Highlights from IMS 20th meeting 2023

Carolina Terragna

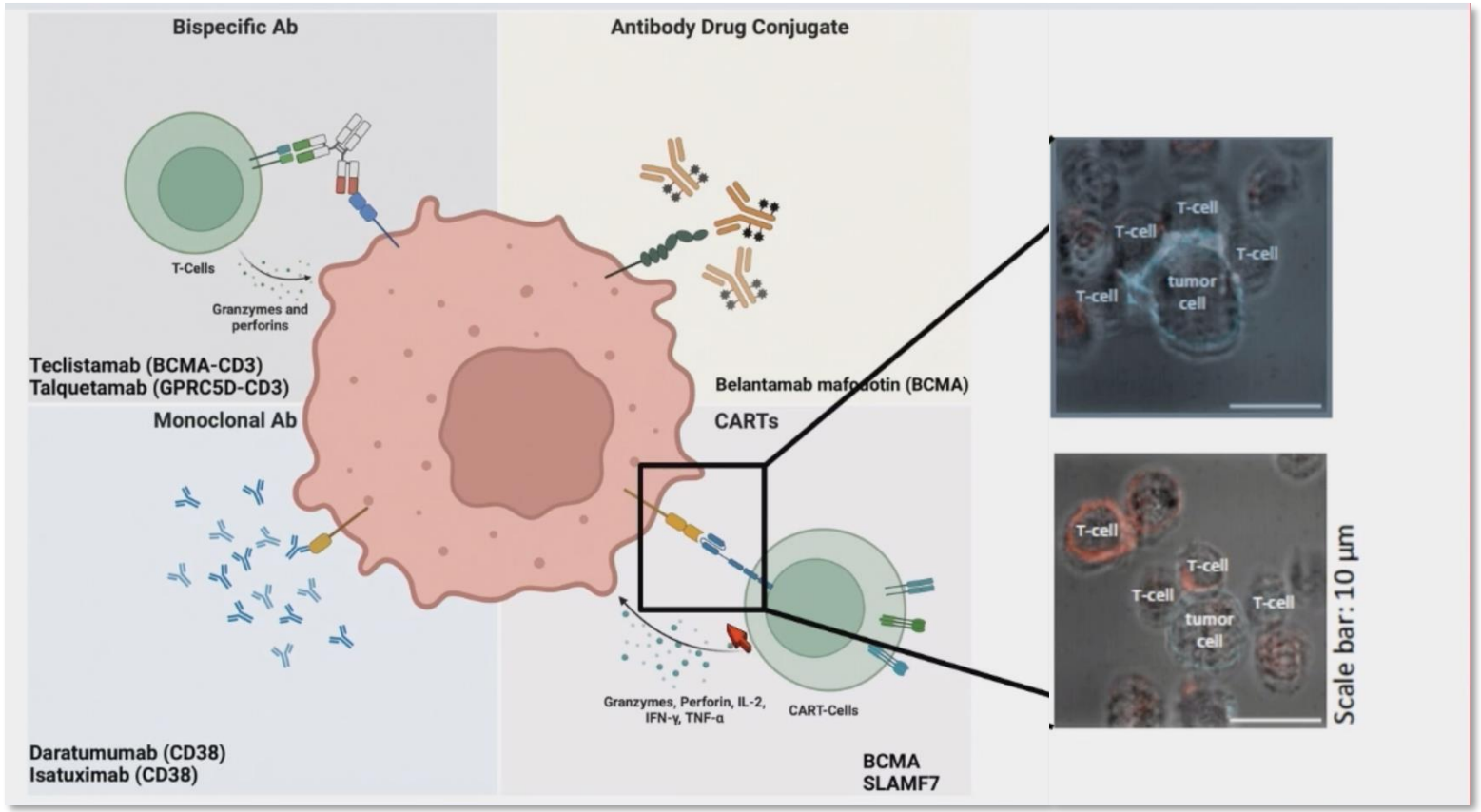
Meccanismi di perdita dell'antigene

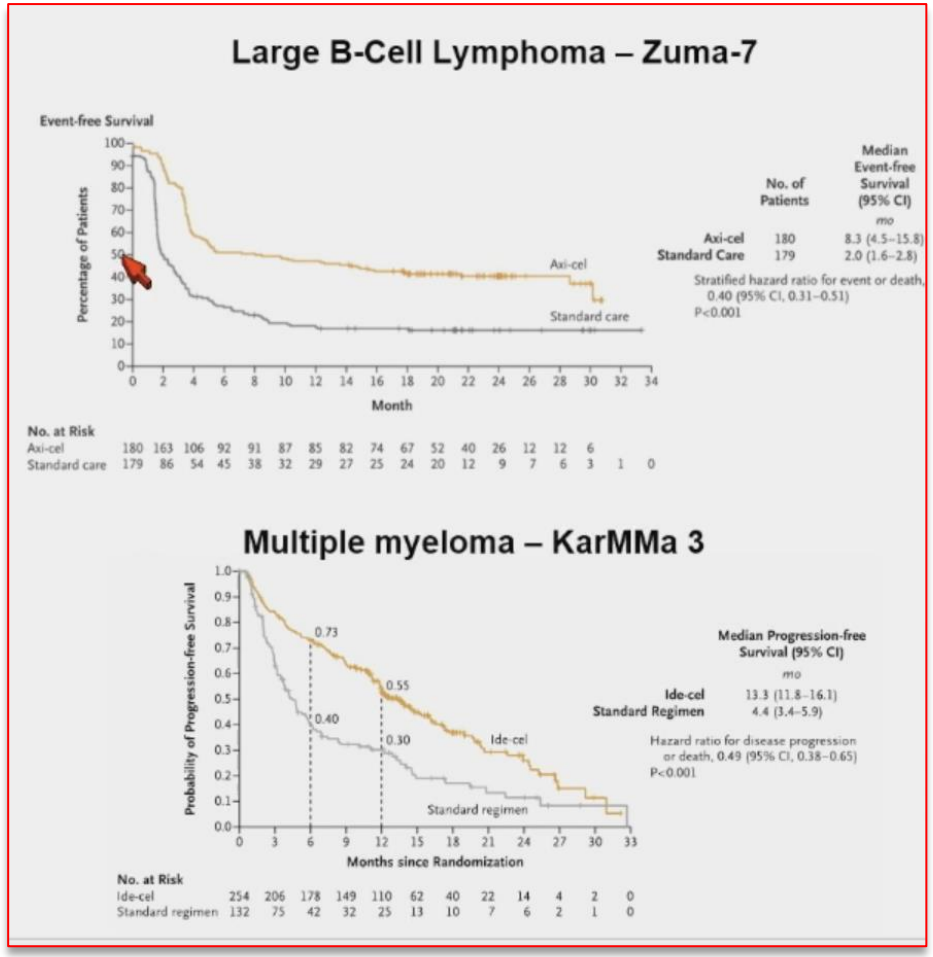
30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

Carolina Terragna

nothing to disclose

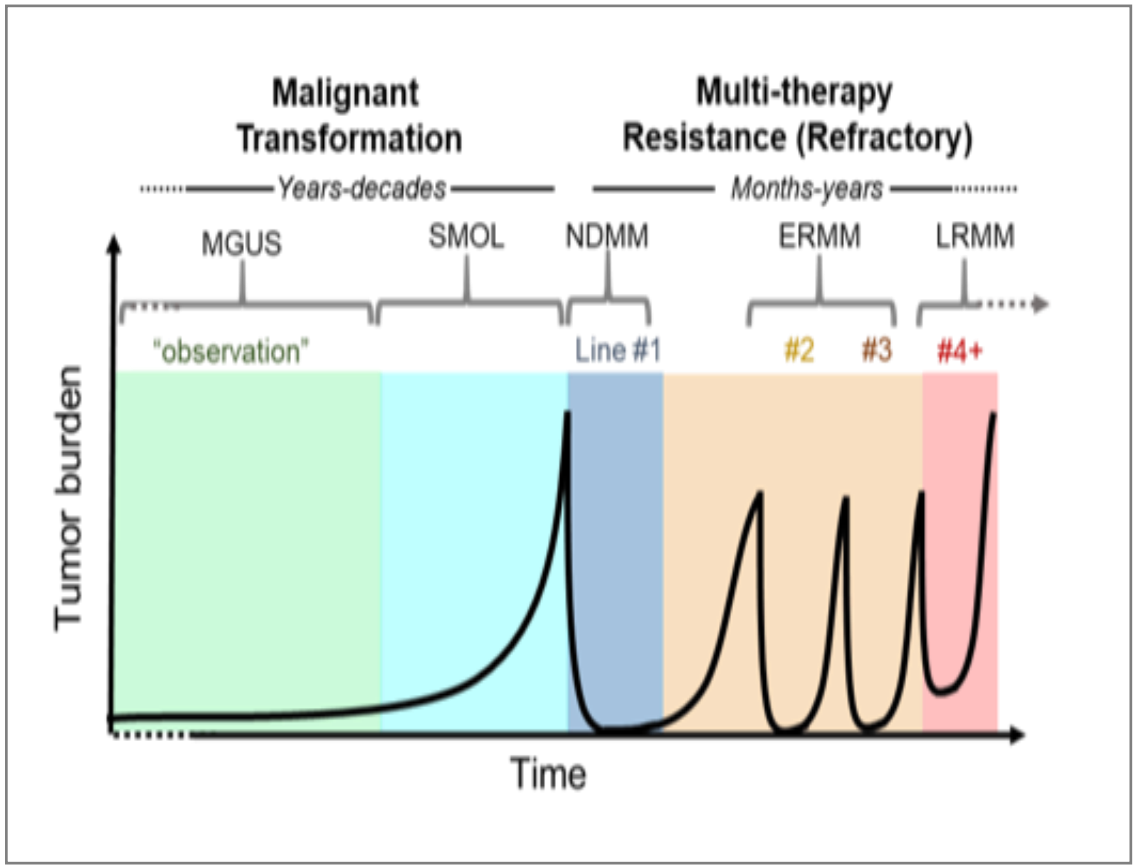
mechanism of resistance to immunotherapy

