Advances in Non-PD(L)1 immunotherapies

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Outline

- Other Immune Checkpoint Inhibitors
- TIGIT-PVR-NECTIN family axis
- Bispecific T Cell Engagers
- Cellular Therapies
  - CAR-T
  - Natural Killer Cells
  - Tumor Reactive And Cytokine-induced Killer (TRACK)-NK cells

Old dogs, new tricks- novel CTLA-4 antibodies
Fc-Enhanced CTLA-4 Antibody

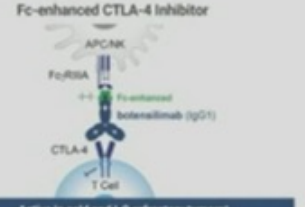
- ✓ CTLA-4 is an "old target"
- ✓ Only in melanoma it has approval as single agent
- ✓ Limited number of malignancies with role for combo
- ✓ Makes sense to improve outcomes in cold tumor
- ✓ Novel antibody designs

Novel Immunotherapy Agents

2022

botensilimab

Fc-enhanced CTLA-4 Inhibitor

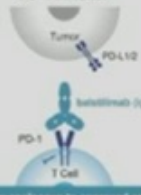


Active in cold and I-O refractory tumors[1]

- ↑ T cell priming, expansion, memory[2,3]
- ↑ Frequency of activated DCs
- ↑ Treg depletion
- ↓ Complement mediated toxicity

balstilimab

PD-1 Inhibitor



Safety and efficacy analogous to approved anti-PD-1 mAbs[4,5]

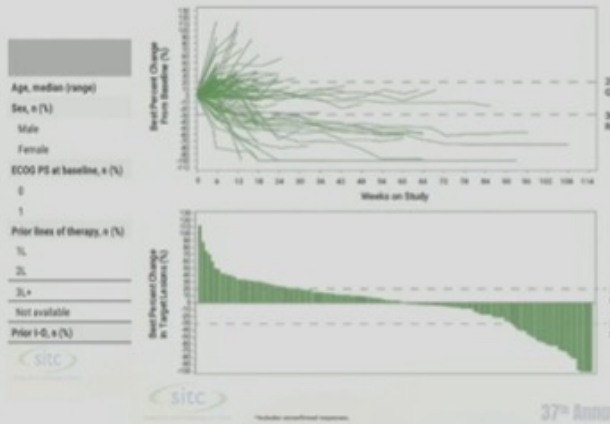
- >750 patients treated; 10 ongoing trials / 2 completed
- Complete blocker of PD-1-PD-L1/2 interactions
- Enhanced T cell activation and effector function

Wilkly, et al. SITC 2022.

Botensilimab + Anti-PD1 activity

Patient Ch Efficacy in Combination Patients (N=125)

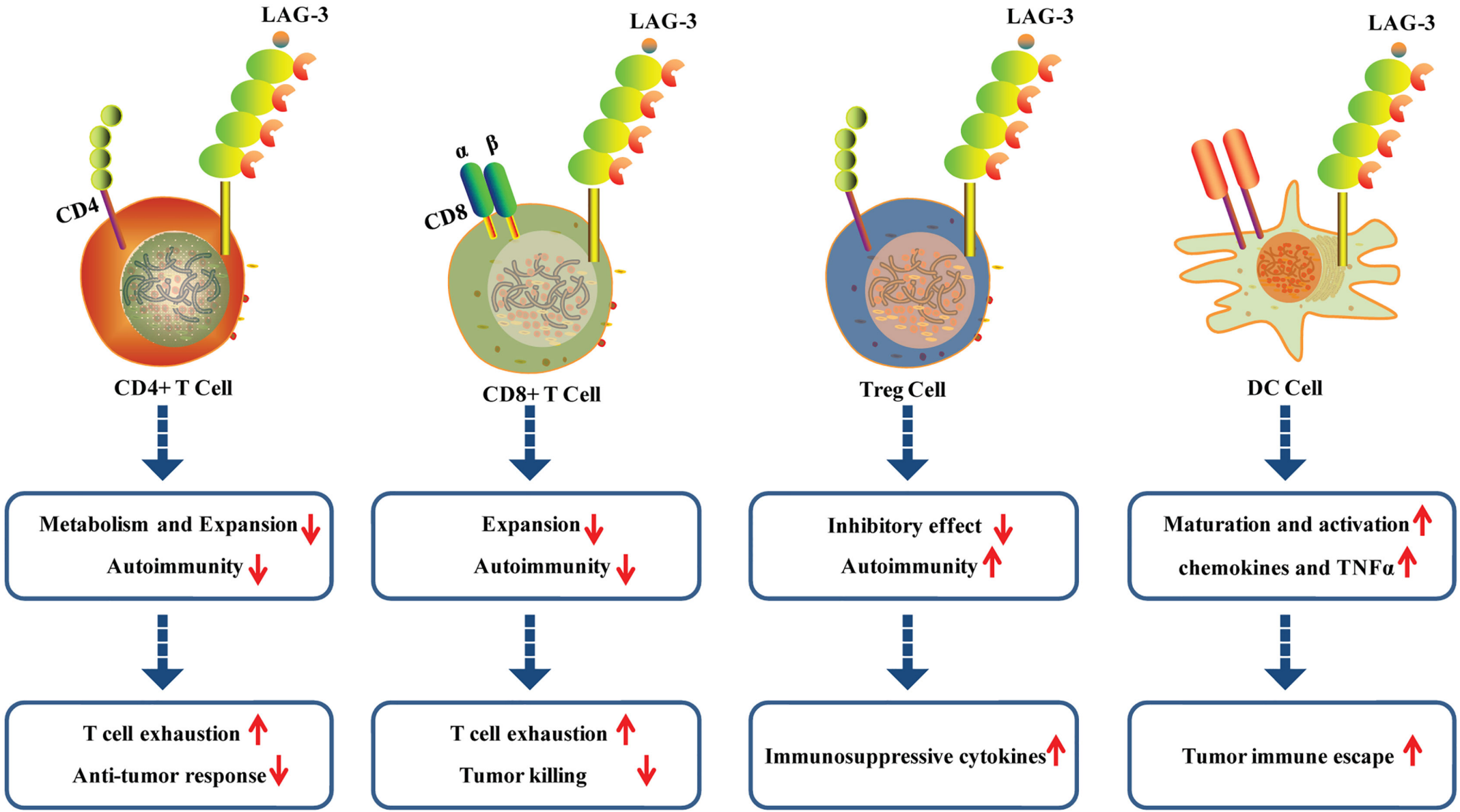
2022



Age, median (range)	
Sex, n (%)	
Male	
Female	
ECOG PS at baseline, n (%)	
0	
1	
Prior lines of therapy, n (%)	
1L	
2L	
3L+	
Not available	
Prior I-O, n (%)	

ALL PATIENTS		GRADE 4
		3 (2)
ORR, %*	28% (95% CI, 13-28%)	1 (1)
BOR, n (%)		0
CR	3 (2)	0
PR	22 (18)	0
SD	58 (46)	0
PD	42 (34)	0
DCR (CR + PR + SD), %	66% (95% CI, 57-74%)	0
Median DOR, months	NR (95% CI, 4.5-NR)	0
Median PFS, months	2.8 (95% CI, 2.7-4.2)	0
Median OS, months	NR (95% CI, 12.9-NR)	0
12-month OS, months	66% (95% CI, 54-76%)	0
Median F/U, months	6.2 (Range, 1.1-29.3)	0

Wilkly, et al. SITC 2022.



Front. Immunol., Sec. Cancer Immunity and Immunotherapy, Volume 13 - 2022

RELATIVITY 047: Combination anti-LAG3 + anti-PD1 in First Line Met. Melanoma

- RELATIVITY-047 is a global, randomized, double-blind, gated, phase 2/3 study

Key eligibility criteria
- Previously untreated, unresectable, or metastatic melanoma
- ECOG PS 0-1

Stratification factors
- LAG-3[a]
- PD-L1[b]
- *BRAF*
- AJCC v8 M stage

N = 714

R 1:1

- NIVO 480 mg + RELA 160 mg FDC IV Q4W
- NIVO 480 mg IV Q4W

	Primary disclosure	Updated disclosure
Database lock date	March 9, 2021	October 28, 2021
Median follow-up, mo	13.2	19.3
Minimum follow-up, mo[d]	1.3	8.7
Data disclosed	Primary endpoint • PFS	Primary endpoint • Updated PFS
		Secondary endpoints • OS[e] • ORR

Primary endpoint
- PFS by BICR[c]

Secondary endpoints
- OS
- ORR by BICR[c]

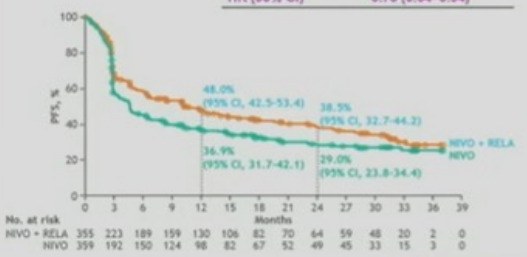
Endpoints were tested in hierarchy
- PFS → OS → ORR

Tawbi, et al. *NEJM*, Jan 2022.

RELATIVITY 047: PFS, OS, and ORR in all randomized patients

Updated PFS by BICR

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo (95% CI)	10.22 (6.51-14.75)	4.63 (3.48-6.44)
HR (95% CI)	0.78 (0.64–0.94)	



OS

	NIVO + RELA (n = 355)	NIVO (n = 359)
mOS, mo (95% CI)	NR (34.20–NR)	34.10 (25.23–NR)
HR (95% CI)	0.80 (0.64–1.01)	
P value	0.0593	

Confirmed ORR by BICR	NIVO + RELA (n = 355)	NIVO (n = 359)
ORR % (95% CI)	**43.1** (37.9-48.4)	**32.6** (27.8-37.7)

DBL date: October 28, 2021. Median follow-up: 19.3 mo

Tawbi, et al. *NEJM*, Jan 2022.

