preparation

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

BCMA is NOT "all or none"

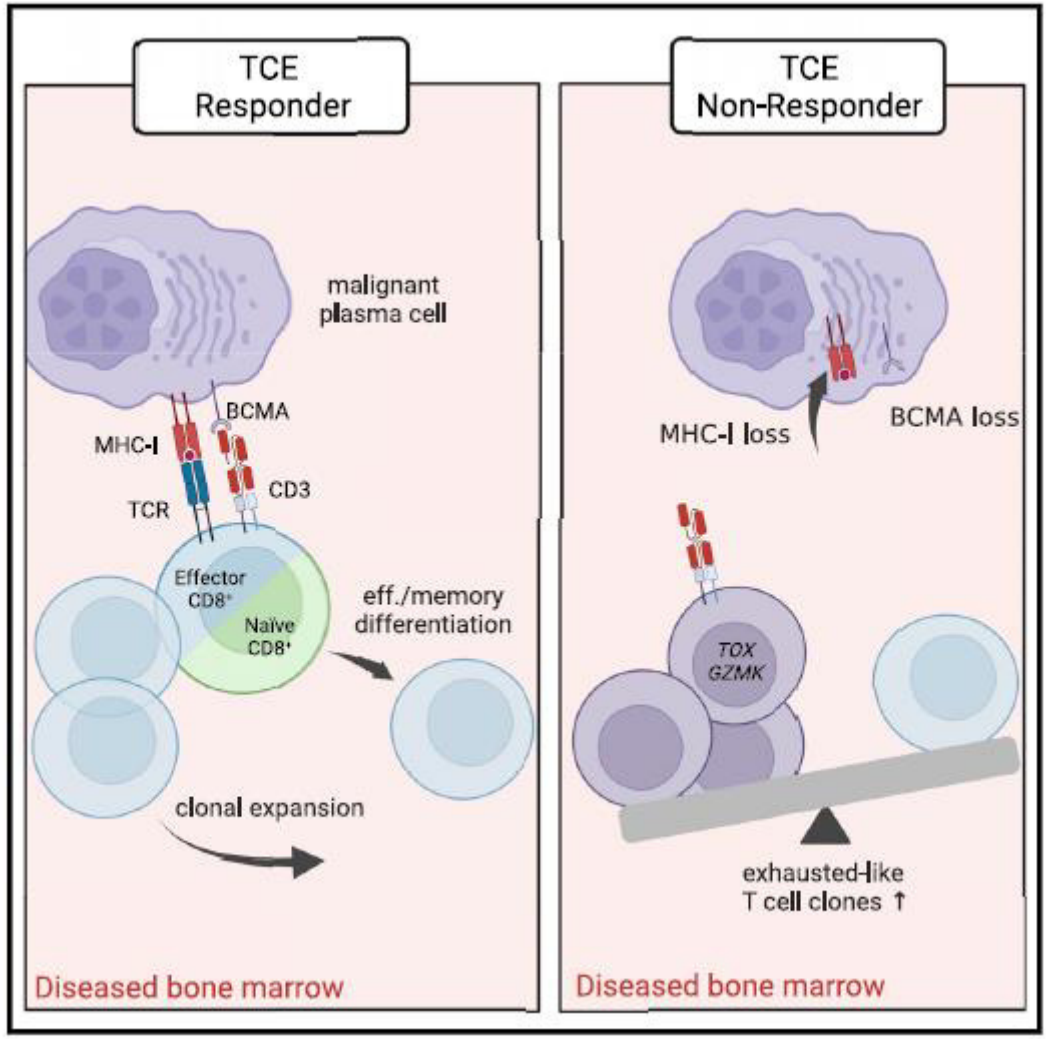
Heterogeneity of Tumor Surface Antigens



- EMD mimics the architectural complexity of solid tumors marked by diverse Microenvironments & multiclonality
- EMD shows infiltration of active T-cells spatially confined to niches segregated from MM cells, potentially affecting therapeutic response

