Anticorpi bispecifi: dalla somministrazione al profilo di tossicità

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LE NUOVE FRONTIERE DELL'IMMUNOTERAPIA PER LA CURA DEL
MIELOMA MULTIPLO
dalla teoria alla pratica

TORINO 3-4 MARZO 2023

Disclosures of Carmelo Carlo-Stella

Company name	Research support	Consultant	Advisory board	Other
Sanofi	X	X	X	
ADC Therapeutics	X	X	X	
Karyopharm Therapeutics			X	
Celgene/Bristol-Myers Squibb			X	
Incyte				Honoraria
F. Hoffmann-La Roche Ltd	X		X	Travel grants
Janssen Oncology				Travel grants, Honoraria
Takeda				Travel grants, Honoraria
Merck Sharp & Dohme				Honoraria
AstraZeneca				Honoraria
Gilead				Honoraria

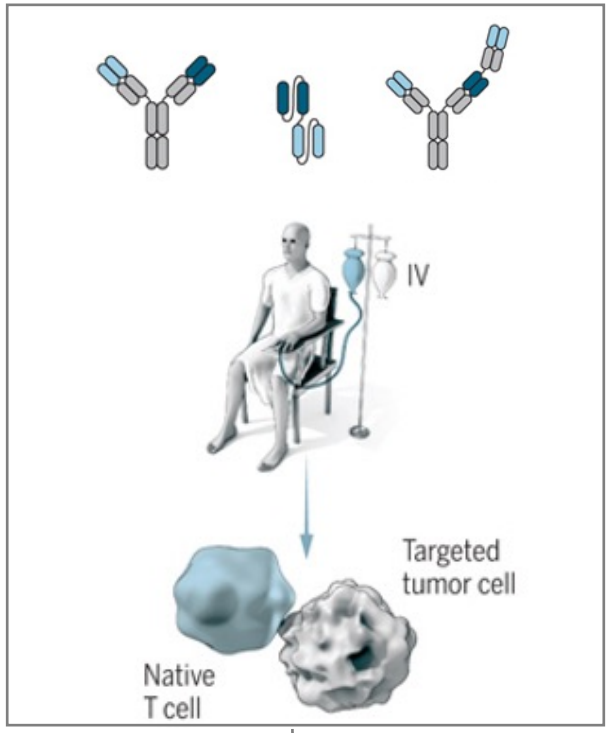
Background

- T-cell activating immunotherapy, including CAR-T cells and BiTEs, results in a significant clinical benefit for MM

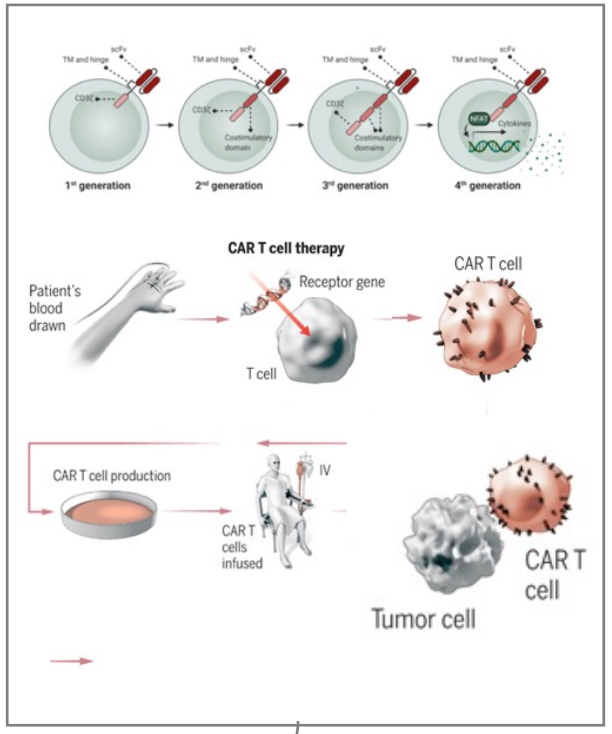
Forced into Battle

Bispecific antibodies unleash T cells against Cancer
by physically tethering them to tumor cells.