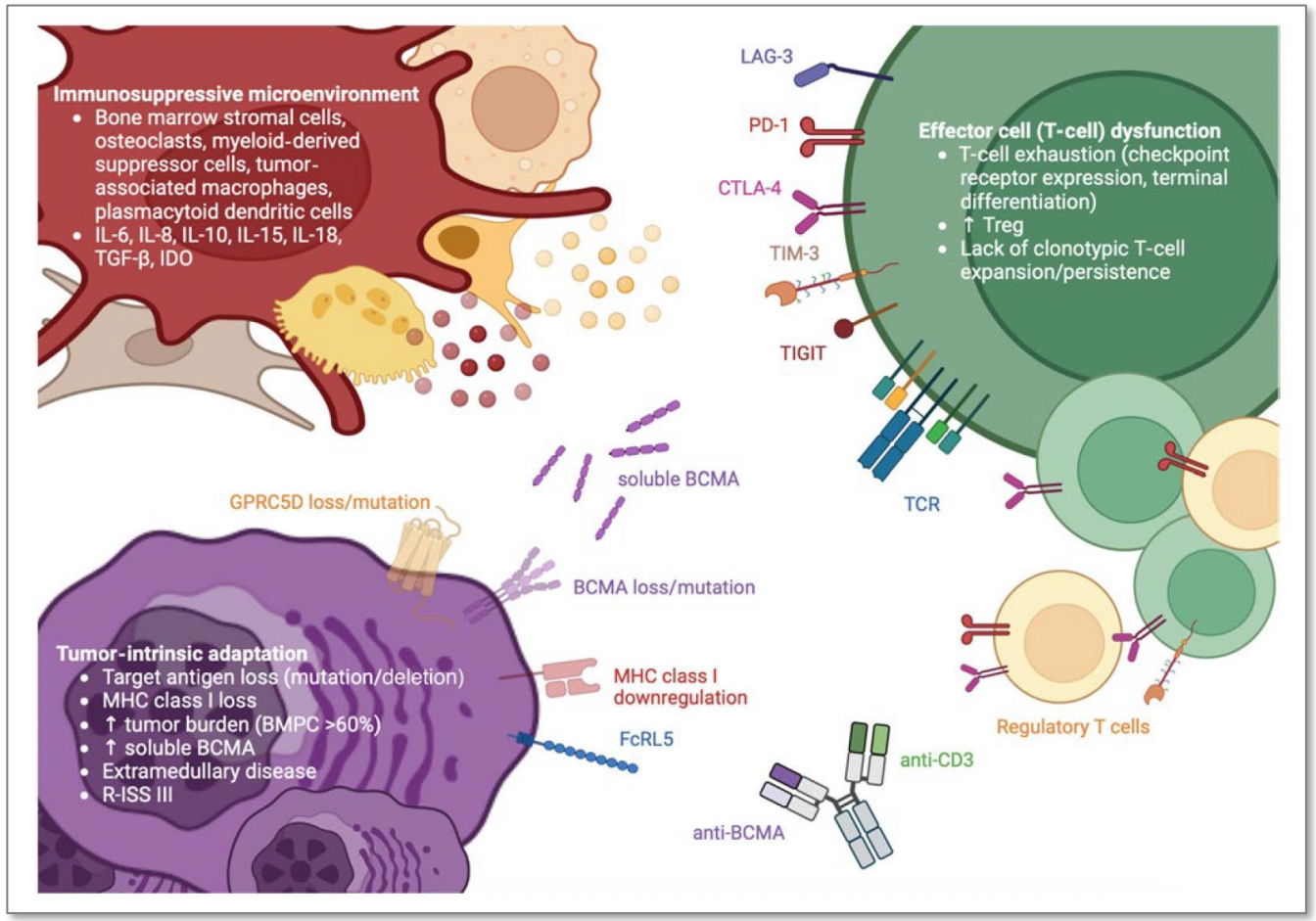




H.Lee et al, Hematology 2023
F.Maura, ASH 2023

mechanism of resistance to immunotherapy

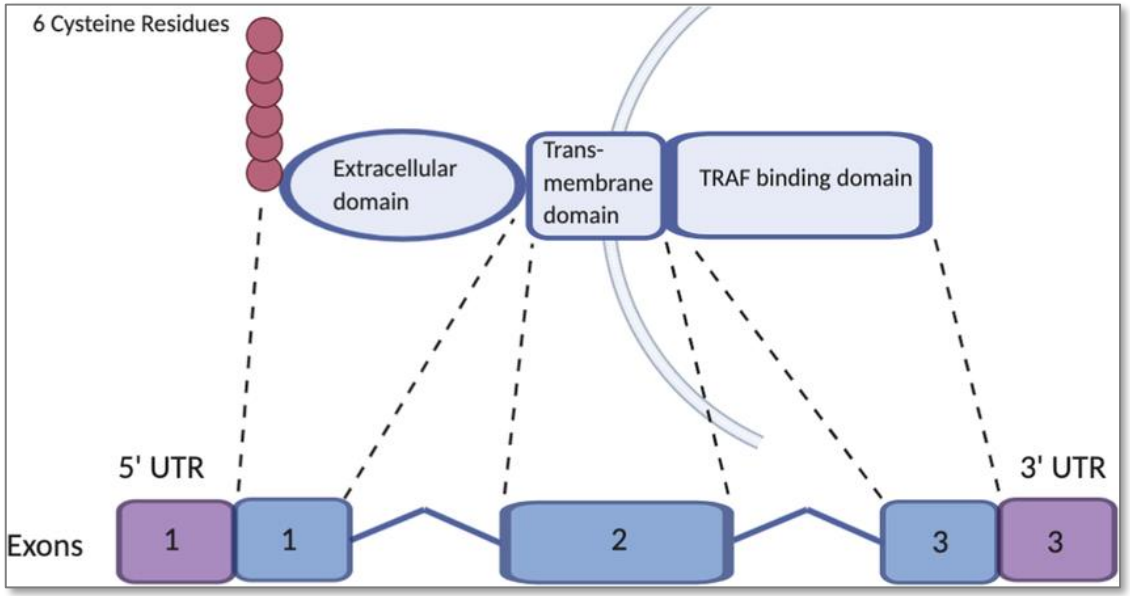




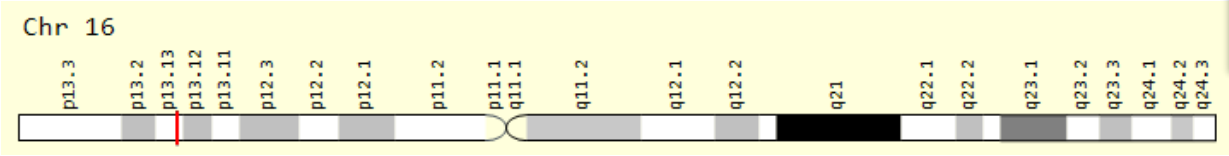
H.Lee et al, Hematology 2023

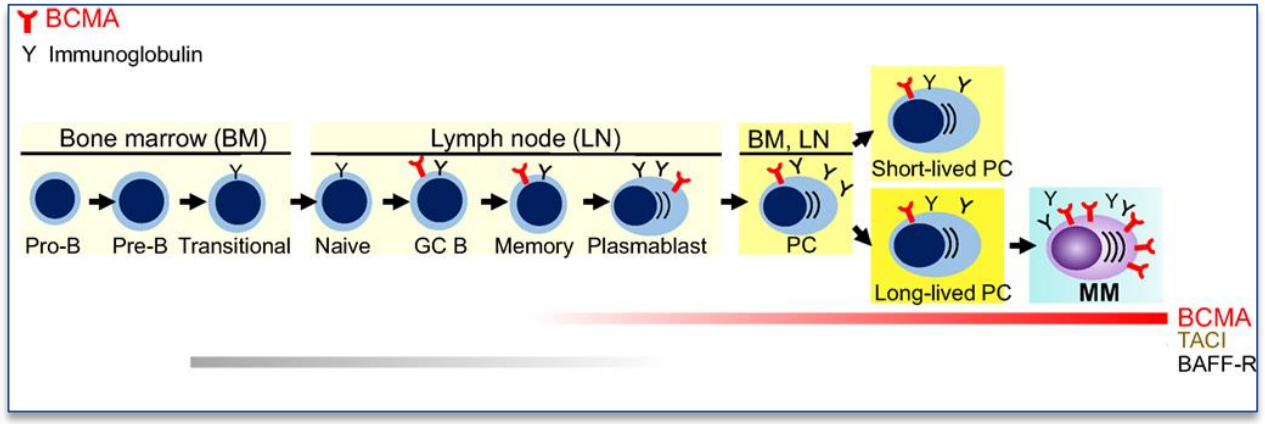
know your enemy

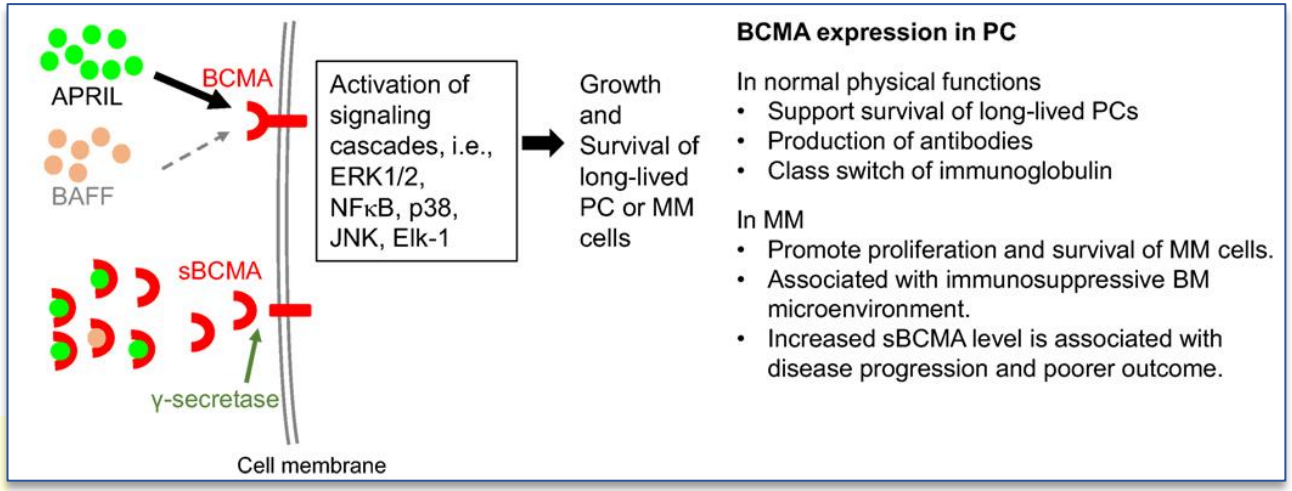
B-cell Maturation Antigen, **BCMA**



TNFRSF17 – chromosome 16p

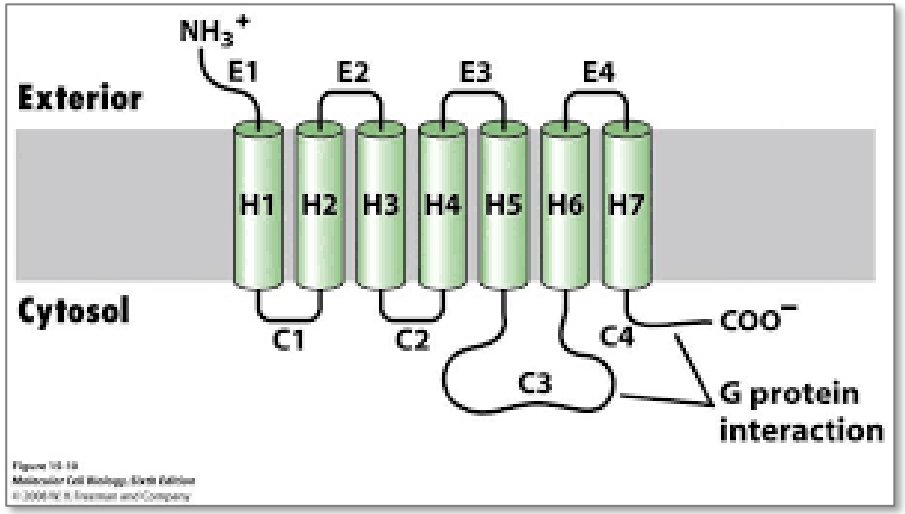


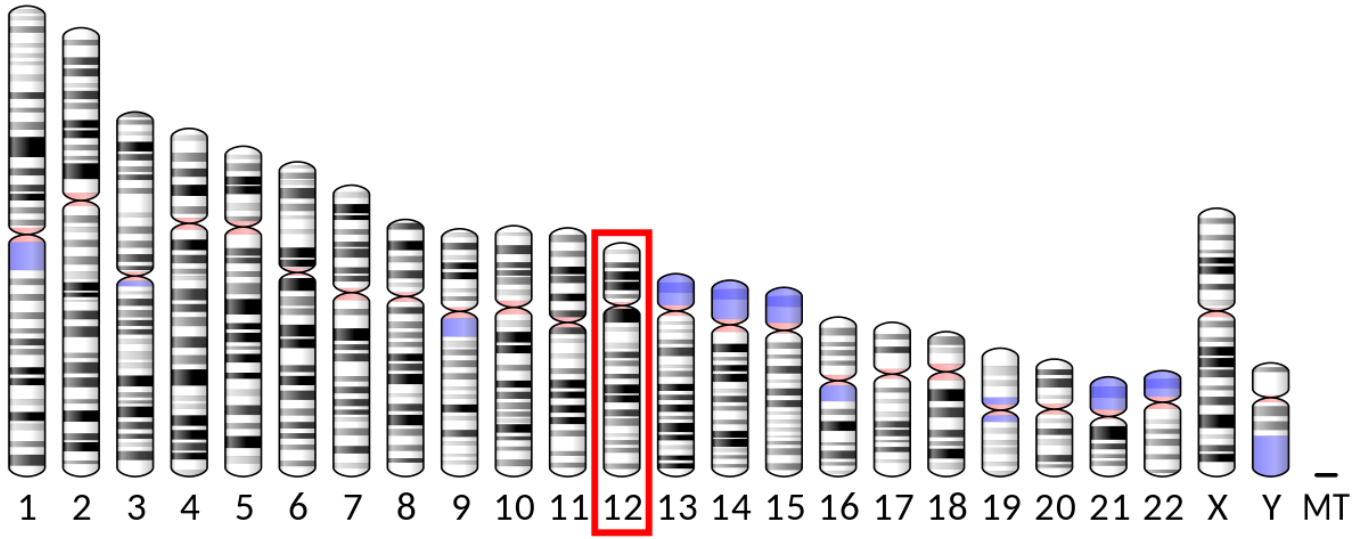




know your enemy

