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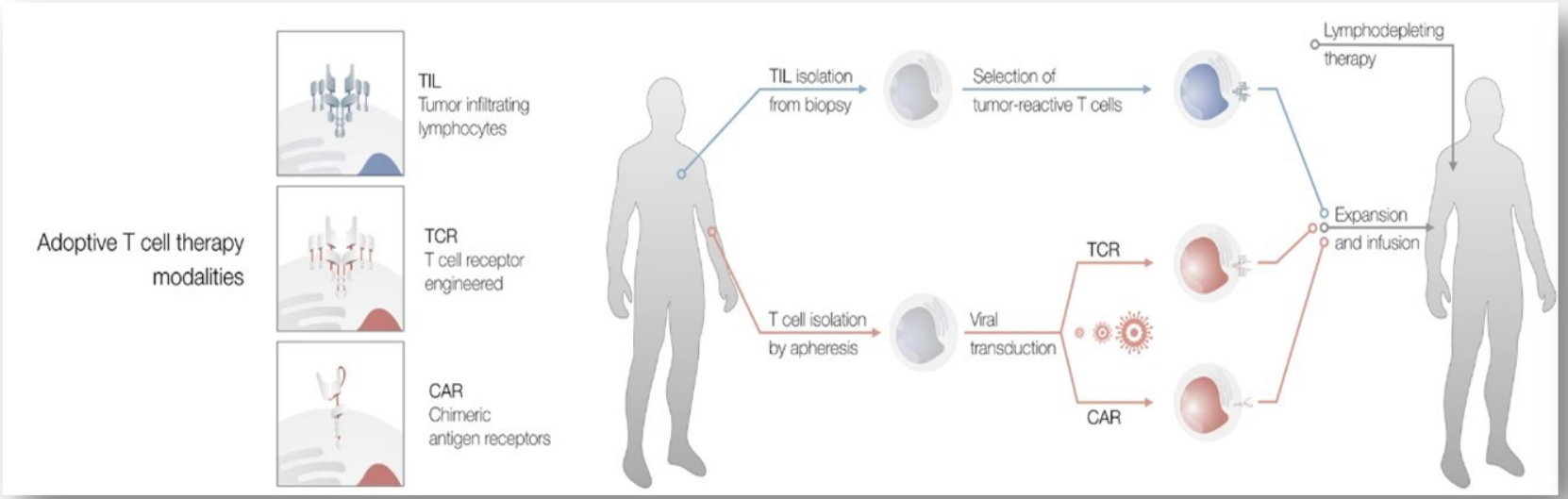
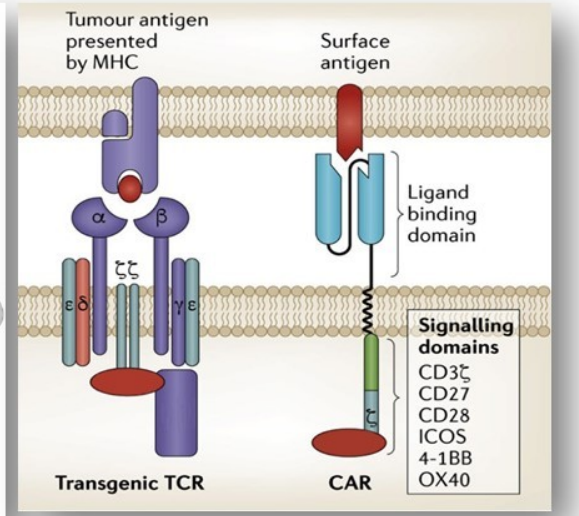
Cellular therapy in GU cancers

Prof Vijay M Patil

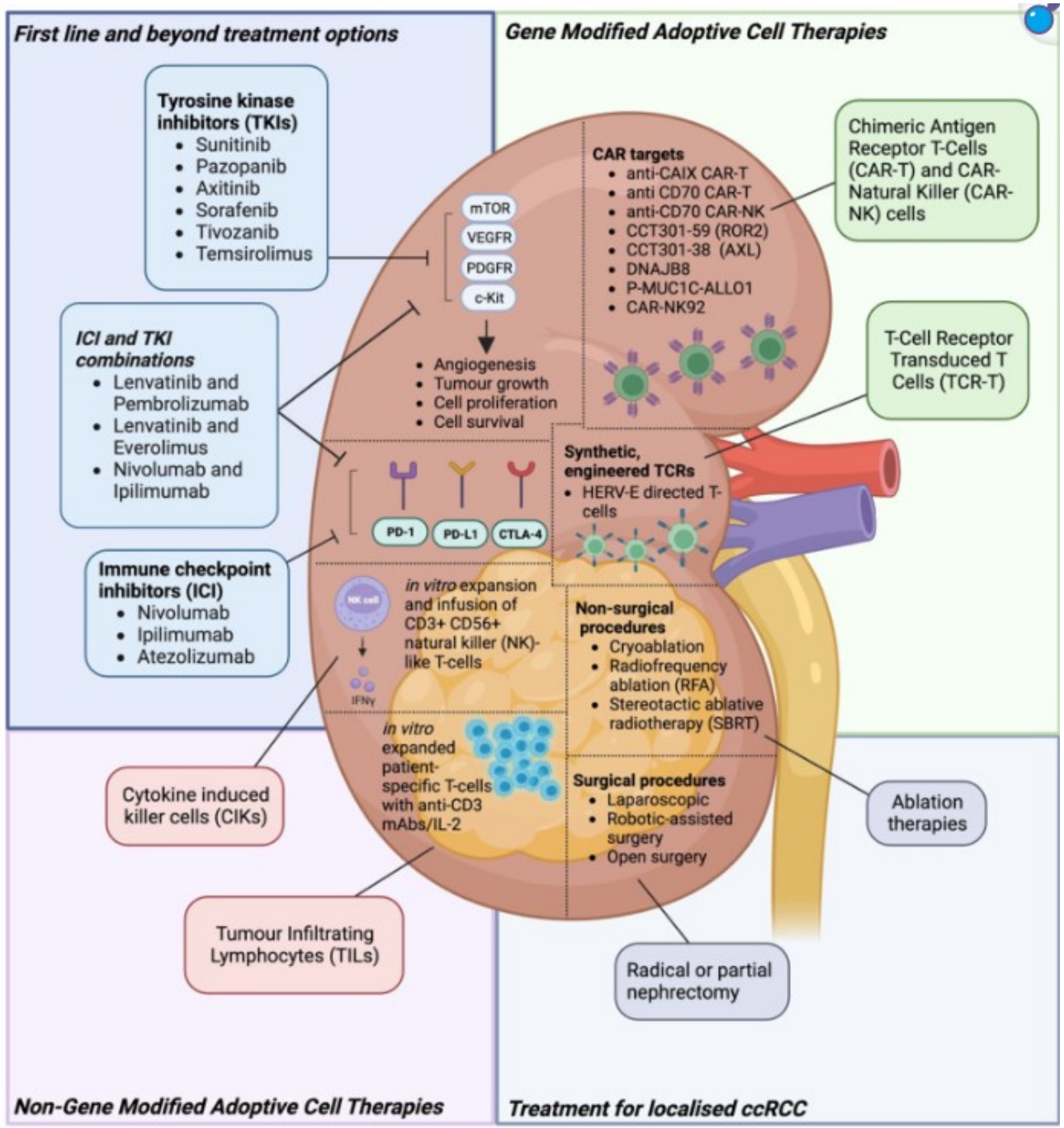
Adoptive T-cell therapy: CAR-T vs TCR-T vs TIL therapy





ACT	CAR-T	TCR-T	TIL
Cell source	PBMC, iPSC	PBMC, iPSC	TIL from tumor tissue
Recognition	CAR-dependent	TCR-dependent	Natural antigen recognition
Infiltration	Low	Low	High
Killing by	Perforin, granzyme, cytokine		
Off the shelf	Low possibility	Low possibility	-

Kruger et al. Journal of Experimental & Clinical Cancer Research 2019; Zhang P, et al. J of hematology and Oncology 2023; Garber K, et al. Nature Biotechnology 2018



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RCC is a immunogenic tumour

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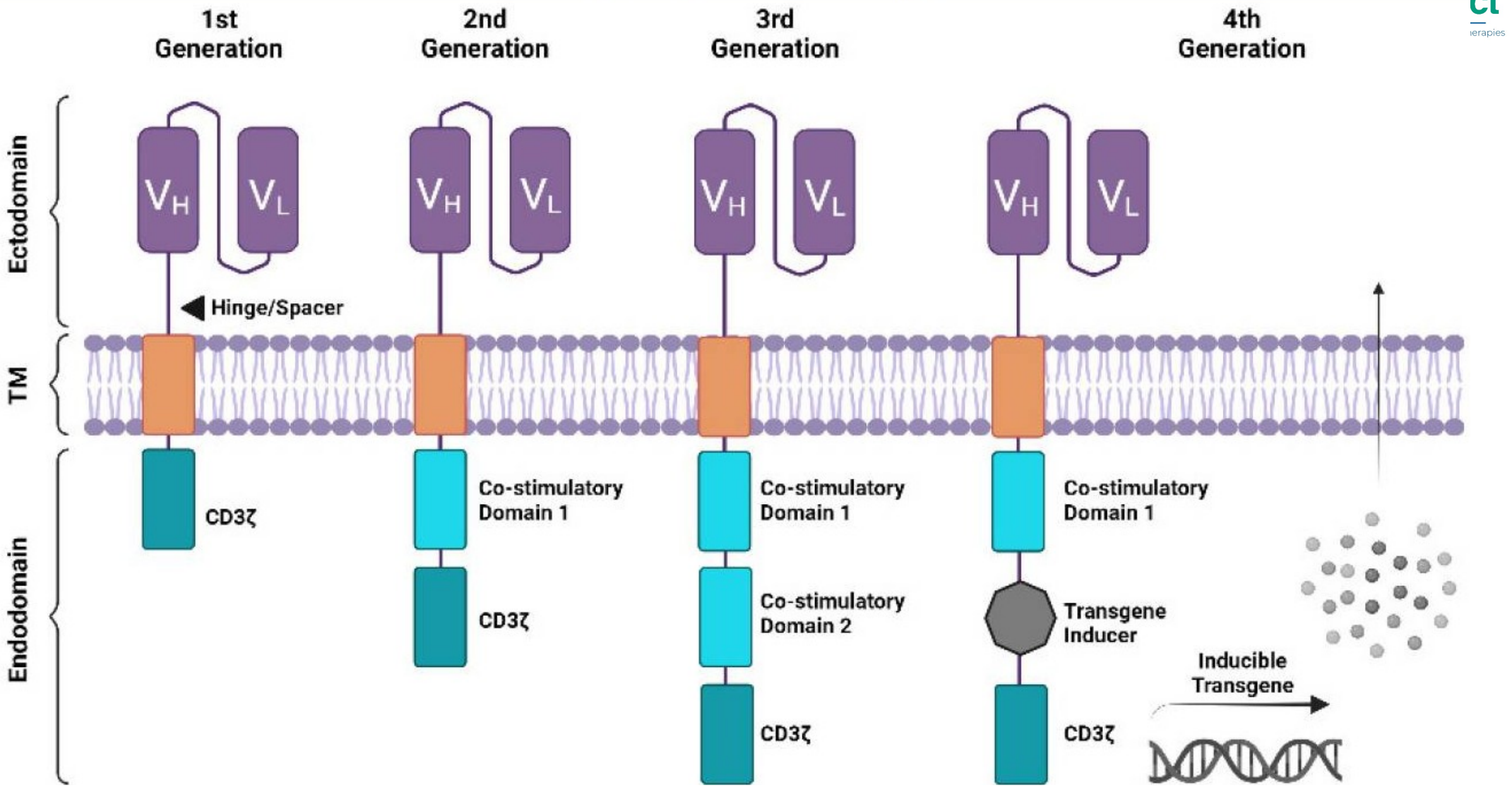
CAR-T


1st Generation
2nd Generation
3rd Generation
4th Generation
Ectodomain
TM
Endodomain
VH
VL
Hinge/Spacer
CD3ζ
Co-stimulatory Domain 1
Co-stimulatory Domain 2
Transgene Inducer
Inducible Transgene

Target	Study phase	Target accrual	Arms	Primary endpoints	Country	NCT identifier
CAIX	I	20	Lymphodepleting chemotherapy + G250 mAb + CAR T cells + IL-2	MTD	China	NCT04969354
MUC1-C	I	100	Allogeneic CAR T cells	MTD, AEs, ORR	USA	NCT05239143
CD70	I	48	Intravenous infusion vs intraperitoneal injection of autologous CAR T cells	RP2D; safety of RP2D	China	NCT06010875
CD70	I	24	Autologous CAR-T cells	MTD	China	NCT05420519
CD70	I	24	Intravenous infusion vs intraperitoneal injection of autologous CAR T cells	MTD	China	NCT05518253
CD70	I	36	Autologous CAR-T cells	MTD	China	NCT05420545
CD70	I	48	Intravenous infusion vs intraperitoneal injection of autologous CAR T cells	MTD	China	NCT05468190
CD70	I	120	Lymphodepleting chemotherapy + allogeneic CAR T cells	DLT	USA	NCT04696731
CD70	I/II	124	Lymphodepleting chemotherapy + autologous CAR T cells	AEs, ORR	USA	NCT02830724
CD70	I/II	250	Lymphodepleting chemotherapy + allogeneic CAR T cells	DLT, ORR	USA	NCT05795595

AEs: Adverse Events; CAIX: Carbonic anhydrase IX; CAR: chimeric antigen receptor DLT: Dose Limiting Toxicity; IL-2: interleukin 2; MTD: Maximal Tolerated Dose; MUC1-C: Mucin 1 C-terminal; ORR: Overall Response Rate; RP2D: Recommended Phase 2 Dose.