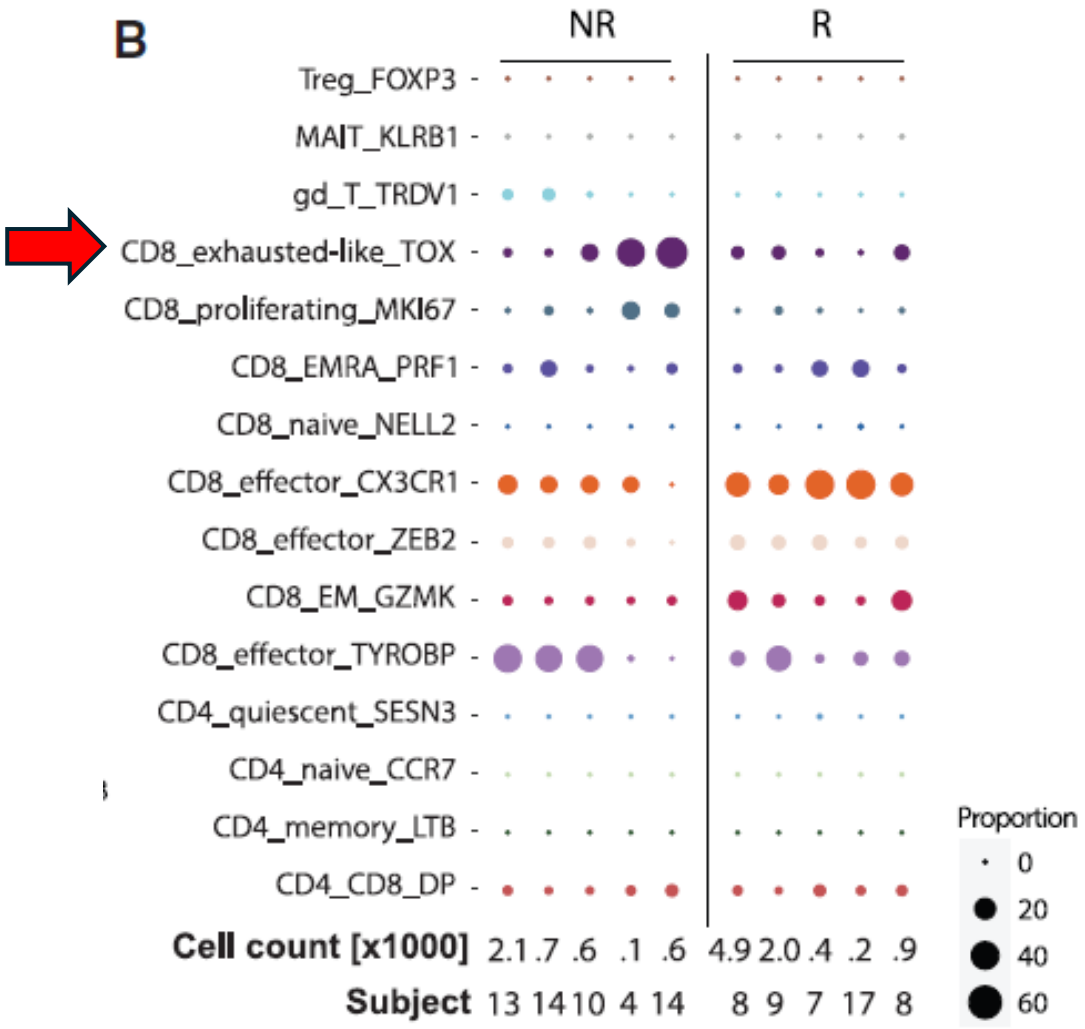
Mara J et al. Blood 2024.

