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

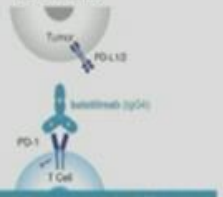
Fc-enhanced CTLA-4 Inhibitor

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.

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Hussein Tawbi, MD, PhD @HTawbi_MD

ASCO KNOWLEDGE CONQUERS CANCER

nature medicine

Article https://doi.org/10.1038/s41591-024-03083-7

Botensilimab plus balstilimab in relapsed/refractory microsatellite stable metastatic colorectal cancer: a phase 1 trial

Andrea J. Bullock[1,20], Benjamin L. Schlechter[2,20], Marwan G. Fakih[3,20], Apostolia M. Tsimberidou[4,20], Joseph E. Grossman[5], Michael S. Gordon[6], Breelyn A. Wilky[7], Agustin Pimentel[8], Daruka Mahadevan[9], Ani S. Balmanoukian[10], Rachel E. Sanborn[11], Gary K. Schwartz[12], Ghassan K. Abou-Alfa[12,14,15], Neil H. Segal[12,14], Bruno Bockorny[1], Justin C. Moser[6], Sunil Sharma[6], Jaymin M. Patel[5], Wei Wu[5], Dhan Chand[5], Katherine Rosenthal[5], Gabriel Mednick[5], Chloe Delepine[5], Tyler J. Curiel[16], Justin Stebbing[17] ✉, Heinz-Josef Lenz[18], Steven J. O'Day[5,19,20] & Anthony B. El-Khoueiry[18,20] ✉

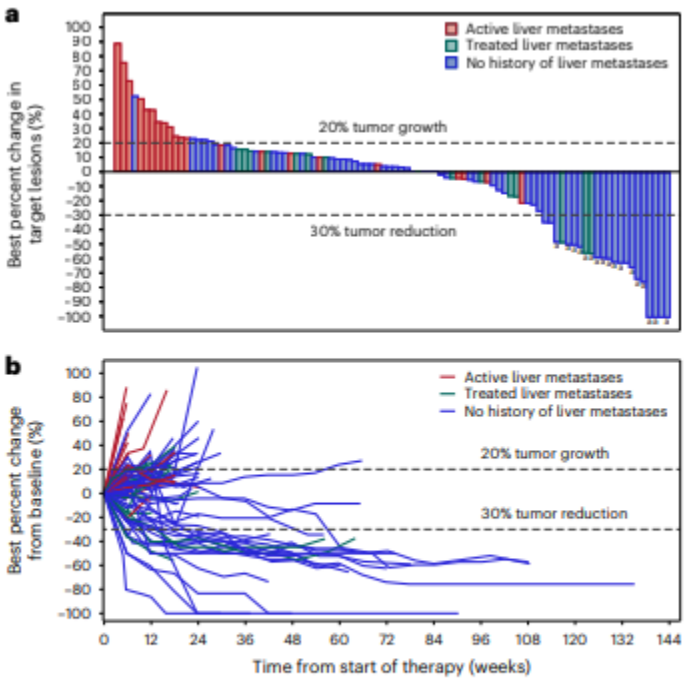
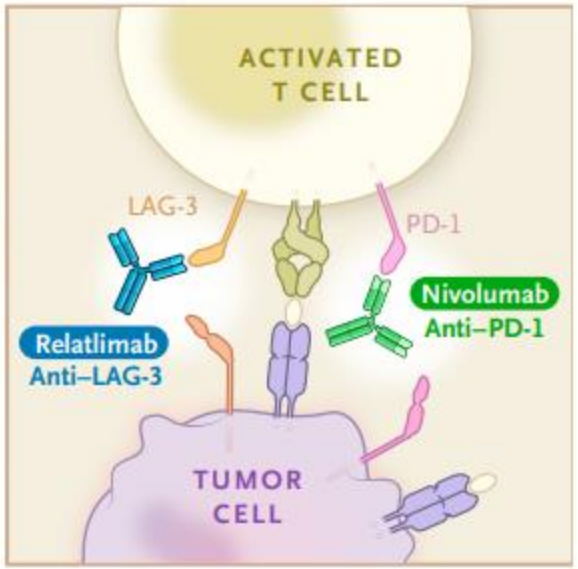
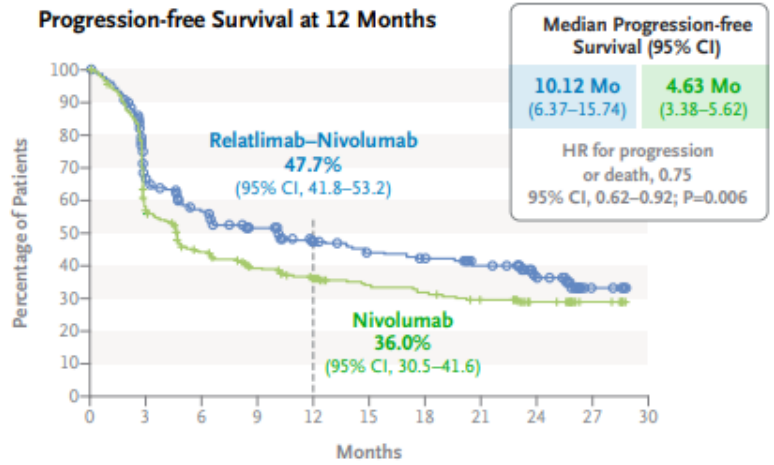


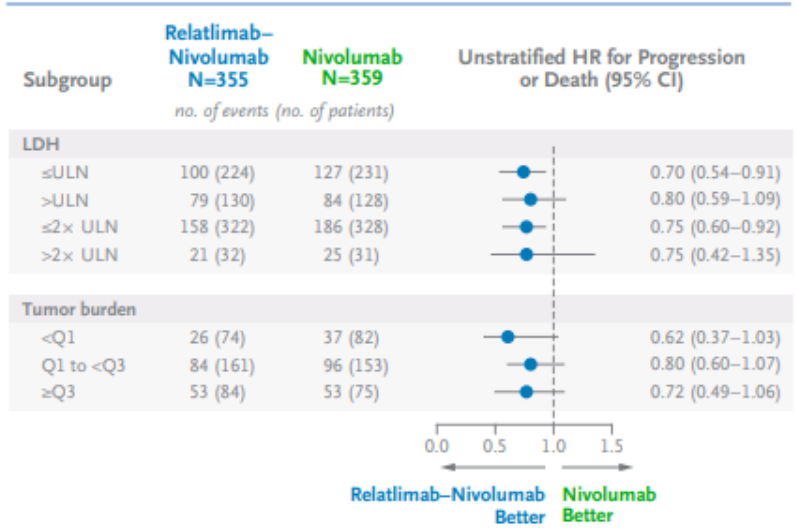
Fig. 2 | Clinical efficacy by liver involvement in response-evaluable patients with MSS mCRC (n = 101). Liver involvement was characterized as patients with active LM, treated LM that were resected or ablated without recurrence or no history of LM. **a**, Best overall response. **b**, Response over time. [a] Indicates a RECIST 1.1–confirmed CR or PR. The first blue bar on the right represents the CR.

Relatlimab and Nivolumab vs. Nivolumab in Untreated Advanced Melanoma

Tawbi HA et al. DOI: 10.1056/NEJMoa2109970







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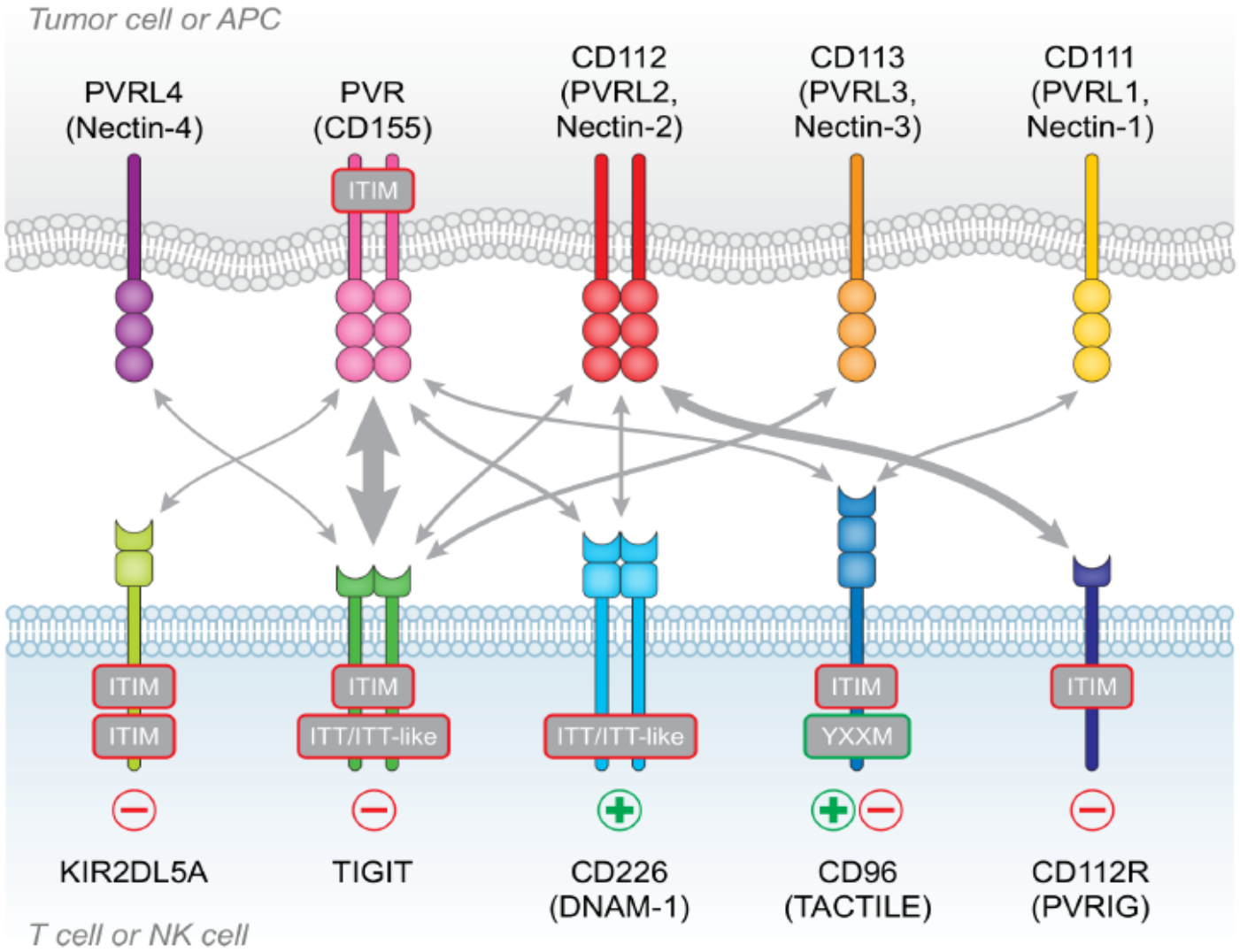
Chiang EY, Mellman I. *J Immunother Cancer* 2022;**10**:e004711. doi:10.1136/jitc-2022-004711



