La personalizzazione del trattamento: Il caso degli anticorpi bispecifici

Angelo Belotti
ASST Spedali Civili di Brescia

LE NUOVE FRONTIERE DELL'IMMUNOTERAPIA PER LA CURA DEL

MIELOMA MULTIPLO

dalla teoria alla pratica

TORINO 3-4 MARZO 2023

Disclosures of NAME SURNAME

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						x	
Janssen						x	
Celgene						x	
Takeda						x	
GSK						x	

La personalizzazione del trattamento: Il caso degli anticorpi bispecifici

ADC

CAR-T

BISPECIFICI

Esiste un paziente ideale per i bispecifici?

Quali aspetti clinici considerare?

Pros and Cons of Bispecifics

- off-the-shelf treatment → promptly treatment start
- older patients with RRMM or those with comorbidities may not be able to receive CAR T-cell therapy, but it may be easier for these patients to receive bispecific antibodies
- Require recurrent administrations (weekly or biweekly basis)
- Rely on endogenous T cells (T cell exhaustion)

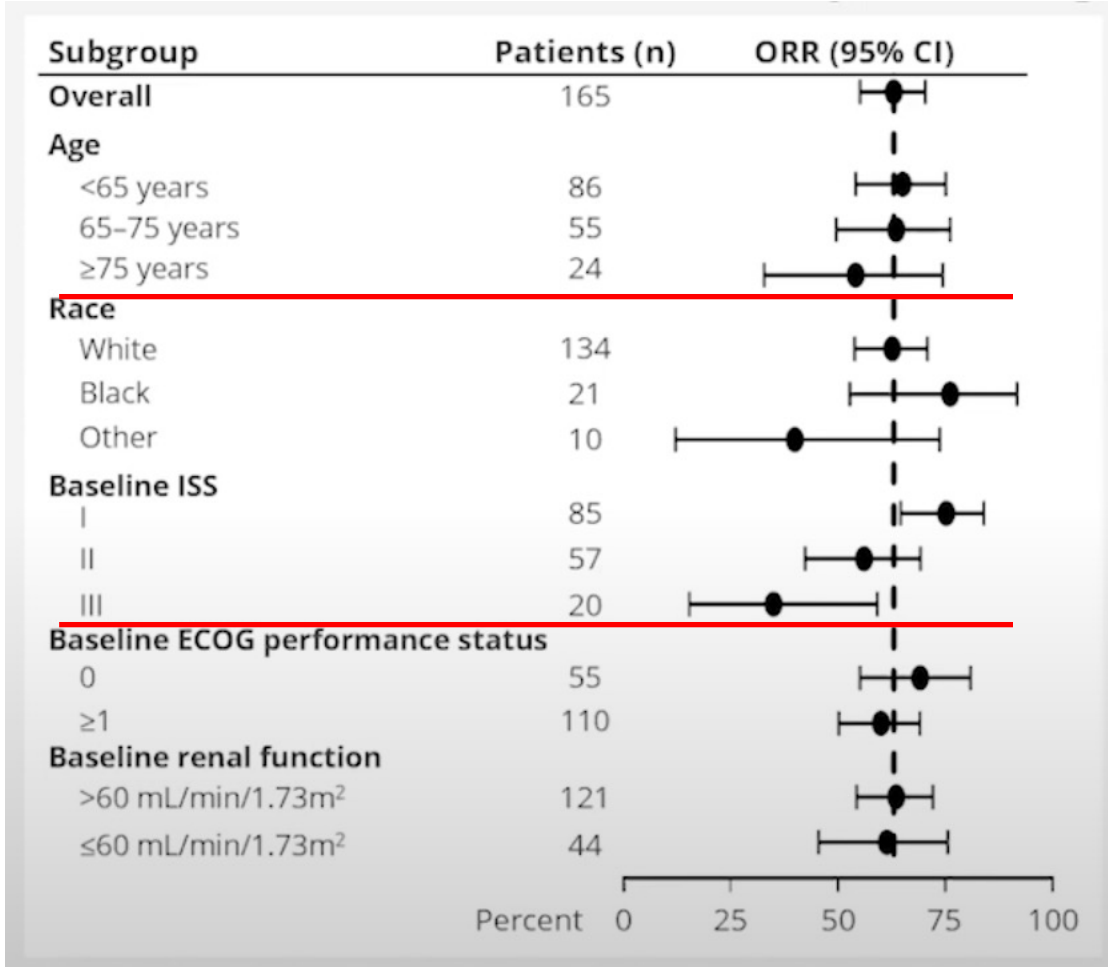
	Target	N	Age (range)	Prior lines	Triple refract	EMD (%)	% High risk-cyto	Reference
Teclistamab[1]	BCMA	165	**64 (33-84)** **14.5% ≥ 75y**	**5**	77.6%	17%	26%	*Nooka A et al, ASCO 2022*
REGN5458[2]	BCMA	73	**64 (41-81)** **21% ≥ 75y**	**5**	89%	NA	18%	*Zonder J et al, EHA 2022*
Alnuctamab[3]	BCMA	68	**64 (36-79)**	**4**	67%	21%	26%	*Wong SW et al, ASH 2022*
ABBV-383[4]	BCMA	124	**68 (35-92)**	**5**	82%	NA	18%	*D'Souza A et al, JCO 2022*
Elranatamab[5]	BCMA	123	**68 (36-89)**	**5**	97%	32%	25%	*Bahlis N et al, ASH 2022*
Talquetamab[6]	GPRC5D	143 145	**67 (38-84)** **30% ≥70y** **64% ≥ 65y**	**6**	74%/ 69%	23% 27%	31% 29%	*Chari A et al, ASH 2022*
Forimtamig[7] **(IV/SC)**	GPRC5D	51/57	**62 (27-79)**	**5/4**	62/72%	27% 32%	47%	*Carlo Stella C et al, ASH 2022*
Cevostamab[8]	FcRH5	161	**64 (33-82)**	**6**	84.5%	21%	70%	*Trudel S et al, ASH 2021*