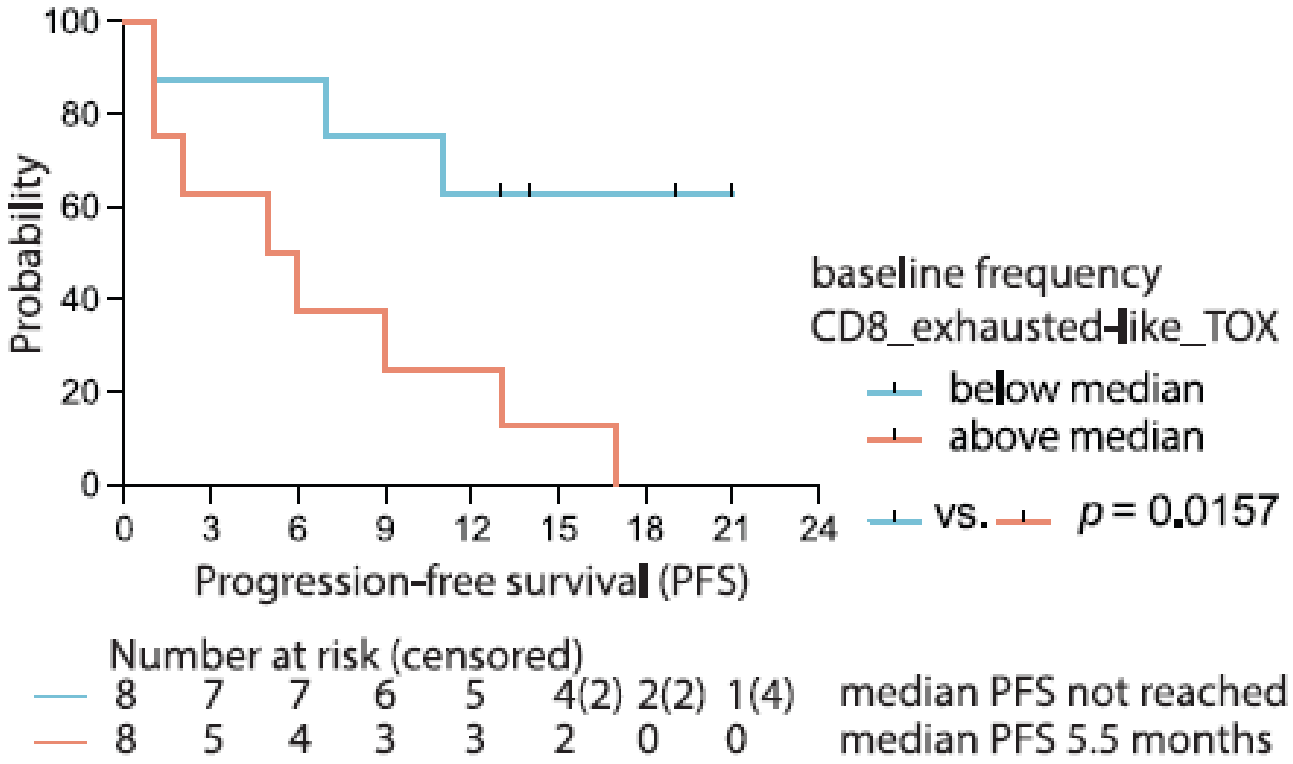
Effect of Tumor Microenvironment



Friedrich et al., 2023, Cancer Cell *41*, 711–725

Exhausted CD8 phenotype associated with poor response to BCMA-TCE





Friedrich et al., 2023, Cancer Cell *41*, 711–725

Pharmacodynamic Signatures and Correlatives of Response in Patients With Relapsed/Refractory Multiple Myeloma Treated With Talquetamab or Teclistamab Plus Daratumumab and Pomalidomide

Deeksha Vishwamitra[1], Sheri Skerget[1], Diana Cortes-Selva[1], Kalpana Bakshi[1], Lien Vandenberk[2], Weili Sun[3], Jaszianne Tolbert[1], Colleen Kane[1], Hein Ludlage[4], Bas D Koster[5], Julie S Larsen[3], Tobias Kampfenkel[6], Ching Li [1], Farheen Zishan[7], Thomas Prior[1], Luciano J Costa[8], Jesus G Berdeja[9], Cyrille Touzeau[10], Aurore Perrot[11], Emma Searle[12], Jeffrey V Matous[13], Ajai Chari[14], Donna Reece[15], Manisha Bhutani[16], Bhagirathbhai Dholaria[17], Anita D'Souza[18], Thomas G Martin[14], John McKay[19], Alfred L Garfall[20], Amrita Y Krishnan[21], Niels WCJ van de Donk[22], Nizar J Bahlis[23], Ricardo Attar[1]

ASH2024

PD Signatures and Correlatives of Response to Tal-Dara-Pom or Tec-Dara-Pom

Key inclusion criteria and baseline characteristics

TRIMM-2 (Tal-Dara-Pom)

≥3 prior LOT, including a PI and IMiD, or double-refractory to a PI and IMiD

Patients (n [%]) **refractory to**
Anti-CD38 (64 [83.1])
Pomalidomide (58 [75.3])

MajesTEC-2 (Tec-Dara-Pom)

