Advances in Adoptive Cellular Therapy: The Progress in Solid Tumors

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New Orleans, Louisiana

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Disclosures

- None

William B. Coley

His Hypothesis, His Toxin, and the Birth of Immunotherapy

ANNALS *of* SURGERY

WILLIAM BRADLEY COLEY

1862–1936

"Ffight on, my men," sayes Sir Andrew Barton,
"I am hurt, but I am not slaine;
I'le lay mee downe and bleed a-while,
And then I'll rise and fight againe!"

Journal of Cancer 2018, Vol. 9

Zhang and Chen. Current status and future directions of cancer immunotherapy

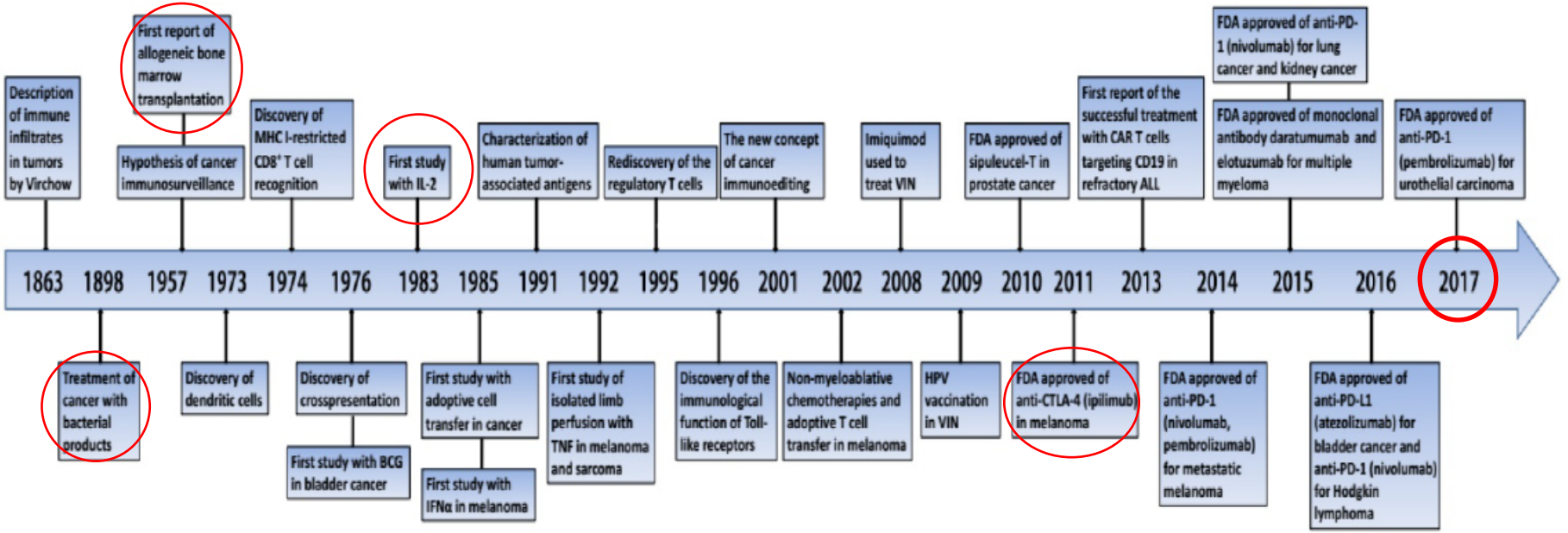


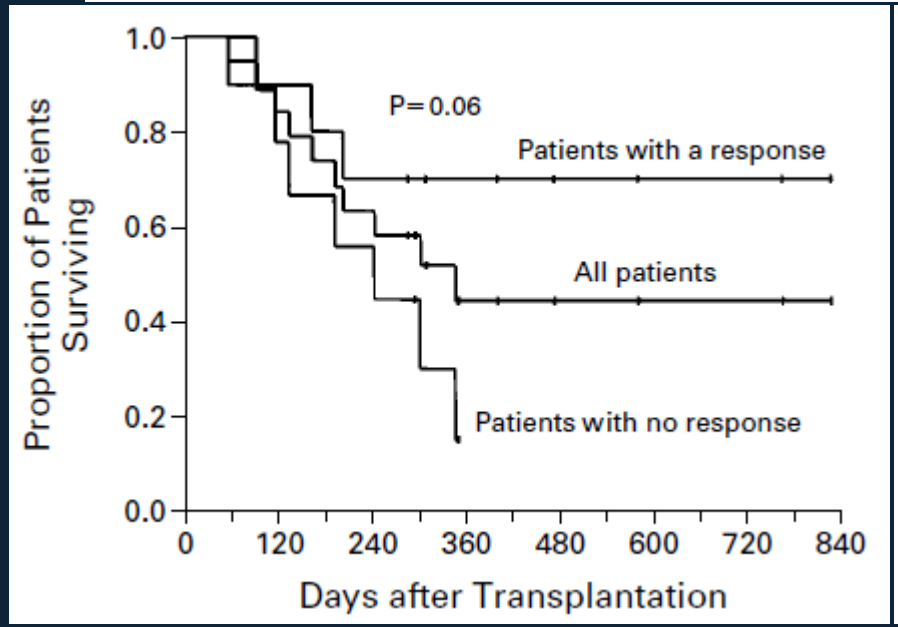
Figure 1. Important events in the history of cancer immunotherapy. BCG, bacilli Calmette-Guérin; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; FDA, Food and Drug Administration; IFNα, interferon-α; IL-2, interleukin-2; MHC, major histocompatibilty complex; PD-1, programmed death 1; TNF, tumor necrosis factor; VIN, vulvar intraepithelial neoplasia

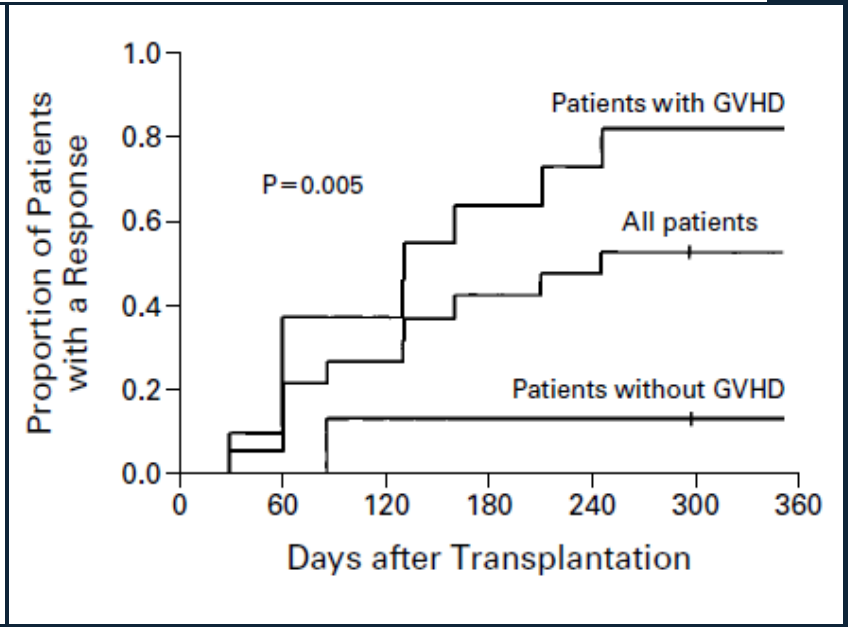
The New England Journal of Medicine

VOLUME 343 SEPTEMBER 14, 2000 NUMBER 11

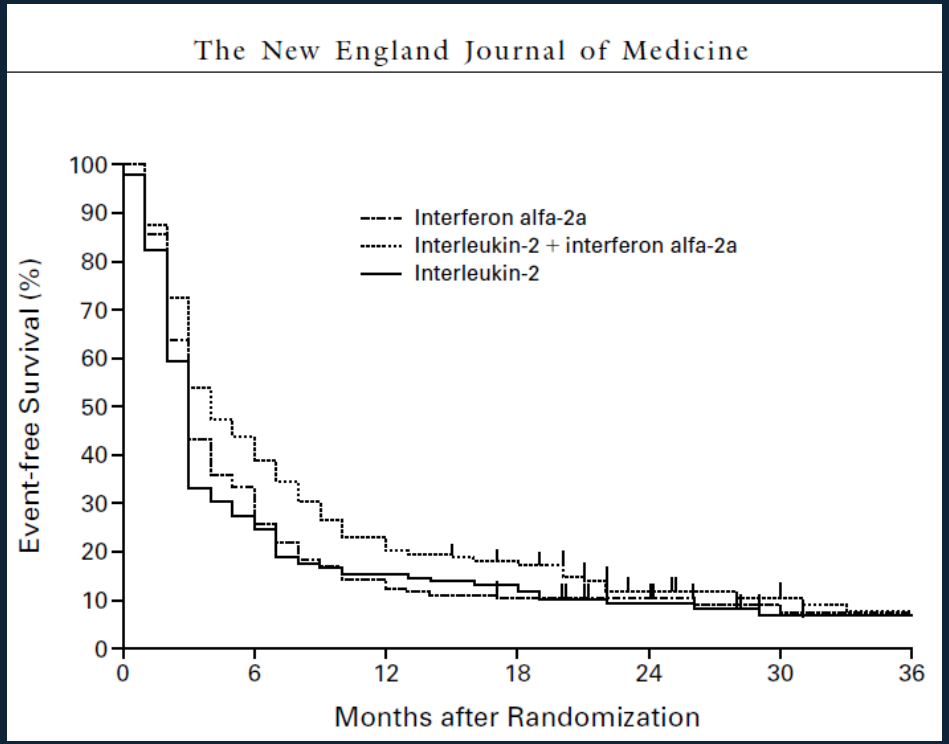
REGRESSION OF METASTATIC RENAL-CELL CARCINOMA AFTER NONMYELOABLATIVE ALLOGENEIC PERIPHERAL-BLOOD STEM-CELL TRANSPLANTATION

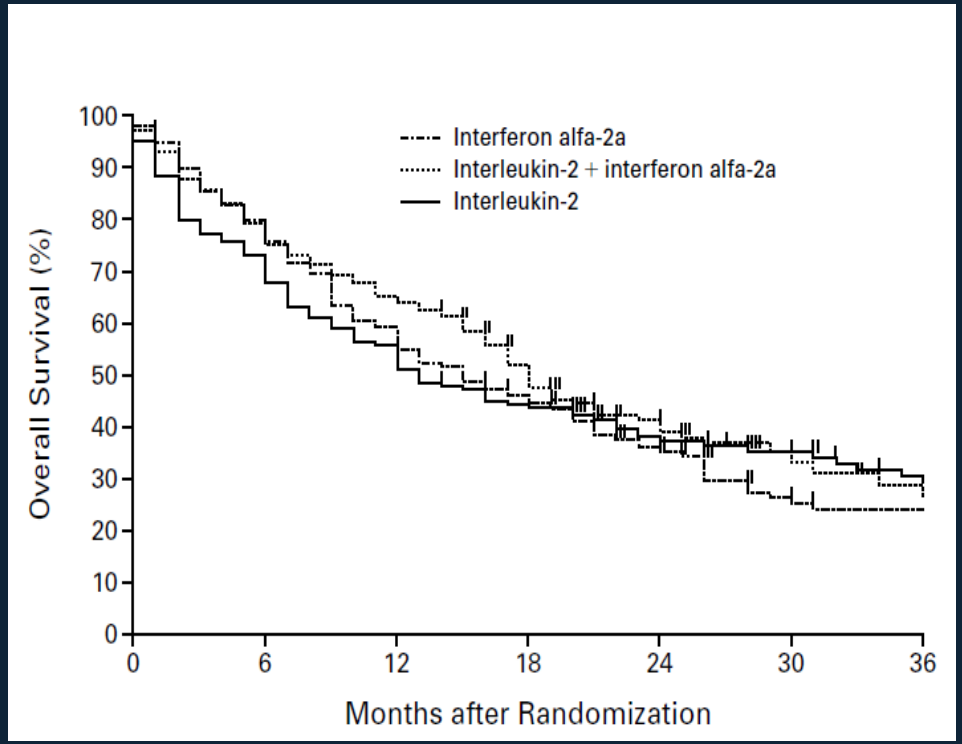
RICHARD CHILDS, M.D., ALLEN CHERNOFF, M.D., NATHALIE CONTENTIN, M.D., ERKUT BAHCECI, M.D., DAVID SCHRUMP, M.D., SUSAN LEITMAN, M.D., ELIZABETH J. READ, M.D., JOHN TISDALE, M.D., CYNTHIA DUNBAR, M.D., W. MARSTON LINEHAN, M.D., NEAL S. YOUNG, M.D., AND A. JOHN BARRETT, M.D.