Bispecific Antibodies



CAR T Cells



Synthetic Immunity

Kaiser et al, Science 2020

Clinical Trials for TCB in MM

CD3 × BCMA

NCT04557098 (MajesTEC-1)

NCT04722146 (MajesTEC-2)

NCT05083169 (MajesTEC-3)

NCT04108195 (TRIMM-2)

NCT04586426

NCT05243797 (MajesTEC-4)

NCT05231629 (Master-2)

NCT03269136 (MAGNETISMM-1)

NCT04649359 (MAGNETISMM-3)

NCT05090566 (MAGNETISMM-4)

NCT05020236 (MAGNETISMM-5)

NCT05137054

NCT03933735

NCT04184050

NCT04735575

GPRC5D × CD3

NCT03399799 (MONUMENTAL-1)

TRIMM-2 NCT04108195

NCT05050097 (MONUMENTAL-2)

FCRH5 × CD3

NCT03275103 (GRACE)

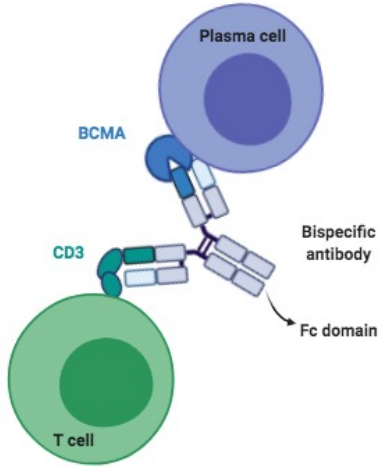
CD38 × CD3

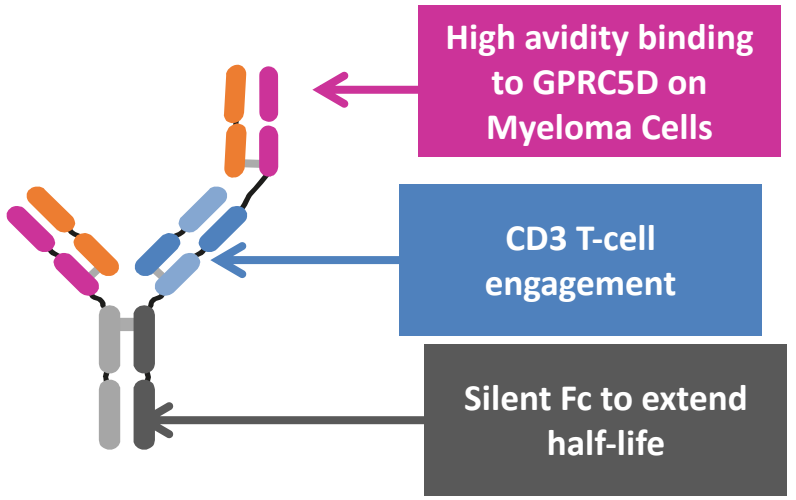
NCT03309111

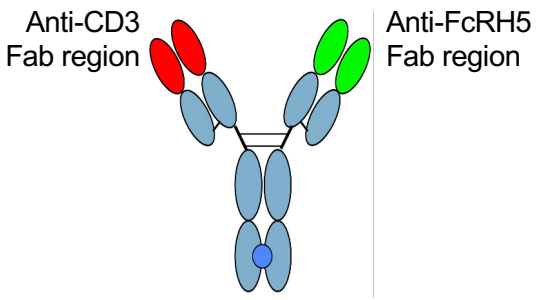
NCT05011097

Bispecifics in Development

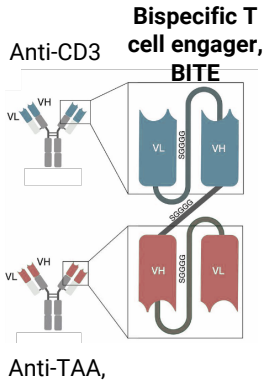
- BCMA
  - Teclistamab
  - Alnuctamab
- GPRC5D
  - Talquetamab (1:1)
  - Forimtamig (2:1)
- FcRH5
  - Cevostamab





