



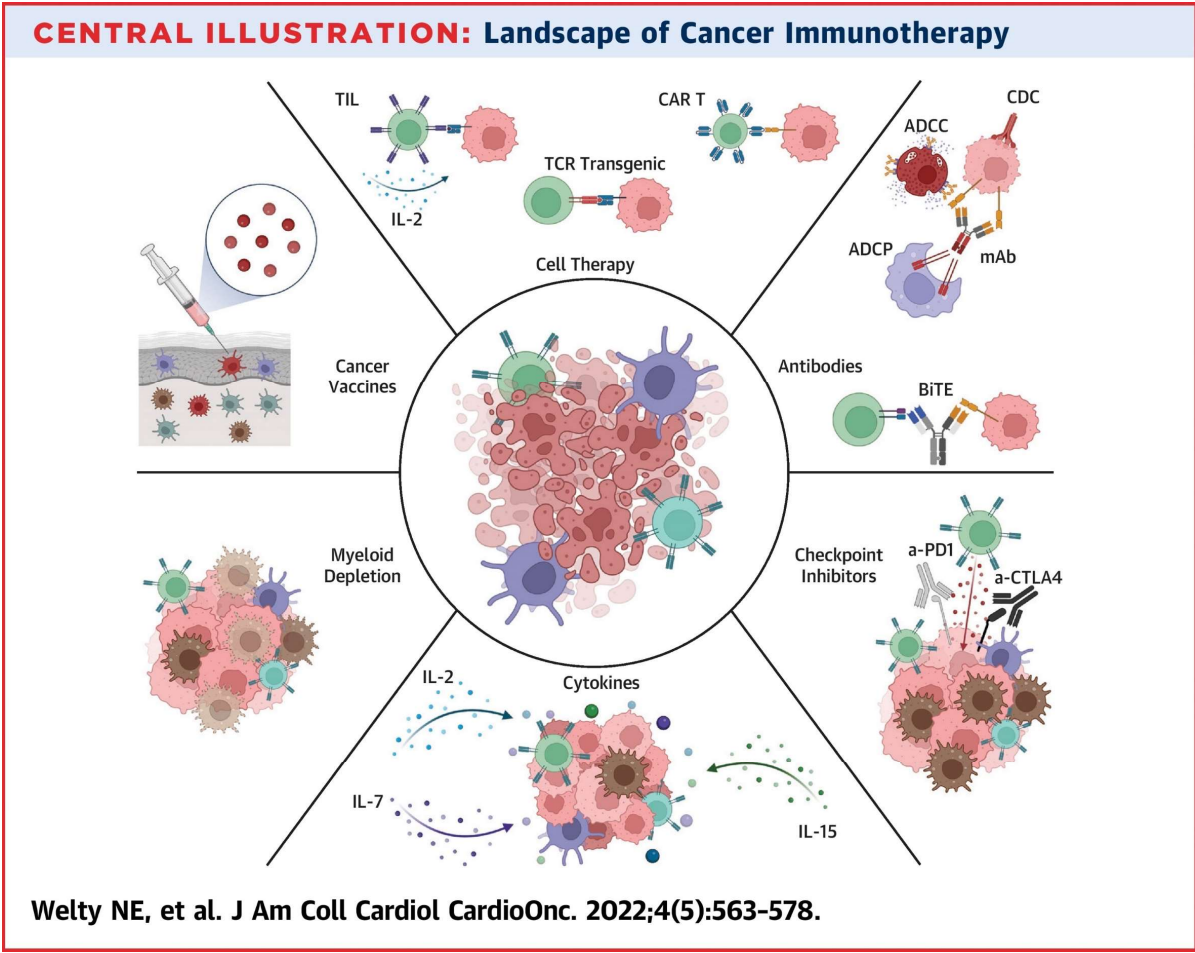
## MULTISPECIFIC ANTIBODIES

JANUARY 10TH 2024

IMMUNOSCIENCE ACADEMY

Prof. Dr. Tessa Kerre

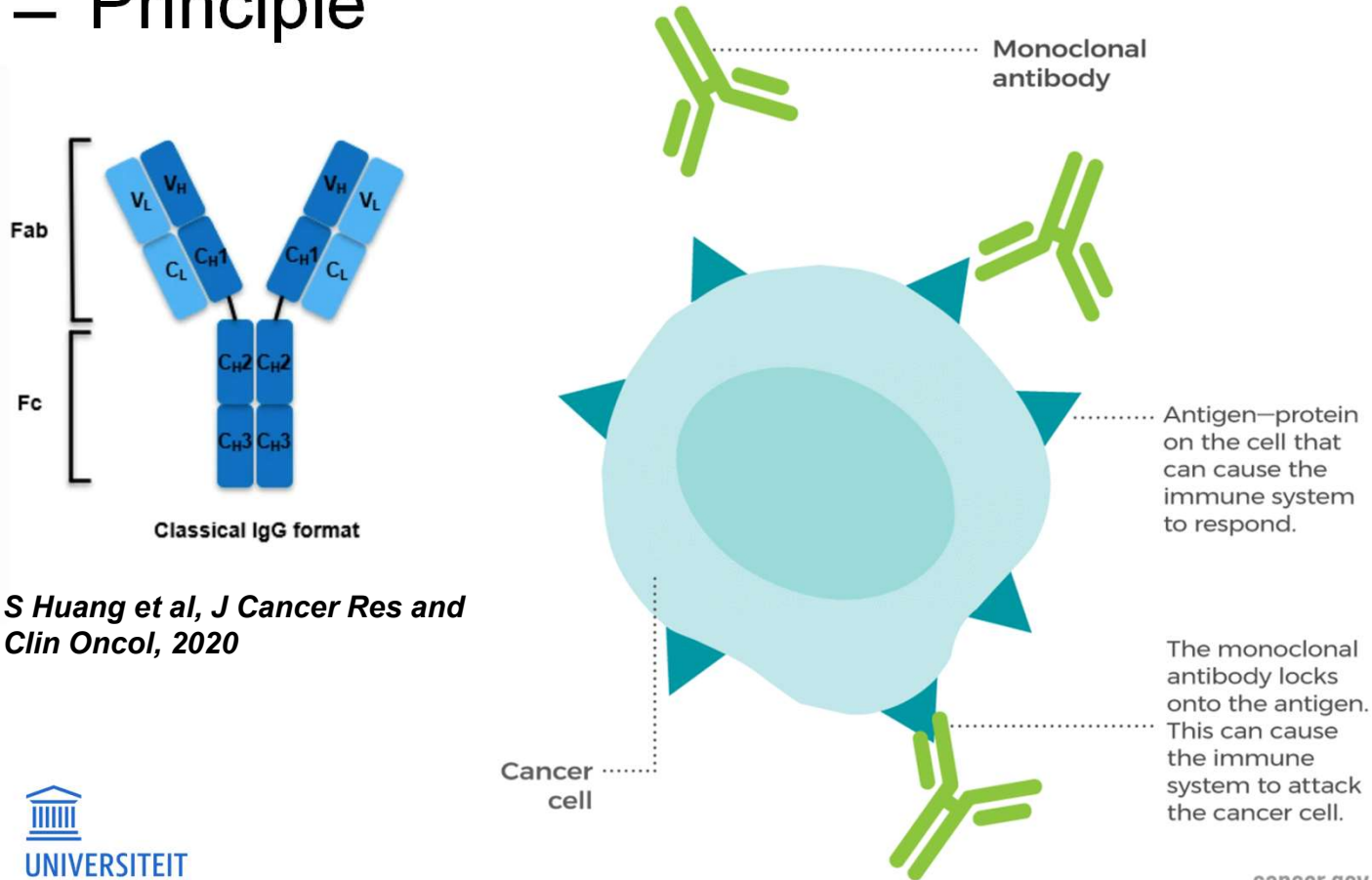
# OVERVIEW: IMMUNOTHERAPY



# MONOCLONAL ANTIBODIES

# MONOCLONAL ANTIBODIES

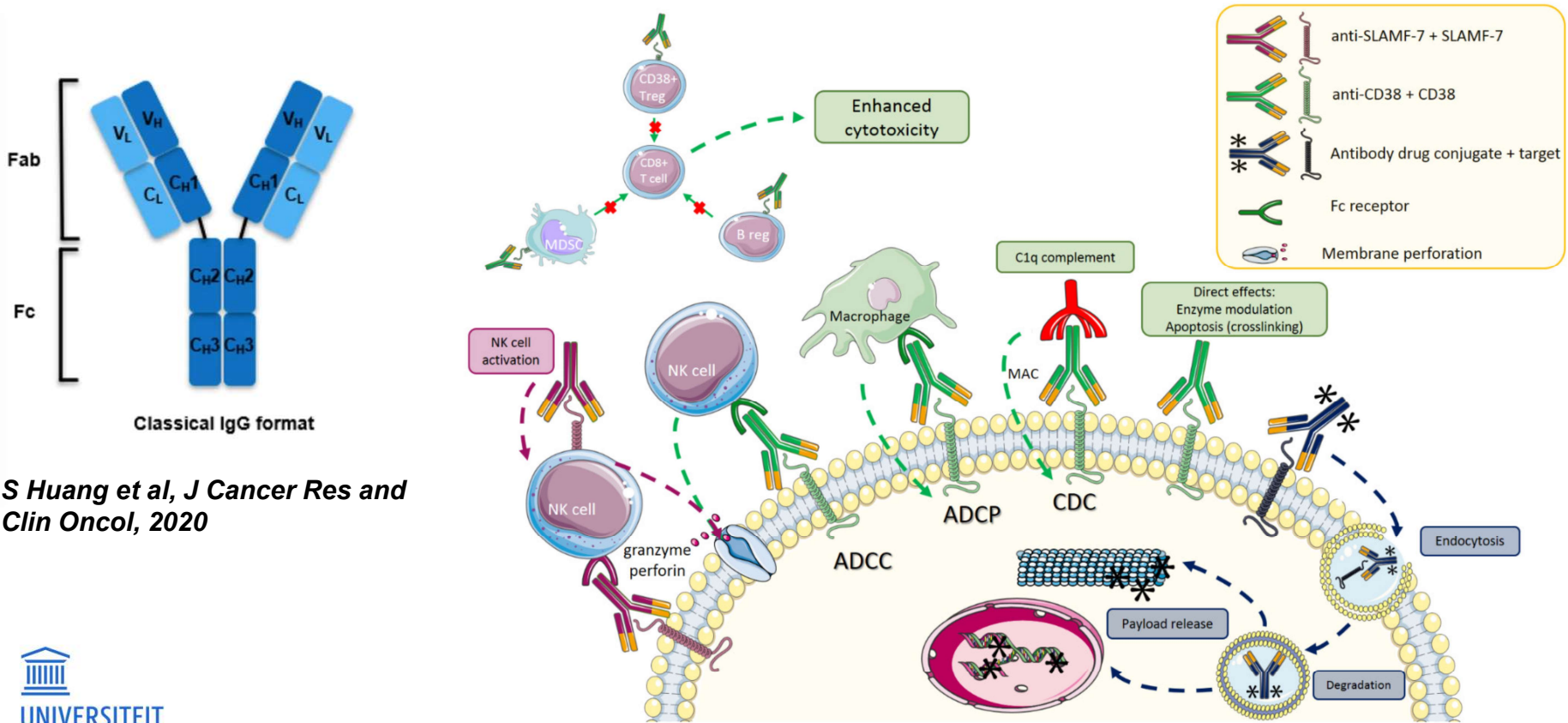
## – Principle



*S Huang et al, J Cancer Res and Clin Oncol, 2020*

# MONOCLONAL ANTIBODIES

## – Mechanisms of action

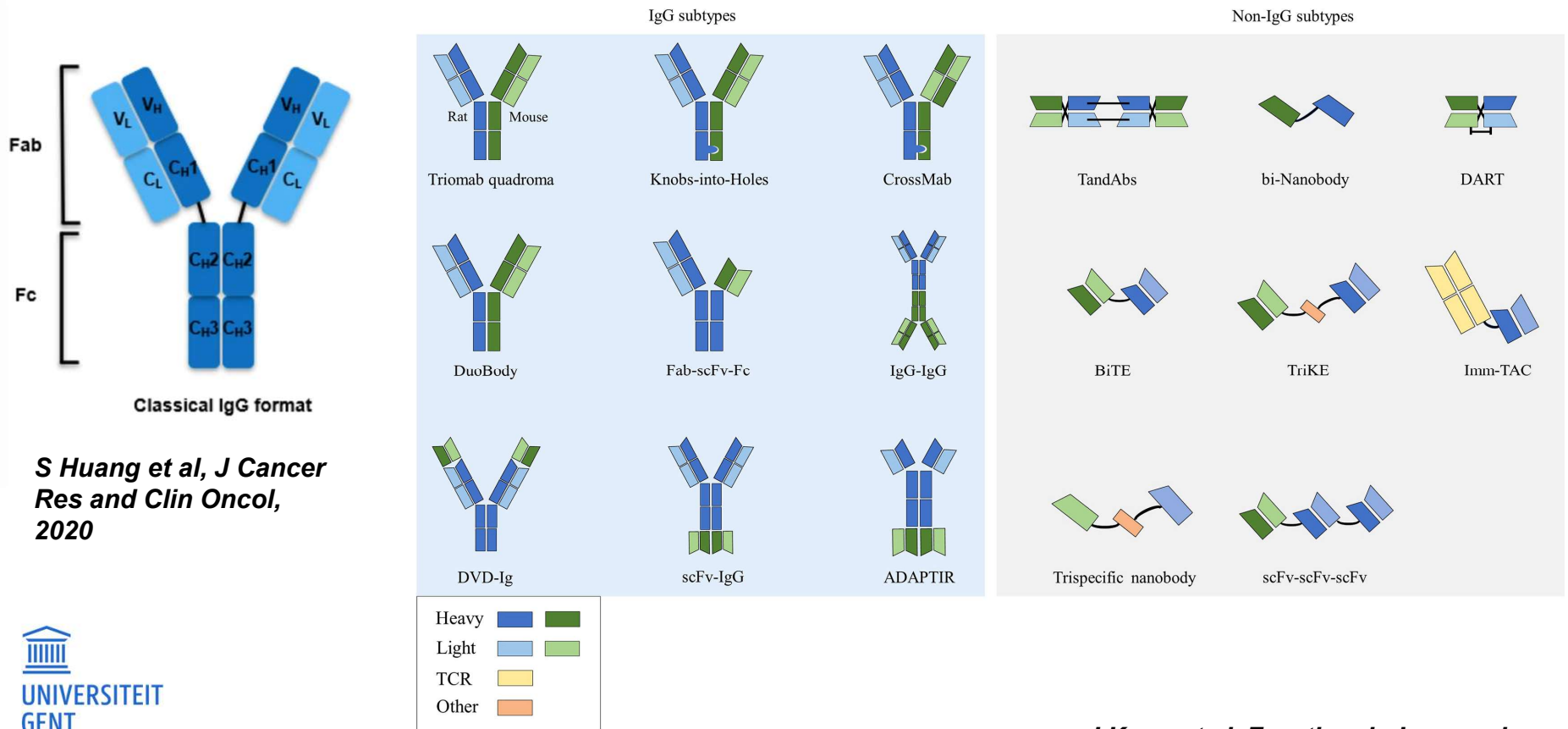