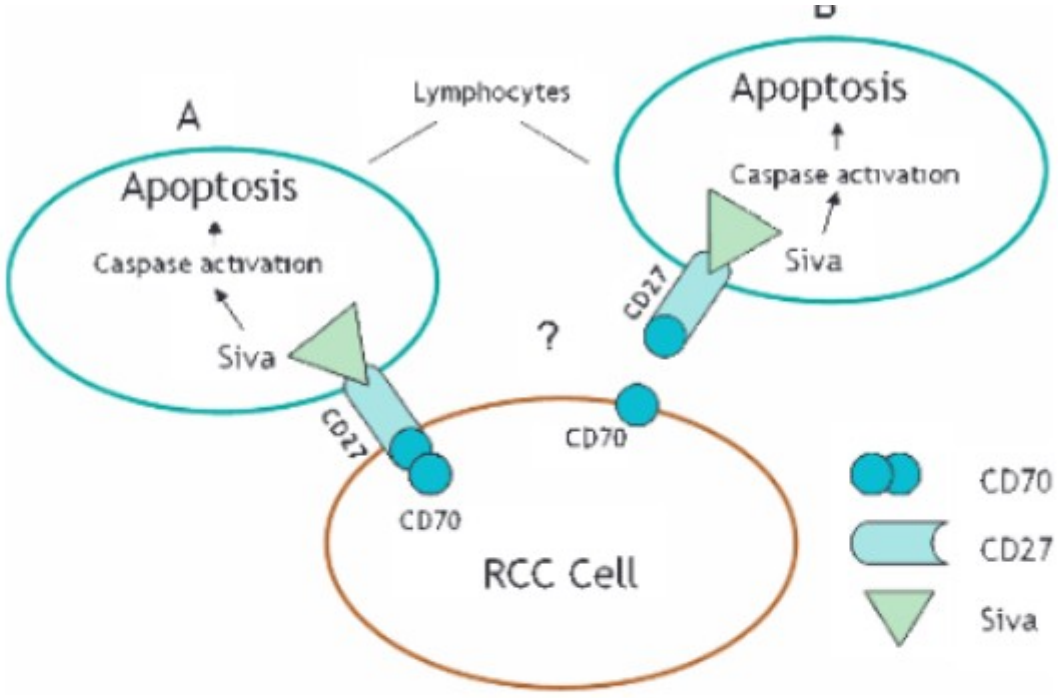


Figure 4. *Schematic representation of apoptosis induction through CD70 expression in RCC cells. (A) Apoptosis induction through cell–cell contact. CD27 receptor is expressed by lymphocytes, and CD70 ligand is membrane-bound in RCC cells. Apoptosis is induced after the binding of death-domain substitute SIVA, which initiates caspase activation. (B) Apoptosis induction without cell–cell contact. Membrane-bound CD70 ligand is cleaved and binds to the CD27 receptor. Apoptosis is induced after the binding of death-domain substitute SIVA, which initiates caspase activation.*

Immune Escape for Renal Cell Carcinoma: CD70 Mediates Apoptosis in Lymphocytes

Meeting Abstract: 2022 ASCO Genitourinary Cancers Symposium

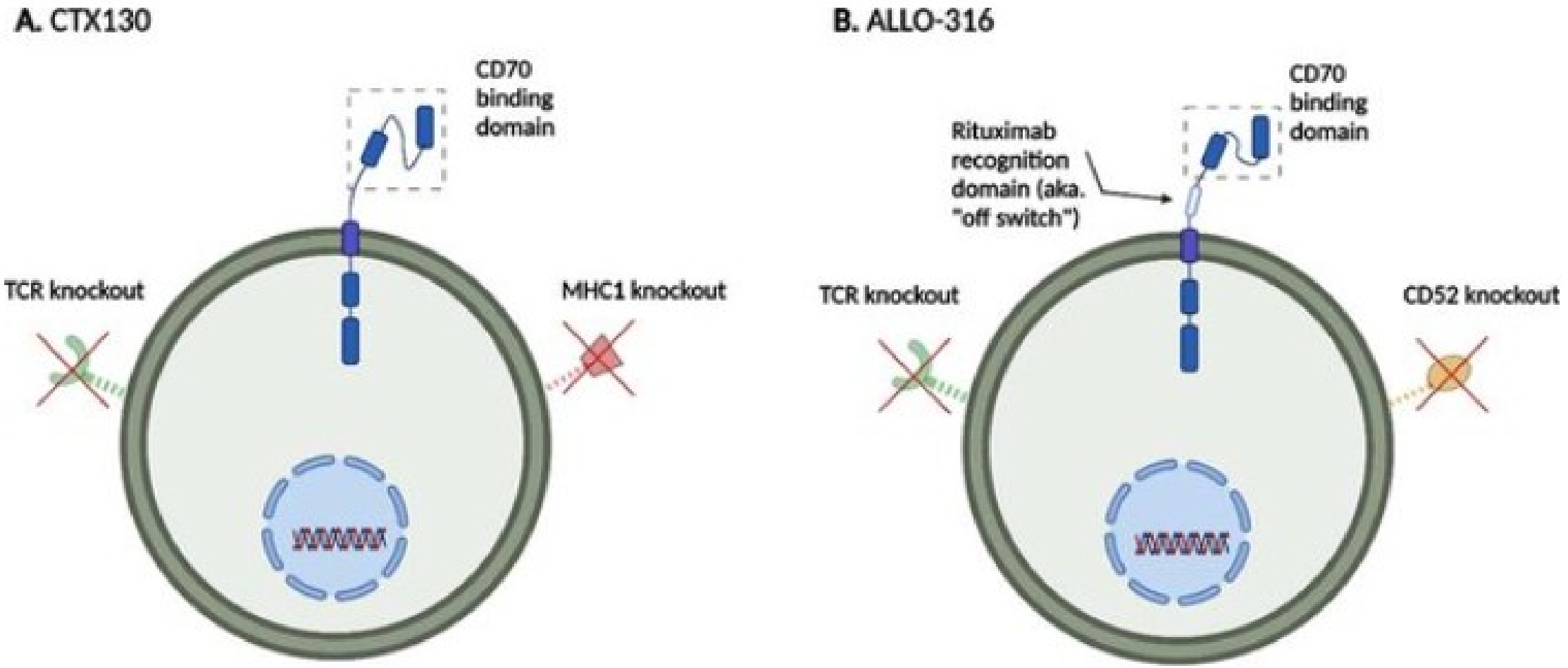
FREE ACCESS | Renal Cell Cancer | February 16, 2022

CD70 is a promising CAR-T cell target in patients with advanced renal cell carcinoma.

Authors: Huihui Ye, Rong Rong Huang, Brian M. Shuch, Zhengshan Chen, Jonathan W. Said, Allan J. Pantuck, and Siler Panowski | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 40, Number 6_suppl • https://doi.org/10.1200/JCO.2022.40.6_suppl.384

- When the positive cutoff was defined as ≥1% of tumor cells demonstrating CD70 staining, the positive rate in CCRCC, pRCC, ChRCC, CDC, and SarRCC was 98%, 32%, 0%, 11%, and 46%, respectively.
- When the positive cutoff was defined as ≥ 25% of tumor cells stained positive for CD70, the positive rate in CCRCC, pRCC, ChRCC, CDC, and SarRCC was 41%, 10%, 0%, 0%, and 23%, respectively.
- Finally, when the positive cutoff was defined as ≥50%, the positive rate in CCRCC, pRCC, ChRCC, CDC, and SarRCC was 22%, 2%, 0%, 0%, and 8%, respectively.


A. CTX130
CD70 binding domain
TCR knockout
MHC1 knockout
B. ALLO-316
CD70 binding domain
Rituximab recognition domain (aka. "off switch")
TCR knockout
CD52 knockout

Regular and Young Investigator Award Abstracts
Clinical Trials Completed

558 CTX130 allogeneic CRISPR-Cas9–engineered chimeric antigen receptor (CAR) T cells in patients with advanced clear cell renal cell carcinoma: Results from the phase 1 COBALT-RCC study FREE

Sumanta Pal [1], Ben Tran [2], John Haanen [3], Michael Hurwitz [4], Adrian Sacher [5], Neeraj Agarwal [6], Nizar Tannir [7], Elizabeth Budde [1], Simon Harrison [2], Sebastian Klobuch [3], Sagar Patel [6], Mary Lee Dequeant [8], Verena Karsten [9], Kaitlyn Cohen [8], Ellen Gurary [8], Henia Dar [8], Anna Ma [8], Anjali Sharma [8] and Samer Srour [7]

- All patients had stage IV disease, and received a median of 3 (range, 1-6) prior treatments.
- Six (out of 14) patients had documented refractory disease at study entry.
- Median CD70 expression level on the tumors was 100% (range, 1-100%).

Efficacy & Adverse event

- Adverse event
  - Seven (50%) patients experienced grade (Gr) 1-2 cytokine release syndrome (CRS); there was no Gr≥3 CRS.
  - Three patients experienced serious adverse events (SAEs) related to CTX130; all were episodes of CRS.
- Efficacy
  - One patient (7.7%) had a durable complete remission (CR) maintained at 18+ months and 9 (69.2%) patients had stable disease (SD) with 4 patients (30.8%) in SD at 4 months.
  - The disease control rate (CR + partial response + SD) was 76.9%.

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ORAL PRESENTATIONS - PROFFERED ABSTRACTS | APRIL 05 2024

Abstract CT002: CTX130 allogeneic CRISPR-Cas9-engineered chimeric antigen receptor (CAR) T cells in patients with advanced clear cell renal cell carcinoma: Long-term follow-up and translational data from the phase 1 COBALT-RCC study FREE

Sumanta Kumar Pal; Ben Tran; John B. Haanen; Michael Hurwitz; Adrian Sacher; Neeraj Agarwal; Nizar Tannir; Elizabeth Budde; Simon Harrison; Sebastian Klobuch; Sagar S. Patel; Mary-Lee Dequeant; Qiuling Ally He; Alissa Keegan; Henia Dar; Anna Ma; PK Morrow; Samer A. Srour

- 1 patient (6.3%) achieved a complete response (CR) (now extending over 36+ months)
- 12 additional patients (75%) achieved stable disease (SD) (1 patient in excess of 18 months), reflecting a disease control rate (CR/partial response/SD) of 81.3%.

Durable response

Expansion of CAR-T

- Using digital droplet PCR assays of the CAR construct, we assessed expansion.
- CTX130 was detected in 20 minutes after infusion, declined to a nadir 2-3 days later, followed by rapid expansion between days 7 and 15.
- In general, expansion increased at each dose level.

Abstract CT011: A phase 1 multicenter study (TRAVERSE) evaluating the safety and efficacy of ALLO-316 following conditioning regimen in pts with advanced or metastatic clear cell renal cell carcinoma (ccRCC) FREE

Samer Srour; Ritesh Kotecha; Brendan Curti; Jad Chahoud; Alexandra Drakaki; Lily Tang; Lovely Goyal; Sacha Prashad; Victoria Szenes; Kevin Norwood; Sumanta Pal

- 18 pts with ccRCC (median age: 63 yrs; 82% male) were enrolled
- All (100%) 17 pts who received ALLO-316, had metastatic disease with 3 lines (median) of prior therapy.

ALLO-316 is an anti-CD70 allogeneic CAR T cell product that utilizes TALEN® gene editing to knock out TCRα constant gene to reduce the risk of graft-versus-host disease (GvHD) and knock out CD52 gene to permit use of ALLO-647 (a humanized anti-CD52 mAb) to selectively deplete host T cells without affecting allogeneic CAR T cells

Efficacy & Adverse event

- Adverse event
  - Eleven (65%) of these pts experienced CRS, all low Gr except one (6%) Gr 3.
  - No ICANS or GVHD was observed.
- Efficacy
  - Three pts achieved best overall response of PR at all time points with two PRs confirmed at subsequent visits; ORR = 12% and disease control rate (DCR) = 71%.
  - In pts with confirmed CD70+ tumors (n=9), confirmed ORR = 22% (unconfirmed ORR = 33%) and DCR = 100%.

CAR-T (CD 70)

- ✓Allogenic
- ✓No waiting
- ✓GVHD risk
- ✓DCR are seen durable

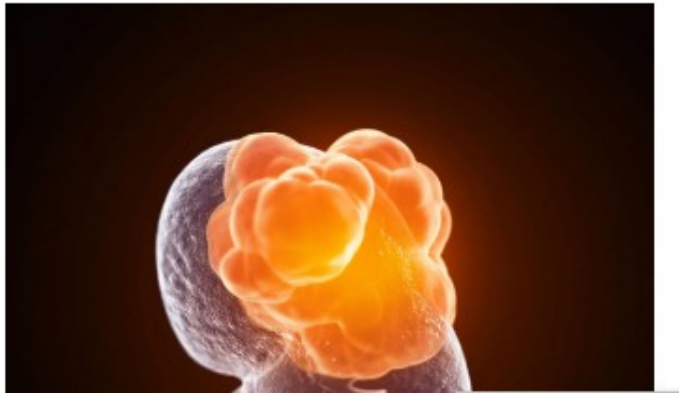
FDA Grants Fast Track Designation to ADI-270 in Advanced Clear Cell RCC

July 9, 2024
By Russ Conroy

News *Article*

Developers designed ADI-270 to potentially improve clinical responses in patients with renal cell carcinoma and other CD70-positive tumors.