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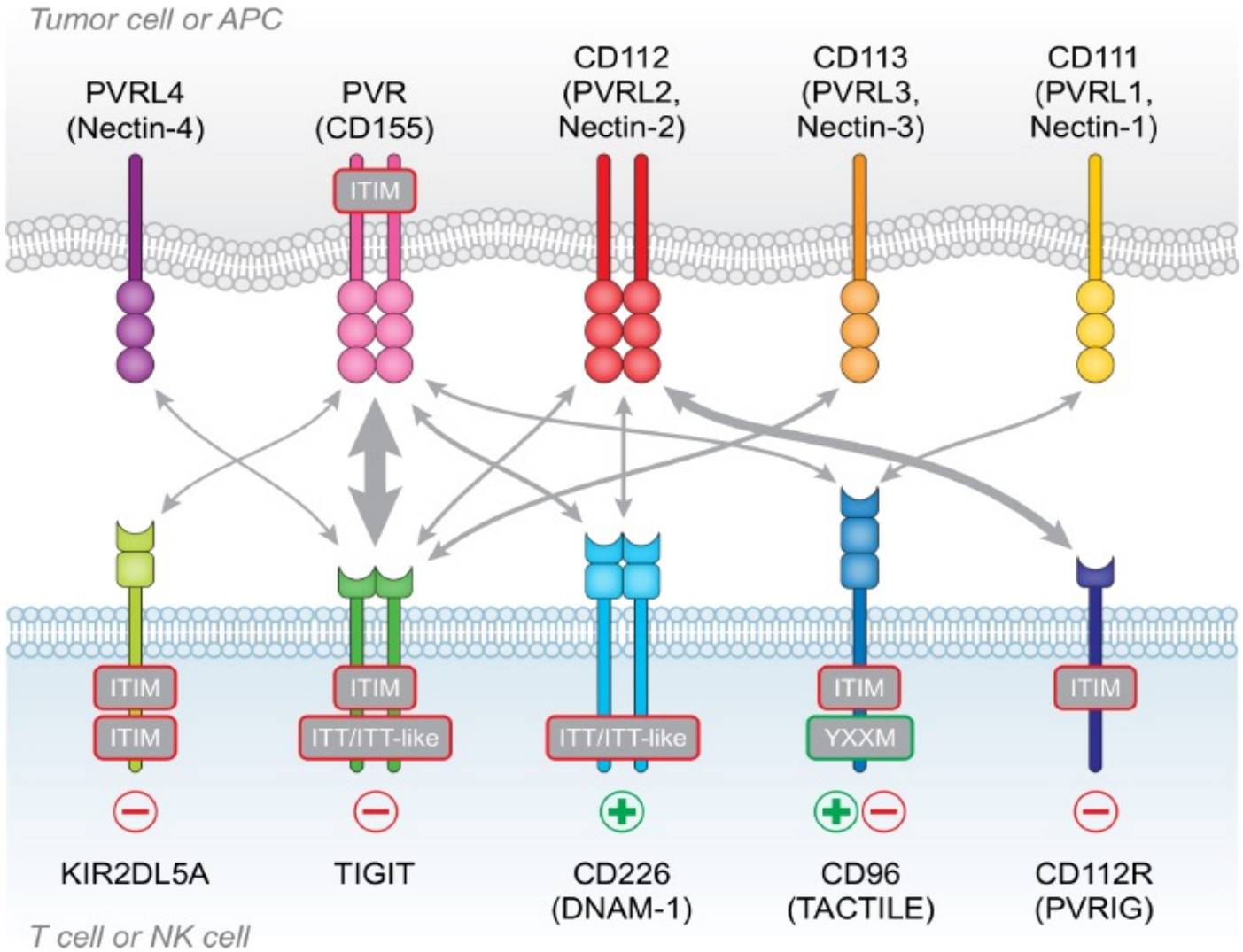
Chiang EY, Mellman I. *J Immunother Cancer* 2022;**10**:e004711. doi:10.1136/jitc-2022-004711



Anti TIGIT Monoclonal Antibodies in Clinical Development

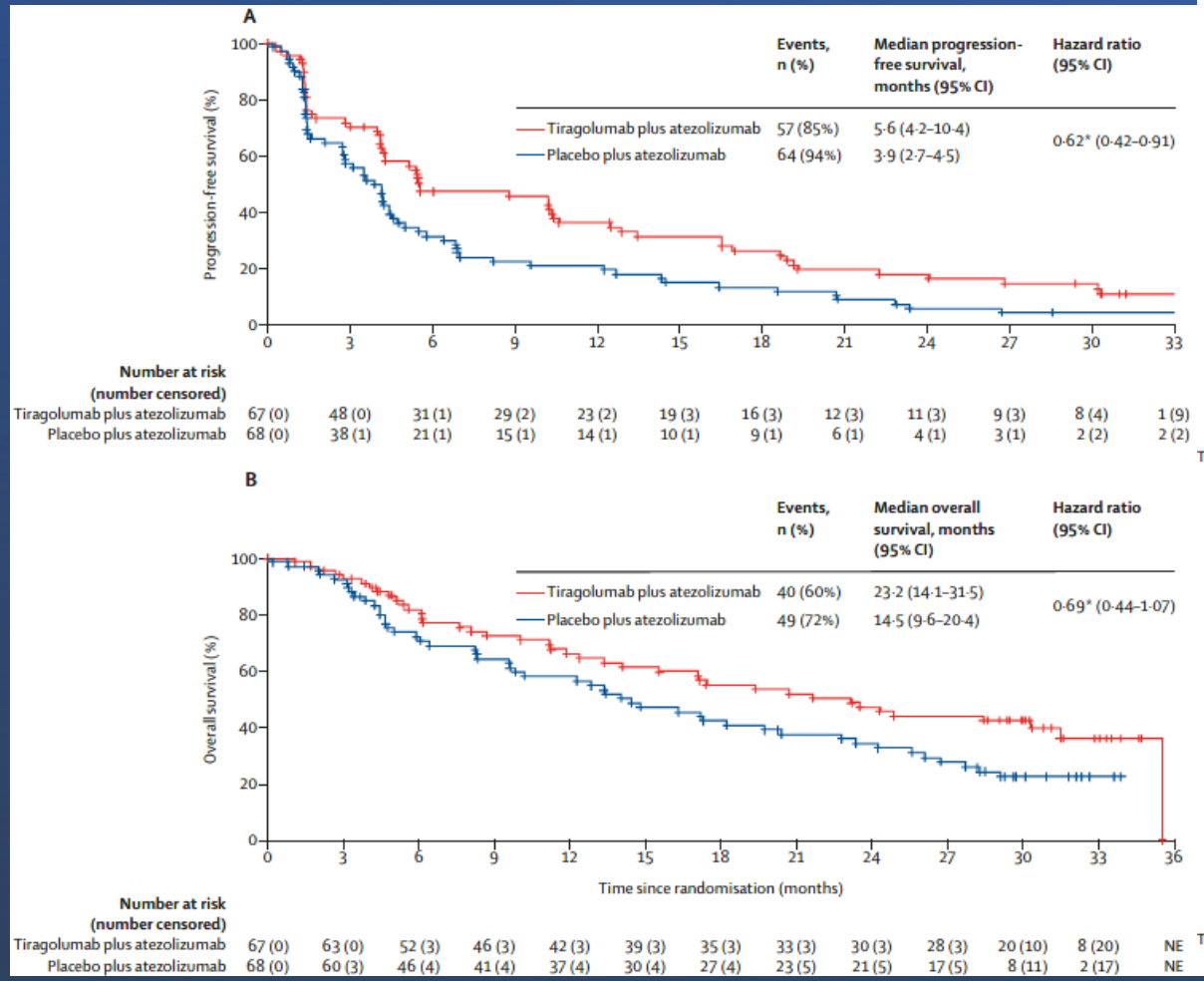
Anti-TIGIT mAbsc	Phase*	Fc Region
Tiragolumab	III	Active
Domvanalimab	III	Inactive
Ociperlimab	III	Active
Vibostolimab	III	Active
BMS-986207	II (Planned)	Inactive
Etigilimab	II (Planned)	Active
EOS-448	I/II	Active
AZD-2936	I/II	Active
SEA-TGT	I	Active
COM-902	I	Inactive
IBI-939	I	Active
IBI-321	I	Unknown
AB308	I	Active
BAT-6005	I	Active
JS-006	I	Unknown
M-6223	I	Active
HB0030	I (as per pipeline)	Unknown

Anti-TIGIT mAbs	Phase*	Fc Region
AGEN1777	I (Planned)	Active
BAT-6021	I (Planned)	Inactive
ZG005	I (Planned)	Unknown
AGEN1327	Preclinical	Active
AK-127	Preclinical	Unknown
HLX-301	Preclinical	Unknown
LP-010	Preclinical	Active
MIL-100	Preclinical	Unknown
Ori-Ab-007	Preclinical	Unknown
Ori-Ab-008	Preclinical	Unknown
PH-804 TME	Preclinical	Unknown
PH-804 ACT / RXI-804	Preclinical	Unknown
SL-9258	Preclinical	Active
TJ-L1T6	Preclinical	Unknown
NTX-901	Preclinical	Unknown
HB0036	Preclinical	Unknown

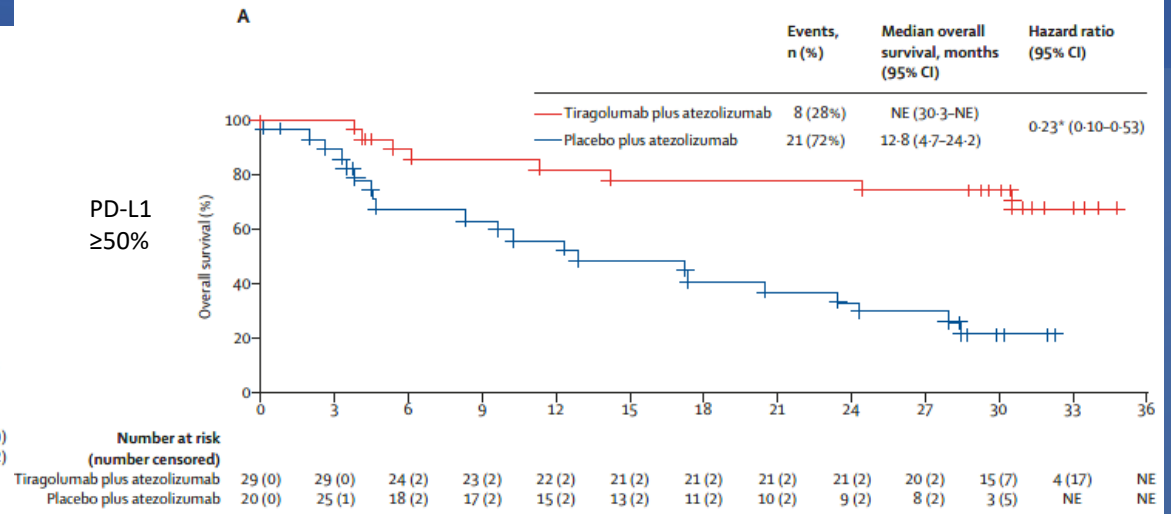
Chiang EY, Mellman I. *J Immunother Cancer* 2022;**10**:e004711. doi:10.1136/jitc-2022-004711

