

Innovations in immunotherapy and CAR-T cells

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COI/Disclosures

Research support

Abbvie, Merck, and Roche/Genentech

Scientific advisor

Abbvie, Actym, Arsenal, Astra Zeneca, Bioatla, Bristol Myer Squibb, Daiichi Sankyo, Dendreon, Immunogenesis, Innovent, Juri, Merck, Sutro, Roche/Genentech, and Xilio

Equity

Actym, Bioatla, Immunogenesis, Juri, Sutro, Therapaint

FDA-approved and non-approved investigational therapies will be discussed.

Bezos Family Immunotherapy Clinic

Opened in 2016 dedicated to experimental cellular immunotherapy.

15 patient care suites built for intensive patient monitoring and treatment administration.

>1000 patients treated with CAR T cells

Liso-cel developed at Fred Hutch

	Current	Pending	Total
Heme Malignancies	19	16	35
Solid Tumor	19	23	42
Autoimmune	2	7	9
	40	46	86



Immunotherapeutic approaches

Enhancing endogenous immunity



Blocking inhibitors
Stimulating effectors

- Vaccines
- Immune checkpoints
- TIL
- Cytokines



Redirecting immune effectors



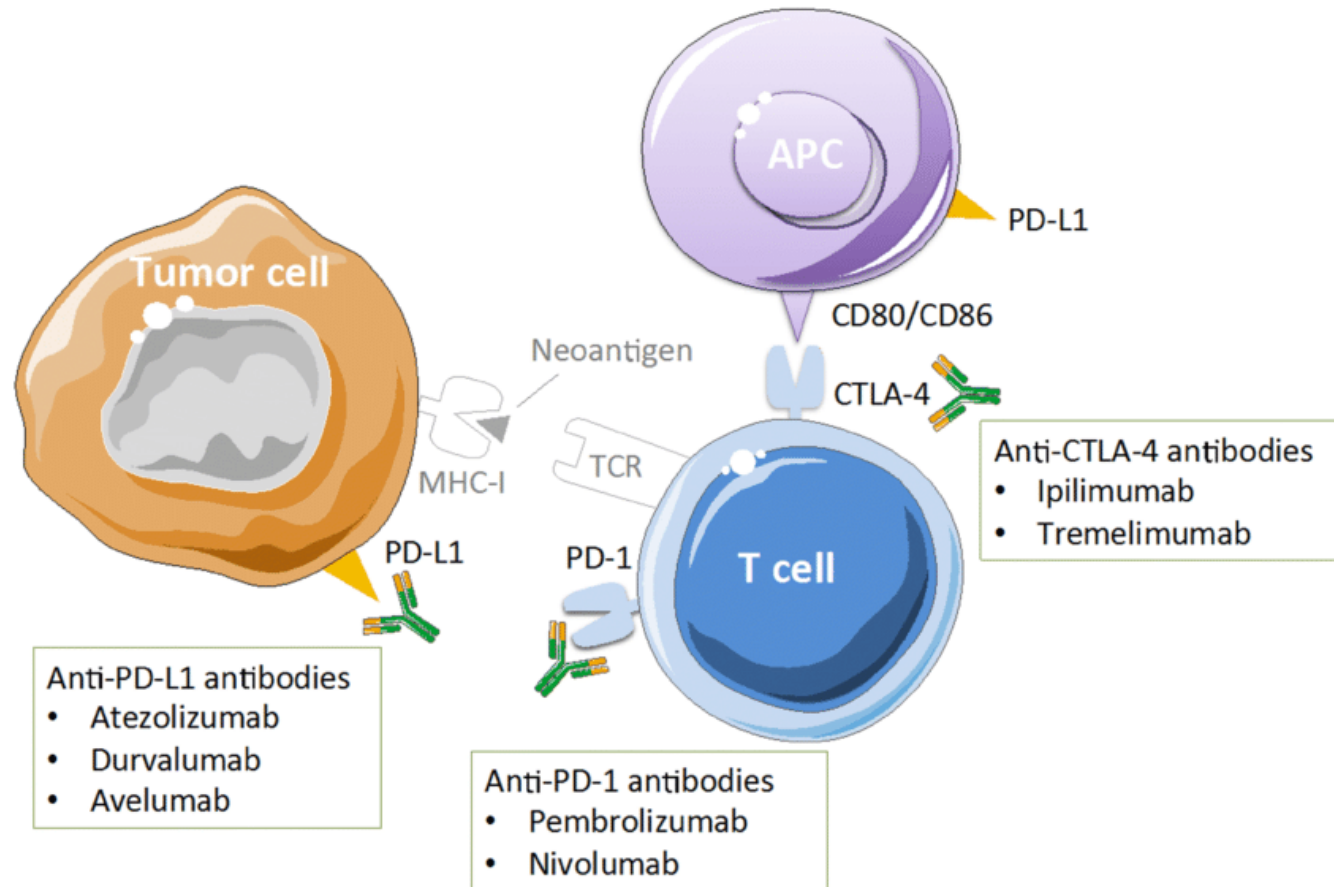
Engineering cellular specificities
Colocalizing effectors to tumors

- T cell engagers
- CAR-T cells
- TCR-T cells

Outline

- Immune checkpoint inhibitors
- Cancer vaccines
- T cell engagers/bispecifics
- CAR-T cells

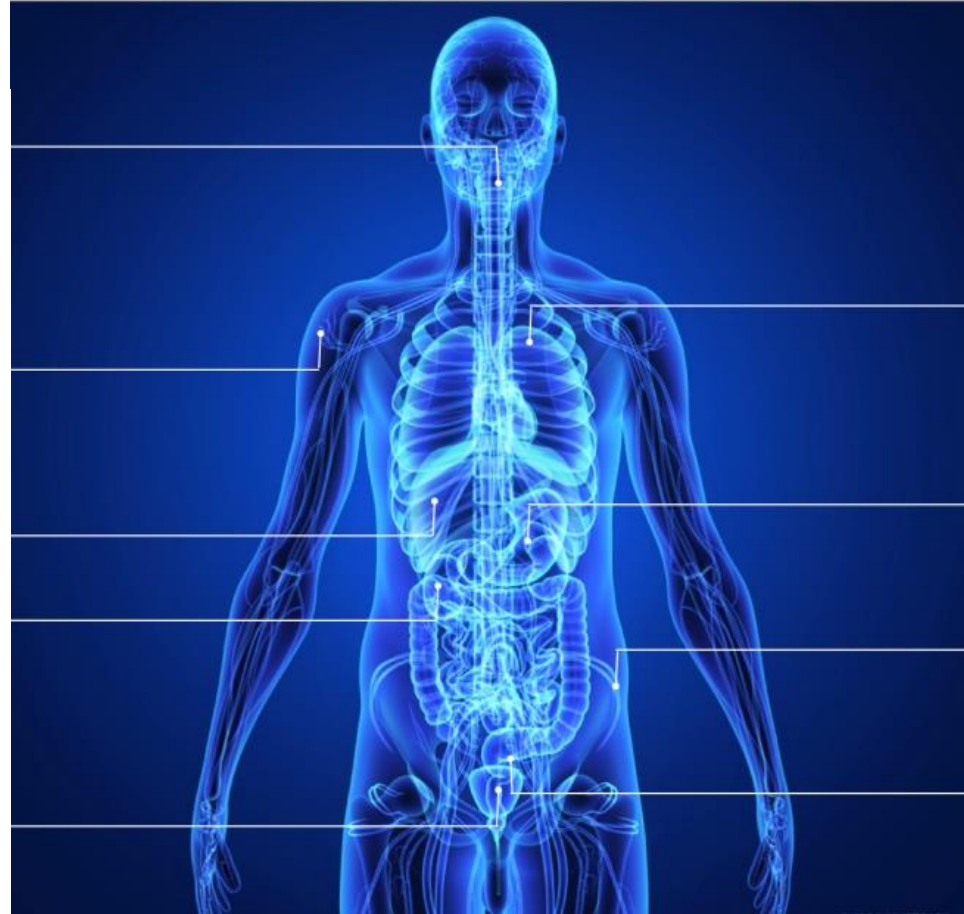
Immune checkpoint inhibitors



PD-1 blockade has transformed oncology

Head & Neck Squamous
Melanoma
Merkel Cell
Squamous
Basal
Hepatocellular
Kidney

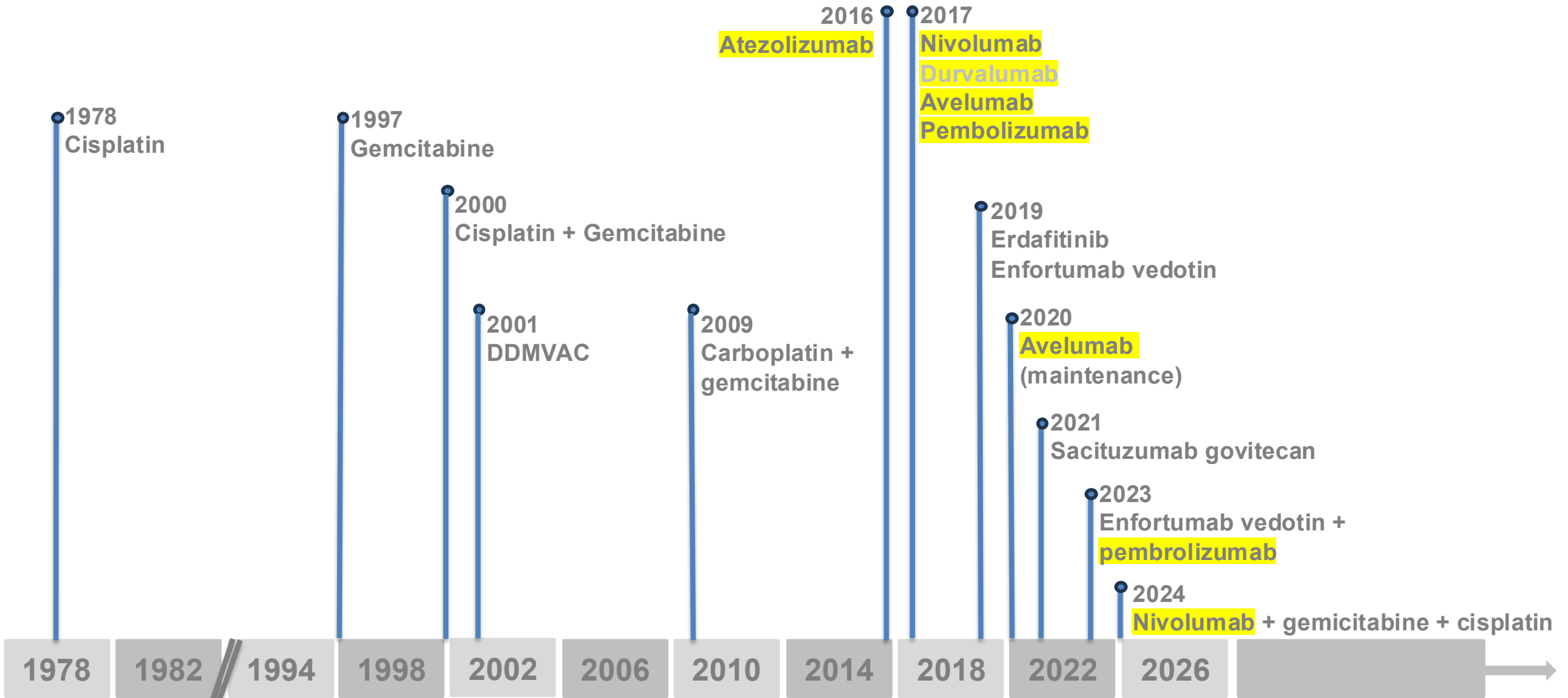
Urothelial
Cervical



Non-small cell
Small cell
TNBC
Gastric
Esophageal
Hodgkins

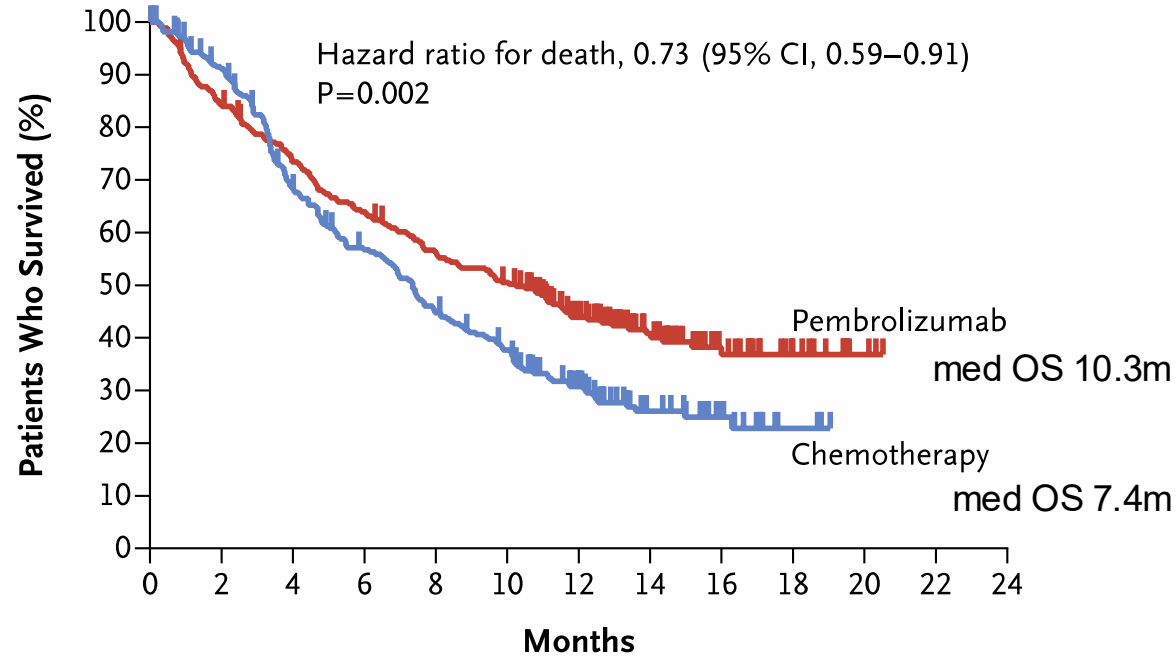
MSI-hi/DNA mismatch
repair defective

Treatments for metastatic urothelial cancer



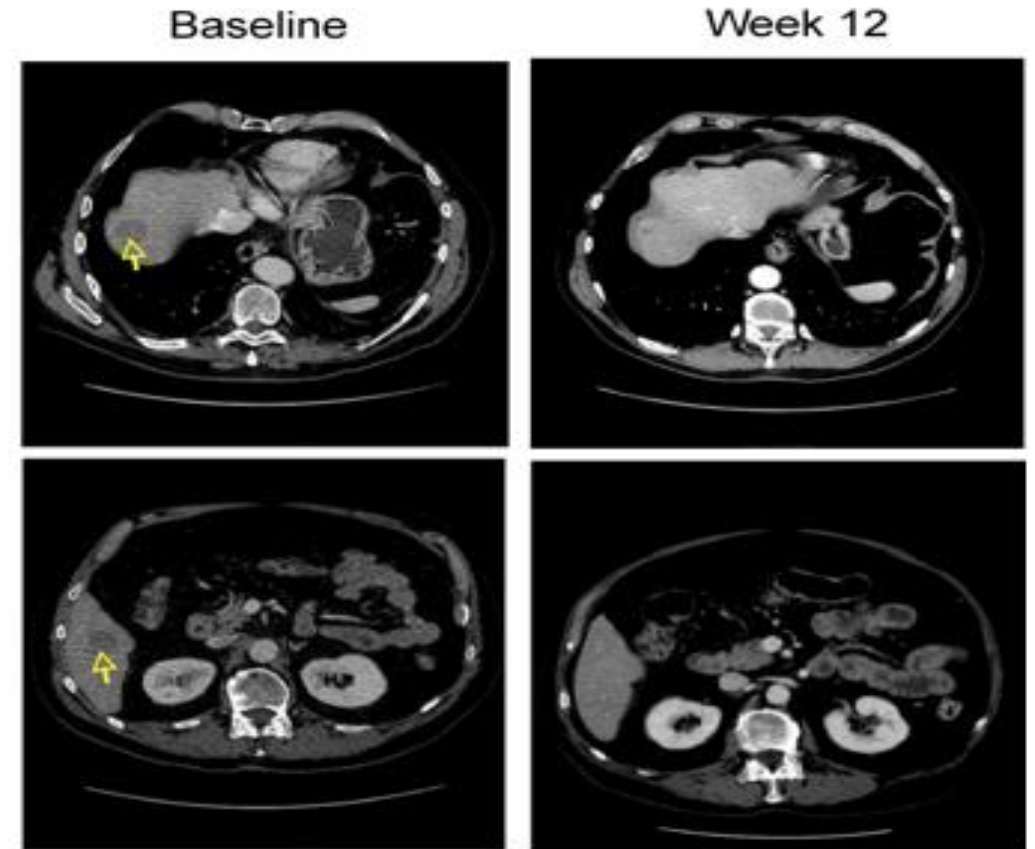
Anti-PD-1 in urothelial cancer patients

A Overall Survival



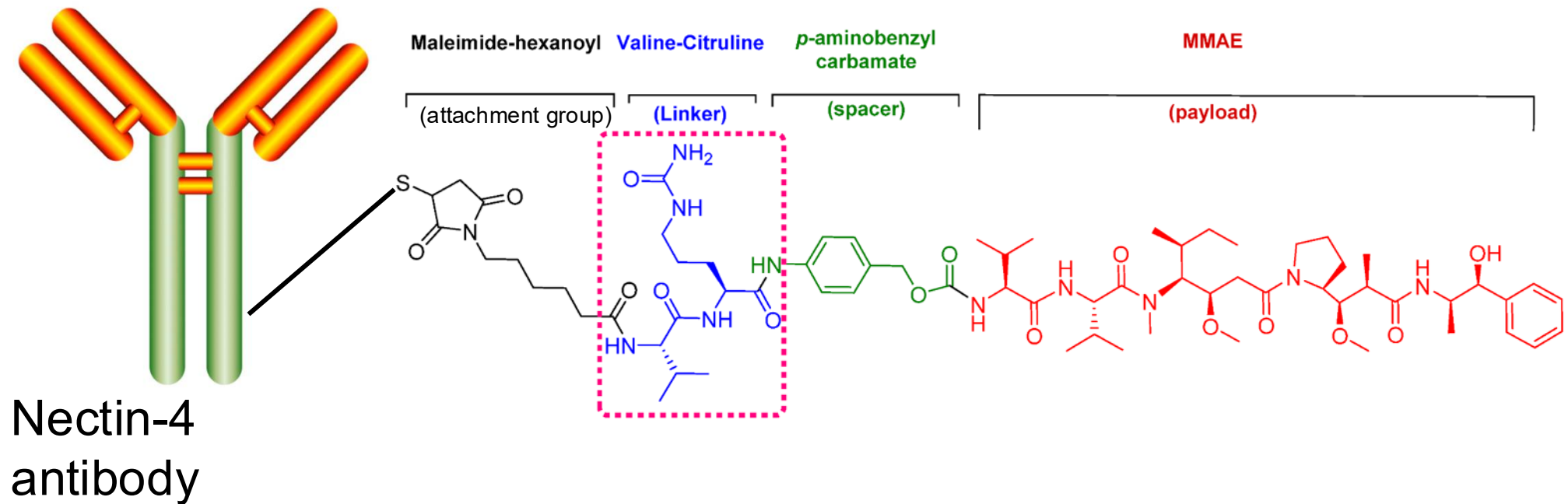
No. at Risk

Pembrolizumab	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemotherapy	272	232	171	138	109	89	55	27	14	3	0	0	0