The FDA has granted fast track designation to the investigational CAR T-cell therapy ADI-270 as a treatment for patients with metastatic or advanced clear cell renal cell carcinoma (RCC) previously treated with an immune checkpoint inhibitor and a VEGF inhibitor, according to a press release from the developer, Adicet Bio, Inc.[1]



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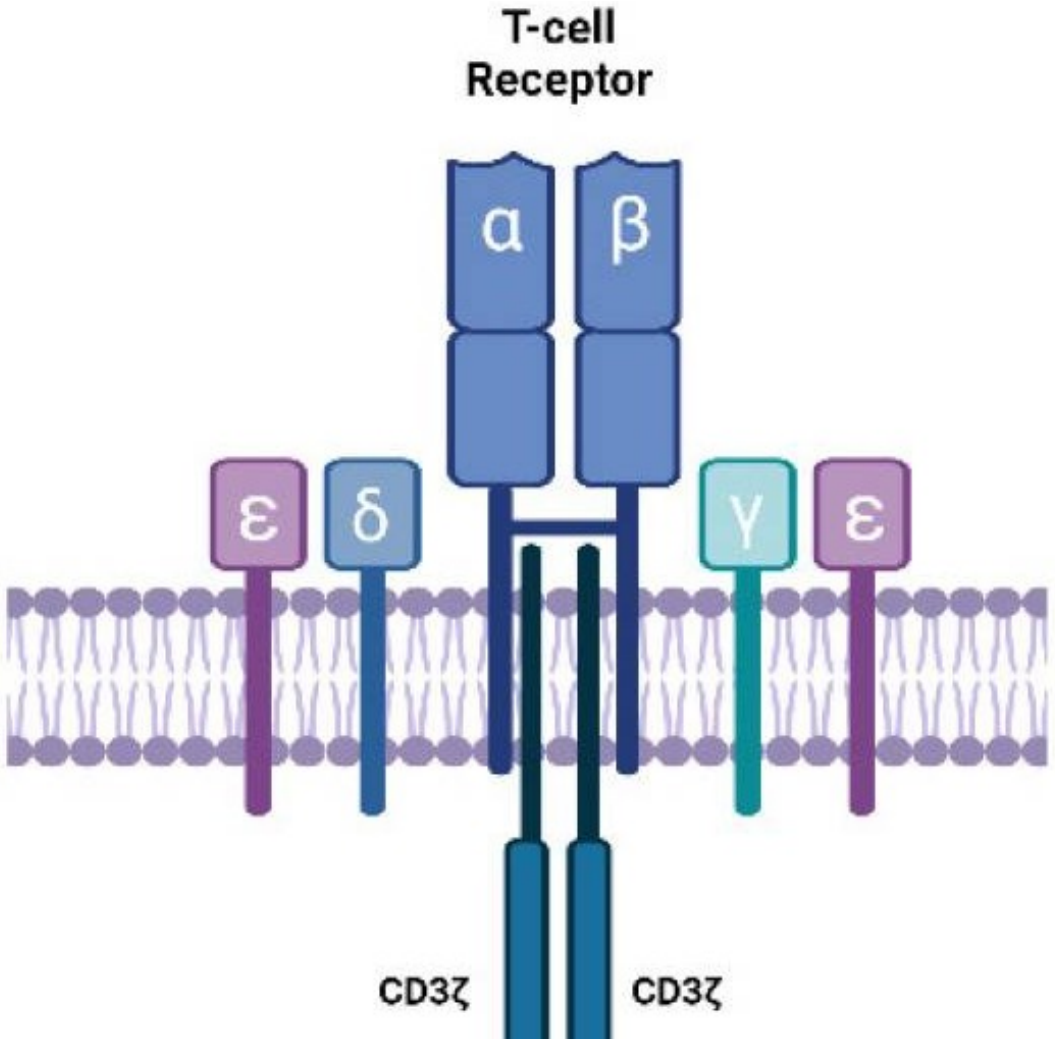
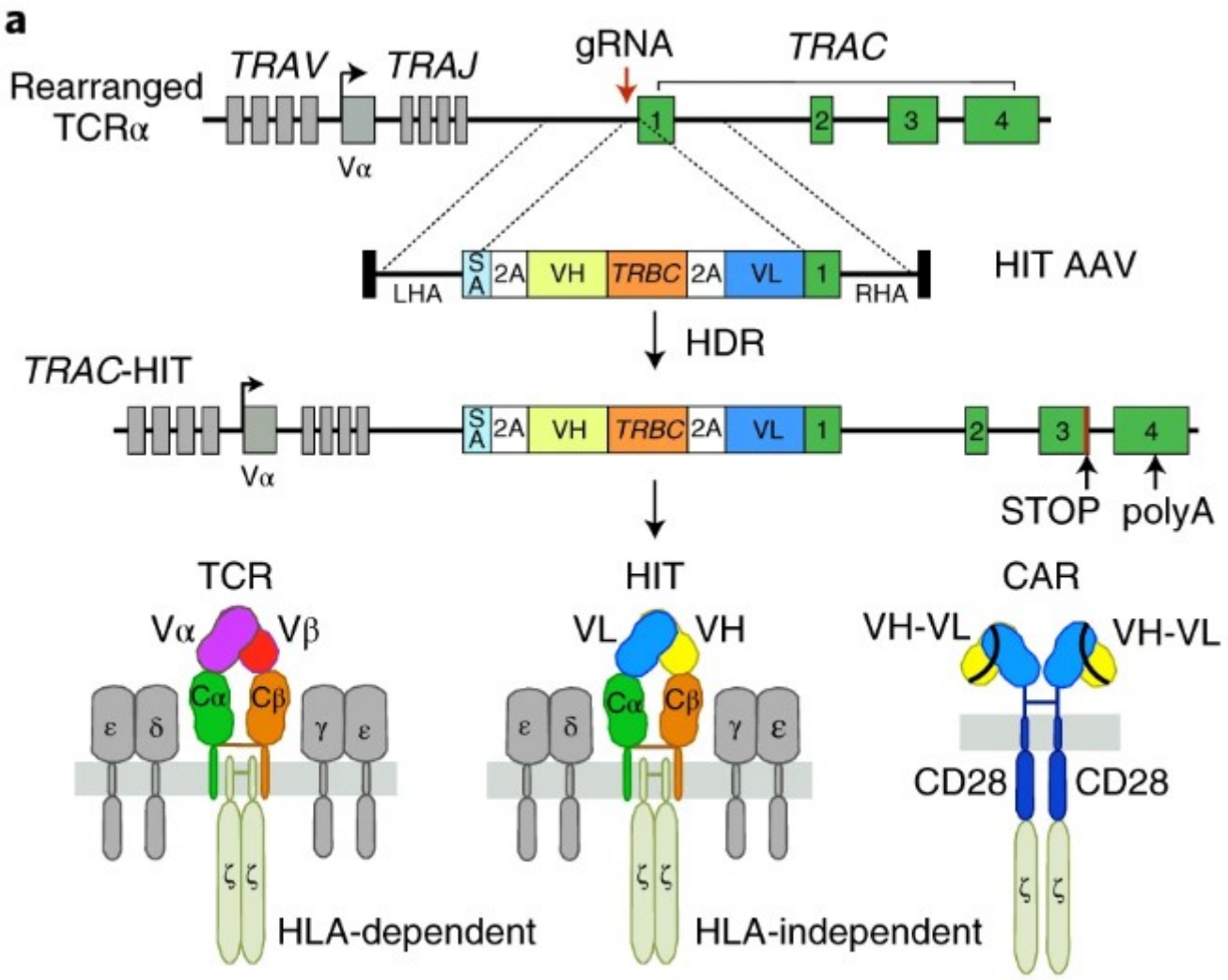
TCR


T-cell
Receptor
α
β
ε
δ
γ
ε
CD3ζ
CD3ζ


a
Rearranged
TCRα
TRAV
TRAJ
Vα
gRNA
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4
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VH-VL
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CD28
CD28
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Meeting Abstract: 2023 ASCO Annual Meeting I

FREE ACCESS | Developmental Therapeutics—Immunotherapy | May 31, 2023

Phase I results of human endogenous retrovirus type-E (HERV-E) TCR transduced T-cells in patients (pts) with metastatic clear cell renal cell carcinoma (mccRCC).

Authors: Rosa Nadal, Stefan Barisic, Gina M. Scurti, Elena Cherkasova, Long Chen, Kristen Wood, Steven L. Highfill, ... SHOW ALL ..., and Richard W. Childs | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 41, Number 16_suppl • https://doi.org/10.1200/JCO.2023.41.16_suppl.2549

- HERV-E TCR contain T-cells engineered to express an HLA-A*11 restricted HERV-E TCR and a truncated CD34 cassette for *in vivo* monitoring.

- 14 HLA-A*11+ pts (median age 56) were treated including 3 pts in each DLs 1-3 & 5 pts in DL4. 86% had ≥ 3 prior treatment lines (range 1-7): 36% had high-dose IL2, 57% Ipilimumab-Nivolumab & 50% ≥ 3 lines of anti-VEGFR therapy.
- Best response included 7% pts with partial response & 29% with stable disease ≥ 8 weeks.

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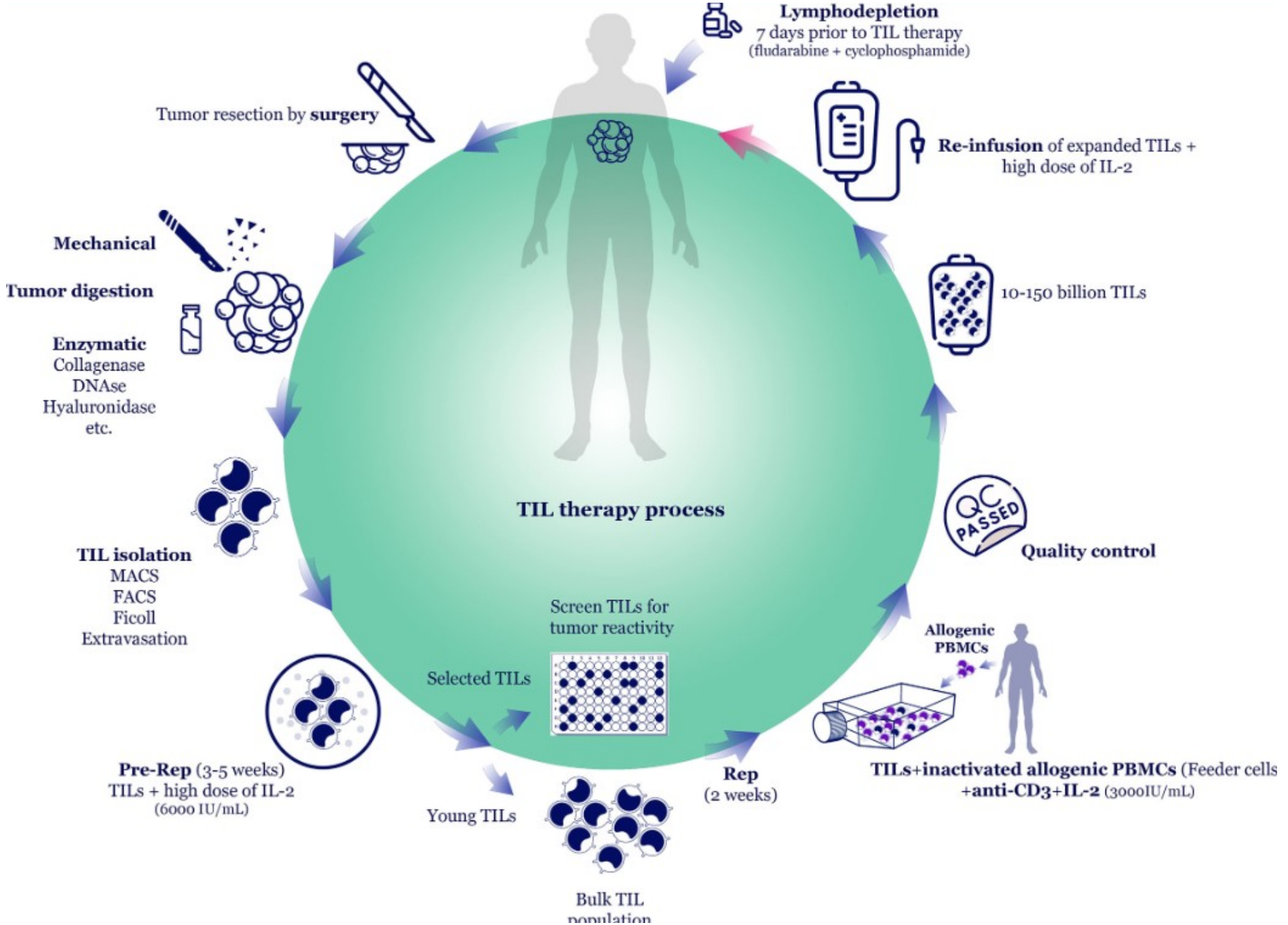
TIL


Lymphodepletion
7 days prior to TIL therapy
(fludarabine + cyclophosphamide)
Re-infusion of expanded TILs + high dose of IL-2
10-150 billion TILs
Quality control
QC PASSED
Allogenic PBMCs
TILs+inactivated allogenic PBMCs (Feeder cells +anti-CD3+IL-2 (3000IU/mL)
Rep
(2 weeks)
Bulk TIL population
Young TILs
Selected TILs
Screen TILs for tumor reactivity
Pre-Rep (3-5 weeks)
TILs + high dose of IL-2
(6000 IU/mL)
TIL isolation
MACS
FACS
Ficoll
Extravasation
Enzymatic
Collagenase
DNAse
Hyaluronidase
etc.
Mechanical
Tumor digestion
Tumor resection by surgery
TIL therapy process

Meeting Abstract: 2025 ASCO Genitourinary Cancers Symposium

FREE ACCESS | Renal Cell Cancer | February 18, 2025

Optimizing clear cell renal cell carcinoma tumor-infiltrating lymphocytes under controlled hypoxic conditions.