Anti TIGIT Monoclonal Antibodies in Clinical Development

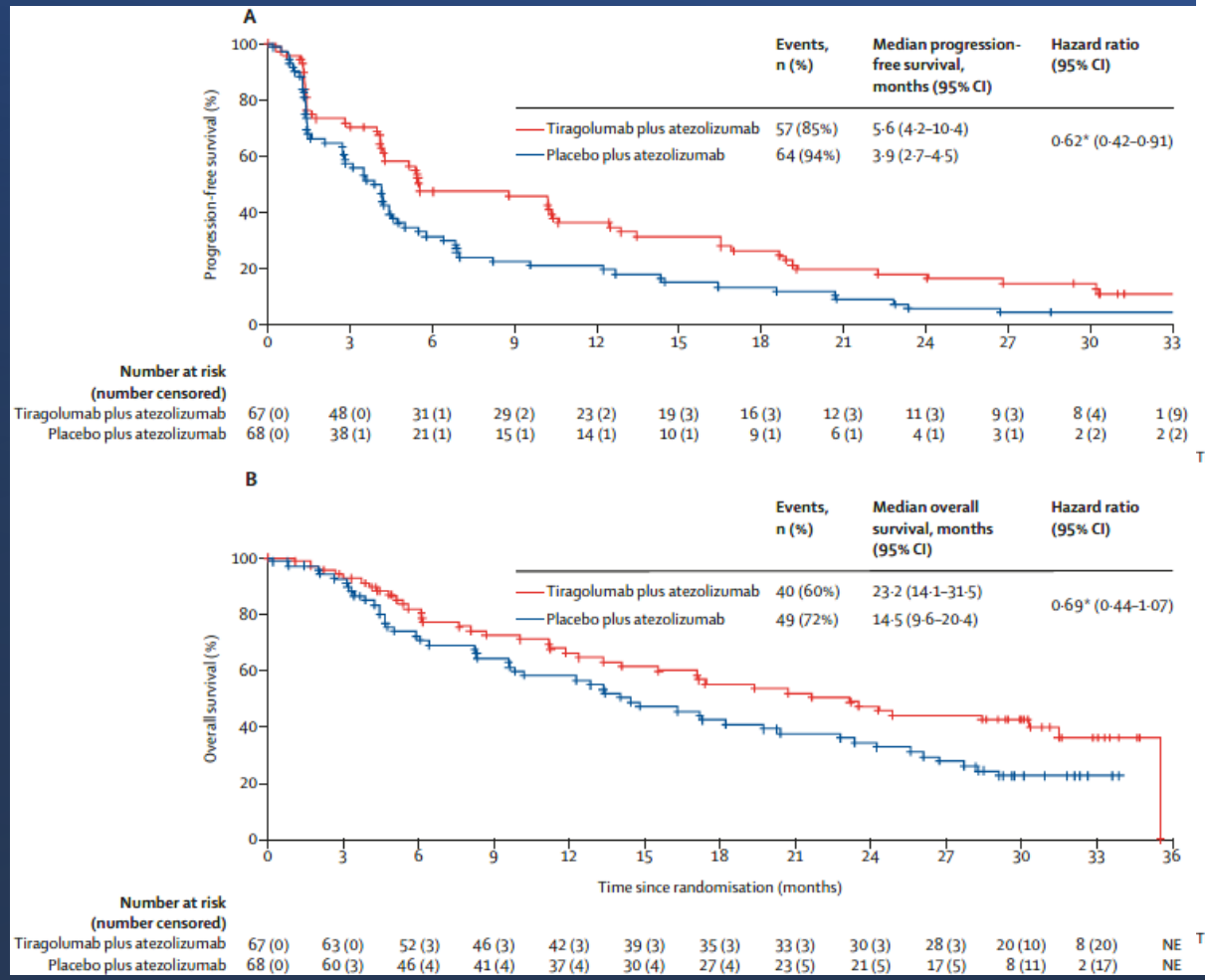
Anti-TIGIT mAbsc	Phase*	Fc Region
Tiragolumab	III	Active
Domvanalimab	III	Inactive
Ociperlimab	III	Active
Vibostolimab	III	Active
BMS-986207	II (Planned)	Inactive
Etigilimab	II (Planned)	Active
EOS-448	I/II	Active
AZD-2936	I/II	Active
SEA-TGT	I	Active
COM-902	I	Inactive
IBI-939	I	Active
IBI-321	I	Unknown
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

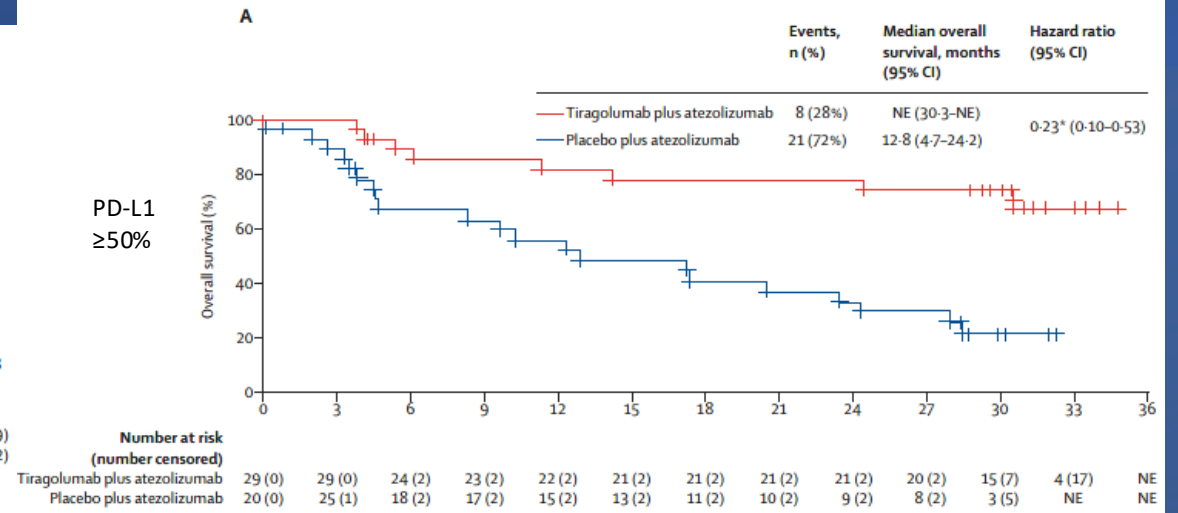
Chiang EY, Mellman I. *J Immunother Cancer* 2022;**10**:e004711. doi:10.1136/jitc-2022-004711

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

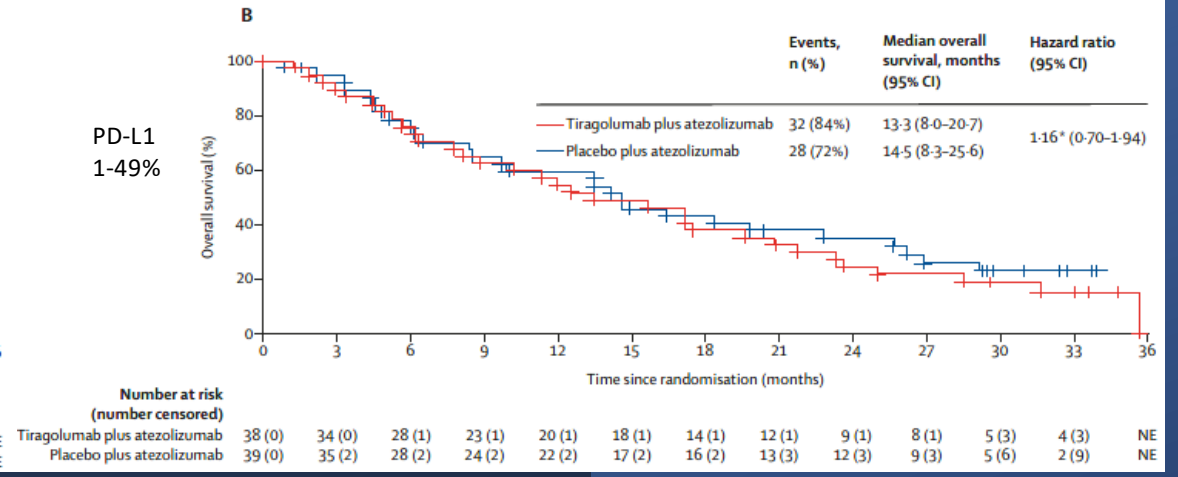
Lancet Oncol 2022; 23: 781–92



PD-L1 ≥50%



PD-L1 1-49%



A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer (SKYSCRAPER-01)

ClinicalTrials.gov ID NCT04294810

Sponsor Hoffmann-La Roche

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

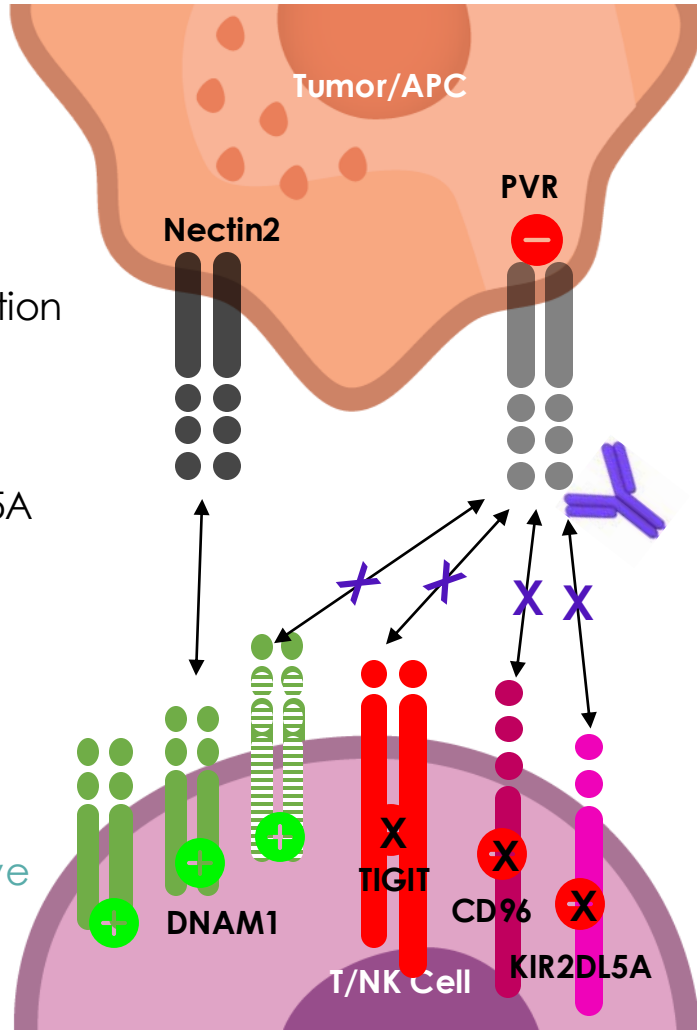
Efficacy Population	Z (n = 44)	DZ (n = 44)	EDZ (n = 45)
Confirmed ORR n (%) [95% CI]	12 (27) [15.0, 42.8]	18 (41) [26.3, 56.8]	18 (40) [25.7, 55.7]
Median PFS (mo) [95% CI]	5.4 [1.8, 9.6]	12.0 [5.5, NE]	10.9 [4.8, NE]
PFS Hazard Ratio vs Z [95% CI]	-	0.55 [0.31, 1.0]	0.65 [0.37, 1.1]
6-mo PFS % (95% 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)