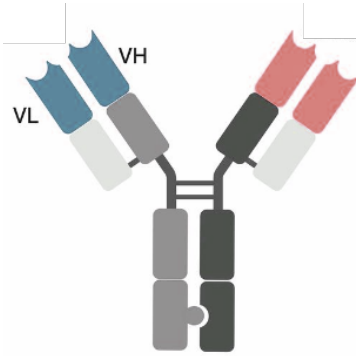


Format of Bispecific Antibodies Determines Pharmakokinetics & Target Antigen Affinity



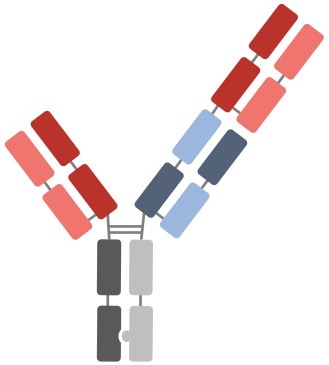
Bispecific T cell engager, BiTE, e.g. Blinatumomab

50 – 60 kDa



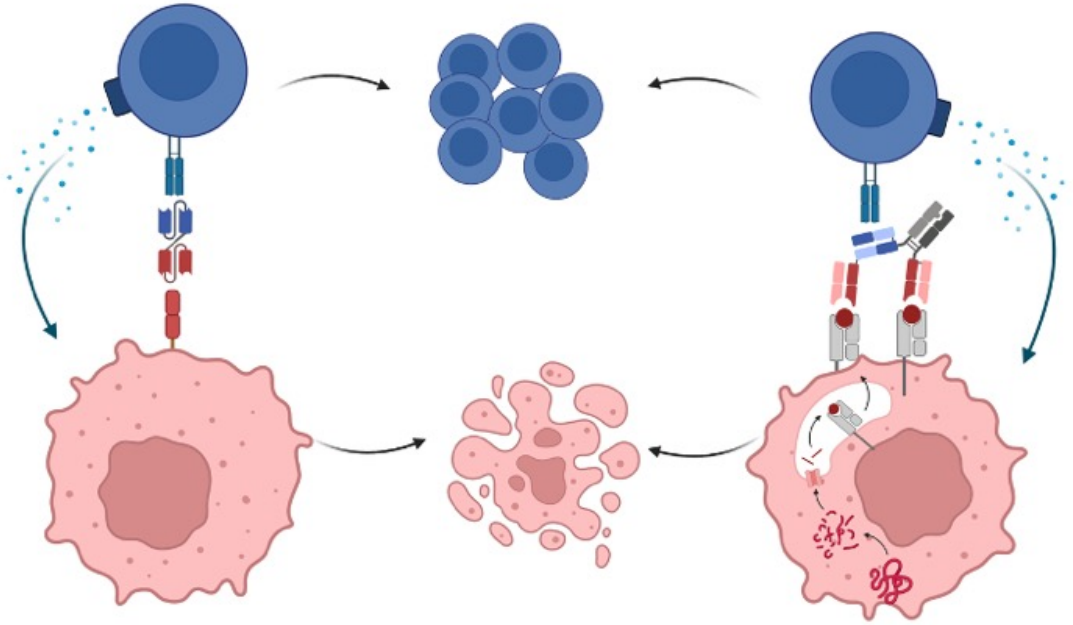
Extended Half-Life BiTEs, Example: Mosunetuzumab