G protein-coupled Receptor class C group 5 member D, **GPRC5D**

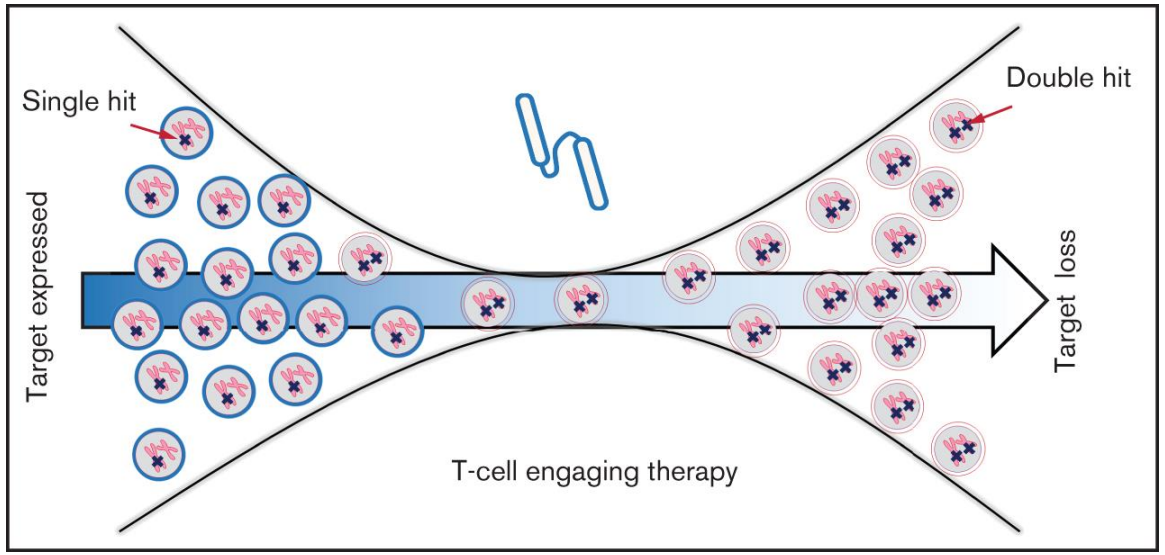




12p32

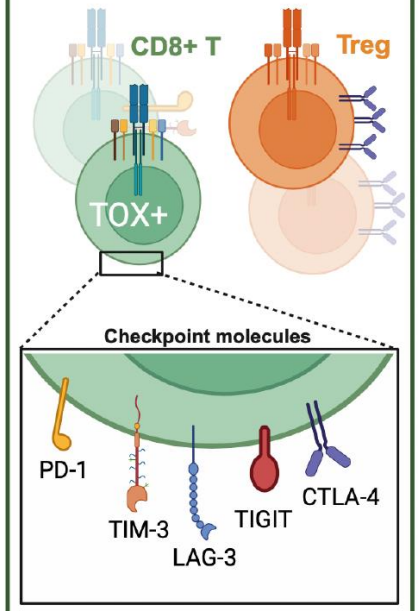
a stressful situation

what affects the response to immunotherapy



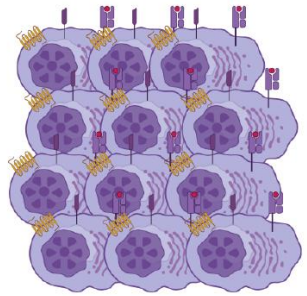
T cell dysfunction

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

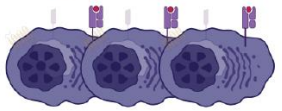


Tumor intrintsic

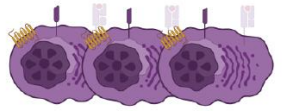
Tumor Biology
BMPC >50-60%
R-ISS stage III
Extramedullary disease