Authors: Jad Chahoud, Marine Potez, Christopher Guske, Justin Miller, Johannes Ali, Michael Carter, Fatema Khambati, ... SHOW ALL ..., and Shari Pilon-Thomas | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 43, Number 5_suppl • https://doi.org/10.1200/JCO.2025.43.5_suppl.581

Meeting Abstract: 2025 ASCO Genitourinary Cancers Symposium

FREE ACCESS | Renal Cell Cancer | February 18, 2025

The feasibility of tumor-infiltrating lymphocyte expansion in non-clear cell renal cell carcinoma.

Authors: Christopher Guske, Marine Potez, Justin Miller, Jeffrey S Johnson, Johannes Ali, Michael Carter, Fatema Khambati, ... SHOW ALL ..., and Jad Chahoud | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 43, Number 5_suppl • https://doi.org/10.1200/JCO.2025.43.5_suppl.580

Clinical Trial > J Urol. 1997 Sep;158(3 Pt 1):740-5. doi: 10.1097/00005392-199709000-00012.

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Treatment of metastatic renal cell carcinoma with nephrectomy, interleukin-2 and cytokine-primed or CD8(+) selected tumor infiltrating lymphocytes from primary tumor

R A Figlin [1], W C Pierce, R Kaboo, C L Tso, N Moldawer, B Gitlitz, J deKernion, A Belldegrun

Affiliations + expand

PMID: 9258071 DOI: 10.1097/00005392-199709000-00012

N=62

Overall 5 patients (9.1%) achieved a complete response and 14 (25.5%) achieved a partial response.

The responses were durable with a median duration of 14 months (range 0.8+ to 64+). The actuarial survival was 65% at 1 year and 43% at 2 years from the time of nephrectomy, with an overall median survival for all patients of 22 months (range 2 to 70+).

The median survival for the responding patients has not yet been reached (range 2 to 63+).

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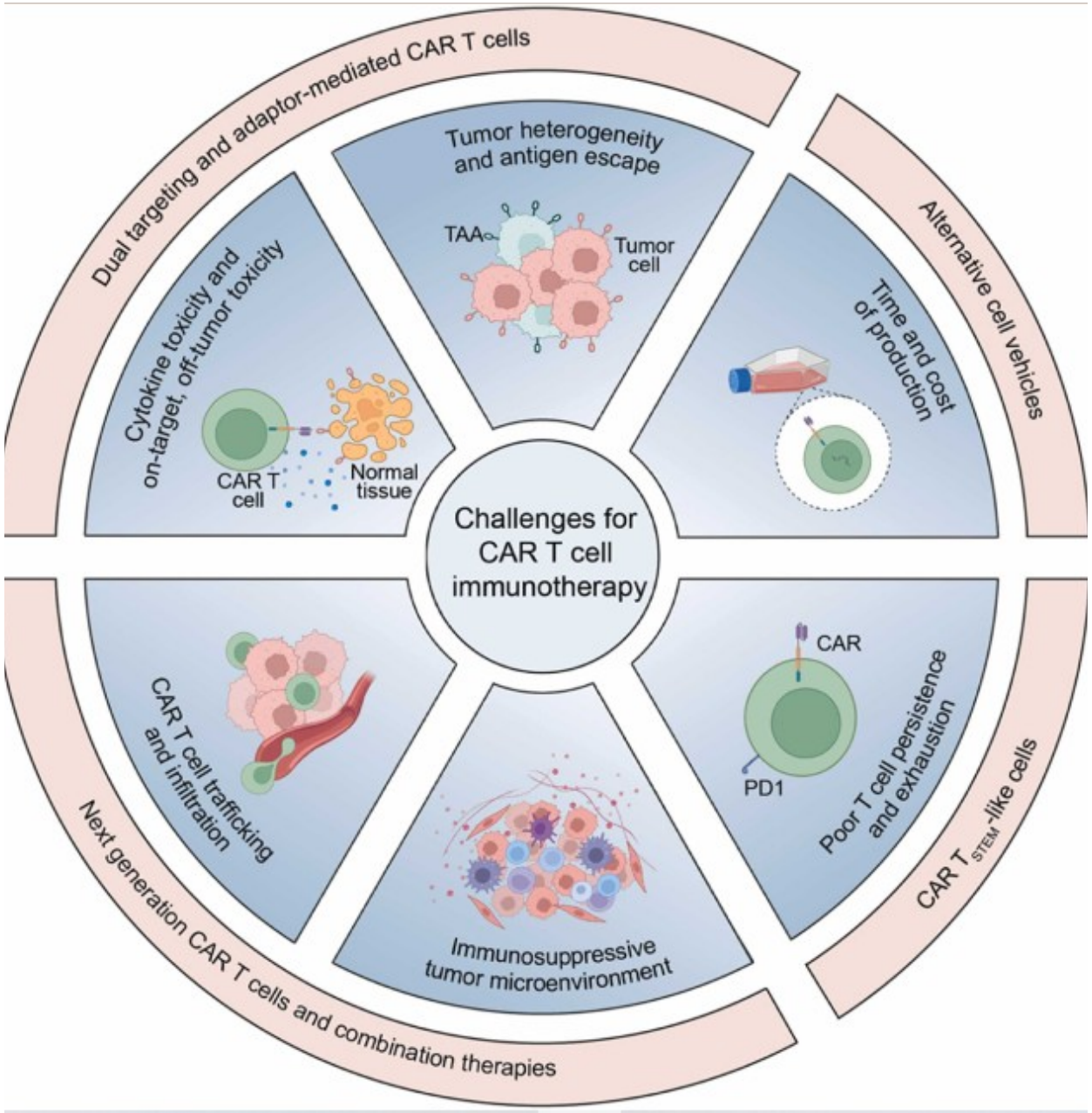
Prostate



Current challenges of CAR T cell immunotherapy for the treatment of prostate cancer and strategies to overcome them.

Porter et al
https://doi.org/10.1016/j.jsbmb.2024.106571

Table 1
Tumor-associated antigens in development for prostate cancer.

Tumor-associated antigen	Cellular localisation	Cellular expression	Immunotherapeutic clinical trials with TAA targets
PSCA	Serine protease	Prostate, bladder and placental epithelium and NE cells within kidney and stomach	Phase 1a and 1b PSCA-CAR T cells (NCT03873805 and NCT05805371) [136]
PSMA	Transmembrane protein	Prostate, renal and breast epithelium, salivary gland, brain and small intestine	Phase 1 PSMA-CAR T cells (NCT04249947) [137,138]
Lewis Y	Oligosaccharide on glycolipds or glycoproteins	Prostate, breast, ovarian, pancreatic, colonic and lung epithelium [139]	Phase 1 Le^{Y}-CAR T cells (NCT03851146) [64]
STEAP1 (Six- Transmembrane Epithelial Antigen of the Prostate 1)	Transmembrane protein	Prostate epithelial cells	Phase 1 STEAP-1 targeted T-cell engager immunotherapy (NCT04221542) Phase 1/2 STEAP-1-CAR T cells (NCT06236139) respectively) [140]
STEAP2 (Six- Transmembrane Epithelial Antigen of the Prostate 2)	Transmembrane protein	Prostate epithelial cells [25]	Phase 1/2 STEAP-2-CAR T cells (NCT06267729) [25]
MUC1-C (Mucin 1)[141]	Heterodimer: transmembrane target unit MUC1-C	Prostate, lung, liver, colon, breast, pancreatic and ovarian epithelial cells [141,142]	Phase 1/2 MUC1-C-CAR T cells (NCT05812326)[143]
DLL3 (Delta-like ligand 3)	Intracellular compartments in normal tissue, cell surface expression on cancer cells	Small cell lung carcinoma; Neuroendocrine prostate cancer; High-grade NED tumors; minimal to no expression on normal cells [144–146]	Phase 1 trial in relapsed/refractory small cell lung cancer (SCLC) Phase 1 trial of DLL3-CAR-NK cells in patients with relapsed/refractory ES-SCLC (NCT05507593)
CEACAM5	Cell surface and cytoplasmic	Overexpressed in tumors including non-small cell lung cancer (NSCLC) and pancreatic ductal adenocarcinoma (PDAC) and NEPC [147,148]	Phase I trial of CAR T cells (C-13–60) in the treatment of carcinoembryonic antigen (CEA) positive advanced malignant solid tumors (NCT06043466) [149]

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PSCA

Article | Open access | Published: 12 June 2024

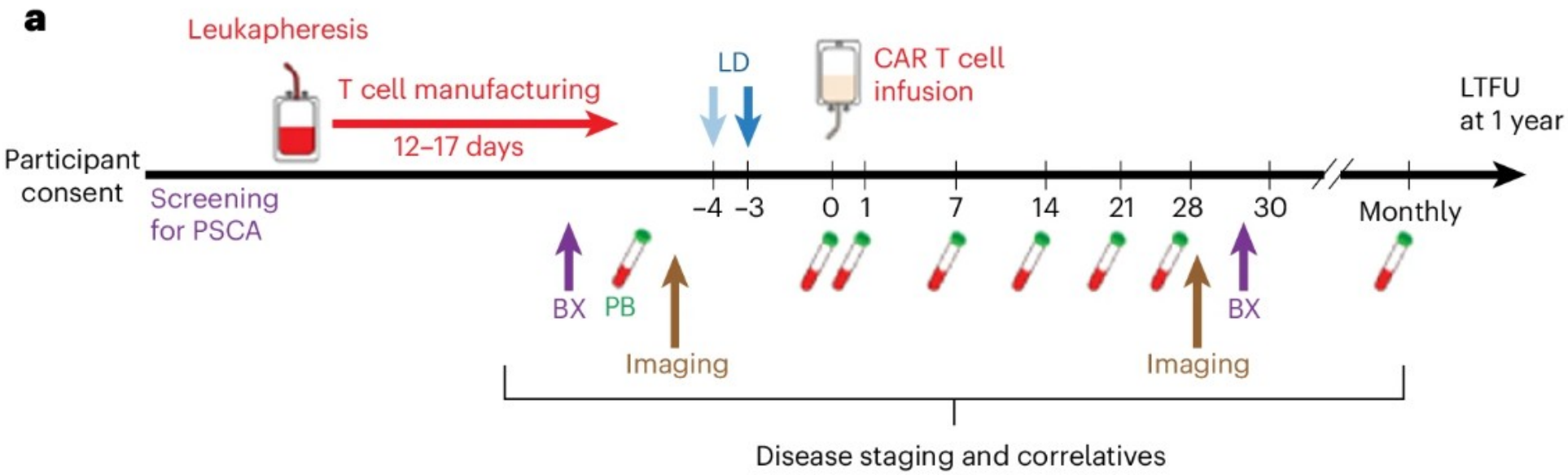
PSCA-CAR T cell therapy in metastatic castration-resistant prostate cancer: a phase 1 trial

Tanya B. Dorff, M. Suzette Blanchard, Lauren N. Adkins, Laura Luebbert, Neena Leggett, Stephanie N. Shishido, Alan Macias, Marissa M. Del Real, Gaurav Dhapola, Colt Egelston, John P. Murad, Reginaldo Rosa, Jinny Paul, Ammar Chaudhry, Hripsime Martirosyan, Ethan Gerdts, Jamie R. Wagner, Tracey Stiller, Dileshni Tilakawardane, Sumanta Pal, Catalina Martinez, Robert E. Reiter, Lihua E. Budde, Massimo D'Apuzzo, ... Saul J. Priceman

+ Show authors

Nature Medicine **30**, 1636–1644 (2024) | Cite this article

From: PSCA-CAR T cell therapy in metastatic castration-resistant prostate cancer: a phase 1 trial