ca. 150 kDa

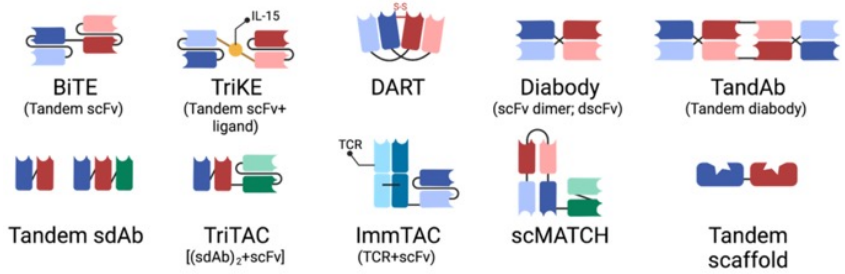


2:1 T cell bispecific; Example: Glofitmab

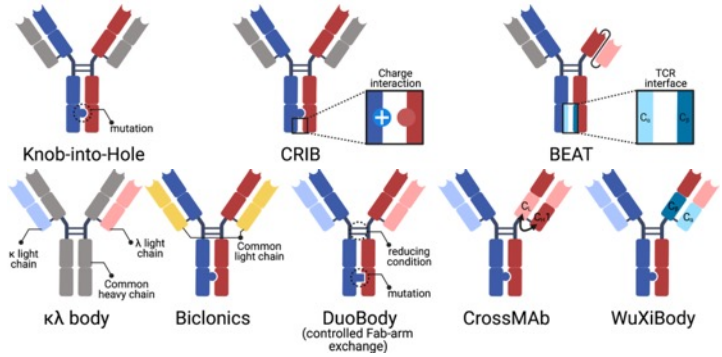
ca. 150 kDa



Fragment-based Bsabs; Can Be Linked To Fc



Heterodimerization Of Heavy Or Light Chains



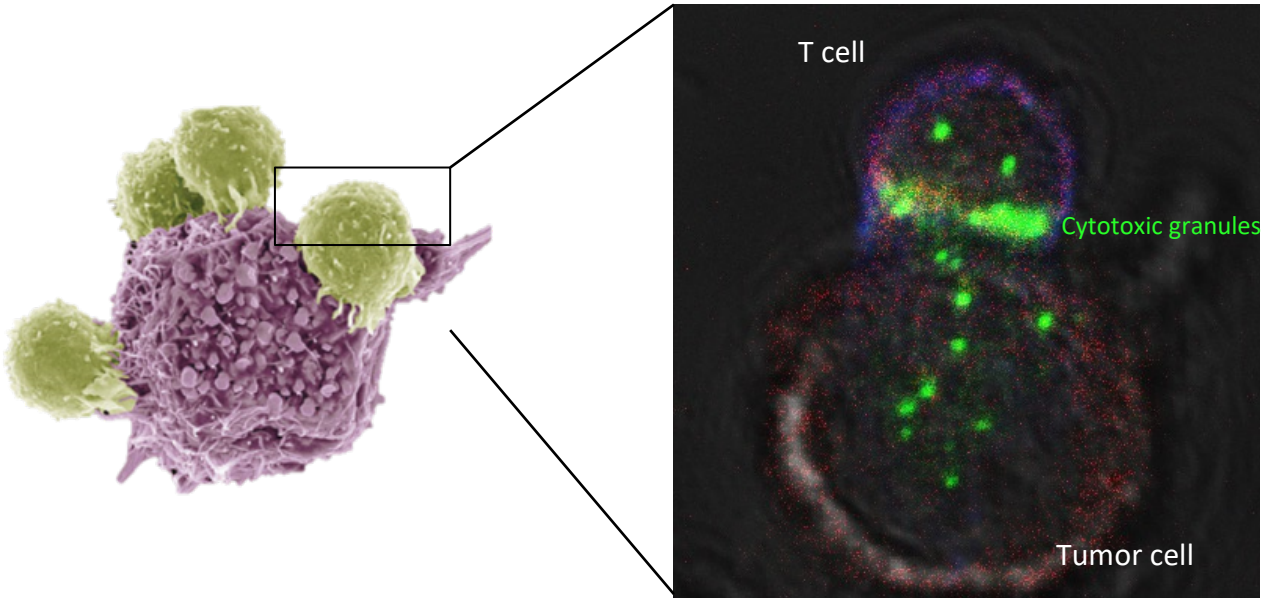
Adpated from You et al, Vaccines 2021, Augsberger et al, Subklewe Blood 2021