Follow up trials STAR-221 (GE) D + Z + Ch vs N + Ch; Pacific 8, post chemo-XRT NSCLC D + Durva vs Durva

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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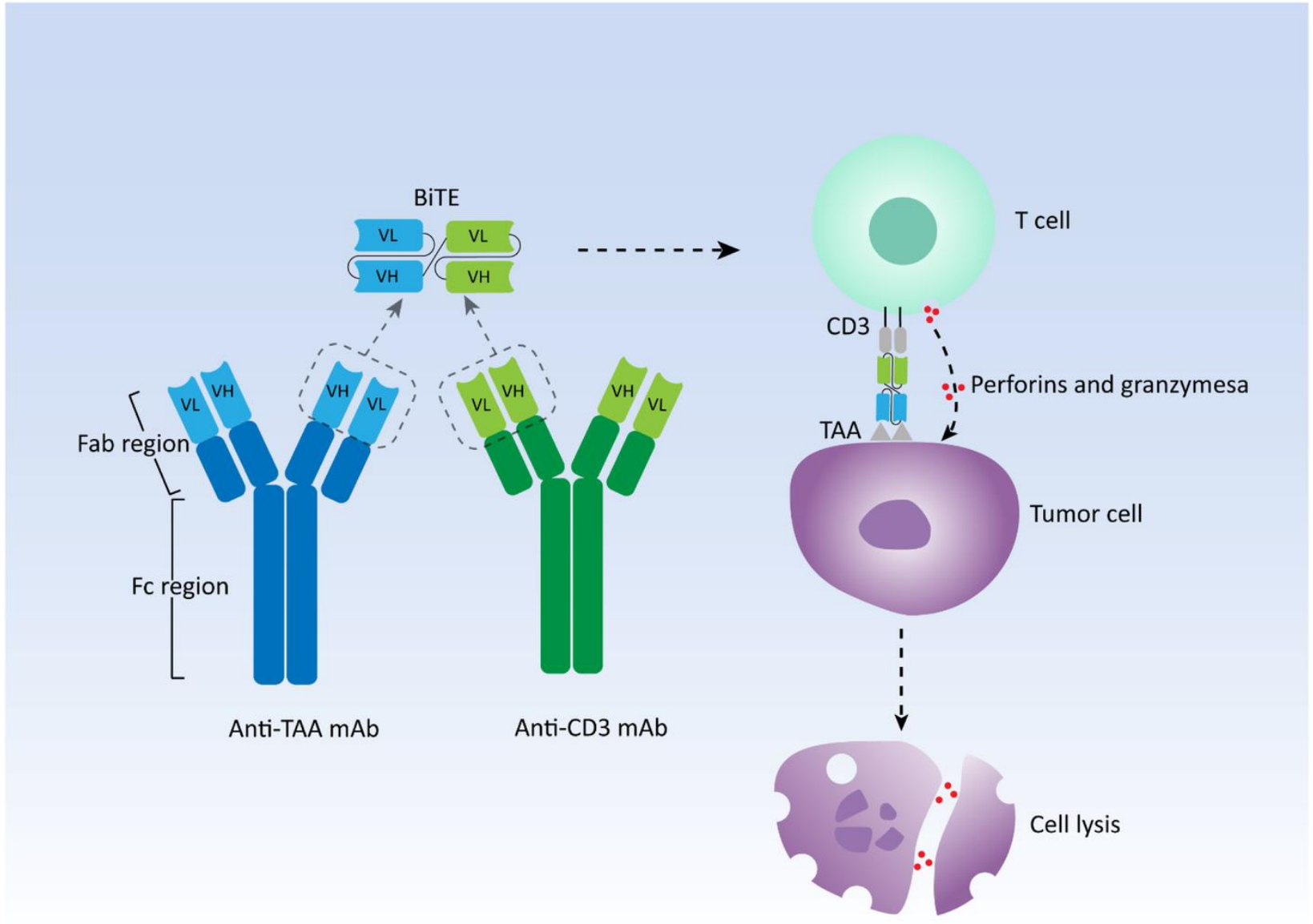


VH: Heavy chain variable region; VL: Light chain variable region; TAA: Tumor-associated antigen

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

Clinical activity of approved bispecific antibodies as of May 2024

Nature Reviews Clinical Oncology | Volume 21 | July 2024 | 539–560

Agent	Target	Indication and activity	Common grade ≥3 adverse events	Year of approval
Blinatumomab[77–80]	CD3×CD19	RR B-ALL: CR/CRh in 43–44%, mRFS 5.9 months, mOS 6.1–6.9 months	Neutropenia (37.8–41%), infection (34.1%), elevated circulating liver enzymes (6–12.7%), neurological events (9.4–11%), CRS (4.9%)	2014[a], 2017 (FDA); 2015[a], 2018 (EMA), 2020 (NMPA) Subsequently, expanded to include patients with MRD[+] B-ALL
Mosunetuzumab[88]	CD3×CD20	RR FL: CRR 60%, ORR 80%, mPFS 17.9 months, mOS NR	Neutropenia or reduced neutrophil count (26%), hypophosphataemia (17%), anaemia (8%), increased serum ALT (5%), CRS (2%)	2022[a] (EMA), 2022[a] (FDA)
Tebentafusp[240,247]	CD3×gp100–HLA-A*02:01	HLA-A*02:01-positive uveal melanoma: ORR 11%, mPFS 3.4 months, mOS 21.6 months	Rash (19%), elevated circulating liver enzymes (10%), pyrexia (5%), pruritus (5%), CRS (1%)	2022 (FDA), 2022 (EMA)
Teclistamab[115,117]	CD3×BCMA	RR MM: CRR 39.4%, ORR 63%, mPFS 11.3 months, mOS 18.3 months	Neutropenia (64.2%), anaemia (37.0%), lymphopenia (32.7%), thrombocytopenia (21.2%), CRS (0.6%)	2022[a] (FDA), 2022[a] (EMA)
Glofitamab[91]	CD3×CD20	RR DLBCL: CRR 39%, ORR 52%, mPFS 4.9 months, mOS 12 months	Neutropenia (27%), thrombocytopenia (8%), anaemia (6%), CRS (4%)	2023[a] (FDA), 2023[a] (EMA), 2023[a] (NMPA)
Amivantamab[198–200]	EGFR×MET	Advanced-stage NSCLC harbouring *EGFR* exon 20 insertion mutations (in combination with chemotherapy): ORR 73%, mPFS 11.4 months, mOS NR	Neutropenia (33%), rash (11%), leukopenia (11%), anaemia (11%), thrombocytopenia (10%)	2021[a] (FDA)
Epcoritamab[94]	CD3×CD20	RR DLBCL: CRR 38.9%, mPFS 4.4 months, mOS NR	Neutropenia (14.6%), anaemia (10.2%), thrombocytopenia (5.7%), CRS (2.5%)	2023[a] (FDA) 2023[a] (EMA)
Elranatamab[118–120]	CD3×BCMA	RR MM: ORR 61%, estimated 15-month PFS 50.9%, estimated 15-month OS 56.7%	Neutropenia (48.8%), anaemia (37.4%), lymphopenia (25.2%), thrombocytopenia (23.6%)	2023[a] (FDA), 2024[a] (EMA)
Cadonilimab[168]	PD-1×CTLA4	Advanced-stage cervical cancer: ORR 32.3%, mPFS 3.7 months, mOS NR	Anaemia (5%), reduced appetite (4%), dyspnoea (2%)	2022 (NMPA)
Talquetamab[130]	GPRC5D×CD3	RR MM: ORR 72%, mDOR 9.5 months, mPFS NR	Lymphopenia (47%), anaemia (33%), neutropenia (26%), leukopenia (16%)	2023[a] (FDA)
Tarlatamab[141,142]	CD3 x DLL3	RR SCLC: ORR 40%, mDOR 9.7 months, mPFS 4.9 months	CRS (26%), neutropenia (8%)	2024[a] (FDA)

FDA approves amivantamab-vmjw for EGFR exon 20 insertion-mutated non-small cell lung cancer indications

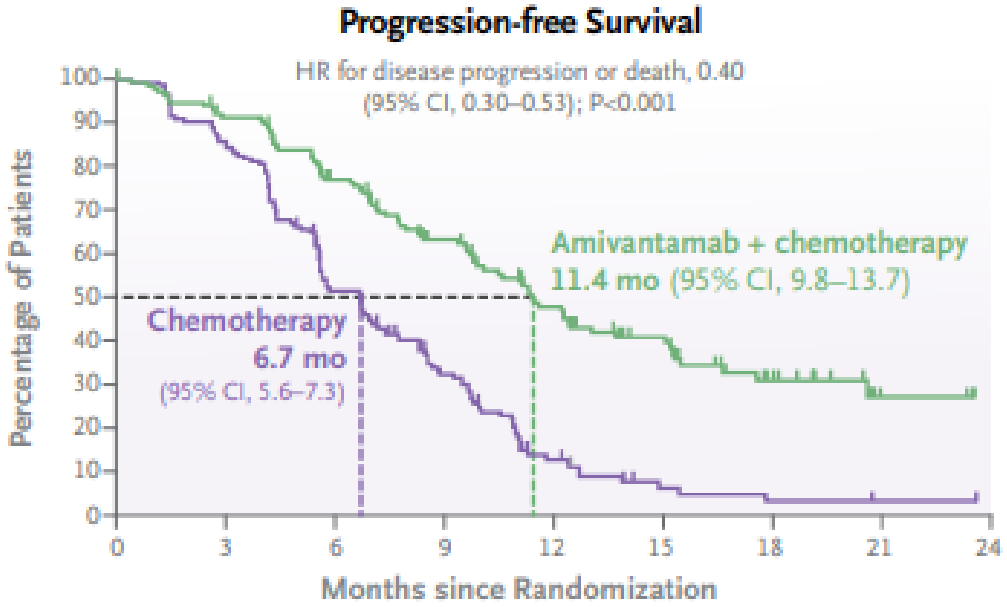
On March 1, 2024, the Food and Drug Administration approved amivantamab-vmjw with carboplatin and pemetrexed for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test.