*S Huang et al, J Cancer Res and Clin Oncol, 2020*

# MULTISPECIFIC ANTIBODIES

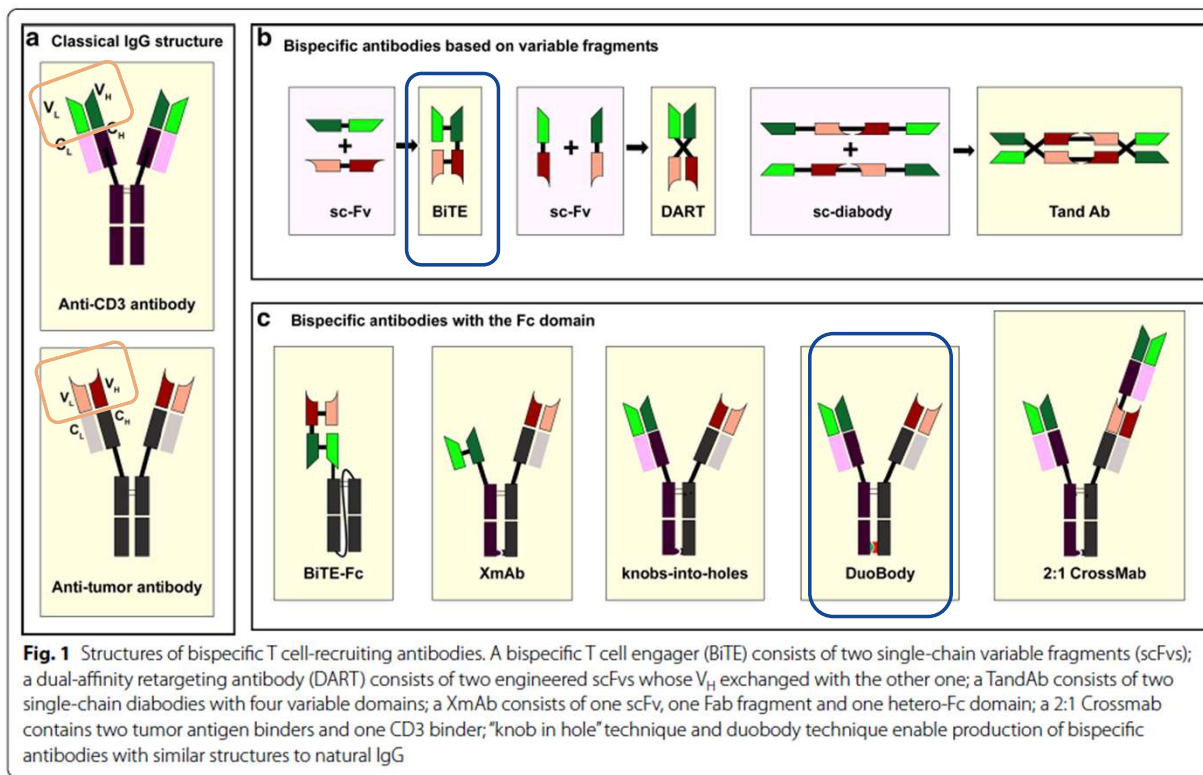
# MULTISPECIFIC ANTIBODIES

## Structure



# MULTISPECIFIC ANTIBODIES

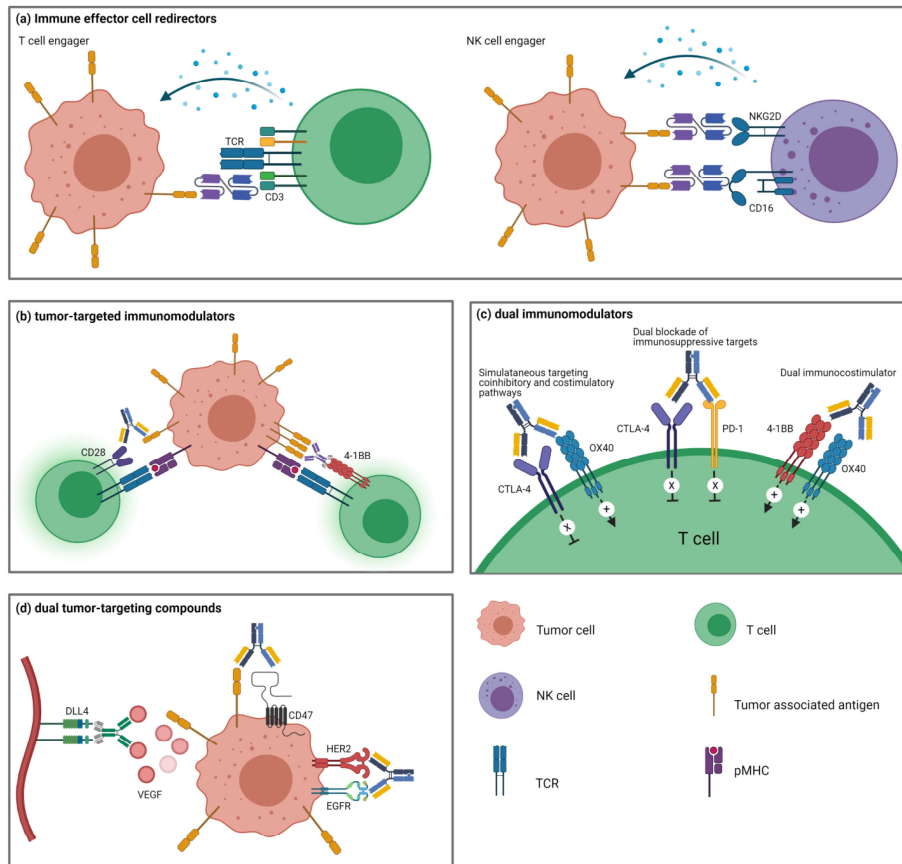
## Structure





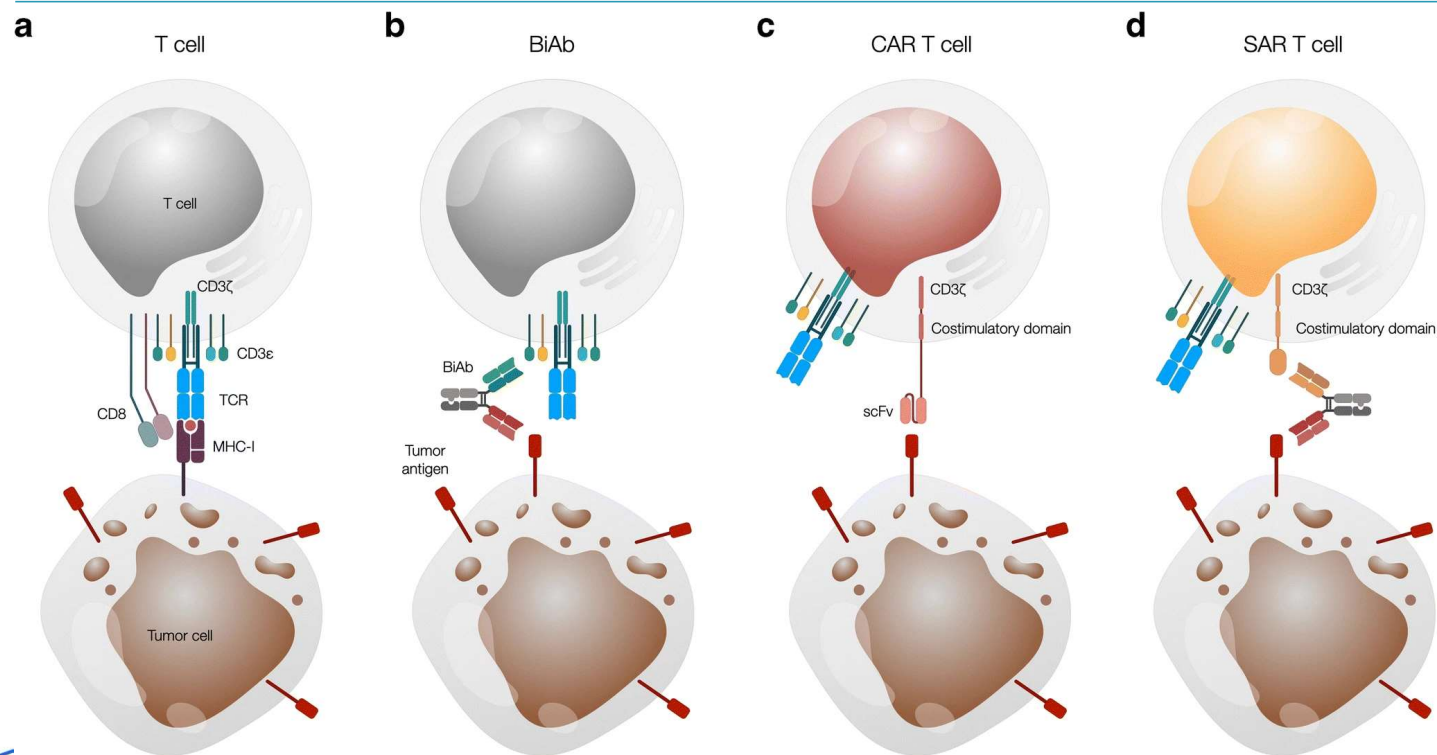
# MULTISPECIFIC ANTIBODIES

## Mechanisms of action



# MULTISPECIFIC ANTIBODIES

## Mechanisms of action



## Slide 10

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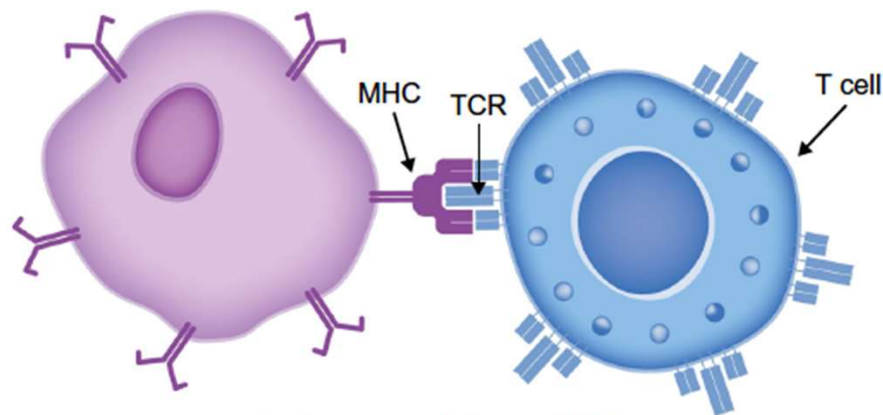