Target antigen loss

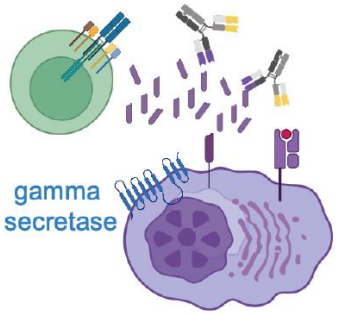


MHC downregulation

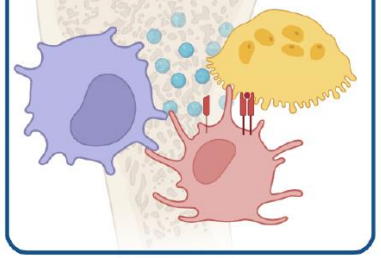


Tumor microenvironment

Soluble BCMA sink



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



H.Lee. et al, Blood 2024
M.S.Truger, Blood Adv 2021

pre-therapy mutations

pre-existing focal *TNFRSF17* and *GPRC5D* (*and other possible target*) mutations

➔ 100 patients *T cell immunotherapy-naive*

=> WGS screening for genomic alteration

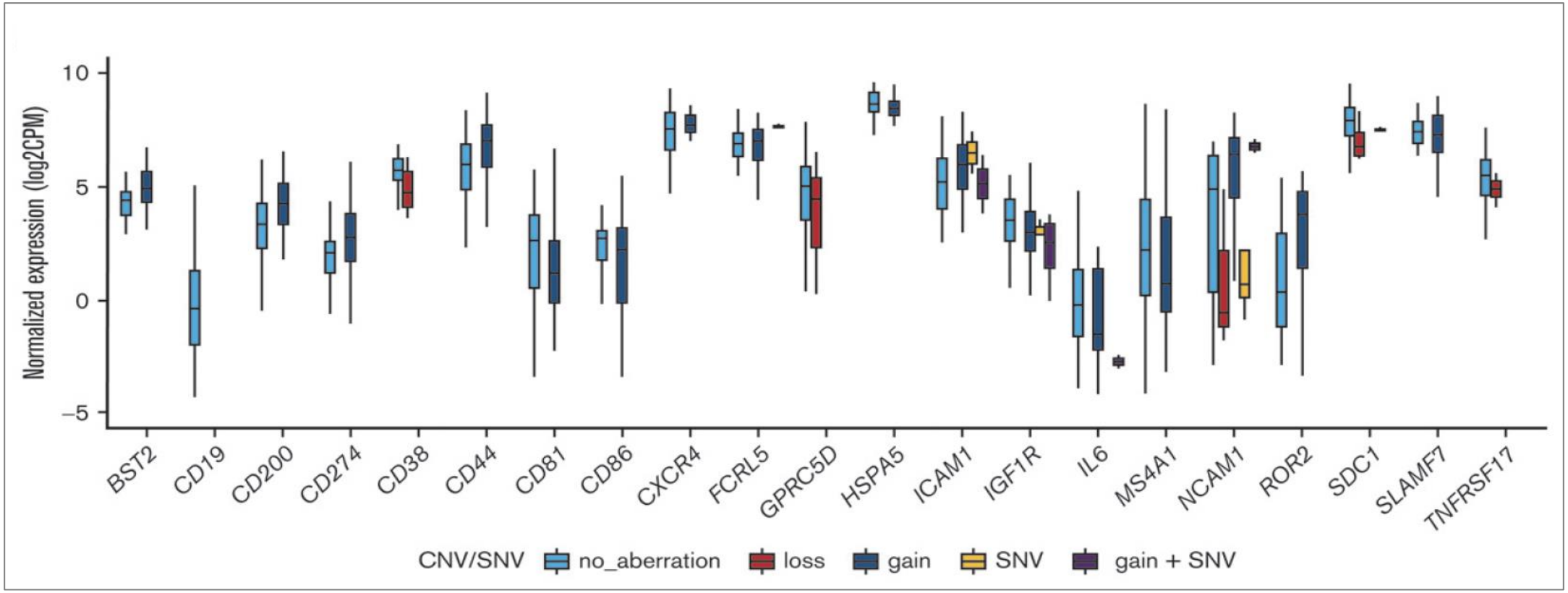
	monoallelic CN loss/SNVs			
gene	NDMM (=50)	RRMM (=50)	CoMMpass dataset (=896 NDMM)	MLL dataset (=400 NDMM)
TNFRSF17	1-5%	8%	3%	2%
GPRC5D	10-20%%	20%	15%	13%
NCAM1 (CD56)	2%	4%	/	/
CD38	2%	18%	/	/
SLAMF7	3%	4%	/	/

Gene	Chromosome	Genomic position (hg19) start	end	Examples of currently available preclinical and clinical immunotherapies
TNFRSF17 (*BCMA*)	16p13.13	12058964	12061925	multiple uni- and multispecific CAR T-cells, bispecific antibodies and antibody drug conjugates under clinical investigation
CD19	16p11.2	28943260	28950667	CAR T-cell under clinical investigation
GPRC5D	12p13.1	13093709	13105081	bispecific antibody under clinical investigation
CD38	4p15.32	15779898	15854853	uni- and multispecific CAR T-cells under clinical investigation, daratumumab, isatuximab
SLAMF7	1q23.3	160709037	160724611	CAR T-cell, antibody drug conjugate under clinical investigation, elotuzumab
FCRL5 (*CD307*)	1q23.1	157483167	157522310	bispecific antibody under clinical investigation
IL6	7p15.3	22765503	22771621	monoclonal antibody tocilizumab, siltuximab
IGF1R	15q26.3	99192200	99507759	monoclonal antibody AVE1642
			94	CAR T-cell, antibody drug conjugate under clinical investigation
			158	CAR T-cell in preclinical setting
			609	monoclonal antibody PAT-SM6 under clinical investigation
			735	monoclonal antibody ulocuplumab under clinical investigation
			233	monoclonal antibody rituximab
			49	monoclonal antibody in preclinical setting
			66	monoclonal antibody nivolumab under clinical investigation
			57	monoclonal antibody in preclinical setting
			659	monoclonal antibody samalizumab under clinical investigation
			949	CAR T-cell under clinical investigation
			291	antibody drug conjugate in preclinical setting
			983	monoclonal antibody CTLA4Ig in preclinical setting
ROR2	9q22.31	94325373	94712444	potential target in preclinical setting

M.S.Truger, Blood Adv 2021

pre-therapy mutations

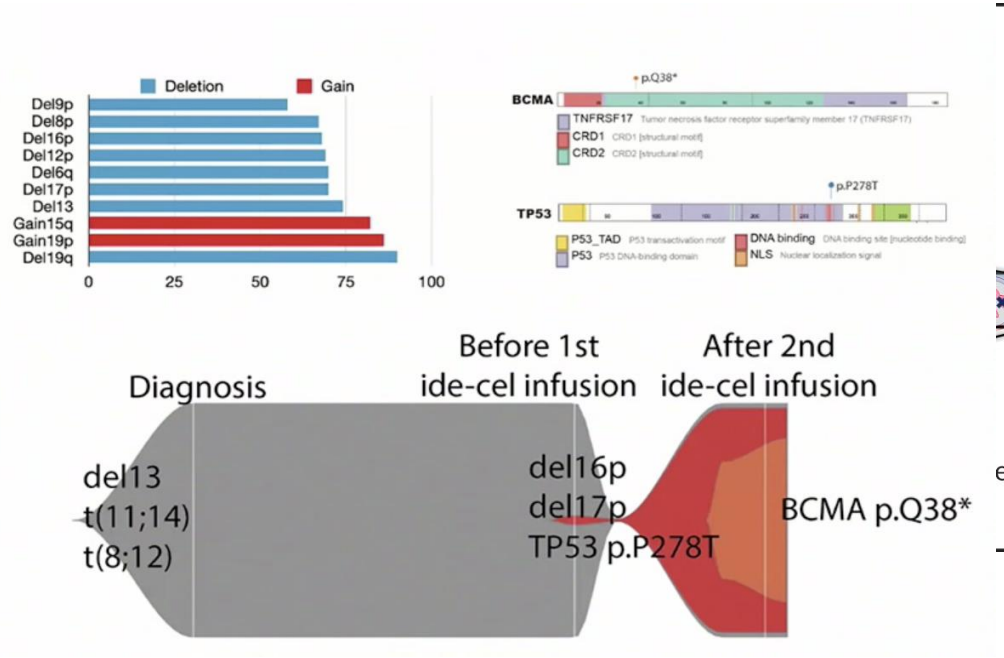
TNFRSF17 and *GPRC5D* (*and other possible target*) expression profile