Tiragolumab plus atezolizumab versus placebo plus atezolizumab as a first-line treatment for PD-L1-selected non-small-cell lung cancer (CITYSCAPE): primary and follow-up analyses of a randomised, double-blind, phase 2 study

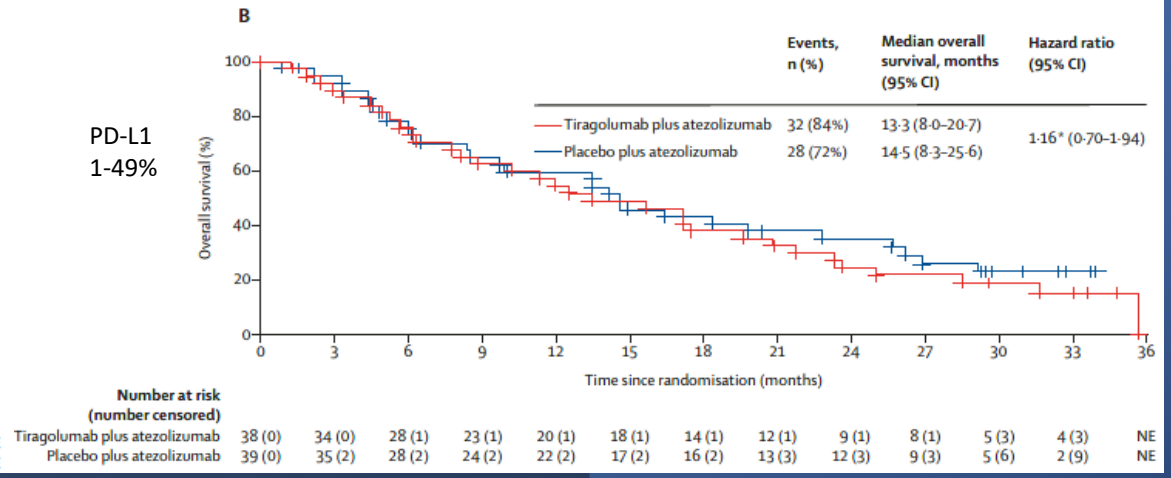
Lancet Oncol 2022; 23: 781–92



PD-L1 ≥50%



PD-L1 1-49%



ARC-7: Randomized phase 2 study of domvanalimab + zimberelimab ± etrumadenant versus zimberelimab in first-line, metastatic, PD-L1-high non-small cell lung cancer (NSCLC). Meeting Abstract | 2022 ASCO Monthly Plenary Series

Efficacy Population	Z (n = 44)	DZ (n = 44)	EDZ (n = 45)
Confirmed ORR n (%) [95% CI]	12 (27) [15.0, 42.8]	18 (41) [26.3, 56.8]	18 (40) [25.7, 55.7]
Median PFS (mo) [95% CI]	5.4 [1.8, 9.6]	12.0 [5.5, NE]	10.9 [4.8, NE]
PFS Hazard Ratio vs Z [95% CI]	-	0.55 [0.31, 1.0]	0.65 [0.37, 1.1]
6-mo PFS % (95% CI)	43 (27, 59)	65 (49, 80)	63 (48, 78)
Safety Population	**Z (n = 50)**	**DZ (n = 49)**	**EDZ (n = 50)**
IRAEs, n (%)	24 (48)	23 (47)	30 (60)
Infusion-related reactions	2 (4)	2 (4)	5 (10)
Rash	6 (12)	5 (10)	9 (18)

The Journal of Clinical Investigation RESEARCH ARTICLE

J Clin Invest. 2022;132(22):e163620. https://doi.org/10.1172/JCI163620.

Blockade of the immunosuppressive KIR2DL5/PVR pathway elicits potent human NK cell–mediated antitumor immunity

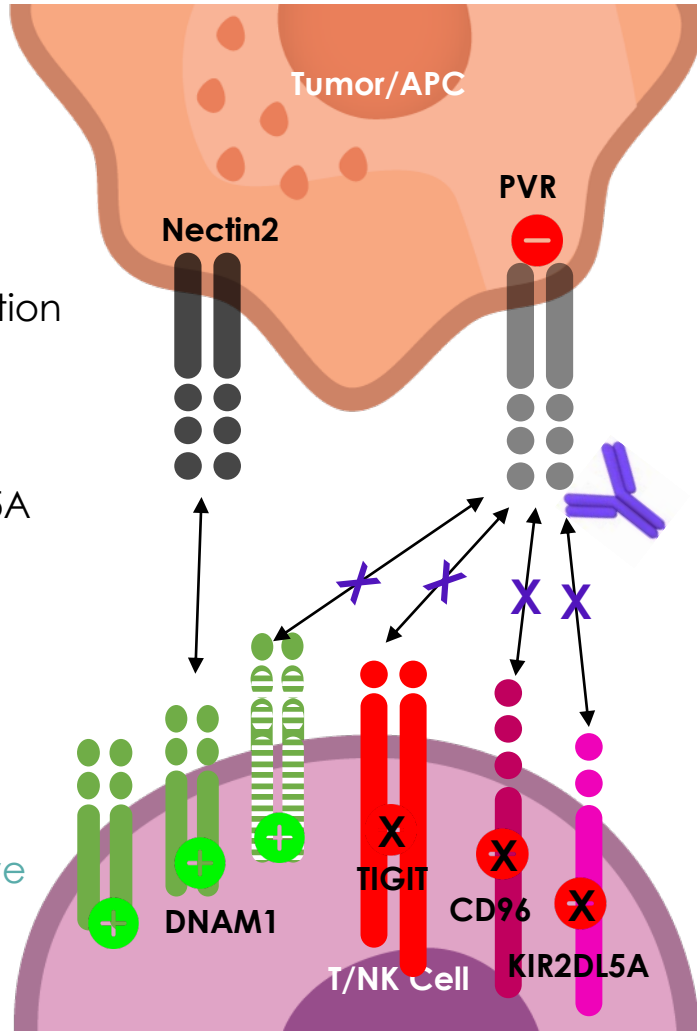
Xiaoxin Ren,[1] Mou Peng,[1] Peng Xing,[1] Yao Wei,[1] Phillip M. Galbo Jr.,[1,2] Devin Corrigan,[1] Hao Wang,[1] Yingzhen Su,[1] Xiaoshen Dong,[1] Qizhe Sun,[1] Yixian Li,[1,3] Xiaoyu Zhang,[1] Winfried Edelmann,[4] Deyou Zheng,[2,5] and Xingxing Zang[1,6,7,8]

Cancer immunotherapy targeting the TIGIT/PVR pathway is currently facing challenges. KIR2DL5, a member of the human killer cell, immunoglobulin-like receptor (KIR) family, has recently been identified as another binding partner for PVR. The biology and therapeutic potential of the KIR2DL5/PVR pathway are largely unknown. Here we report that KIR2DL5 was predominantly expressed on human NK cells with mature phenotype and cytolytic function and that it bound to PVR without competition with the other 3 known PVR receptors. The interaction between KIR2DL5 on NK cells and PVR on target cells induced inhibitory synapse formation, whereas new monoclonal antibodies blocking the KIR2DL5-PVR interaction robustly augmented the NK cytotoxicity against PVR$^+$ human tumors. Mechanistically, both intracellular ITIM and ITSM of KIR2DL5 underwent tyrosine phosphorylation after engagement, which was essential for KIR2DL5-mediated NK suppression by recruiting SHP-1 and/or SHP-2. Subsequently, ITIM/SHP-1/SHP-2 and ITSM/SHP-1 downregulated the downstream Vav1/ERK1/2/p90RSK/NF-κB signaling. KIR2DL5$^+$ immune cells infiltrated in various types of PVR$^+$ human cancers. Markedly, the KIR2DL5 blockade reduced tumor growth and improved overall survival across multiple NK cell–based humanized tumor models. Thus, our results revealed functional mechanisms of KIR2DL5-mediated NK cell immune evasion, demonstrated blockade of the KIR2DL5/PVR axis as a therapy for human cancers, and provided an underlying mechanism for the clinical failure of anti-TIGIT therapies.

PVR – A Promising New Oncology Target

DNAM1 Restoration - Novel MOA

- PVR is a transmembrane protein, expressed on cancer cells and associated with immune exhaustion
- High PVR expression is associated with resistance to PD1 and PDL1 blockers
- PVR blockade by **NTX1088** uniquely restores DNAM1 on T and NK cells and prevents TIGIT, KIR2DL5A and CD96 suppressive signaling
- DNAM1 restoration represents a novel and promising therapeutic approach never seen before
- PVR blockade offers potent monotherapy and combination activity with PD1 blockers
- The various Nectin family members of receptors and ligands will be explored as relevant predictive and pharmacodynamic biomarker



Mechanism of Action	Anti-TIGIT	Anti-CD96	NTX1088
Block TIGIT signaling	✓	✗	✓
Block CD96 signaling	✗	✓	✓
Block KIR2DL5A signaling	✗	✗	✓
Increase DNAM1 surface expression and signaling	✗	✗	✓

COH# 23219 | NTX-1088-01. A Phase 1, First-in-Human Study of NTX-1088, a Monoclonal Antibody Targeting the Poliovirus Receptor (PVR), as Monotherapy and Combined with Pembrolizumab, in Patients with Advanced Solid Malignancies