The FDA also granted traditional approval to amivantamab-vmjw for adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. FDA previously granted (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-amivantamab-vmjw-metastatic-non-small-cell-lung-cancer) accelerated approval for this indication.

CLINICAL TRIAL

Design: A phase 3, international, randomized trial assessed the efficacy and safety of amivantamab–chemotherapy as compared with chemotherapy alone as first-line therapy in patients with advanced NSCLC with *EGFR* exon 20 insertions.

Intervention: 308 adults were assigned to receive intravenous amivantamab (1400 mg weekly for the first 4 weeks; 1750 mg every 3 weeks starting at week 7 until progression occurred) plus carboplatin–pemetrexed chemotherapy or chemotherapy alone, in 21-day cycles. Patients assigned to chemotherapy alone could receive amivantamab monotherapy after disease progression was documented. The primary outcome was progression-free survival.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

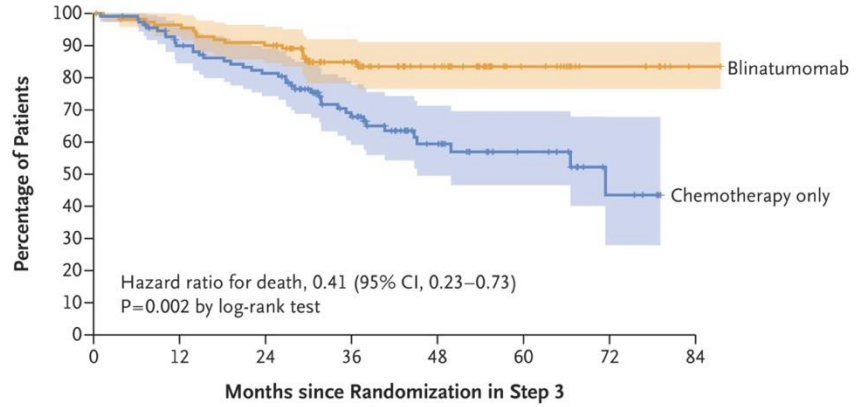
Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults

M.R. Litzow, Z. Sun, R.J. Mattison, E.M. Paietta, K.G. Roberts, Y. Zhang, J. Racevskis, H.M. Lazarus, J.M. Rowe, D.A. Arber, M.J. Wieduwilt, M. Liedtke, J. Bergeron, B.L. Wood, Y. Zhao, G. Wu, T.-C. Chang, W. Zhang, K.W. Pratz, S.N. Dinner, N. Frey, S.D. Gore, B. Bhatnagar, E.L. Atallah, G.L. Uy, D. Jeyakumar, T.L. Lin, C.L. Willman, D.J. DeAngelo, S.B. Patel, M.A. Elliott, A.S. Advani, D. Tzachanis, P. Vachhani, R.R. Bhave, E. Sharon, R.F. Little, H.P. Erba, R.M. Stone, S.M. Luger, C.G. Mullighan, and M.S. Tallman

CONCLUSIONS

The addition of blinatumomab to consolidation chemotherapy in adult patients in MRD-negative remission from BCP-ALL significantly improved overall survival.

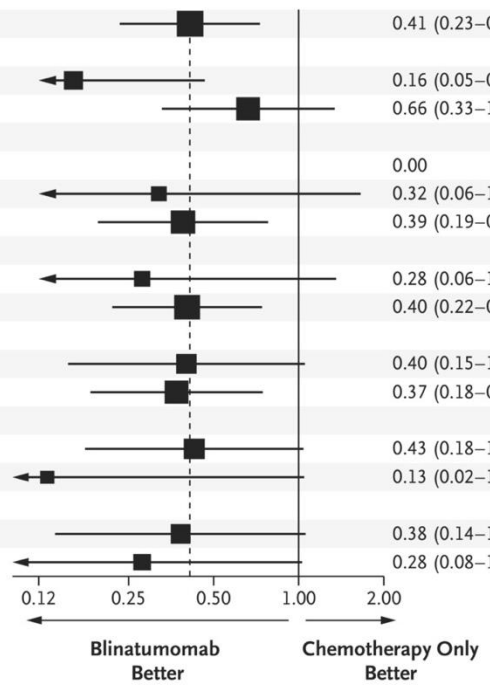
A Overall Survival among Patients with MRD-Negative Status



No. at Risk								
Blinatumomab	112	106	99	65	41	19	8	1
Chemotherapy only	112	96	85	53	28	15	5	0

B Subgroup Analysis

Subgroup	Blinatumomab	Chemotherapy Only	Hazard Ratio for Death (95% CI)
	no. of deaths/total no.		
All MRD-negative patients	17/112	40/112	0.41 (0.23–0.73)
Age			
<55 yr	4/66	21/65	0.16 (0.05–0.47)
≥55 yr	13/46	19/47	0.66 (0.33–1.35)
Combined molecular risk			
Favorable	0/19	6/28	0.00
Intermediate	2/22	5/19	0.32 (0.06–1.65)
Unfavorable	12/50	24/45	0.39 (0.19–0.78)
BCR::ABL1–like genotype			
BCR::ABL1–like	2/16	7/15	0.28 (0.06–1.36)
Not *BCR::ABL1*–like	15/96	33/97	0.40 (0.22–0.74)
Transplantation intended			
Yes	6/36	13/35	0.40 (0.15–1.05)
No	11/76	27/77	0.37 (0.18–0.75)
CD20 status			
Positive	7/45	16/46	0.43 (0.18–1.04)
Negative	1/26	7/26	0.13 (0.02–1.05)
Rituximab use			
Yes	5/33	14/36	0.38 (0.14–1.06)
No	3/38	9/36	0.28 (0.08–1.03)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer

M.-J. Ahn, B.C. Cho, E. Felip, I. Korantzis, K. Ohashi, M. Majem, O. Juan-Vidal, S. Handzhiev, H. Izumi, J.-S. Lee, R. Dziadziuszko, J. Wolf, F. Blackhall, M. Reck, J. Bustamante Alvarez, H.-D. Hummel, A.-M.C. Dingemans, J. Sands, H. Akamatsu, T.K. Owonikoko, S.S. Ramalingam, H. Borghaei, M.L. Johnson, S. Huang, S. Mukherjee, M. Minocha, T. Jiang, P. Martinez, E.S. Anderson, and L. Paz-Ares, for the DeLLphi-301 Investigators*

n engl j med 389;22 nejm.org november 30, 2023

Table 2. Treatment Response According to Blinded Independent Central Review (Analysis Population for Antitumor Activity).*

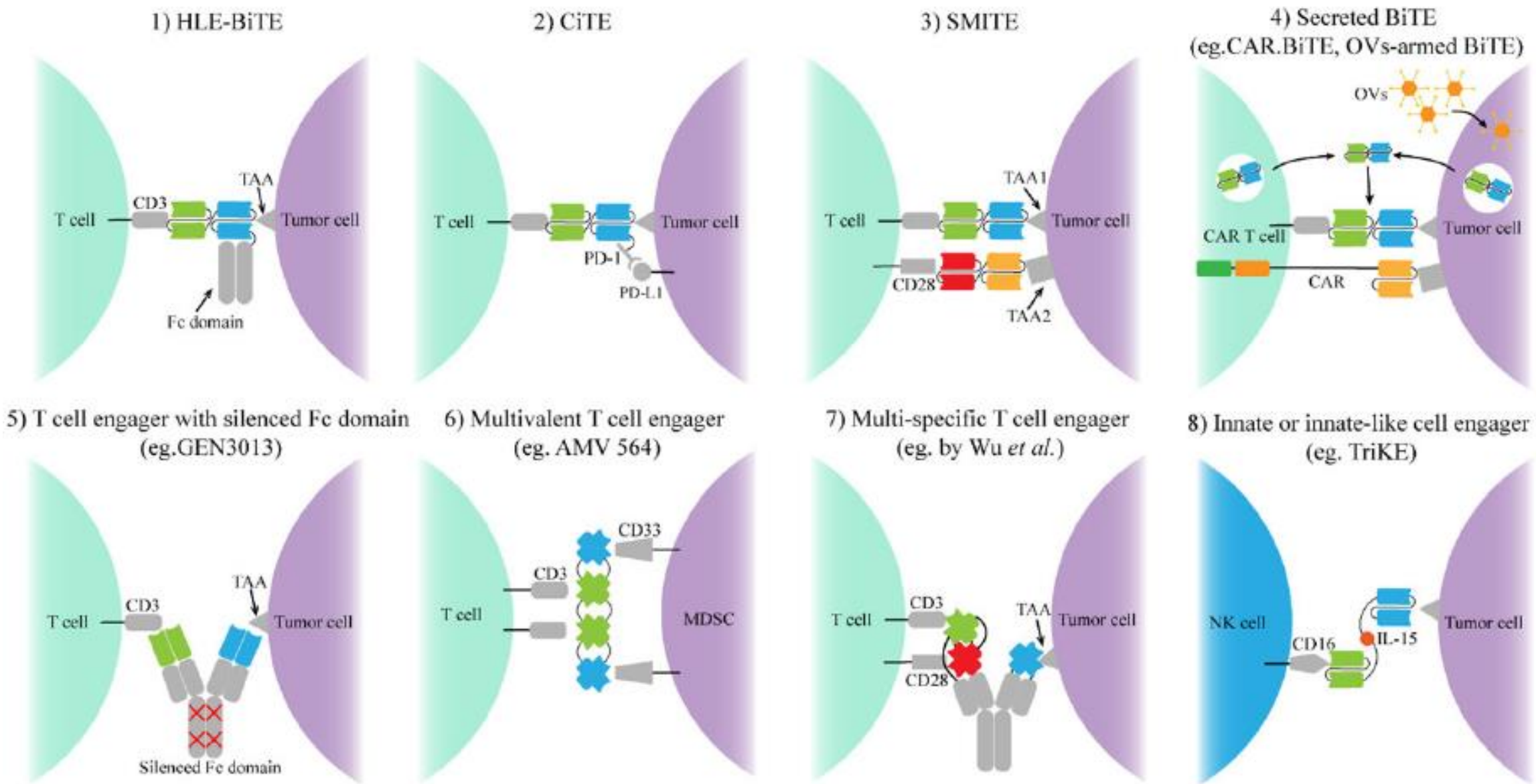
Variable	Tarlatamab, 10 mg (N=100)	Tarlatamab, 100 mg (N=88)
Best overall response — no. (%)		
Objective response		
Confirmed complete response	1 (1)	7 (8)
Confirmed partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable†	2 (2)	4 (5)
Death before postbaseline scan†	6 (6)	13 (15)
No postbaseline scan†	2 (2)	3 (3)
Percentage of patients with objective response (97.5% CI)	40 (29–52)	32 (21–44)
Median duration of objective response (95% CI) — mo		
Overall	NE (5.9–NE)	NE (6.6–NE)
25th percentile	4.4 (2.8–7.1)	5.6 (2.8–7.6)
75th percentile	NE (NE–NE)	NE (NE–NE)
Observed duration of objective response — no./total no. (%)		
≥3 mo	35/40 (88)	25/28 (89)
≥6 mo	23/40 (58)	17/28 (61)
≥9 mo	10/40 (25)	10/28 (36)
Median time to objective response (range) — mo	1.4 (1.1–2.8)	1.4 (1.2–9.6)
Ongoing objective response at data cutoff — no./total no. (%)	22/40 (55)	16/28 (57)
Percentage of patients with disease control (95% CI)	70 (60–79)	63 (52–73)
Median duration of disease control (95% CI) — mo	6.9 (5.4–9.7)	6.7 (4.2–NE)

* The primary end point was objective response (complete or partial response), as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Data from parts 1 and 2 of the trial are reported for the 10-mg group, and data from part 1 are reported for the 100-mg group. Percentages may not total 100 because of rounding. No adjustment for multiplicity was prespecified, so the width of the confidence intervals should not be used in place of hypothesis testing. NE denotes not evaluable.