Features of T-cell Bispecific Antibodies

Simultaneous binding to

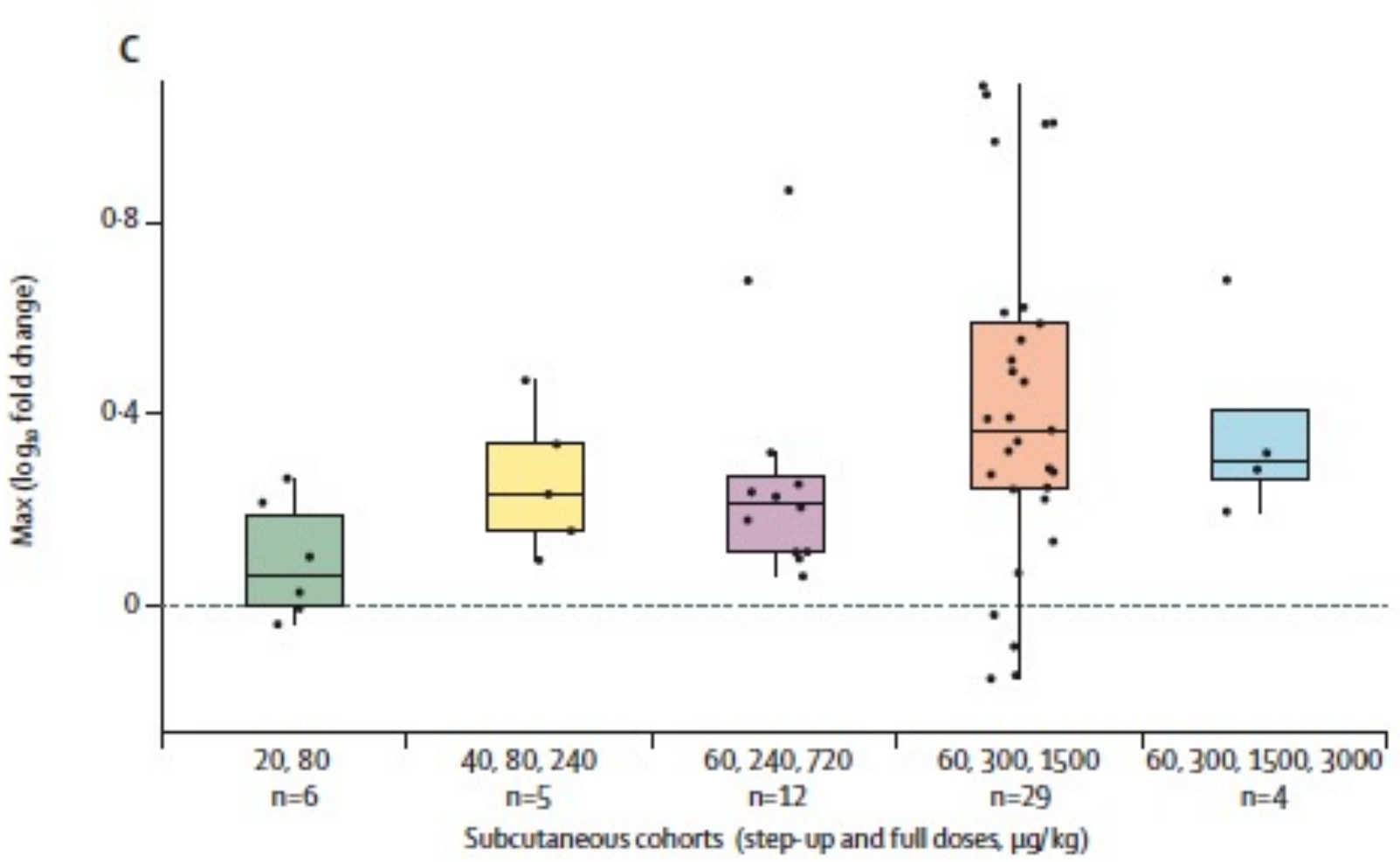
tumor antigen and CD3ε chain of TCR independent of peptide-MHC complex;