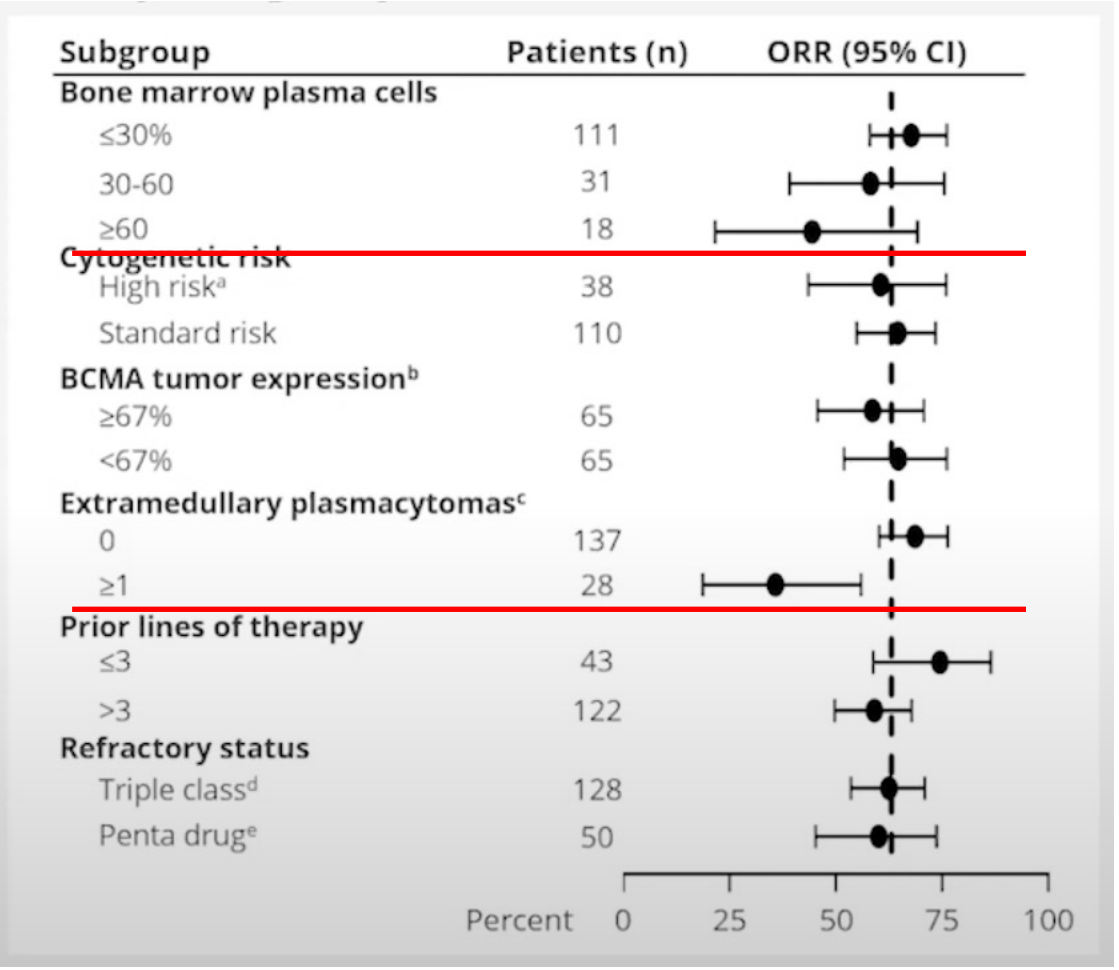
	Target	N	ORR	DOR (months)	PFS (months)	OS (months)	Follow-up (months)
Teclistamab[1]	BCMA	165	**63**% (CR:7%)	18.4	11.3	18.3	14
REGN5458[2]	BCMA	73	**75**% @highest dose (≥CR: 16%)	NR	NA	NA	3
Alnuctamab[3]	BCMA	68	**65%** @highest dose (≥CR: 19%)	NA	NA	NA	4.1
ABBV-383[4]	BCMA	124	**57**% (≥CR 28%)	NR (67% @1y)	10.4	NA	10.8
Elranatamab[5]	BCMA	123	**66**% @RP2D (≥CR: 30%)	NR (71% @1y)	NR (58% @1y)	NR (63.6% @1y)	10.4
Talquetamab[6]	GPRC5D	143 145	**70**% (CR: 7%) **64%** (CR: 11.4%)	9.3 (≥CR: NR) 13 (≥CR: NR)	7.5 11.9	NA	14 8
Forimtamig[7] (IV/SC)	GPRC5D	51/ 57	**71%** (≥CR: 35%) **64%** (≥CR: 25%)	10.8 12.5	NA	NA	11.6 8
Cevostamab[8]	FcRH5	161	**56.7**% @highest dose (≥CR: 18%)	11.5	NA	NA	14.3/6.5