Cytokine therapy in RCC

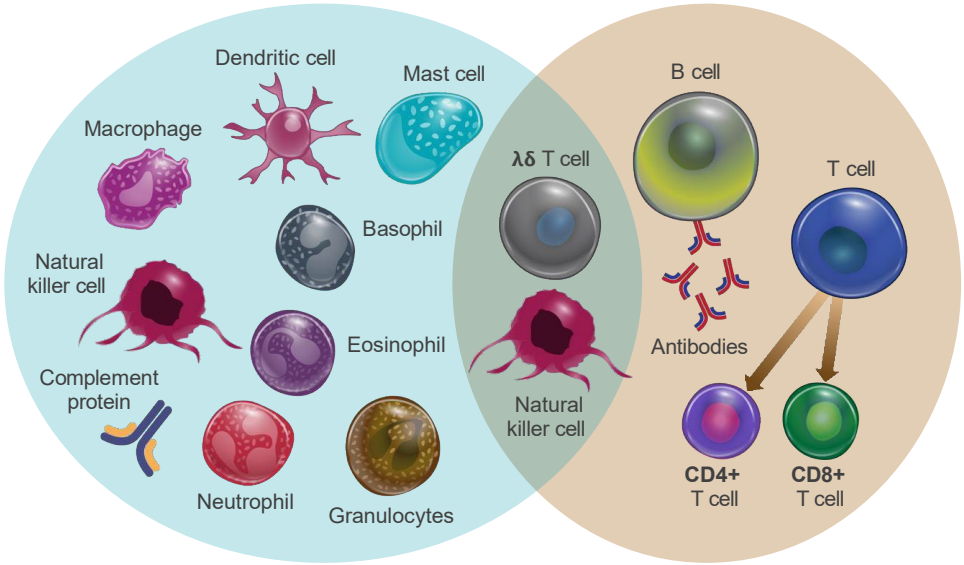




Negrier et al. NEJM 1998

Innate and Adaptive Immunity

Innate Immunity
Nonspecific first line of defense

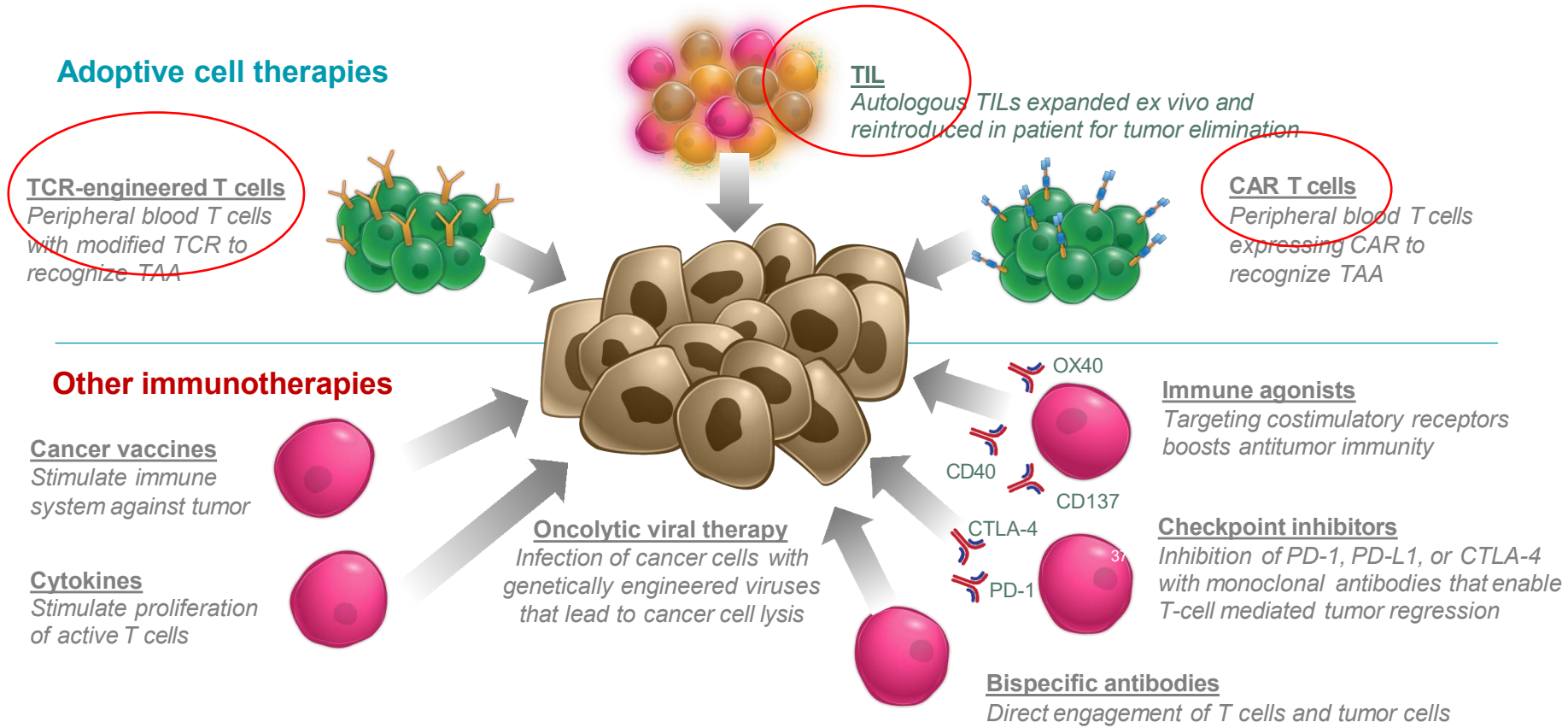


Adaptive Immunity
Specific response, memory functions

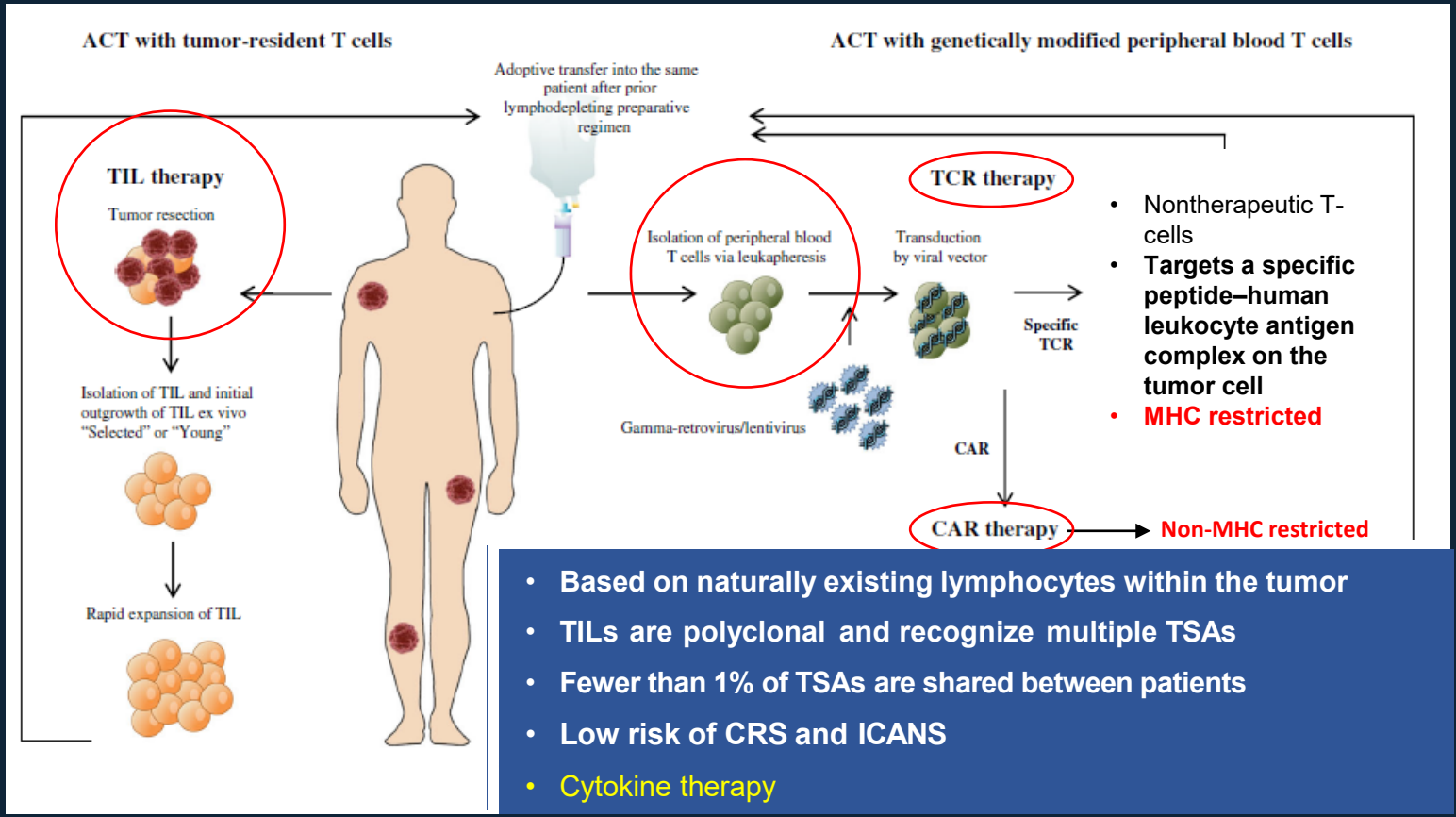
Immune Surveillance
Identification and destruction of foreign or abnormal cells by innate and adaptive immunity

Powell J. Overview of Adaptive Immunity. SITC 2018; Rahma OE. Overview of Immunotherapyfor Cancer. Clinical Care Options 2016; Zhang and Chen. Journal of Cancer 2018

Different methods to harness the immune system to treat cancer



Rahma OE. Overview of Immunotherapyfor Cancer. Clinical Care Options. 2016.
Courtesy of Ganguly S. ASTCT 2023.



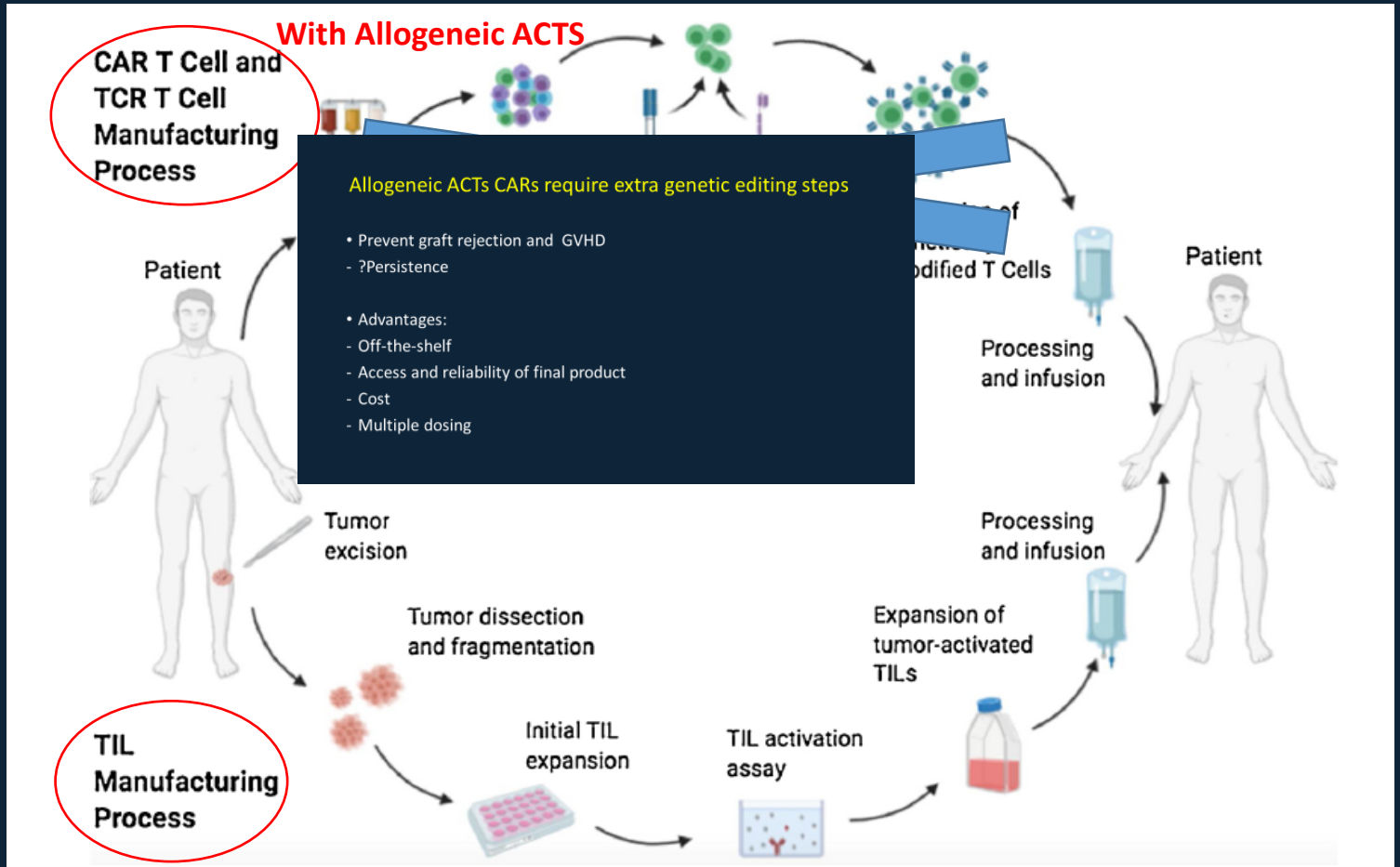
Rohaan et al. Virchos Archic 2019
Srour and Akin. JIPO 2023

Relative advantages and disadvantages of TILs, TCR T Cells, and CAR T Cells.

	TILs	CAR T Cells	TCR T Cells
Advantages	• Multiple lymphocyte clones target patient-specific antigens • Reduced on-target, off-tumor toxicity risk • Persistent responses achievable with lymphodepletion	• MHC independent; no HLA matching requirement • Relatively faster manufacturing time • Off-the-shelf potential	• Target intracellular and extracellular antigens, including neoantigens • Relatively faster manufacturing time • Off-the-shelf potential
Disadvantages	• Longer, more costly manufacturing period • Tumor escape via MHC downregulation	• Target extracellular antigens only, with few neoantigen options • On-target, off-tumor toxicity • Poor persistence, even with lymphodepletion • Tumor escape via target downregulation	• HLA matching requirement • On-target, off-tumor toxicity • Poor persistence, even with lymphodepletion • Tumor escape via MHC downregulation and/or target downregulation