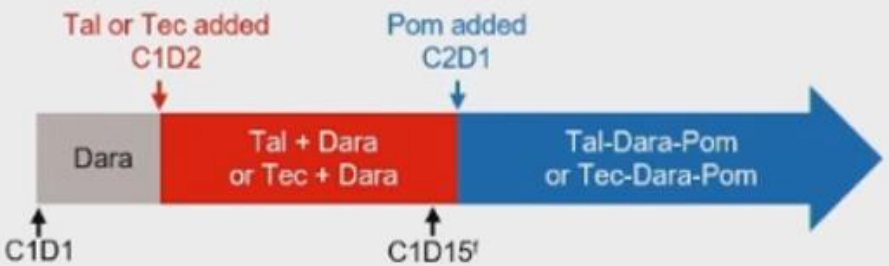
1–3 prior LOT, including a PI and lenalidomide

Patients (n [%]) **refractory to**
Anti-CD38 (1 [5.9])
Pomalidomide (1 [5.9])

Prior BsAb exposure was permitted in both studies[a]

Patients (n [%]) **refractory to BsAbs**
Tal-Dara-Pom: (29 [37.7])
Tec-Dara-Pom: (0 [0])

TRIMM-2[b,c] (N=77) or MajesTEC-2[d,e] (N=17)



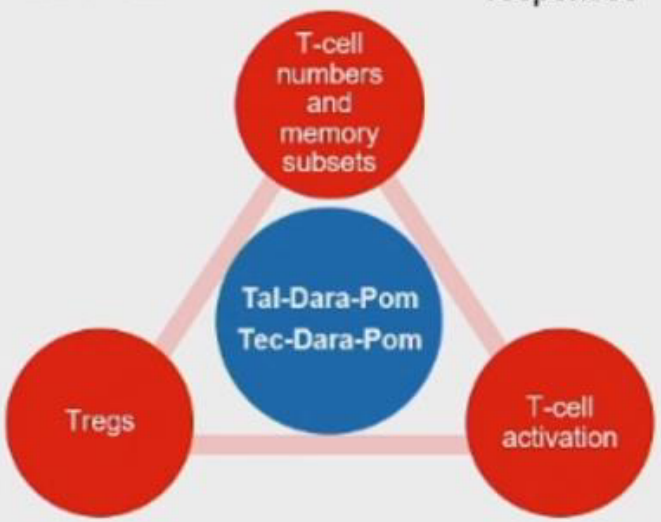
Peripheral blood

Flow cytometry

Analyses

PD:
Immune profiling demonstrating the added effects of Dara + Pom to Tal or Tec

Mechanisms of depth and DOR:
Assessment of immune-cell profiles correlating with deep and durable responses



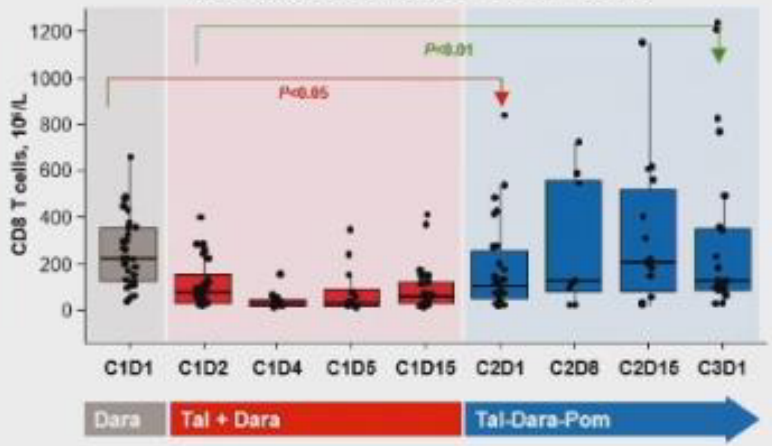
Tal-Dara-Pom data presented first, followed by Tec-Dara-Pom