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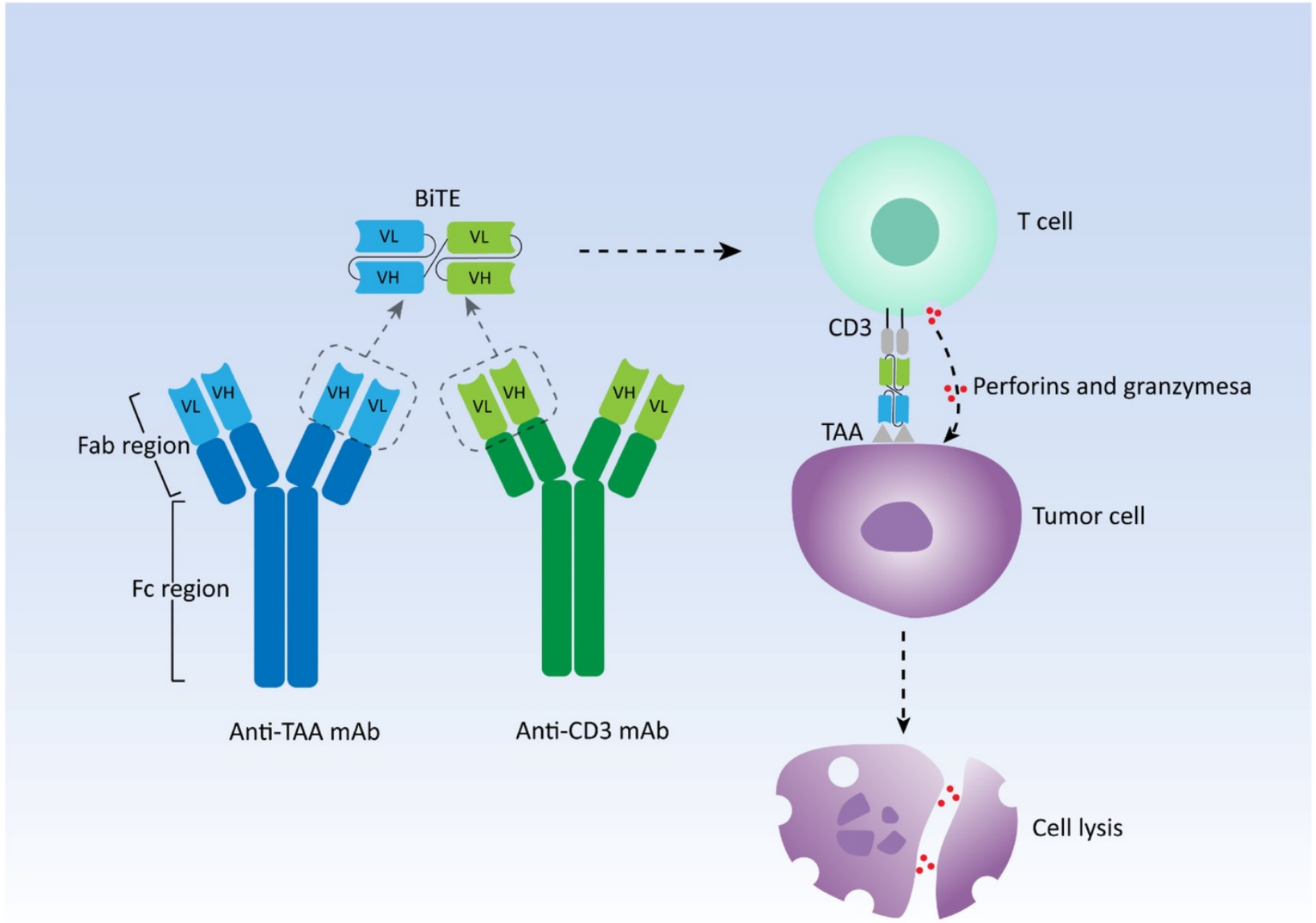


VH: Heavy chain variable region; VL: Light chain variable region; TAA: Tumor-associated antigen

Zhou, S., *et al.* The landscape of bispecific T cell engager in cancer treatment. *Biomark Res* **9**, 38 (2021).

BISPECIFIC ANTIBODY DRUG APPROVALS

Drug Name	Targets	Approved Date (Country)	Indications
Blinatumomab	**CD3/CD19**	Dec 2014 (USA)	Relapsed or refractory precursor B-cell acute lymphoblastic leukemia (**ALL**)
Emicizumab	FIXa/FX	Nov 2017 (USA)	Bleeding due to hemophilia A
Amivantamab-vmjw	**EGFR/cMet**	May 2021 (USA)	**Non-small cell lung cancer**
Tebentafusp-tebn	**GP100/CD3**	Jan 2022 (USA)	unresectable or metastatic **uveal melanoma**
Faricimab-svoa	Ang-2/VEGF-A	Jan 2022 (USA)	Wet AMD and DME
Cadonilimab	PD-1/CTLA-4	Jun 2022 (China)	cervical cancer
Mosunetuzumab-axgb	**CD20/CD3**	Jun/Dec 2022 (EU/USA)	relapsed or refractory (R/R) **follicular lymphoma** (FL)
Teclistamab-cqyv	**BCMA/CD3**	Aug/Oct 2022 (EU/USA)	relapsed and refractory **multiple myeloma**
Ozoralizumab	TNFα /TNFα	Sep 2022 (Japan)	inflammatory diseases

Select bispecific antibodies in phase III trials in oncology

Drug	Targets	Key indications
Glofitamab	CD20 ×CD3	DLBCL
Epcoritamab	CD20 ×CD3	DLBCL
Elranatamab	BCMA ×CD3	Multiple myeloma
Erfonrilimab	PDL1 ×CTLA4	NSCLC, PDAC
Tebotelimab*	PD1 ×LAG3	Gastric/GOJ cancer
Ivonescimab	PD1 ×VEGF	NSCLC
Navicixizumab	DLL4 ×VEGF	Ovarian cancer
SI-B001*	EGFR ×HER3	NSCLC
Zanidatamab	HER2 ×HER2	Gastro-oesophageal adenocarcinoma
Catumaxomab	EpCAM ×CD3	Gastric adenocarcinoma
Bintrafusp alfa	PDL1 ×TGFβ	NSCLC, biliary tract cancer
SHR-1701	PDL1 ×TGFβ	NSCLC, cervical cancer, gastric/GOJ cancer

Nature Reviews Drug Discovery, https://doi.org/10.1038/d41573-022-00040-2

Phase 1 Updated Exploration and First Expansion Data for DLL3-Targeted T-cell Engager Tarlatamab in SCLC (DeLLphi-300 Study)

Hossein Borghaei,[1*] Luis Paz-Ares,[2] Melissa Johnson,[3] Stephane Champiat,[4] Taofeek Owonikoko,[5] Victoria Lai,[6] Michael Boyer,[7] Horst-Dieter Hummel,[8] Ramaswamy Govindan,[9] Neeltje Steeghs,[10] Fiona Blackhall,[11] Noemi Reguart,[12] Afshin Dowlati,[13] Yiran Zhang,[14] Nooshin Hashemi Sadraei,[14] Amanda Goldrick,[14] Hiroki Izumi[15]

Borghaei, IASLC, 2022
Paz-Ares, JCO, 2023

Treatment-Related Adverse Events Summary

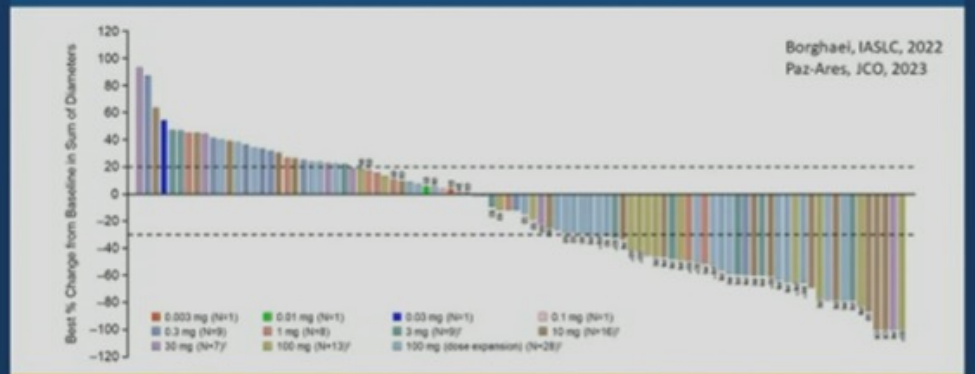
Treatment-related AEs (by preferred term)	Patients (N = 106) All Grades, n (%)	Grade ≥ 3, n (%)*
Any treatment-related AE	97 (92)	33 (31)
Treatment-related AEs occurring in > 15% of patients (by preferred term)		
CRS	56 (53)	1 (1)
Pyrexia	40 (38)	2 (2)
Dysgeusia	24 (23)	0
Fatigue	23 (22)	3 (3)
Nausea	21 (20)	0

- 4/106 (4%) patients discontinued tarlatamab due to treatment-related AEs: encephalopathy (n=1), neurotoxicity (n=1), and pneumonitis (n=2, including one grade 5 AE)

*Includes one patient with grade 5 pneumonitis; AE, adverse event; CRS, cytokine release syndrome.

Borghaei, IASLC, 2022
Paz-Ares, JCO, 2023

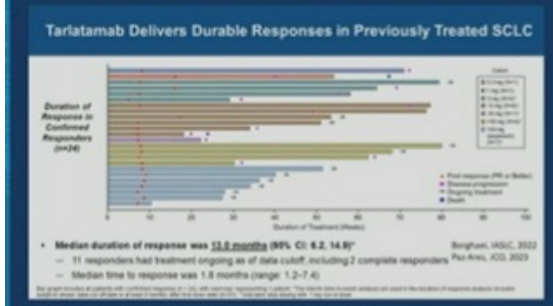
Tarlatamab Induces Response in Previously Treated SCLC



