Bispecific antibody development in Immuno-Oncology: redirecting immune effector cells towards tumors

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IUPHAR
INTERNATIONAL UNION OF BASIC AND CLINICAL PHARMACOLOGY

Joint Meeting of NC-IUPHAR and the British Pharmacological Society
Nov. 19-20, 2020

Agenda

- **Introduction – General concepts**
- **T cell engagers**
  - Prototypical TCE: blinatumomab
- **NK cell engagers**
  - Case study: AFM13 in T cell lymphoma
- **Immune checkpoint modulators**
  - Case study: MGD013, a PD1xLAG3 DART®
- **Other bispecific Ab-based molecules**
- **Take home messages**

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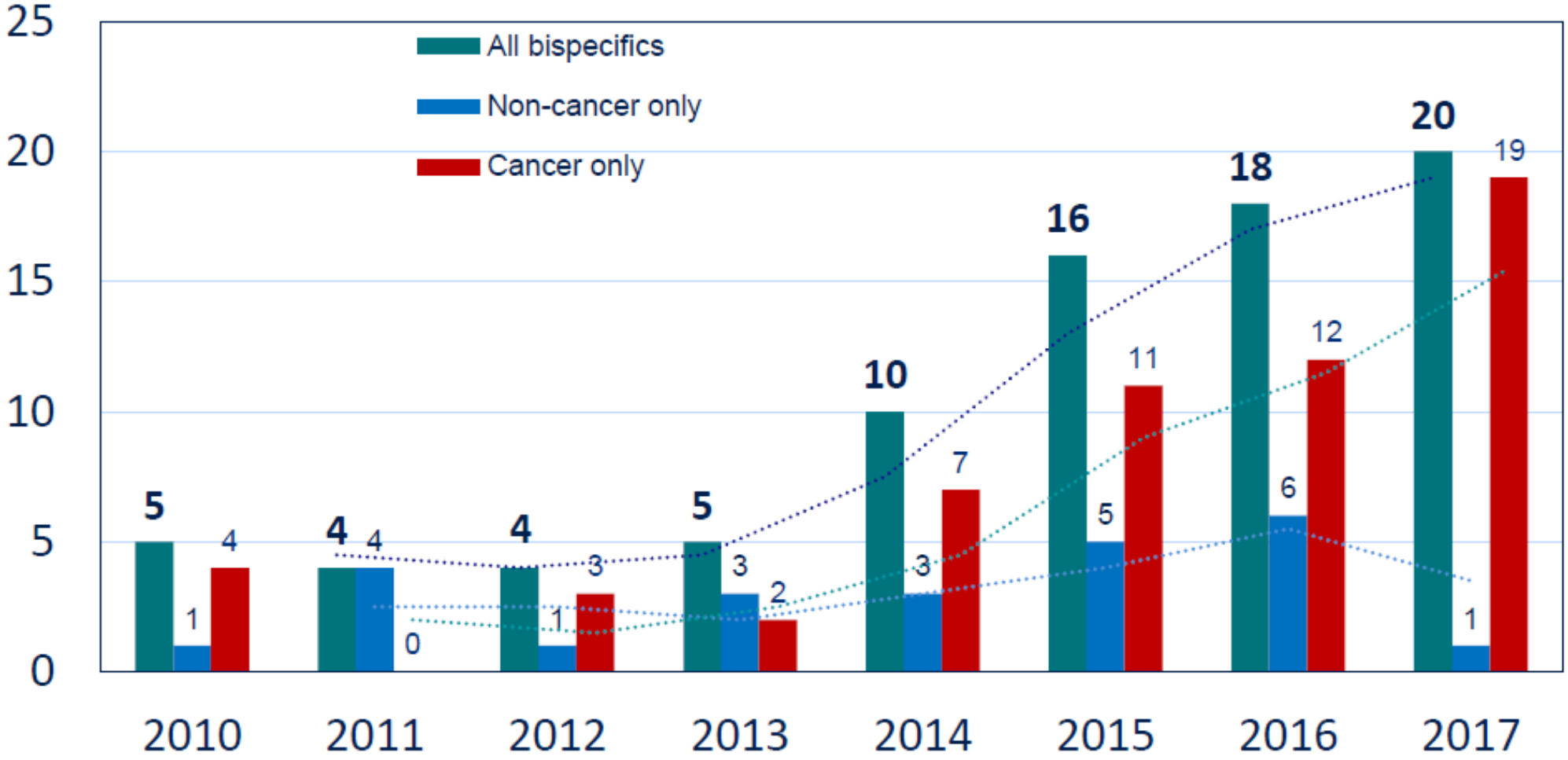
Bispecifics: Year of FiH study entry



Reichert, J, 2018, The Antibody Society website

Bispecifics in Oncology

- **Most (80%) are for cancer; 51 at Ph1 and 9 at Ph2**
  - T-cell redirection (38/60, 63%) most common mechanism of action
  - Most frequent TAAs are CD20 and B-cell maturation antigen (5 bsAbs each), followed by CD33 and CD123 (4 bsAb each)
- **EGFR family, Immune checkpoints targets also popular**
  - VEGF, EGFR, HER2 (5, 4, 2 bsAbs, respectively), with DLL3/VEGF most frequent (3 bsAbs)
  - PD-1, PD-L1 (4, 2 bsAbs, respectively) with PD-1/CTLA4 most frequent (3 bsAbs)

Reichert, J, 2018, The Antibody Society website

Bispecifics in non-cancer indications

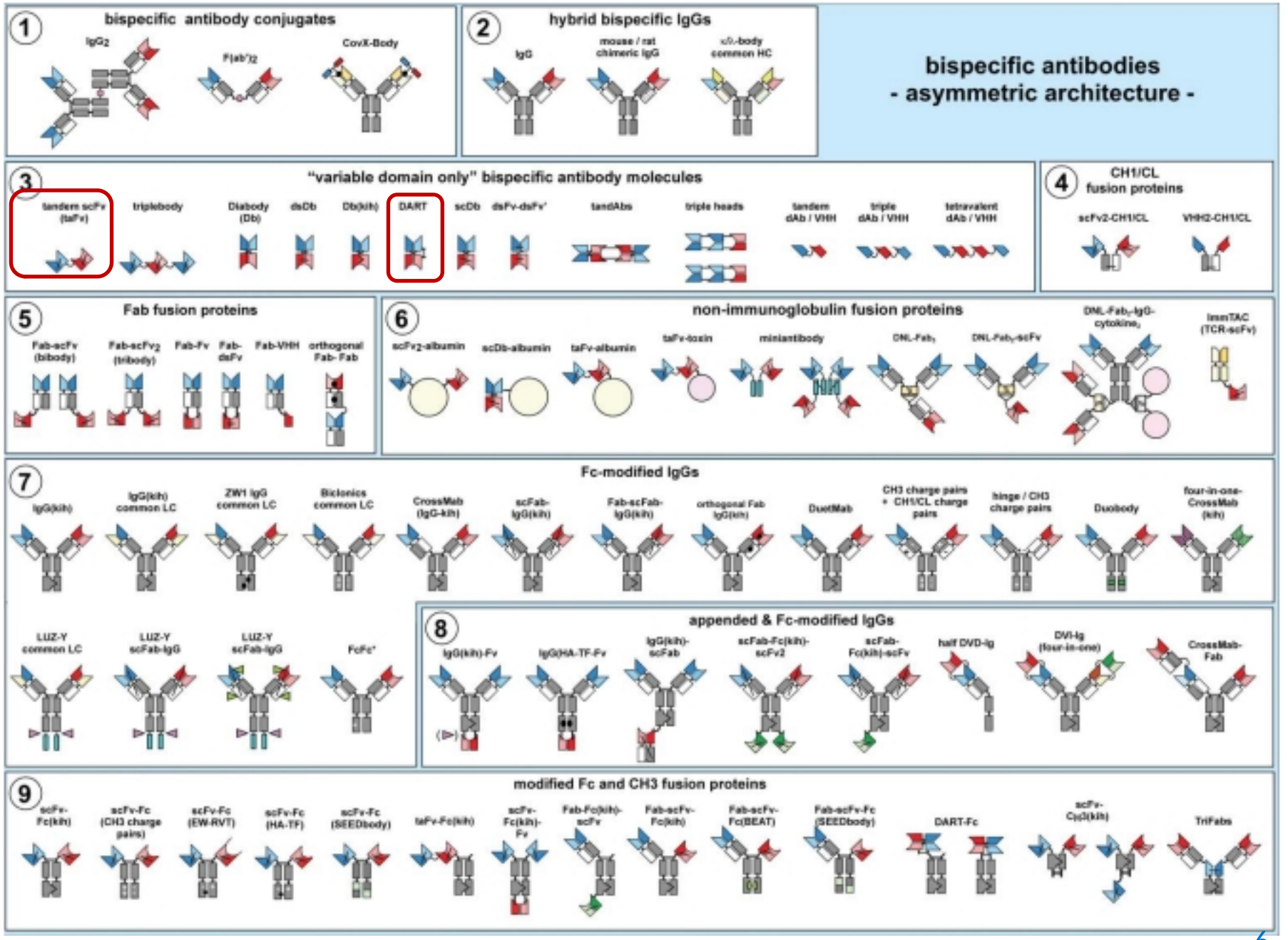
- **Only 15 (20%) bsAbs currently in clinical studies are for non-cancer indications**
  - 10 at Phase 1, 5 at Phase 2
- **Disorders include immune-mediated/inflammatory (9 bsAb), metabolic, neurological, ophthalmic, respiratory disorders and infectious disease**
  - Diverse array of targets, with IL-17 (3 bsAb) and TNF (2 bsAb) most frequent
- RO6867461 VEGF-A/Ang-2 CrossMab ready to enter Phase 3 in diabetic macular edema