**PKO** added abbreviations

Put, Karen, 2024-01-04T14:29:25.471

# BITES

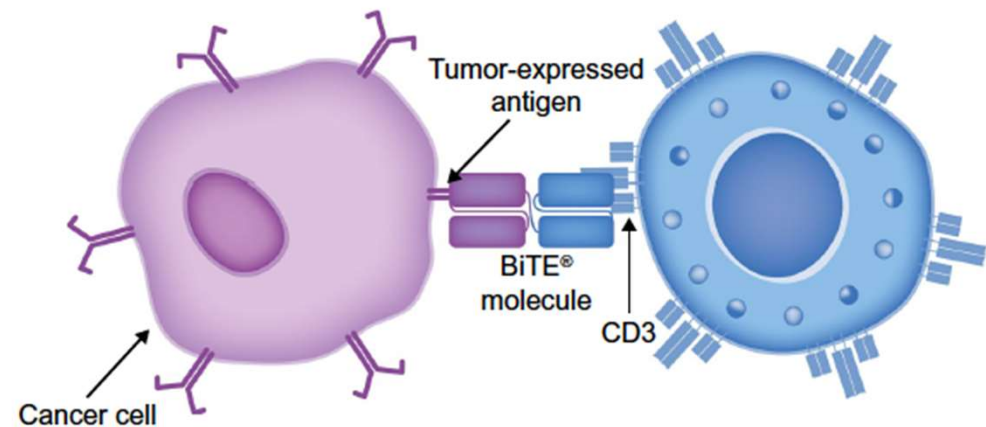
## Mechanisms of action

Normal Immune Recognition Systems



Antigen presentation by MHC and recognition by TCR

BiTE<sup>®</sup> Molecule-Mediated T cell Engagement



Engagement independent of MHC/TCR

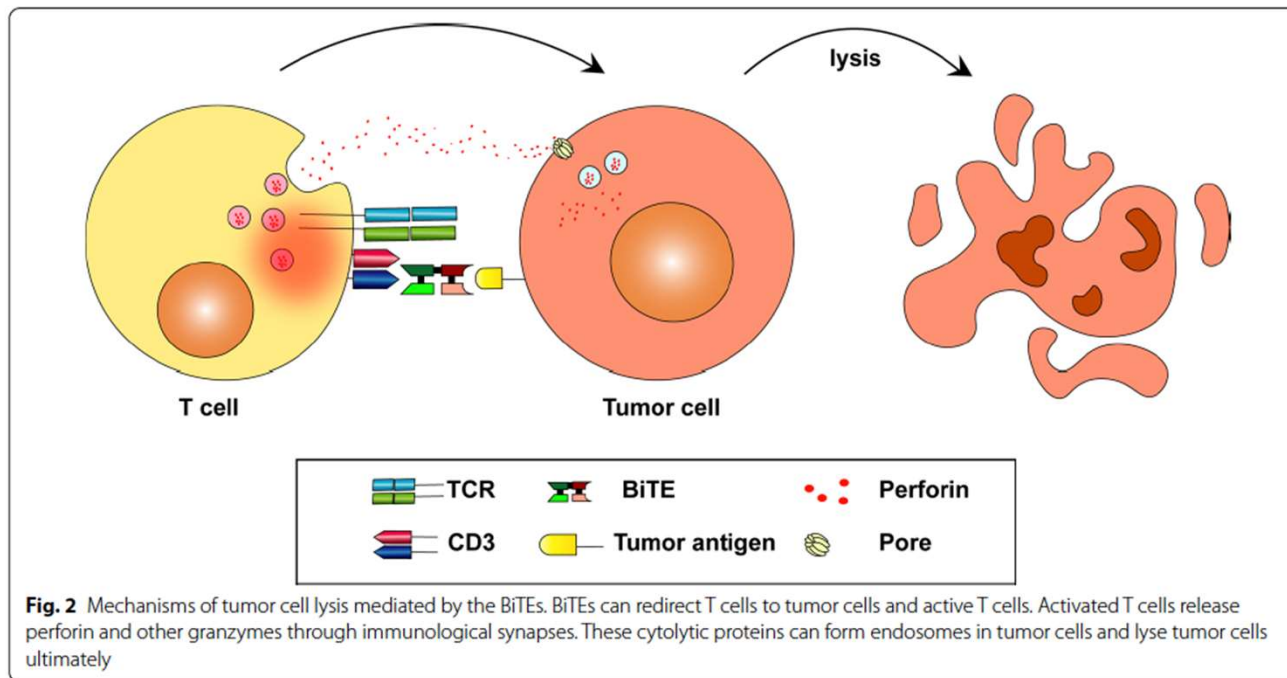
## Slide 11

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**PKO** added abbreviations  
Put, Karen, 2024-01-04T14:29:41.754