Borghaei, IASLC, 2022
Paz-Ares, JCO, 2023

Confirmed ORR, 23% (2 CRs, 22 PRs); 37% of patients with tumor shrinkage ≥ 30%

Tarlatamab Delivers Durable Responses in Previously Treated SCLC

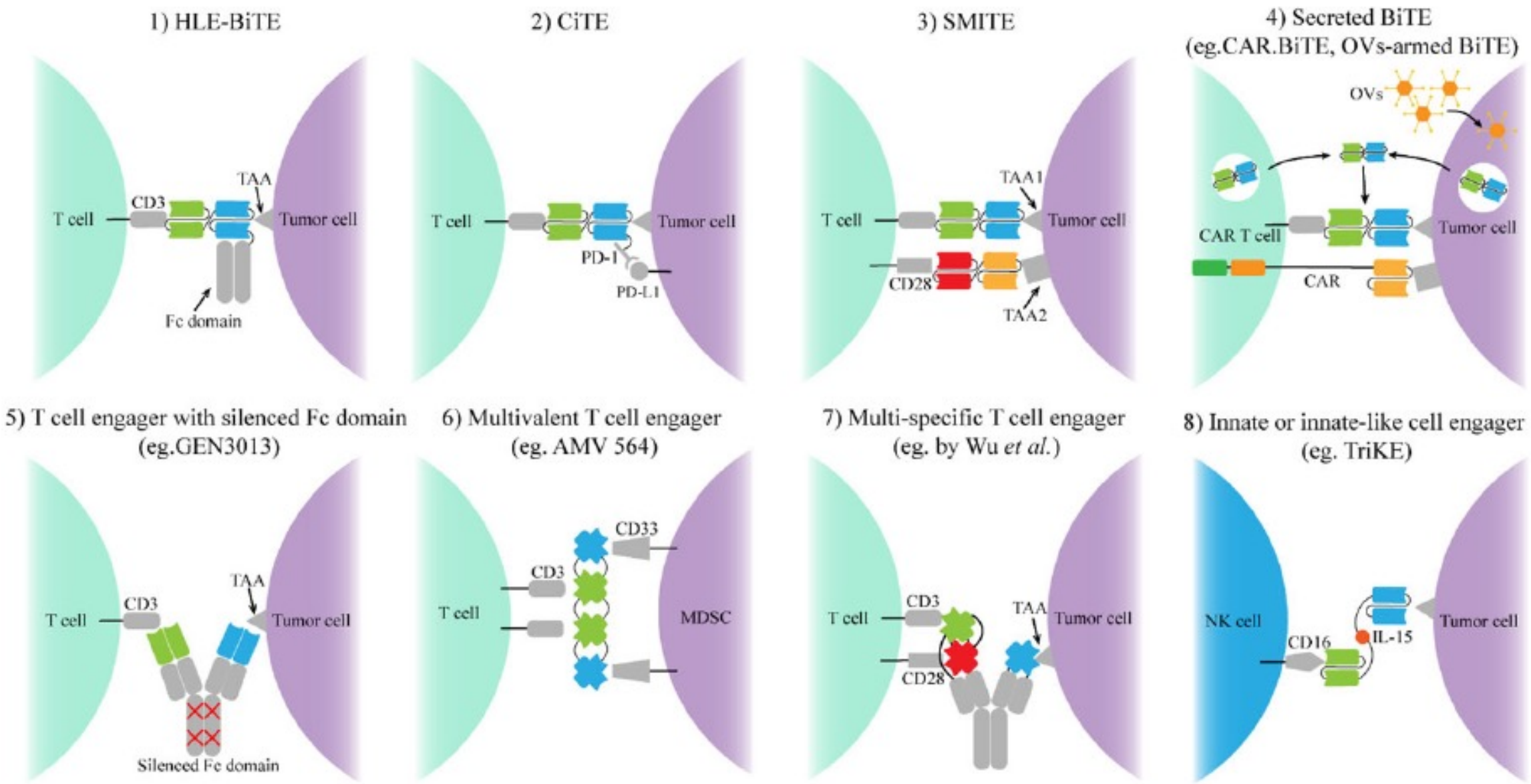


Survival with Tarlatamab in Previously Treated SCLC

Median overall survival of 13.2 months (95% CI: 8.8, -)

Mechanisms of Resistance

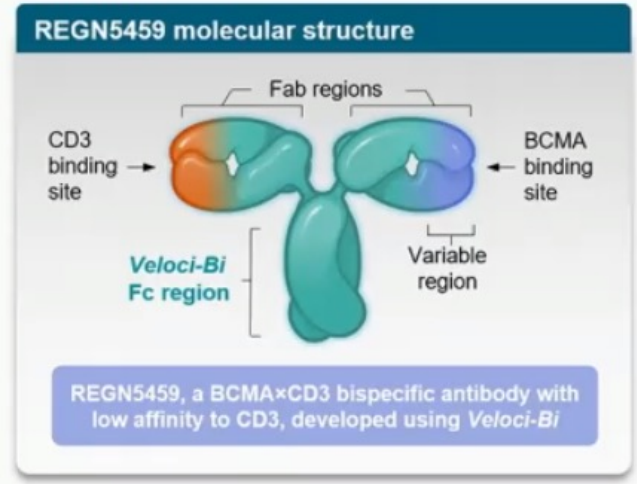
- Immunosuppressive Factors
  - Upregulation of Immune checkpoints, e.g., PD-L1
  - Increase of T regs (CD4/CD25/FOXP3)
  - Myeloid-derived suppressor cells (CD11b/CD13/CD16)
- Loss of Antigen

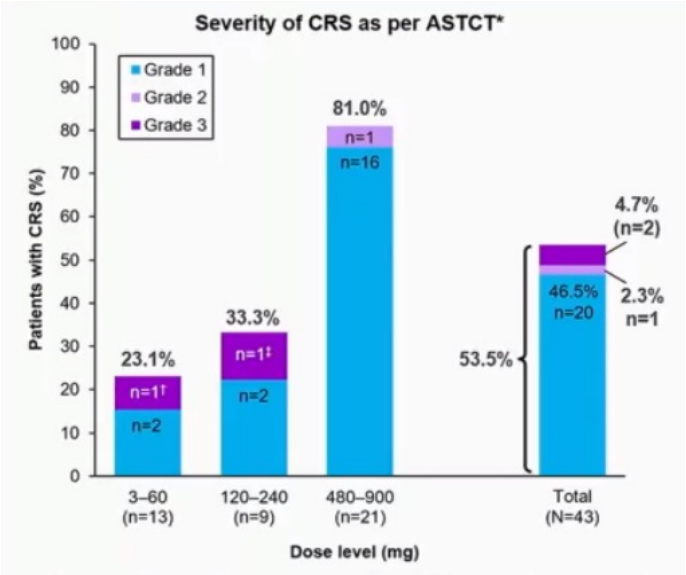


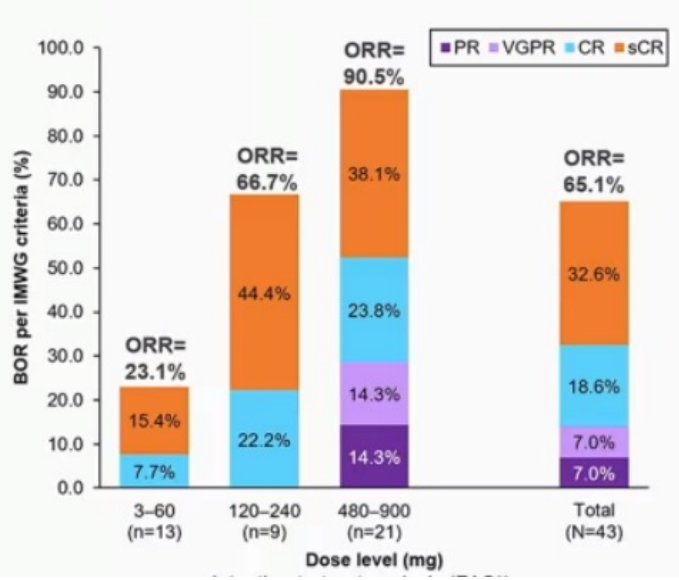
Zhou, S., *et al.* The landscape of bispecific T cell engager in cancer treatment. *Biomark Res* **9**, 38 (2021).

Safety and Efficacy from the Phase 1/2 First-in-Human Study of REGN5459, a BCMA×CD3 Bispecific Antibody with Low CD3 Affinity, in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

Attaya Suvannasankha[1,2], Prashant Kapoor[3], Matthew J. Pianko[4], Joshua Richter[5], Anita D'Souza[6], Larry D. Anderson, Jr.[7], Andrew Magyar[8], Oluwaseun Aina[8], Anita Boyapati[8], Damien Cronier[8], Nikhil Singh[8], Karen Rodriguez Lorenc[8], Glenn S. Kroog[8], Hans C. Lee[9]







Cytokine Release Syndrome: Uncontrolled systemic inflammatory response with elevated levels of cytokines, primarily IL6, which is triggered by T cell activation.

Table B1. Clinical signs and symptoms associated with CRS

Organ System	Symptoms
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

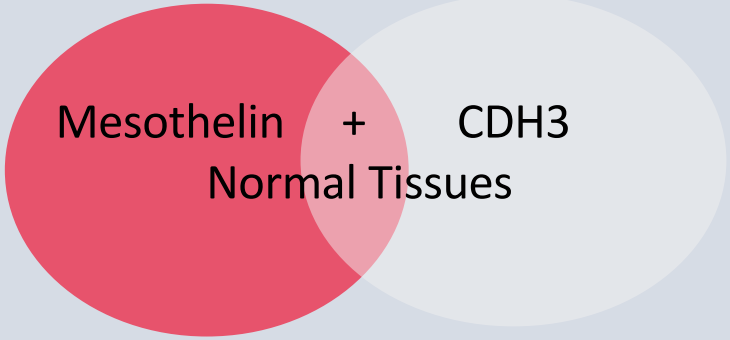
Table B2. ASTCT CRS consensus grading system (14)

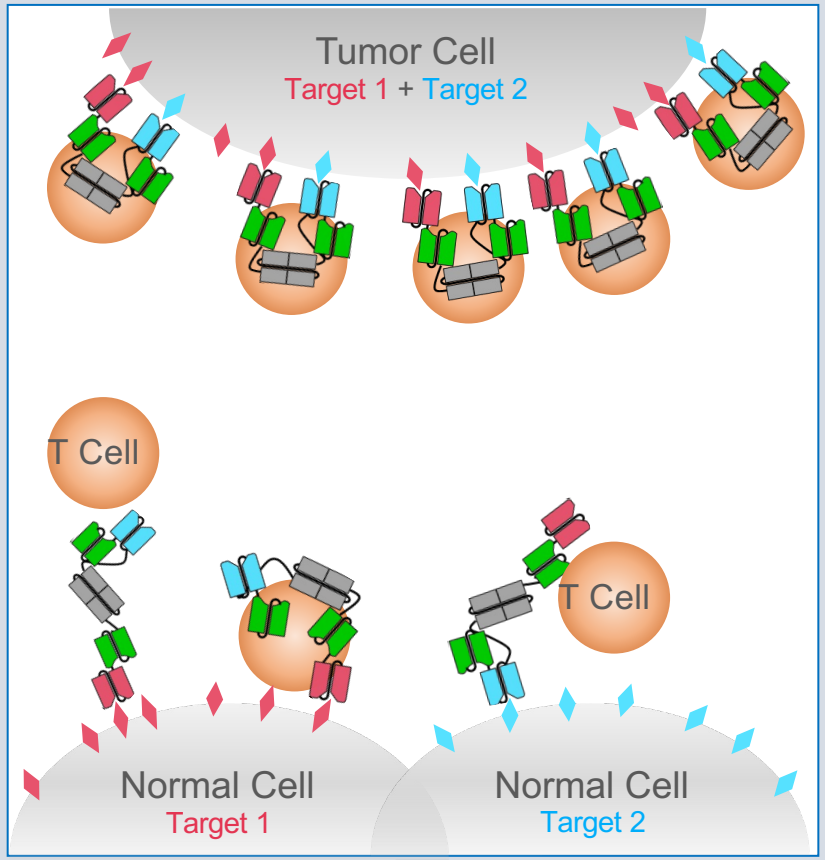
CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temp ≥ 38°C	Temp ≥38°C	Temp ≥ 38°C	Temp ≥ 38°C
		with	With	with
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		and/or†	and/or†	and/or†
Hypoxia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