Reichert, J, 2018, The Antibody Society website

A zoo of formats exists

Asymmetric

Generally associated with extensive engineering



Brinkmann & Kontermann, MABS 2017

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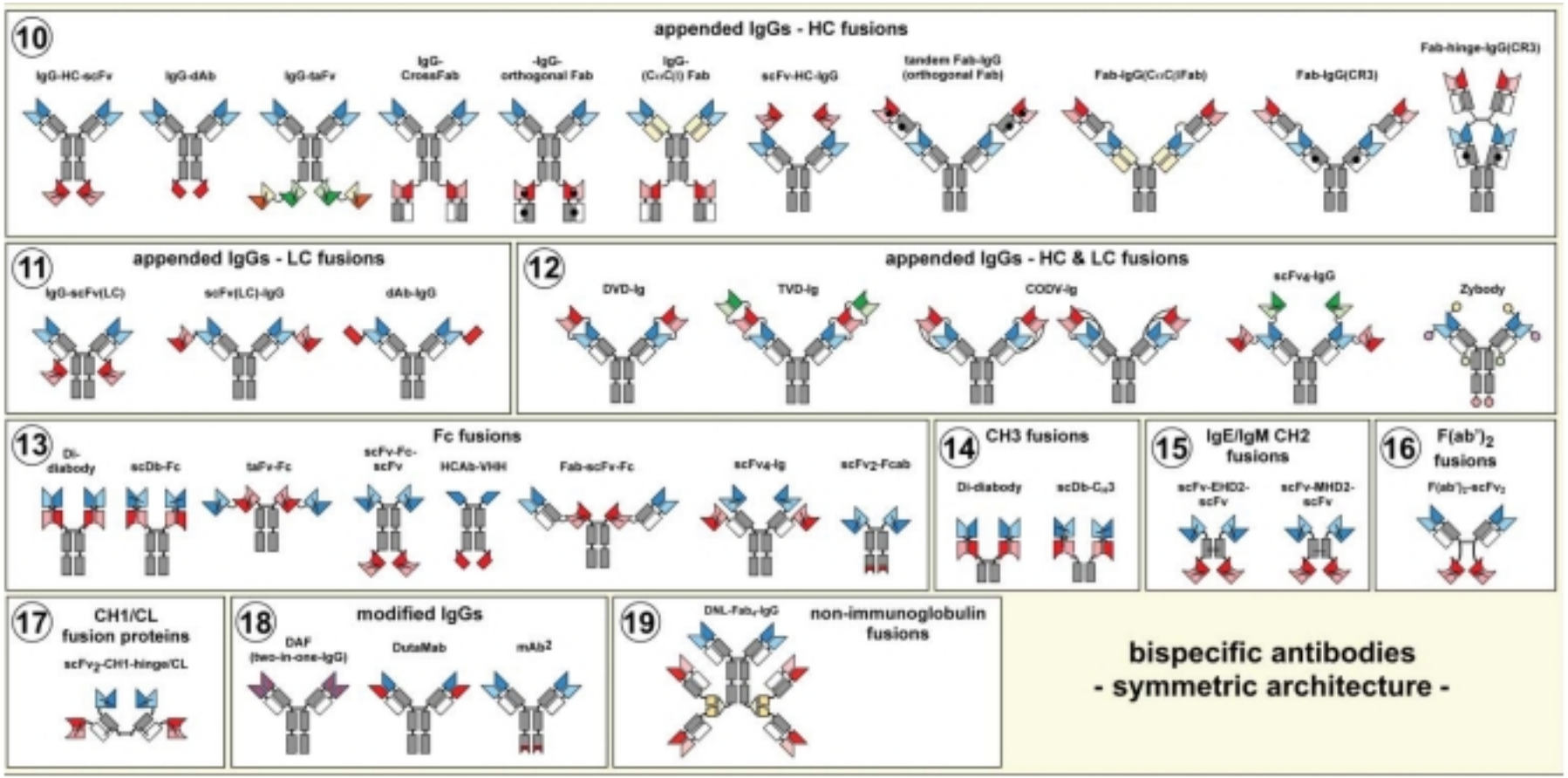
A zoo of formats exists

Symmetric

Unable to have differential valencies



Brinkmann & Kontermann, MABS 2017

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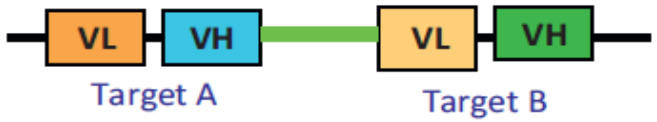
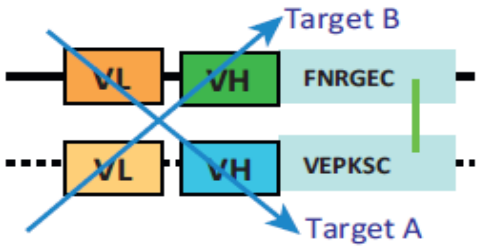
Examples of bispecific diabody-based scaffolds

BiTE
(Bi-specific T-cell engager)



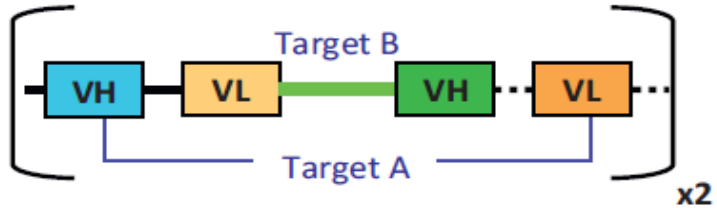
- 1 single polypeptide chain
- Flexible linker
- No chain dimerization

DART
(Dual affinity retargeting)

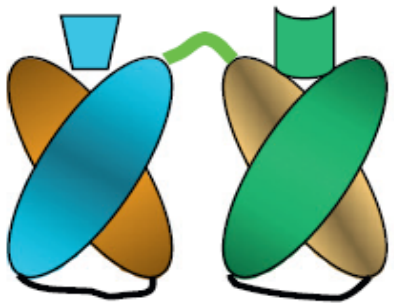


- 2 polypeptide chains
- No linker – interchain disulfide bridge
- Fusion to Ckappa and IgG1 upper hinge

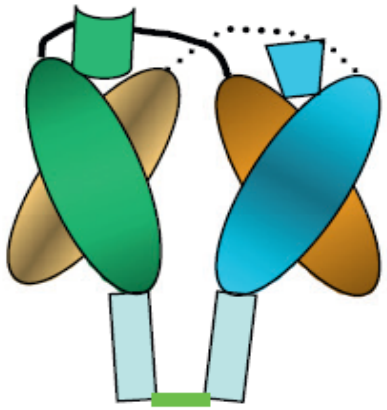
TandAb
(Tetravalent tANDem antibody)

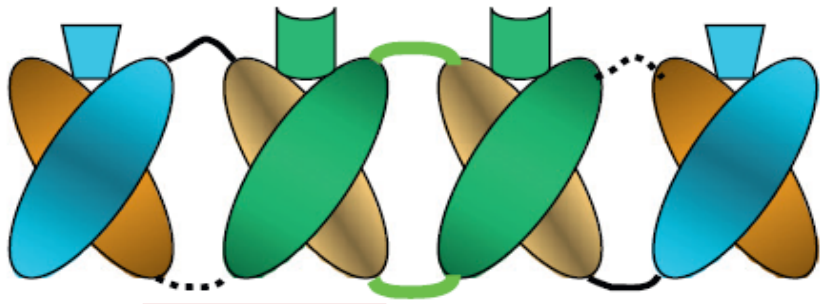


- 1 single polypeptide chain
- Highly flexible linkers
- Chain dimerization



TCEs





NKCEs

TRENDS in Biotechnology

BISPECIFIC T CELL ENGAGERS OR BITE®

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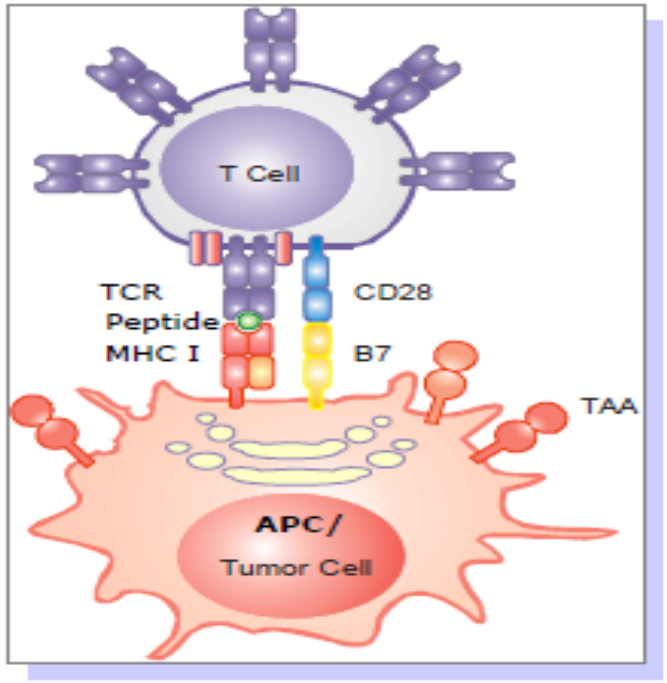
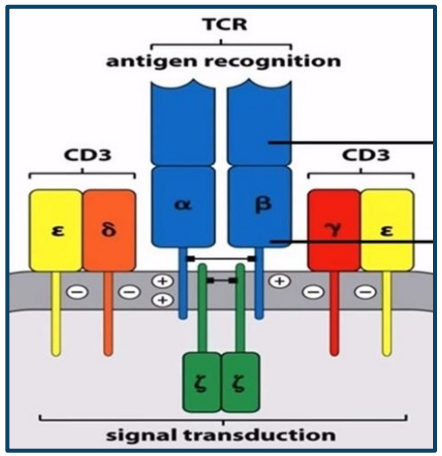
T cell engagers create an immunological synapse