# BISPECIFIC ANTIBODIES AND BITES

## Mechanisms of action



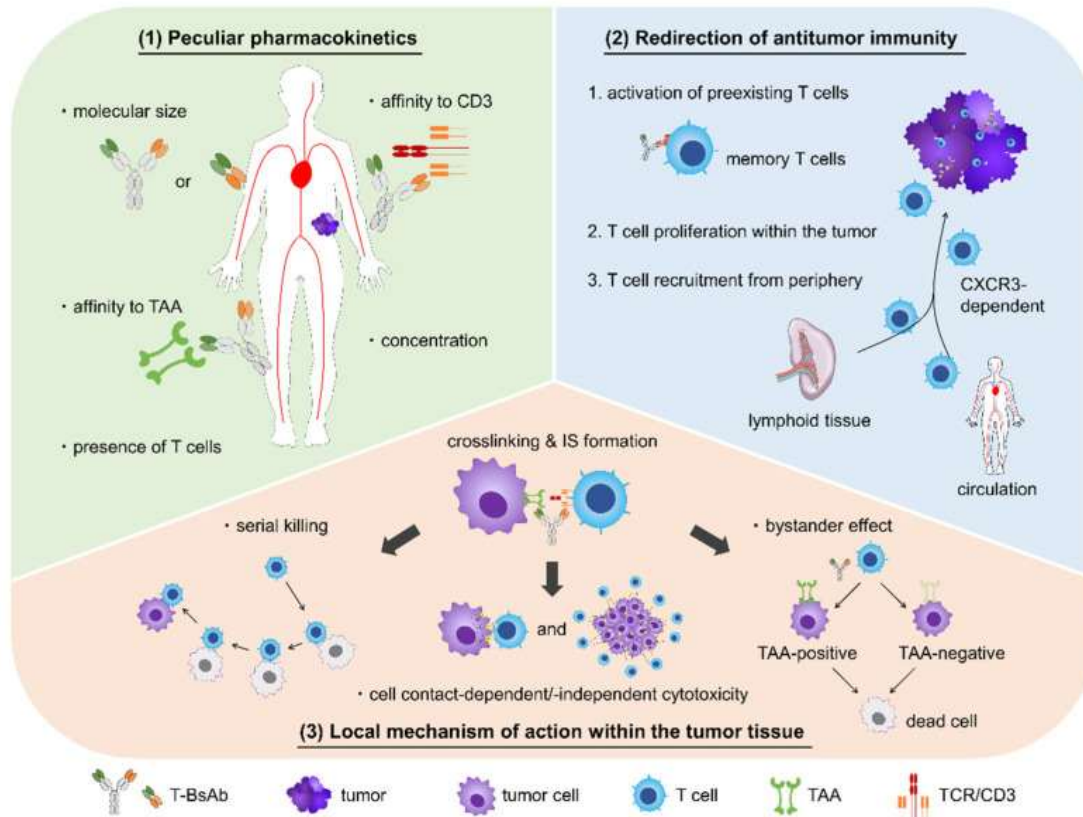
## Slide 12

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**PKO** added abbreviations  
Put, Karen, 2024-01-04T14:52:09.946

# MULTISPECIFIC ANTIBODIES

## Mechanisms of action





# MULTISPECIFIC ANTIBODIES

Multi(bi)specifics for hematologic malignancies reimbursed in Belgium

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## B-ALL

- **Blinatumumab** – CD19/CD3 BiTE – B-ALL

## Lymphoma

## Multiple myeloma

- **Teclistamab** = BCMA/CD3 bispecific Ab (duobody) – MM

## Slide 14

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**PK0** Please note we removed the brand names due to the educational nature of this symposium