Recruitment of endogenous T cells: 4 x 10^{11} in the circulation



- **T cell engagement, activation and killing** of tumor cells by cytotoxic granules
- **T cell proliferation** (expansion) at site of activation
- **Cytokine, chemokine release leading to recruitment of additional T-cells**
- Very high potency with EC_{50} values in the fM to pM range
- **Serial killing of tumor cells, activity at low effector-to-target (E:T) ratio**
- T cell killing independent of specificity, activation and differentiation status

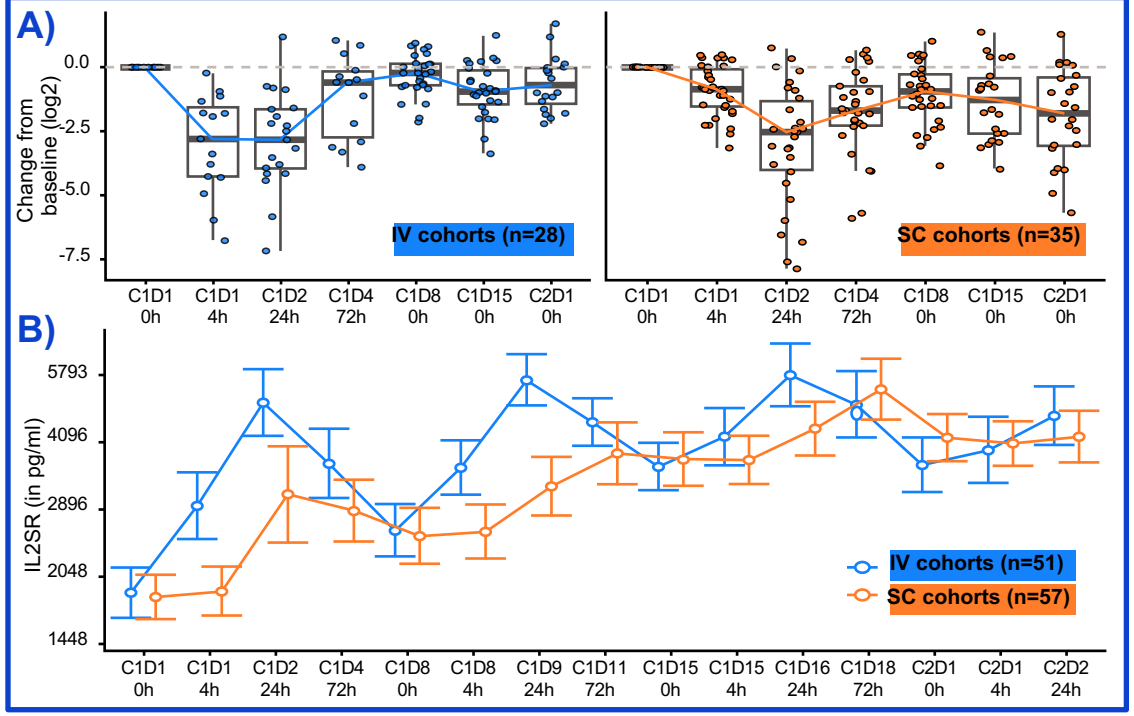
Teclistamab-Induced PD-1-pos T Cells



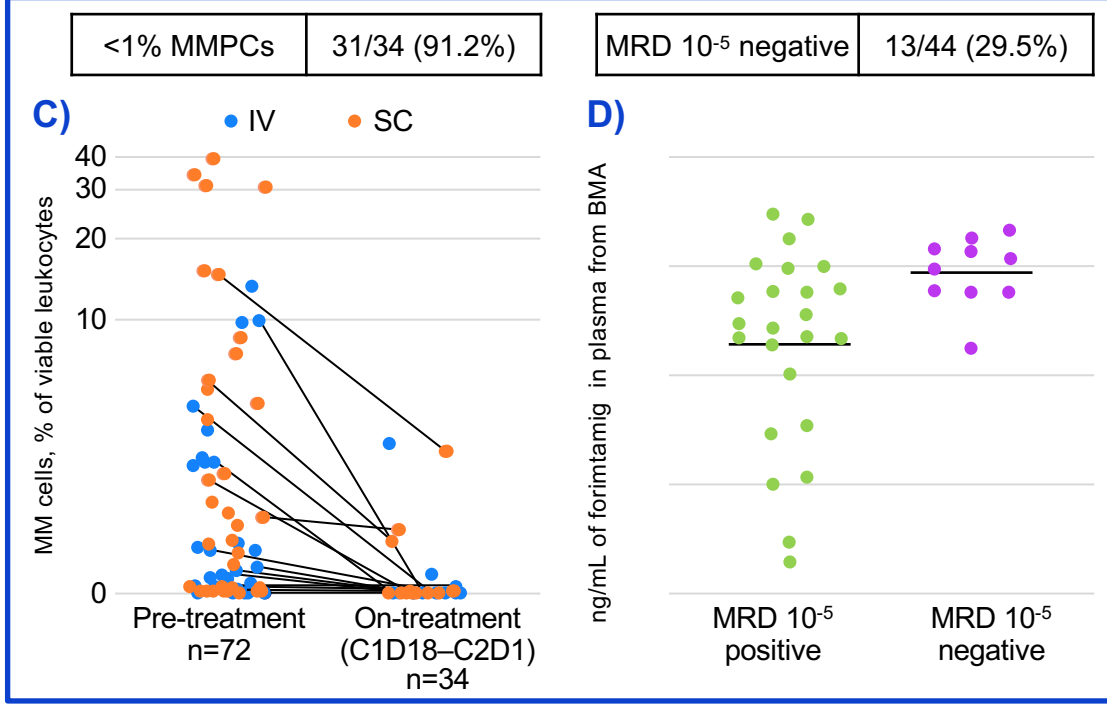
The Lancet, 398:665-674, 2021

Pharmacodynamic responses to Forimtamig

T-cell activation shown by A) CD8+ T cells margination and B) sCD25 increase after IV and SC administration



C) Rapid decrease of MM cells upon treatment and D) association of 10^{-5} MRD status with time-matched forimtamig exposure in BM (individual data)*