Regular T cell activation

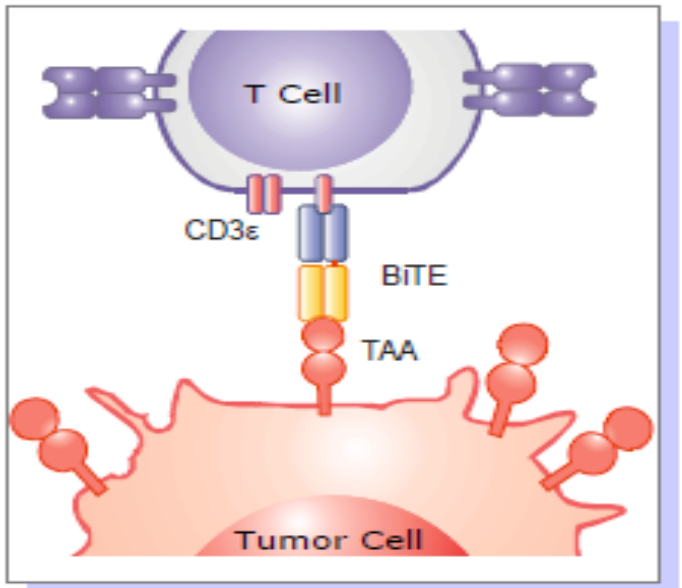


- Specific T Cell Receptor
- Peptide Antigen Presentation and Processing
- MHC I/β2 Microglobulin
- Co-stimulatory Molecules

TCR structure



CD3-engaging scaffold



- Any Cytotoxic T Cell (= Polyclonal)
- No Peptide Antigen
- No Antigen Processing
- No APCs needed
- No MHC I/β2 Microglobulin
- No Co-stimulatory Molecules

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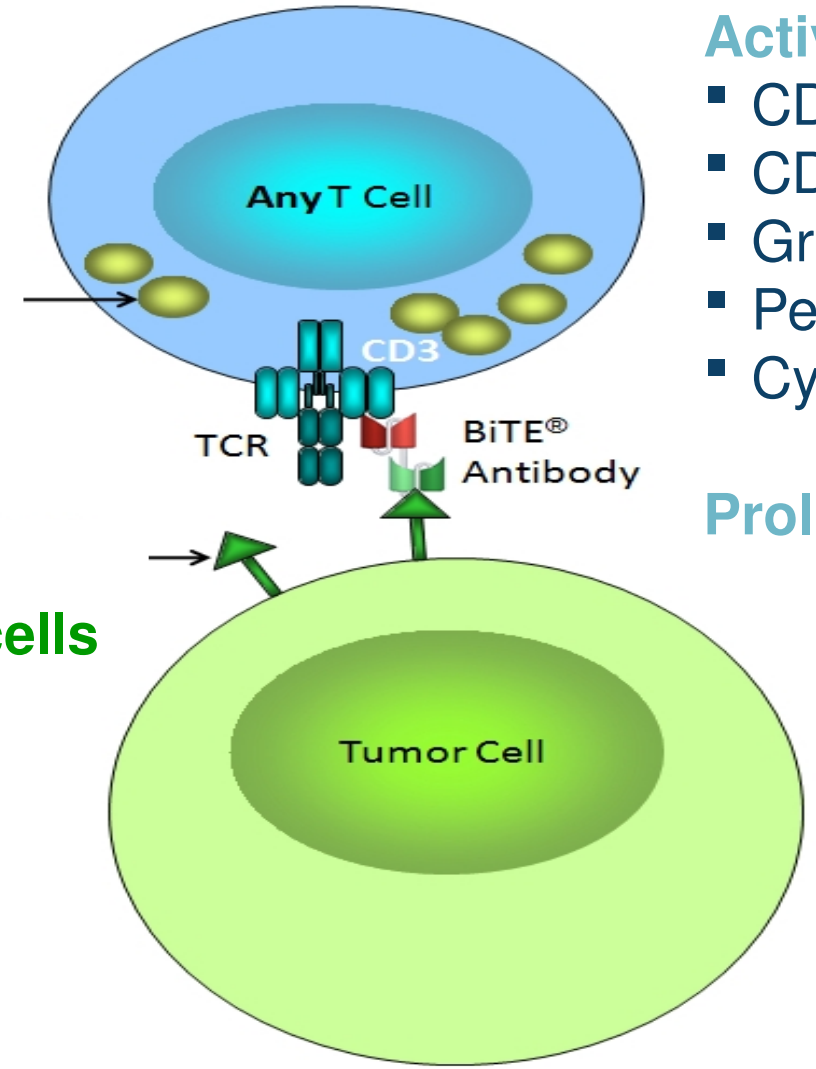
Cytolytic Immune Synapse



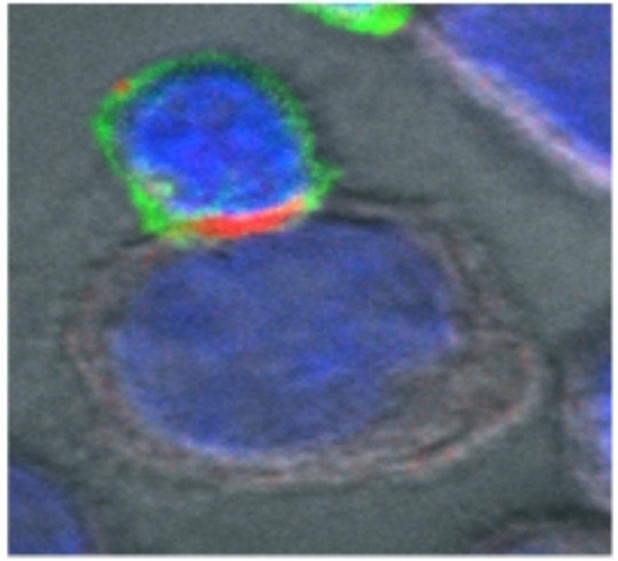
Cytolytic granule

TAA on tumor cells

Activation markers

- CD69 ⇄
- CD25 ⇄
- Granzymes ⇄
- Perforin ⇄
- Cytokines ⇄

Proliferation



Apoptosis

- Caspase activation ⇄
- DNA fragmentation ⇄
- PARP cleavage ⇄
- Morphological changes

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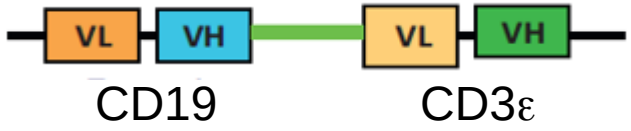
T cell engagers in clinical development

	Specificities (Target × Effector Cell)	Drug	Stage	Comments	Trial Identifier
Heme	CD19 × CD3	Blinatumomab[a]	Market and multiple phase II/III ongoing studies	Treatment of refractory/relapsed ALL and phase II for r/r NHL	NCT02811679
	CD19 × CD3	AFM11	Phase I	NHL and ALL	NCT02106091; NCT02848911
	CD20 × CD3	RG6026[a] and REGN1979[a]	Phase I	NHL and CLL	NCT02290951; NCT02290951
	CD20 × CD3	Mosunetuzumab[a]	Phase I	NHL, CLL, and DLBCL	NCT02500407; NCT03677154
	CLEC12A × CD3	MCLA-117[a]	Phase I	AML	NCT03038230
	CD33 × CD3	AMsG 330, GEM333, and AMV564	Phase I	AML and MDS	NCT02520427; NCT03516760; NCT03516591
	CD123 × CD3	MGD006, JNJ-63709178[a], and APVO436[a]	Phase I	AML	NCT02152956; NCT02715011; NCT03647800
	BCMA × CD3	BI 836909, JNJ64007957[a], PF-06863135[a], and REGN5458	Phase I	Multiple myeloma	NCT02514239; NCT03145181; NCT03269136; NCT03761108
	CD38 × CD3	GBR 1342[a]	Phase I	Multiple myeloma	NCT03309111
Solid	HER2 × CD3	GBR 1302[a]	Phase I	HER2-positive solid tumors	NCT02829372
	PSMA × CD3	AMG 160 and ES414[a]	Phase I	Prostate cancer	NCT03792841; NCT02262910
	DLL3 × CD3	AMG 757	Phase I	Small-cell lung cancer	NCT03319940
	NYESO1/LAGE-1A × CD3	IMCnyeso	Phase I	NYESO1 or LAGE-1A solid tumors	NCT03515551
	SSTR2 × CD3	XmAb18087[a]	Phase I	Neuroendocrine tumors and gastrointestinal stromal tumors	NCT03411915
	GPC3 × CD3	ERY974[a]	Phase I	GPC3-positive solid tumors	NCT02748837
	Gp100 × CD3	IMCgp100	Phase I/II	Uveal melanoma	NCT02570308
	GD2 × CD3	Hu3F8-BsAb[a] (GD2/CD3)	Phase I/II	Neuroblastoma, osteosarcoma, and other GD2-expressing solid tumors	NCT03860207

Mostly Pre-PoC assets

Strohl & Naso, Antibodies 2019

Prototypical TCE: blinatumomab – BLINCYTO®



- **Engineering**:
  - 1 single polypeptide chain
  - Flexible linker
  - No chain dimerization
- **Dosing**
  - Continuous IV infusion
  - Dose weight-adapted
  - Lead-in dose (1/3 of target) to diminish CRS risk