Complementary PD Effects Observed With Tal + Dara, Which Was Synergized by Pom

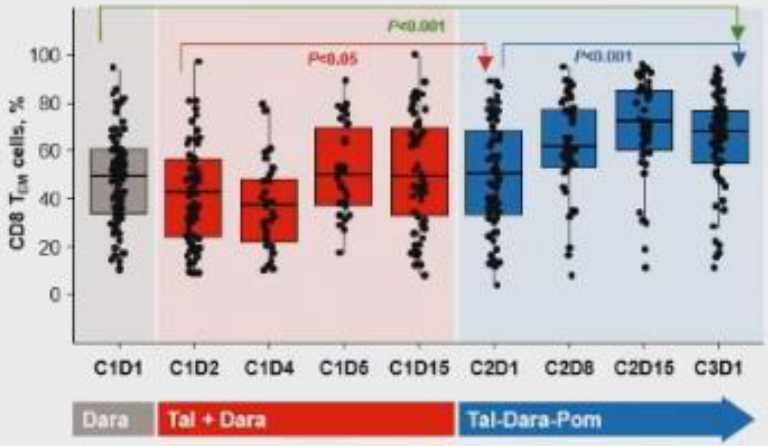
Tal-Dara-Pom

T-cell dynamics

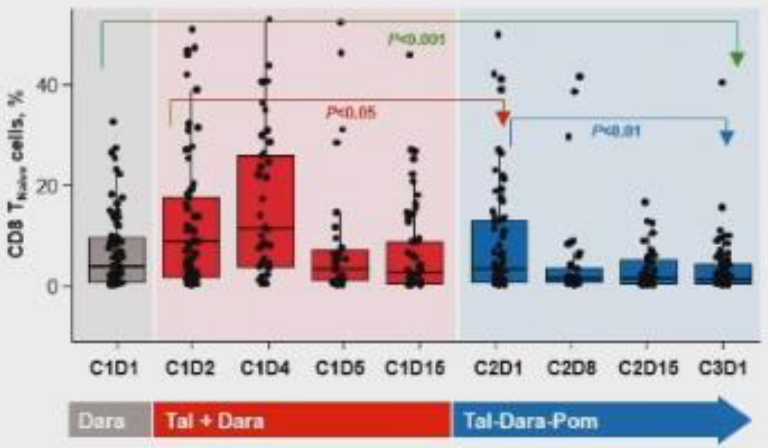
Tal-Dara-Pom–mediated recovery of absolute counts of CD8 T cells[a]



Tal-Dara-Pom–mediated CD8 T_{EM} cell expansion



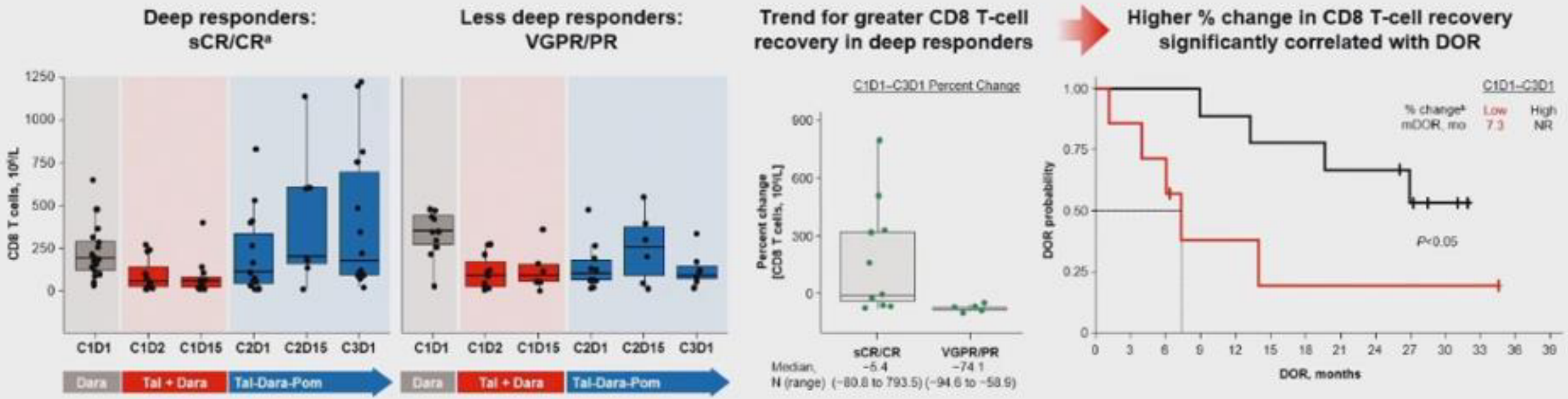
Tal-Dara-Pom–mediated CD8 T_{Naive} cell reduction[a]