	Target	Dosing	N	CRS % (any G; G ≥3)	Neurotox % (any G; G ≥3)	Infections % (any G; G ≥3)
Teclistamab[1]	BCMA	QW SC	165	72%; 0.6%	14.5%; 0.6%	76.4%; 44.8%
REGN5458[2]	BCMA	Q2W IV	73	38%; 0%	12%; 0%	23%; 11% (pneumonia)
Alnuctamab[3]	BCMA	QW SC then Q2W→ Q4W	68	53%; 0%	3%; 0%	34%; 9%
ABBV-383[4]	BCMA	Q3W IV	124	57%, 2%	0%	41%; 25%
Elranatamab[5]	BCMA	QW then Q2W SC	123	56%; 0%	3%; 0%	67%; 35%
Talquetamab[6]	GPRC5D	QW 0.4mg/kg SC Q2W 0.8 mg/kg SC	143 145	79%; 2.1%; 72%; 0.7%	11%; 1.6% 10%; 1.8%	57%; 16.8% 50%; 11.3 %
Forimtamig[7] **(IV/SC)**	GPRC5D	Q2W IV/SC	51/ 57	82%; 2% 79%; 1.8%	10%; 2% 12%; 3.6%	61%; 21% 45%; 26%
Cevostamab[8]	FcRH5	Q3W IV	161	80.7%; 1.2%	14%; 0.6%	43%; 20%