Enfortumab Vedotin

Antibody-Drug Conjugate Targeting Nectin-4
Monomethylauristatin E (MMAE) “payload”



Enfortumab vedotin + pembrolizumab for metastatic urothelial cancer

Patient population

- Previously untreated la/mUC
- Eligible for platinum, EV, and P
- PD-(L)1 inhibitor naive
- GFR ≥ 30 to <60 mL/min^a
- ECOG PS ≤ 2 ^b

N=886

R
1:1

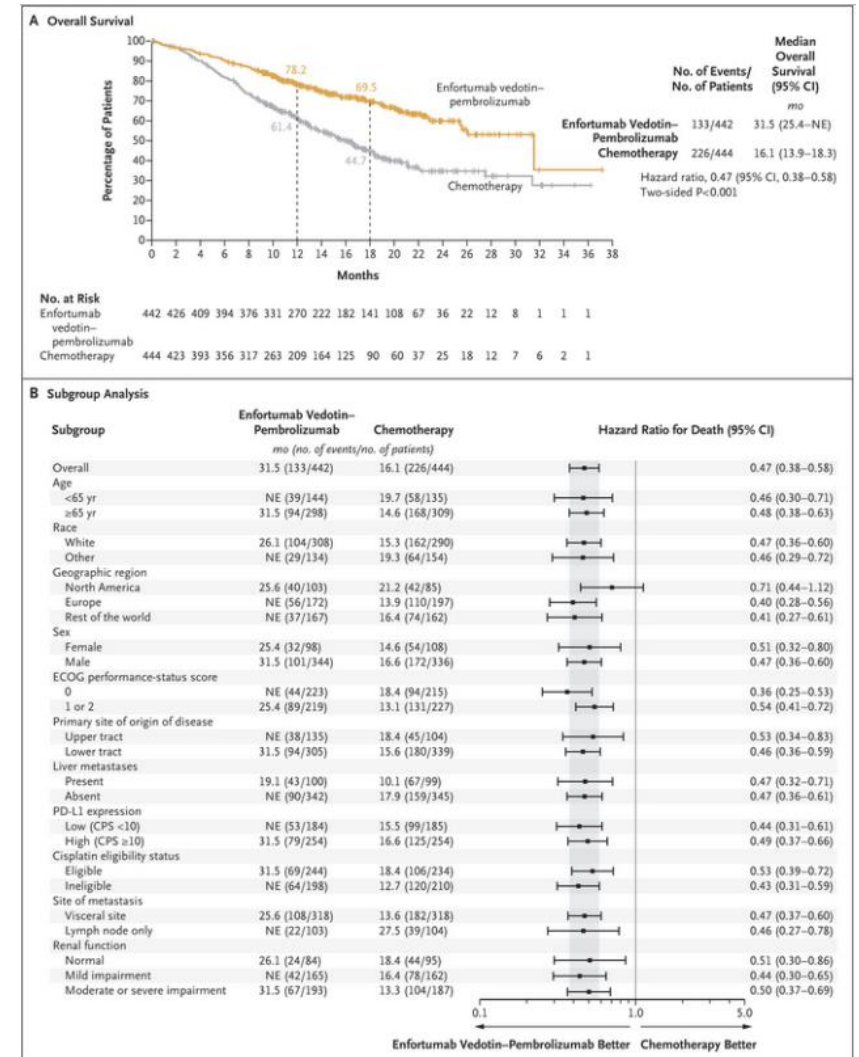
EV + Pembrolizumab

No maximum treatment cycles for EV,
maximum 35 cycles for P

Treatment until disease progression per
BICR, clinical progression, unacceptable
toxicity, or completion of maximum cycles

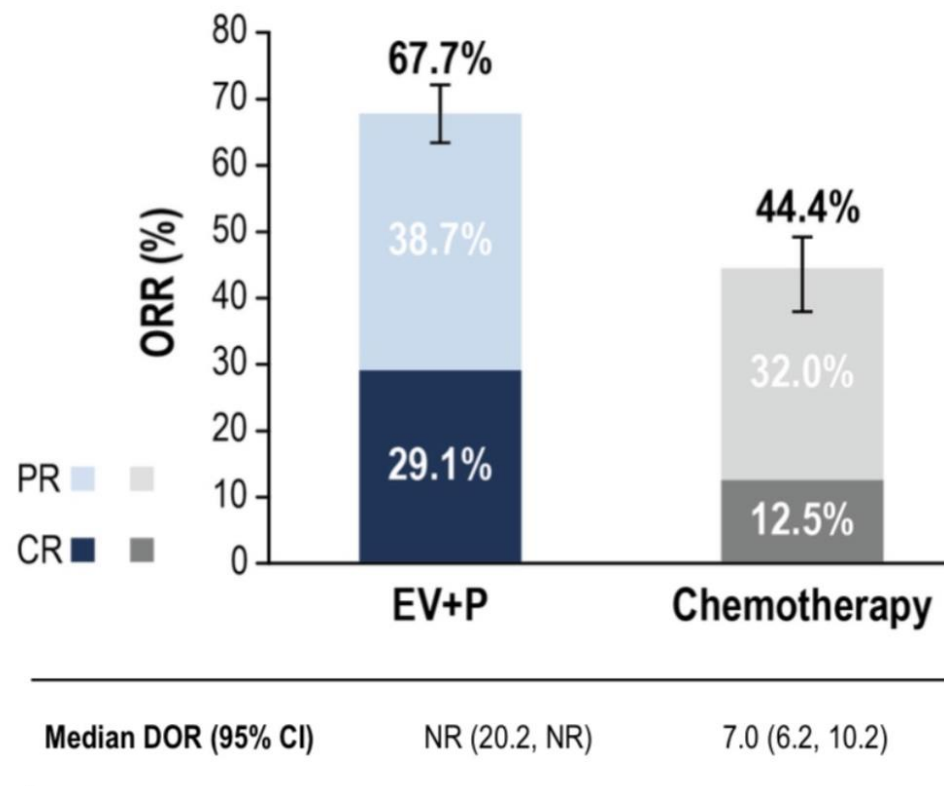
Chemotherapy^c

(Cisplatin or carboplatin + gemcitabine)
Maximum 6 cycles



(Powels T et al. *NEJM* 2024)

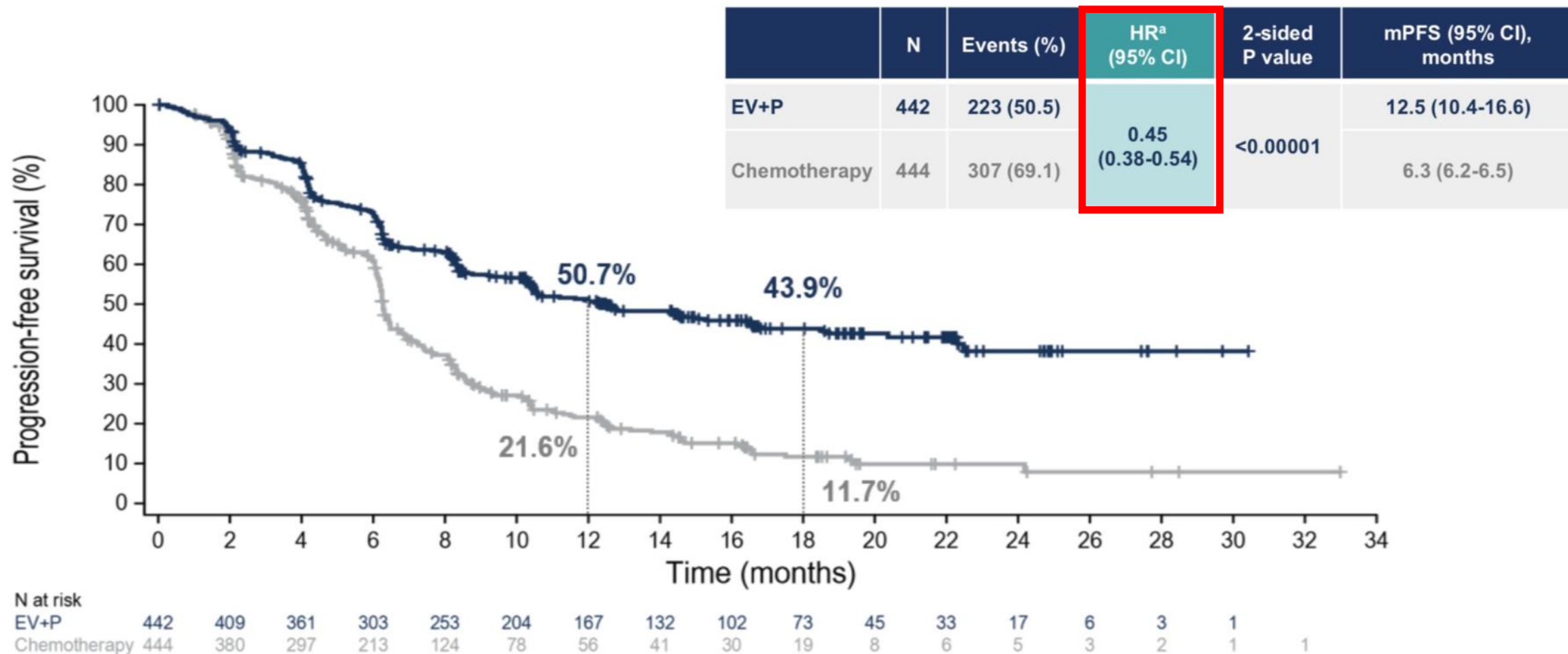
Enfortumab vedotin + pembrolizumab for metastatic urothelial cancer



	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	296 (67.7) (63.1-72.1)	196 (44.4) (39.7-49.2)
2-sided P value	<0.00001	
Best overall response^a, n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment ^b	21 (4.8)	36 (8.2)

Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P



BICR, blinded independent central review; CI, confidence interval; EV+P, enfortumab vedotin + pembrolizumab; HR, hazard ratio; mPFS, median progression-free survival.

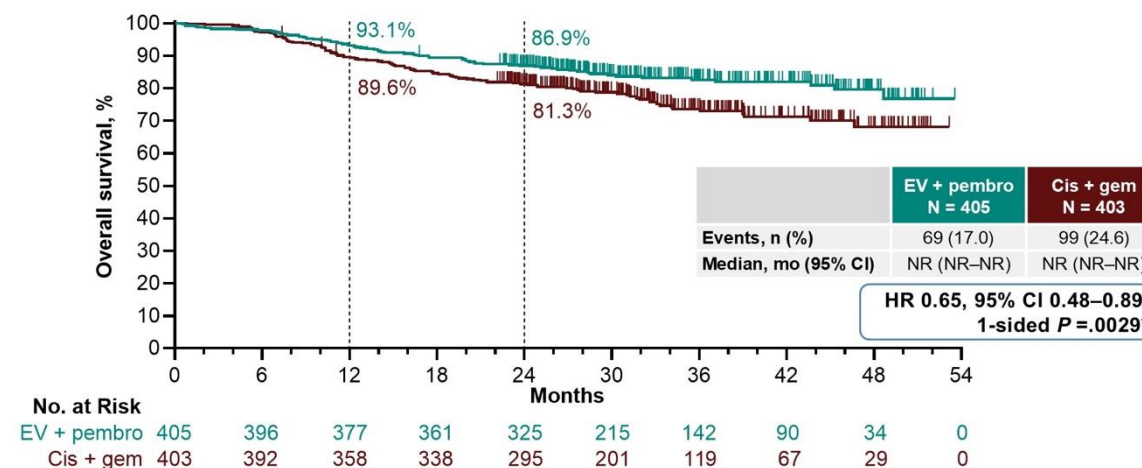
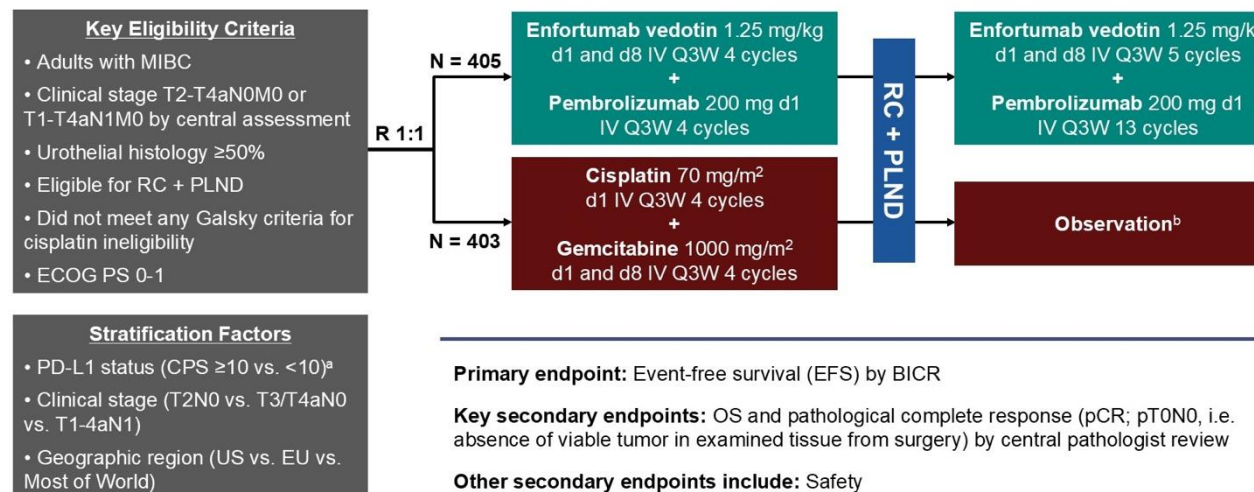
mPFS at 12 and 18 months as estimated using Kaplan-Meier method.

^aCalculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm.

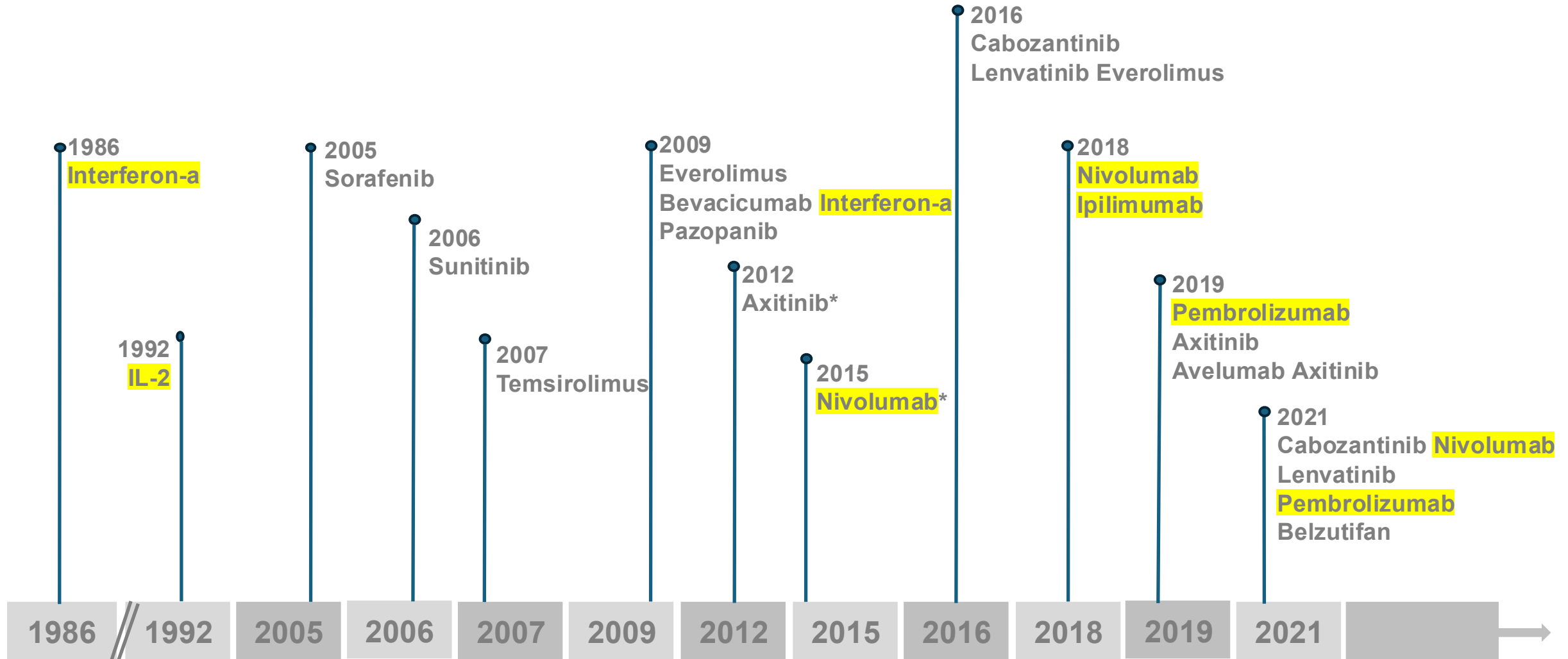
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