† In the response analysis, patients who could not be evaluated, who died before the postbaseline scan, or who did not have a postbaseline scan were considered not to have had an objective response.

Mechanisms of Resistance

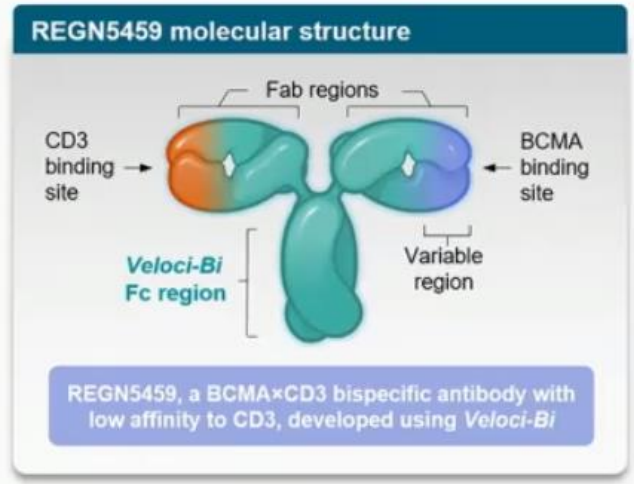
- Immunosuppressive Factors
  - Upregulation of Immune checkpoints, e.g., PD-L1
  - Increase of T regs (CD4/CD25/FOXP3)
  - Myeloid-derived suppressor cells (CD11b/CD13/CD16)
- Loss of Antigen

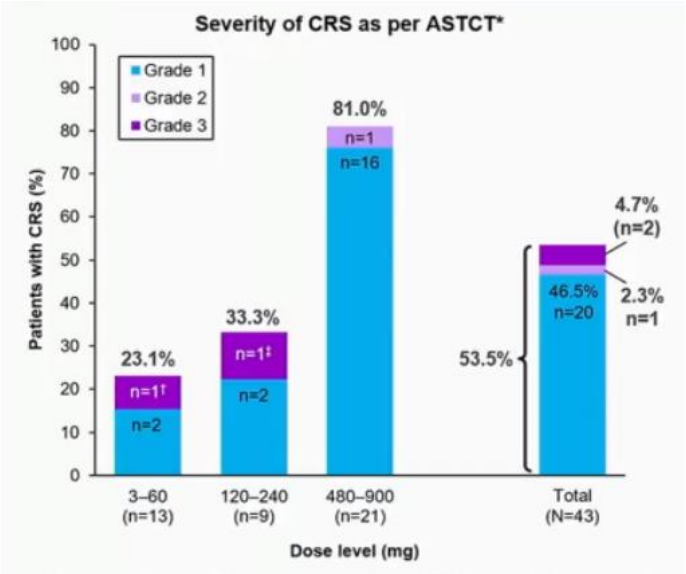


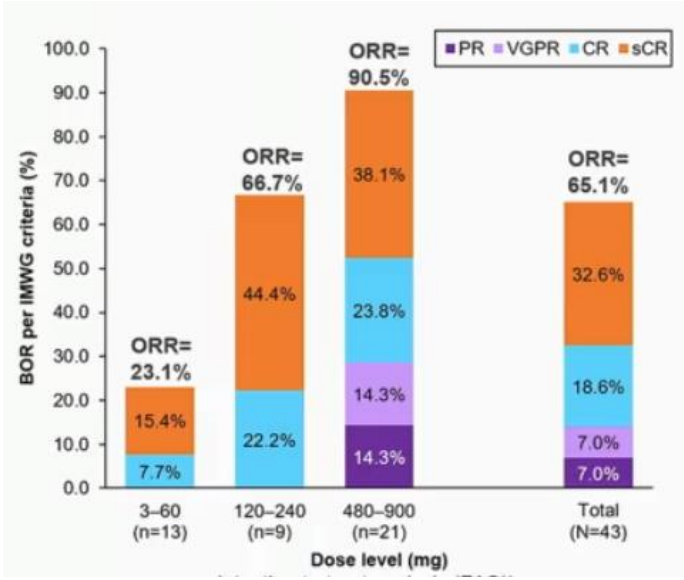
Zhou, S., *et al.* The landscape of bispecific T cell engager in cancer treatment. *Biomark Res* **9**, 38 (2021).

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[9], Karen Rodriguez Lorenc[9], Glenn S. Kroog[8], Hans C. Lee[9]







Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer

N Engl J Med 2023;389:2063-2075 VOL. 389 NO. 22

Table 3. Adverse Events (Safety Analysis Population).*

Adverse Events	Tarlatamab, 10 mg		Tarlatamab, 100 mg
	Parts 1 and 2 (N=99)	Part 3, Reduced Monitoring (N=34)	Part 1 (N=87)
	number of patients (percent)		
Events during treatment period			
According to severity			
Any grade	96 (97)	34 (100)	87 (100)
Grade ≥2	86 (87)	33 (97)	83 (95)
Grade ≥3	57 (58)	22 (65)	56 (64)
Grade ≥4	16 (16)	7 (21)	13 (15)
Fatal	3 (3)	4 (12)	5 (6)
Serious adverse event	58 (59)	14 (41)	62 (71)
Event leading to dose interruption, dose reduction, or both	31 (31)	5 (15)	39 (45)
Event leading to tarlatamab discontinuation	7 (7)	3 (9)	6 (7)
Events of interest during treatment period			
Cytokine-release syndrome†			
Overall	49 (49)	19 (56)	53 (61)
Grade ≥3 severity	0	1 (3)	5 (6)
Serious	26 (26)	5 (15)	32 (37)
Leading to tarlatamab discontinuation	0	0	1 (1)
Fatal	0	0	0
ICANS and associated neurologic events‡			
Overall	7 (7)	4 (12)	24 (28)
Grade ≥3 severity	0	0	4 (5)
Serious	2 (2)	2 (6)	11 (13)
Leading to tarlatamab discontinuation	1 (1)	0	1 (1)
Fatal	0	0	0
Neutropenia			
Overall	18 (18)	5 (15)	14 (16)
Grade ≥3 severity	6 (6)	2 (6)	9 (10)
Serious	2 (2)	0	3 (3)
Leading to tarlatamab discontinuation	0	0	0
Fatal	0	0	0
Events related to treatment			
According to severity			
Any grade	89 (90)	29 (85)	81 (93)
Grade ≥2	69 (70)	23 (68)	66 (76)
Grade ≥3	29 (29)	5 (15)	29 (33)
Grade ≥4	5 (5)	2 (6)	3 (3)
Fatal	0	1 (3)	0
Serious	37 (37)	7 (21)	46 (53)
Event leading to dose interruption, dose reduction, or both	14 (14)	3 (9)	25 (29)
Event leading to tarlatamab discontinuation	4 (4)	0	3 (3)

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)

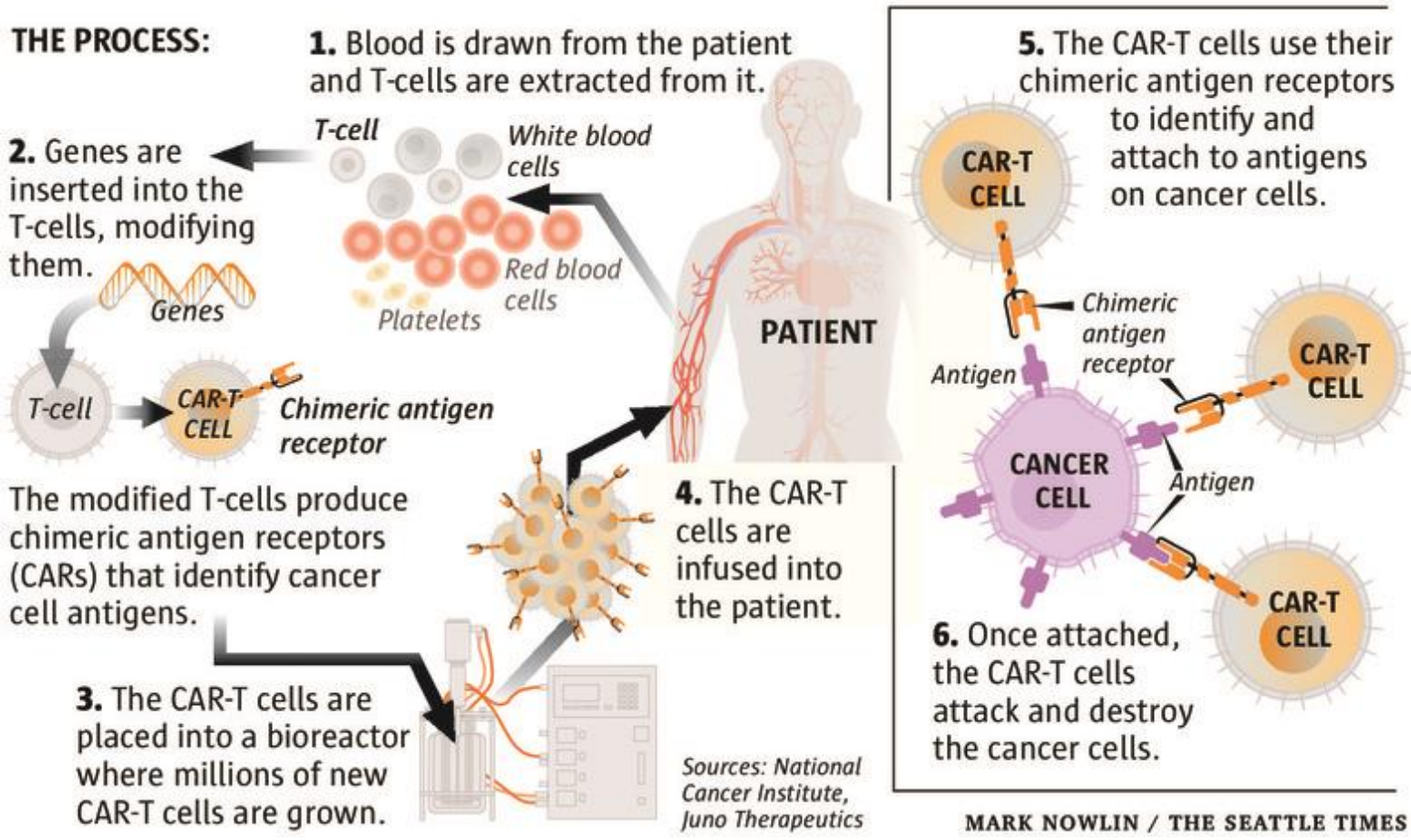
Table B3. ASTCT immune effector cell-associated neurotoxicity syndrome (ICANS) consensus grading system for adults (14)

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

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.