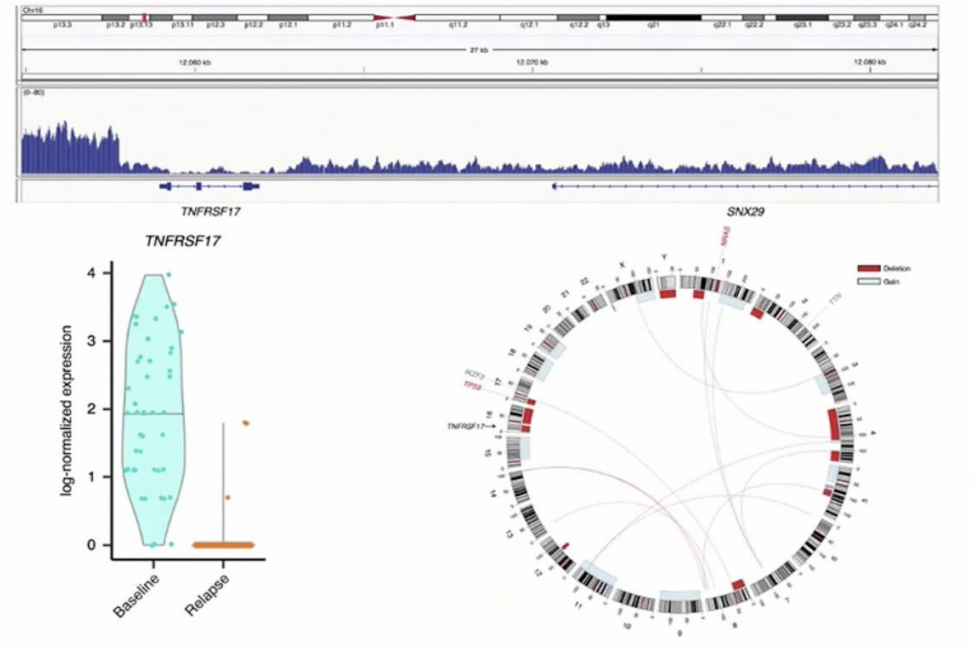
M.S.Truger, Blood Adv 2021

post T-cell immunotherapy landscape

resistance to anti BCMA & anti-GPRC5D immunotherapy ➔ the loss of antigen



M.Samur et al., 2021

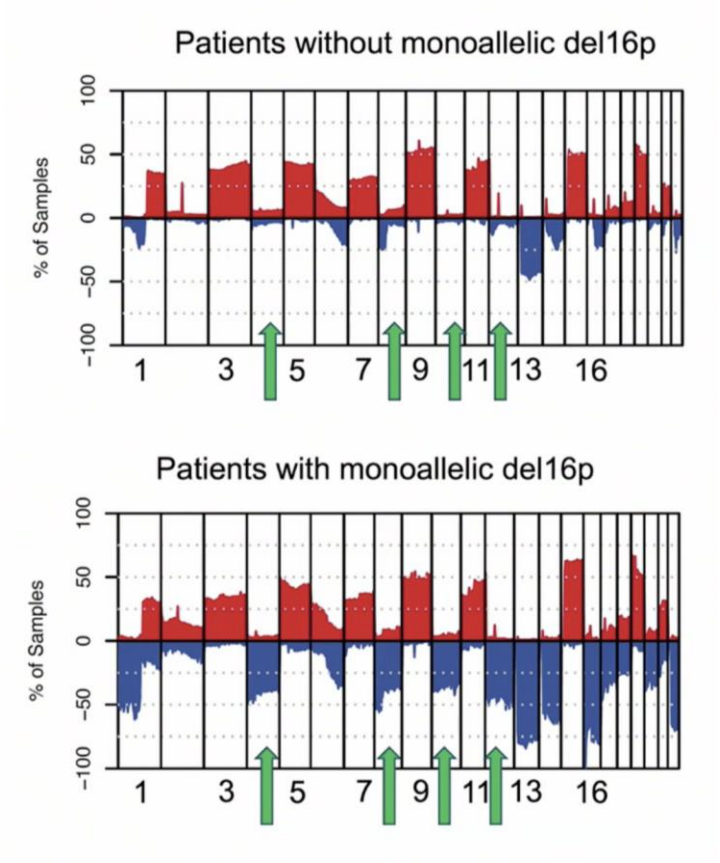


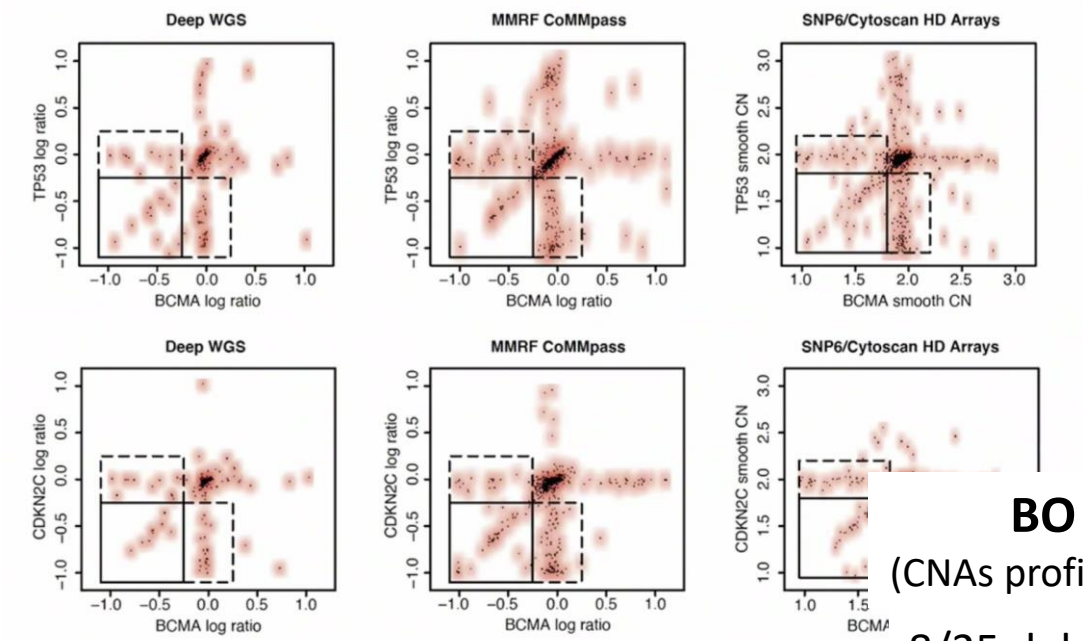
M.Da Vià et al., 2021

Lee H. et al., Nature Medicine 2023

post T-cell immunotherapy landscape

resistance to anti BCMA & anti-GPRC5D immunotherapy ➔ the loss of antigen





BO dataset

(CNAs profile by SNPs array)

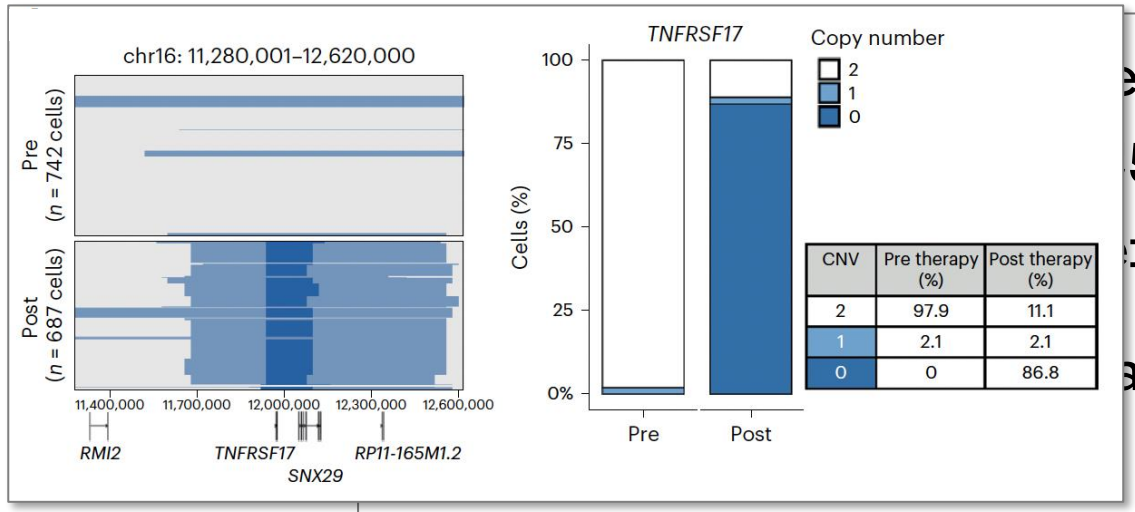
8/25 del *BCMA* & del *TP53* (**44%**)