Data cutoff: 08 Aug 2023

Front-line EV-P in urothelial cancer



Treatments for metastatic renal cell cancer

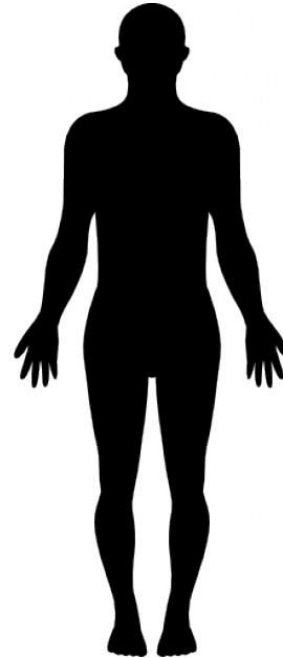


Non-small cell lung cancer treatments

Current

PD-(L)1 immune checkpoint inhibitor +/- chemotherapy

PD-1 + CTLA-4 immune checkpoint inhibitors



Emerging

Personalized cancer vaccines: mRNA (V940), peptide (PNV-21)

PD-1 x VEGF bispecific (Ivonescimab)

Novel PD-1 x IL-2 bispecifics (XT501, IBI363)

T cell engagers: masked EGFR x CD3 (VIR-5525),
ULBP2/5/6 x CD3 x CD2 (EVOLVE104)

Tumor infiltrating lymphocyte therapy (LN-145)

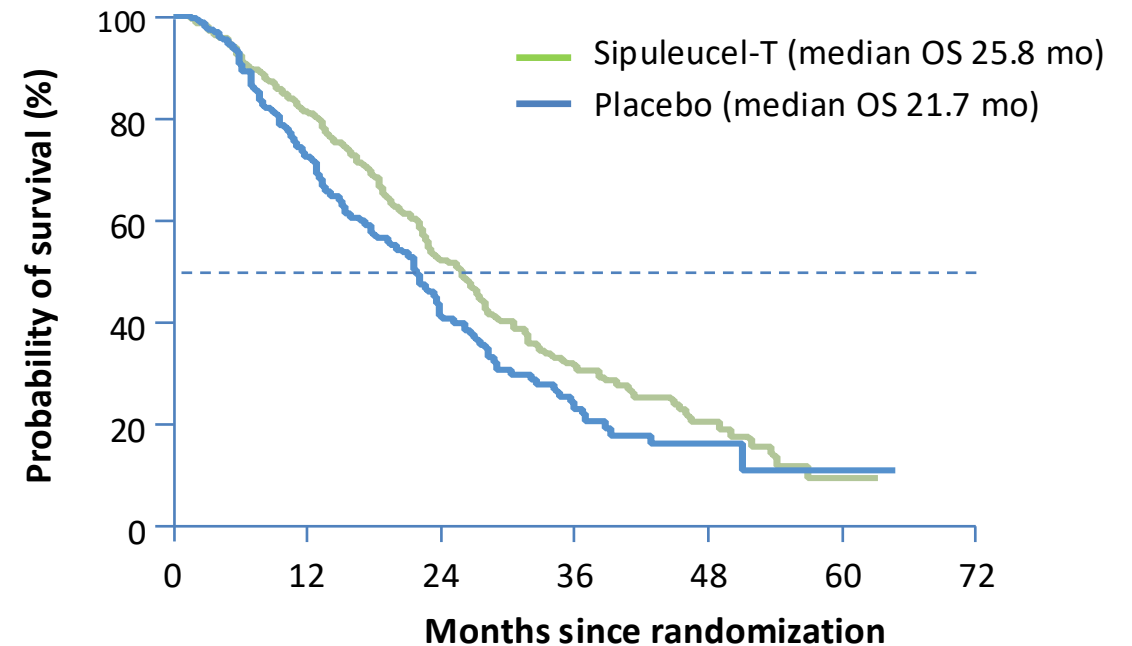
Engineered T cell therapy trials

Outline

- Immune checkpoint inhibitors
- Cancer vaccines
- T cell engagers/bispecifics
- CAR-T cells

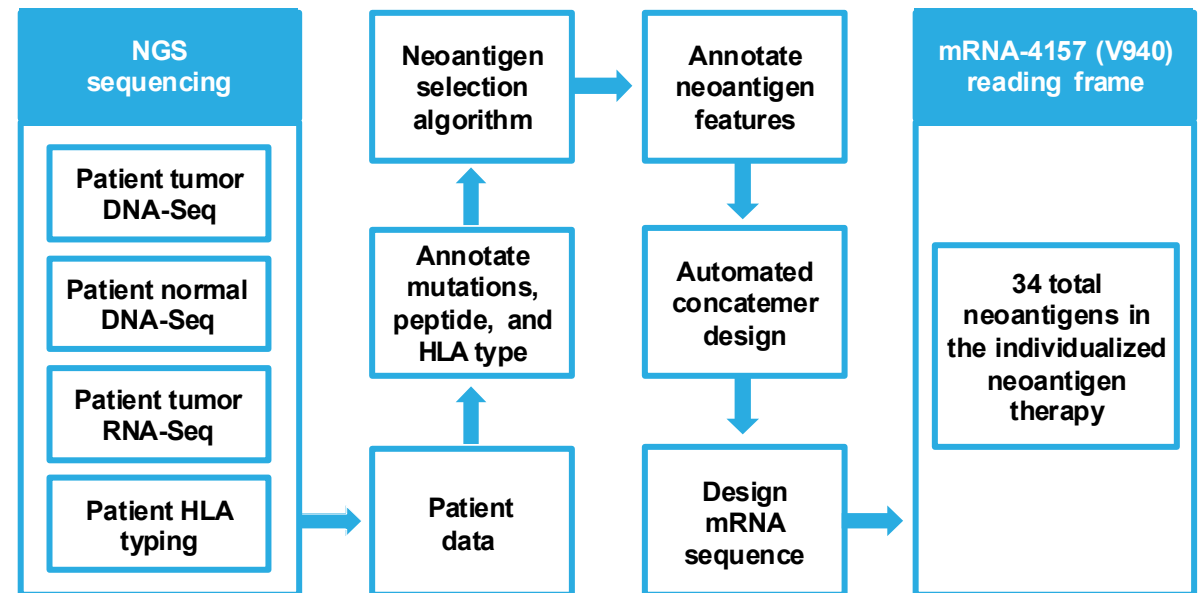
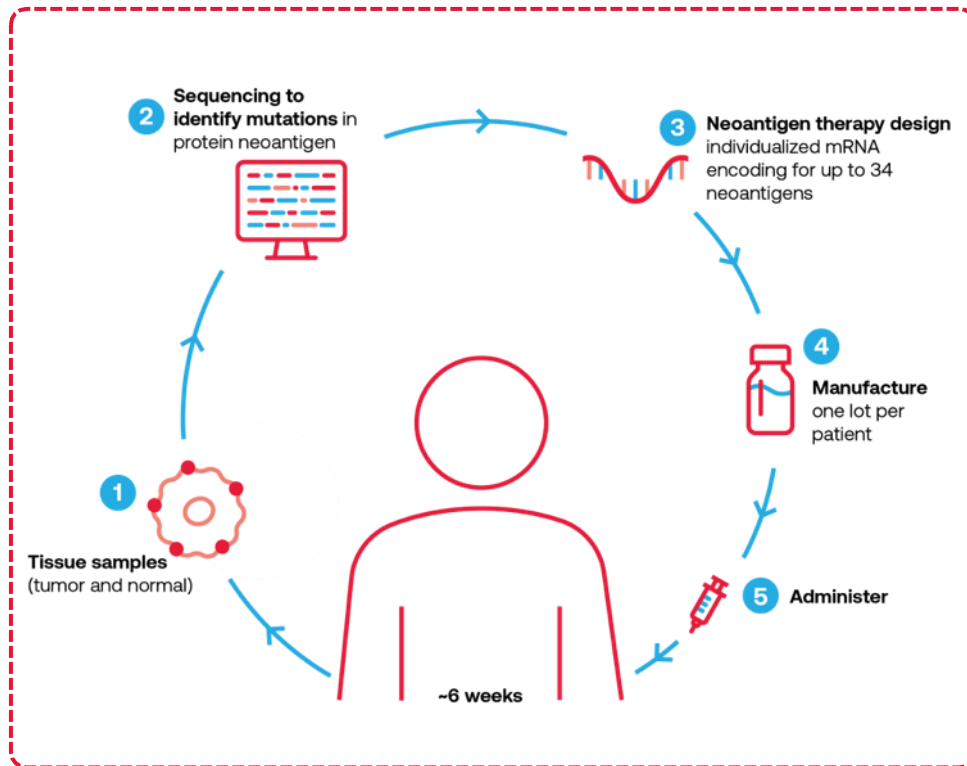
Sipuleucel-T: an FDA-approved prostate cancer immunotherapy

- Autologous cellular immunotherapy that works as a vaccine
- Targets prostatic acid phosphatase (PAP)
- Induces T and B cell responses that correlate with outcomes
- Improved OS without PFS or PSA responses
- Longer OS in patients with lower baseline PSAs

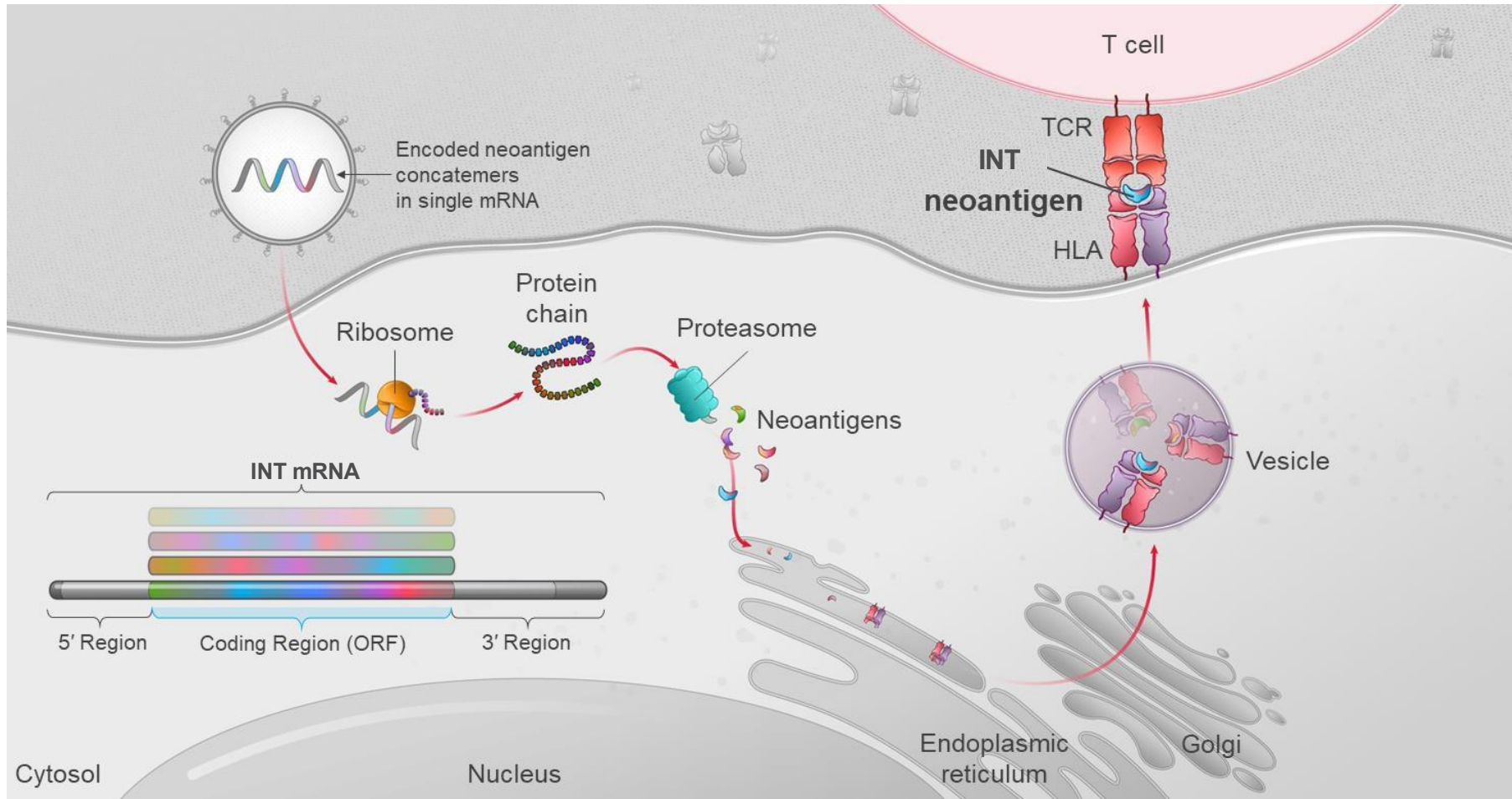


Individualized Neoantigen Vaccines

- Identify mutations in a patient's tumor
- Predict what could be seen by T cells
- Produce the bespoke vaccine (peptides, RNA)



mRNA-4157 (V940) Mechanism of Action



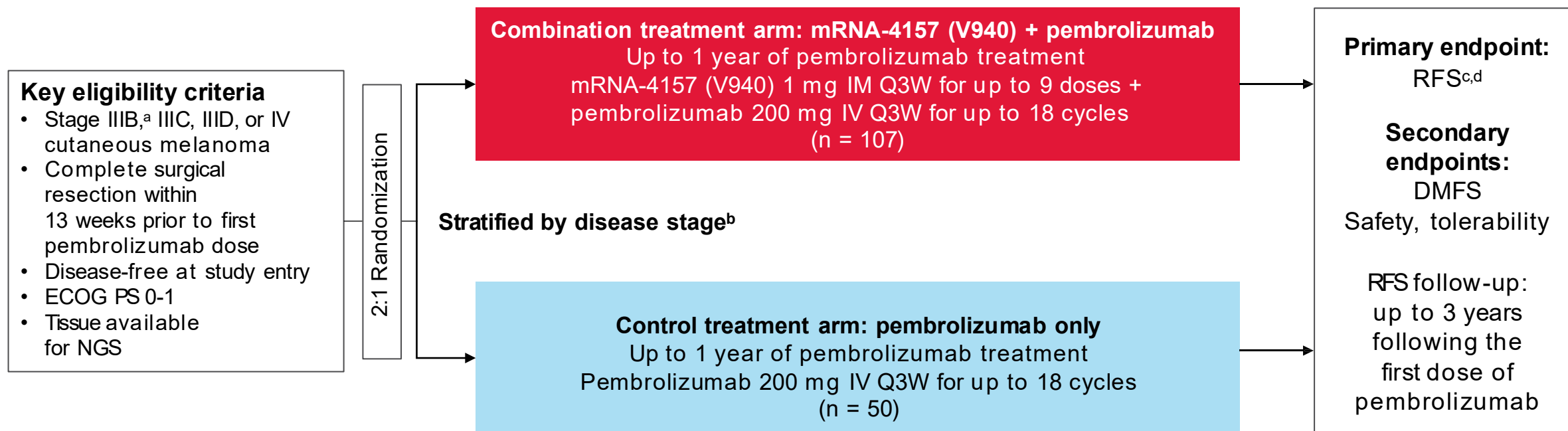
mRNA-4157 (V940) is a **customizable** individualized neoantigen therapy encoding up to 34 neoantigens

Targeting of neoantigens by T-cells has been demonstrated to **drive antitumor responses**¹

The modified mRNA **platform** was implemented for the COVID-19 vaccine (mRNA-1273), demonstrating **utility and adaptability**²

mRNA-4157-P201/KEYNOTE-942 (NCT03897881)

Randomized, phase 2 study in adjuvant resected melanoma patients at high risk of recurrence



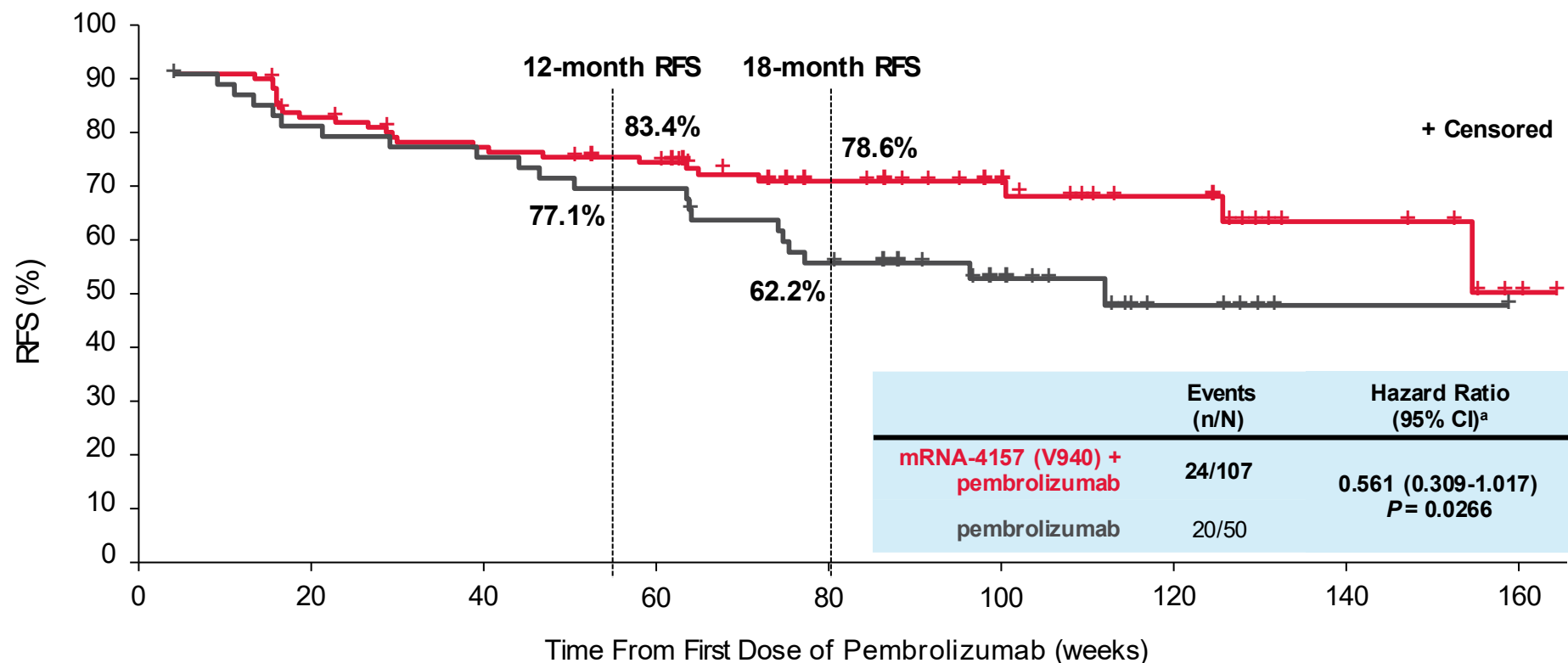
Designed with 80% power to detect an HR of 0.5 with ≥40 RFS events (with 1-sided alpha of 0.1)

Median follow-up^e: 23 months for mRNA-4157 (V940) + pembrolizumab
24 months for pembrolizumab only

DMFS, distant metastasis-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IM, intramuscular; IV, intravenous; mRNA, messenger RNA; NGS, next-generation sequencing; Q3W, every 3 weeks; RFS, recurrence-free survival.