FDA approval history

Mar 29, 2018	APPROVAL FDA Expands Approval of Blincyto (blinatumomab) to Treat Minimal Residual Disease-Positive B-Cell Precursor Acute Lymphoblastic Leukemia
Jul 11, 2017	APPROVAL FDA Grants Full Approval for Blincyto (blinatumomab) to Treat Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia in Adults and Children
Sep 1, 2016	APPROVAL FDA Approves Blincyto (blinatumomab) For Use In Pediatric Patients With Philadelphia Chromosome-Negative Relapsed Or Refractory B-cell Precursor Acute Lymphoblastic Leukemia
Dec 3, 2014	APPROVAL FDA Approves Blincyto (blinatumomab) for Precursor B-Cell Acute Lymphoblastic Leukemia

BLINCYTO® TOWER Ph.3 study: SAFETY

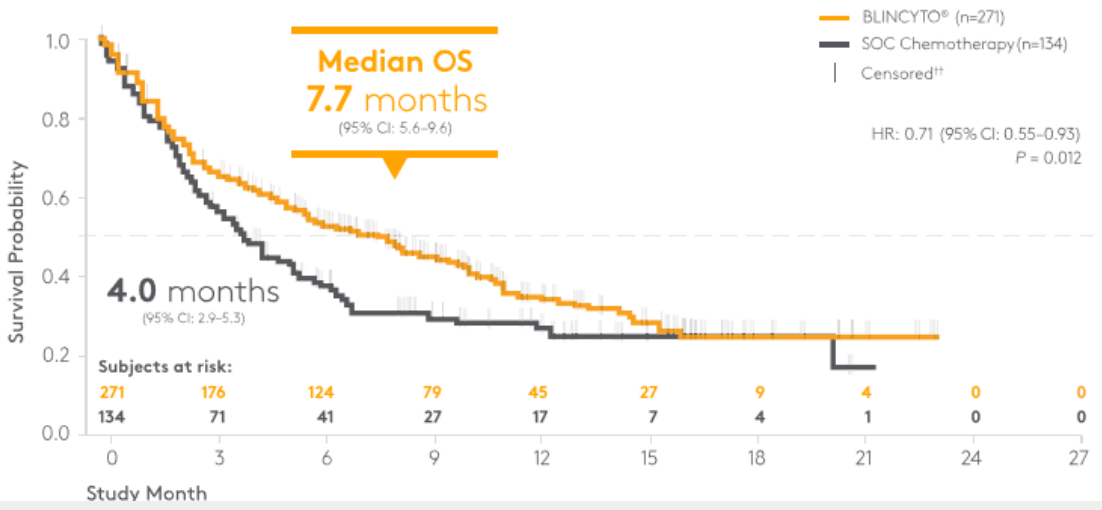
Two black boxed warnings issued by FDA:

- **CRS**
- **Neurological toxicities**

Adverse reaction	BLINCYTO® (N=267)		SOC chemotherapy (N=109)	
	Any Grade* n (%)	≥ Grade 3* n (%)	Any Grade* n (%)	≥ Grade 3* n (%)
Blood and lymphatic system disorders				
Neutropenia[a]	84 (31)	76 (28)	67 (61)	61 (56)
Anemia[b]	68 (25)	52 (19)	45 (41)	37 (34)
Thrombocytopenia[c]	57 (21)	47 (18)	42 (39)	40 (37)
Leukopenia[d]	21 (8)	18 (7)	9 (8)	9 (8)
Cardiac disorders				
Arrhythmia[e]	37 (14)	5 (2)	18 (17)	0 (0)
General disorders and administration-site conditions				
Pyrexia	147 (55)	15 (6)	43 (39)	4 (4)
Edema[f]	48 (18)	3 (1)	20 (18)	1 (1)
Immune system disorders				
Cytokine release syndrome[g]	37 (14)	8 (3)	0 (0)	0 (0)
Infections and infestations				
Infections — pathogen unspecified	74 (28)	40 (15)	50 (46)	35 (32)
Bacterial infectious disorders	38 (14)	19 (7)	35 (32)	21 (19)
Viral infectious disorders	30 (11)	4 (1)	14 (13)	0 (0)
Fungal infectious disorders	27 (10)	13 (5)	15 (14)	9 (8)
Injury, poisoning, and procedural complications				
Infusion-related reaction[h]	79 (30)	9 (3)	9 (8)	1 (1)
Investigations				
Hypertransaminasemia[i]	40 (15)	22 (8)	13 (12)	7 (6)
Nervous system disorders				
Headache	61 (23)	1 (<1)	30 (28)	3 (3)
Skin and subcutaneous tissue disorders				
Rash[j]	31 (12)	2 (1)	21 (19)	0 (0)

BLINCYTO® TOWER Ph.3 study: EFFICACY

Primary endpoint: Overall survival (intent-to-treat population)[1,4]



Primary endpoint: **Overall survival**[4]

2:1 Randomization

2

BLINCYTO® single-agent immunotherapy[4] n=271

- Continuous IV infusion for 1 to 2 induction cycles (4 weeks on, 2 weeks off)
- 9 mcg/day on days 1–7 of cycle 1 and 28 mcg/day on subsequent days

1

Standard-of-care chemotherapy[4] (investigator's choice of one of the regimens below) n=134

- FLAG ± anthracycline–based regimen
- HiDAC-based regimen
- High-dose methotrexate–based regimen
- Clofarabine-based regimens

Consolidation, maintenance,† and follow-up, depending on response to induction

Overall response

BLINCYTO® significantly increased complete remission rates compared with SOC chemotherapy[1]

CR/CRh*, §§

$P < 0.001$***

SOC n=27/134 (95% CI: 14-28)

BLINCYTO® n=115/271 (95% CI: 37-49)

Median duration of remission (DOR)

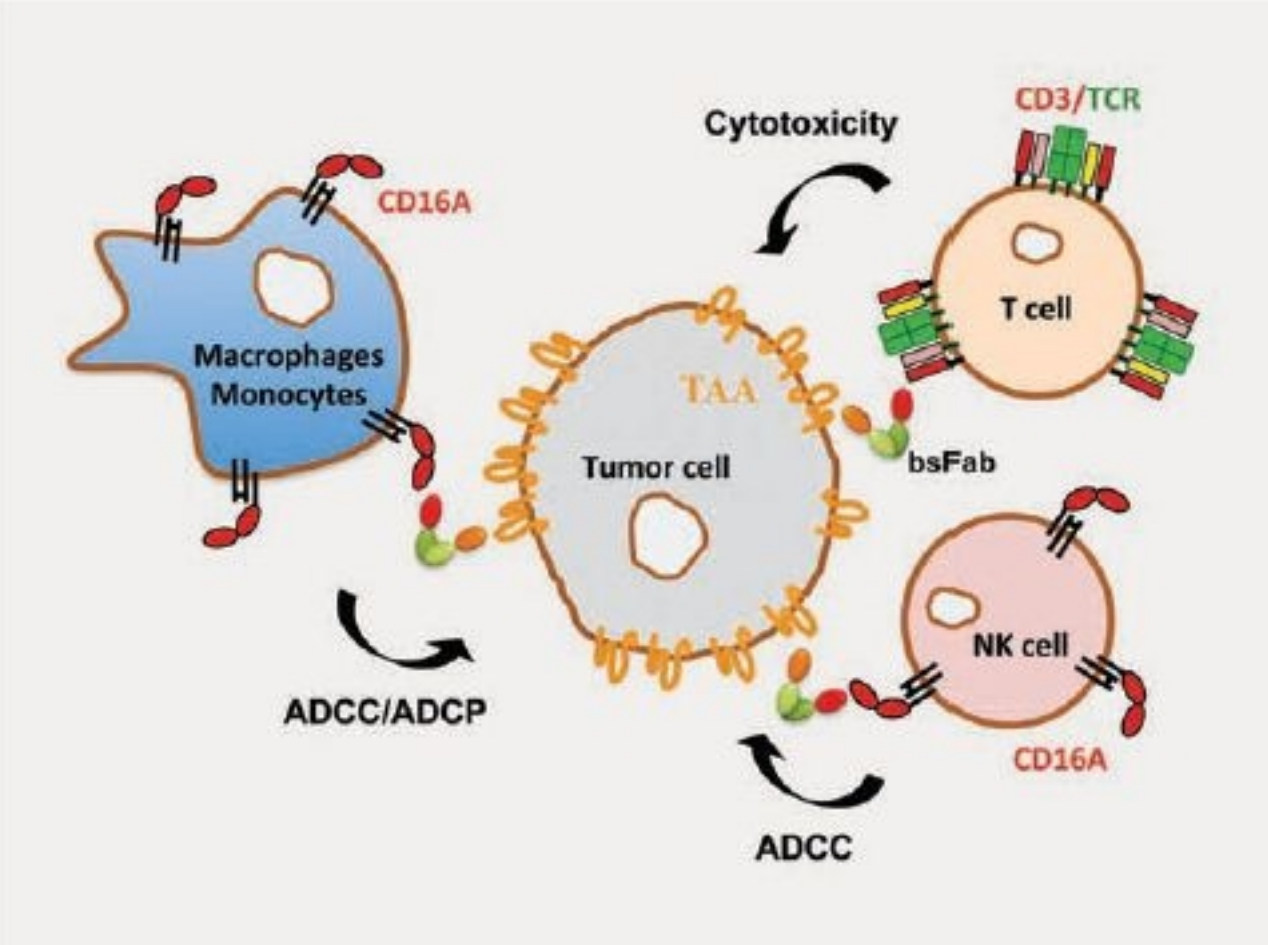
BLINCYTO® produced a more durable remission compared with SOC chemotherapy among patients who had CR/CRh*[8]

SOC n=27/134 (95% CI: 1.8–19.0)

BLINCYTO® n=115/271 (95% CI: 5.8–10.2)