SC administration induces delayed and lower cytokine release compared with IV infusion; there is rapid and deep clearance from bone marrow independent of administration route

Data cut-off: October 21, 2022; *four patients (two MRD-positive and two MRD-negative) had samples collected at the CR confirmation visit rather than at the end of C1
IL2SR, soluble interleukin-2 receptor; MM, multiple myeloma; MMPC, multiple myeloma plasma cell

Adverse Events Summary

		Teclistamab*	Talquetamab		Forimtamig	Cevostamab
Target		BCMA	GPRC5D		GPRC5D	FcRH5
Dose/RoA		1.5 mg/kg SC Until PD / SUD	0.4 mg/kg SC Until PD / SUD	0.8 mg/kg SC Until PD / SUD	0.006-10mg IV Fix Dur / SUD	0.3-160mg IV Fix Dur / SUD
Any related AEs	Any Grade	165 (100)	30 (100)	44 (100)	49 (96.1)	160 (99.4)
	Grade 3-4	156 (94.5)	26 (87)	38 (86)	35 (68.6)	99 (61.5)
Grade 5(Fatal) AEs	Any	19 (11)	0 (0)	3 (6)	3 (5.9)	6 (3.7)
	Related	5 (3)	0 (0)	0 (0)	0 (0)	1 (0.6)
AEs leading to discontinuation	Any	2 (1)	0 (0)	1 (2)	3 (5.9)	21 (13.0)
	Related	2 (1)	0 (0)	0 (0)	2 (3.9)	7 (4.3)
AEs leading to dose reduction	Any	1 (0.6)	NR	NR	6 (11.8)	NR
	Related	1 (0.6)	NR	NR	3 (5.6)	NR