^aPatients with stage IIIB disease were eligible only if relapse occurred within 3 months of prior surgery of curative intent. ^bAccording to the 8th edition of the American Joint Committee on Cancer staging manual. ^cThe primary endpoint was investigator-assessed RFS (defined as the time from first dose of pembrolizumab until the date of first recurrence [local, regional, or distant metastasis], a new primary melanoma, or death from any cause) in the intention-to-treat population. ^dThe primary analysis for RFS was specified to occur after all patients completed ≥12 months on study and ≥40 RFS events were observed. Descriptive analysis specified to occur when ≥51 RFS events observed. ^eTime of database cutoff was November 14, 2022.

mRNA-4157 (V940) and pembrolizumab combination treatment demonstrated an improvement in RFS



	Number at Risk								
mRNA-4157 (V940) + pembrolizumab	107	92	85	73	49	24	20	8	1
pembrolizumab	50	42	40	37	28	13	6	1	0

CI, confidence interval; mRNA, messenger RNA; RFS, recurrence-free survival.

^aThe hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. The *P* value is based on a 1-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization.

INTerpath-001: Phase 3 Trial Schema

Adjuvant intismeran autogene + pembrolizumab in completely resected high-risk melanoma



Population

- Completely resected cutaneous melanoma
- Stage IIB / IIC / III / IV
- High risk
- No prior systemic therapy

 N = 1,137



Personalized therapy workflow



Tumor tissue collection



Neoantigen identification



Individualized intismeran manufacturing

Synthetic mRNA encoding up to 34 neoantigens

Randomization
2:1
Double-blind

Experimental arm

Intismeran autogene (V940 / mRNA-4157)

1 mg IM Q3W × up to 9 doses



Pembrolizumab

400 mg IV Q6W × up to 9 cycles



Treatment duration: ~1 year (up to ~56 weeks)

Control arm

Placebo

IM Q3W × up to 9 doses



Pembrolizumab

400 mg IV Q6W × up to 9 cycles



Treatment duration: ~1 year (up to ~56 weeks)



Topline result



RFS met



DMFS met



OS follow-up ongoing



No new safety signals



Primary endpoint

RFS



Key secondary endpoints

DMFS • OS • Safety • Tolerability • Quality of life

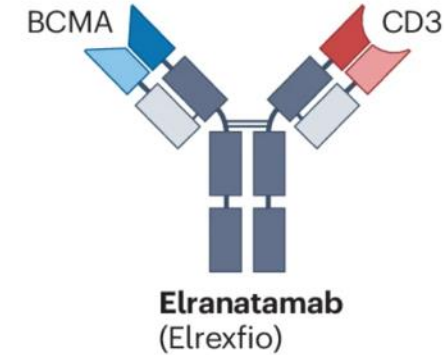
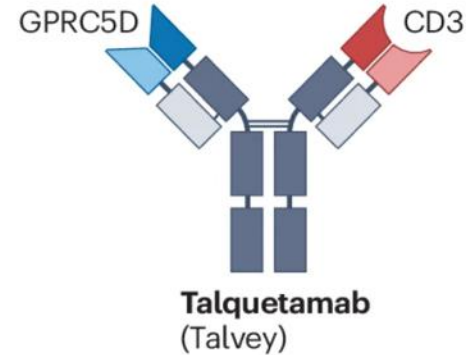
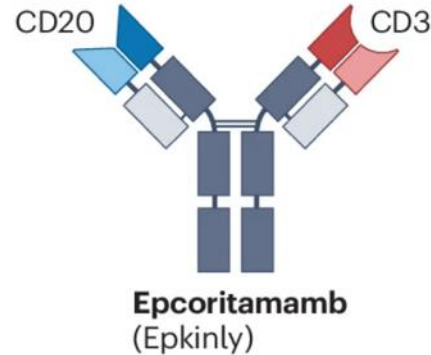
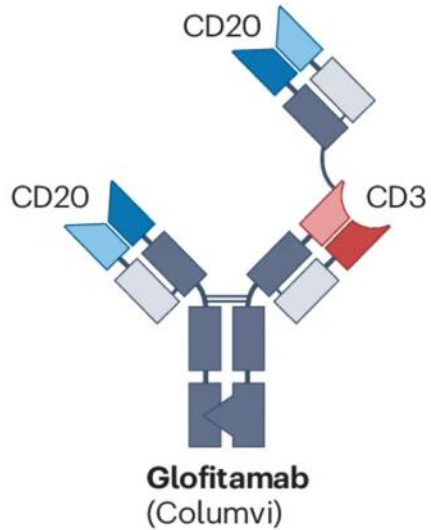
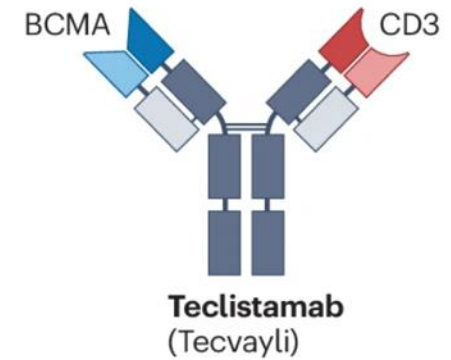
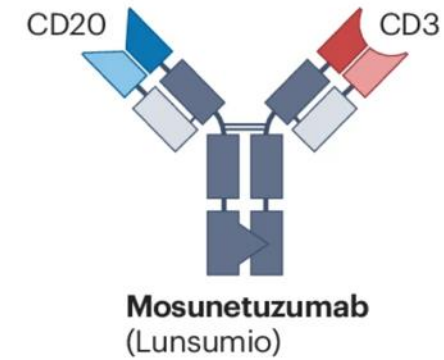
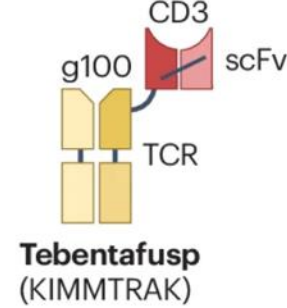
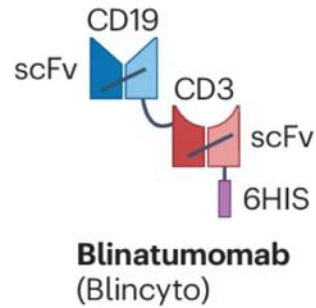
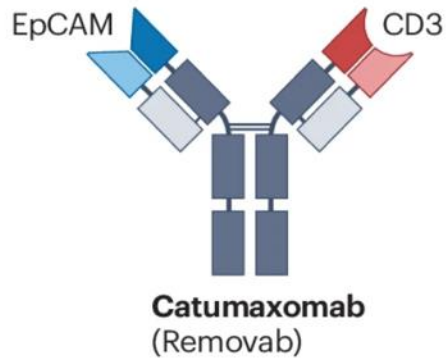


Merck and Moderna Announce Phase 3
INTerpath-001 Trial of Intismeran
Autogene Plus KEYTRUDA® Met
Endpoints of Recurrence-Free Survival
(RFS) and Distant Metastasis-Free
Survival (DMFS) in Patients With
Completely Resected Stage IIB-IV
Melanoma

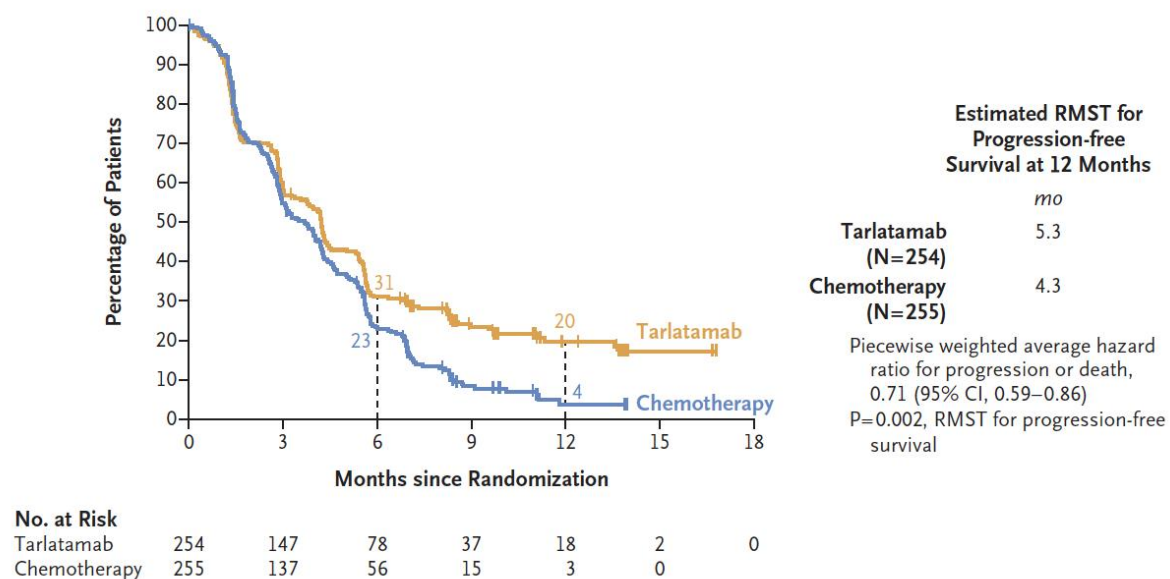
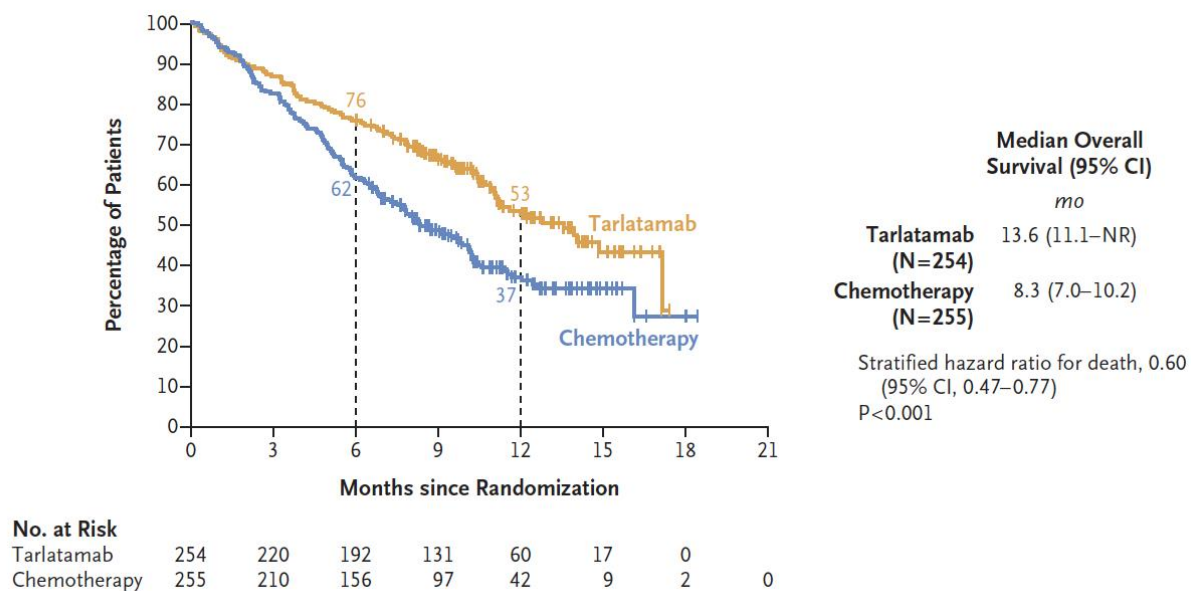
Outline

- Immune checkpoint inhibitors
- Cancer vaccines
- T cell engagers/bispecifics
- CAR-T cells

T cell engagers/Bispecifics



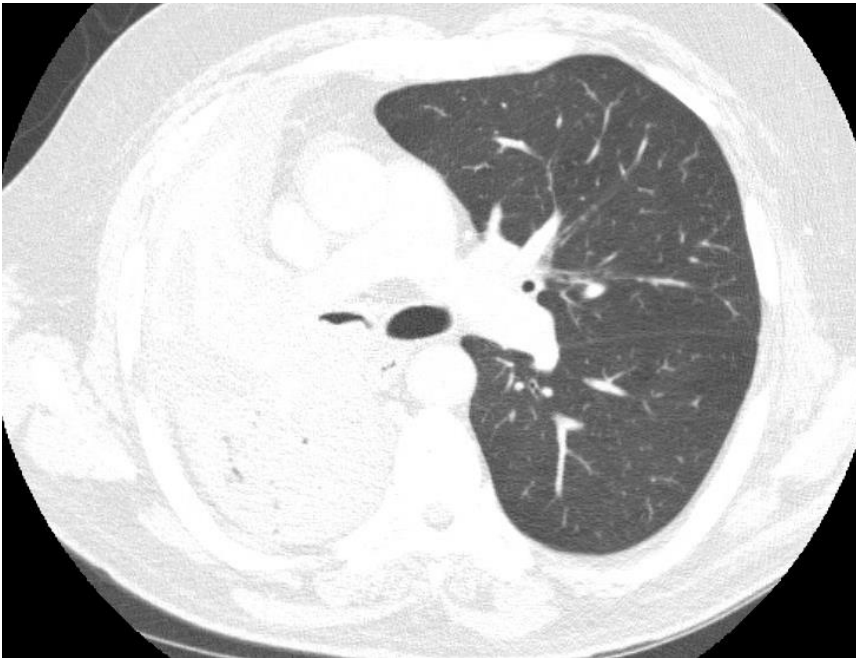
Tarlatamab in 2nd line small cell lung cancer



Tarlatamab has changed the treatment landscape for ES-SCLC

62 year old gentleman with extensive-stage small cell lung cancer receives tarlatamab after progression on carboplatin/etoposide/atezolizumab

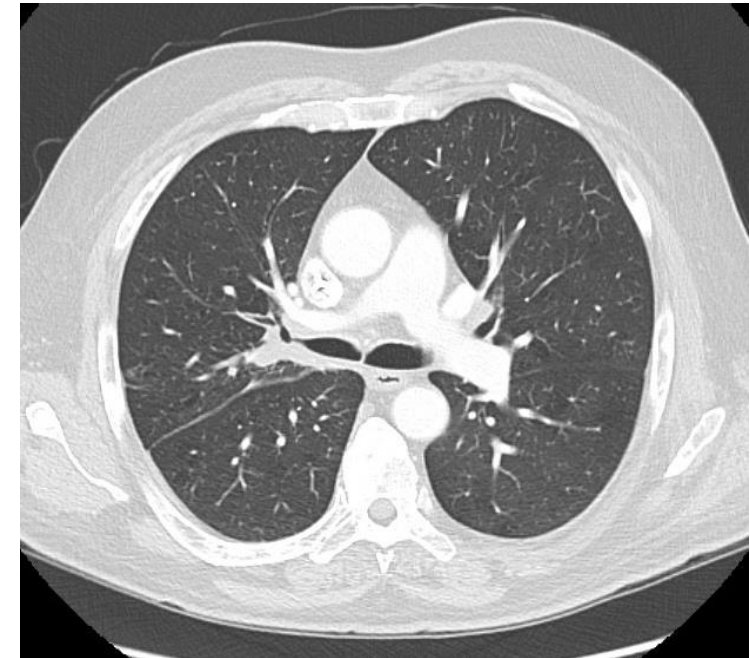
Pre-treatment



Tarlatamab



2 months Post-treatment



He is now enjoying camping with his family

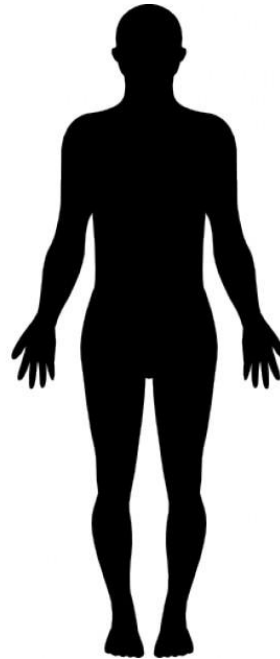
Extensive-stage small cell lung cancer treatments

Current

Platinum + Etoposide + PD-L1 inhibitor

Lurbinectedin

Tarlatamab (2L)



Emerging

Next-generation DLL3 T cell engagers (ZG006)

Bispecific antibodies: DLL3 x CD47 (PT217)