BISPECIFIC NK CELL ENGAGERS

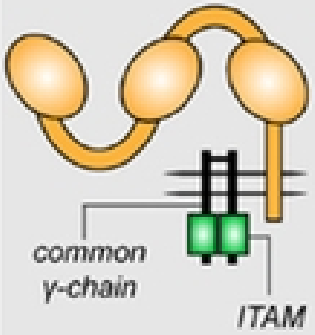
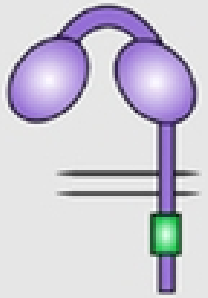
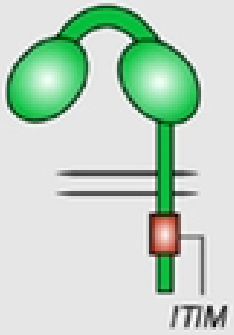
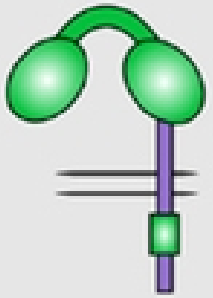
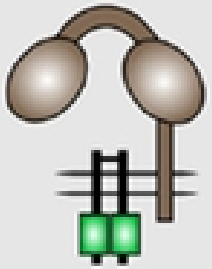
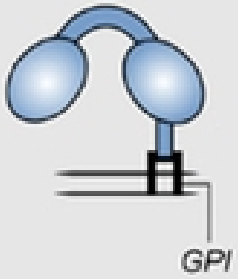
NK cell engagers: mimicking the TCE concept



- Mimicking Mab Fc properties: ADCC/ADCP
- Selective binding to CD16a/FcγRIIIa
- No binding to inhibitory FcγRIIa
- Independent of CD16a polymorphism (V/F158)

Major NK cell activators: CD16 and/or NKp46

Reminder: human FcγRs

Name	FcγRI CD64	FcγRIIa CD32a	FcγRIIb C32b	FcγRIIc CD32c	FcγRIIIa CD16a	FcγRIIIb CD16b
Structure						
Function	Activating	Activating	Inhibitory	Activating	Activating	Activating
Affinity	High	Low	Low	Low	Low	Low
SNP		131H/R R: reduced affinity to IgG2	232I/T T: decreased inhibitory activity	57Q/X X: stop codon (non-functional protein)	158F/V V: increased affinity to IgG1/3/4	NA1/2 NA2: reduced affinity to IgG1/3

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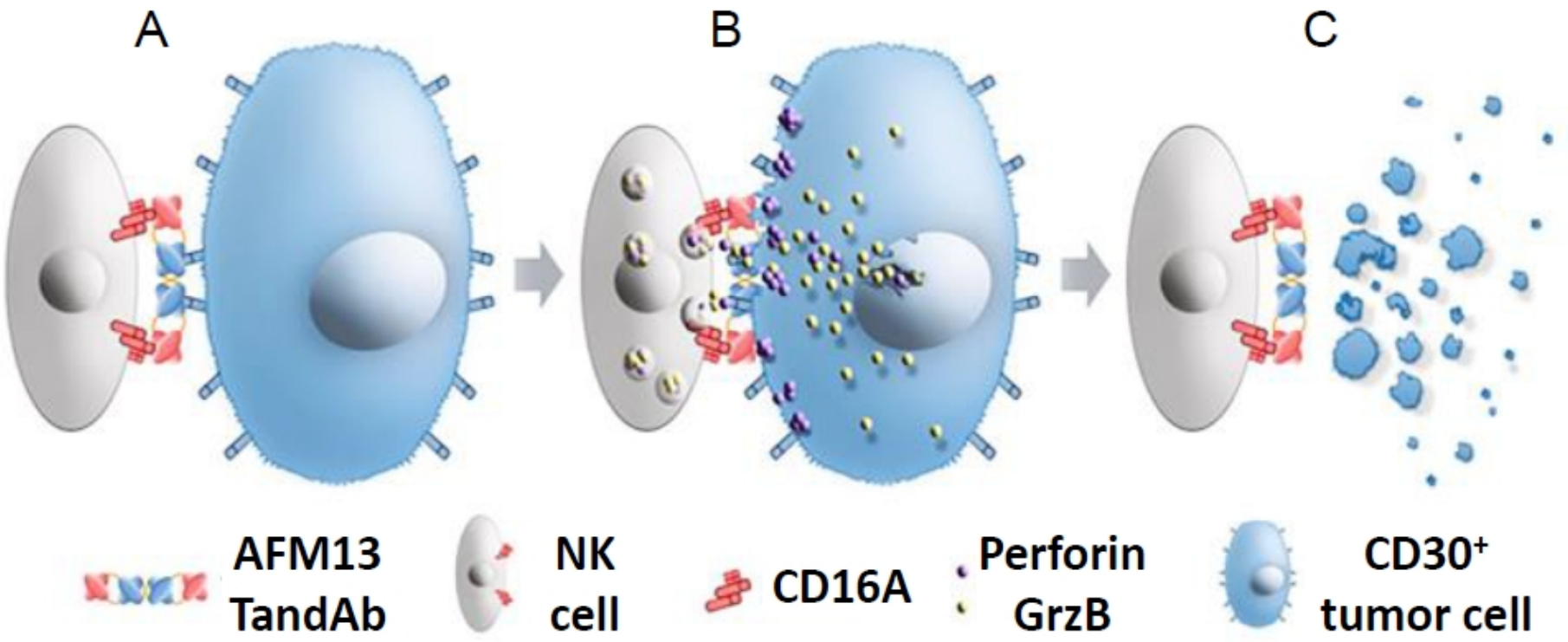
Activated by hIgG1

Examples of NK cell engagers

Mode of Action	Format	Targets	Molecules/ *Biotech*	Development stage
NK cell redirection	Tandab	CD30xCD16	AFM13	Ph.2
	Tandab	BCMAxCD16	AFM26	PC
	triKE	CD133xCD16	N.A.	PC
	aTriFlex	BCMAxCD200xCD16	N.A.	PC
	BiKE	CS1xNKG2D	N.A.	PC
	IgG like	CD20xNKp46	*Innate Pharma*	PC

Wurch & Chames, Médecines&Sciences 2019

AFM13 induces CD30-specific NK cell activation & proliferation



Activation markers

- CD25 ⇄
- CD137 ⇄
- Granzymes ⇄
- Perforin ⇄
- Cytokines (IL15, IFNγ) ⇄

Apoptosis

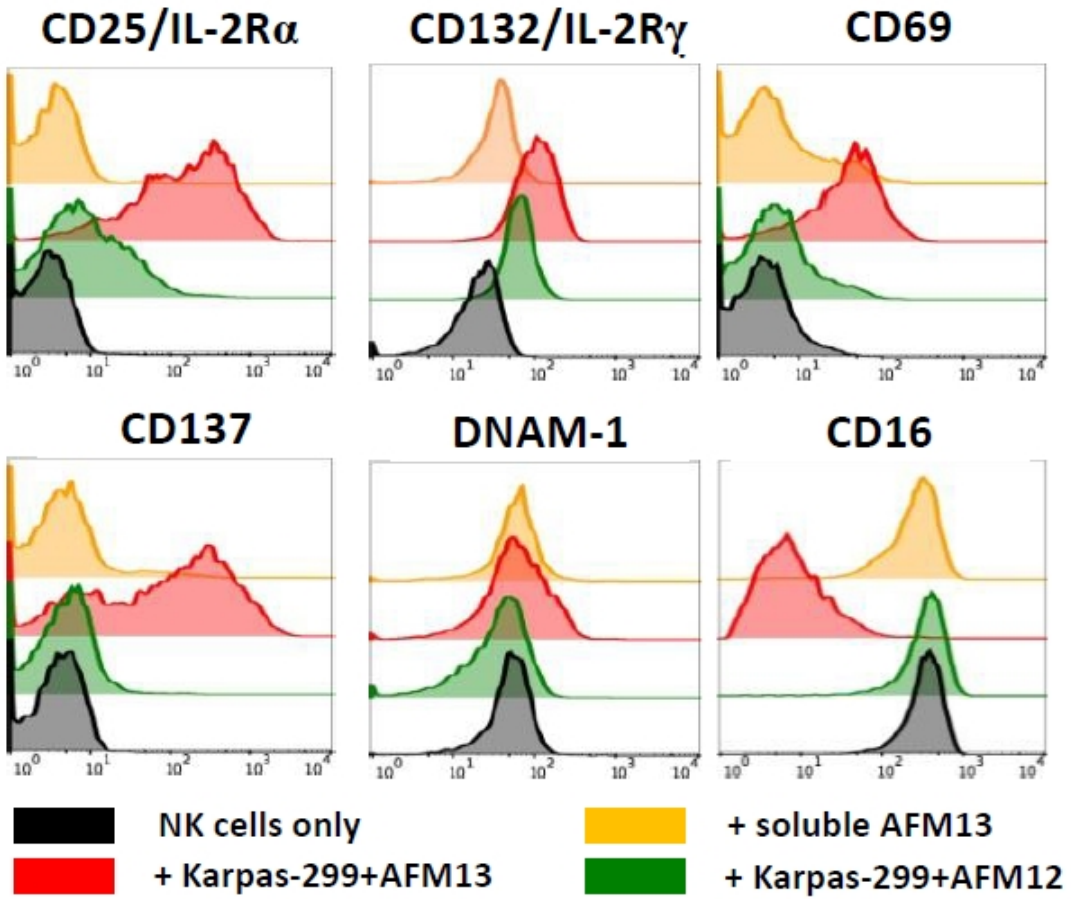
- Caspase activation ⇄
- DNA fragmentation ⇄
- PARP cleavage ⇄