- Complementary PD effects resulted in a **durable, activated immune response, a shift toward an antigen experienced memory phenotype, and a less immunosuppressed environment**
- Synergistic potential observed with Tal + Dara for an initial immune response and enhanced with the addition of Pom to extend the immune effects

Durable Recovery of CD8 T Cells Observed in Deep Responders to Tal-Dara-Pom and Correlated Significantly With Longer DOR

Tal-Dara-Pom



- Following T-cell margination, **a more durable recovery of CD8 T cells was observed in deeper responders (sCR/CR vs VGPR/PR)** and correlated with longer DOR

Molecular Correlates of response to T-ell re-directional therapy in Myeloma – Current State

- It is complex, much still unknown, yet our understanding is advancing
- Path towards tailored therapy –
  - **Mapping Tumor landscape** – target mutations & deletion as well as downstream tumorigenic pathways of escape
  - **Mapping & monitoring TME fitness**
- Impact can be highly significant -- to select, sequence, avoid under/over treatment & reduce development of resistance

Myeloma Molecular Diagnostic Lab
Hematology Division, Tel Aviv Sourasky Medical Center

Goal:

Provide multi-dimensional correlative measures to predict response of Myeloma patients to therapy, focus on resistance to BisAb and CART therapy → towards decision a support tool for optimizing therapy selection and sequencing

Study will cover different molecular levels of tumor, DNA, RNA & antigen expression on the cells surface, as well as characterization of TME

Team:

Prof. Yael Cohen
Head of Myeloma Unit,
Hematology Institute

Dr. Dalit Hecht
Head of Molecular Myeloma
Research Center

Collaborators:

Dr David Hagin, MD PhD
Head, Allergy and Clinical
Immunology Unit

Dr Ayala Lagzuel, PhD
Director, Clinical Genetics
Laboratory

Dr Avraham (Rami) Unterman, MD, MBA
Head, Pulmonary Fibrosis Center of Excellence
PI, Genomic Research Laboratory for Lung Fibrosis
Institute of Pulmonary Medicine