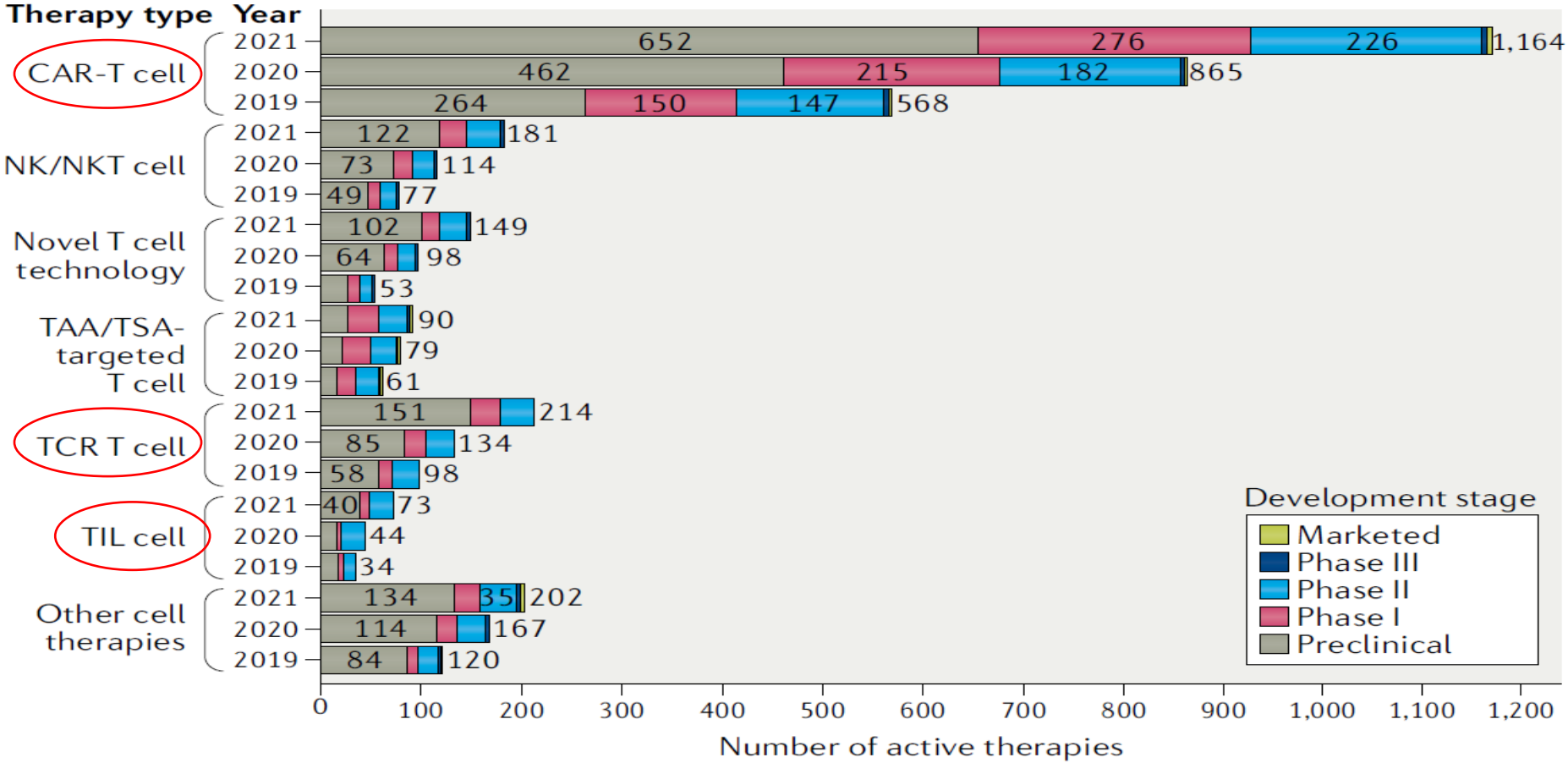
TIL: tumor infiltrating lymphocyte; TCR: T cell receptor; CAR: Chimeric antigen receptor.

Grimes JM, et al. Transfusion and Apheresis Science 2021

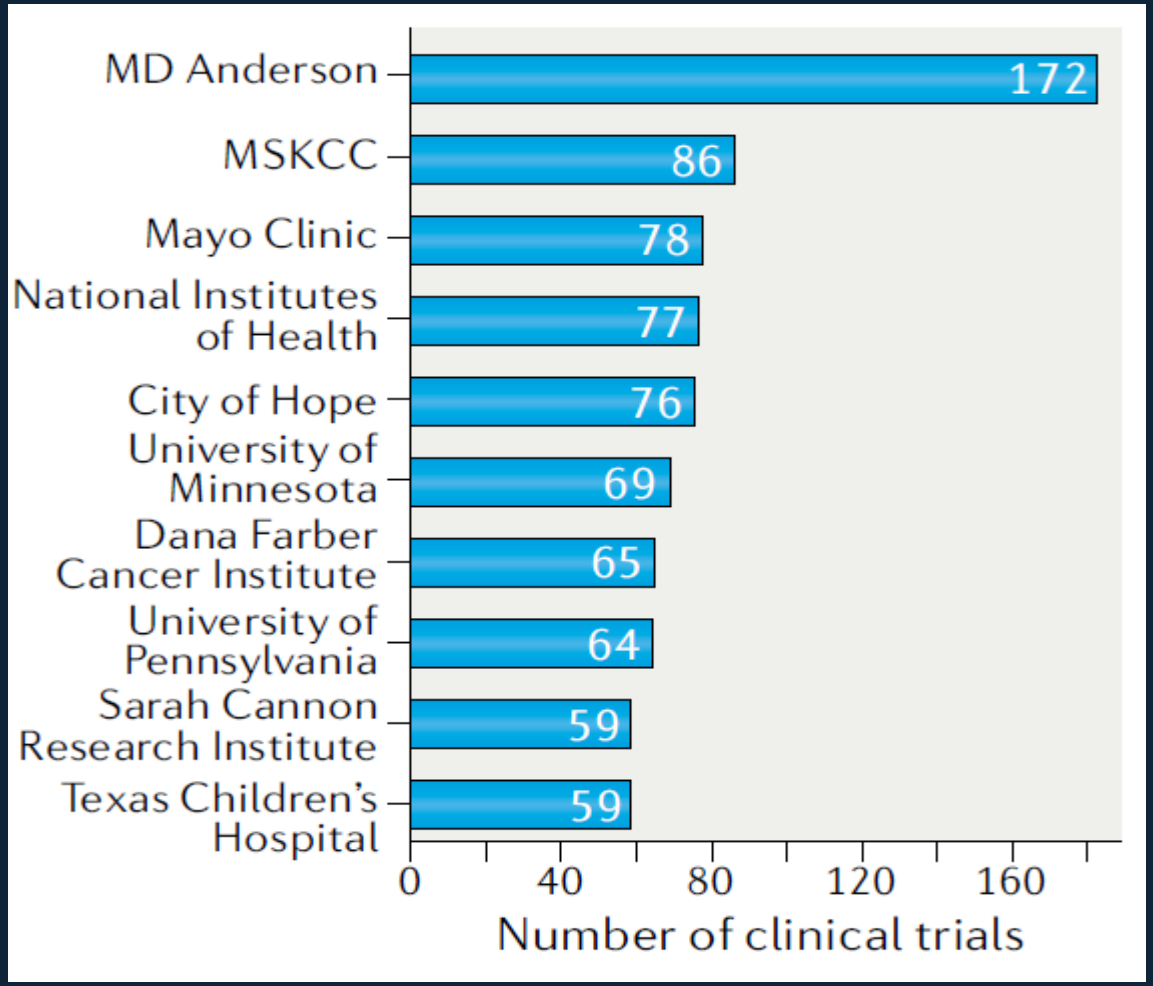


Manufacturing steps for TILs and for engineered T cell therapies, including CAR T Cells and TCR T Cells.

Adapted from Grimes JM, et al. Transfusion and Apheresis Science 2021

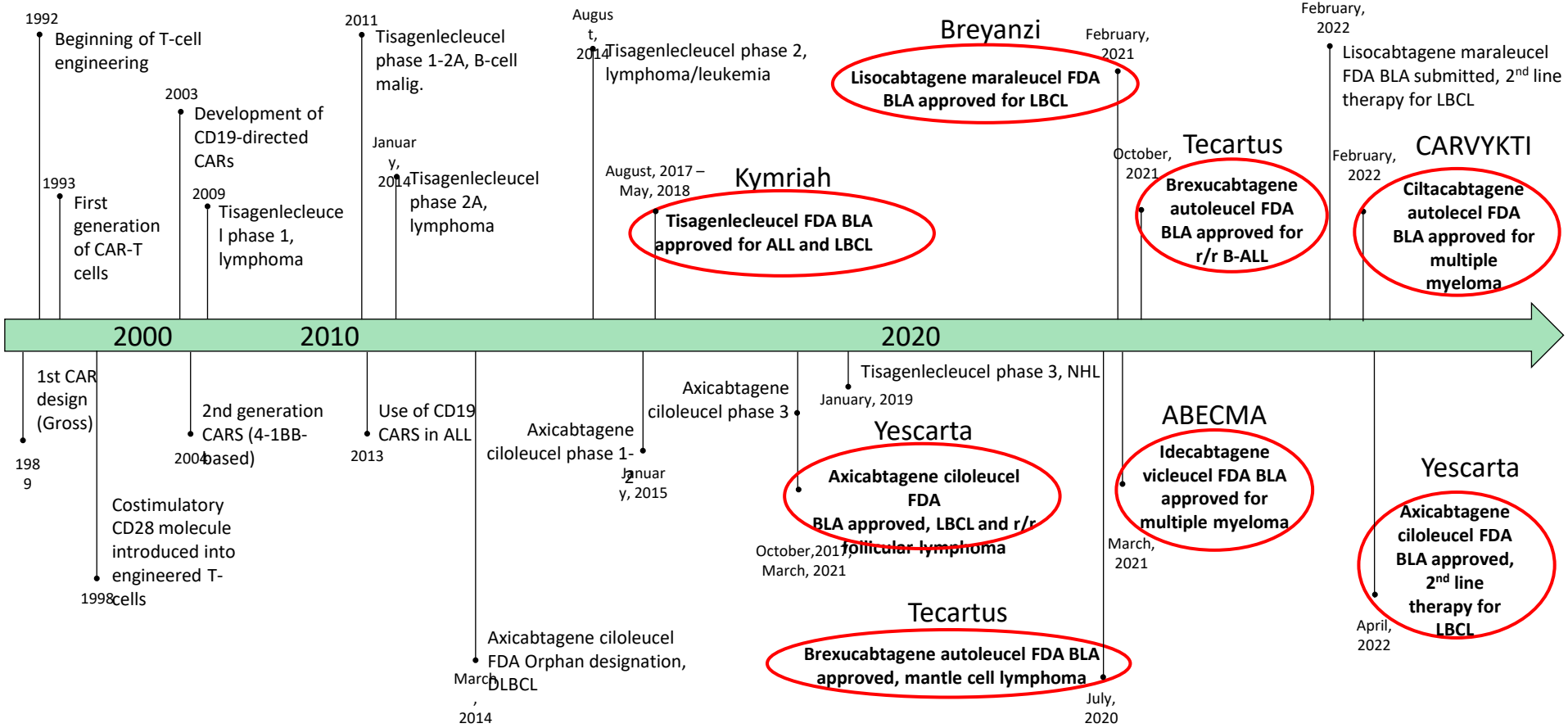


Upadhaya S. Nature Reviews 2021



Upadhaya S. Nature Reviews 2021

Paradigm Shift for CAR T Cell in Heme Tumors



SOC IEC Products by Disease

Lymphoma

Product	FDA Approval Date
Tisagenlecleucel (Kymriah)	August 2017
Axicabtagene Ciloleucel (Yescarta)	October 2017
Brexucabtagene Autoleucel (Tecartus)	July 2020
Lisocabtagene Maraleucel (Breyanzi)	February 2021

Myeloma

Product	FDA Approval Date
Idecabtagene Vicleucel (Abecma)	February 2021
Ciltacabtagene Autoleucel (Carvykti)	April 2022

Melanoma

Product	FDA Approval Date
Lifileucel (Amtagvi)	February 2024

Leukemia

Product	FDA Approval Date
Tisagenlecleucel (Kymriah)	August 2017
Brexucabtagene Autoleucel (Tecartus)	October 2021
Lisocabtagene Maraleucel (Breyanzi)	March 2024
Obecabtagene Autoleucel (Aucatzyl)	November 2024

Sarcoma

Product	FDA Approval Date
Afamitresgene Autoleucel (Tecelra)	August 2024

Lessons from our CAR T-Cell Experience?

- Durable responses in Heme Malignancies

- Associated with unique and potentially serious toxicities:
  - Cytokine Release Syndrome
  - Immune Cell Associated Neurotoxicity Syndrome
  - High rates of ICU admissions
  - Infections, HLH, Prolonged Cytopenias, Neurological Toxicities
  - NRM

  - Construct-specific toxicities

  - Multi-departmental infrastructure management is critical

NEWS BRIEF

Emily Whitehead, First Pediatric Patient to Receive CAR T-Cell Therapy, Celebrates Cure 10 Years Later

May 10, 2022

Pictured: Emily with Dr. Grupp

www.cjop.edu
www.emilywhiteheadfoundation.org

Estimated New Cases

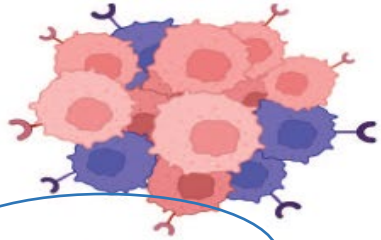
Seigel R, et al. Cancer Statistics, 2023. CA Cancer J Clin 2023

Males				Females		
Prostate	288,300	29%		Breast	297,790	31%
Lung & bronchus	117,550	12%		Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%		Colon & rectum	71,160	8%
Urinary bladder	62,420	6%		Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%		Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%		Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%		Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%		Pancreas	30,920	3%
Leukemia	35,670	4%		Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%		Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**		**All Sites**	**948,000**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	67,160	21%		Lung & bronchus	59,910	21%
Prostate	34,700	11%		Breast	43,170	15%
Colon & rectum	28,470	9%		Colon & rectum	24,080	8%
Pancreas	26,620	8%		Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%		Ovary	13,270	5%
Leukemia	13,900	4%		Uterine corpus	13,030	5%
Esophagus	12,920	4%		Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%		Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%		Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%		Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**		**All Sites**	**287,740**	**100%**

Challenges with CAR T-cells in Solid Tumors

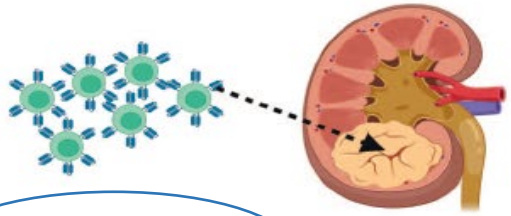


A. Target antigen heterogeneity

1. Clonal complexity in solid tumors
2. Substantial tumor-associated antigen heterogeneity
3. Escape mechanisms due to antigen-negative tumor cells
4. Off-tumor on-target toxicity

Solutions:

- Develop dual and tandem CARs to target multiple antigens
- Target neoantigens
- Use "adapter-mediated" CARs
- Use strategies that can induce "epitope spreading"

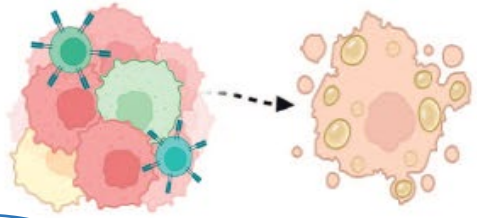


B. Trafficking into tumor tissue

1. Discrete masses in different organs
2. Impaired T-cell fitness
3. Suboptimal CAR T-cell expansion and persistence
4. Suppressive tumor microenvironment

Solutions:

- Improve lymphodepletion strategies
- Improve CAR constructs (e.g. co-express functional chemokine receptors)
- Intracavitary/tumor delivery of CAR T-cells
- Other strategies to overcome the suppressive tumor microenvironment

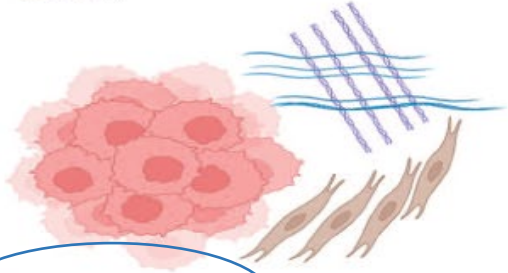


D. Toxicity

1. On-target off-tumor toxicity
2. Indirect CAR T-cell-related end organ toxicity

Solutions:

- Select highly tumor-specific antigen
- Engineer CARs with "suicide genes" (e.g. inducible Caspase9 suicide gene system)
- Design CARs with non-functional targeted receptors
- Design adapter-mediated and tandem/dual CARs
- CARs using the Boolean logic gates technology

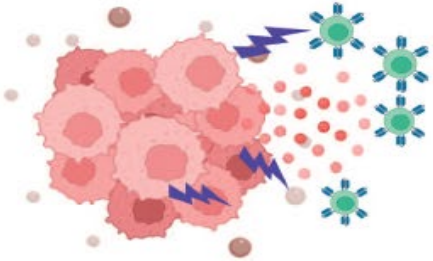


C. Tumor microenvironment

1. Extracellular matrix, tumor stroma
2. Suppressive surveillance immune cells
3. Inhibitory effect of checkpoint molecules
4. Inhibitory cytokine milieu (e.g. IL-10)

Solutions:

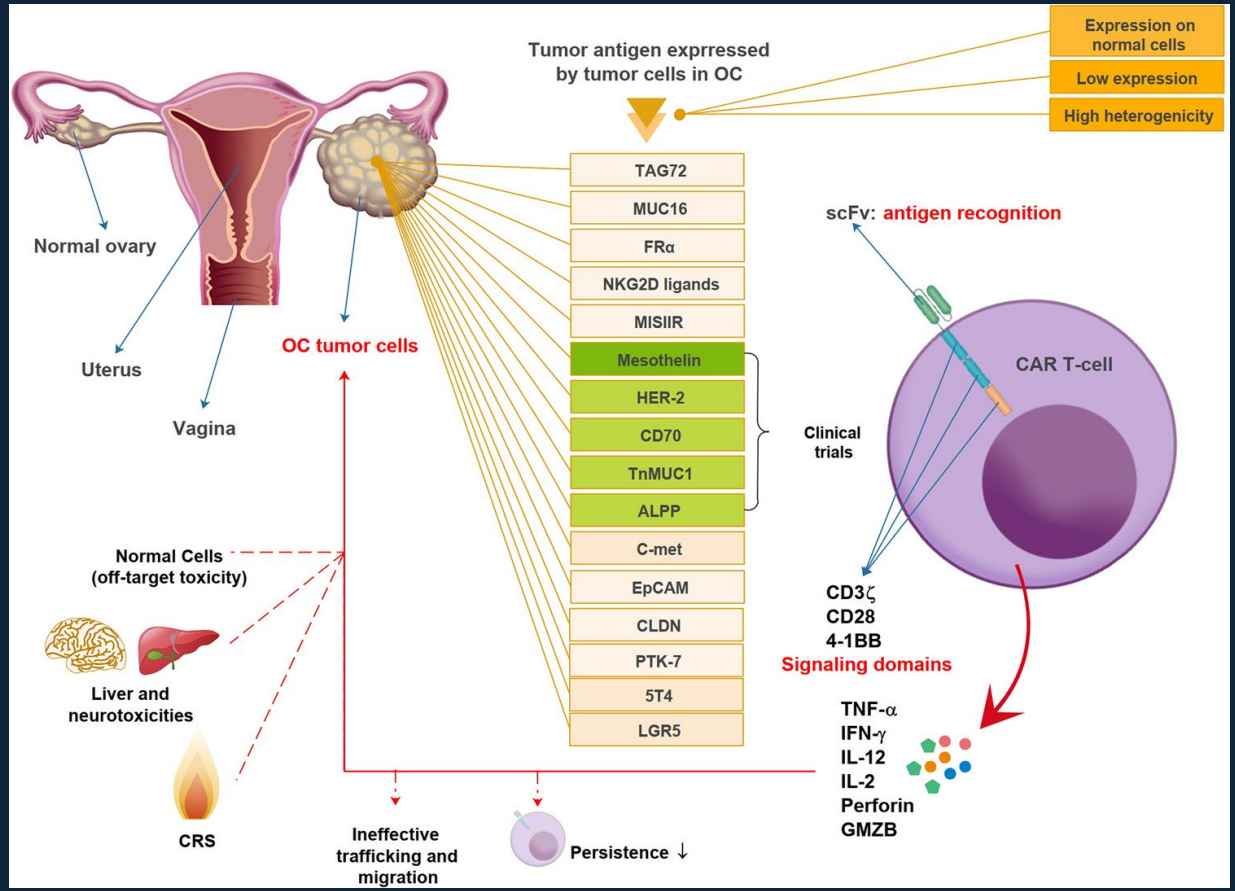
- Use modified CARs capable to target tumor stroma



- Knocked out CARs to resist some of the inhibitory cytokines
- Armored CARs with cytokines (e.g. IL-12 armored CARs) to overcome the suppressive microenvironment
- Combination strategies (e.g. with checkpoint inhibitors)

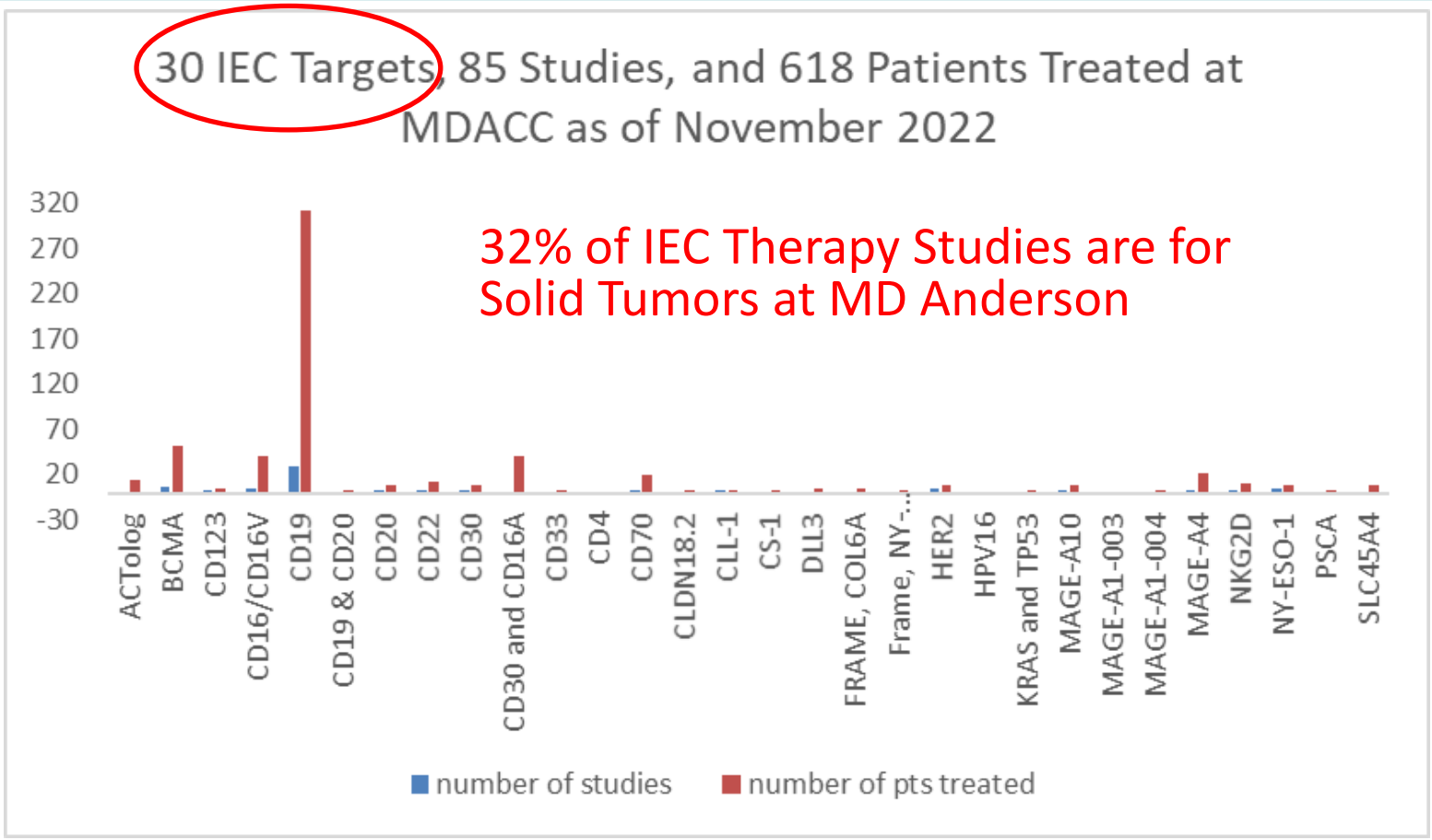
Srour and Akin. JIPO 2022

Target antigen heterogeneity

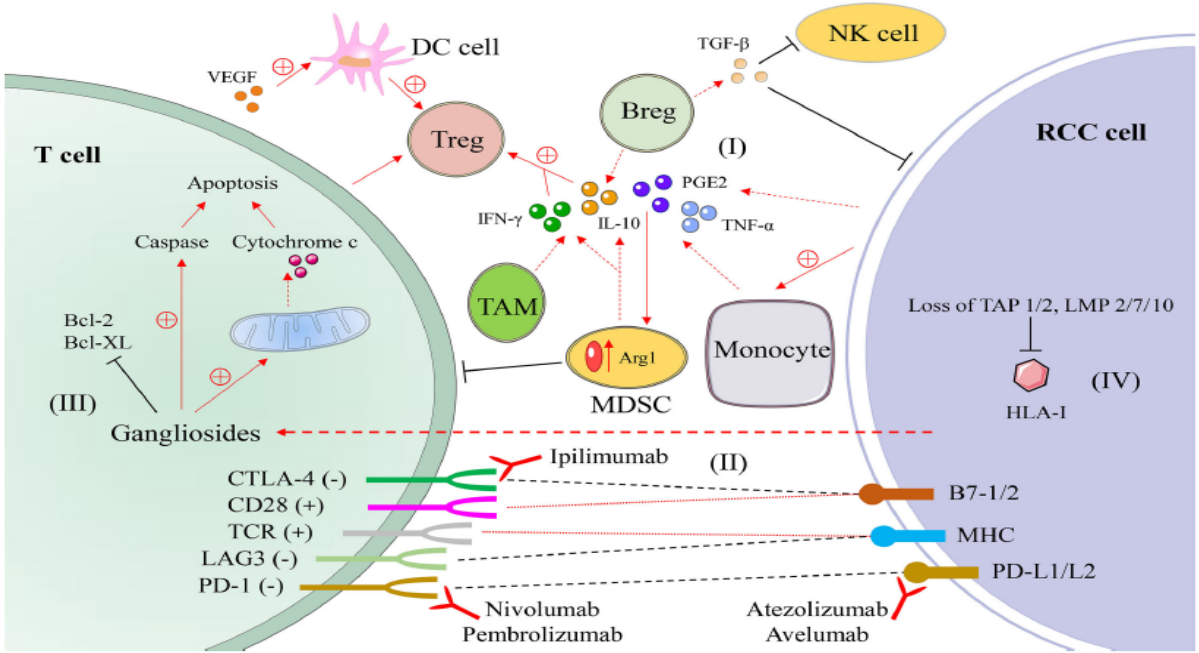


Ding et al. Medical Oncology 2022

IEC Targets Studied at MD Anderson



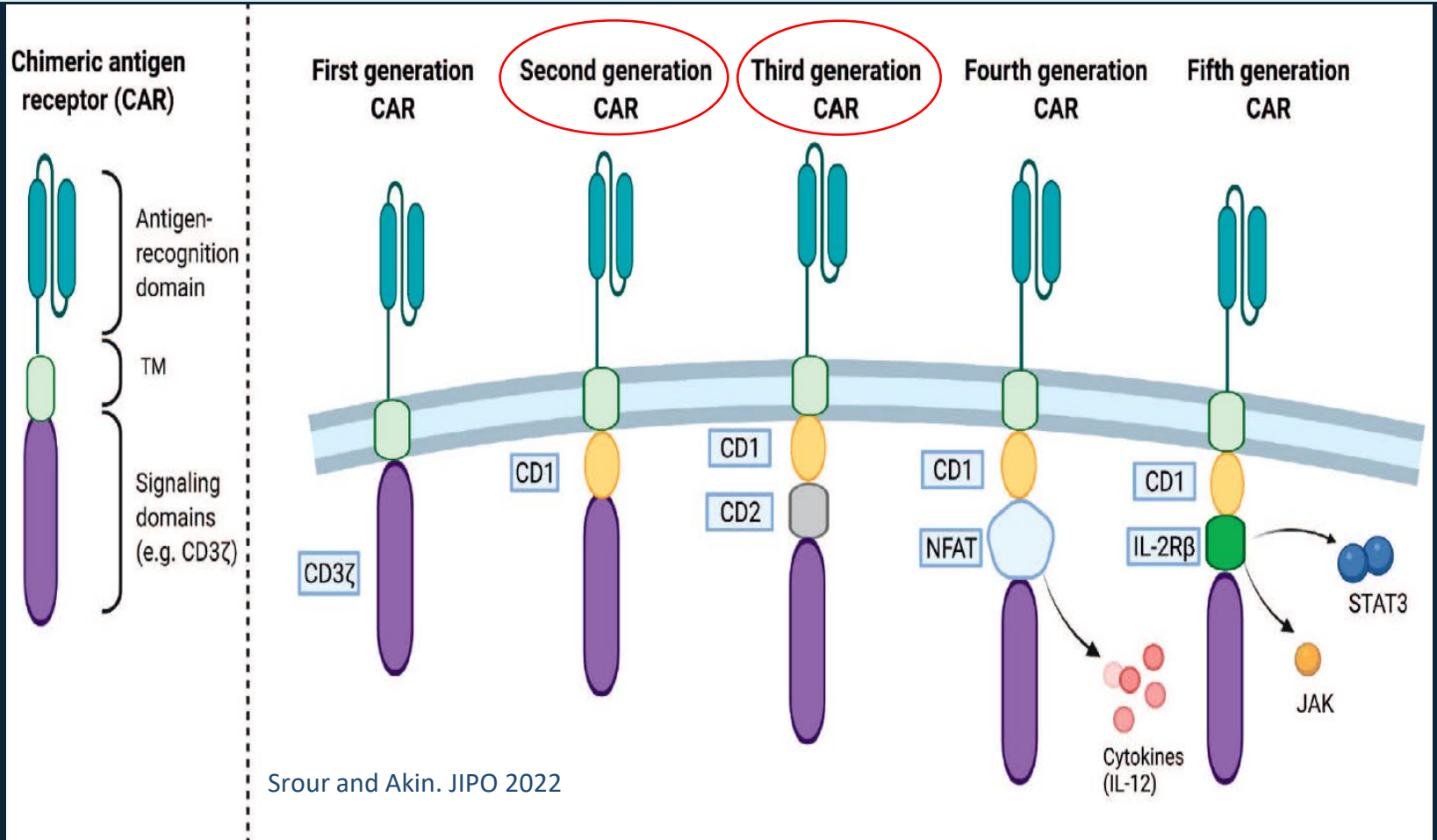
Immune evasion mechanisms and suppressive TME