AFM13 Is the Most Advanced Bispecific NK-Cell Engaging Antibody in Clinical Development Substantially Enhancing NK-Cell Effector Function and Proliferation

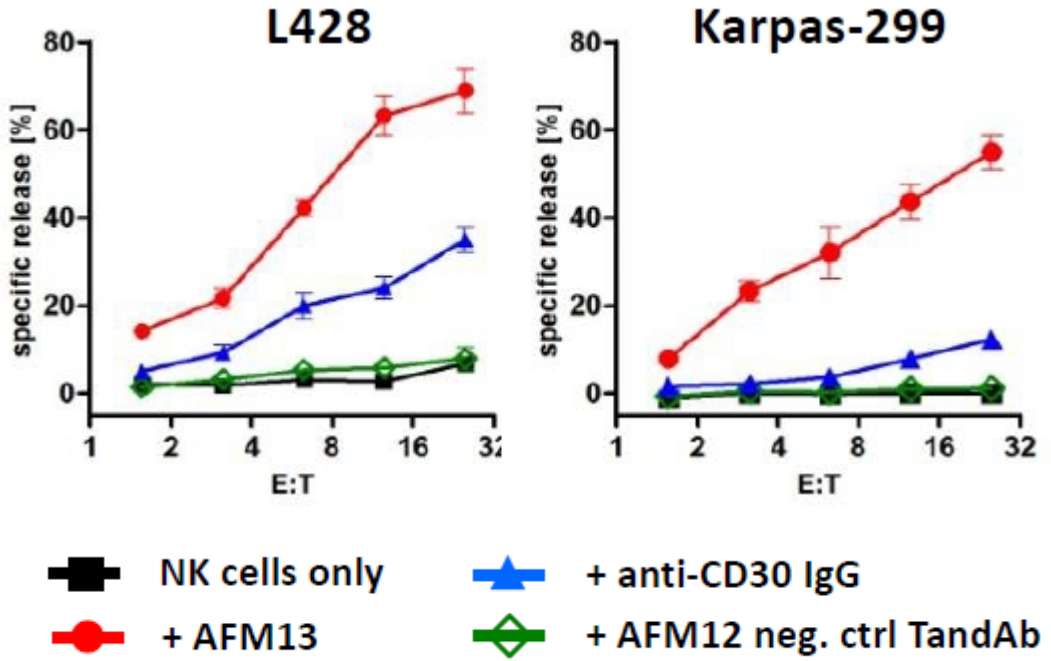
Jens Pahl, PhD[1]; Uwe Reusch, PhD[2]; Thorsten Gantke, PhD[2]; Anne Kerber, MD[2]; Joachim Koch, PhD[2]; Martin Treder, PhD[2#] and Adelheid Cerwenka, PhD[1#]

[1]Innate Immunity, DKFZ, 69120 Heidelberg, Germany; [2]Affimed GmbH, 69120 Heidelberg, Germany

AFM13-mediated NK cell activation



AFM13-mediated tumor cell killing



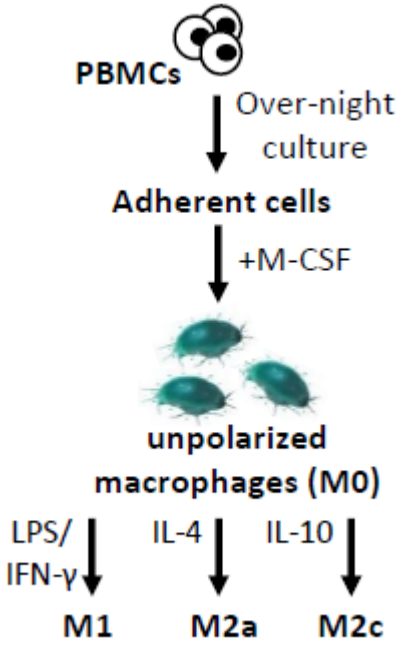
AFM12: CD19xCD16a

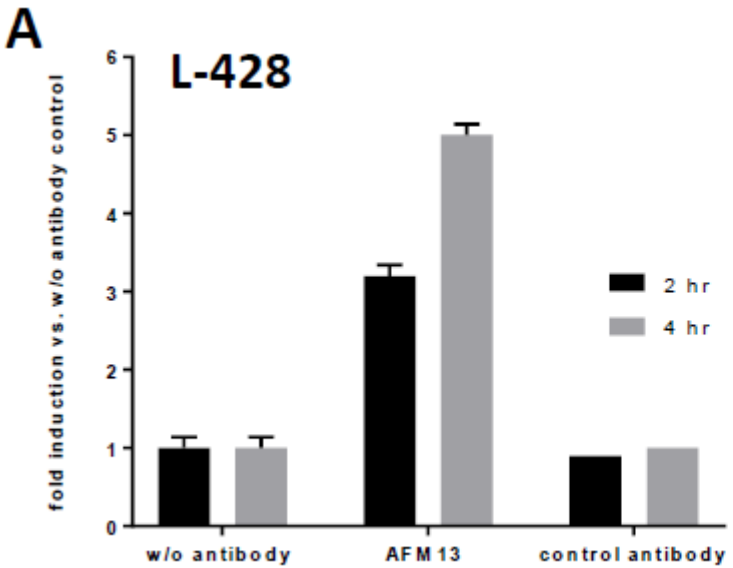
Pahl J et al, ASH2016

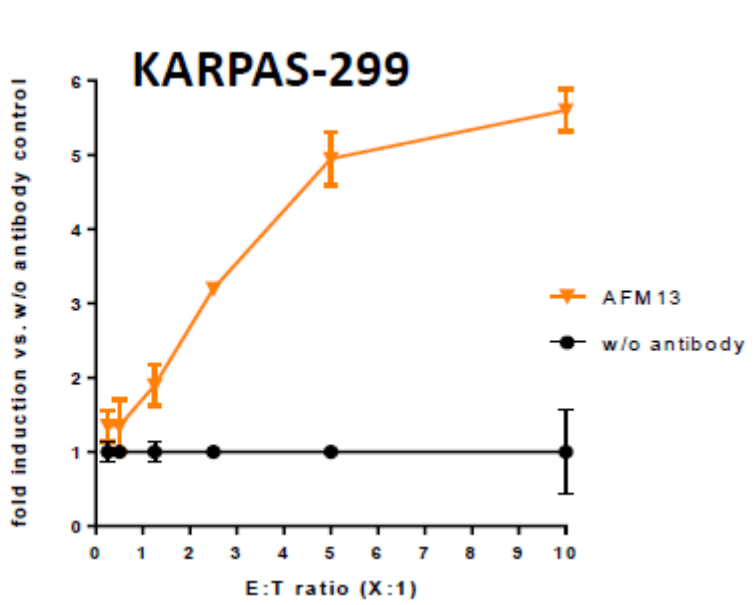
CD16A-Specific Tetravalent Bispecific Immuno-Engagers Potently Induce Antibody-Dependent Cellular Phagocytosis (ADCP) by Macrophages

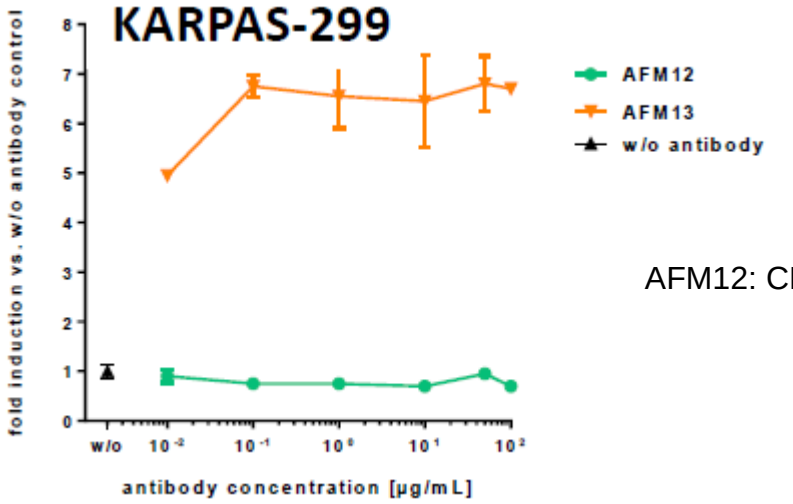
Susanne Wingert[1], Uwe Reusch[1], Armin Beez[1], Jens Pahl[2], Adelheid Cerwenka[2], Joachim Koch[1], Martin Treder[1#]

[1] Affimed GmbH, Im Neuenheimer Feld 582, 69120 Heidelberg, Germany; [2]Department for Immunobiochemistry, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany









AFM12: CD19xCD16a

AFM13-induced ADCP is:

- tumor antigen-specifc
- depends on binding to both CD16a on macrophages AND TA on tumor cells

Wingert et al, ASH2018

Clinical and Biological Evaluation of the Novel CD30/CD16A Tetravalent Bispecific Antibody (AFM13) in Relapsed or Refractory CD30-Positive Lymphoma with Cutaneous Presentation: A Biomarker Phase Ib/IIa Study (NCT03192202).