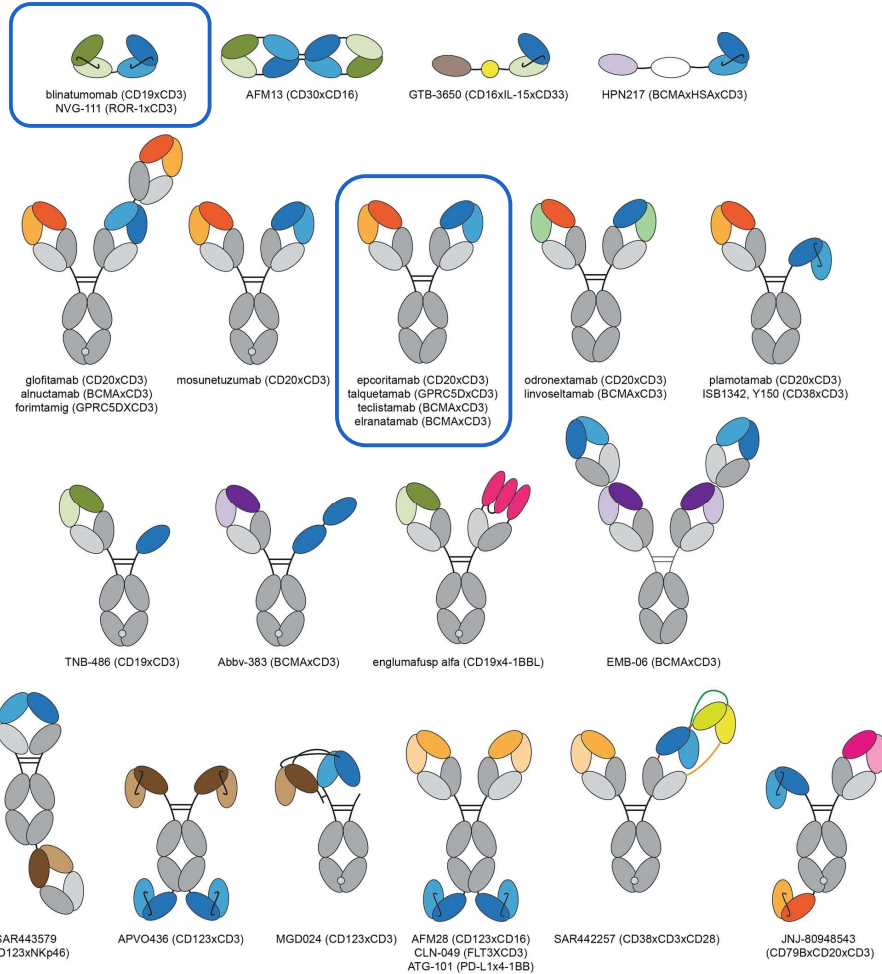
Put, Karen, 2024-01-04T14:27:48.323

**PK1** added abbreviations

Put, Karen, 2024-01-04T14:29:47.301

# MULTISPECIFIC ANTIBODIES

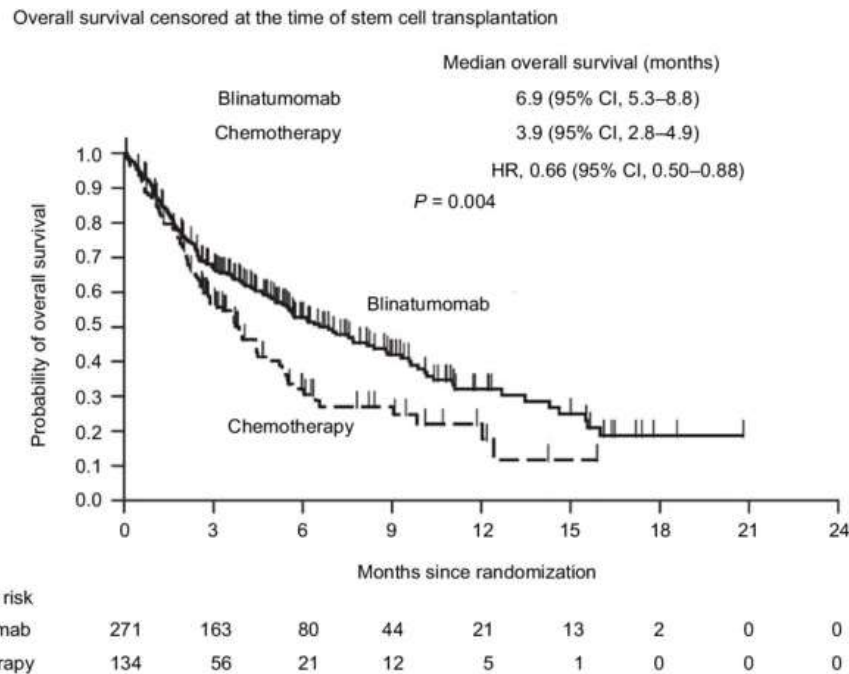
## Structure



# MULTISPECIFIC ANTIBODIES

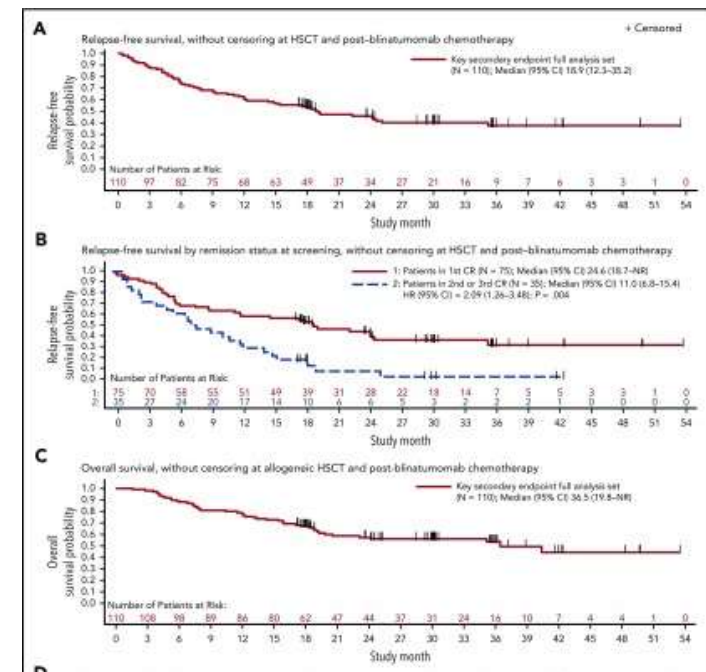
Blinatumomab = anti-CD19/anti-CD3 BiTE = the pioneer

## R/R B-ALL



H Kantarjian *et al*, *NEJM*, 2017 - TOWER

## MRD+ B-ALL

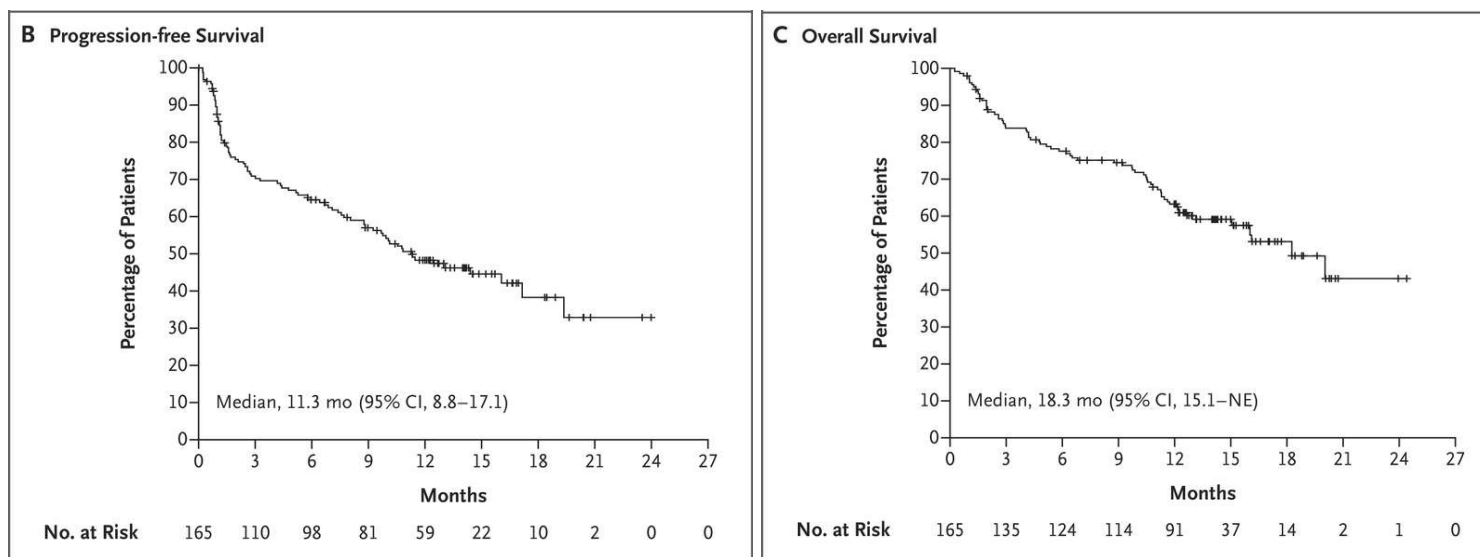


N Gökbueğ, *Blood*, 2018 - BLAST

# MULTISPECIFIC ANTIBODIES

## Teclistamab = anti-BCMA/anti-CD3 BiAb

Relapsed/refractory myeloma after at least three therapy lines, including triple-class exposure (immunomodulatory drug, proteasome inhibitor, and anti-CD38 antibody)



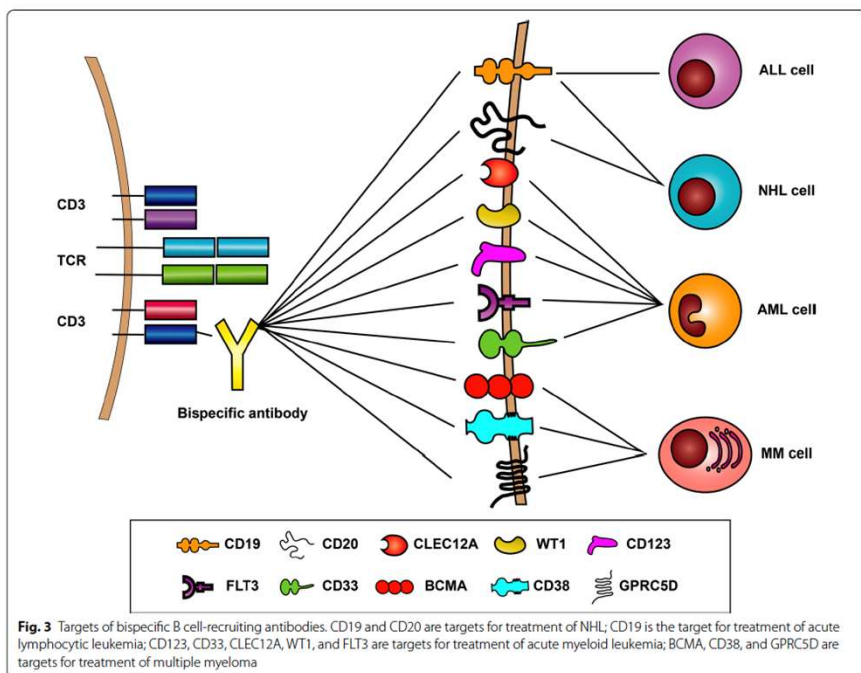
## Slide 17

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**PKO** added abbreviations  
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# MULTISPECIFIC ANTIBODIES

## Bispecific antibodies for hematologic malignancies



**Table 1** Bispecific T cell-recruiting antibodies for the treatment of hematologic malignancies

Disease	Target	Name	Antibody format
AML	CD123-CD3	MGD006	DART
		XmAb14045	XmAb
	CD33-CD3	AMG 330	BiTE
		AMV 564	TandAb
	FLT3-CD3	7370	BiTE
ALL	CLEC12A-CD3	MCLA-117	Biclonics
	WT1-CD3	ESK1-BITE	BiTE
	CD19-CD3	Blinatumomab	BiTE
MM	BCMA-CD3	AMG420	BiTE
		AMG701	BiTE-Fc
	GPRC5D-CD3	Talquetamab	DuoBody
	CD38-CD3	AMG424	XmAb
		Bi38-3	BiTE
NHL	FCRL5-CD3	anti-FcRH5/CD3 TDB	Knobs-into-holes
	CD19-CD3	Blinatumomab	BiTE
	CD20-CD3	REGN1979	Veloci-Bi platform
MDS		Mosunetuzumab	Knobs-into-holes
		RG6026	2:1 CrossMab
	CD33-CD3	AMV564	TandAb
	CD123-CD3	MGD006	DART

**PKO** abbreviations

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# MULTISPECIFIC ANTIBODIES

Multi (bi) specifics for hematologic malignancies coming (soon?)...

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## Lymphoma

- **Epcoritamab** = CD20/CD3 bispecific Ab (duobody) – DLBCL – CUP
- **Glofitamab** = CD20/CD3 bispecific Ab (crossbody) - DLBCL (DLBCL - 3<sup>rd</sup> line) – CUP
- **Mosunetuzumab** = CD20/CD3 KIH – FL
- **Odronextamab** = CD20/CD3 VelociBi - NHL

## Multiple myeloma

- **Talquetamab** = GPRC5D/CD3 bispecific Ab (duobody) - MM - CUP

## Slide 19

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**PK0** please note we removed the brand names due to the educational nature of the symposium

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**PK1** added abbreviations

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# MULTISPECIFIC ANTIBODIES

## Multispecifics for solid tumors

Table 1. Bispecific T-cell engagers therapy in solid tumors (clinicaltrials.gov accessed on 1 November 2022).