Antibody drug conjugates (DLL3, SEZ6, B7H3)

DLL3 CAR T cells (DJI136, ML261)

Epigenetic modulation with HDAC6/LSD1 inhibition (JBI-802)

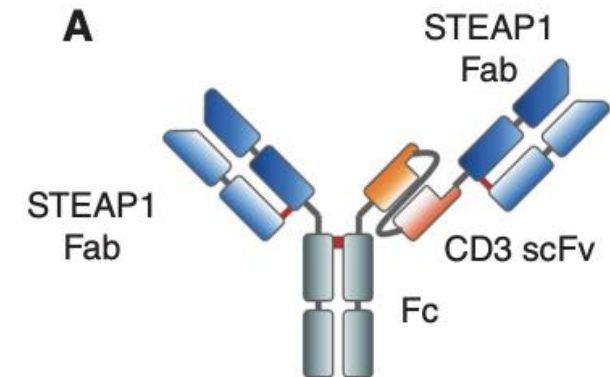
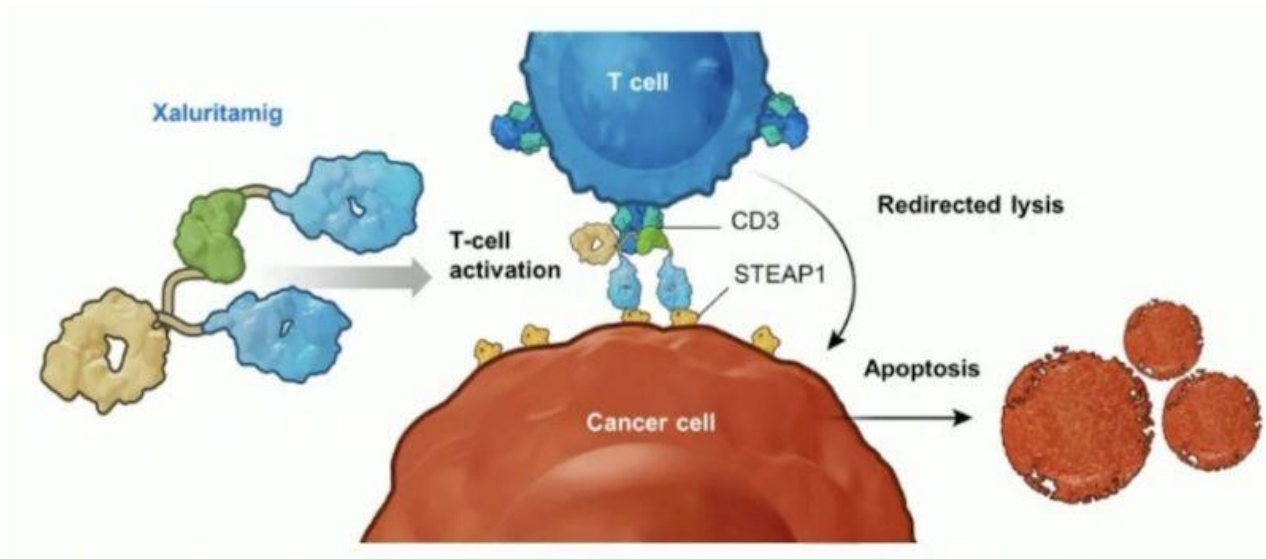
Transcriptional subtype-specific therapies

Tarlatamab (1L maintenance)

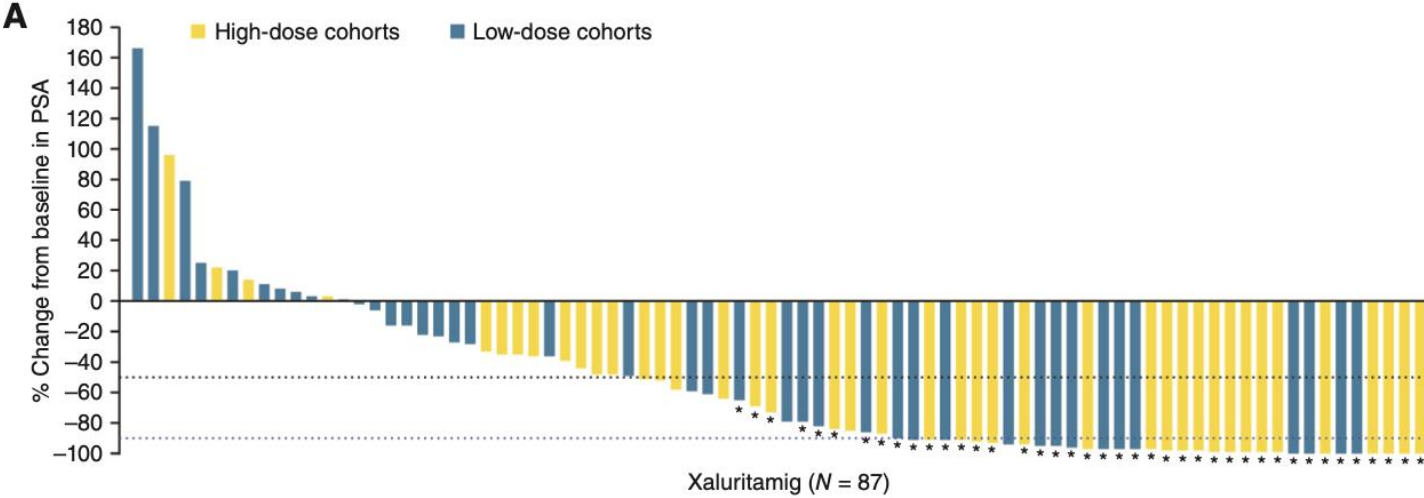
IMFINZI® (durvalumab) plus tarlatamab demonstrated a statistically significant and highly clinically meaningful improvement in overall survival and progression-free survival in 1st-line extensive-stage small cell lung cancer

STEAP1 x CD3 T cell engager (xaluritamig)

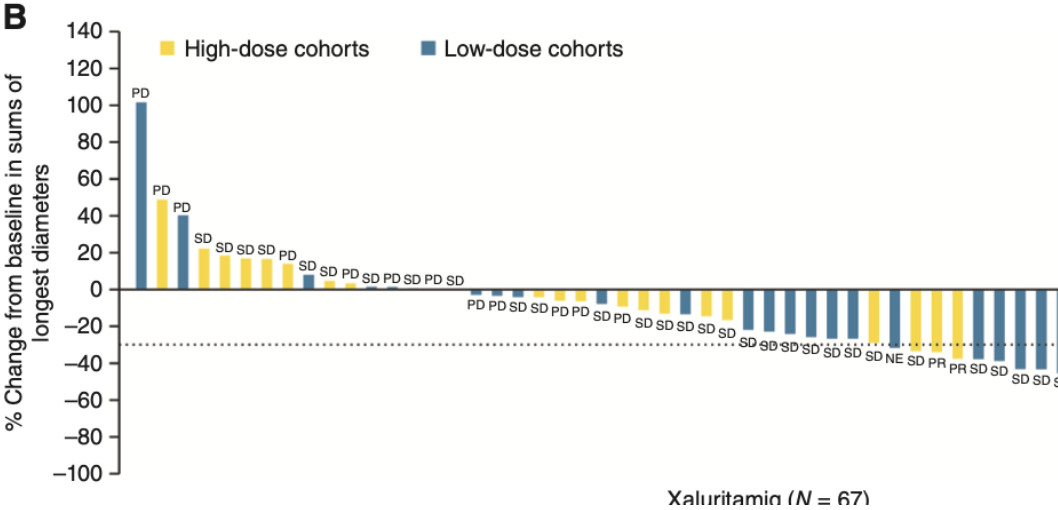
- Potent, selective bispecific T-cell engaging antibody targeting STEAP1
 - Dual anti-STEAP1 Fabs
- Preferentially targets tumor cells with high STEAP1 expression.



Clinical efficacy with xaluritamig in mCRCP

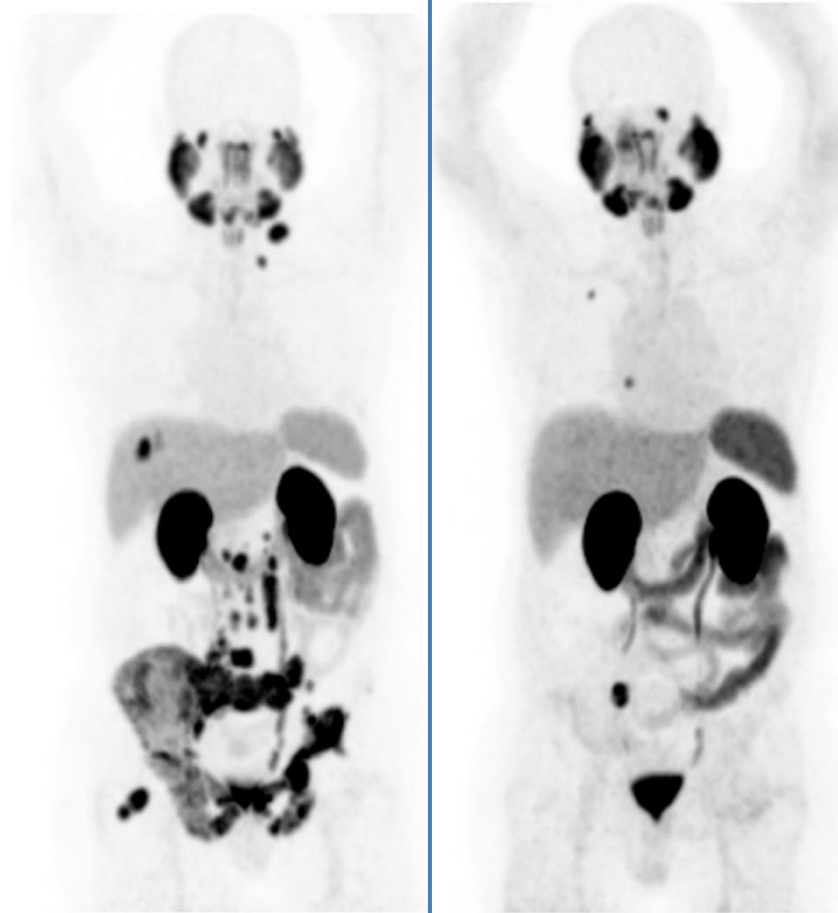


- PSA50 Response:
 - All Cohorts: 43/87 (49%)
 - Low-Dose Cohorts (1-7a): 17/43 (40%)
 - High-Dose Cohorts (7b-13): 26/44 (59%)
- PSA90 Response:
 - All Cohorts: 24/87 (28%)
 - Low-Dose Cohorts (1-7a): 8/43 (19%)
 - High-Dose Cohorts (7b-13): 16/44 (36%)



	All Cohorts	Low-Dose Cohorts (1-7a)	High-Dose Cohorts (7b-13)
RECIST v1.1 Evaluable, n	67	30	37
RECIST v1.1 response, confirmed, n (%)			
PR	16 (24%)	1 (3%)	15 (41%)
SD	32 (48%)	18 (60%)	14 (38%)
PD	13 (19%)	6 (20%)	7 (19%)
Not evaluable*	6 (9%)	5 (17%)	1 (3%)

Patient's response to treatment

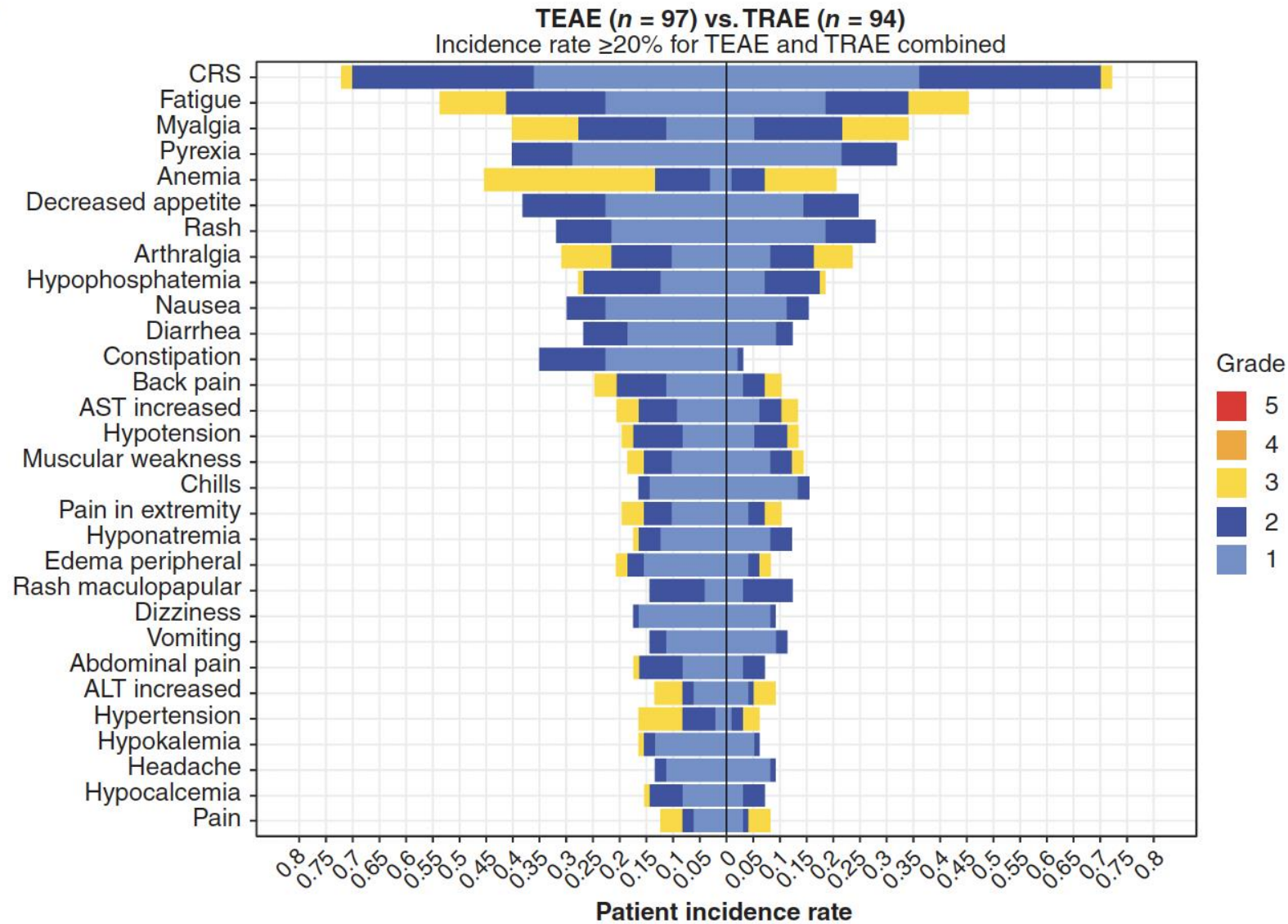


Baseline

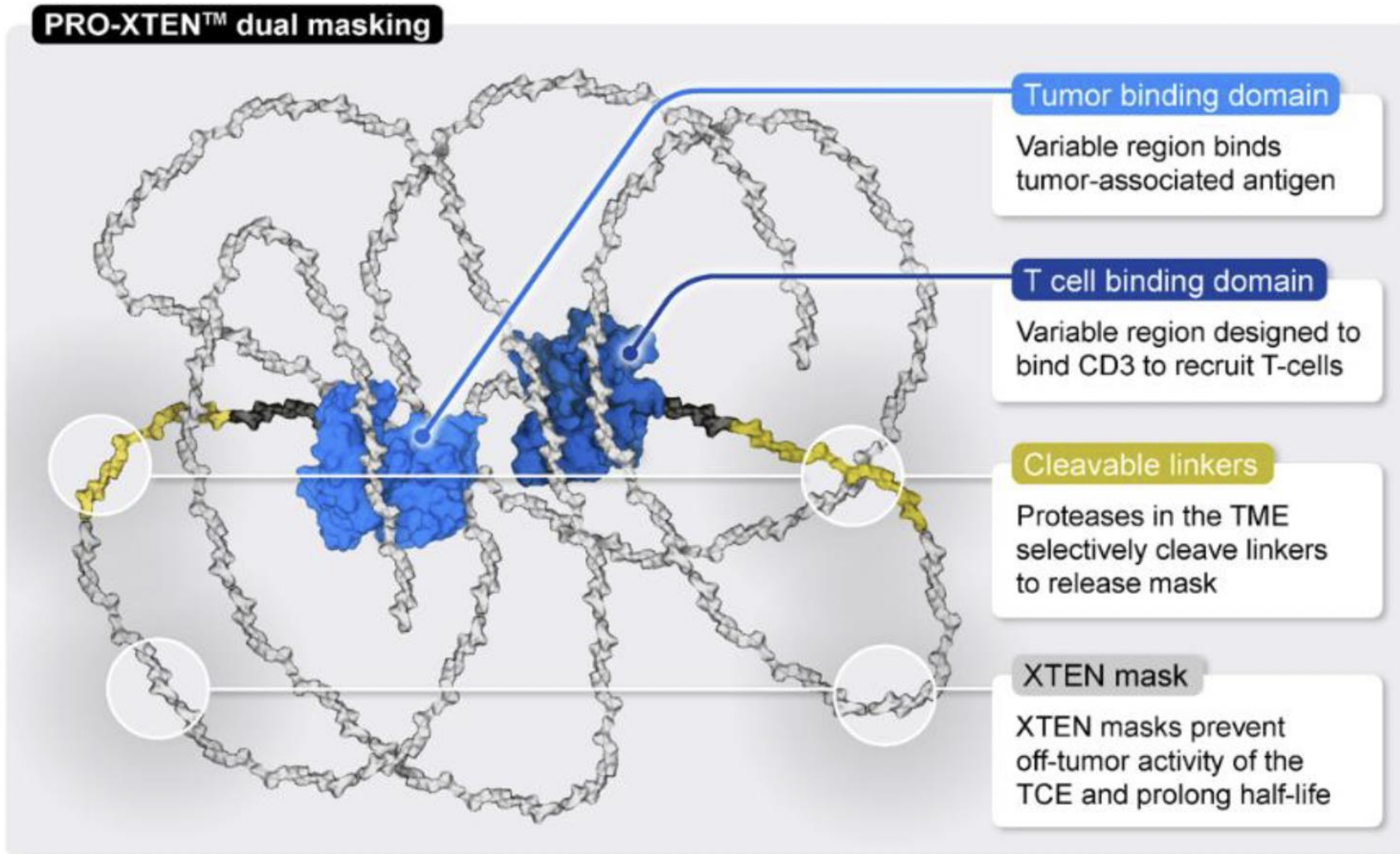
After Cycle 6

Toxicity with xaluritamig (AMG 509)