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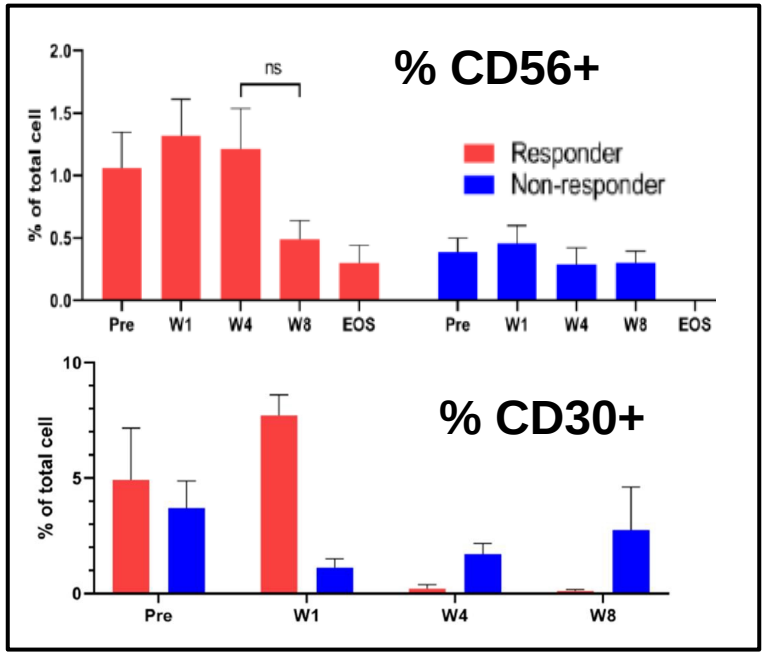
Cohort	Dose regimen			Total exposure
	Dose	Schedule	Duration	
Cohort 1	1.5 mg/kg	weekly	weeks 1-8	12 mg/kg
Cohort 2	7.0 mg/kg	weekly	weeks 1-8	56 mg/kg
Cohort 3	7.0 mg/kg CIVI *	weekly	weeks 1-8	56 mg/kg
Cohort 4	200mg flat dose	weekly	weeks 1-8	1600 mg

*1 mg/kg loading 6mg/kg as continuous infusion for 5 days per week

Cohort	Disease	Toxicity	Response
1	S-ALCL, Alk (-)	No AE	PR
	T-MF	No AE	POD
	C- ALCL	Rash (G4) Skin infection (G3)	CR
2	MF	IRR (G1)	SD
	T-MF	IRR (G1)	SD
	T-MF	Skin infection (G3) IRR (G1)	Not assessed
3	T-MF	No AE	PR
	S-ALCL, Alk (-)	No AE	PR
	MF	No AE	POD
4	T-MF	No AE	PR



- AFM13 well tolerated
- AFM13 high ORR 50% & active post-Adcetris
- Biomarkers indicated increased NKs in responders

Sawas A et al, ICML2019

Disease: forms of cutaneous T cell lymphoma:
S-ALCL: systemic anaplastic large cell lymphoma
T-MF: transformed mycosis fungoides

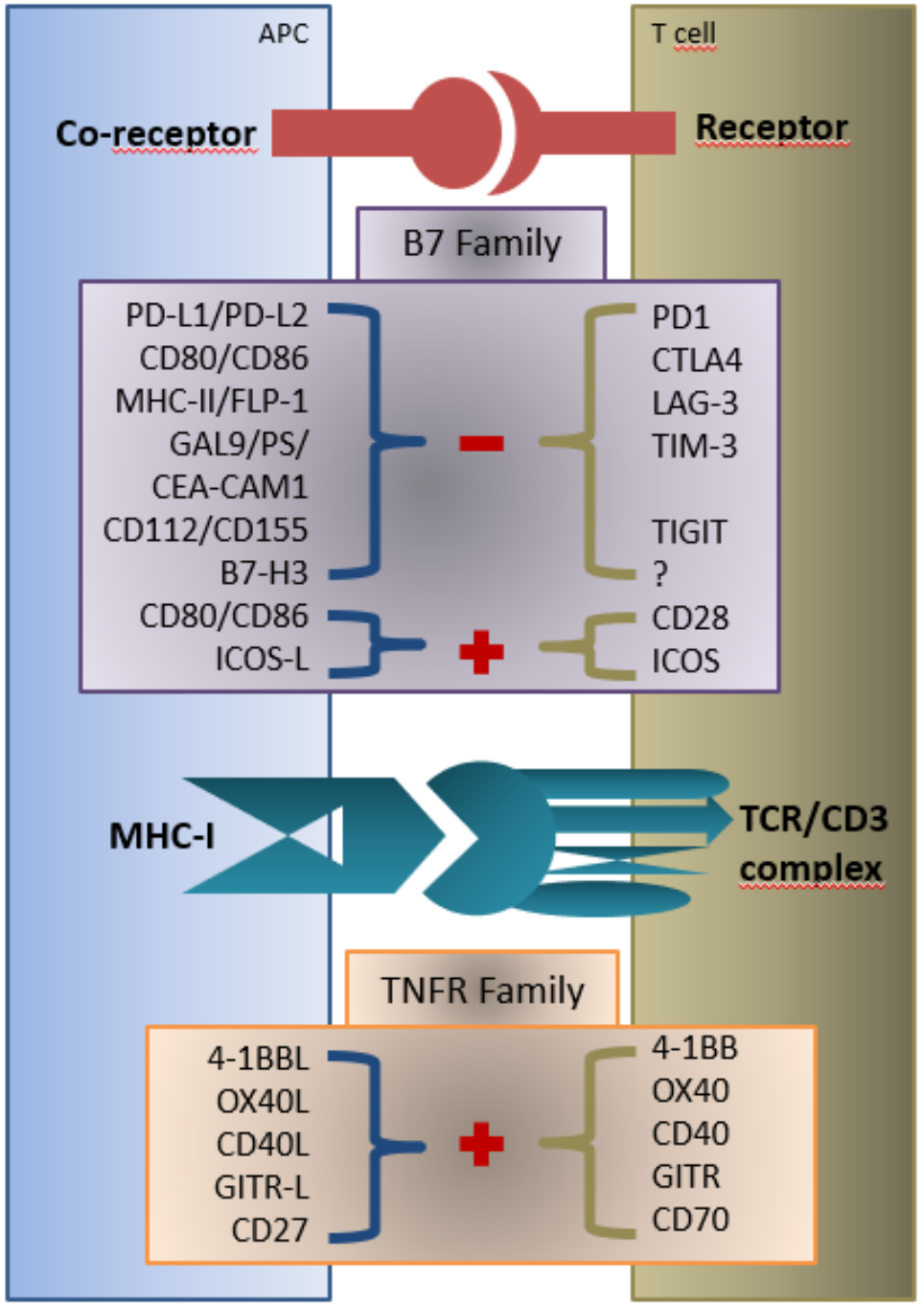
Clinical response: CR, complete response, PR: partial response, PoD: progression of disease

BISPECIFIC IMMUNE CELLS MODULATORS

Major immune receptors controlling T cell activation

Bispecific MoAs engaging immune checkpoints:

- Dual Targeting of 2 inhibitory ICPs *i.e., PD1xLAG3*
- Dual co-targeting of one inhibitory and one co-stimulatory ICP *i.e., PD-L1x4-1BB*
- Tumor-restricted co-stim. ICP targeting *i.e., Her2x4-1BB*



Examples of Bispecific ICP modulators

	Mode of Action	Targets	Molecule	Development stage
Co-inhibitory immune modulators	Co-engagement of two inhibitory ICPs to enhance T cell activation	PD-1xLAG-3	MGD013	Ph. I
		PD-1xTIM-3	RO7121661	Ph. I
		PD-1xTIM-3	MCLA-134	PC
		PD-L1xLAG-3	FS118	Ph. I
		CTLA-4xLAG-3	XmAb22841	Ph. I
		CTLA-4xPD1	XmAb20717	Ph. I
		CTLA-4xPD1	MGD019	Ph. I
Dual immune modulators	Co-engagement of both inhibitory & co-stimulatory ICPs to maximize T cell activation	PD-1xICOS	XmAb23104	Ph. I
		PD-L1x4-1BB	PRS-344	PC
		PD-L1x4-1BB	MCLA-145	Ph. I
		PD-L1x4-1BB	FS222	PC
		PD-L1x4-1BB	ND021	PC
		PD-L1x4-1BB	-	PC
		PD-L1x4-1BB	-	PC
		CTLA-4xOX40	ATOR-1015	Ph. I
		CTLA-4xGITR	ATOR-1144	PC
Tumor-retargeted immune-modulators	Selective tumor targeting of a co-stimulatory ICP by co-engagement of a tumor-associated antigen	HER2x4-1BB	PRS-343	Ph. I
		GPC3x4-1BB	PRS-342	PC
		5T4x4-1BB	AGL.APV-527	PC
		FAPx4-1BB	MP310	PC
		FAPxCD40	-	PC
Immune modulators & cytokines	ICP engagement coupled to a cytokine	PD-L1 xTGF-βtrap	M7824	Ph. II
		CTLA-4 xTGF-βtrap		PC

Wurch & Chames, Médecines&Sciences 2019

IPSEN Innovation for patient care

VIRTUAL 2020 ESMO congress

A Phase 1 Dose Escalation Study of PRS-343, a HER2/4-1BB Bispecific Molecule, in Patients with HER2-positive Malignancies

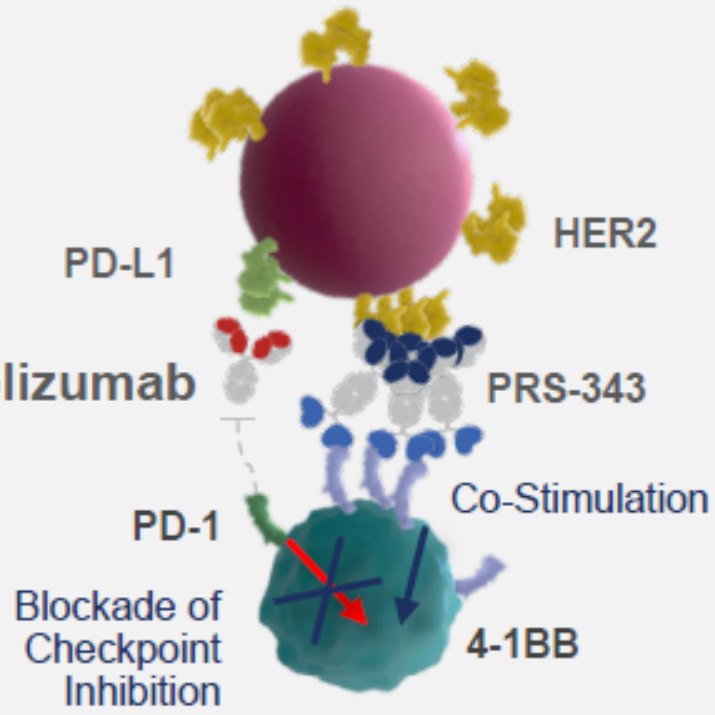
HER2-targeting moiety of the drug localizes to the tumor microenvironment and facilitates 4-1BB cross-linking