TECLISTAMAB

MAJESTEC-1: ORR across subgroups





Nooka A et al, ASCO 2022

TALQUETAMAB

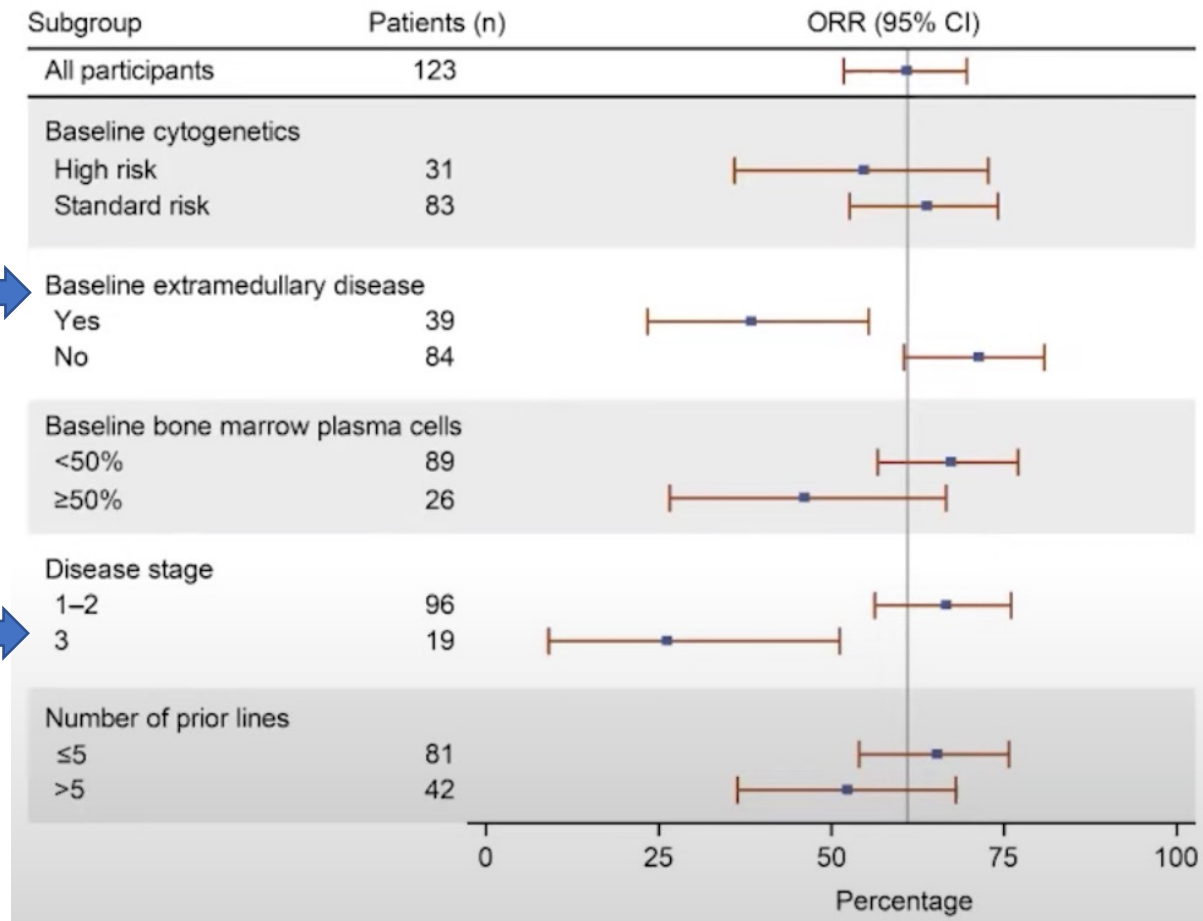
MONUMENTAL-1: ORR across subgroups

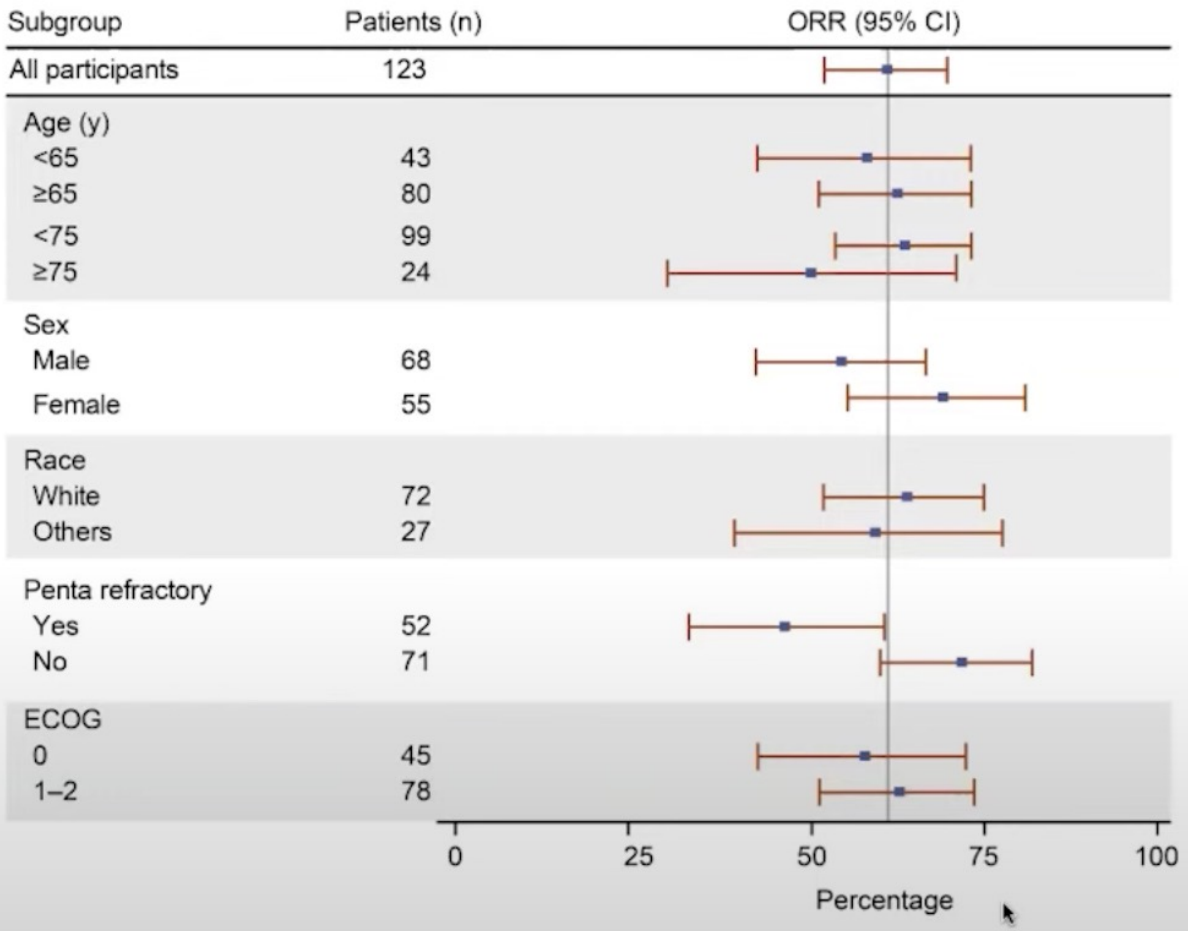
	Triple-class–exposed		Penta-drug–exposed		High-risk Cytogenetics		Extramedullary Plasmacytomas	
	405 µg/kg QW (n=30)	800 µg/kg Q2W (n=43)	405 µg/kg QW (n=24)	800 µg/kg Q2W (n=30)	405 µg/kg QW (n=3)	800 µg/kg Q2W (n=9)	405 µg/kg QW (n=11)	800 µg/kg Q2W (n=15)
Response rate, no. of patients (%)	**21 (70.0)**	**28 (65.1)**	**15 (62.5)**	**20 (66.7)**	**2 (66.7)**	**5 (55.6)**	**5 (45.5)**	**6 (40.0)**
Best response, no. of patients (%)								
Stringent complete response	7 (23.3)	5 (11.6)	6 (25.0)	4 (13.3)	1 (33.3)	1 (11.1)	1 (9.1)	1 (6.7)
Complete response	0	5 (11.6)	0	4 (13.3)	0	3 (33.3)	0	1 (6.7)
Very good partial response	10 (33.3)	13 (30.2)	6 (25.0)	10 (33.3)	1 (33.3)	1 (11.1)	1 (9.1)	3 (20.0)
Partial response	4 (13.3)	5 (11.6)	3 (12.5)	2 (6.7)	0	0	3 (27.3)	1 (6.7)
Stable disease	9 (30.0)	12 (27.9)	9 (37.5)	8 (26.7)	1 (33.3)	3 (33.3)	6 (54.5)	6 (40.0)
Progressive disease	0	3 (7.0)	0	2 (6.7)	0	1 (11.1)	0	3 (20.0)