NCT	Phase	Drug (Format)	Target	Indication	Status	Results	Ref.
EpCAM							
NCT00836654	2/3	Catumaxomab or Removab® (Triomab®)	EpCAM xCD3	Malignant ascites and EpCAM-positive tumors	Completed	N = 258 (129 ovarian cancer) Puncture-free survival: 46 vs. 11 days AE: fever (60%); abdominal pain (43%)	[51]
NCT01065246	2	Catumaxomab	EpCAM xCD3	Malignant ascites due to epithelial carcinoma	Completed	N = 8 (rechallenge of intraperitoneal catumaxomab) Puncture-free survival: 47.5 days	[57]
NCT00326885	2	Catumaxomab	EpCAM xCD3	Malignant ascites ovarian cancer	Completed	N = 32 Puncture-free survival: 29.5 days Ascites symptoms improved	[58]
NCT01246440	2	Catumaxomab	EpCAM xCD3	Ovarian cancer	Completed	N = 46 (consolidation therapy) Median duration treatment: 13 days Grade 3-4 AE in 29 pts (74.4%) Treatment interruption in 4 (10.2%)	[59]
NCT00189345	2	Catumaxomab	EpCAM xCD3	Platinum refractory ovarian, fallopian tube, and peritoneal neoplasms	Completed	N = 46 (low dose 23 + high dose 22) No difference AE low vs. high Stable disease in 2 pts (low) and 5 pts (high)	[60]
NCT01815528	2	Catumaxomab	EpCAM xCD3	Recurrent epithelial ovarian cancer	Completed	Not reported	
NCT00563836	2	Catumaxomab	EpCAM xCD3	Ovarian cancer	Completed	Not reported	
NCT04222114	3	Catumaxomab	EpCAM xCD3	Gastric cancer	Recruiting		
CEA							
NCT01504256	2	Catumaxomab + FLOT	EpCAM xCD3	Gastric adenocarcinoma with peritoneal carcinomatosis	Completed	N = 31 (FLOT + catumaxomab 15 pts (A) vs. FLOT alone 16 pts (B)) Complete remission of carcinomatosis: 27% (A) vs. 19% (B) (p = 0.69). Severe AE: fever (23%), abdominal pain (31%), elevated liver enzymes (31%). Median PFS: 6.7 (A) vs. 5.4 months (B) (p = 0.71).	[61]
NCT00464893	2	Catumaxomab	EpCAM xCD3	Gastric cancer	Completed	Not reported	
NCT00352833	2	Catumaxomab	EpCAM xCD3	Gastric cancer	Completed	Not reported	
NCT04501744	1	M701	EpCAM xCD3	Malignant ascites	Recruiting		
NCT00635996	1	Solitumab or MT110 or AMG110	EpCAM xCD3	Relapsed/refractory solid tumors	Completed	N = 65 (35 colorectal; 10 ovarian; 8 gastric; 6 NSCLC; 3 SCLC; 3 mCRC) 95% Grade ≥ 3 AE, mainly diarrhea, elevated liver parameters and lipase	[54]
CEA							
NCT02324257 NCT02650713	1	RO6958688 or RC7802 + atezolizumab	CEA xCD3	CEA-positive tumors	Completed	N = 36 pts in monotherapy + 10 pts in combination Grade ≥ 3 AEs: infusion related reaction (16.3%) and diarrhea (5%)	[55]
NCT01284231	1	AMG211 or MEDI-565	CEA xCD3	Gastrointestinal adenocarcinomas	Completed	N = 39 (28 colorectal, 6 pancreatic, 5 other) Grade ≥ 3 AE in 5 pts (hypoxia n = 2, diarrhea, and CRS) Stable disease in 11 pts (28%)	[62]
NCT02291614	1	AMG211 or MEDI-565	CEA xCD3	Gastrointestinal adenocarcinomas	Completed	Terminated due to high immunogenicity at high doses of >3.2 mg	[63]
NCT03337698	1/2	RO6958688 + atezolizumab	CEA xCD3	NSCLC	Recruiting		[64]

NCT	Phase	Drug (Format)	Target	Indication	Status	Results	Ref.
EGFR							
NCT02620865	1/2	EGFR Bi-armed activated T-cells (BATs)	EGFR xCD3	Advanced pancreatic cancer	Completed	N = 7 No dose-limiting toxicities (DLTs), Median time to progression: 7 months	[65]
NCT03269526	1/2	EGFR BATs	EGFR xCD3	Advanced pancreatic cancer	Recruiting		
NCT03296696	1	AMC596	EGFRvIII xCD3	Glioblastoma	Completed	Not reported	[66]
NCT03344250	1	EGFR BATs + Temozolomide + RT	EGFR xCD3	Glioblastoma	Active, not recruiting		
gpA33							
NCT02248805	1	MGD007 (DART®)	gpA33 xCD3	Metastatic CRC	Completed	Not reported	[67]
NCT03531632	1/2	MGD007 + MGA012	gpA33 xCD3	Metastatic CRC	Completed	Not reported	
HER2							
NCT04501770	1	M802	HER2 xCD3	HER2-positive advanced solid tumors	Not yet recruiting		
NCT03448042	1	Runimotamab + trastuzumab + tocilizumab	HER2 xCD3	Locally advanced or metastatic HER2-expressing solid tumors	Recruiting		
NCT03272334	1/2	HER2 BATs + Pembrolizumab	HER2 xCD3	Metastatic breast cancer	Recruiting		
Other							
NCT03411915	1	Tidutamab (XmAb18087)	SSTR2 xCD3	NET and GIST	Completed	N = 41 Grade ≥ 3 AE: lymphopenia (29.3%); transaminase and GGT increase (19.5%); hypophosphatemia (9.8%) and lipase increase (7.3%)	[56]
NCT04590781	1/2	Tidutamab (XmAb18087) + Pembrolizumab	SSTR2 xCD3	Advanced Merkel cell carcinoma and ES-SCLC	Completed	Not reported	
NCT04424641	1/2	GEN1044 (DuoBody®)	574 xCD3	Solid tumors	Completed	Results on submission clinicaltrials.gov (accessed on 1 November 2022)	
NCT05180474	1	GEN1047 (DuoBody®)	B7H4 xCD3	Solid tumors	Recruiting		
NCT04083599	1/2	GEN1042	4-1BB xCD40	Solid tumors	Recruiting		
NCT04496674	1	CC-1 + Tocilizumab	PSMA xCD3	NSCLC	Recruiting		
NCT04260191	1	AMG910	CLDN18.2 xCD3	Gastric and gastroesophageal junction adenocarcinoma	Active, not recruiting		
NCT03146637	2	Activated CIK	MUC1/CEA/EpCAM/GPC3xCD3	Advanced liver cancer	Recruiting		
NCT03319940	1	AMG757 (HLE) + Pembrolizumab	DLL3	SCLC	Recruiting		[68]
SCLC							
NCT	Phase	Drug (Format)	Target	Indication	Status	Results	Ref.
NCT04471727	1/2	HPN328 (TriTAC)	DLL3	SCLC	Recruiting		
NCT04590326	1/2	REGN4018 or REGN5668 + Cemiplimab	MUC16 xCD3 or MUC16 xCD28	Ovarian cancer, fallopian tube cancer, peritoneal cancer	Recruiting		[69]
NCT03564340	1/2	REGN4018 + Cemiplimab	MUC16 xCD3	Ovarian cancer, fallopian tube cancer, peritoneal cancer	Recruiting		
NCT04117958	1	AMG199 (HLE)	MUC17 xCD3	MUC17-positive solid tumors	Recruiting		

## Slide 20

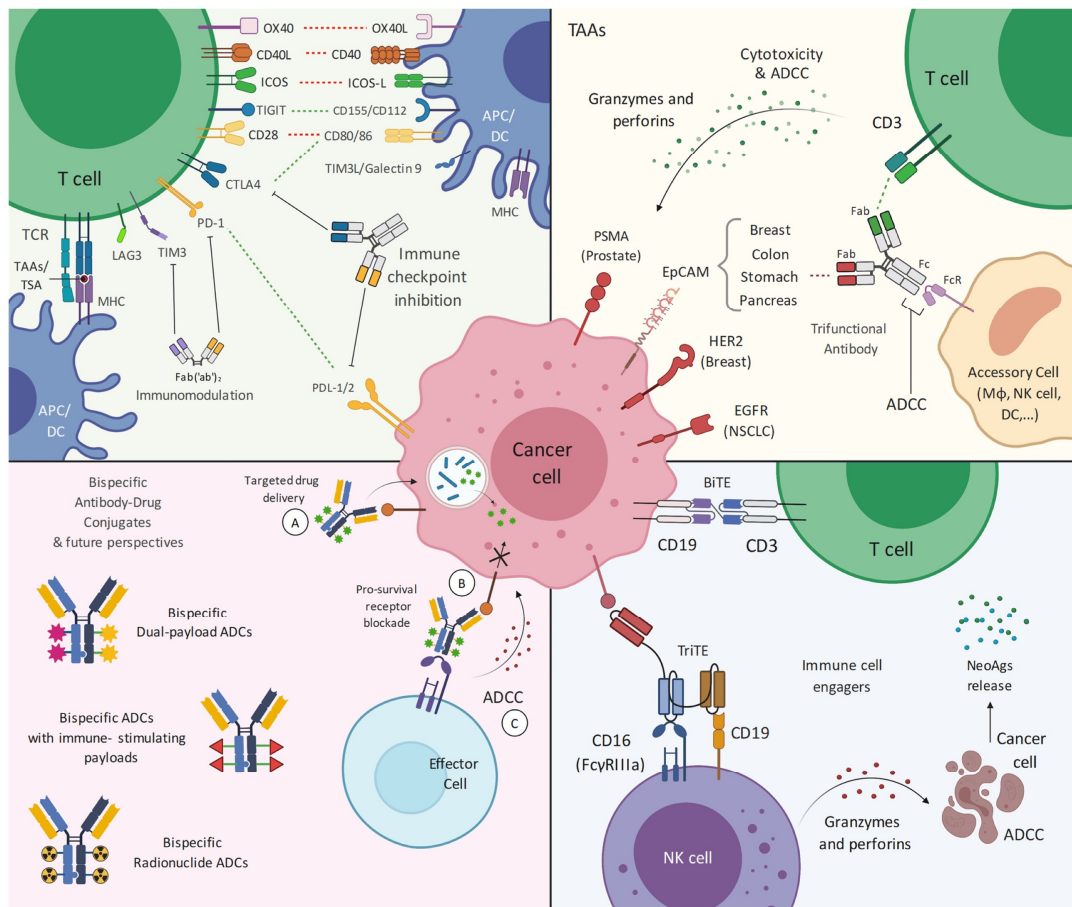
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**PKO** adapted title to multispecific antibodies to be in line with previous and following slides