A schematic diagram of mechanisms of immune evasion in renal cell carcinoma. (I) Immunosuppressive cells and their secreted cytokines, such as interleukin-10 (IL-10), prostaglandin E2 (PGE2), and transforming growth factor-β (TGF-β) secreted by myeloid-derived suppressor cell (MDSC) and other cells. (II) The interaction of T cells and tumor cells and the mode of action of monoclonal antibodies. (III) Gangliosides secreted by renal cell carcinoma cells promote T cell apoptosis. (IV) The absence of components related to antigen processing leads to a decline in antigen presentation function. RCC, renal cell carcinoma; DC, dendritic cell; NK, natural killer cell; Treg, regulatory T cell; Breg, regulatory B cell; TAM, tumor-associated macrophage; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; HLA, human leukocyte antigen; TAP, transport protein proteins associated with antigen processing; LMP, low molecular weight protein; CD28, cluster of differentistion 28; CTLA-4 (CD152), cytotoxic T-lymphocyte associated protein 4; TCR, T cell receptor; LAG3 (CD223), gene 3 activation of lymphocyte; PD-1 (CD279), programmed cell death protein 1; B7-1/2 (CD80/CD86); MHC, major histocompatibility complex; PD-L1/L2 (CD274/CD273), programmed cell death protein ligand 1/2.

Jian et al. Frontiers in Immunology 2021

CAR-T Cell Therapy: Improving on CAR Construct



Srour and Akin. JIPO 2022

CAR-T Cell Therapy: Toxicity

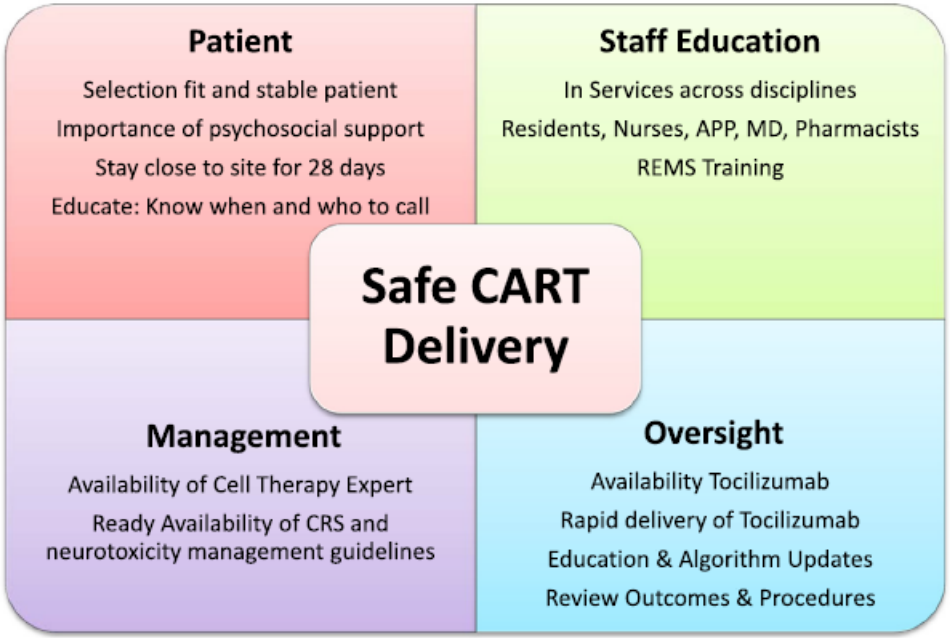
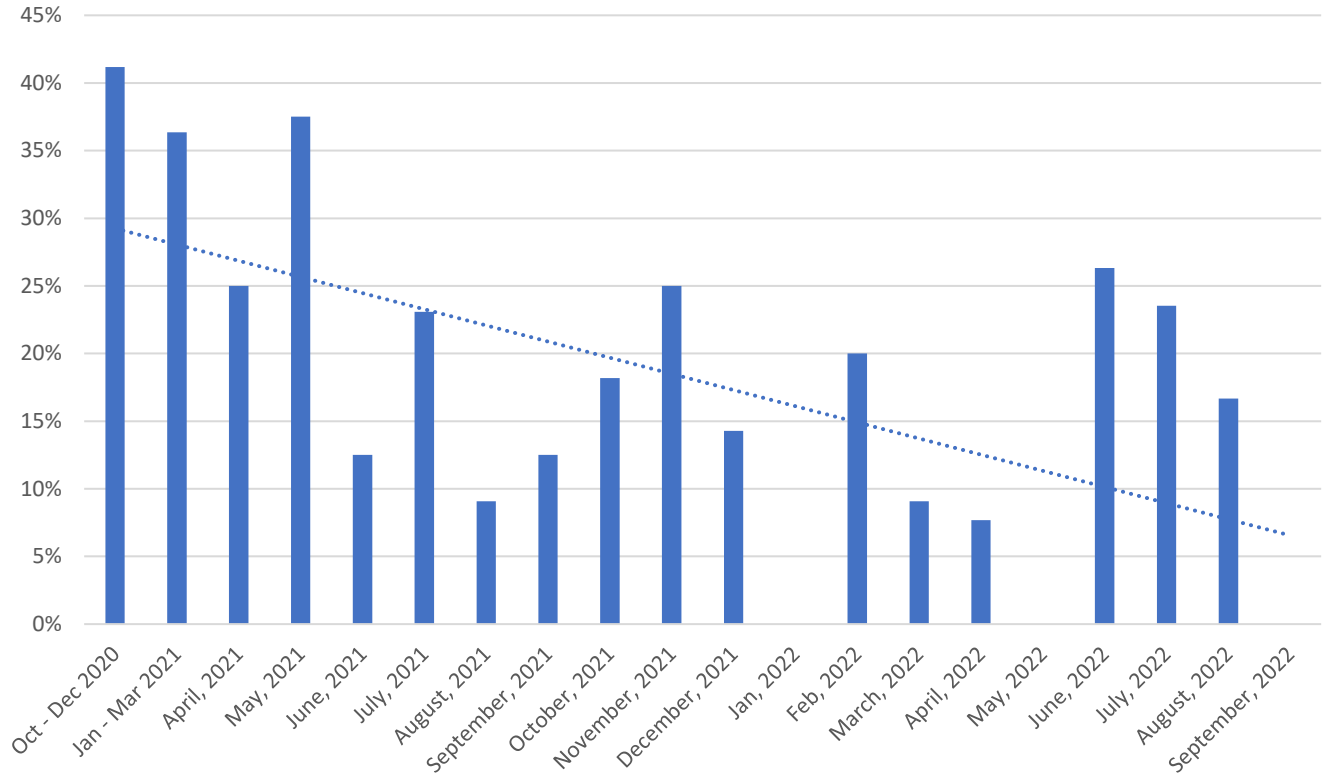


Figure 1. Delivering CAR-Ts safely.

Adapted from Frey & Porter. BBMT, 2019, 25, e123-e127

CARTOX Program Quality Trend: ICU Transfer Rate for Patients Treated with SOCs

- ICU transfer rate at MD Anderson is trending lower over time with improvements in IEC management



Unique challenges with ACT in solid tumors

- Toxicity profile less uniform c/w CAR T in hematologic malignancies
  - ✓Target-, CAR construct- and disease-specific
  - ✓Cytokine therapy, high-dose IL-2
- Shared management between cell therapists and solid tumor oncologists
- Unique challenges not only during the clinical trial development, but more important when it is commercialized
- Data reporting

A Robust Quality Infrastructure is Key to Safe and Effective Delivery of Immune Effector Cells – How "FACT"-Finding Can Help

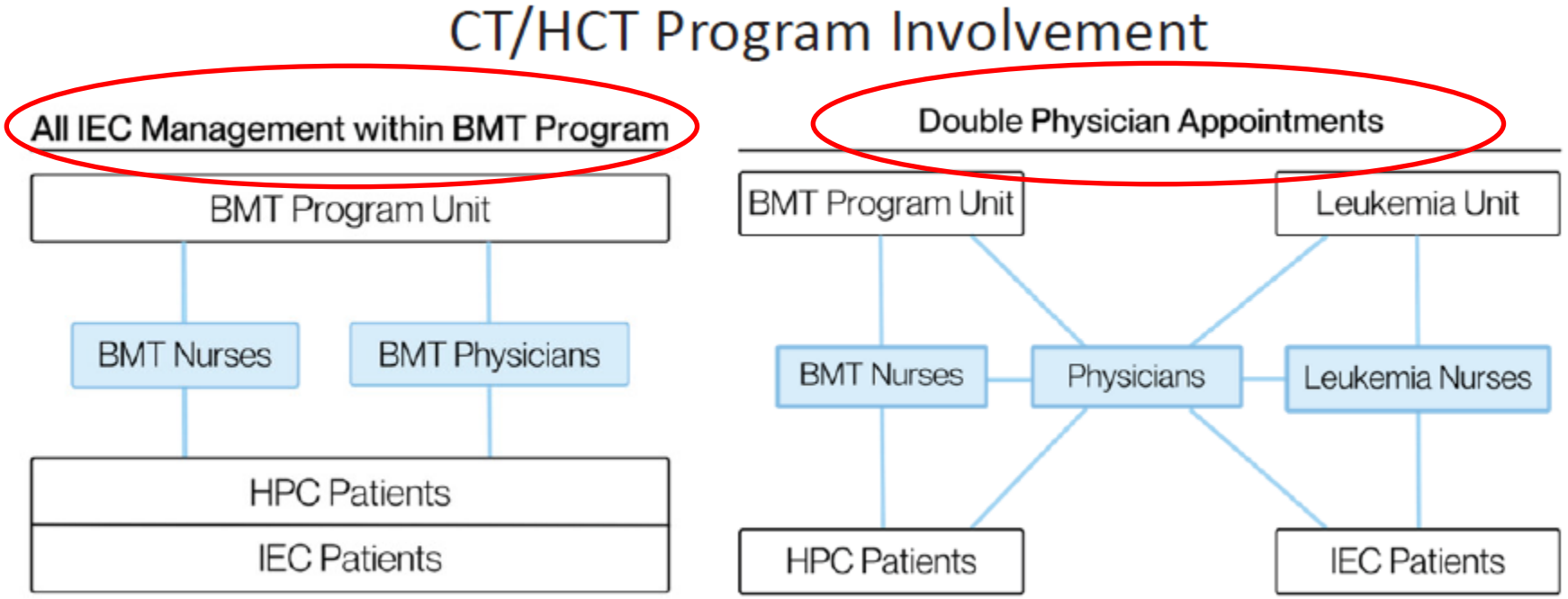
Kevin J. Curran[1], Sarah Nikiforow[2], Carlos Bachier[3], Yen-Michael Hsu[4], David Maloney[5], Marcela V. Maus[6], Philip McCarthy[7], David Porter[8], Patricia Shi[9], Elizabeth J Shpall[10], Basem William[11], Kara Wacker[12], Phyllis Warkentin[12, 13], Helen E Heslop[14]