	DL1: 100 M CAR T cells, *n* = 3	DL2: LD + 100 M CAR T cells, *n* = 6	DL3: reduced LD + 100 M CAR T cells, *n* = 5
Age (years) median (range)	62 (59–69)	70 (42–73)	69 (62–72)
Race:			
White	3 (100)	6 (100)	3 (60)
Black	0	0	2 (40)
Asian	0	0	0
Other/unknown	0	0	0
Previous treatment:			
Enzalutamide	3 (100)	5 (83)	2 (40)
Abiraterone	3 (100)	6 (100)	2 (40)
Both	3 (100)	5 (83)	1 (20)
Previous treatment:			
Docetaxel	2 (67)	5 (83)	5 (100)
Cabazitaxel	2 (67)	3 (50)	3 (60)
Both	2 (67)	3 (50)	3 (60)
Baseline PSA median (range)	16.5 (10.7–20.4)	88.0 (11.7–590.2)	235.3 (1.79–3,260)
Lymph node only	2 (67)	1 (17)	0
Bone ± lymph node	0	4 (67)	4 (80)
Visceral	1 (33)	1 (17)	1 (20)

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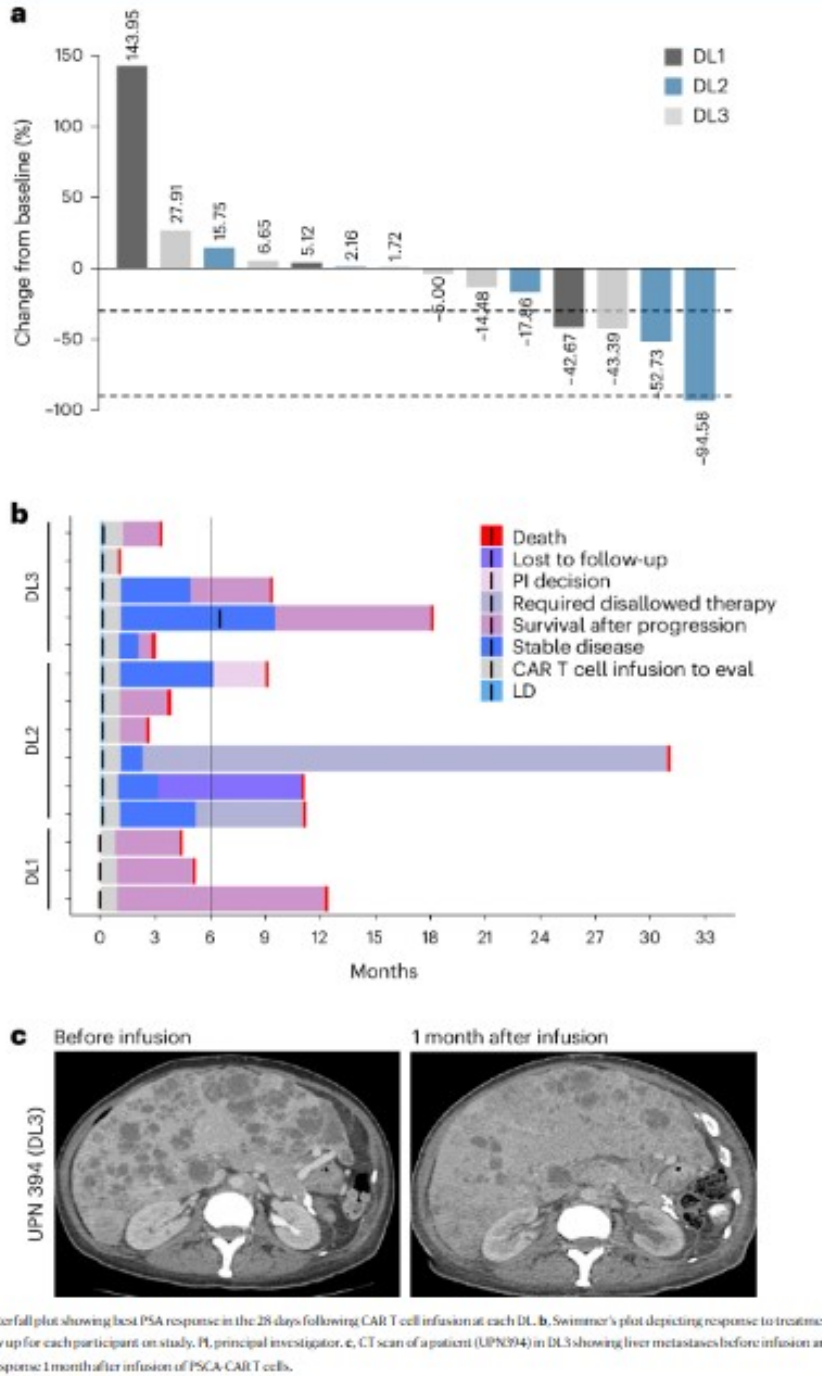
Heavily pretreated
All exposed to Novel hormones and chemotherapy



PSA waterfall plot showing best PSA response in the 28 days following CAR T cell infusion at each DL. **b**, Swimmer's plot depicting response to treatme
d follow up for each participant on study. PI, principal investigator. **c**, CT scan of a patient (UPN394) in DL3 showing liver metastases before infusion a
sease response 1 month after infusion of PSCA-CAR T cells.

No DLTs were observed at DL1, with a DLT of grade 3 cystitis encountered at DL2, resulting in addition of a new cohort using a reduced LD regimen + 100 M CAR T cells (DL3). No DLTs were observed in DL3.

Cytokine release syndrome of grade 1 or 2 occurred in 5 of 14 treated patients.

Prostate-specific antigen declines (>30%) occurred in 4 of 14 patients, as well as radiographic improvements.

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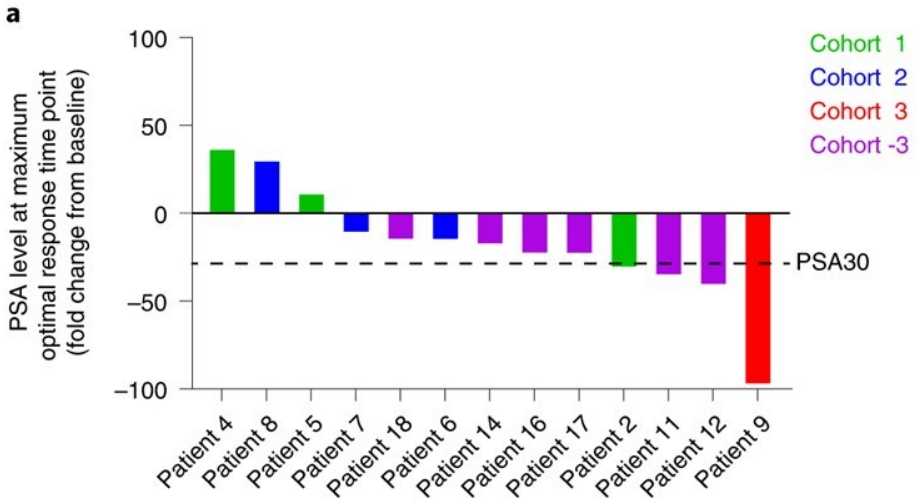
PSMA

PSMA CAR-Ts: Mixed Results To Date

Lower efficacy, unwieldy toxicity

- CART-PSMA with TGFβRDN as functional "armor"
- Pt 9: rapid PSA drop >98%, but fatal toxicity w/ clonal CAR expansion.



Narayan V., et al. *Nat Med* **28**, 724–734 (2022).

- CART-PSMA-TGFβRDN
- Some reductions in PSA
- **Stopped due to severe neurotoxicity & 1 G5 HLH**

McKean M. et al. *J Clin Onc* 40: 6 (Feb 20, 2022) 94

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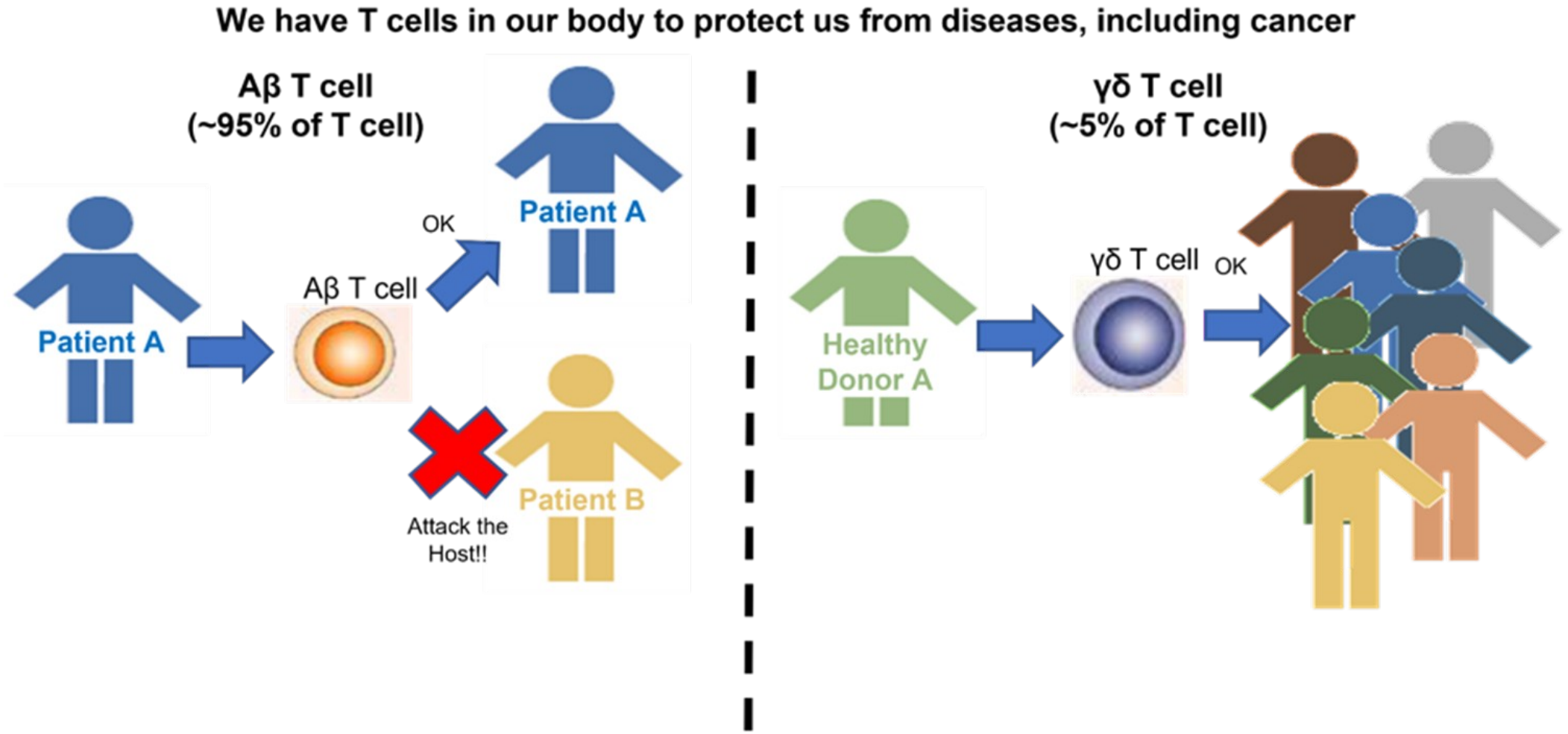
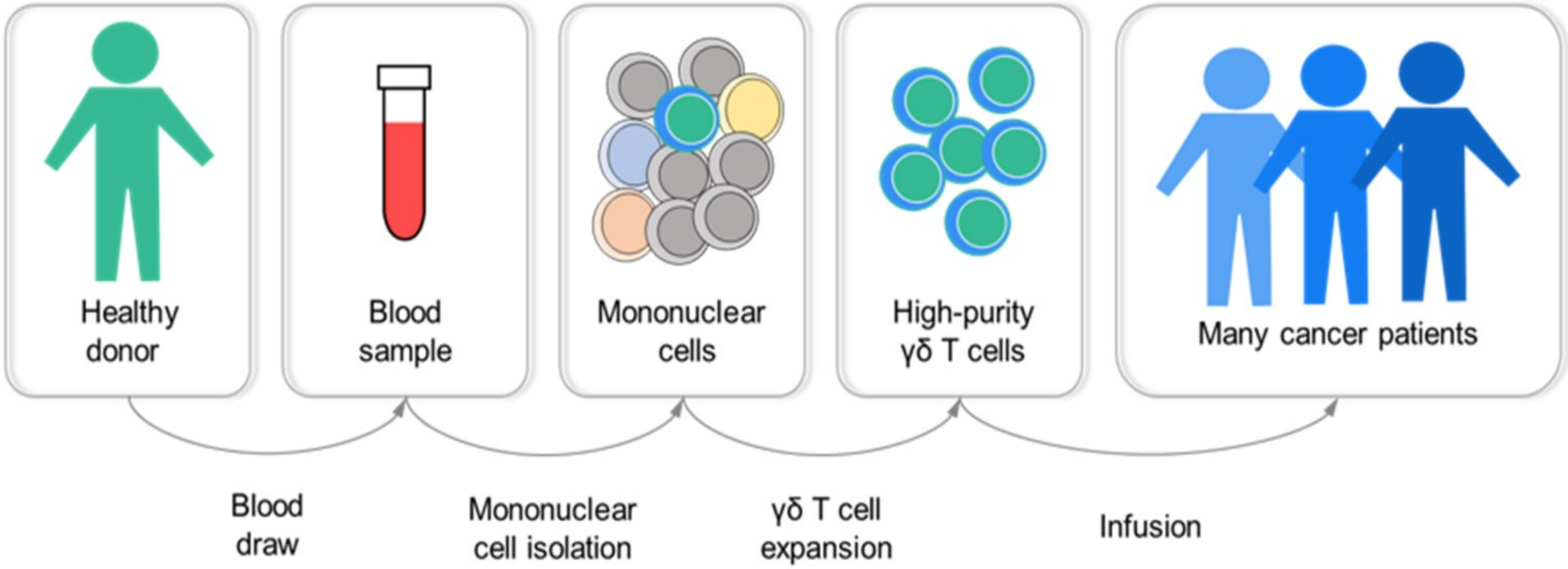
Gamma Delta