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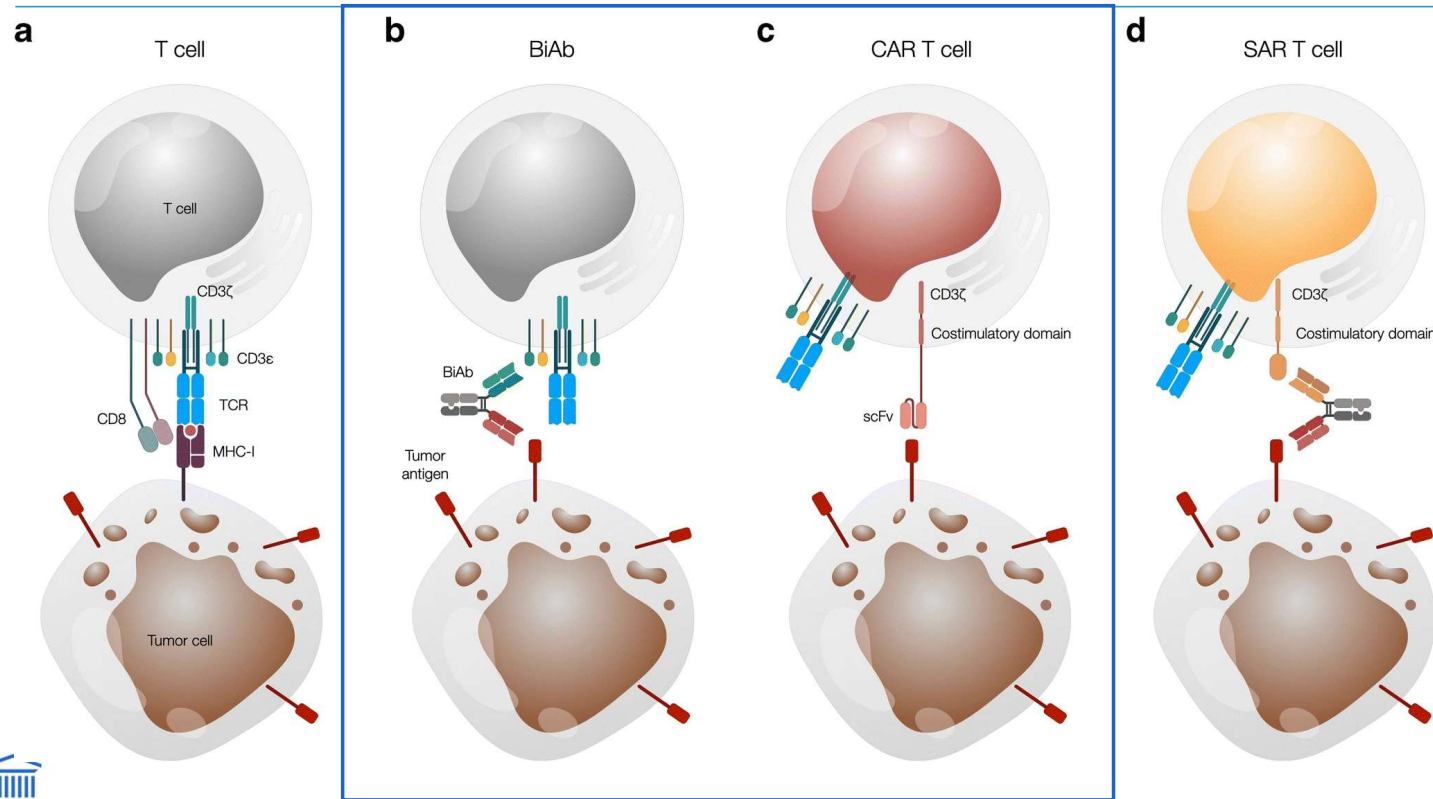
# MULTISPECIFIC ANTIBODIES

## Multispecifics for solid tumors



# MULTISPECIFIC ANTIBODIES

## BiAbs / BiTEs versus CARs

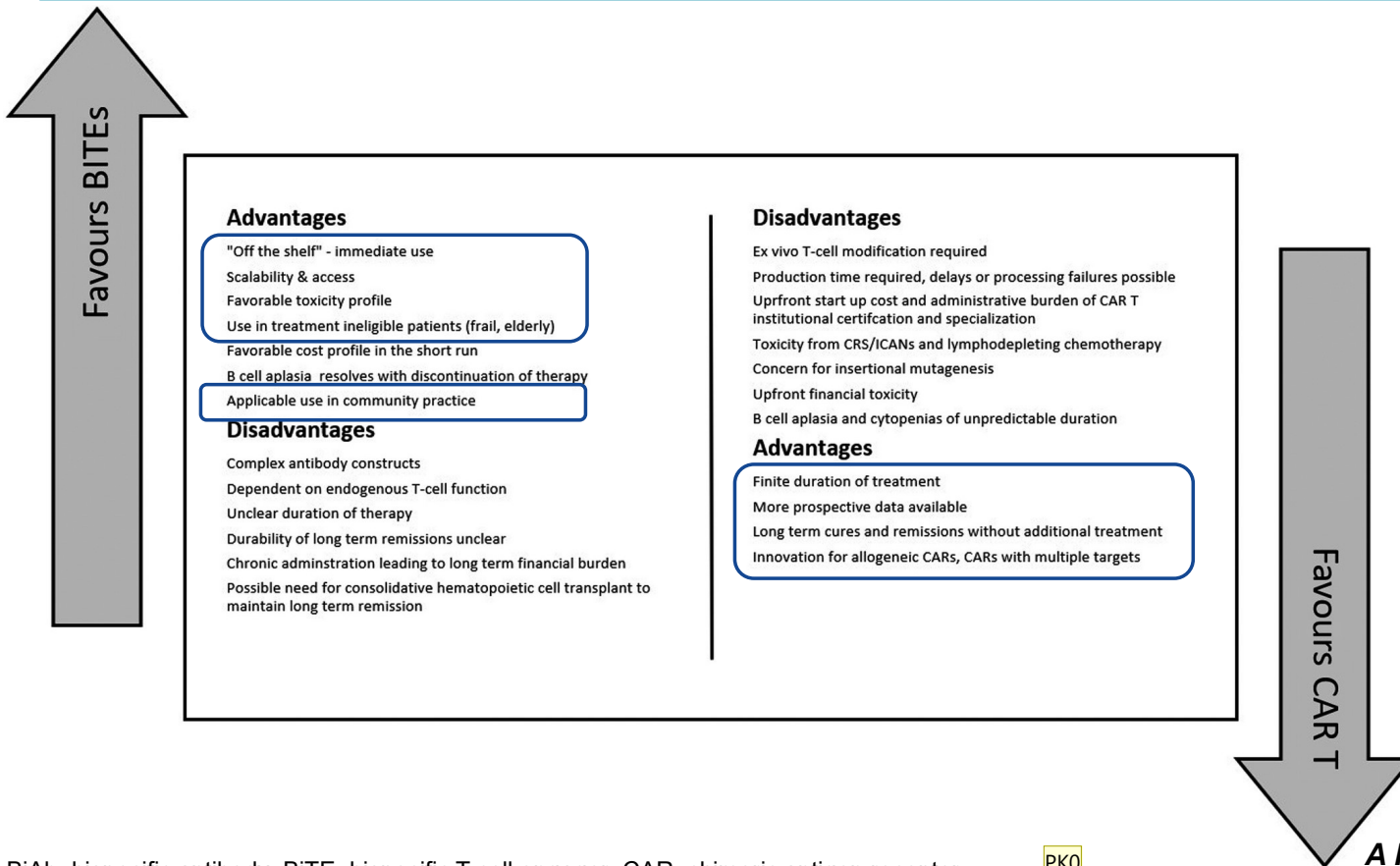


**PKO** added abbreviation

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# MULTISPECIFIC ANTIBODIES

## BiAbs / BiTEs versus CARs



BiAb, bispecific antibody; BiTE, bispecific T cell engager; CAR, chimeric antigen receptor.