Chari A et al, NEJM 2022

ELRANATAMAB

MAGNETISMM-3: ORR across subgroups





Bahlis N et al, ASH 2022

Rates of infections in bispecific antibody trials for RRMM

Drugs	Target	Patients in Trial	ORR, %	≥ VGPRR, %	Incidence of Infections, % (grade ≥ 3, %)	Deaths From Infection, No. (%)	Neutropenia, % (grade ≥ 3, %)	Hypogammaglobulinemia, %
ABBV-383[1]	BCMA	124	57	43	41 (≥ 20)	8 (6.5)	37 (34)	14[a]
Teclistamab[2]	BCMA	165	63	59	76 (45)	≥ 19 (11)	71 (64)	75
Teclistamab + daratumumab[3]	BCMA; CD38	33	78	43	52 (24)	1 (3)	36 (36)	NR
Elranatamab[4]	BCMA	123	61	55	67 (35)	6 (5)	48 (48)	75
Linvoseltamab, REGN5458[5]	BCMA	191	64	45	54 (29)	10 (6)	25 (23)	NR
Pavurutamab (AMG 701)[6]	BCMA	85	26[b]	17	17[c]	2 (2)	25 (NR)	NR
AInuctamab (CC-93269)[7]	BCMA	30	43	30	57 (30)	1 (3)	47 (43)	NR
Talquetamab[8]	GPRC5D	108	68	53	39 (7)	1 (1)	48 (43)	77
Talquetamab + daratumumab[9]	GPRC5D; CD38	46	77	65	50 (13)	—	NR	NR
Cevostamab[10]	FcRH5	160	45[d]	NR	43 (19)	—	38 (36)	NR

Abbreviations: BCMA, B-cell maturation antigen; FcRH5, Fc receptor-homolog 5; GPRC5D, G protein-coupled receptor family C group 5 member D; NR, not reported; ORR, objective response rate; ≥ VGPRR, rate of very good partial responses or better.

[a]In this trial, although only 14% were documented to be hypogammaglobulinemic, 23% received immunoglobulin.

[b]This is overall ORR; higher response rates were observed with higher dose cohorts.

[c]Rate of serious infections.

[d]ORR 55% among the higher (160 mg) dose level cohort.

Scheffer Cliff ER et al, JCO 2023

42 patients (2019-2021, ph1-2 trials), Wisconsin - Milwaukee

Risk of Infection Increases with Longer Duration of Bispecific Antibody Therapy:

- At 3 months: 41%
- at 6 months: 57%;
- at 9 months: 64%
- at 12 months: 67%
- at 15 months: 70%.