Manufacturing of γδ T cells



Flow of manufacturing of γδ T cells:



Tumor type	Ligands Identified
Acute Lymphoblastic Leukemia	28-67% MICA/B 9-20% ULBP1-3
Acute myeloid leukemia	0-75% MICA/B 16-50% ULBP1 4-64% ULBP2 16-100% ULBP3
Bladder carcinoma	70% MICA
Brain cancer	90% MICA/B and ULBP1-3
Breast cancer	35-100% MICA/B, ULBP1-5
Cervical cancer	20% MICA, ULBP2
Chronic lymphatic leukemia	0-85% MICA/B 10-20% ULBP1-3
Chronic myeloid leukemia	28-80% MICA/B 12-20% ULBP1-3
Colorectal cancer	80-100% MICA/B ULBP1-5
Gastric carcinoma	40-100% MICA/B, ULBP2

Tumor type	Ligands Identified
Hepatocellular carcinoma	60-100% MICA
Lymphoma	20-44% MICA/B 12-20% ULBP1-3
Melanoma	50% MICA/B
Multiple myeloma	10-60% MICA 0-34% ULBP1-3
Neuroblastoma	86% MICA/B, ULBP1-3
Non-small-cell lung cancer	20-30% MICA/B, ULBP1-3
Ovarian carcinoma	50-97% MICA/B, ULBP1-5
Pancreatic cancer	68-89.3% MICA/B
Prostate cancer	**75-95% MICA/B, sMICA/B**
Renal carcinoma	>95% MICA/B
Sarcoma	100% MICA/B, ULBP1-3

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Cancer Res. Author manuscript; available in PMC: 2014 Feb 6.

Published in final edited form as: Cancer Res. 2007 Aug 1;67(15):7450–7457. doi: 10.1158/0008-5472.CAN-07-0199

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Targeting Human γδ T Cells with Zoledronate and Interleukin-2 for Immunotherapy of Hormone-Refractory Prostate Cancer

Francesco Dieli [1], David Vermijlen [3], Fabio Fulfaro [2], Nadia Caccamo [1], Serena Meraviglia [1], Giuseppe Cicero [2], Andrew Roberts [3], Simona Buccheri [1], Matilde D'Asaro [1], Nicola Gebbia [2], Alfredo Salerno [1], Matthias Eberl [4,5], Adrian C Hayday [3]

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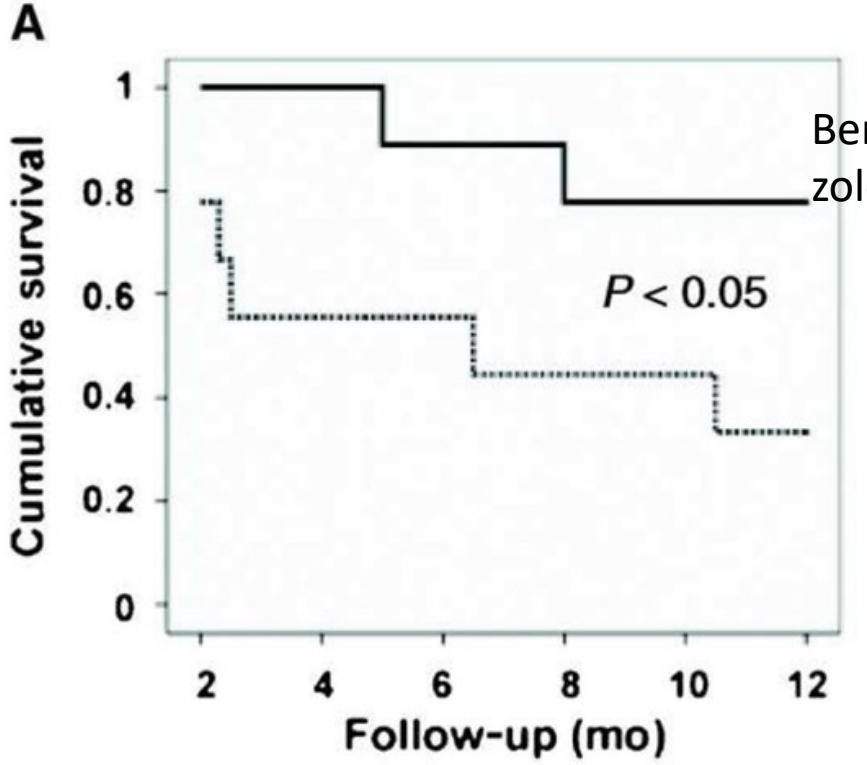
PMCID: PMC3915341 EMSID: EMS55526 PMID: 17671215



Benefit with zolendronic

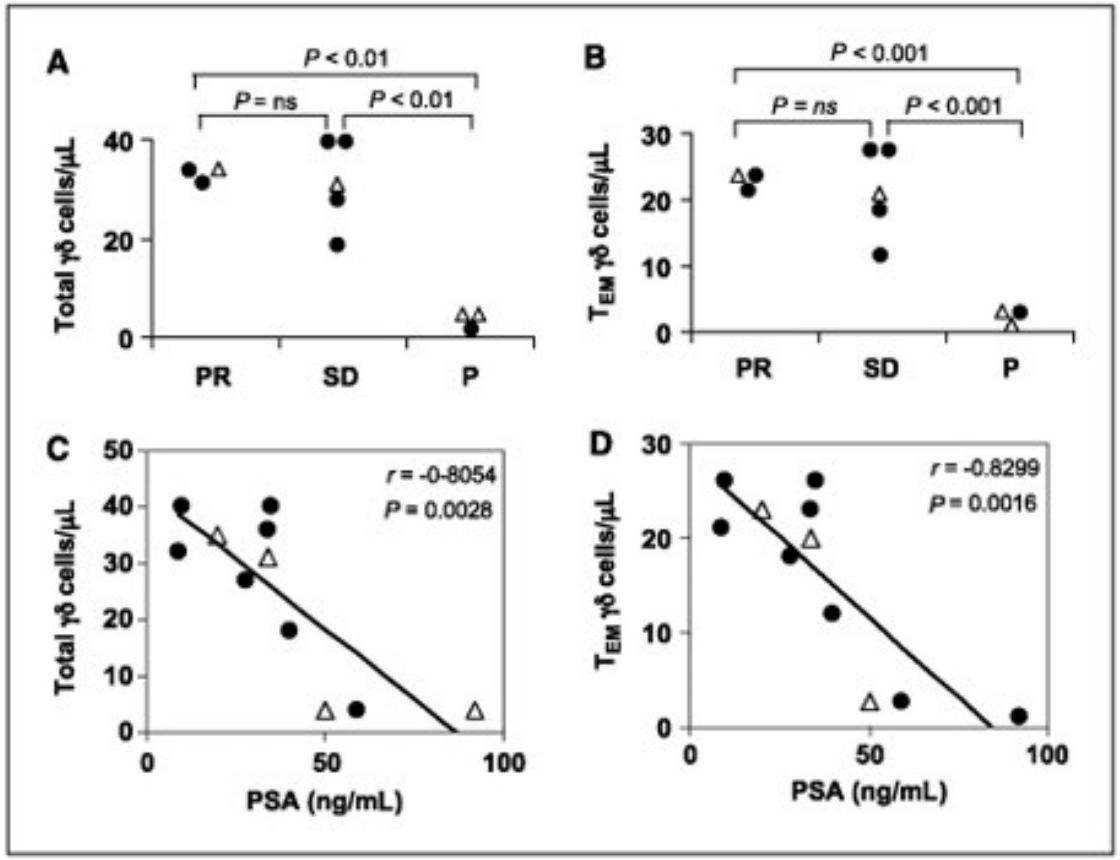


FIGURE 5.
Correlation between γδ T-cell numbers and clinical outcome. *A*, numbers of total γδ cells and (*B*) Vδ2+ γδ T_{EM} cells assessed at 9 mo after therapy are shown in three patients with partial remission, five patients with stable disease, and three patients with progression. •, patients treated with zoledronate + IL-2; △, patients treated with zoledronate alone. *C*, inverse correlation between numbers of total γδ cells and (*D*) of Vδ2+ γδ T_{EM} cells and PSA levels, as assessed at 9 mo after therapy, in three patients with partial remission, five patients with stable disease, and three patients with progression (*P*). •, patients treated with zoledronate+IL-2; △, patients treated with zoledronate alone.

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Gamma Delta CAR-T

Science Advances | AAAS
SIGNIFICANT RESEARCH, GLOBAL IMPACT

In Vivo & animal results

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Sci Adv. 2023 May 3;9(18):eadf0108. doi: 10.1126/sciadv.adf0108

γδ-Enriched CAR-T cell therapy for bone metastatic castrate-resistant prostate cancer

Jeremy S Frieling [1,*,†], Leticia Tordesillas [2,*,†], Xiomar E Bustos [2], Maria Cecilia Ramello [2], Ryan T Bishop [1], Junior E Cianne [2], Sebastian A Snedal [2], Tao Li [1], Chen Hao Lo [1], Janis de la Iglesia [3], Emiliano Roselli [2], Ismahène Benzaïd [2], Xuefeng Wang [4], Youngchul Kim [4], Conor C Lynch [1,*,‡], Daniel Abate-Daga [2,*,‡]

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PMCID: PMC10156127 PMID: 37134157

Journal for ImmunoTherapy of Cancer
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Regular and Young Investigator Award Abstracts
Cell Therapies

286 Systemic distribution of gamma-delta PSCA-CAR T cells in combination with zoledronate in a model of bone metastatic prostate cancer FREE

Leticia Tordesillas , Junior Cianne , Jeremy Frieling , Xiomar Bustos , Conor Lynch and Daniel Abate-Daga

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

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Meeting Abstract: 2023 ASCO Genitourinary Cancers Symposium
FREE ACCESS | Prostate Cancer - Advanced | February 21, 2023

Early dose escalation of LAVA-1207, a novel bispecific gamma-delta T-cell engager (Gammabody), in patients with metastatic castration-resistant prostate cancer (mCRPC).

Authors: Niven Mehra, Debbie Robbrecht, Jens Voortman, Paul WHI Parren, Sonia Macia, Jorden Veeneman, Sanjana Umarale, Benjamin Winograd, Hans J. van der Vliet, and David R Wise | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 41, Number 6_suppl • https://doi.org/10.1200/JCO.2023.41.6_suppl.153

Open label, 3+3 design, phase 1/2a study in patients with therapy refractory metastatic castration resistant prostate cancer

A total of 16 patients have been treated with LAVA-1207 with treatment duration ranging from 1 to 25+ weeks.

PD data show a consistent early reduction in Vγ9Vδ2-T cell frequencies at 2hrs after the first dose, which could be indicative of Vγ9Vδ2-T cell redistribution after treatment, often accompanied by an increase in Vγ9Vδ2-T cell activation markers. Vγ9Vδ2-T cell numbers are restored in the subsequent 3 to 5 days to at least pre-dose levels. Additionally, receptor occupancy of Vγ9Vδ2-T cells was detectable up to 5 days after first dosing.