A



Masked PSMA x CD3 TCE (VIR5500)



VIR-5500-V101 First in Human Phase 1 Study

VIR-5500
(PSMA)

No Dose Limiting Toxicities; CRS Mainly Grade 1, Despite No Prophylaxis

- 12% (7/58) Grade ≥ 3 TRAEs, Limited CRS 50% (29/58) primarily seen in the first cycle, Mostly Grade 1 (Fever Only)¹, and No DLTs²

Dose-dependent and Meaningful Anti-Tumor Activity

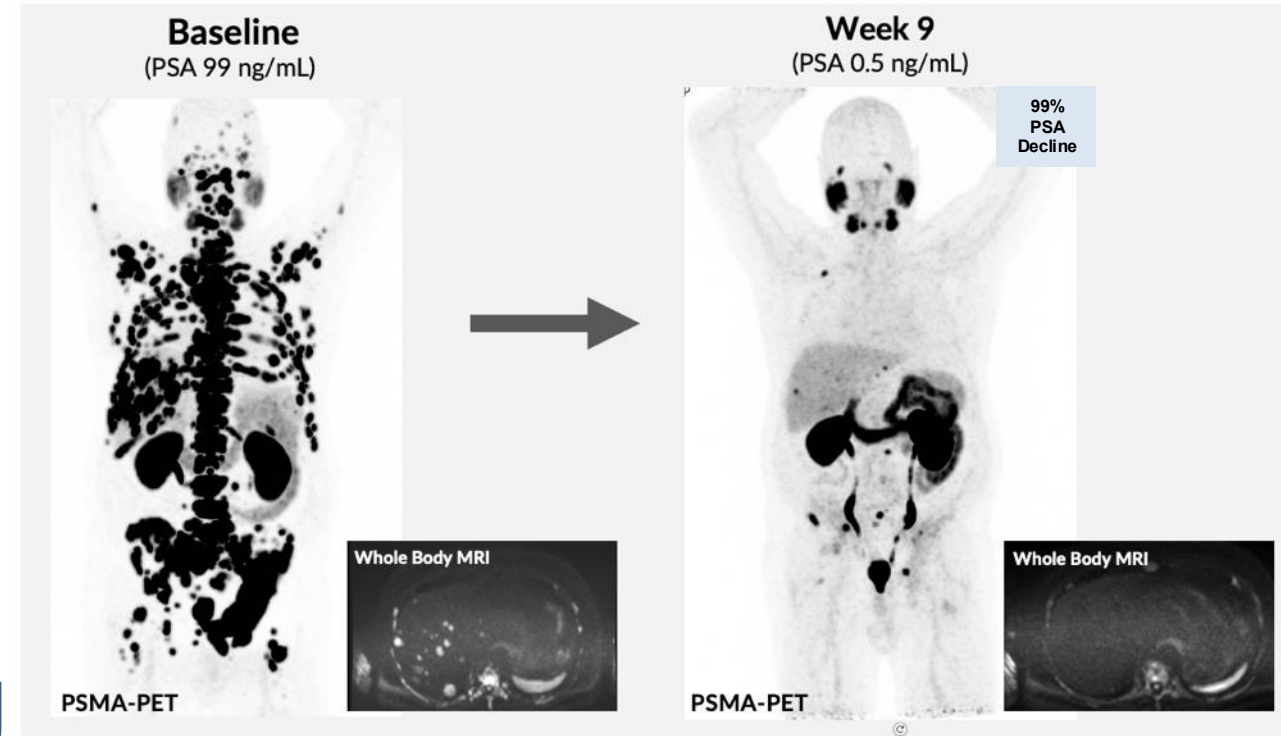
- Dose-response relationship with deeper PSA declines and confirmed PSA responses observed at higher doses

Doses $\geq 3,000$ $\mu\text{g/kg}$ Q3W	
PSA ₅₀	82% (14/17) ³
PSA ₉₀	53% (9/17) ³
PSA ₉₉	29% (5/17) ³
ORR (RECIST v1.1)	45% (5/11), 4 evaluable confirmed up to Week 27

Early Signs of PSA and Radiographic Durability

- Emerging evidence of durable PSA₅₀, PSA₉₀ and RECIST responses

Q3W Cohort 800/1500/3000 $\mu\text{g/kg}$



¹Prophylactic steroids explored in cycle 1 of 1000-2000-4000 $\mu\text{g/kg}$ Q3W cohort (N=3)

²Two blurred vision events were reviewed and incorporated into dose-escalation considerations and ongoing study conduct

³Unconfirmed & Confirmed

RECIST-evaluable population is defined as having measurable disease documented at baseline according to RECIST v1.1 criteria and at least one follow-up tumor assessment after a full cycle of treatment

PSA evaluable population is defined as participants who received ≥ 1 cycle of VIR-5500 and must have at least one pre-treatment and at least one post-treatment PSA measurement.

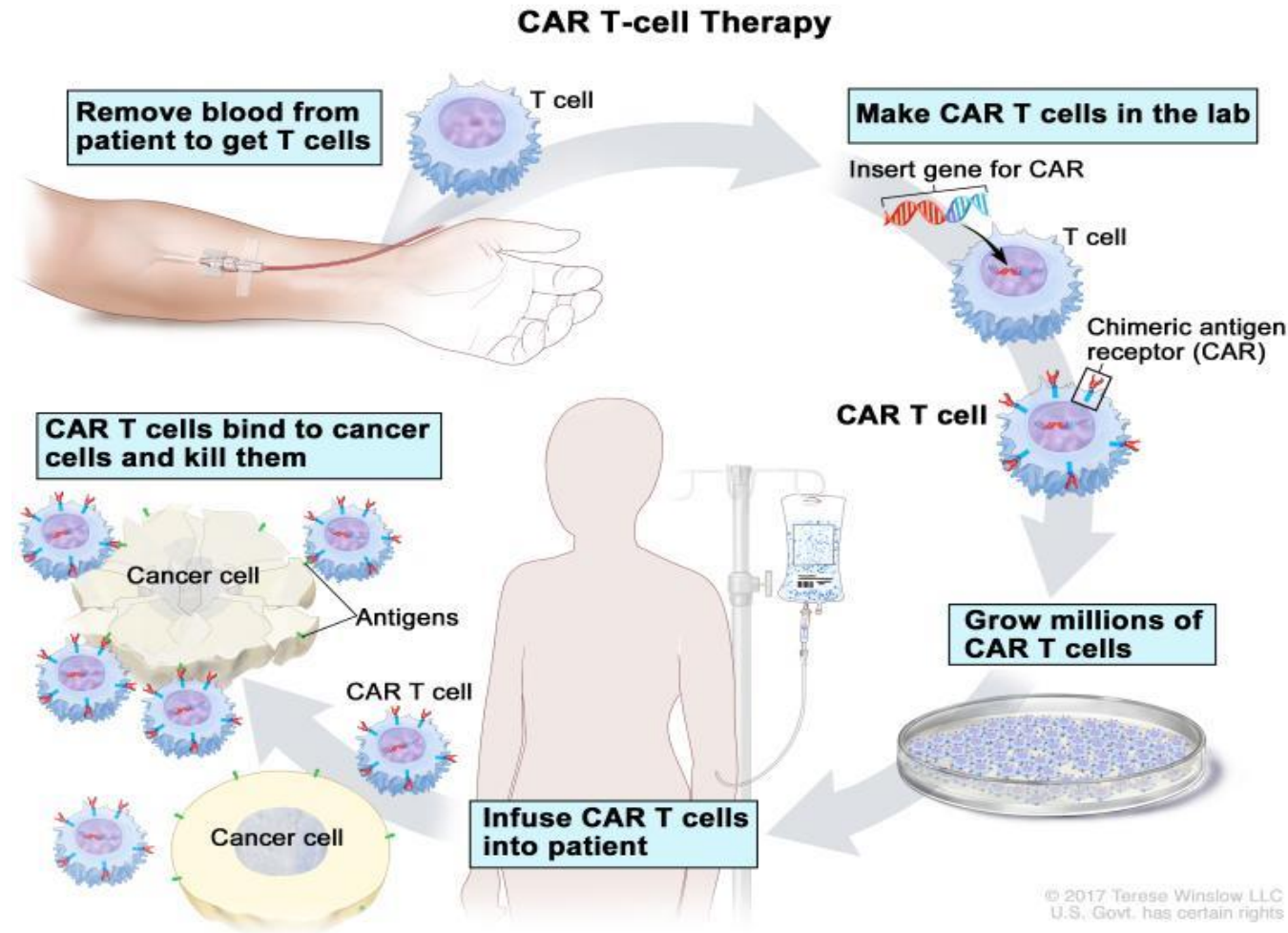
CRS: cytokine release syndrome; DLT: dose limiting toxicities; G3+: Grade ≥ 3 ; ORR: objective response rate; PSA: prostate-specific antigen; Q3W: once every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; TRAE: treatment related adverse event

VIR-5500-V101 ClinicalTrials.gov Identifier: NCT05997615. Data as of: January 9, 2026

Outline

- Immune checkpoint inhibitors
- Cancer vaccines
- T cell engagers/bispecifics
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Cell therapy is advancing from treating hematologic malignancies to solid tumors

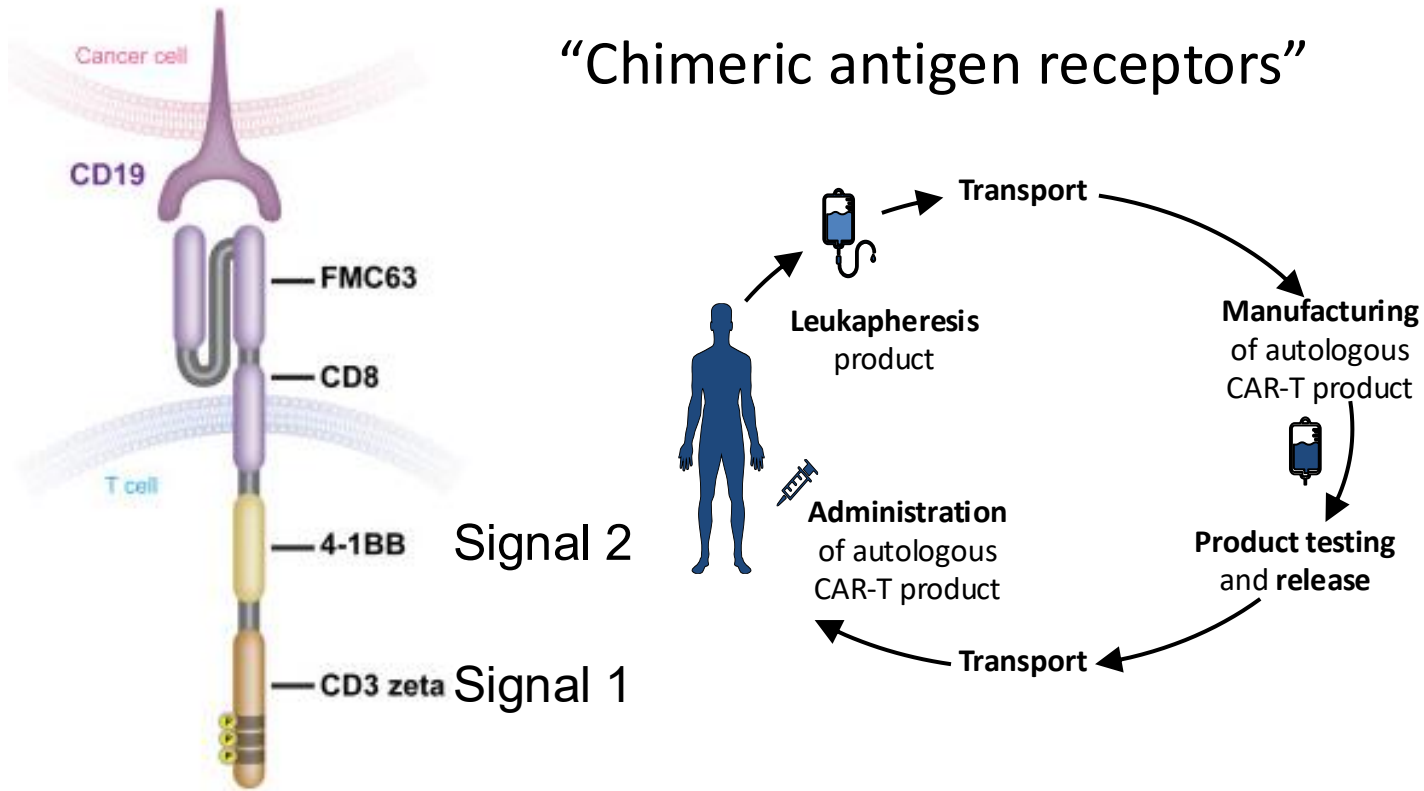


**Preparative
lymphodepleting
chemotherapy given prior
to cell infusion**

<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy>

FDA-approved CAR-T cells

“Chimeric antigen receptors”



Product	Price	Indication	Target	Clinical Outcomes
Kymriah, Novartis	\$475,000	Acute Lymphoblastic Leukemia (ALL) (Relapsed or Refractory)	CD19	83% complete remission
Yescarta, Kite, Gilead	\$373,000	Large B Cell Lymphoma (NHL) (Relapsed or Refractory)	CD19	54% complete response
Tecartus, Kite, Gilead	\$373,000	Mantle Cell Lymphoma (NHL) (Relapsed or Refractory)	CD19	62% complete response
Breyanzi, Juno, BMS	\$410,300	Large B Cell Lymphoma (NHL) (Relapsed or Refractory)	CD19	51% complete response
Abecma, BMS & BlueBird Bio	\$437,968	Multiple Myeloma (Relapsed or Refractory)	BCMA	54% complete response
Carvykti, Legend, Janssen	\$465,000	Multiple Myeloma (Relapsed or Refractory)	BCMA	78% complete response

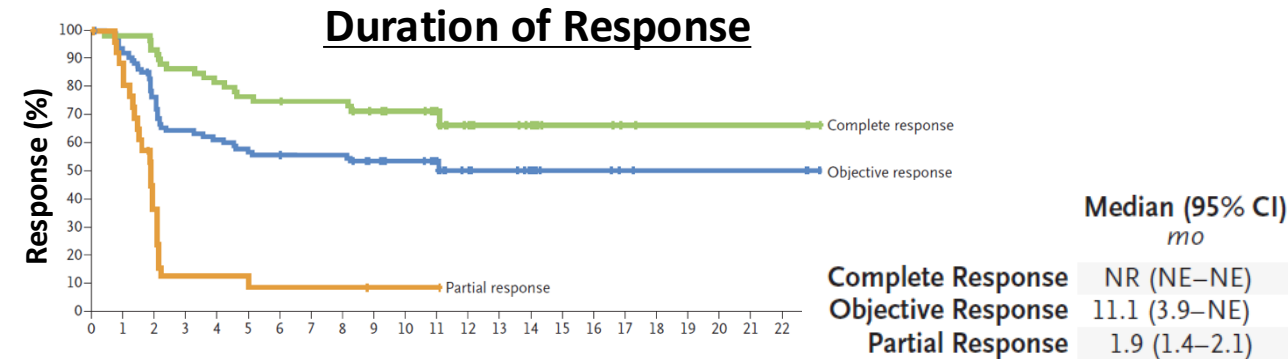
- 6 FDA-approved CAR T cells
- Anticipate more FDA approvals in hematologic, solid tumors and non-cancer disease indications