4-1BB cross-linking ameliorates T-cell exhaustion and is critical for T-cell expansion

HER2
targeting
Antibody

4-1BB
targeting
Anticalin®
Proteins

PRS-343

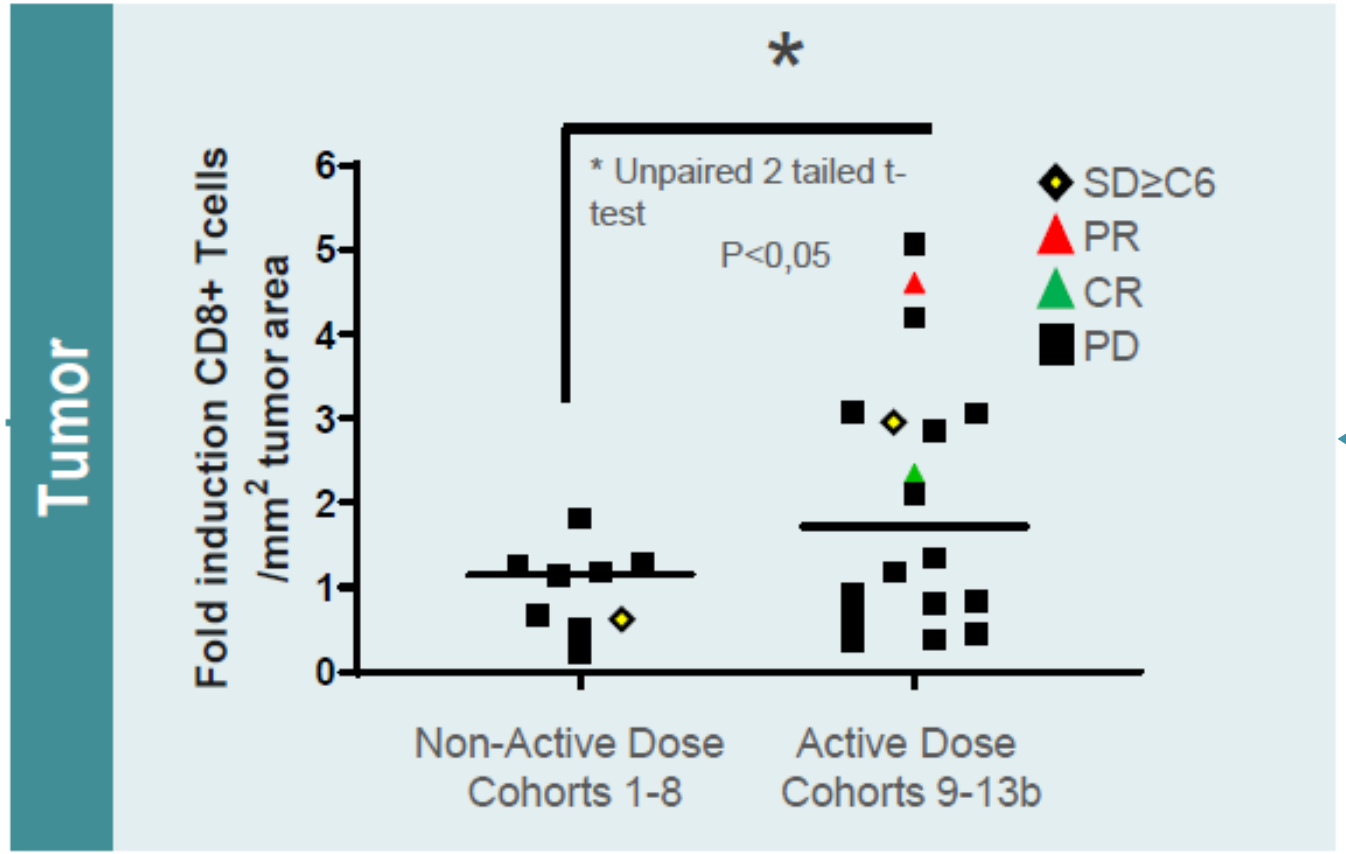


Summary of Responses of PRS-343 in Monotherapy

Cohort	13b	12b	11c	Obi	11b	11	10	9	Total
Best Response	18 mg/kg, Q2W	12 mg/kg, Q2W	8 mg/kg, QW	8 mg/Kg, Q2W	8 mg/kg, Q2W	8 mg/kg, Q3W	5 mg/kg, Q3W	2.5 mg/kg, Q3W	
Evaluable Patients	3	2	4	2	7	4	6	5	33
CR	1	-	-		-	-	-	-	1
PR	-	-	-		3	-	-	-	3
SD	-	-	1	1	3	3	3	2	13
ORR	33%	0%	0%	0%	43%	0%	0%	0%	12%
DCR	33%	0%	25%	50%	86%	75%	50%	40%	52%

ACTIVE SCHEDULES	
	Schedule 1: Q3W dosing on day 1; 21-day cycle
	Schedule 2 (b): Q2W dosing on days 1, 15; 28-day cycle
	Schedule 3 (c): Q1W dosing on days 1, 8, 15; 21-day cycle
	In combination with atezolizumab: Q3W dosing on day 1; 21-day cycle

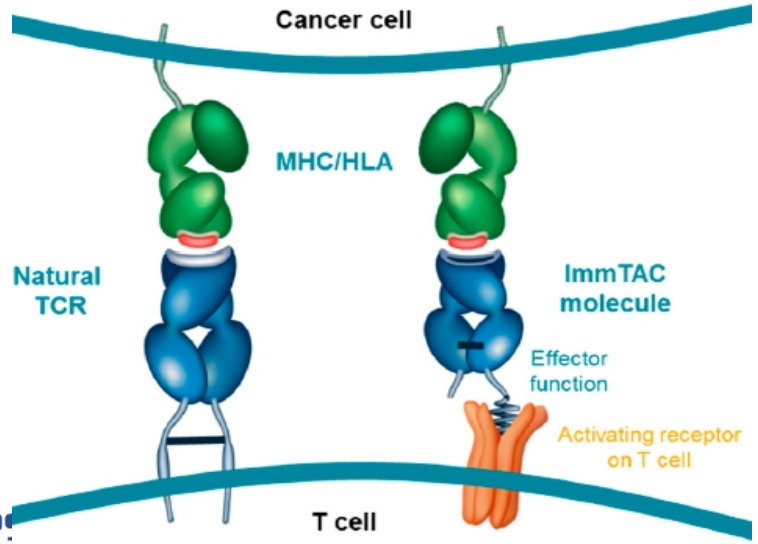
Increase in CD8+T Cells Support 4-1BB Engagement by PRS-343



Other examples of bispecific Ab-based molecules

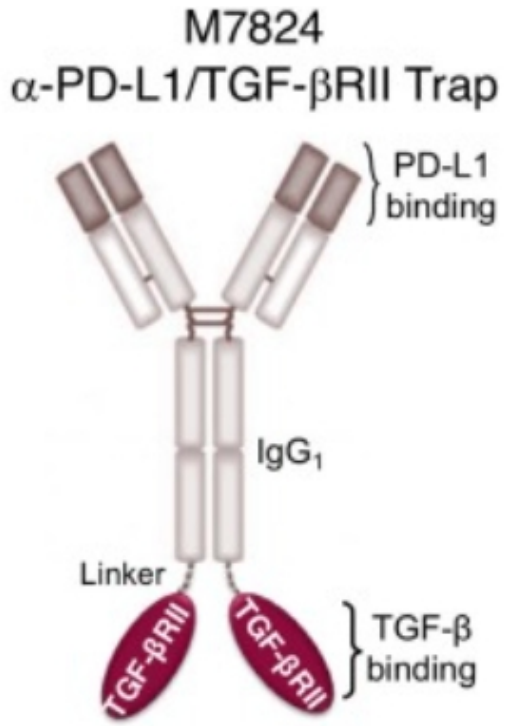
TCR-based TCE

- Product: IMCgp100
- Biotech: Immunocore (UK)
- Engineered solTCR against gp100 fused to CD3 scFv
- Pivotal study in metastatic uveal melanoma on-going



Immunocytokines

- Product: bintrafusp alfa/M7824
- Pharma: Merck Serono/NCI
- PD-L1 Mab fused to TGFβ trap
- Pivotal study in 1st line NSCLC



Take-Home messages

- Novel immune cell activators have emerged in the last decades thanks to the increased knowledge in tumor immunology and the engineering and design of numerous novel antibody- & non-Ig-based formats
- Most of these novel therapeutics showed promising preclinical data & for the most advanced early signs of clinical efficacy
- Despite the approval of blinatumomab in 2014 & first ICP inhibitors in 2011 (ipi) and 2014 (nivo), next generation molecules with potential BiC profile show difficulties to gain approval
- Solid tumors remain a real challenge for these novel classes of immune cell modulators
- Combination treatments will certainly be needed to increase the clinical benefit for patients

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THANK YOU FOR YOUR ATTENTION

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