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.

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

OPTIMIZED MANUFACTURING PROCESS

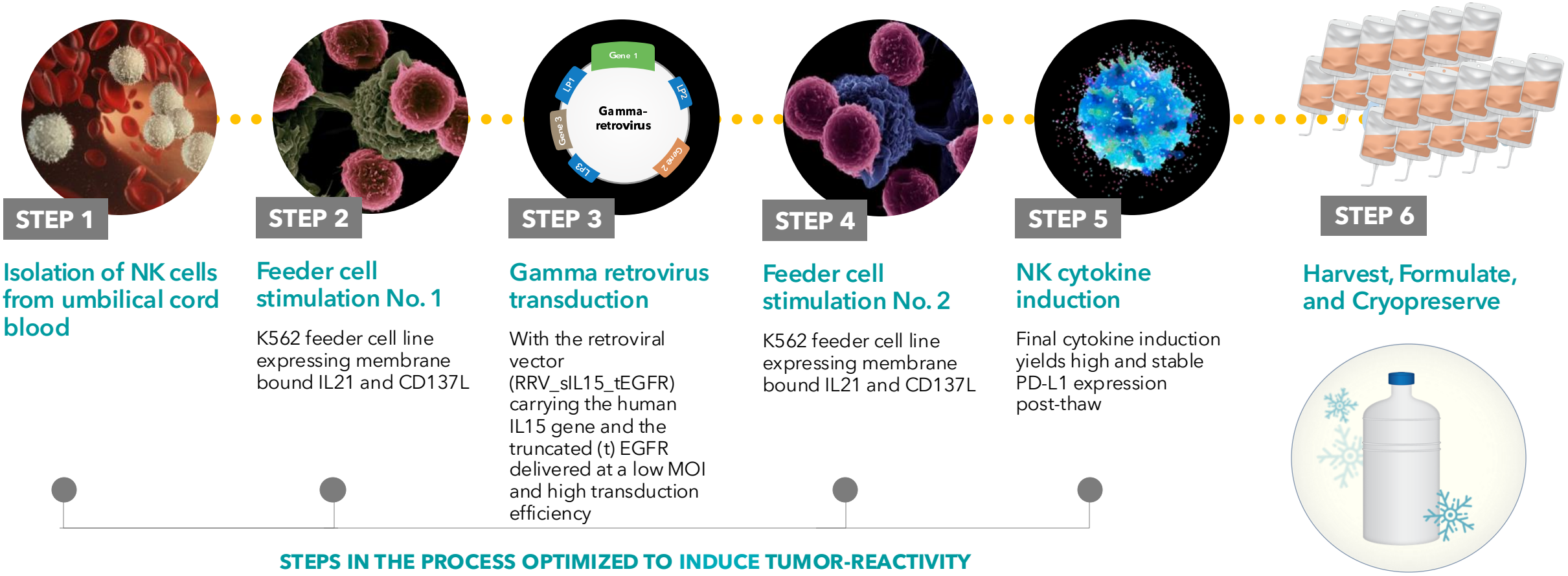


Figure 2. Schematic summarizing the process of sIL15_TRACK NK cell manufacturing and cryopreservation processes.

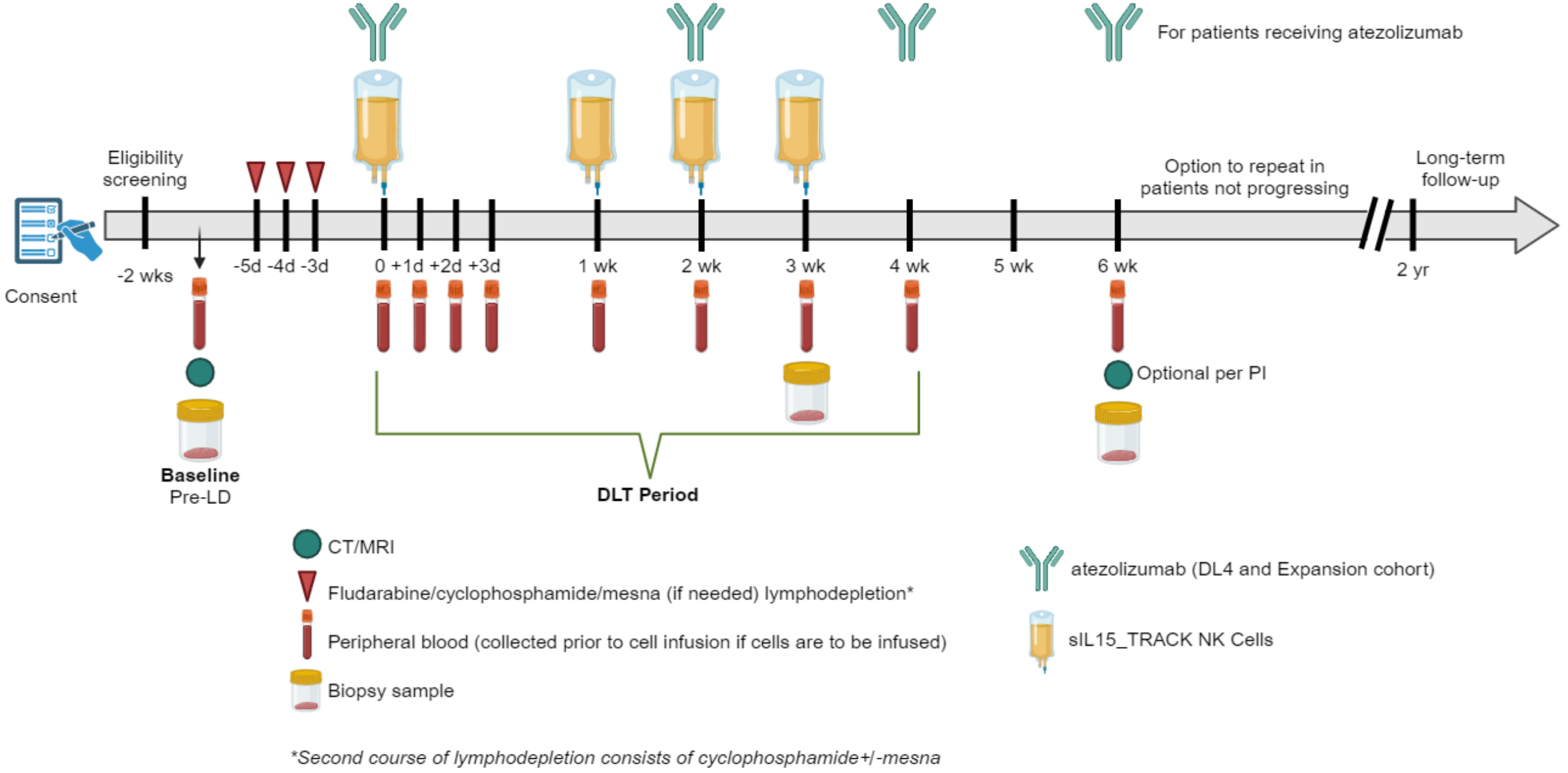


Figure 1. Protocol schema for first-in-human phase 1 trial of sIL15_TRACK NK cells in NSCLC (NCT05334329).

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/ kgǂ	Atezolizumab Dose
-2	4.0×10^5	---
-1	7.0×10^5	---
1 (starting dose)	1.50×10^6	---
2	4.0×10^6	---
2a (intermediate dose)	7.5×10^6	
3*	1.2×10^7	---
4	1.2×10^7**	840 mg IV
5	2.0×10^7	840 mg IV

* If unacceptable toxicity (>1/3 or >1/6 DLTs) is observed at dose level 3, an intermediate dose level (2a) may be explored. If this dose is deemed safe, will be considered for combination treatment.
** 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.
ǂ Transduced cells are tEGFR+ cells as determined by flow cytometry.