Table B3. ASTCT immune effector cell-associated neurotoxicity syndrome (ICANS) consensus grading system for adults (14)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging^	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

DUAL-TARGETING MOLECULES HAVE THE POTENTIAL TO INCREASE THERAPEUTIC INDEX





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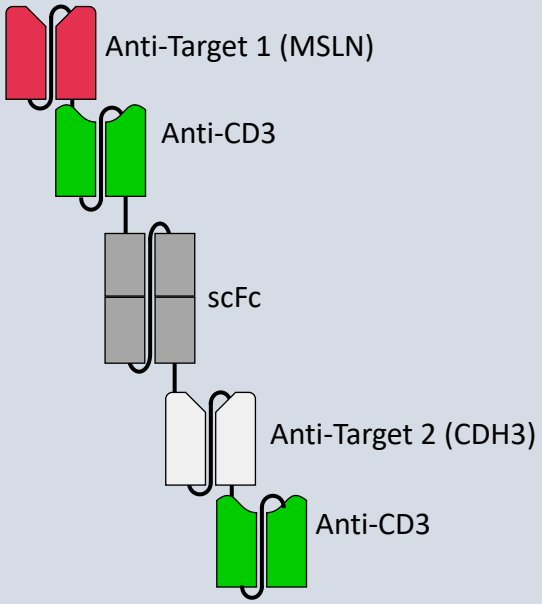


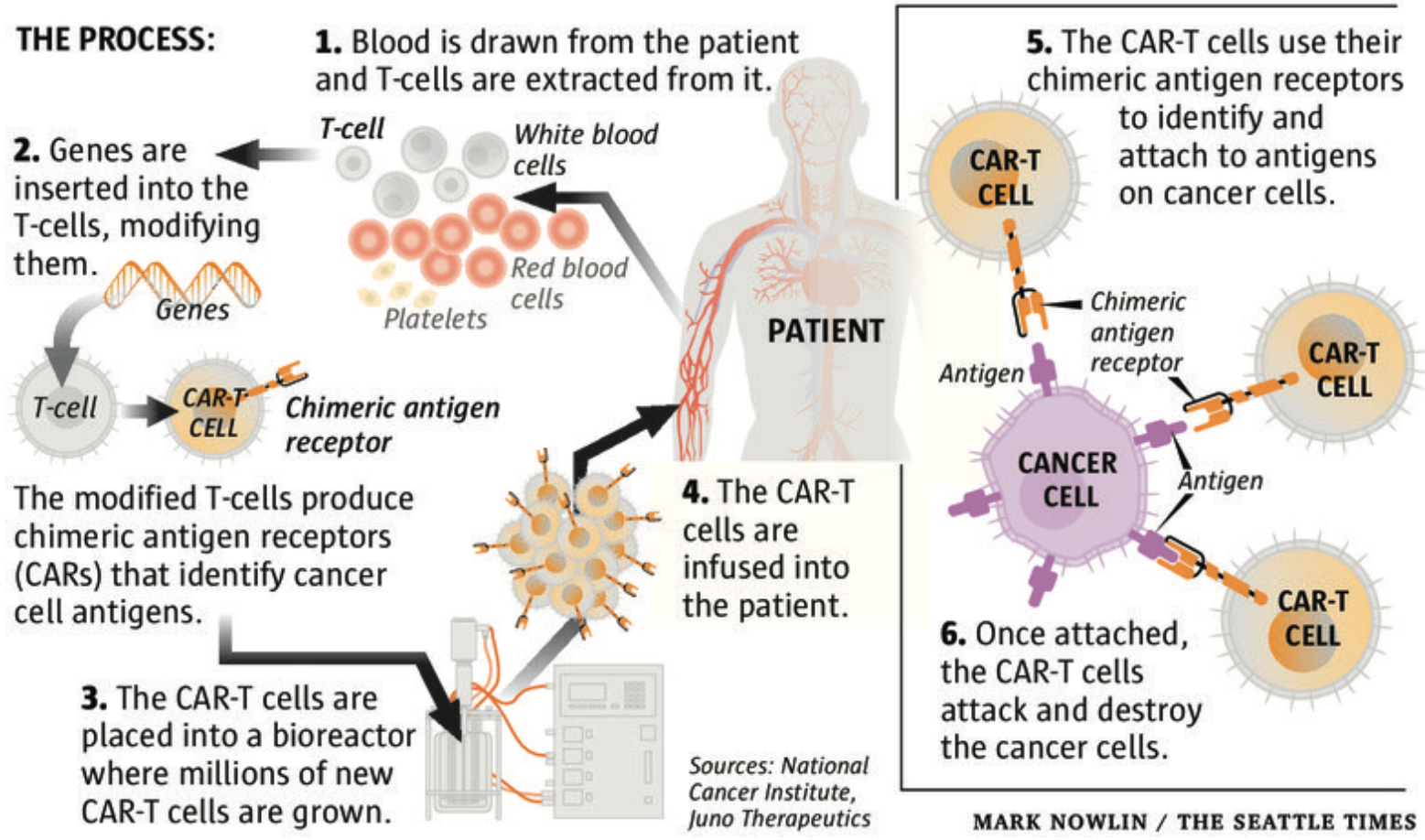
Simultaneous binding to two tumor-associated antigens and CD3 required for potent activity

IRB 23240: Phase 1 First-In-Human Study to Explore the Safety, Tolerability, and Pharmacokinetics of AMG 305 in Subjects With Advanced Solid Tumors. NCT05800964

Outline

- Other Immune Checkpoint Inhibitors
- TIGIT-PVR-NECTIN family axis
- Bispecific T Cell Engagers
- Cellular Therapies
  - CAR-T
  - Natural Killer Cells
  - Tumor Reactive And Cytokine-induced Killer (TRACK)-NK cells

Cellular Therapies: T cells with Chimeric Antigen Receptor (CAR-T)

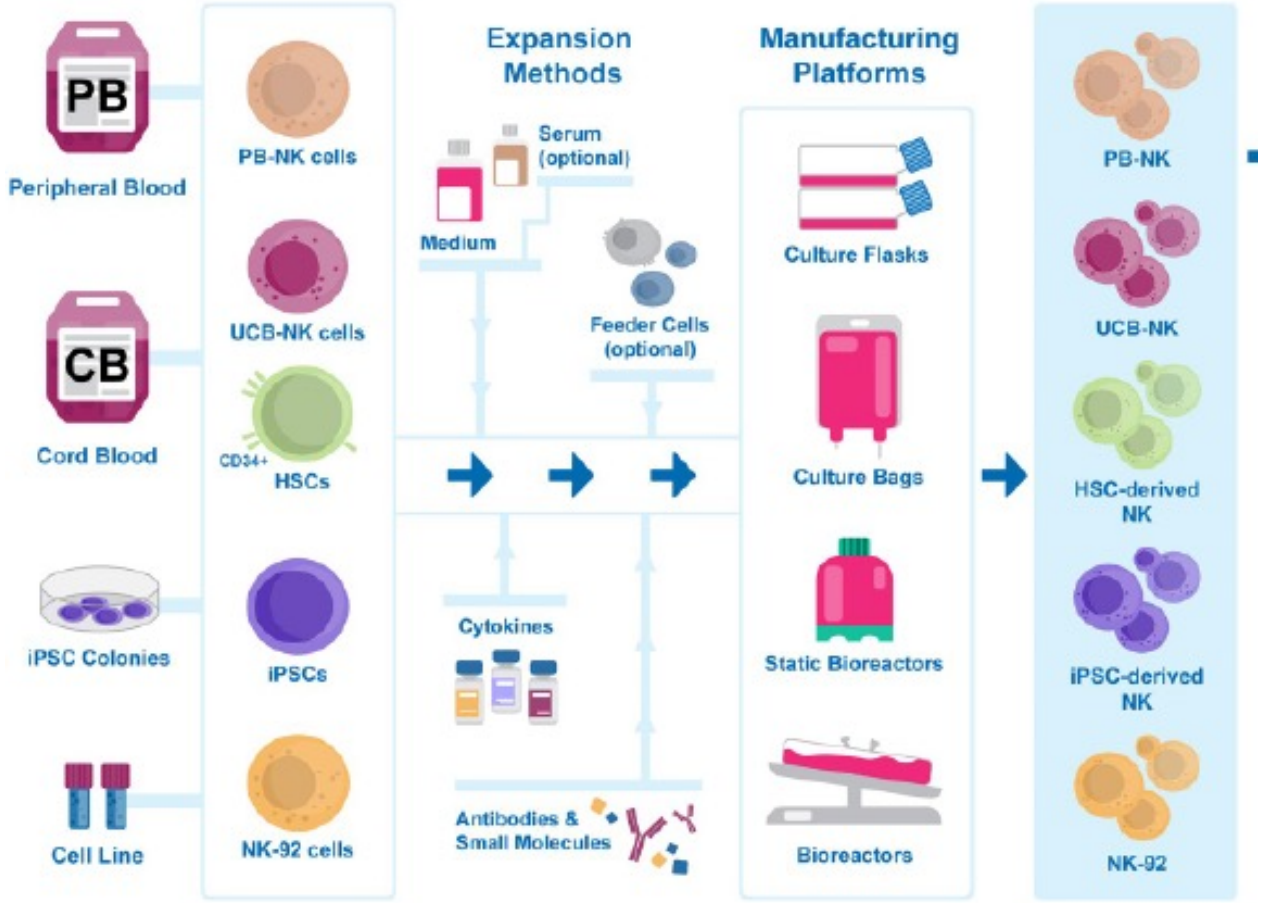


Natural Killer Cells

NK cells are a subset of immune cells that can target malignancies without the necessity of chimeric antigen receptors or prior antigen exposure and do not require matching to recipient's human leukocyte antigen for potential activity.