CD19 CAR T cells for R/R large B-cell lymphomas can induce durable remissions

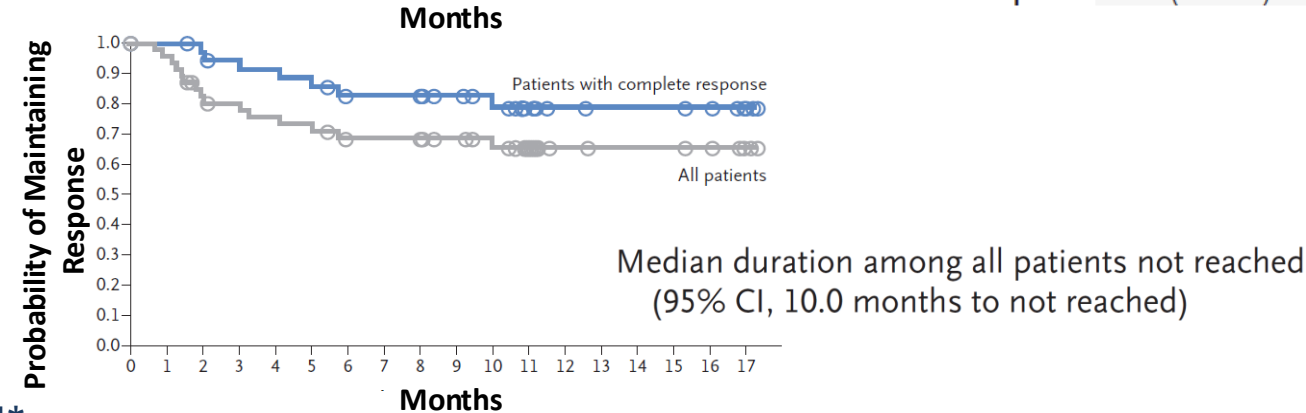
ZUMA-1: Axicabtagene ciloleucel

101 adults treated
ORR 82%, CR 58% (updated analysis)
Median duration of CR – NR



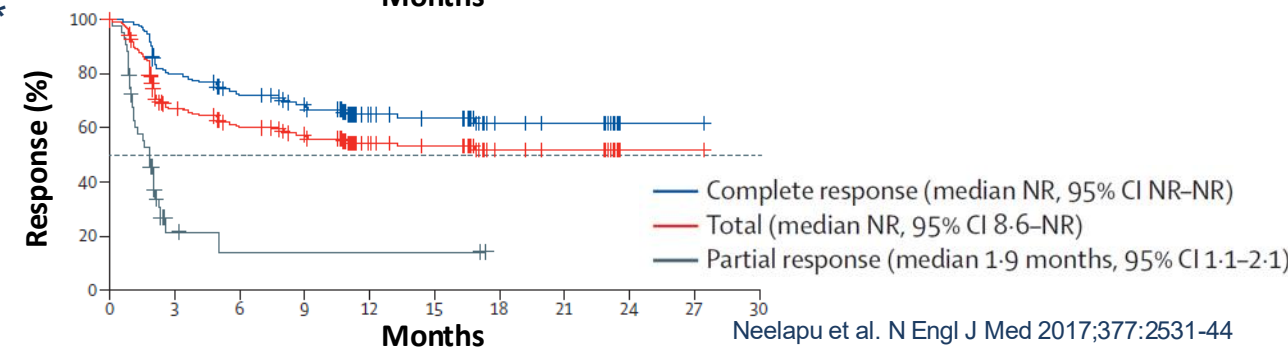
JULIET: Tisagenlecleucel

111 adults treated
ORR 52%, CR 40%
Median duration of CR – NR



TRANSCEND NHL 001: Lisocabtagene maraleucel*

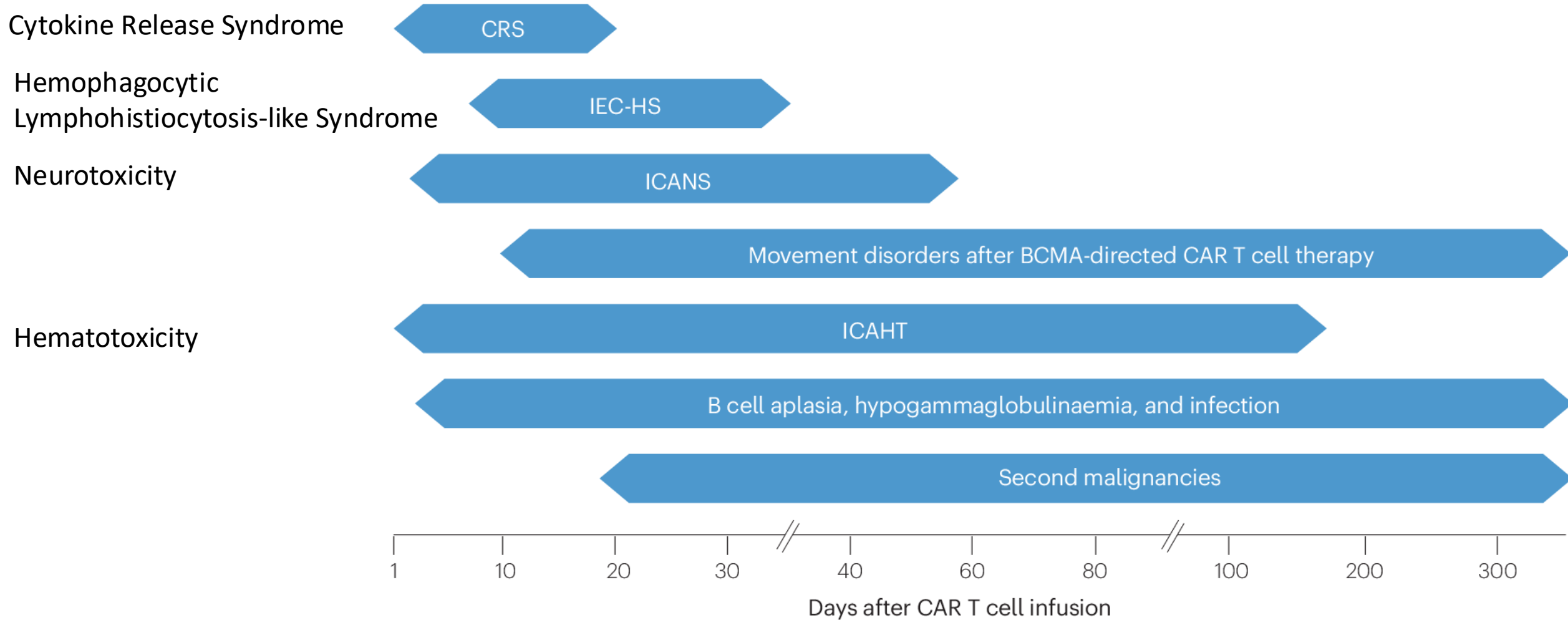
269 adults treated
ORR 73%, CR 53%
Median duration of CR – NR



Neelapu et al. N Engl J Med 2017;377:2531-44
Schuster et al. N Engl J Med 2019;380:45-56.
Abramson et al. Lancet 2020; 396: 839-52.

*1:1 CD4+:CD8+ ratio

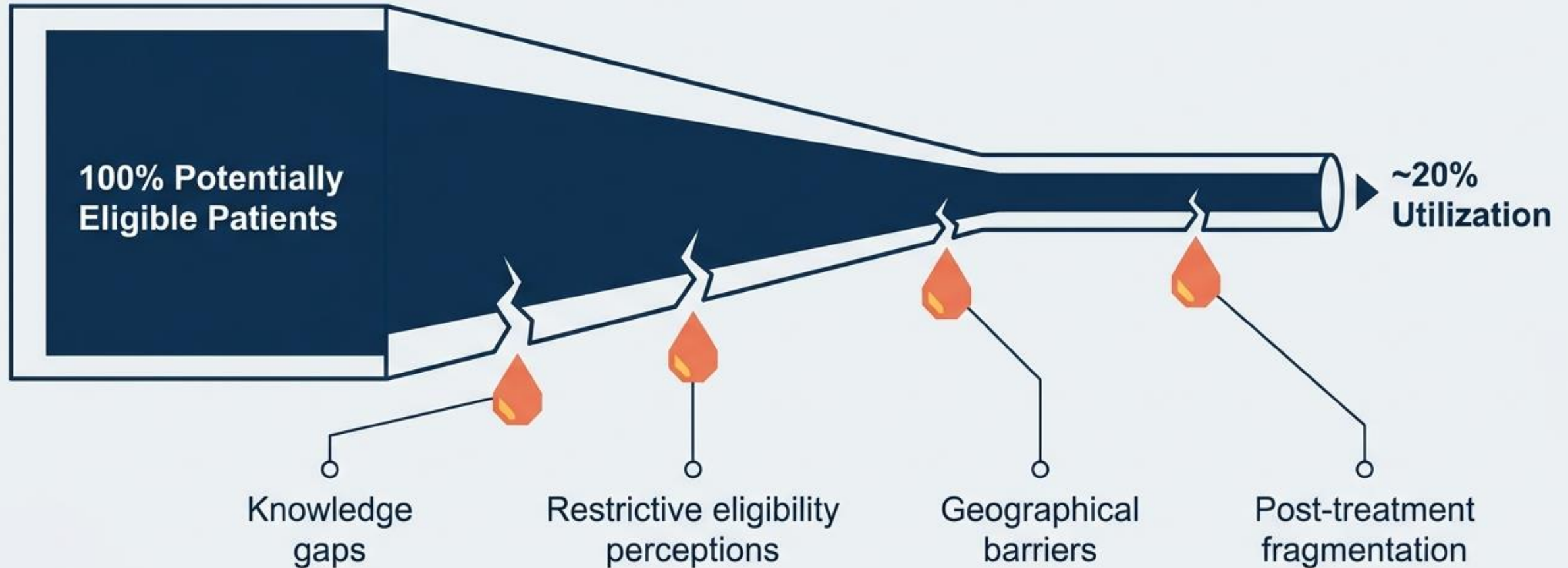
CAR-T cell therapy toxicities



(Brudno et al. *Nat Rev Clin Oncol* 2024)

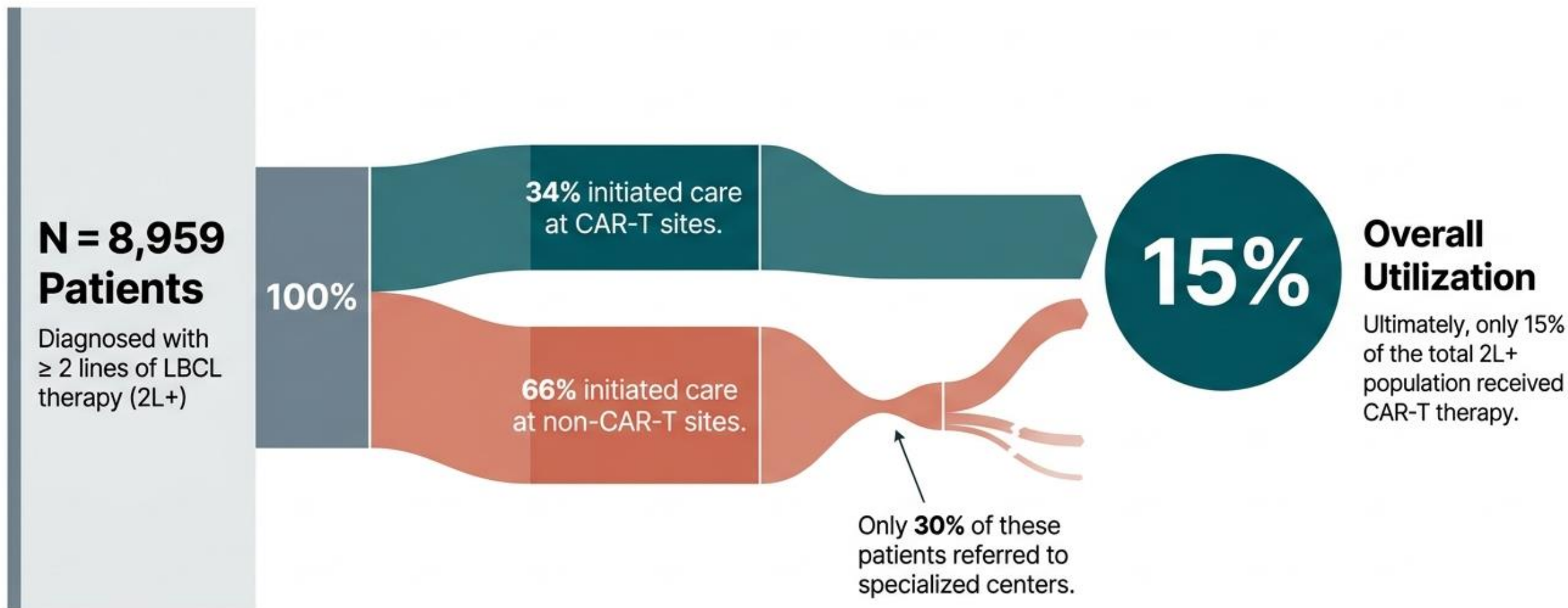
The CAR-T Utilization Paradox

Despite randomized trials demonstrating an overall survival benefit compared with standard-of-care therapy, CAR-T utilization remains unsustainably low.



CAR-T Patient Journey: A Steep Funnel of Attrition in 2L+ LBCL

Komodo Health Claims Analysis (October 2016 – May 2025)



Demographics and Distance: Key Barriers to Specialized Care

Structural and geographic friction significantly limits patient access

Age & Demographics



Referred Patient Profile

Mean Age: 61.5 years



Non-Referred Patient Profile

Mean Age: 67.3 years

Referred patients are significantly younger, highlighting a stark demographic divide in access to specialized care.

Geography & Proximity



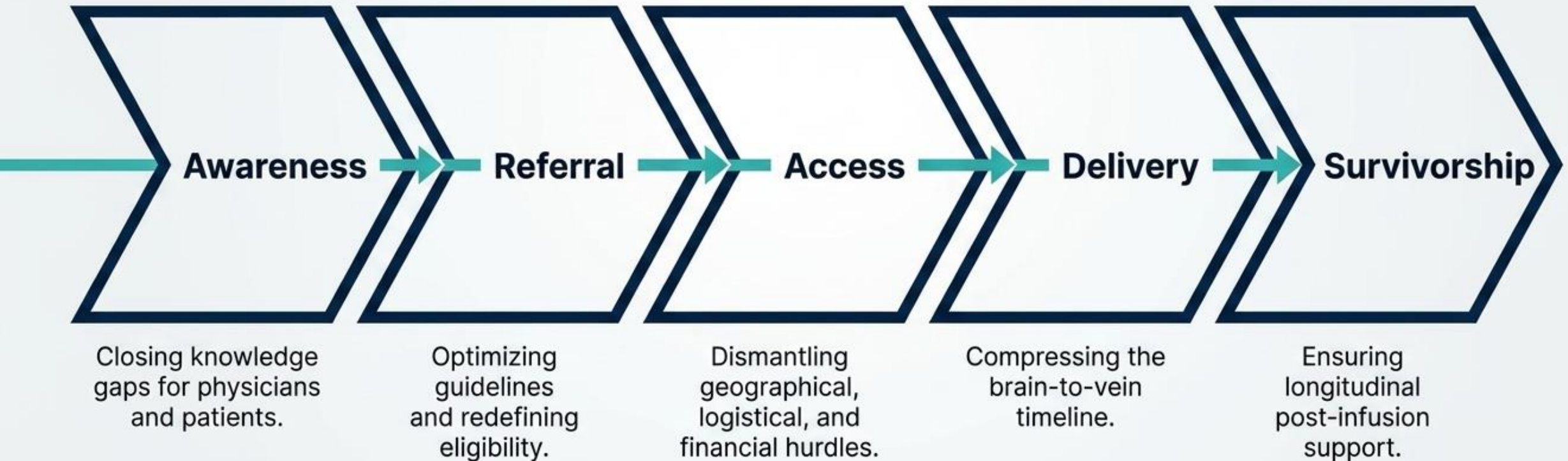
of referred patients live within a 25-mile radius of a CAR-T center.



of non-referred patients live within this same radius.

The Five-Domain Optimization Framework

Increasing CAR-T utilization requires a systemic approach beyond simply expanding manufacturing capacity. We must optimize every stage of the patient journey.



Cellular Therapy

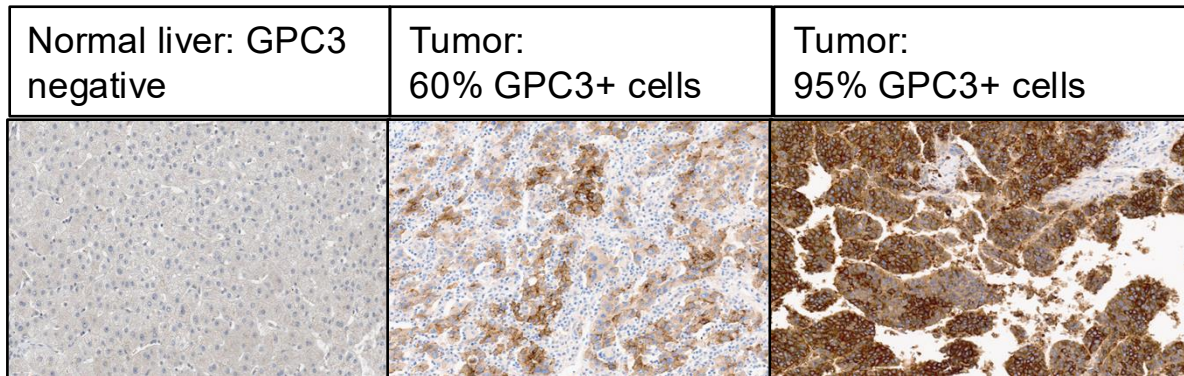
Who Is Eligible for Chimeric Antigen Receptor T Cell Therapy? Expert Perspectives on Overcoming Referral Barriers

Mazyar Shadman^{1,*}, Sairah Ahmed², Michael T. Byrne³, Julio C. Chavez⁴,
Manali Kamdar⁵, Mohamed L. Sorrow¹, Miguel-Angel Perales^{6,7}, Joshua A. Hill¹,
Javid Moslehi⁸, David B. Miklos⁹

Patient Characteristic		CAR T-cell Therapy	ASCT
	Advanced age	Refer for further assessment; consider together with other factors	Age ≥70 or refer for further analysis to be considered together with other factors
	Poor performance status	Refer for further assessment (even those with marginal PS)	ECOG PS ≤2; KPS ≥60
	Lack of response to chemotherapy	Consult with CAR T-cell therapy specialist in choosing bridging therapy for disease control	Response to salvage chemotherapy required
	Impaired cardiovascular function	Involve cardiologists/onco-cardiologists early to optimize cardiac status	NYHA class I or II; LVEF ≥40 and no uncontrolled cardiovascular disease or arrhythmia
	Impaired pulmonary function	Consult pulmonologists early in the process for patients with concerning pulmonary condition/history	DLCO ≥50%
	Impaired renal function	Consider CAR T-cell therapy in select patients with significant renal dysfunction	Serum creatinine <2 mg/dL; CrCl >50 mL/min
	Impaired hepatic function	Refer and consult hepatologists an/or GI specialists	No cirrhosis
	Unresolved, active, or chronic infections	Refer and consult ID specialists; give special consideration to patients with aggressive disease or poor prognosis who may proceed to CAR T-cell therapy despite active infections	No unresolved, active infections; seropositivity for HIV, hepatitis B, or hepatitis C should not contraindicate referral
	Poor psychological health	Refer and solicit support from psychiatric unit	Well-controlled psychological illnesses; no active use of illicit drugs; safe post-ASCT environment

GPC3 CAR T cell therapy in Hepatocellular Carcinoma

- Glypican 3 (GPC3) is a heparan sulfate proteoglycan overexpressed in HCC but absent in healthy tissues
- C-CAR031: GPC3-specific TGF β RIIDN CAR T cell
- ATHENA: AZD5851 Armored GPC3 CAR T
Global Phase 1/2 for advanced/recurrent 2L+ HCC - ongoing



Kelley et al, unpublished data



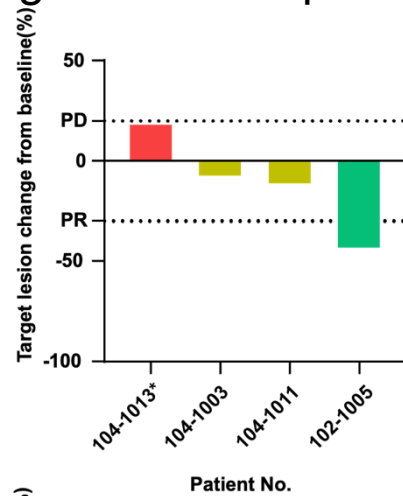
Clinical Response	DL1	DL2	DL3	DL4	Overall
n (%)	N = 1	N = 6	N = 8	N = 7	N = 22
PR	0	3 (50.0%)	4 (50.0%)	4 (57.1%)	11 (50.0%)
uPR	0	0	0	1 (14.3%)	1 (4.5%)
SD	1 (100%)	2 (33.3%)	4 (50.0%)	1 (14.3%)	8 (36.4%)
PD	0	1 (16.7%)	0	1 (14.3%)	2 (9.1%)

With 5.82-month median follow-up, Kaplan-Meier estimation of median progression-free survival was 4.27 months (95% CI, 2.86-8.90). Median overall survival has not been reached. C-CAR031 showed a robust cellular kinetic profile with a median T_{max} , C_{max} and $AUC_{0-28Day}$ of 10 days, 367,711.5 copies/ μ g gDNA and 4,105,036 days*copies/ μ g gDNA respectively.