*FDA approved, R/R MM, ≥4 lines

CRS, ICANS and Infections

		Teclistamab	Talquetamab		Forimtamig	Cevostamab
Target		BCMA	GPRC5D		GPRC5D	FcRH5
Dose/RoA		1.5 mg/kg SC	0.4 mg/kg SC	0.8 mg/kg SC	0.006-10mg IV	0.3-160mg IV
Cytokine release syndrome	Any Grade	119 (72.1)	23 (77)	35 (80)	42 (82.4)	130 (80.7)
	Grade 3	1 (0.6)	1 (3)	0	1 (2)	1 (1.2)
ICANS-related events	Any Grade	24 (14.5)	3 (10.0)	2 (4.5)	5 (9.8)	23 (14.3)
	Grade 3	1 (0.6)	0	0	1 (2.0)	1 (0.6)
Infections	Any Grade	126 (76-4)	17 (57)	22 (50)	31 (60.8)	68 (42.5)
	Grade 3-4	74 (44.8)	6 (19)	6 (14)	11 (21.5)	30 (18.8)
Covid-19	Any Grade	29 (17.6)	4 (13)	1 (2)	11 (21.6)	NR
	Grade 3-4	20 (12.1)	1 (3)	0	1 (2.0)	NR

ASTCT CRS Grading System

Table 2
ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Hematological Adverse Events

		Teclistamab	Talquetamab		Forimtamig	Cevostamab
Target		BCMA	GPRC5D		GPRC5D	FcRH5
Dose/RoA		1.5 mg/kg sc	0.4 mg/kg SC	0.8 mg/kg SC	0.006-10mg IV	0.3-160mg IV
Neutropenia	Any Grade	117 (70.9)	20 (67)	16 (36)	12 (23.5)	29 (18.1)
	Grade 3 or 4	106 (64.2)	18 (60)	14 (32)	6 (11.8)	26 (16.3)
Anemia	Any Grade	86 (52.1)	18 (60)	19 (43)	17 (33.3)	51 (31.9)
	Grade 3 or 4	61 (37)	9 (30)	10 (23)	8 (15.7)	35 (21.9)
Thrombocytopenia	Any Grade	66 (40)	11 (37)	10 (23)	16 (31.4)	NR
	Grade 3 or 4	35 (21.2)	7 (23)	5 (11)	7 (13.7)	NR

Skin & Mucosal Adverse Events

		Talquetamab		Forimtamig
Target		GPRC5D		GPRC5D
Dose/RoA		0.4 mg/kg SC	0.8 mg/kg SC	0.006-10mg IV
Skin AEs	Any Grade	20 (67)	31 (70)	40 (78.4)
	Grade 3 or 4	0	1 (2)	6 (11.8)
Nail/Hair AEs	Any Grade	17 (57)	12 (27)	12 (23.5)
	Grade 3 or 4	0	1 (2)	0
Mucosal toxicity	Any Grade	NR	NR	37 (72.5)
	Grade 3 or 4	NR	NR	0
Dysgeusia	Any Grade	19 (63)	25 (57)	NR
	Grade 3 or 4	NA	NA	NR
Dry mouth	Any Grade	9 (30)	25 (57)	NR
	Grade 3 or 4	0	0	NR
Dysphagia	Any Grade	11 (37)	12 (27)	NR
	Grade 3 or 4	0	0	NR

Conclusions

- Toxicity profile is consistent with the mechanism of action class (*Bispecific T-cell Engager*) and the target antigen class (BCMA *vs* GPRC5D)