NK cells can be generated from cord-blood to be used as off-the-shelf allogeneic therapy without gene modifications such as HLA knockdown, considerably reducing the cost of manufacturing with increased availability of dosing product.

Natural Killer Cell Therapy Manufacturing Process Pipeline



Lamers-Kok *et al. Journal of Hematology & Oncology* (2022) 15:164

Challenges for NKC therapeutic impact

- Limited in vivo persistence
- Treatment of solid tumors is restricted by limited infiltration and by the escape of the immune suppressive microenvironment.
- NK cell engineering with CARs improves tumor infiltration and targeting.
- Expression of cytokines by combination of priming agents or genetic engineering can improve persistence and function.
- Combination with tumor targeting antibodies and immune checkpoint inhibitors might increase efficacy.
- NK cell engagers, migration enhancers and immunomodulators targeting the microenvironment and tumor immune escape are being explored.

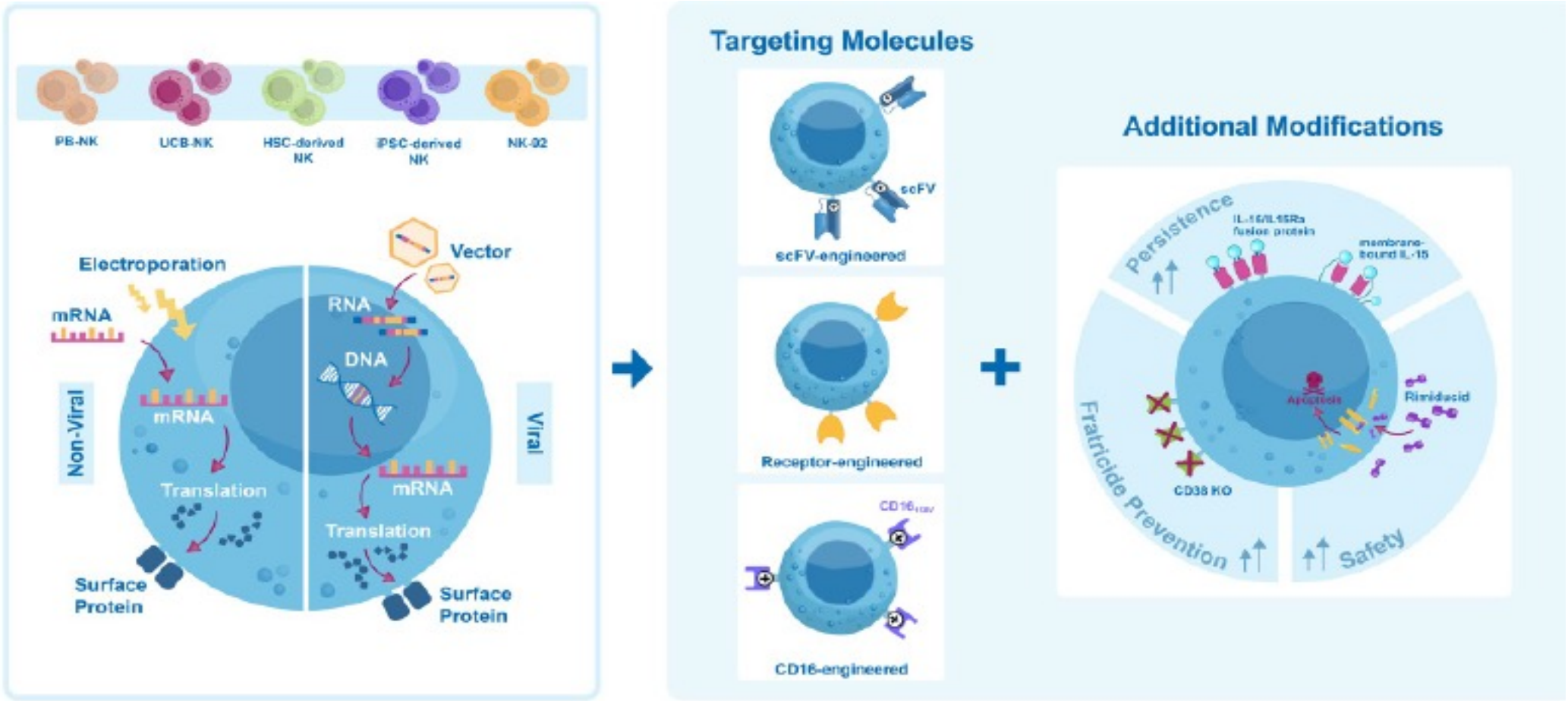


Fig. 4 Overview of engineered NK cell therapies. From left to right: different NK cell sources (PB-NK, UCB-NK, HSC-derived NK, iPSC-derived NK, NK-92) are engineered to express the desired surface protein(s) by means of non-viral electroporation with mRNA (left) or of transduction with γ-retro or lentiviral vectors and stable integration in the host genome (right). Engineered NK cell therapies can be divided in categories, according to the targeting molecule: (1) antibody-derived single-chain variable fragment (scFv-engineered) for tumor antigen binding, (2) NK cell receptor (receptor-engineered) for ligand binding, and (3) Fc receptor CD16 (158 V) high-affinity non-cleavable hnCD16 variant (CD16-engineered) to enhance antibody-dependent cell cytotoxicity (ADCC). Co-expression of scFv and hnCD16 is also reported. Additional modifications of engineered NK cell products under clinical evaluation enhance NK cell persistence in vivo by expression of membrane-bound IL-15 or of IL-15/IL-15 receptor fusion protein IL-15/IL-15Ra, prevent fratricide by CD38 KO, or increase safety through induction of apoptosis by administration of Rimiducid

Natural killer cells in antitumour adoptive cell immunotherapy

Tamara J. Laskowski[1], Alexander Biederstädt[1,2] and Katayoun Rezvani

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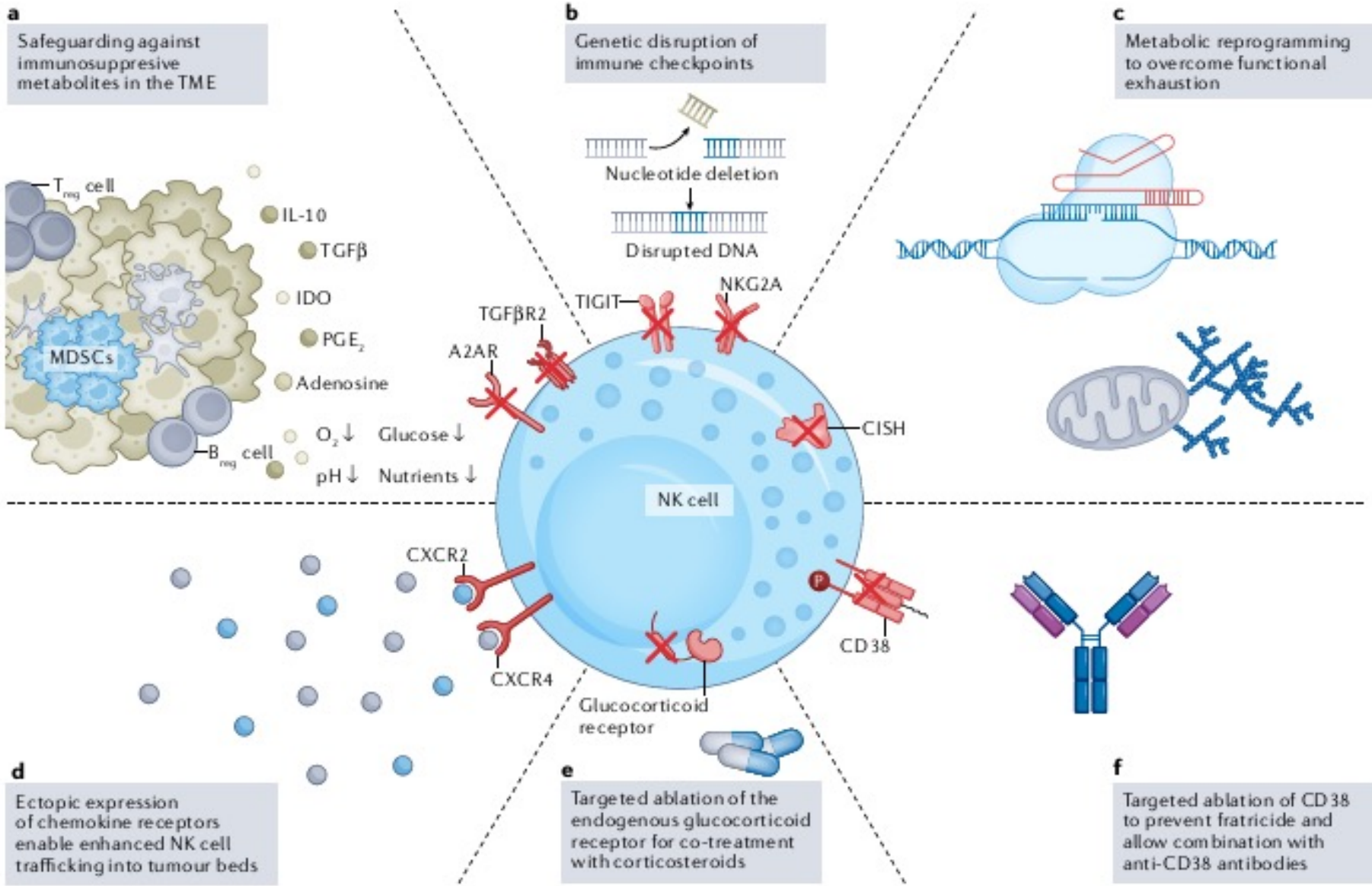


NKC Selected recent/ongoing trials

FT516 – iPS **CD16-eng** allo NK (enhanced ADCC) explored in combination with rituximab or avelumab; Doses of 9 x10^7 (n=4), 3x 10^8 (n=7), or 9 x 10^8 (n=7) FT516 cells/dose were administered. No DLT, ICANS or GVHD. 11/18 resp, 5CR

FT538 - is a multiplexed-engineered NK that incorporates 3 synthetic elements including **CD16, IL15R, KOCD38** showed very favorable safety profile without achieving good clinical benefit

FT596 – co-expressing **hmCD16 and a CD19-scFv-CAR**, tested combined with rituximab/Obinutuzumab. 18/24 resp, 12 CR