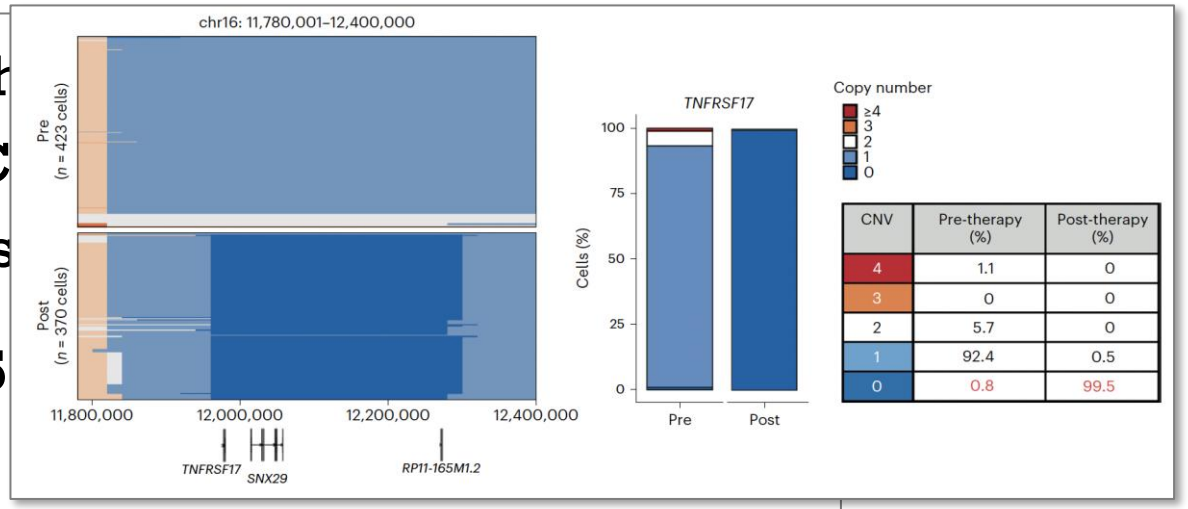
4/25 del *BCMA* & amp *MYC* (16%)

M.Samur et al., IMS 2021

TNFRS17 biallelic loss

biallelic loss of *TNFRS17* upon anti-BCMA treatment ➔ loss of the target





ed with
5D TC
rapies
an of 5

- WGS and/or scCNV-seq

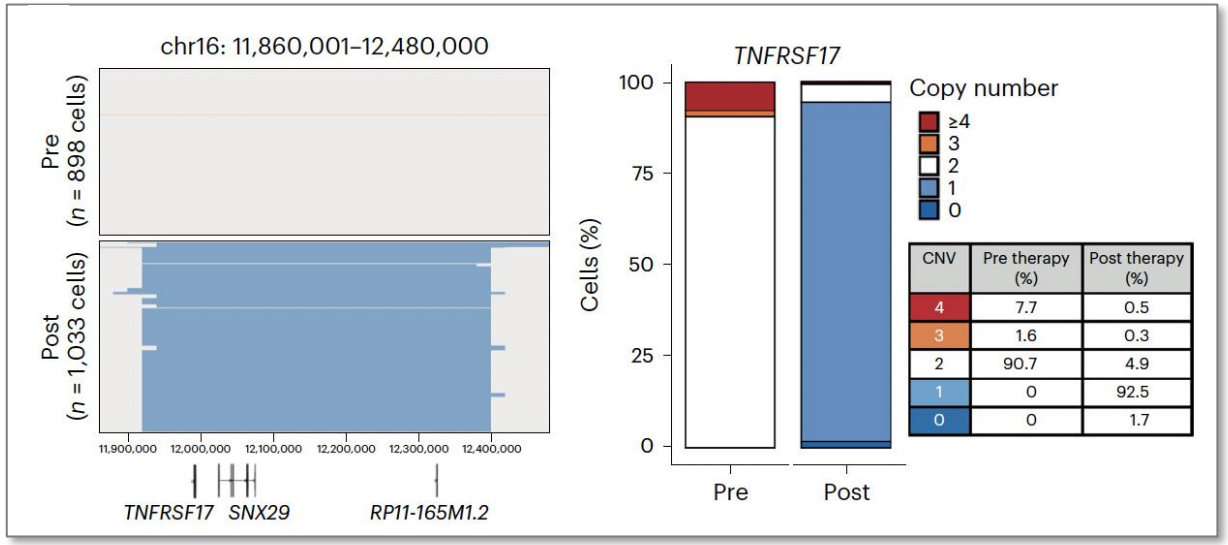
MM-1: RRMM receiving Ide-cel as third-line therapy and relapsed with a BCMA-negative clone

MM-2: triple refractory MM, who relapsed 6 months after anti-BMA TCE therapy with a BCMA-negative clone

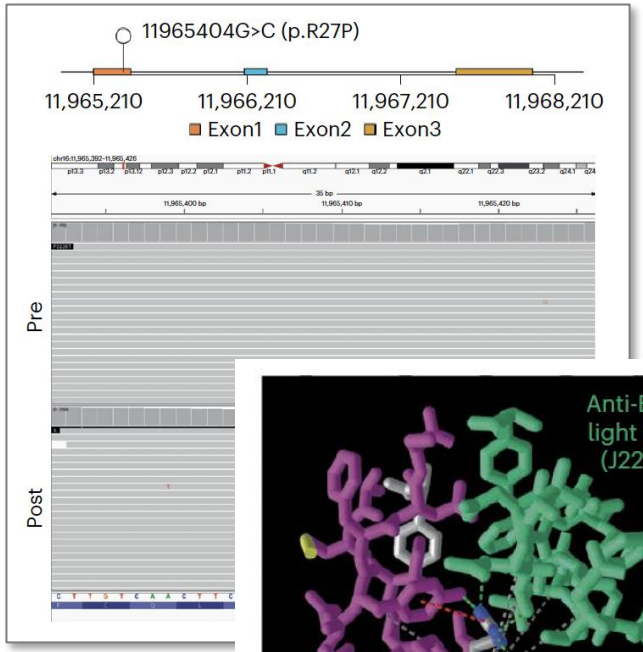
L.Rasche et al., IMS 2023
H.Lee et al., Nat Med, 2023

BCMA extracellular domain mutations

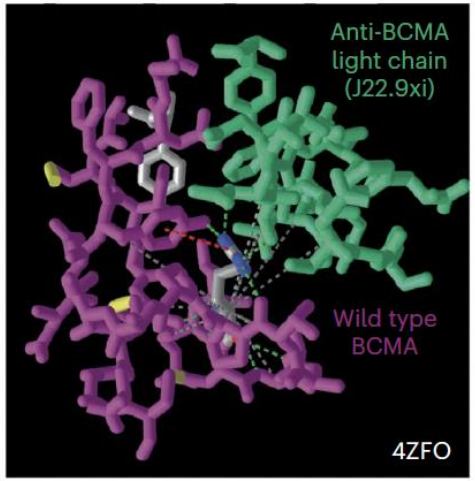
1. non-truncating point mutation in the BCMA extracellular domain (2 patients)

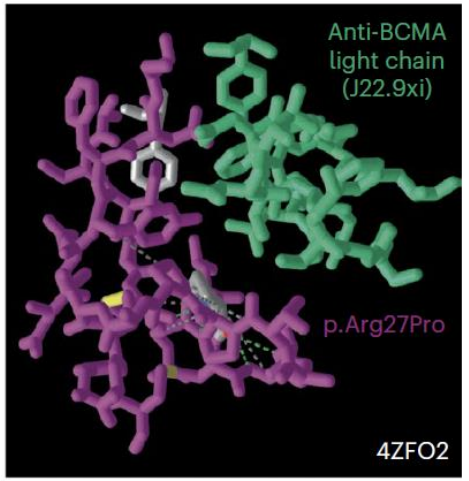


CNV	Pre therapy (%)	Post therapy (%)
4	7.7	0.5
3	1.6	0.3
2	90.7	4.9
1	0	92.5
0	0	1.7



=> monoallelic loss of *TNFRSF17* & clonal missense mutation in exon 1 (80G>C Arg27Pro)



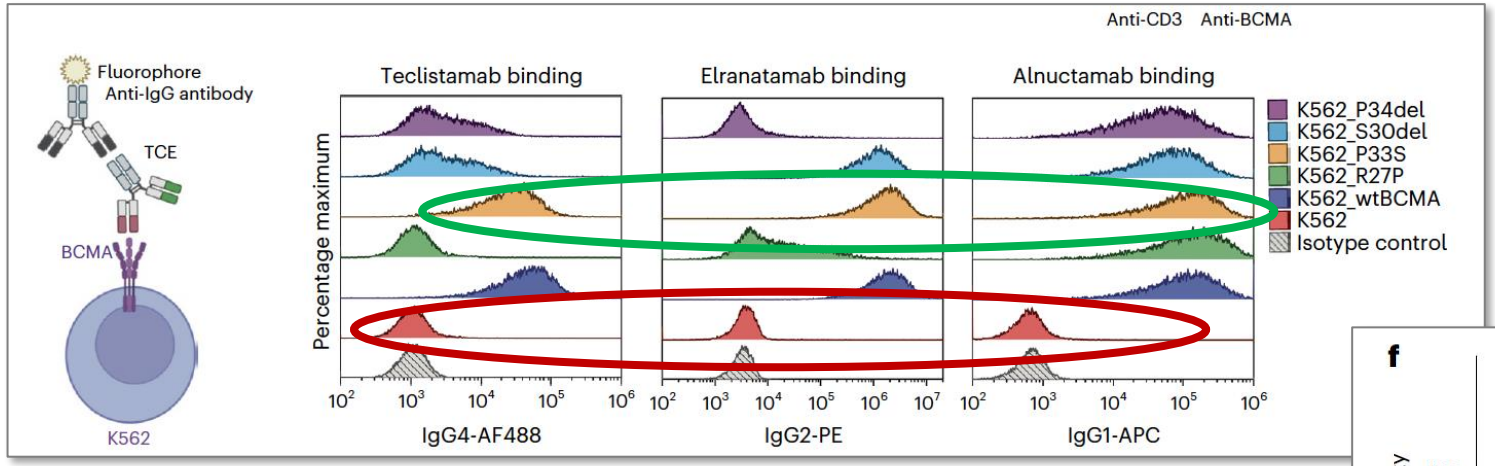


MM-3: penta-drug refractory MM (no previous exposure to anti-BCMA tp) receiving anti-BCMA TCE therapy; 11 months of CR