Median follow-up 9.5 months

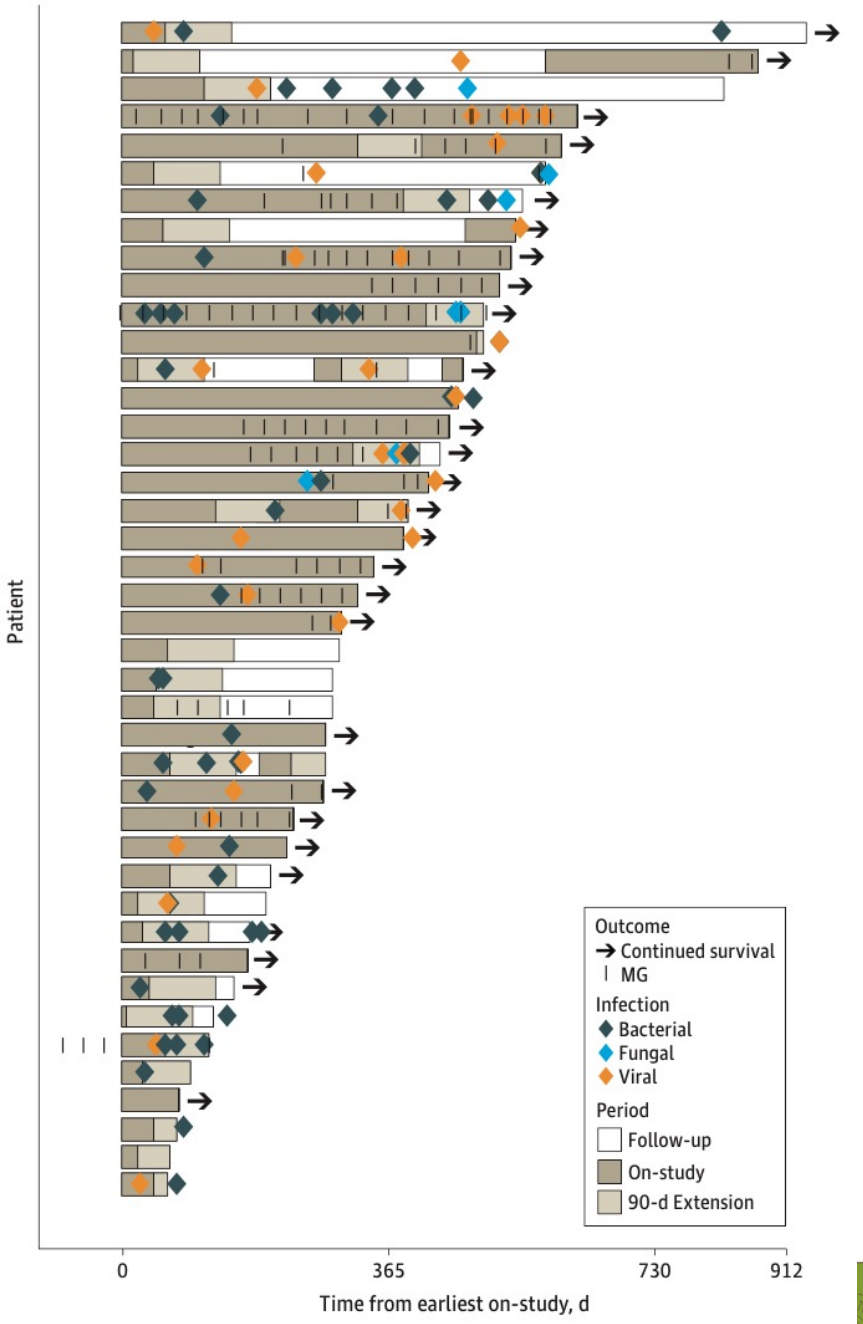
IV Ig administred in 49%

Infections:

- bacterial: 54%
- viral: 41%
- fungal: 5%
- Respiratory tract infections: 51%
- Four deaths were attributed to infections, including 2 patients who died within 90 days of treatment

the risk of infection was associated with the degree of hypogammaglobulinemia and increased further with treatment

Hammons L et al, JAMA Netw Open 2022



COMBINATION STRATEGIES: TRIMM-2 TRIAL

TECLISTAMAB-DARATUMUMAB

Characteristic	N=65
Prior lines of therapy, median (range)	5.0 (1-15)
Exposure status, n (%)	
IMiD[e]	63 (96.9)
Anti-CD38 mAb[f]	49 (75.4)
Triple-class[g]	49 (75.4)
Penta-drug[h]	36 (55.4)
BCMA-targeted therapy[i]	8 (12.3)
Refractory status, n (%)	
IMiD[e]	54 (83.1)
Anti-CD38 mAb[f]	41 (63.1)
Triple-class[g]	38 (58.5)
Penta-drug[h]	20 (30.8)
To last line of therapy	52 (80.0)

Tec + dara dosing schedules

Dara	Tec SC	Patients enrolled
1800 mg SC (per approved schedule[1]) Cycles 1–2: QW Cycles 3–6: Q2W Cycles 7+: Monthly	1.5 mg/kg QW[a]	n=21
	3 mg/kg Q2W[a]	n=39
	3 mg/kg QW	n=5

Median follow-up 8.6 months

- ORR 74-100%
- ORR 73.7% in patients with prior anti-CD38 exposure
- 44/65 (67%) infections (G ≥3: 27.7%)

ALERT: increased fatal infections in a cohort evaluating teclistamab fixed dose

Awaiting more safety data

Rodriguez Otero P et al, EHA 2022

La personalizzazione del trattamento: Il caso degli anticorpi bispecifici

ORR 50-70%

Opzione per pazienti ricaduti dopo precedente terapia BCMA-target

PER TUTTI?

RECIDIVE AGGRESSIVE

EMD ?

TERAPIA DI SUPPORTO/PROFILASSI (Ig ev)

Paziente con infezioni ricorrenti ?

Paziente FRAIL ?