Patient characteristics	***n* (%)**
Total enrolled patients, No.	6 (100%)
Age, y, median (range)	63.5 (45, 80)
Gender	
Female	3 (50%)
Male	3 (50%)
Race/ethnicity	
Non-Hispanic White	2 (33%)
Asian	2 (33%)
Hispanic/Latino	2 (33%)
No. of prior regimens, median (range)	3 (1, 7)
Histology	
Adenocarcinoma	5 (83%)
Squamous	1 (17%)
Site of Metastasis	
Contralateral Lung	4 (67%)
Lymph Nodes	2 (33%)
Pleura	3 (50%)
Liver	1 (17%)
Bone	1 (17%)
Trachea	1 (17%)
Relevant Tumor Genomics	
Kras	
G12D	2 (33%)
G12A	1 (17%)
G12V	1 (17%)
PDL1	
0%	2 (33%)
<1%	2 (33%)
5%	1 (17%)
90%	1 (17%)
TMB	
Low	2 (33%)
6.3 m/MB	1 (17%)
Intermediate	1 (17%)
Not evaluable	2 (33%)
MSI	
Stable	6 (100%)
Prior Immunotherapy	
Ipilimumab/Nivolumab	1 (17%)
Pembrolizumab	4 (67%)
Atezolizumab	1 (17%)
Tiragolumab	1 (17%)

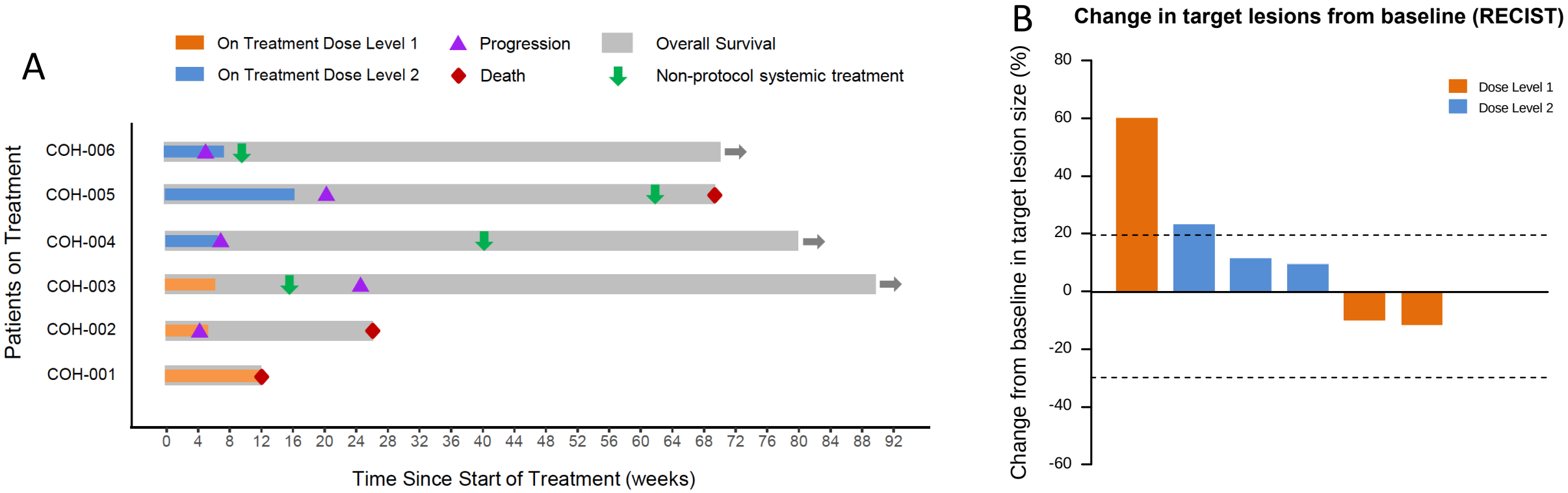


Figure 3. (A) Swimmer plot for all 6 patients. Two of the patients (003, and 005) exhibited stable disease prior to progression, while Patient 001 died unexpectedly of a cardiac event with a diagnosis of COVID while on cycle 2 without progression. Three patients (002, 004, 006) exhibited no stabilization of disease. The swimmer plot also shows systemic palliative treatment following treatment with sIL15_TRACK NK cells. Three patients remain alive 70, 80, and 90 weeks. (B) Waterfall plot for all 6 patients showing change in target lesions based on RECIST. The tumor volume of the target lesions in patient 001 following one cycle of therapy with sIL15_TRACK NK cells was reduced by ~12**% (Suppl Figure 3).**

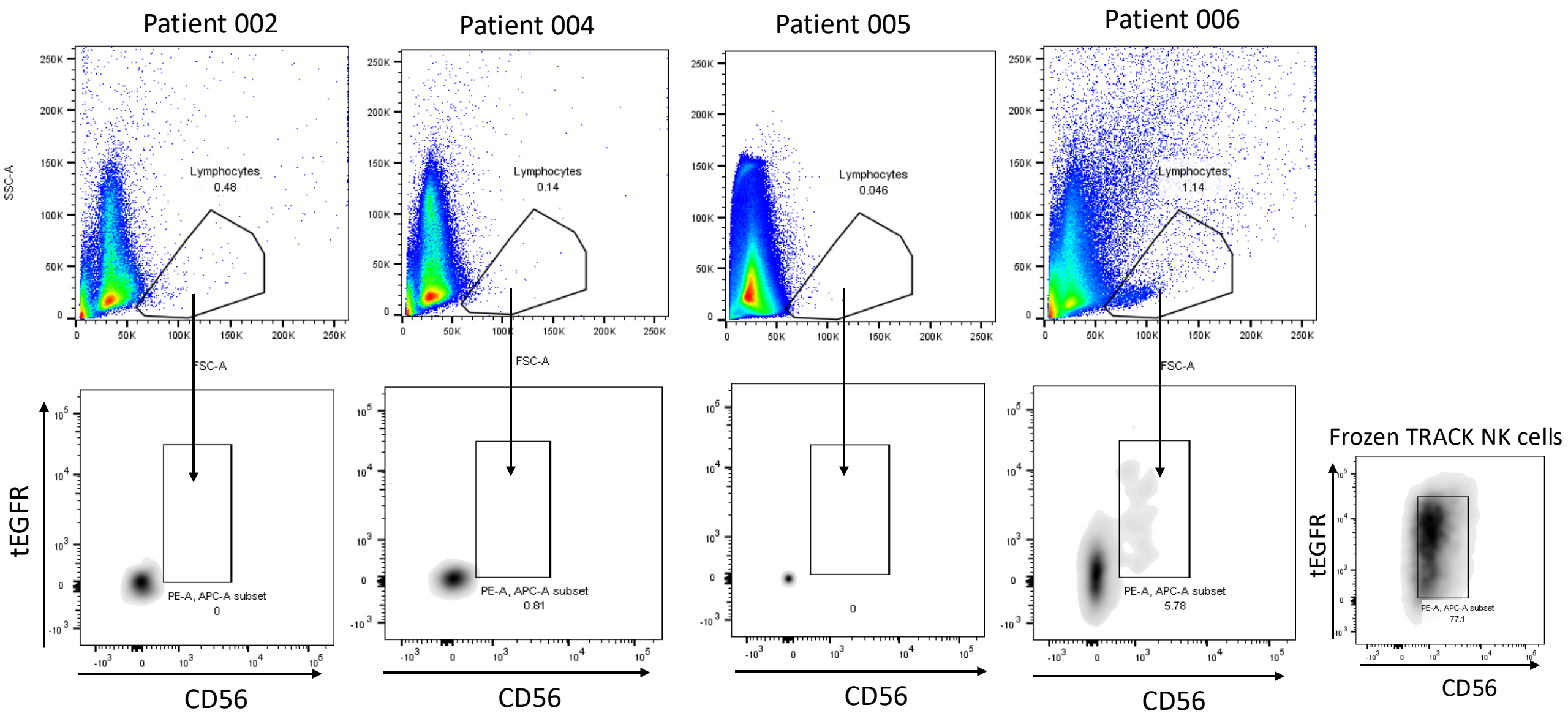


Figure 5. Patient lung biopsies were collected after the 4th infusion of sIL15_TRACK NK cells and digested to single cell suspension using collagenase I and DNase I. Cells were stained for tEGFR and CD56 antibodies and assessed by flow cytometry to identify the presence of dual positive (sIL15_TRACK NK) cells within the lymphocyte gate. In the far right, frozen and thawed sIL15_TRACK NK cells were stained as positive control. It is notable that very few total cells were collected in biopsies from patients 002, 004, and 005 shown here, with a relative abundance from patient 006.