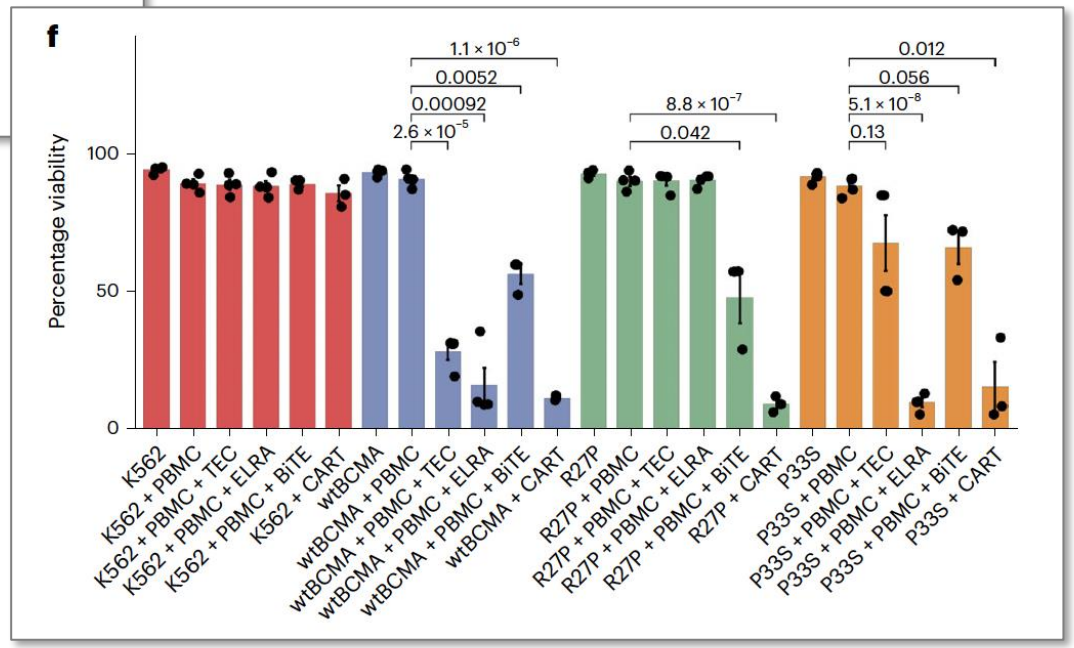
L.Rasche et al., IMS 2023
H.Lee et al., Nat Med, 2023

BCMA extracellular domain mutations

Arg27Pro mutation & TME



1. ***binding efficacy***
(TEC vs elratanamab vs alnuctamab)

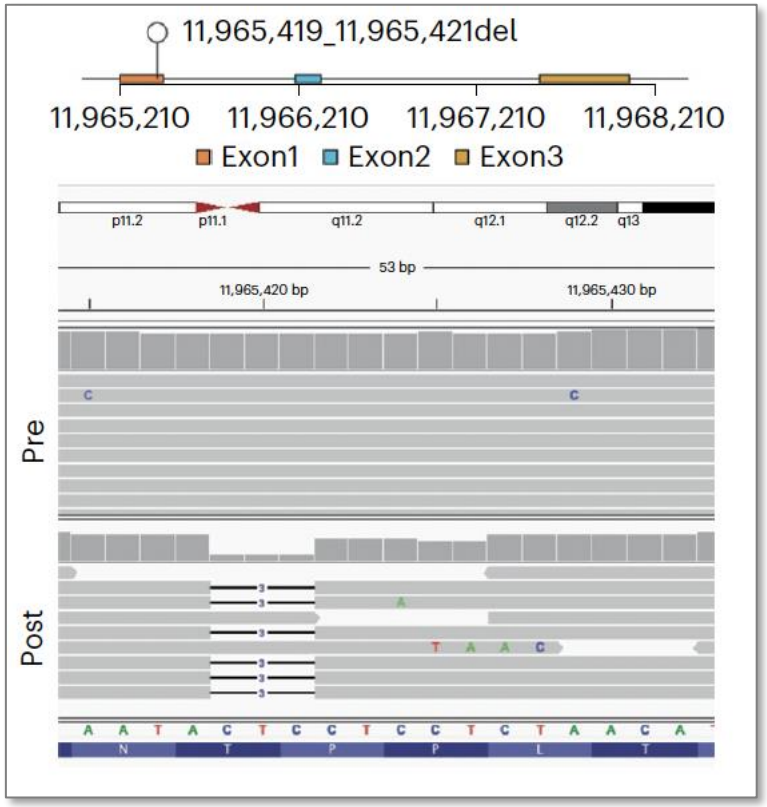


2. ***cytotoxic effect***
(TEC vs elratanamab vs alnuctamab)

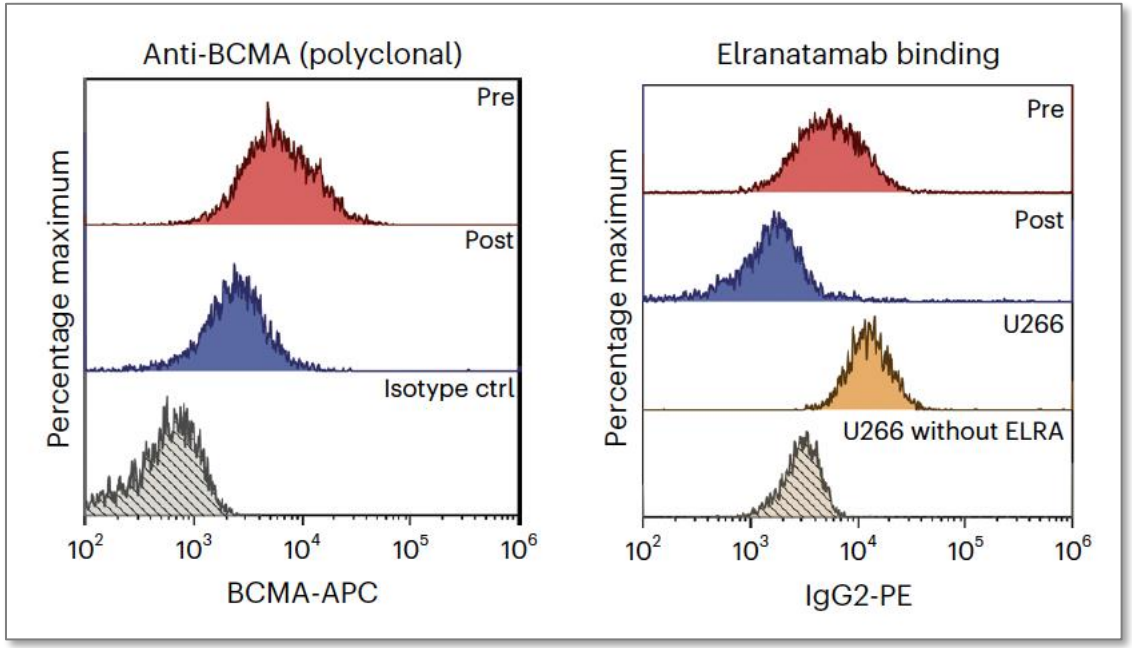
L.Rasche et al., IMS 2023
H.Lee et al., Nat Med, 2023

BCMA extracellular domain mutations

2. in-frame deletions in BCMA extracellular domain (4 patients)



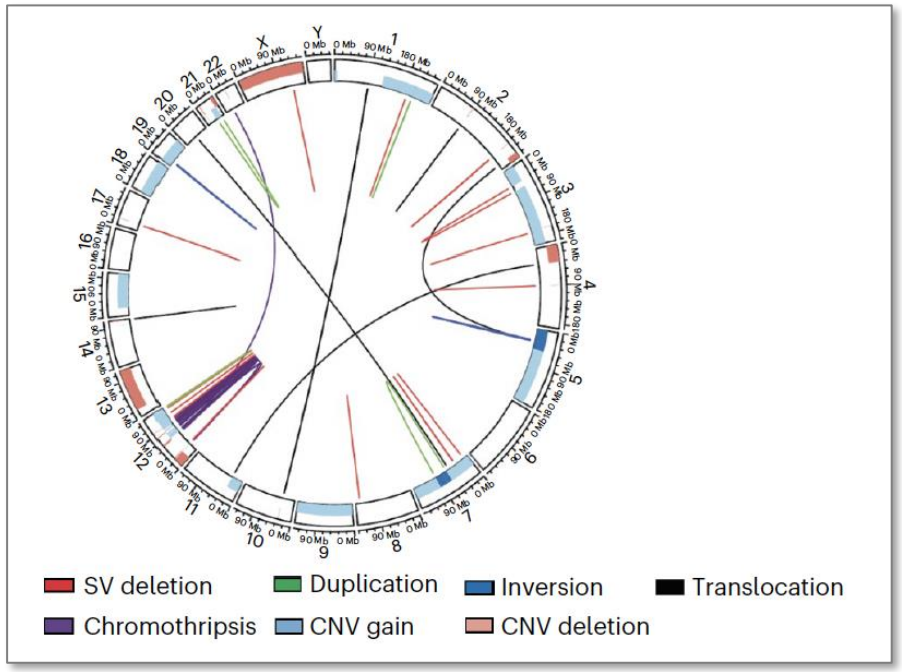
MM-10: penta-drug refractory MM (no previous exposure to anti-BCMA tp) receiving anti-BCMA TCE therapy for 19 months