- Addressed some of the common issues faced by IEC programs including the need to manage resources, proper program structure, and the need for on-going competency assessment
- Through the FACT IEC Standards and accreditation program an institution can develop a quality IEC program which provides safe and effective IEC products for their patients with exceptional outcomes

blood advances

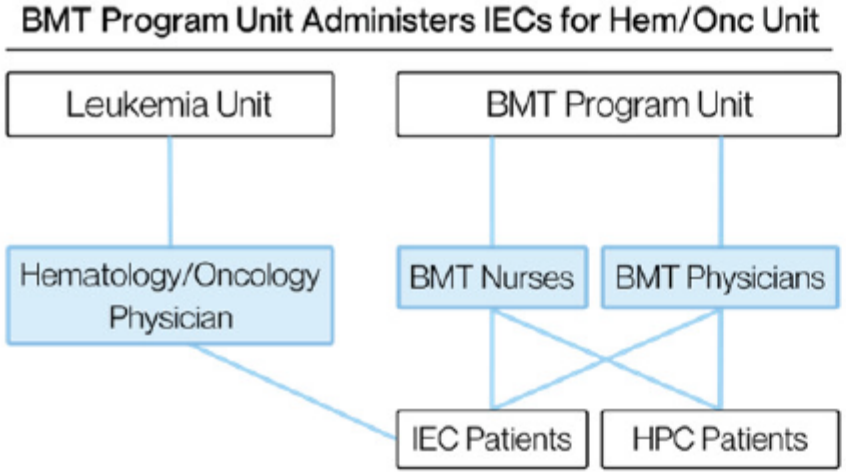
Blood Advances 2023

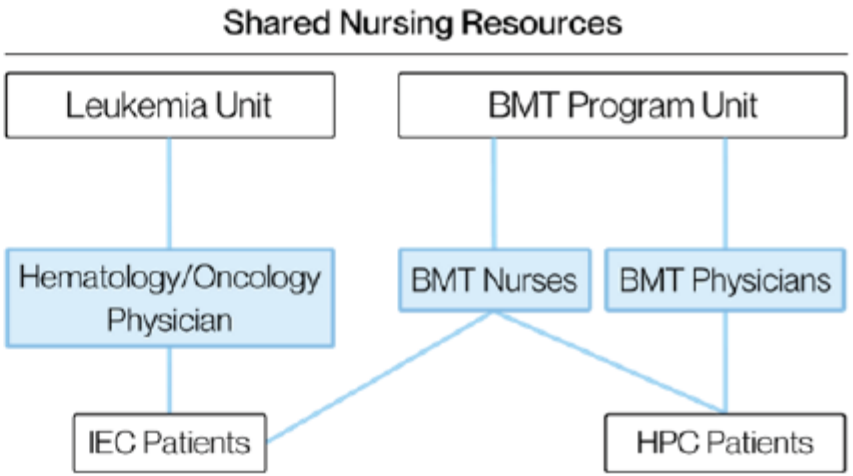
IEC Program Structures



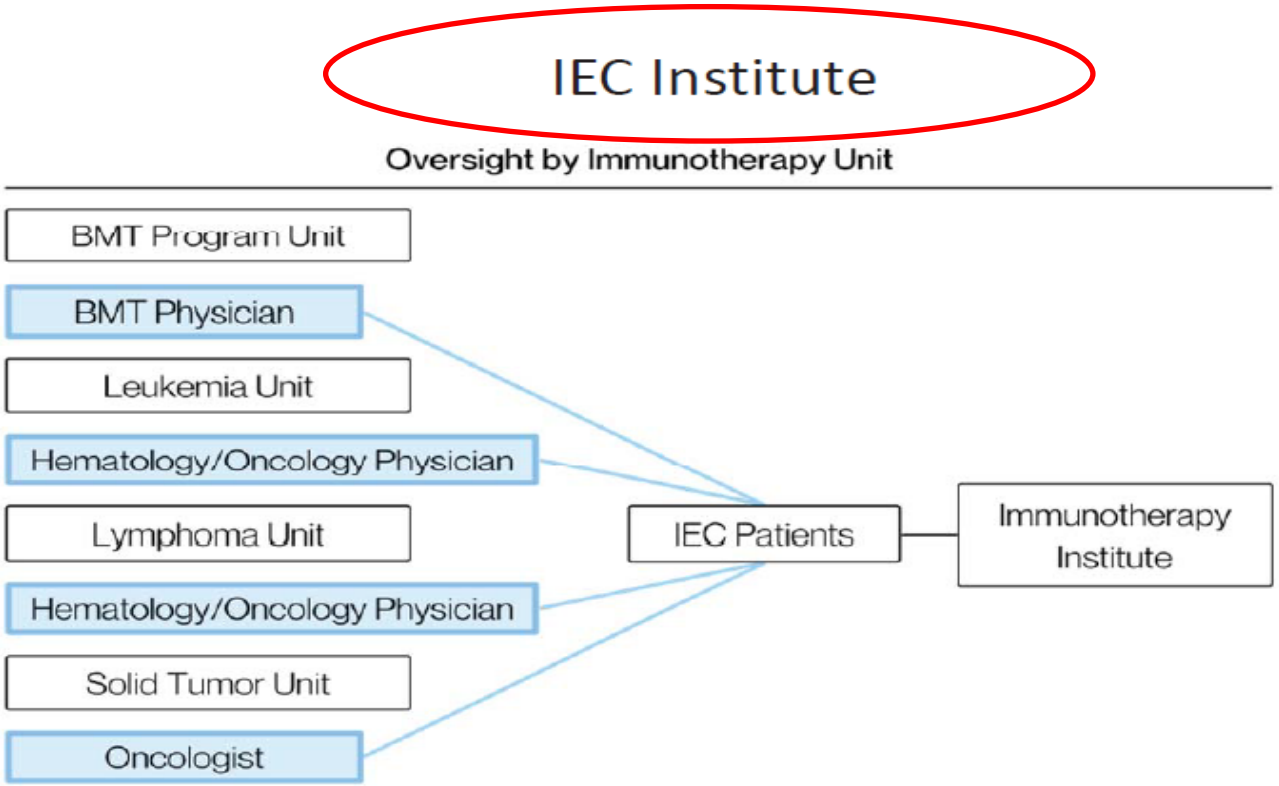
IEC Program Structures

Shared Resources





IEC Program Structures



Caring for IEC solid tumor patients at MDACC: Model 1

- The entire care is provided by the SCT team while on study protocols
- Return to medical oncology upon progression
- Coordinate with referring oncology on bridging and follow up care

Referring Provider

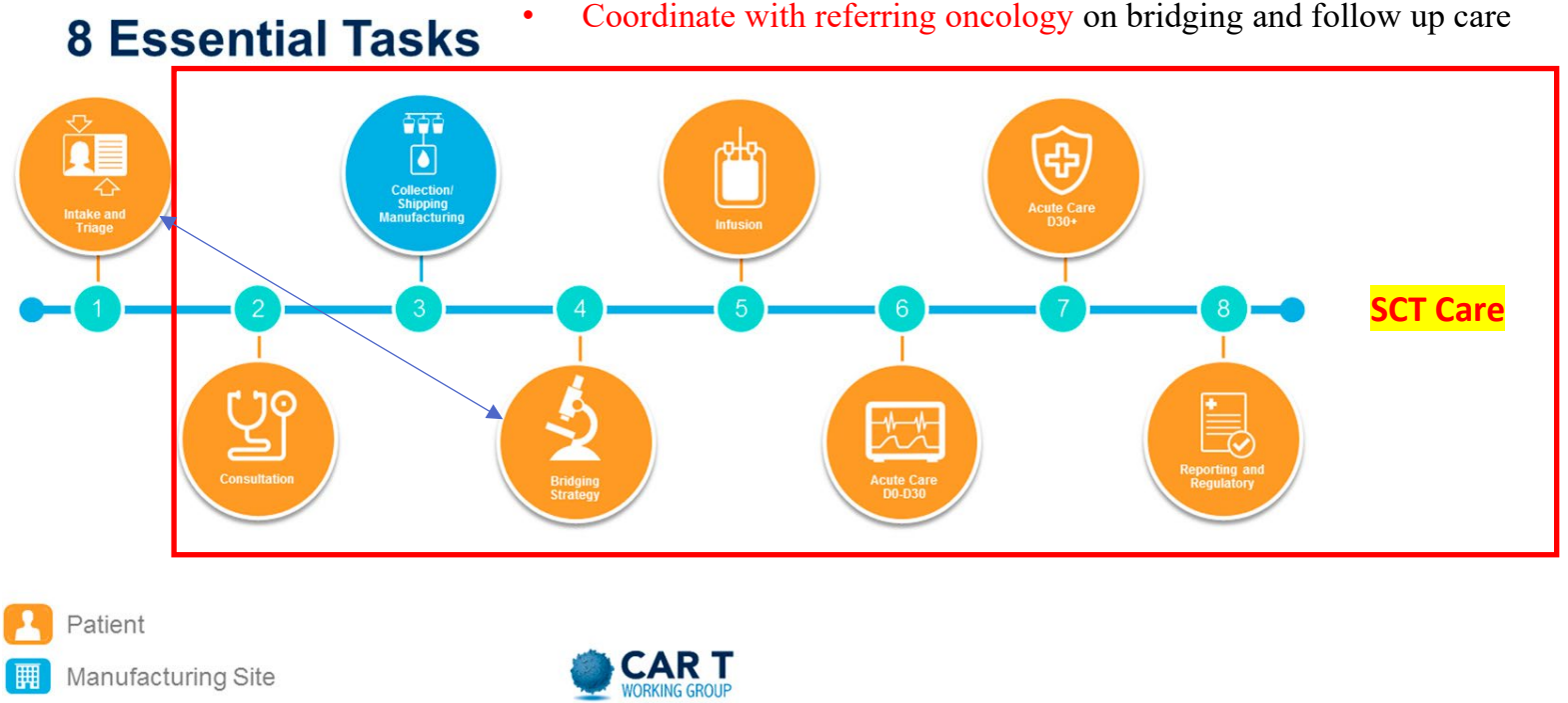


Figure adapted from Berdeja JG. ASH Educ 2020

Caring for IEC solid tumor patients at MDACC: Model 2

- Outpatient, follow up jointly with solid tumor and SCT attending until day 30*
- Return to medical oncology after day 30*

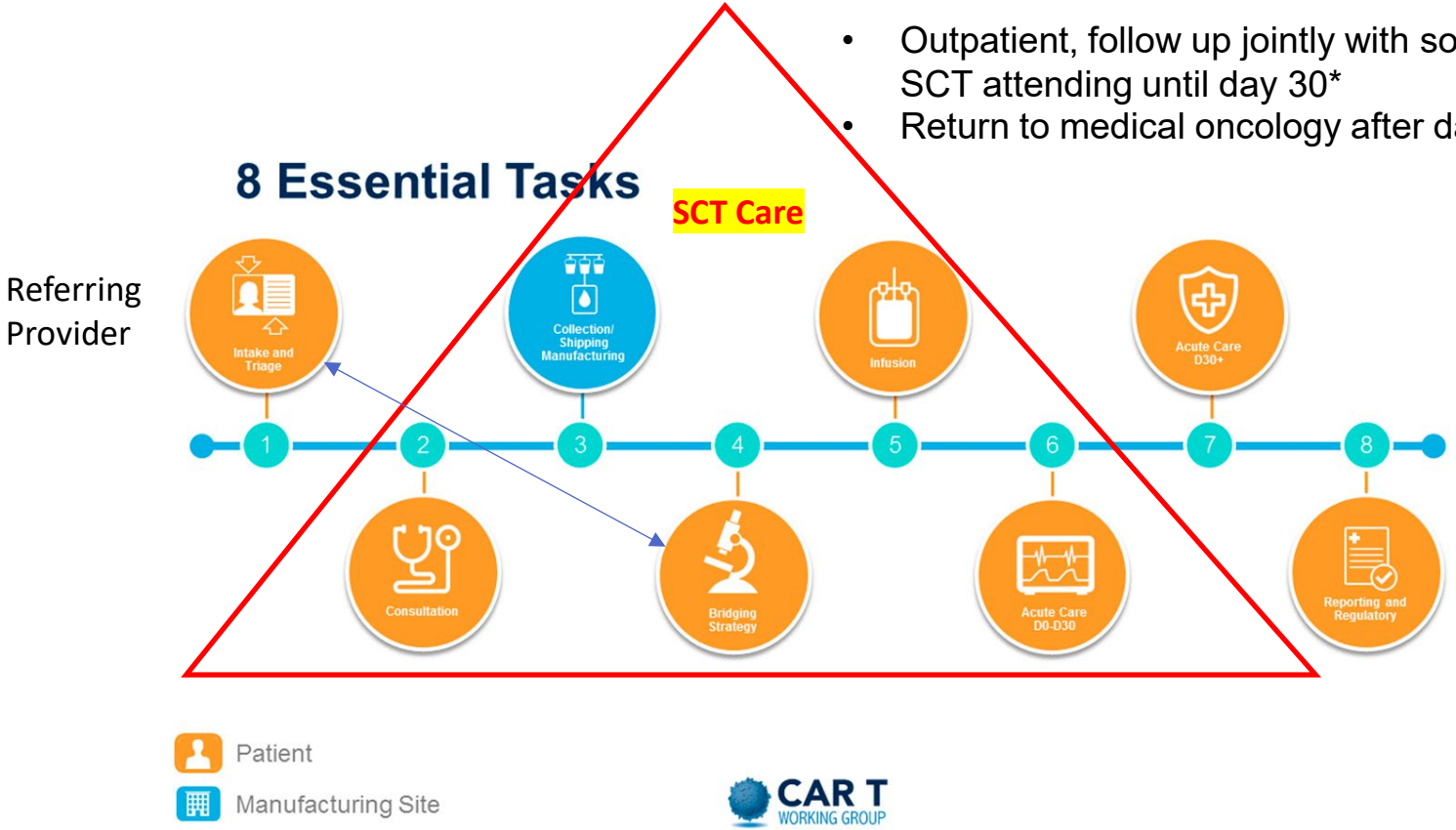
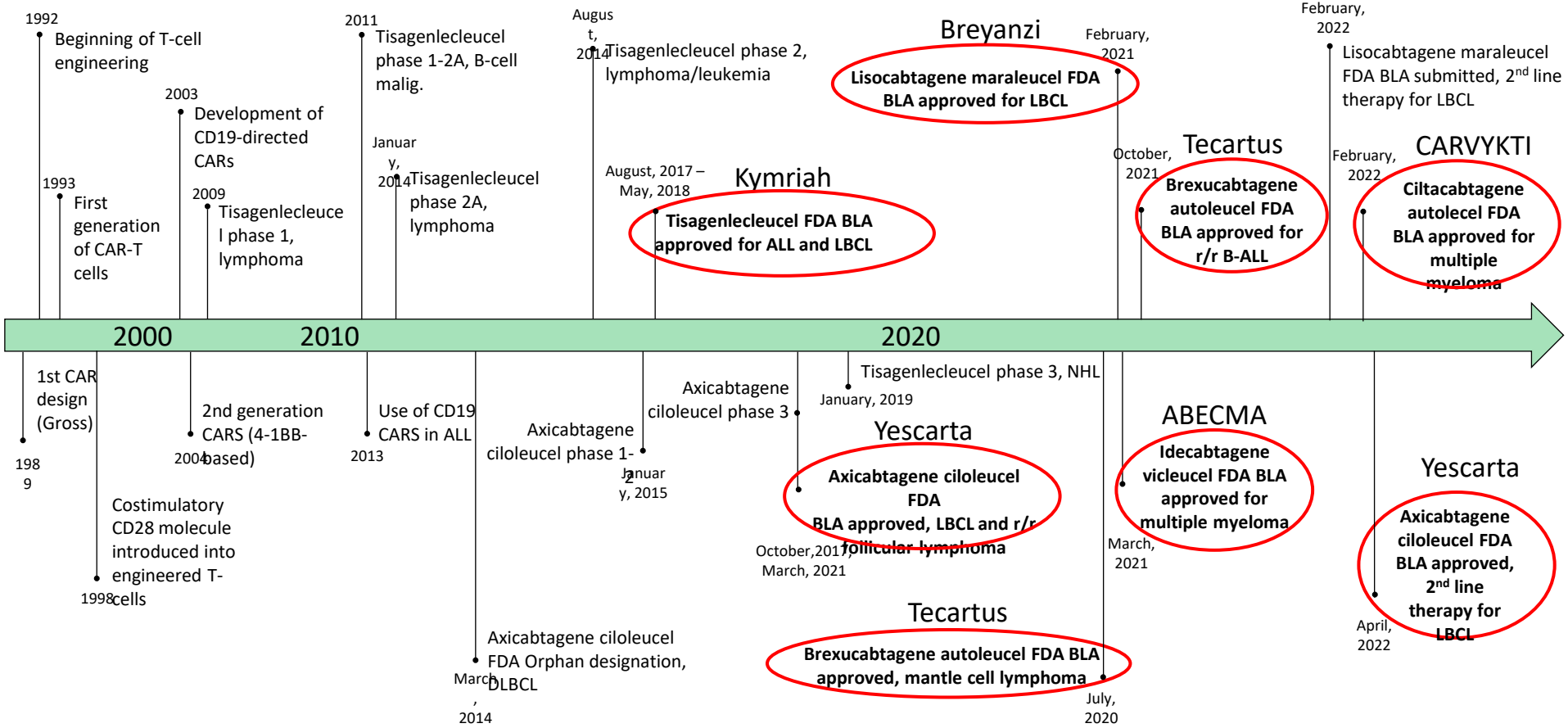


Figure adapted from Berdeja JG. ASH Educ 2020

Paradigm Shift for CAR T Cell in Heme Tumors



What about a Paradigm Shift for CAR T Cell in Solid Tumors?!