Myeloma Molecular Lab

Annotated Clinical Data

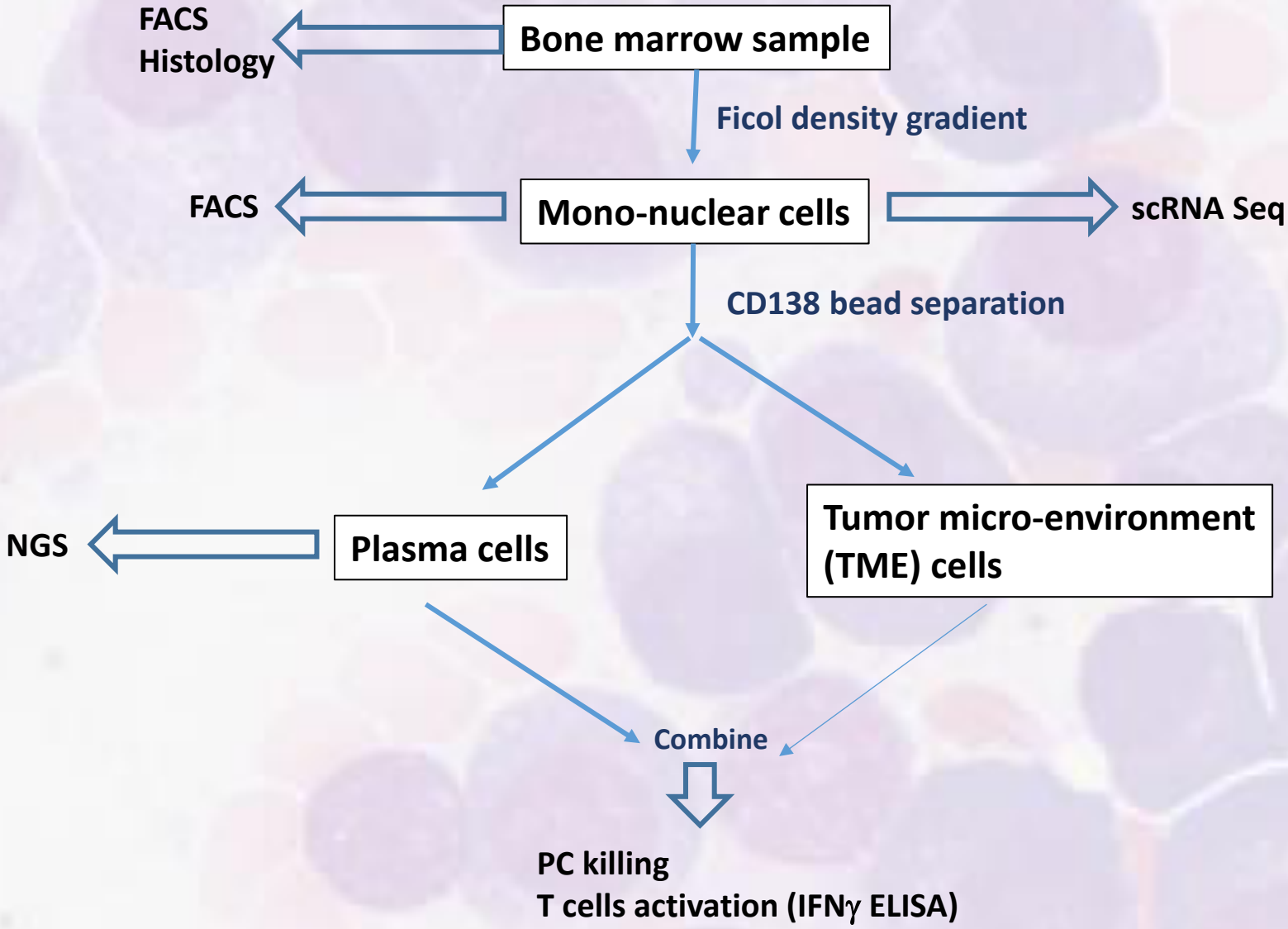
Muti-Omic Data

Decision Support

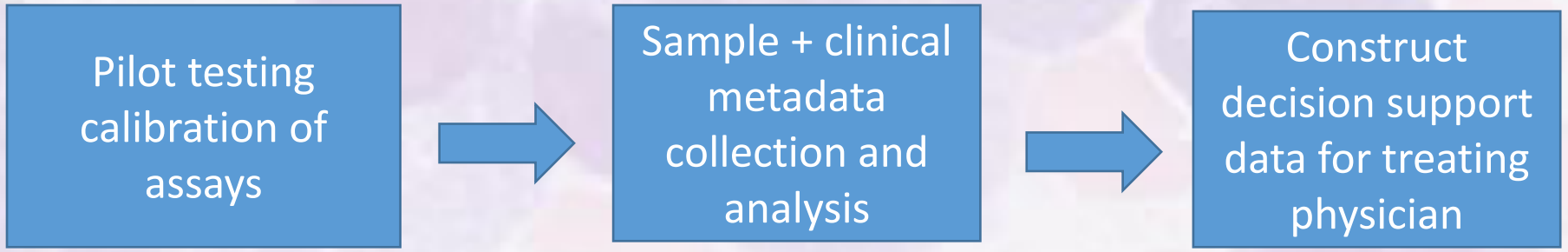
Planned analyses

1. Genomic sequencing of targets –TNFRSF17, GPRC5D, FcRH5 [+WES]
   - Identification of InDel and point mutations - NGS
   - Characterization of copy number variation- bionano (OGM)
2. RNA expression of targets –TNFRSF17, GPRC5D, FcRH5 + pathways of interest (e.g. NFkB)
   - scRNAseq of plasma cells
3. Characterization of cell surface expression of targets
   - FACS – comparison of binding between BisAb and commercial Ab
4. TME analysis – exhaustion markers
   - FACS and scRNAseq
5. Cell-Cell drug dependent interaction assays
   - Killing assay for plasma cells- incucyte
   - Activation of TME –ELISA
6. Soluble BCMA levels
   - Ella (?) / Elisa

From sample to analysis



Lab set-up



- We are currently setting up FACS, cell-cell interactions, genomic DNA NGS, scRNAseq, sBCMA assay
- Using myeloma cell lines as well as Patient BM samples
- We intend to collaborate with multiple centers in Israel

Looking forward to Collaborate !