PKO

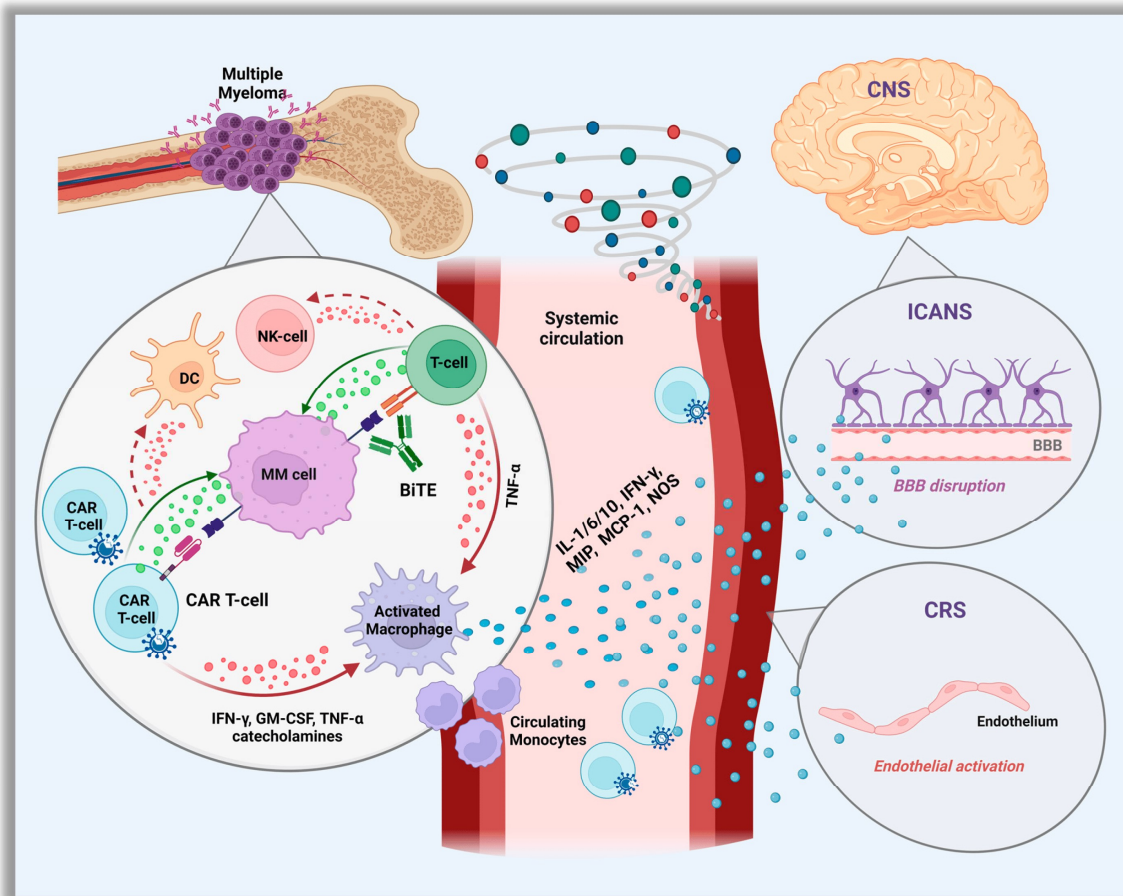
A Patel et al, British J Haemat, 2021 23



**PKO** added abbreviations  
Put, Karen, 2024-01-04T14:45:17.930

# MULTISPECIFIC ANTIBODIES

## Multispecific antibodies: side effects



- CRS
- ICANS
- On-target, off-tumour  
(depending on the targeted Ag)

# MULTISPECIFIC ANTIBODIES

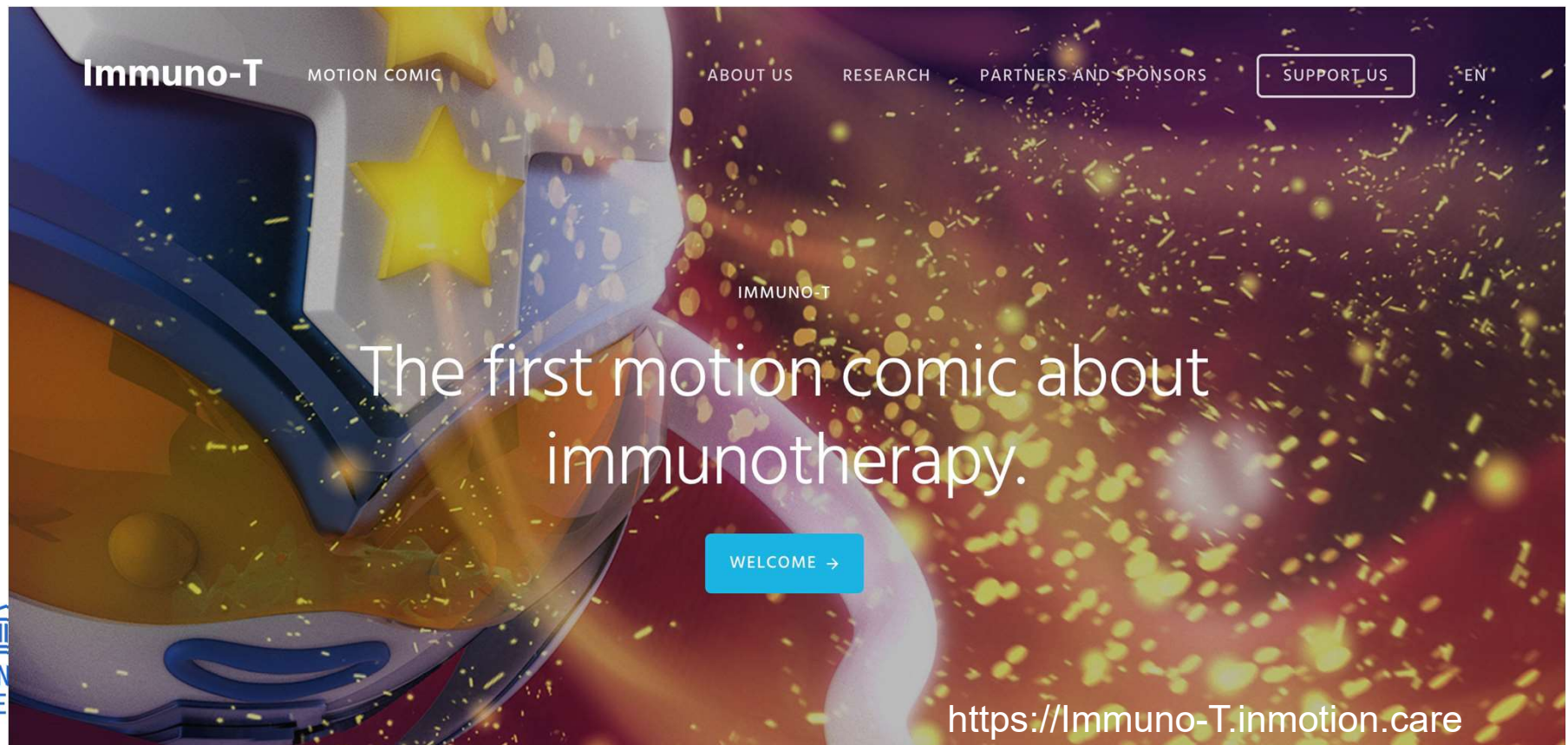
## The future

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- Altering the design of BiAbs/BiTEs to increase safety, patient friendly administration, efficacy
- Combination with checkpoint inhibitors? Other molecules?
- CAR-T vs BiAbs/BiTEs, or consecutive, in what order?

# PATIENT EDUCATION

<https://Immuno-T.inmotion.care>



## Slide 26

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**PKO** We would suggest to add `https://` to the link below to better visualize that this is a web address.

<https://Immuno-T.inmotion.care>

Put, Karen, 2024-01-04T14:48:28.594



immuno-T.inmotion.care

# IMMUNO T

A STORY IN MOTION




Start journey 

Choose your therapy 

Partners & sponsors 

Disclaimer 

Choose language 

<https://Immuno-T.inmotion.care>

## Slide 27

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**PKO** We would suggest to add `https://` to the link below to better visualize that this is a web address.

<https://Immuno-T.inmotion.care>

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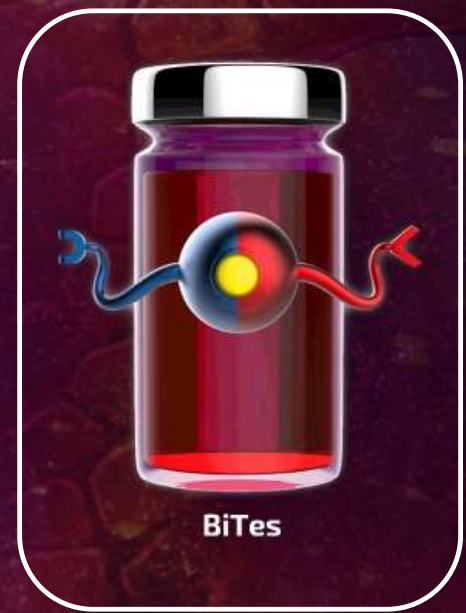
Click on the vials to discover the different forms of immunotherapy.



checkpoint inhibitors



CAR T-cell therapy



BiTes

Back to start

<https://Immuno-T.inmotion.care>



## Slide 28

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**PKO** We would suggest to add `https://` to the link below to better visualize that this is a web address.

<https://Immuno-T.inmotion.care>

Put, Karen, 2024-01-04T14:48:45.657

Tessa Kerre

Hematoloog UZ Gent

Hoofddocent UGent

DIENST HEMATOLOGIE

E tessa.kerre@ugent.be

T +32 9 332 66 54

[www.ugent.be](http://www.ugent.be)

[Immuno-T.inmotion.care](http://Immuno-T.inmotion.care)



during



# Enjoy your second workshop!

18.05-18.20	BREAK			
18.25	<p>18.25 =&gt; 19.05  <b>PLENARY 2</b>            Novel concepts in cancer            Immunotherapy            B ROUTY            T KERRE            S RAUH (Mod)</p>	<p><b>METEOR ROOM</b>            FLOOR 1</p>	<p><b>COMET ROOM</b>            FLOOR 2</p>	<p><b>SATIN ROOM</b>            FLOOR 3</p>
19.10		<p>19.10=&gt;19.50            Patient education:            Examples from academics centers            T KERRE            S STREEL            M VANDELDELDE            J VANSTEENKISTE (Mod)</p>	<p>19.10=&gt;19.50            CAR T vs Bispecifics :            Toxicity and sequencing            P VANDENBERGHE            J CAERS            R SCHOTS (Mod)</p>	<p>19.10=&gt;19.50            Drug Interference during            Immunotherapy            M ILZKOVITZ            B ROUTY            A AWADA (Mod)</p>
19.50	<p>19.50 =&gt; 20.05  <b>CLOSING</b>            P LACANTE &amp; P COULIE</p>			
20.00 - 22.00	WALKING DINNER			



Micros & question  
cards available  
during **workshops**