- In February 2024, first historical approval for TIL (Lifileucel) in melanoma

- In August 2024, first historical approval for TCR (Afamitresgene) in sarcoma

Table 2. Summary of the published clinical trials for CAR T-cell therapy in solid tumors

Year	Tumor Subtypes	Target	Sample Size	Outcome	Reference
2006	Ovary	FRα	14	No response	Kershaw et al[13]
2007	Neuroblastoma	CD171	6	NR	Park et al[82]
2010	CRC	HER2	1	Died	Morgan et al[36]
2011	Neuroblastoma	GD2	19	3 CR of 11 active disease	Louis et al[34]
2013	RCC	CAIX	12	No response	Lamers et al[24]
2015	GBM	IL13Ra2	3	Transient	Brown et al[29]
2015	Ovary	MUC16	6	NR	Koneru et al[83]
2015	GBM	HER2	16	1 PR and 4 SD for up to 24 mo	Ahmed et al[84]
2015	Sarcoma	HER2	19	17 evaluable: 4 with SD for up to 14 mo	Ahmed et al[37]
2016	Prostate	PSMA	5	2 PR	Junghans et al[26]
2017	CRC	CEA	10	2 PR 7 SD up to 30 wk	Zhang et al[48]
2017	Neuroblastoma	GD2	11	5 SD	Heczey et al[35]
2017	CEA-positive tumors	CEA	14	No response	Thistlethwaite et al[49]
2017	GBM	EGFRv3	10	1 SD for 18 wk	O'Rourke et al[3]2
2018	CD133-positive tumors	CD133	23	3 PR, 14 SD	Wang et al[56]
2018	HNSCC	EGFR	13	ORR: 69%	Papa et al[85]
2018	Biliary and pancreatic cancers	HER2	11	1 PR 5 SD	Feng et al[39]
2018	PDAC	Mesothelin	6	3 SD	Beatty et al[40]
2019	Pleural tumors	Mesothelin	20	14 with PD1 therapy: 2 CR, 5 PR, 4 SD	Adusumilli et al[42]
2019	Mesothelin-positive tumors	Mesothelin	15	11 SD	Haas et al[86]
2019	Gastric, pancreas	Claudin18.2	12	1 CR, 3 PR, 5 SD	Zhan et al[51]
2019	MUC1-positive tumors	MUC1	13	9 SD	Li et al[87]
2019	GBM	EGFRv3	18	No response	Goff et al[33]
2019	CEA-positive tumors	CEA	8	2 SD	Katz et al[47]
2019	PSCA-positive tumors	PSCA	15	8 SD	Becerra et al[88]
2019	GD2-positive tumors	GD2	12	1 CR, 2 PR	Yankelevich et al[89]
2019	TNBC	ROR1	4	1 PR 2 SD	Specht et al[90]
2019	CRC	NKG2D	8	NR	Van Cutsem et al[91]
2020	Lung	PD-L1	1	Serious AE	Liu et al[92]
2020	HCC	Glypican-3	13	2 PR and 1 SD for 44 mo	Shi et al[93]

Srour and Akin. JIPO 2022

Table 1 | Summary of selected TCR gene therapy clinical trials

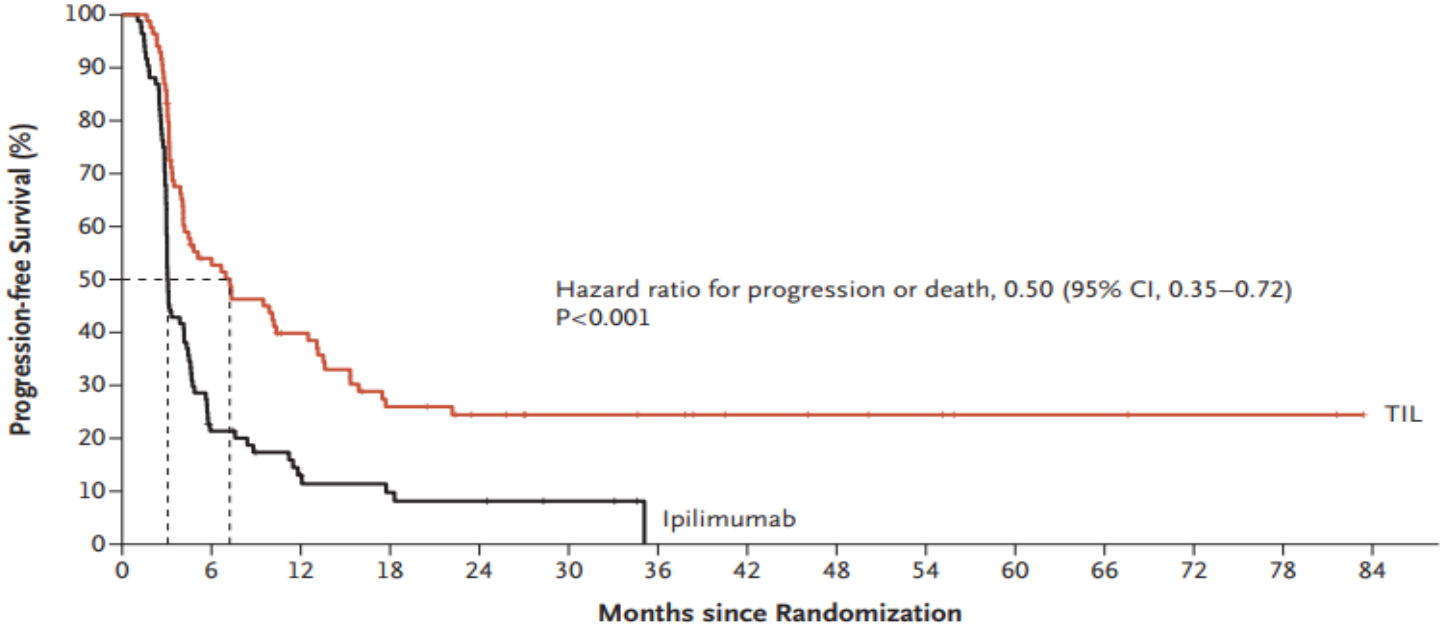
Antigen class	HLA	Co-receptor independent	CDR modification	Tumour	ORR[a]	Ref.
Tissue differentiation						
MART-1	A*02:01	No	No	Melanoma	13%	33
MART-1	A*02:01	Yes	No	Melanoma	30%	34
gp100	A*02:01	Yes	No	Melanoma	19%	34
Tyrosinase	A*02:01	Yes	No	Melanoma	33%	299
CEA	A*02:01	Yes	Yes	CRC	33%	35
Cancer germ line						
NY-ESO-1	A*02:01	Yes	Yes	Melanoma	55%	258
NY-ESO-1	A*02:01	Yes	Yes	SS	61%	258
NY-ESO-1	A*02:01	Yes	Yes	SS	50%	43
NY-ESO-1	A*02:01	Yes	Yes	MRCLS	40%	259
MAGE-A3/9/12	A*02:01	Yes	Yes	Various	56%	36
MAGE-A3/6	DPB1*04:01	Yes	No	Various	24%	38
MAGE-A4	A*24:01	No	No	ESCA	0%	37
MAGE-A4	A*02:01	Yes	Yes	SS and MRCLS	36%	262
MAGE-A4	A*02:01	Yes	Yes	Various	24%	263
MAGE-A4+CD8α	A*02:01	Yes	Yes	Various	36%	264
MAGE-A10	A*02:01	Not defined	Yes	NSCLC	11%	266
PRAME	A*02:01	No	No	Various	50%	268
Overexpressed						
WT1	A*24:02	No	No	MDS/AML	0%	39
WT1	A*02:01	Yes	No	AML	NED	44
Viral						
HPV-16 E6	A*02:01	Yes	No	HPV-16$^+$	17%	40
HPV-16 E7	A*02:01	Yes	No	HPV-16$^+$	50%	41
Neoantigen						
Private	Various	Various	No	Various	0%	47
TP53 (R175H)	A*02:01	Yes	No	BRCA breast cancer	1/1	275
KRAS (G12D)	C*08:02	Yes	No	PDAC	1/2	274
KRAS (G12D)	A*11:01	Yes	No	NSCLC	1/1	300

Klebanoff CA et al. Nat Rev Drug Discovery 2023

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2022 VOL. 387 NO. 23

Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma



No. at Risk															
TIL	84	41	29	18	14	11	10	7	6	5	3	3	2	2	0
Ipilimumab	84	17	8	6	5	3	0	0	0	0	0	0	0	0	0

nature medicine

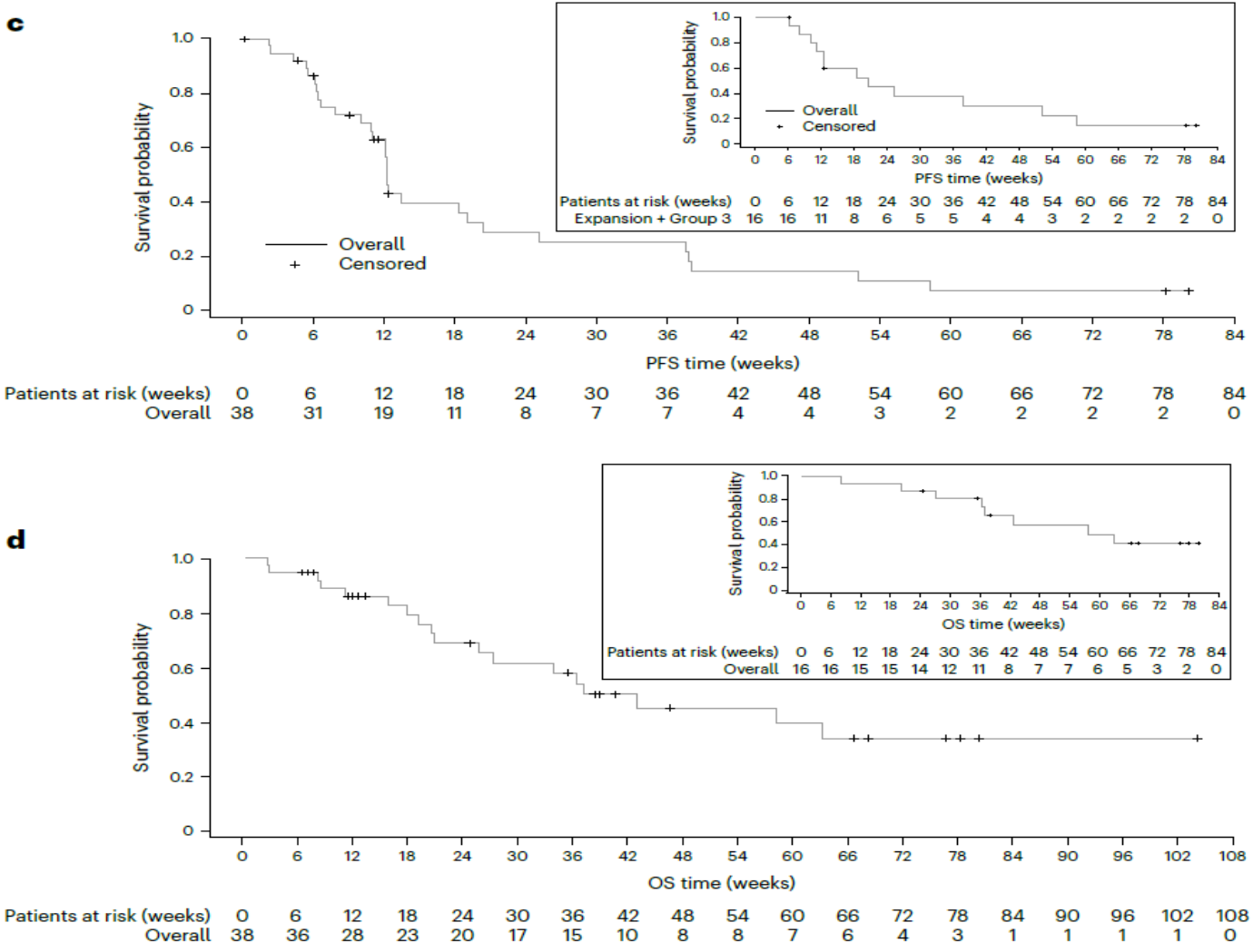
Article

https://doi.org/10.1038/s41591-022-02128-z

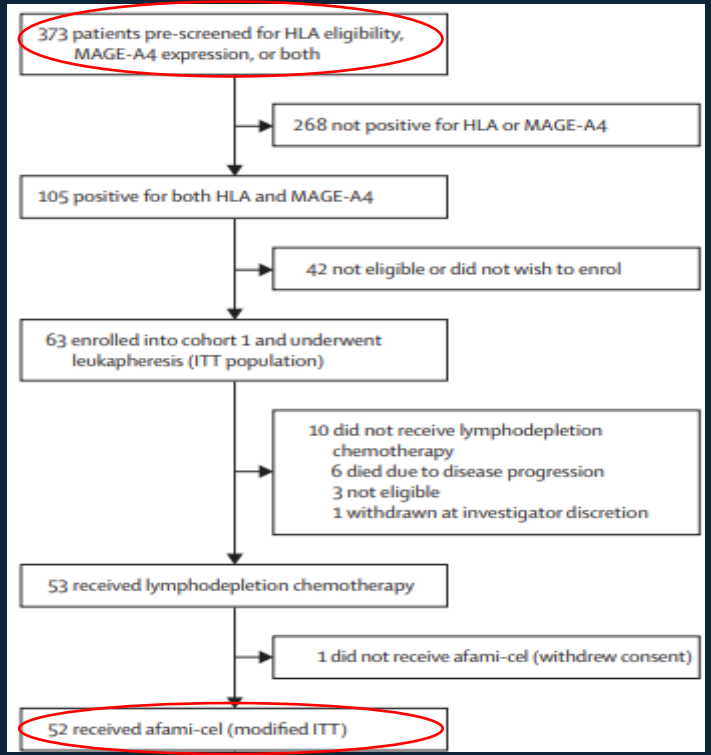
Autologous T cell therapy for MAGE-A4^{+} solid cancers in HLA-A*02^{+} patients: a phase 1 trial