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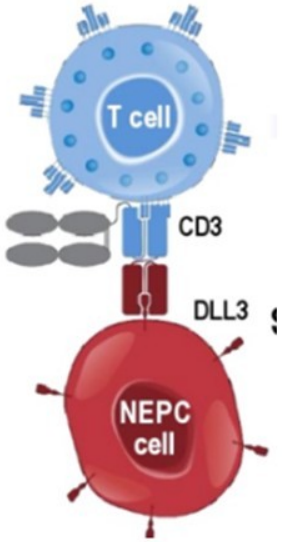
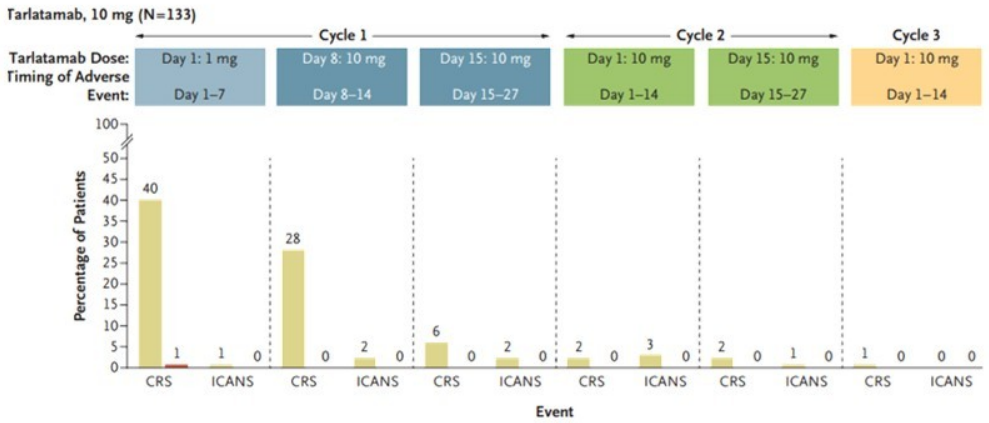
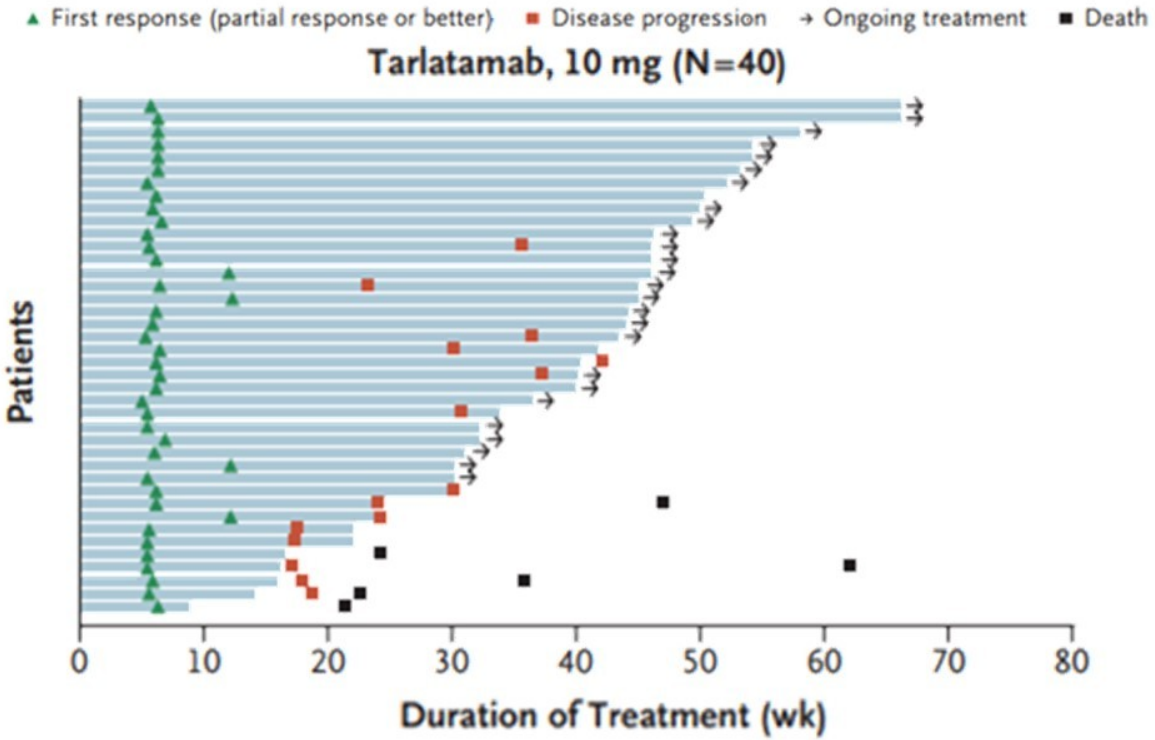
Neuroendocrine differenation

DLL3 Bispecific T cell Engagers for Neuroendocrine Cancers



- DLL3+: 85% of SCLC
- ORR 40%
- **mDOR 9.7m**
- Little CRS after 1st cycle
- mPFS 4.9 m, mOS 14.3 m

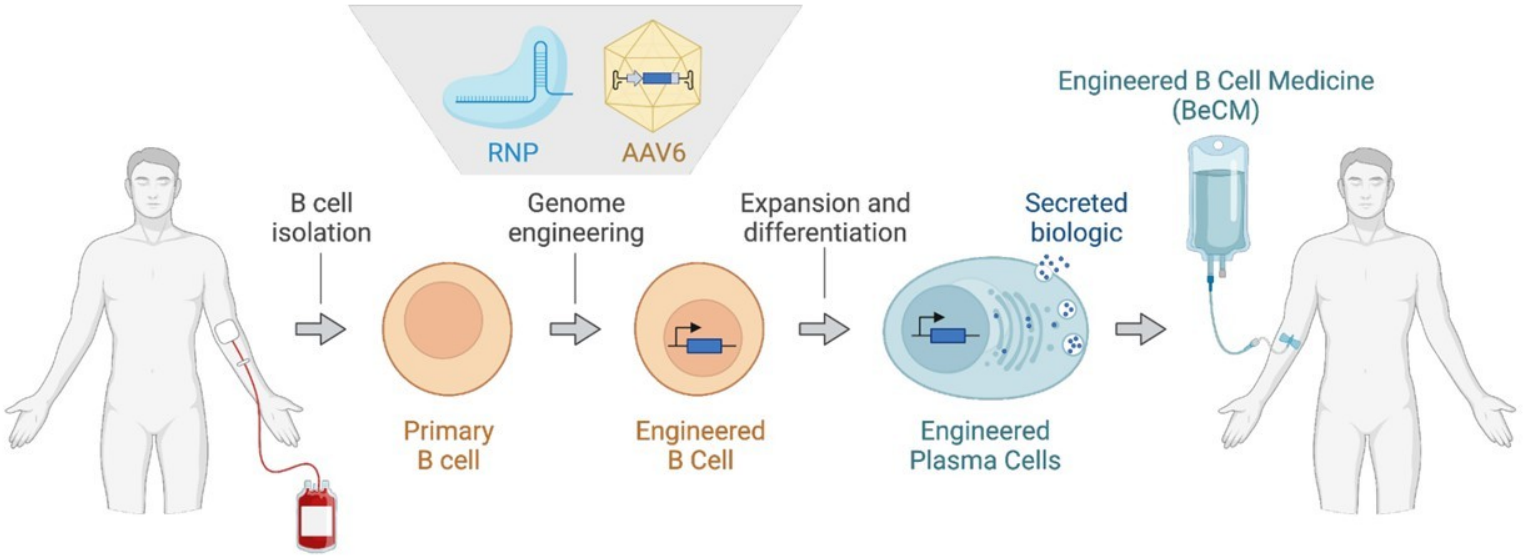




Ahn MJ *et al.* NEJM Oct 2023

Future: Transform BiTEs into a single B cell infusion for sustained secretion of antibodies.

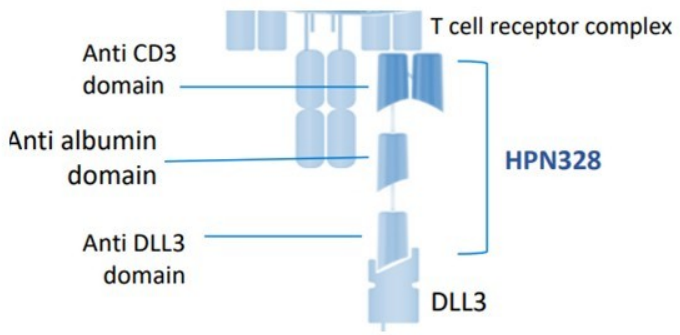
A Future Way to Avoid Need for Multiple Infusions?

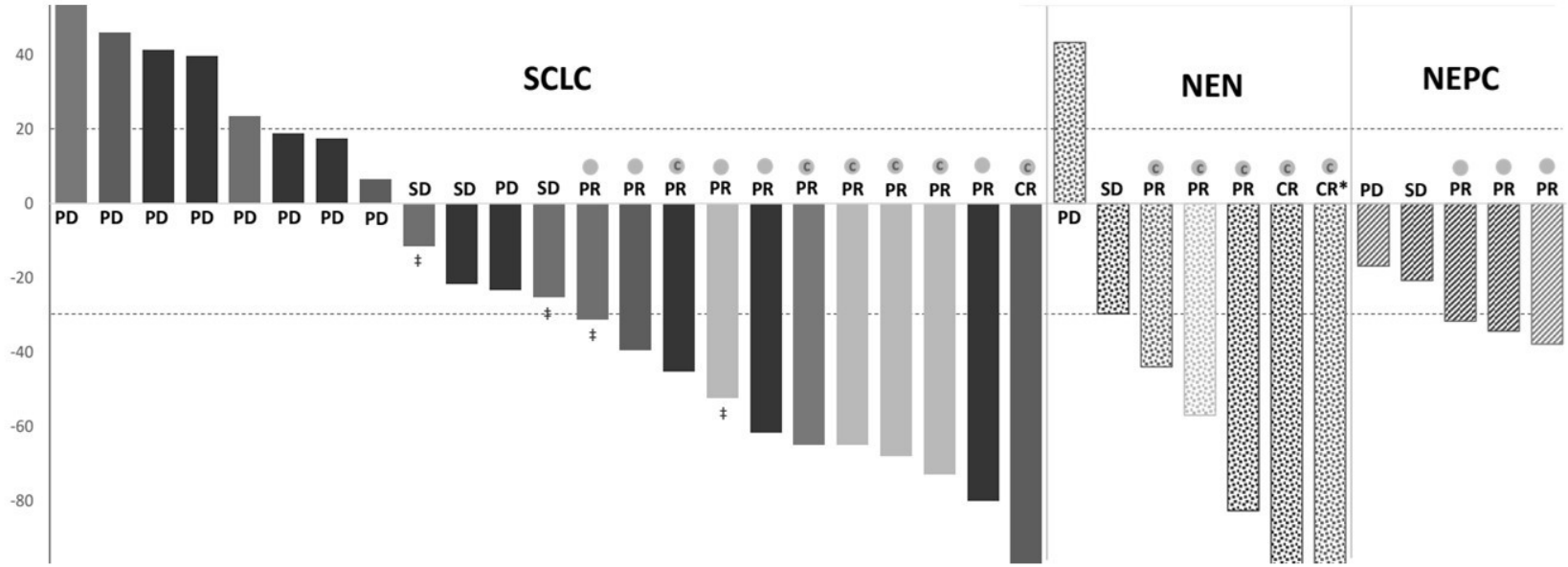


- Engraft without preconditioning
- Continuous secretion
- 1000s of molecules/sec/cell

Hohmann et al. ASGCT May 2023
Arlauckas A. et al. SITC 2023

Multiple Companies Pursuing DLL3 BiTEs in Solid Tumors
HPN328 across Neuroendocrine Histologies



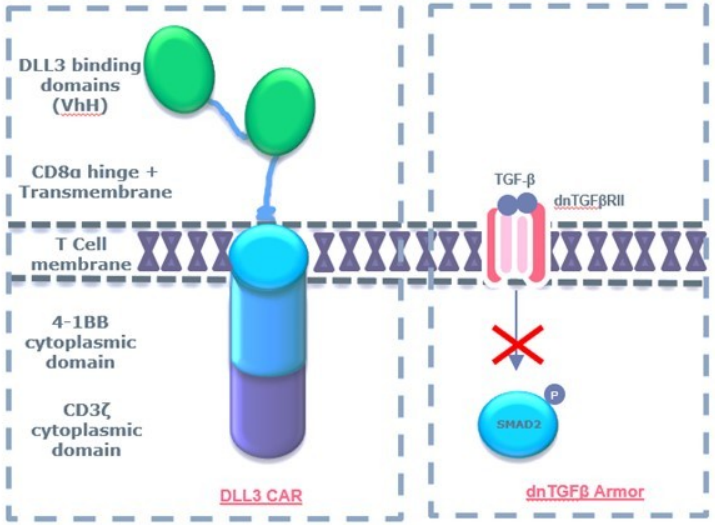


- Median **2.5** prior lines therapy, 56% prior PD1.
- **32%** (6/19) cORR in SCLC (including 1 CR!).
- 42% (5/12) cORR in other neuroendocrine prostate, bladder, GI (2 CRs!).
- Cumulative safety (n =71): CRS 60%, dysgeusia, fatigue: 59%

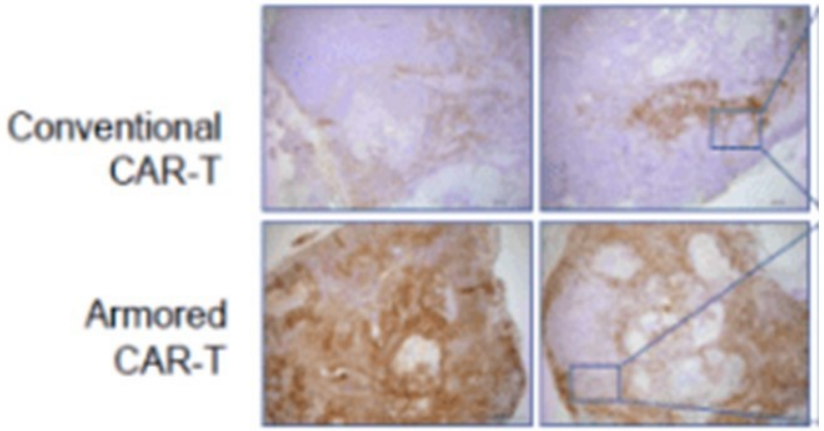
Choudhury N. et al. Annals of Oncology (2023) 34 (suppl_2): S458-S497.