FT576 – carries a BCMA-scFv-CAR

GDA-201 – PBNK combined with rituximab 13/19 CR. Retreatment without LD converted 1 PR in CR

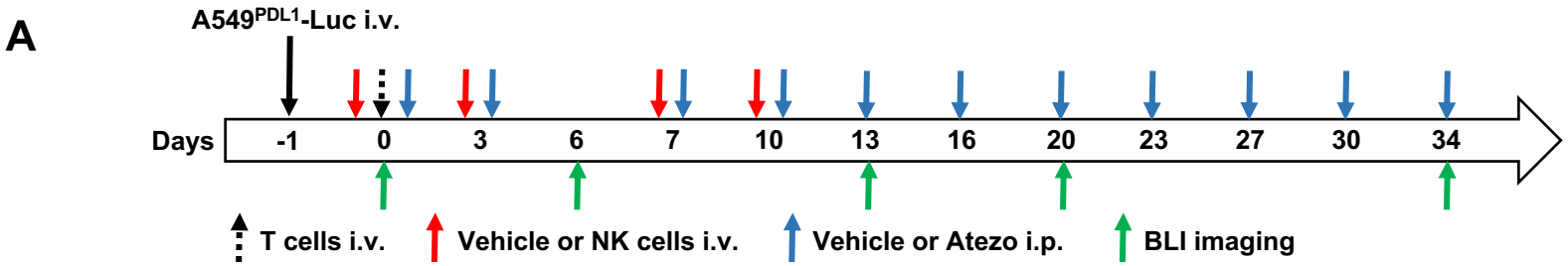
PBNK HANK - Combined with pembro. OS 15.5 m vs 13.3 m pembro alone

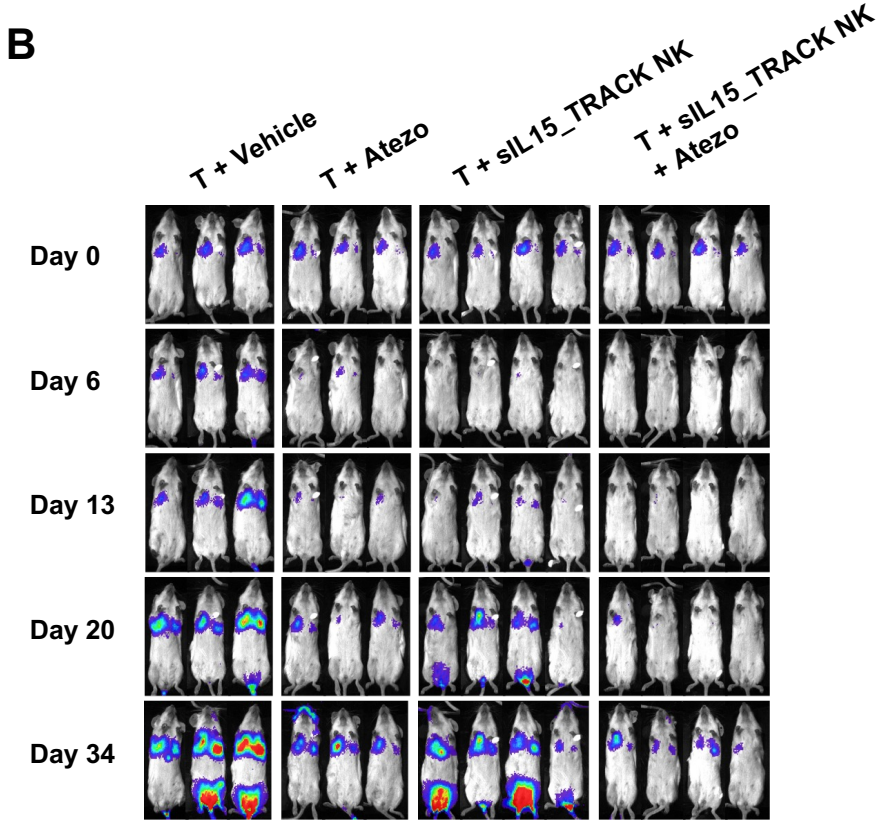
ACE1702 (**anti-HER2 oNK** cells). Repeat dosing 9 x 10^9 cells /cycle (14 days) Dose escalation continues to 15 x 10^9 NK cells/cycle

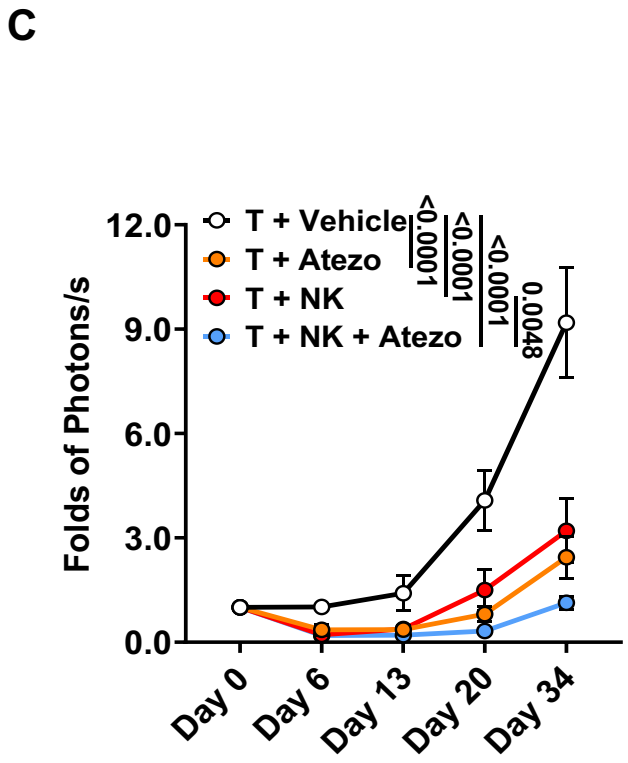
NKX 019 - engineered **anti CD19 CAR and mIL15**. 7/10 patients treated at 1 x 10^9/1.5 x 10^9 had CR

Umbilical cord blood derived tumor-reactive PD-L1+ natural killer cells engineered to express soluble IL-15 (TRACK-NK) as a treatment strategy for non-small cell lung cancer patients

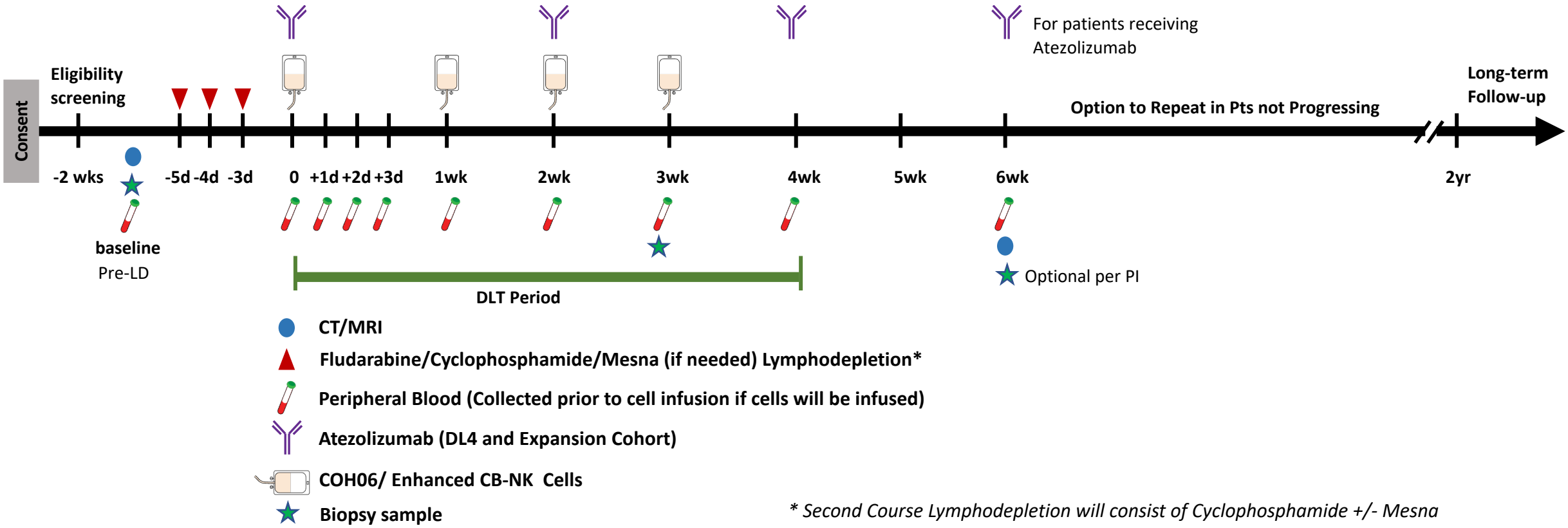
IND-Enabling Study: Combination Therapy







Study Schema



** Second Course Lymphodepletion will consist of Cyclophosphamide +/- Mesna*

Trial Design

- Phase 1 (Cycle: 28 Days/ Course: 6 Weeks)
- Goal: Determine the OBD of COH06
  Not an MTD seeking trial

- Utility Based Bayesian Optimal Interval Design
- Stage 1: Toxicity (3+3)
- Stage 2: Toxicity and Persistence
  Pr(Tox ≤.25)
  Pr(Per ≥.75)

- Persistence is defined as any evidence of detectable COH06 cells by ddPCR measurement on day 28
- Relationship between detectable cells and activity

Dose Level (DL)	Transduced Cells/ kg[ł]	Atezolizumab Dose
-2	4.0×10^5	---
-1	7.0×10^5	---
1 (starting dose)	1.50×10^6	---
2	4.0×10^6	---
3	7.5×10^6	---
4	$7.5 \times 10^{6*}$	840 mg IV

*: The expected COH06 dose for combination treatment.
Note: The starting dose of COH06, as part of the combination therapy, may be less based on adverse events observed on DLs 1-3 -either the highest monotherapy dose tested where no more than 1/6 DLTs are observed, or one dose level below the highest tested safe dose.

łTransduced cells are tEGFR+ cells as determined by flow cytometry

Summary

- Significant Advances had occurred in the understanding of Immune anti tumor response and mechanisms curtailing its action.

- This has resulted in several therapeutics strategies some with already proven benefits while others undergoing adjustments and further evaluation.

- Although significant challenges remain, the outlook is promising and suggest that a significant proportion of patients will derive profound long term benefits.