GCC CAR T cells + CD19 CAR T cells in Colorectal Cancer

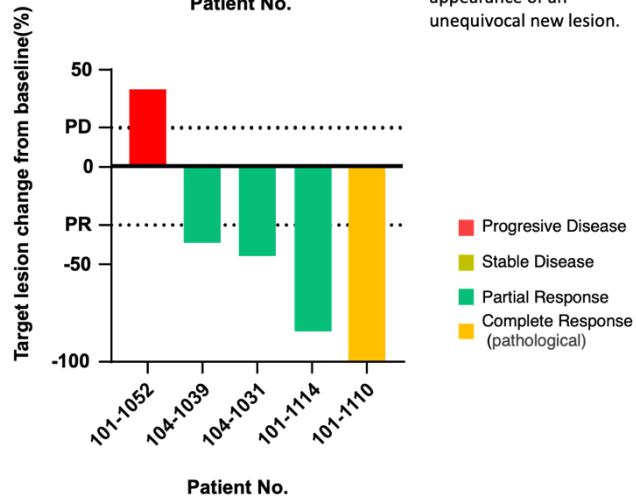
Target lesion responses

Dose Level 1



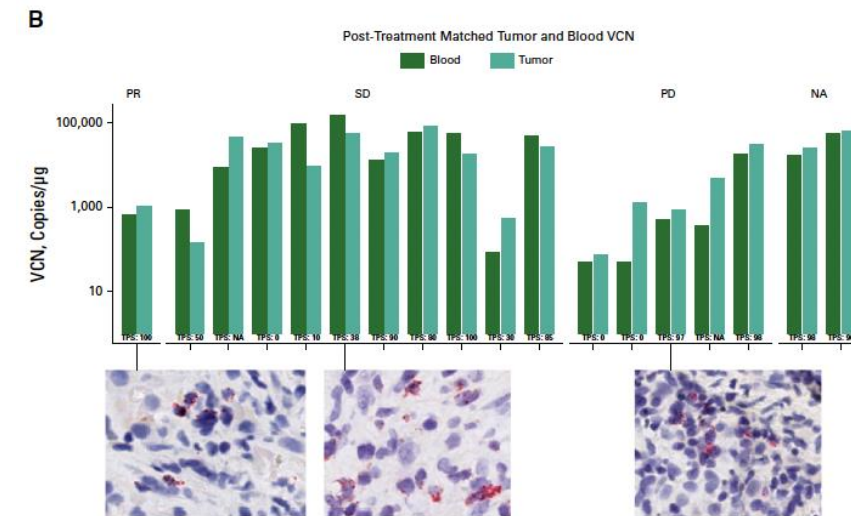
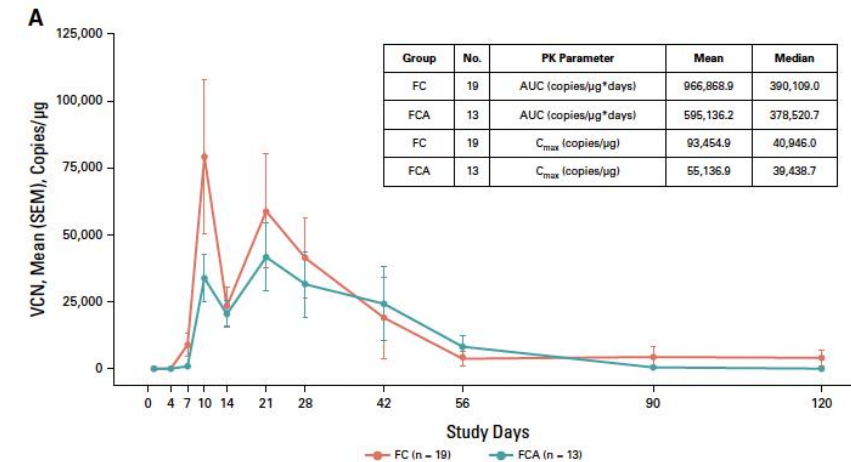
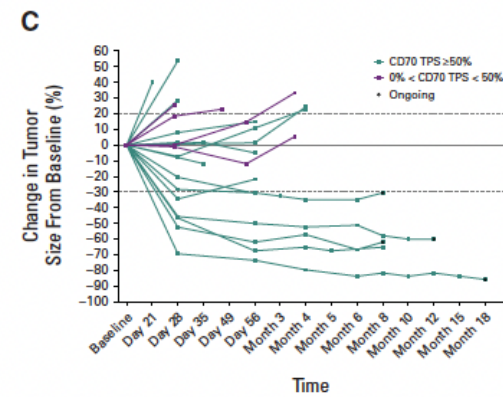
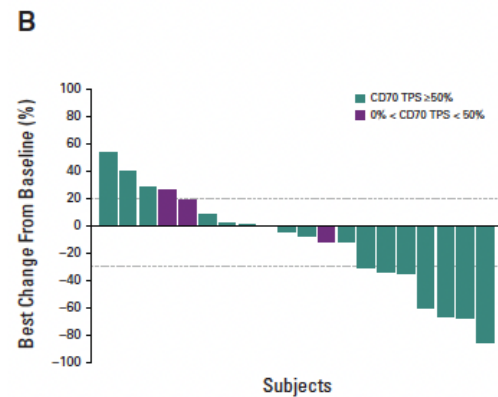
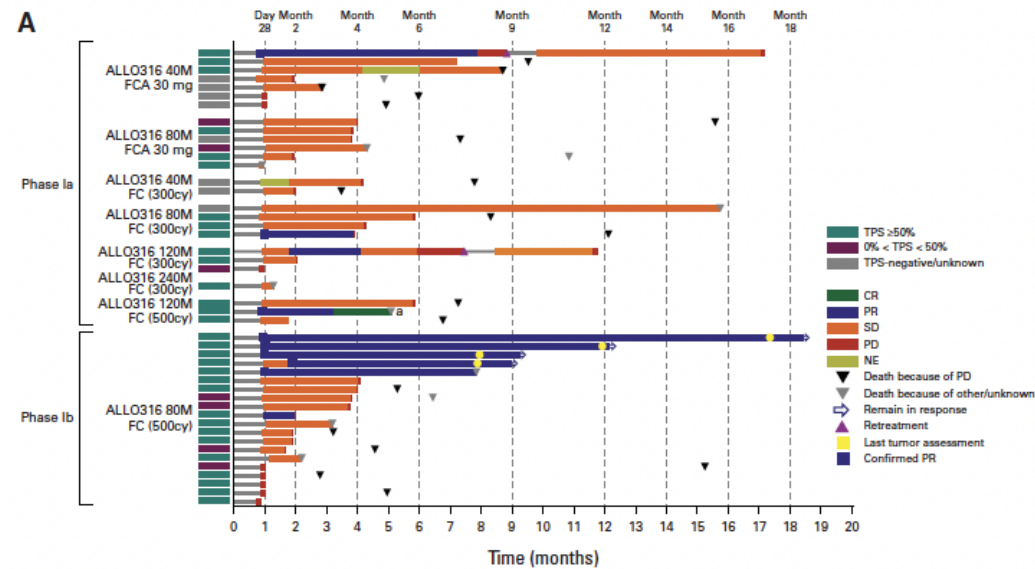
*Subject 104-1013 was assessed as having progressive disease (PD) at month 2 due to the appearance of an unequivocal new lesion.

Dose Level 2

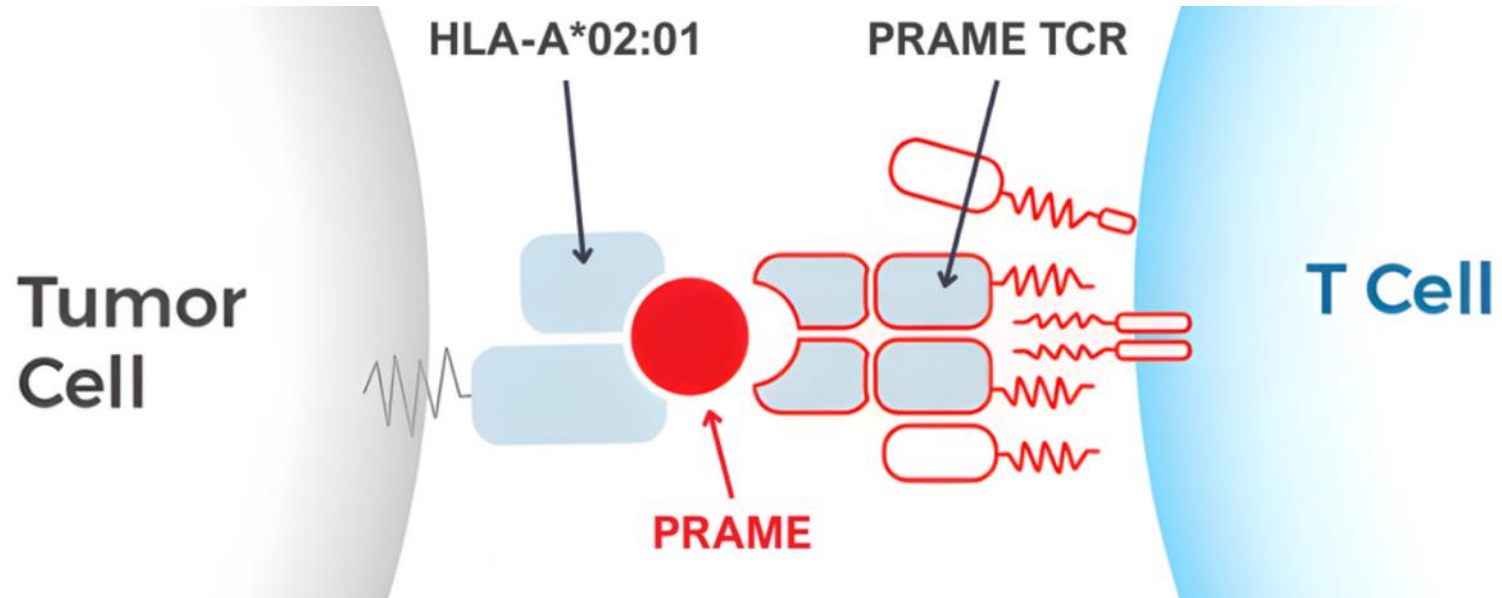


- CD19-targeting CAR T cells act as “bystanders” to help the GCC CAR T cells become activated
- As of December 26, 2024, a total of 9 subjects have been treated in 2 dose levels
- On target/off tumor toxicity of diarrhea/colitis due to GCC expression on gut epithelium as well as colorectal tumor cells

Allogeneic CD70-Targeted CAR T-Cell Therapy for Advanced Renal Cell Carcinoma



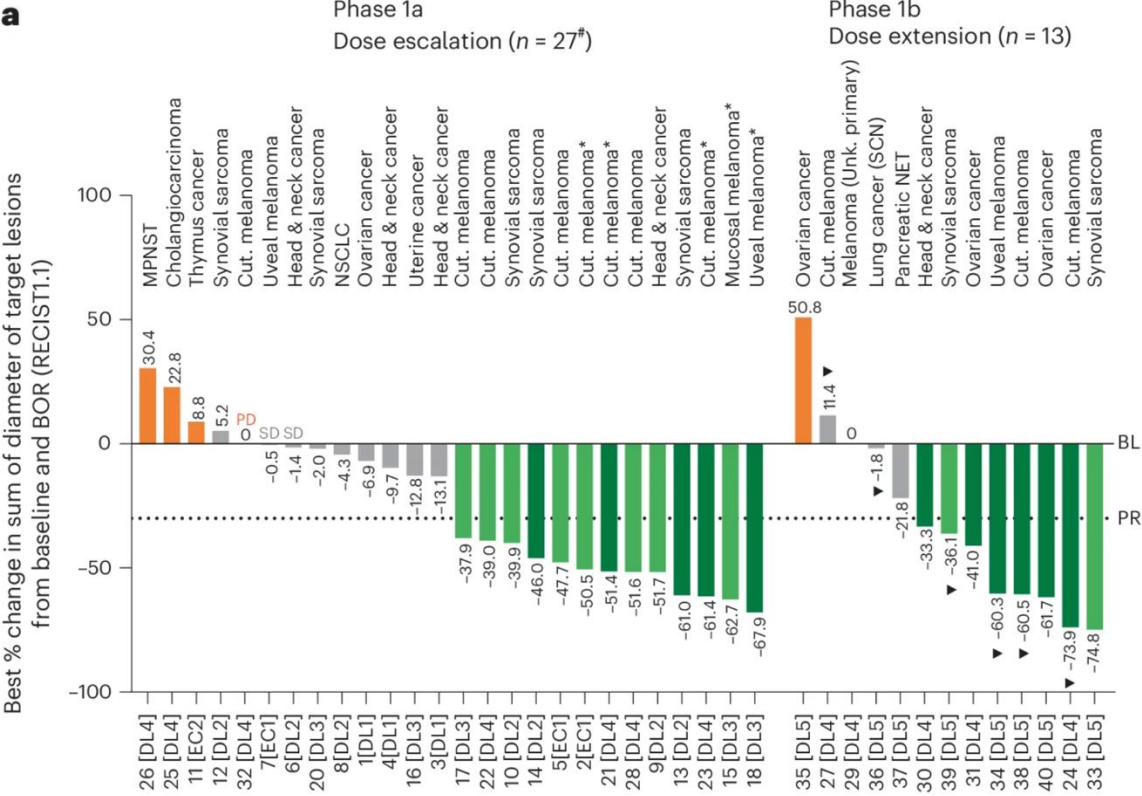
TCR T cell therapy



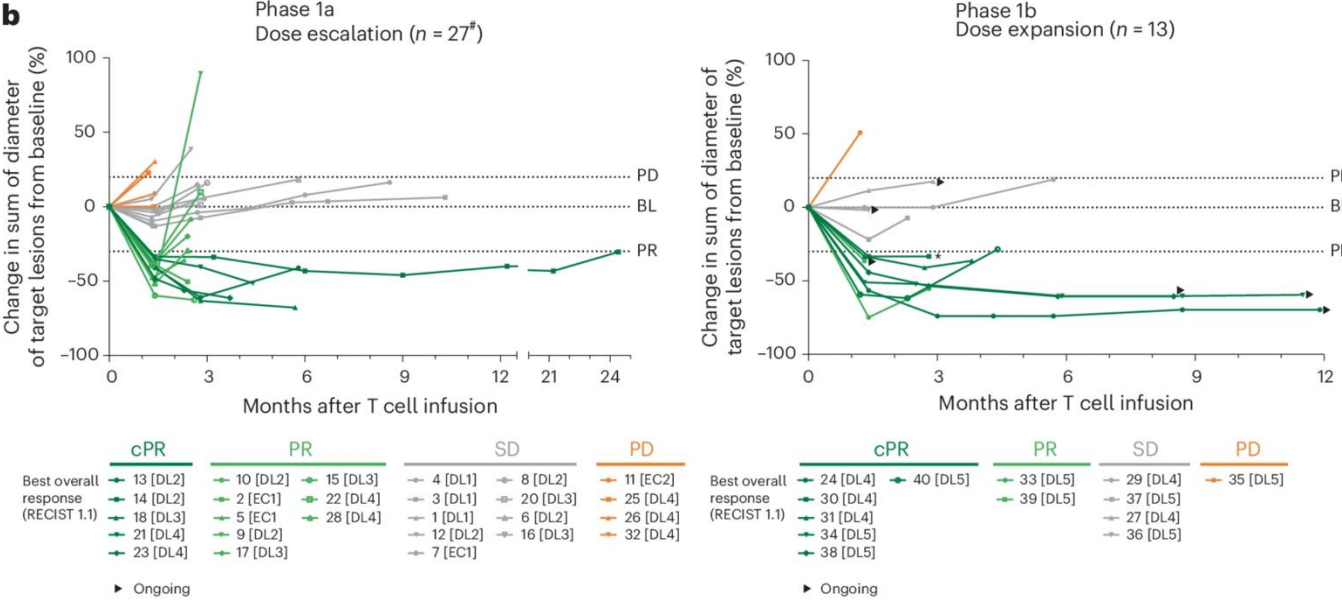
IMA203

PRAME TCR T cell therapy

a



b



Conclusions

- Immune checkpoint inhibitors continue to advance into earlier lines of therapy.
 - Muscle invasive bladder cancer
- Next-generation checkpoint inhibitors are in Phase 3 trials
 - PD-L1 x VEGF
 - PD-1 x IL2
- T cell engagers are gaining traction in solid tumors.
- Only a minority of patients who could benefit from CAR T cells receive them.
- Cell therapies are gaining traction in solid tumors.

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