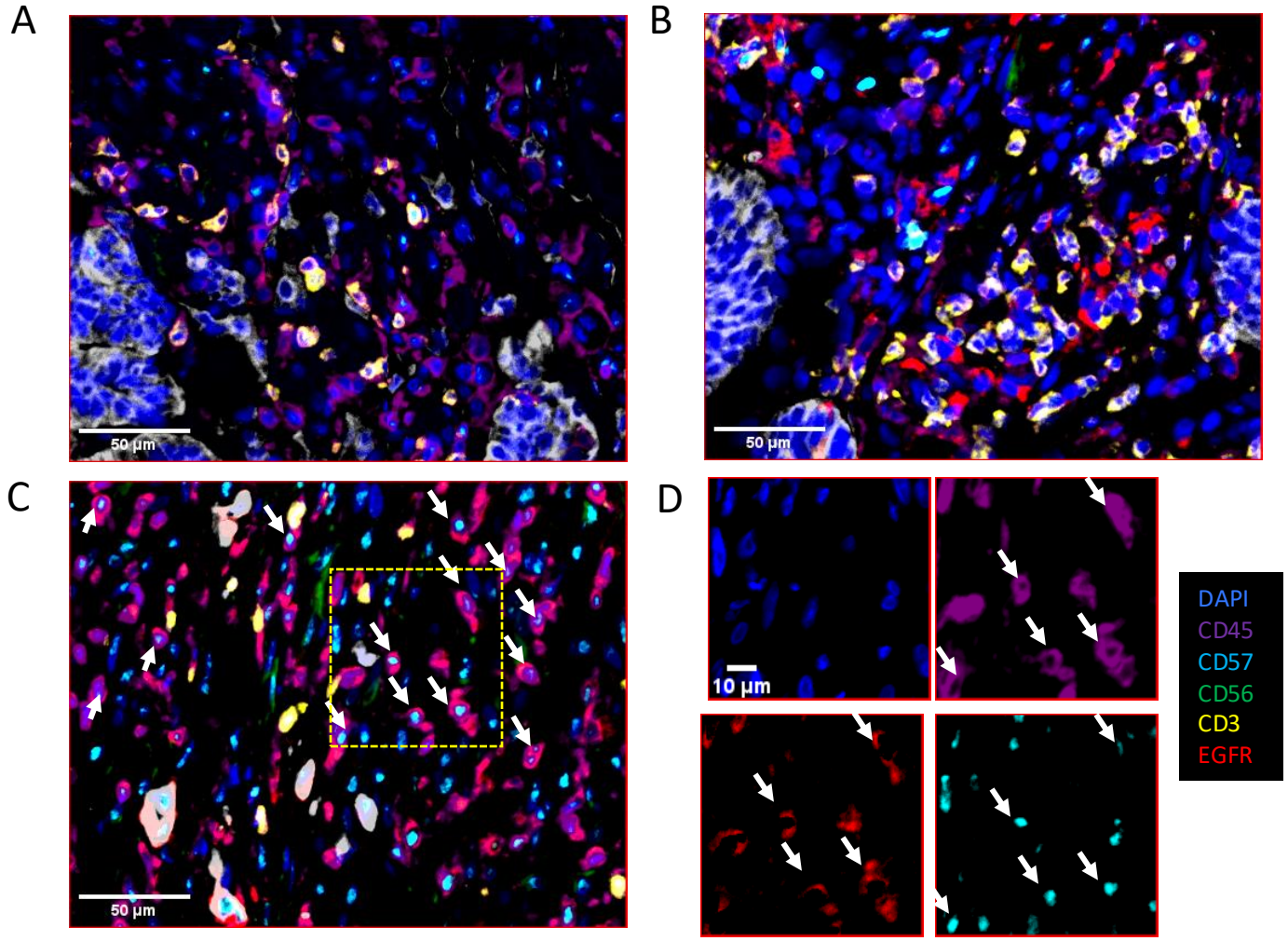
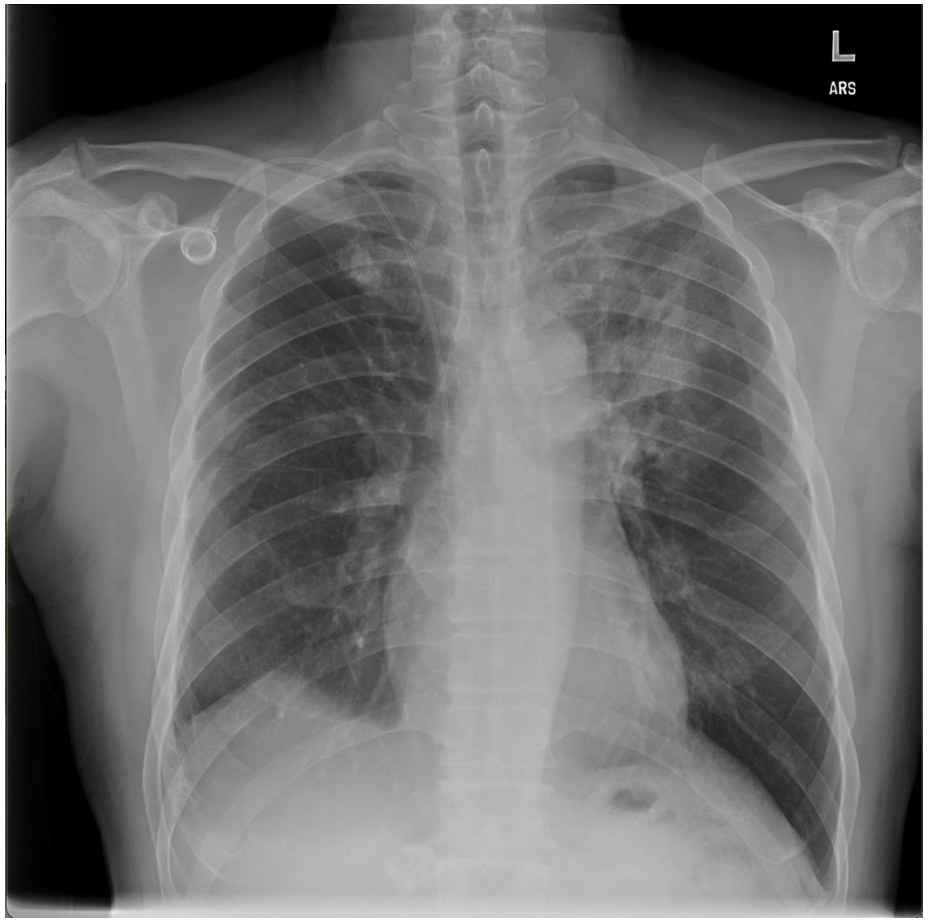
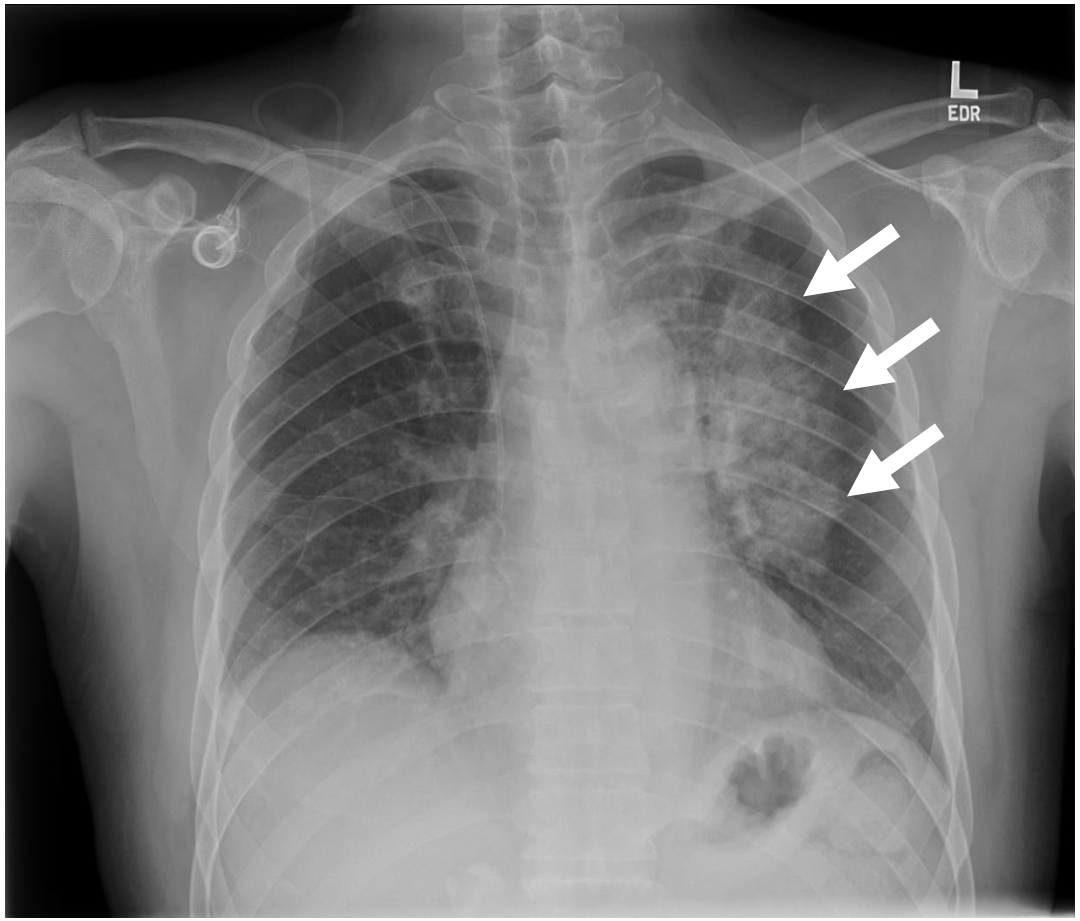


Figure 6. sIL15_TRACK NK cells in patient 006 lung tumor tissues. FFPE tissues from tumor biopsies were collected from pre-treatment (A), 24 hours post-Cycle 4 (B), and 7 days post-treatment (C). stained by multiplex immunofluorescence for DAPI (blue), CD45 (purple), CD57 (cyan), CD56 (green), CD3 (yellow), and tEGFR (red). sIL15_TRACK NK cells were identified in DAPI+CD45+ cells by co-expression of tEGFR (red) with CD57 (cyan) or CD56 (green). Transduced NK cells were observed most notably in the post-treatment sample (C) as marked by white arrows and obtained seven days following completion of Cycle 4. Quadrant D represents selected staining from region shown in the insert from quadrant C. CD56 staining was less prominent than CD57 on tissue infiltrating tEGFR NK cells. Scale bars are as shown.

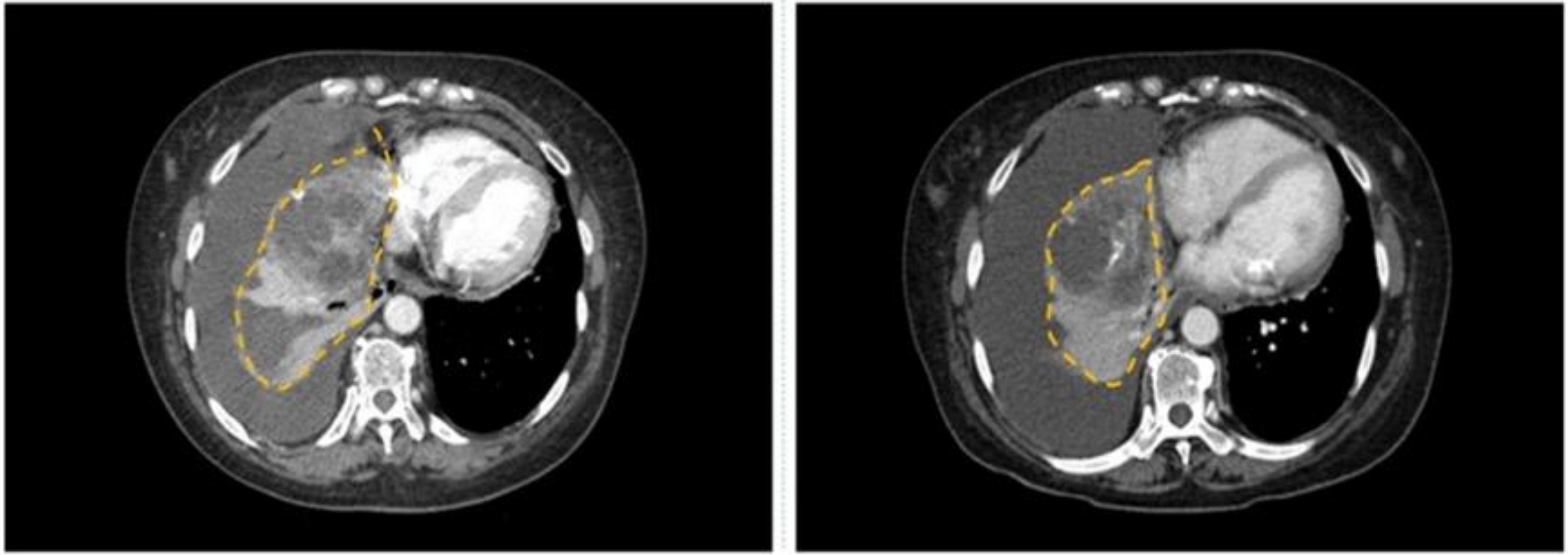




Supplementary Figure 2. The chest X-Ray on the left shows a baseline film of patient 005 before starting cycle 2 of sIL15_TRACK NK cell infusions at a dose of 4.0 x 10^6 transduced cells/kg. The patient became acutely short of breath following the third weekly infusion of cycle 2 and a chest X-Ray was again obtained demonstrating a new infiltrate (white arrows) that subsequently cleared spontaneously without the onset of fever or additional intervention.

Patient 001 Pre-treatment baseline CT Scan

Patient 001 CT scan tumor measurement at week 6



Supplementary Figure 3. The CT scan on the left shows a baseline tumor measurement of patient 001 immediately prior to starting cycle 1 of sIL15_TRACK NK cell infusions at a dose of 1.5 x 10^6 transduced cells/kg. The yellow dashed line indicates the size of the target lesion. The CT scan on the right shows an approximately 12% reduction in tumor volume when measured 6 weeks after the start of cycle 1 and 2 weeks after completion of cycle 1. Patient 001 died unexpectedly of a cardiac event with a diagnosis of COVID while on cycle 2 of sIL15_TRACK NK cells without evidence of progression.

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.