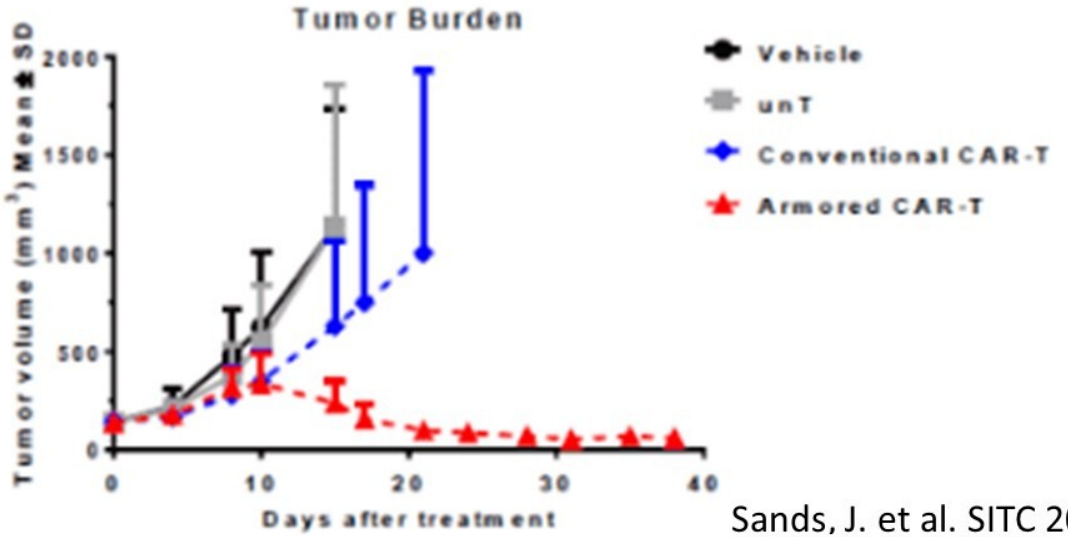
LB2102: CAR-T V_HH targeting DLL3

Can a CAR do even better than a BiTE for SCLC?



- Tandem binders w/ high affinity and specificity
- TGFB for TME to promote infiltration
- Well-tolerated *in vivo* in s.c and pulmonary xenograft
- Accruing 1st pts Q4 2023





Sands, J. et al. SITC 2023

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GCT

Trial	Agent	Target	Mechanism of Action	Phase	Patients enrolled/estimated enrolling
NCT04503278 (100)	BNT211	CLDN6	CAR-T	I	22 (13 testicular cancer)/96
NCT05028933 (101)	IMC001	EpCAM	CAR-T	I	7/48

ESMO ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

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ABSTRACT ONLY · Volume 33, Supplement 7, S1404-S1405, September 2022 · *Open Archive*

LBA38 BNT211-01: A phase I trial to evaluate safety and efficacy of CLDN6 CAR T cells and CLDN6-encoding mRNA vaccine-mediated in vivo expansion in patients with CLDN6-positive advanced solid tumours

A. Mackensen [1] · J.B.A.G. Haanen [2] · C. Koenecke [3] · ... · L. Preussner [10] · Ö. Türeci [10] · U. Sahin [10] ... Show more

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DEVELOPMENTAL THERAPEUTICS · Volume 35, Supplement 2, S489-S490, September 2024

611O Updated results from BNT211-01 (NCT04503278), an ongoing, first-in-human, phase I study evaluating safety and efficacy of CLDN6 CAR T cells and a CLDN6-encoding mRNA vaccine in patients with relapsed/refractory CLDN6+ solid tumors

J.B.A.G. Haanen [1] · A. Mackensen [2] · C. Schultze-Florey [3] · ... · L. Preussner [13] · Ö. Türeci [14] · U. Sahin [14] ... Show more

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GCT

- 43y M
- Comorbidity
  - Hypothyroid on thyroxine 50mcg,
  - History colloid cyst in 3rd ventricle --operated in June 2015 (had H/O giddiness) on levetiracetam
  - Has undescended testis on left side .
- Previous Rx- 2022
  - Symptomatic for with increasing lower abdominal pain and lump lower left abdomen
  - Diagnosed to have Non-Seminoma of testis (cTxN3M0 s2; stage IIIb)
  - Received 3 cycles of BEP & one EP
  - Had a Complete metabolic response

- Previous Rx- 2023
  - Had a recurrence in para aortic region with disease free interval of 1.2 years
  - Tumour markers were S1 status
  - Received VIP 4 cycles
  - Had a complete metabolic response. Declined high dose chemotherapy and stem cell transplant
- Previous Rx-2024
  - Had cough & found to have lung metastasis with a disease free interval of 0.8 years
  - Tumour markers were S2
  - Received TIPX 2 cycles and than had to halt treatment due to COVID-19

- Previous Rx 2024
  - Recurrence in brain and lung with disease free interval of 0.5 years
  - Underwent surgical resection for brain- NSGCT in histopathology
  - Received TIP x 2 cycles and than Gem-ox for 2 cycles
  - Had a stable disease in lung
  - Than had a progression with 3 months- Bone and lung
- Issues
  - Resistant- Refractory disease
  - Neuropathy
  - PS-01

Cellular therapy assessment

- Panel of IHC were done to identify CAR-T markers
  - CD30
  - Claudin
  - GPC-3
  - IL13Ralpha2
- Out of which GPC-3 came positive so was administered GPC3-specific TGFβRIIDN armoured autologous CAR-T
- Adverse event- CRS, Neutropenia, Thrombocytopenia

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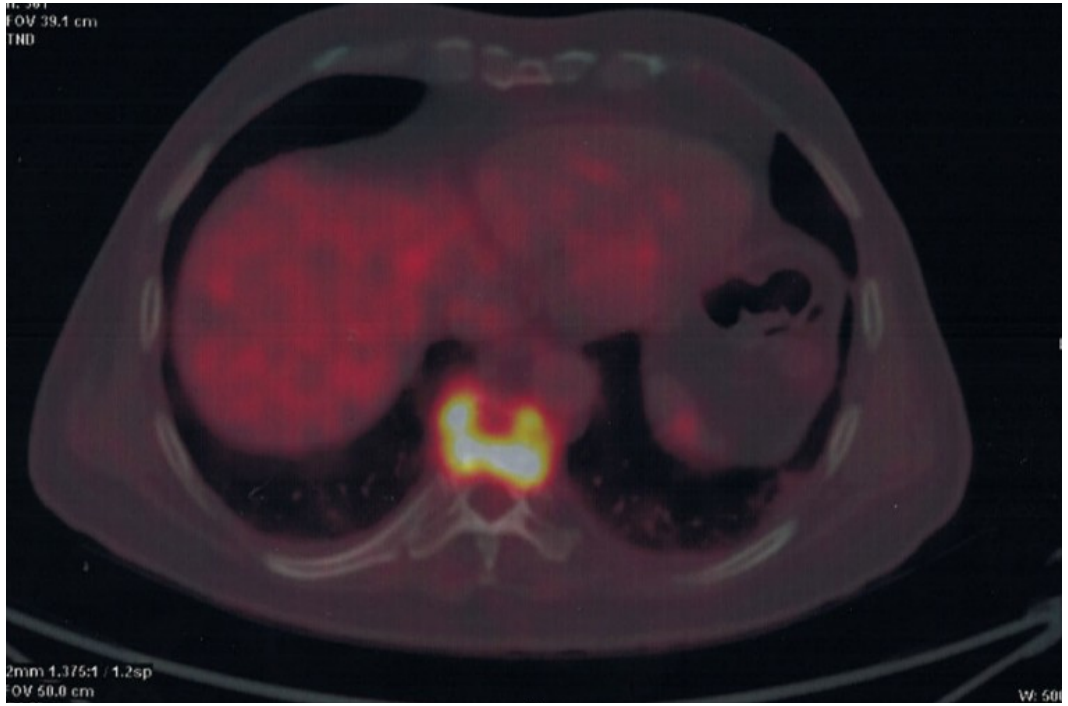
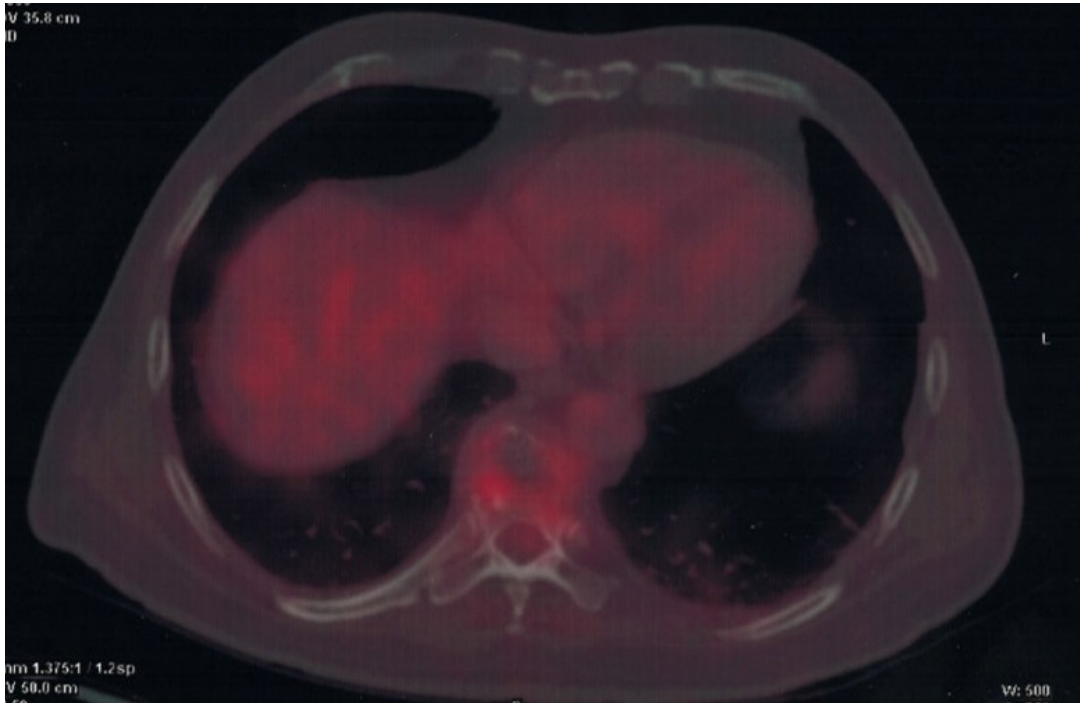
Pre



Post



Gamma Delta T cell

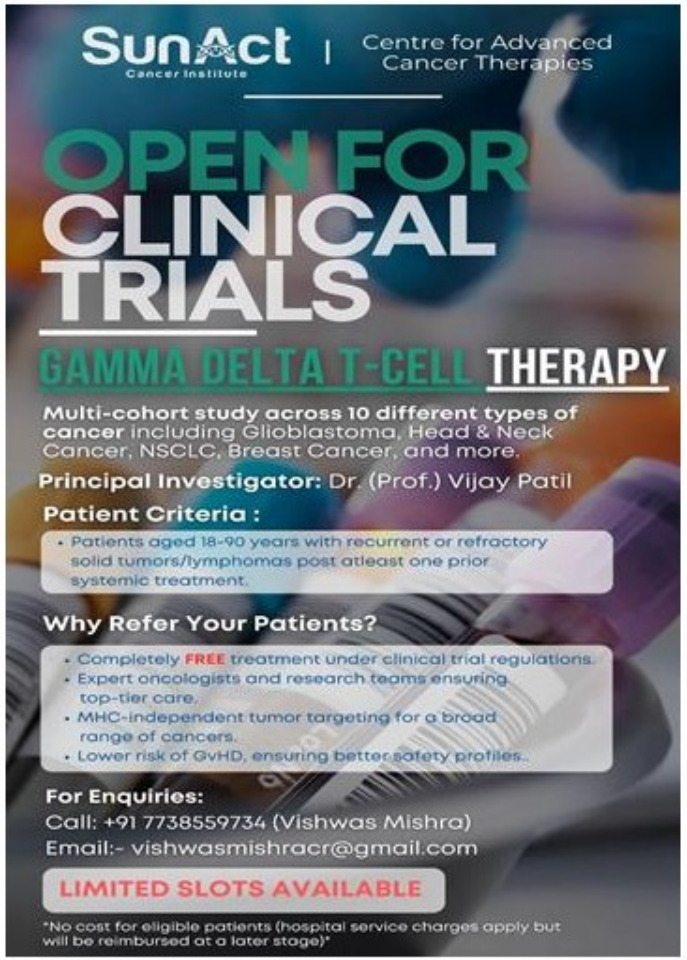
2.6 Trial design

Multi-cohort (10 cohorts), non comparative, open label, prospective, phase 2 study

1. Cohort 1: Glioblastoma
2. Cohort 2: Head & neck squamous cell carcinoma
3. Cohort 3: Non small cell lung cancer
4. Cohort 4 : Cervical Cancer
5. Cohort 5 : Breast Cancer
6. Cohort 6: Colon Cancer
7. Cohort 7: Hepatocellular Cancer
8. Cohort 8 : Non Hodgkin Lymphoma
9. Cohort 9 : Renal Cell Carcinoma
10. Cohort 10: Prostate Cancer

Phase 2 a- RR as the endpoint
Phase 2b- OS as the endpoint

Enrollment – 1.4.2025



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5 Phase 1- Nearly covering Lymphoma, MM & all solid tumors

Conclusion

- Promise
- Requires more studies
- Hope for them where currently no options are available