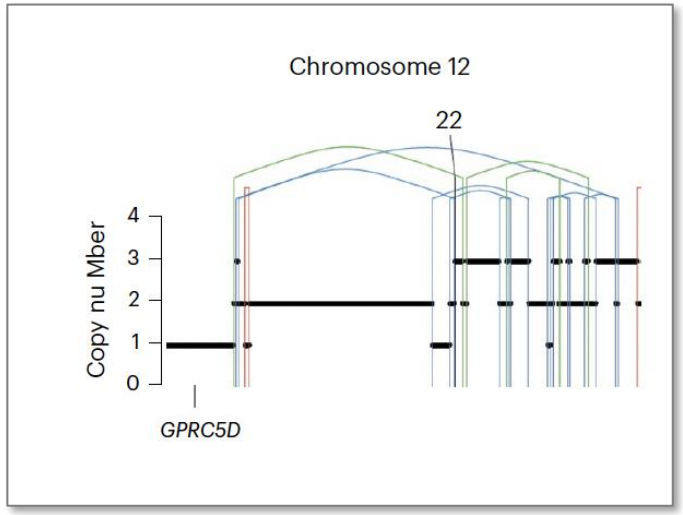


L.Rasche et al., IMS 2023
H.Lee et al., Nat Med, 2023

GPRC5D mutations

GPRC5D biallelic deletion post anti-GPRC5D TCE therapy (4 mutation)





- chormotripisis at baseline on chr 12p and monoallelic GPRC5D loss)

MM-18: relapsed after Talq-DPd (6° line of therapy) and 12 months of remission

L.Rasche et al., IMS 2023
H.Lee et al., Nat Med, 2023

NGS genomic profile: is it prime-time?

MM-NGS panel for the daily practice

=> ***UMA panel***, NGS Unique Molecular Assay has been designed* to detect all the currently validated and suspected genomic DNA aberrations with prognostic value in a single assay (all-in-one panel)

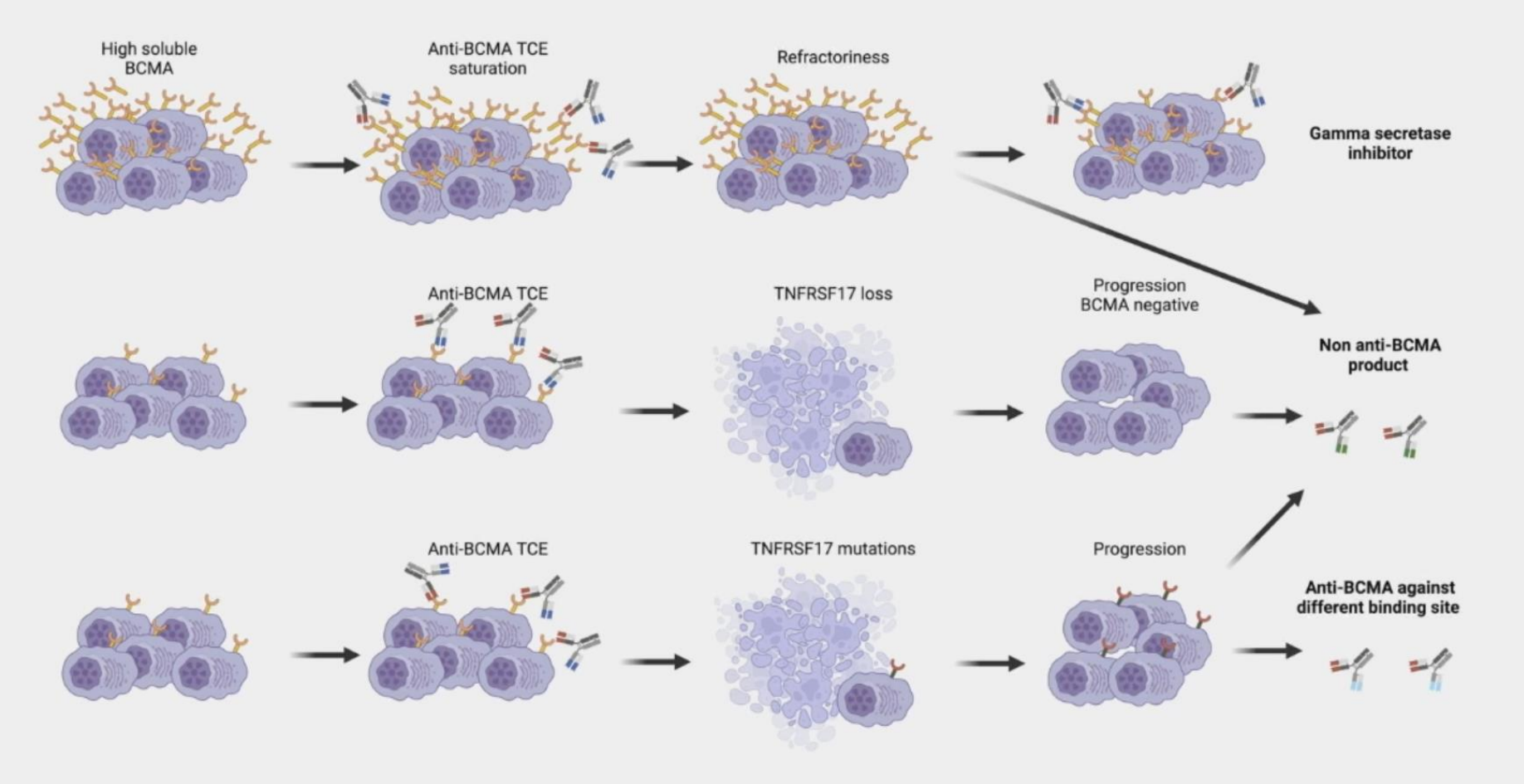
- **CNAs**: pipeline steps and analysis tools that take advantage of off-target reads to compute a whole genome Log2ratio signal precise enough for ARM-level calls
- **IgH traslocations**: custom design on IgH region to minimize costs
- **SNV and Indels**: pipelines already validated (Mutect, Strelka, Seurat)

Number	GENE	Mean cov	Min cov	Max cov	Number	GENE	Mean cov	Min cov	Max cov
1	ATM	255	27	816	42	KDM6A	142	4	358
2	ATR	253	11	643	43	KMT2B	168	1	537
3	BAX	167	10	512	44	KRAS	217	33	409
4	BCL7A	161	3	368	45	LEMD2	180	12	522
5	BIRC2	268	26	866	46	LTB	147	48	394
6	BIRC3	243	9	886	47	MAX	164	23	411
7	BRAF	235	13	689	48	MYC	202	65	520
8	BTG1	143	2	303	49	MYD88	241	53	577
9	CARD11	173	22	559	50	NF1	222	4	534
10	CCND1	145	36	607	51	NFKB1	206	9	544
11	CD19	156	25	415	52	NFKB2	156	19	396
12	CD27	150	21	368	53	NFKBIA	169	14	382
13	CD38	196	18	502	54	NOTCH2	199	11	642
14	CDKN1B	194	47	446	55	NRAS	222	83	402
15	CDKN2C	193	43	368	56	PIK3CA	266	13	675
16	CKS1B	188	53	496	57	PRDM1	196	31	533
17	CRBN	233	25	582	58	PRKD2	182	29	601
18	CUL4B	172	6	425	59	PSMB5	227	41	489
19	CYLD	191	10	448	60	PSMD1	218	4	441
20	DDB1	237	32	757	61	PTEN	175	2	417
21	DIS3	183	25	402	62	PTPN11	189	1	450
22	DNAH5	239	10	622	63	RASA2	234	2	599
23	DTX1	138	17	330	64	RB1	173	1	389
24	DUSP2	110	18	239	65	RBX1	209	42	430
25	EGR1	219	60	492	66	RPL10	155	29	434
26	EVI5	185	31	428	67	RPL5	169	26	455
27	FAF1	197	7	441	68	SAMHD1	229	31	479
28	FAM46C	223	92	373	69	SETD2	240	13	715
29	FANCA	181	3	476	70	SF3B1	225	35	467
30	FBXO4	221	15	610	71	SGPP1	133	10	364
31	FGFR3	81	3	312	72	SNX7	176	3	434
32	HIST1H1B	133	29	303	73	SP140	194	1	457
33	HIST1H1D	159	42	367	74	STAT3	218	57	512
34	HIST1H1E	125	47	243	75	TGDS	178	19	413
35	HIST1H4H	278	106	539	76	TNFRSF17	188	42	413
36	IDH1	230	56	454	77	TNFSF12	95	7	373
37	IDH2	190	1	735	78	TP53	144	10	423
38	IGLL5	68	0	344	79	TRAF2	187	16	624
39	IKZF1	227	36	672	80	TRAF3	184	6	421
40	IL6ST	245	28	670	81	XBP1	173	12	389
41	IRF4	229	26	559	82	XPO1	239	66	543

**in collaboration with N. Bolli, UniMi*
paper in preparation

NGS genomic profile: is it prime-time?

Hhw can genomics guide clinical decisions?



F.Maura, ASH 2023

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