- Phase 1 dose-escalation study
- Autologous T cells that express a high-affinity melanoma-associated antigen A4 (MAGE-A4)-specific T-cell receptor (TCR) targeting MAGE-A4+ tumors
- (HLA)-A*02
- 38 patients, variety of solid tumors, 42% were sarcomas, 24% ovarian

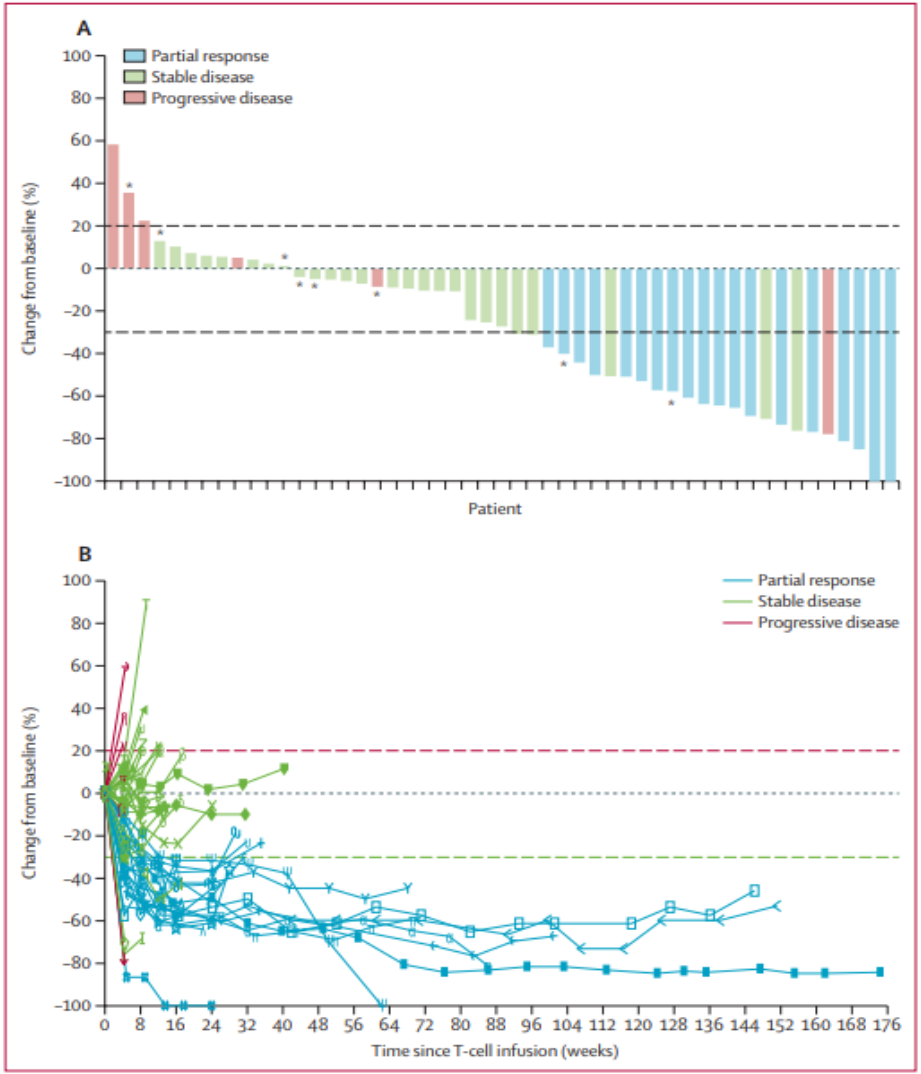
Hong DS, et al. Nature Medicine 2023


c
Survival probability
1.0
0.8
0.6
0.4
0.2
0
Overall
Censored
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
PFS time (weeks)
Patients at risk (weeks) 0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
Overall 38 31 19 11 8 7 7 4 4 3 2 2 2 2 0
Survival probability
Overall
Censored
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
PFS time (weeks)
Patients at risk (weeks) 0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
Expansion + Group 3 16 16 11 8 6 5 5 4 4 3 2 2 2 2 0
d
Survival probability
1.0
0.8
0.6
0.4
0.2
0
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108
OS time (weeks)
Patients at risk (weeks) 0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108
Overall 38 36 28 23 20 17 15 10 8 8 7 6 4 3 1 1 1 1 0
Survival probability
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
OS time (weeks)
Patients at risk (weeks) 0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
Overall 16 16 15 15 14 12 11 8 7 7 6 5 3 2 0

Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial



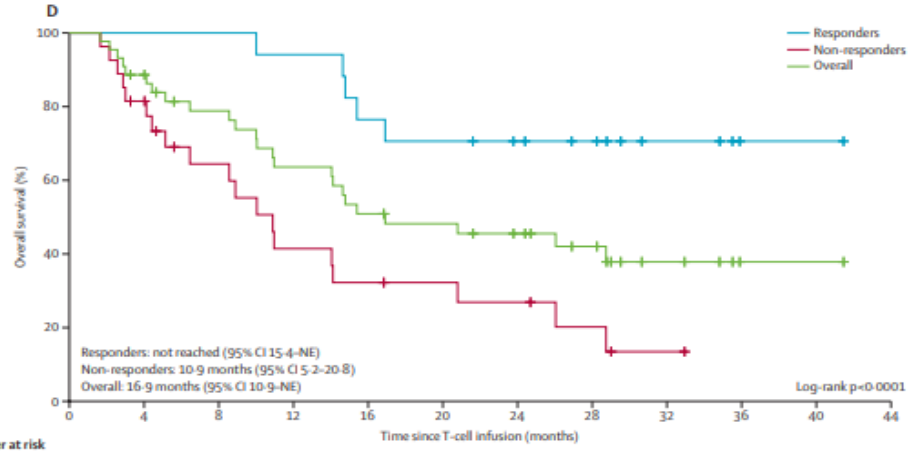
D'Angelo S, et al. Lancet 2024



C

	Events/patients	Overall response rate (95% CI)
Bridging therapy		
Yes	4/16	25% (7-52)
No	13/28	46% (28-66)
Baseline sum of longest diameters of target lesions, mm		
≥100	5/21	24% (8-47)
<100	12/22	55% (32-76)
MAGE-A4 expression H score		
<200	4/13	31% (9-61)
≥200	13/31	42% (25-61)
Sex		
Male	6/22	27% (11-50)
Female	11/22	50% (28-72)
Age, years		
<40	7/21	33% (15-57)
≥40	10/23	44% (23-66)
Previous lines of systemic therapy		
≤2	7/21	33% (15-57)
≥3	10/23	44% (23-66)
Dose of transduced T cells administered, ×10⁹		
<7	8/19	42% (20-67)
≥7	9/25	36% (18-57)
Any-grade cytokine release syndrome		
Occurred	11/33	33% (18-52)
Did not occur	6/11	55% (23-83)
Overall	**17/44**	**39% (24-55)**

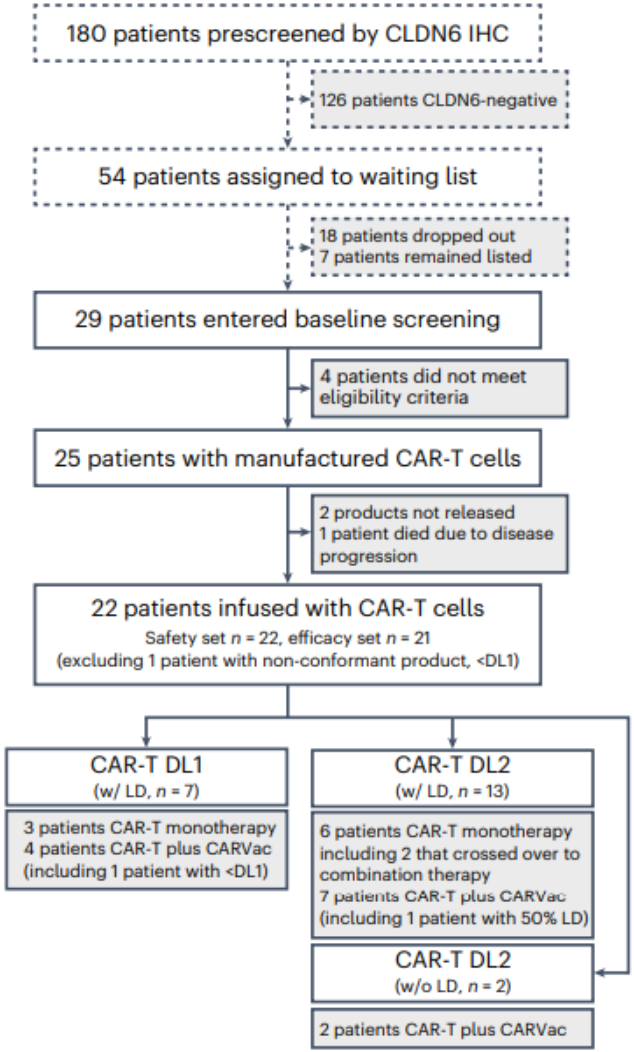
D



Number at risk (number censored)

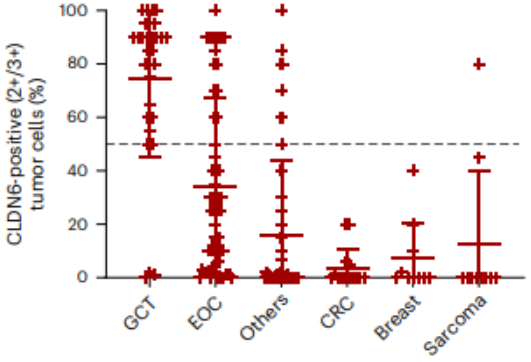
Responders	17 (0)	17 (0)	17 (0)	16 (0)	13 (0)	12 (0)	10 (2)	8 (4)	4 (8)	1 (11)	1 (11)	0 (12)
Non-responders	27 (0)	21 (1)	14 (4)	9 (4)	7 (4)	6 (5)	5 (5)	3 (6)	1 (7)	0 (8)	..	..
Overall	44 (0)	38 (1)	31 (4)	25 (4)	20 (4)	18 (5)	15 (7)	11 (10)	5 (15)	1 (19)	1 (19)	0 (20)

b



c

Cancer type	*n*	Percentage with any positivity	Percentage of 2+/3+
GCT	30	100	90
EOC	55	91	29
Others	61	48	16
CRC	14	43	0
Breast	10	40	0
Sarcoma	10	20	10
Total	180	67	30



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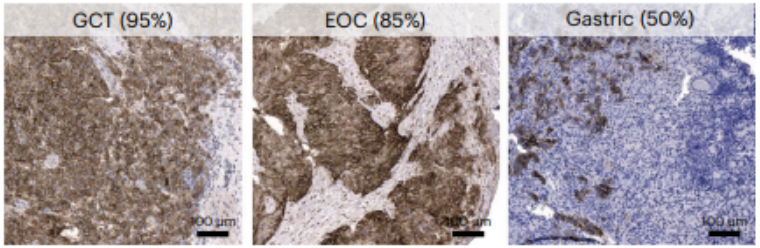
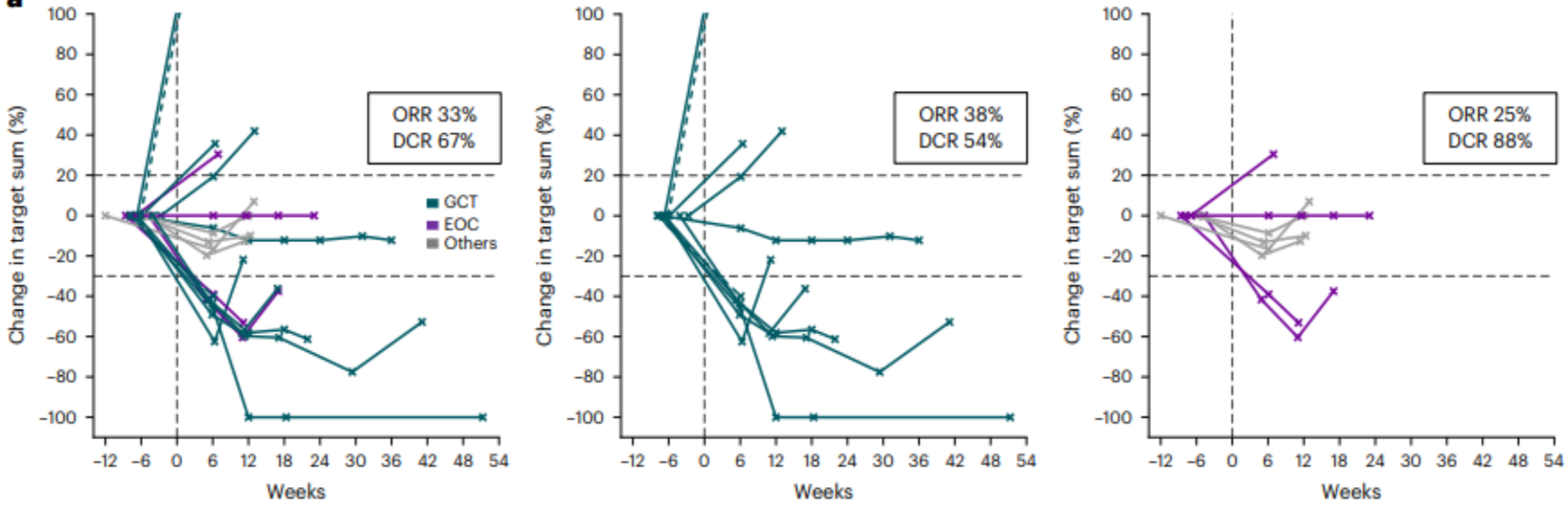


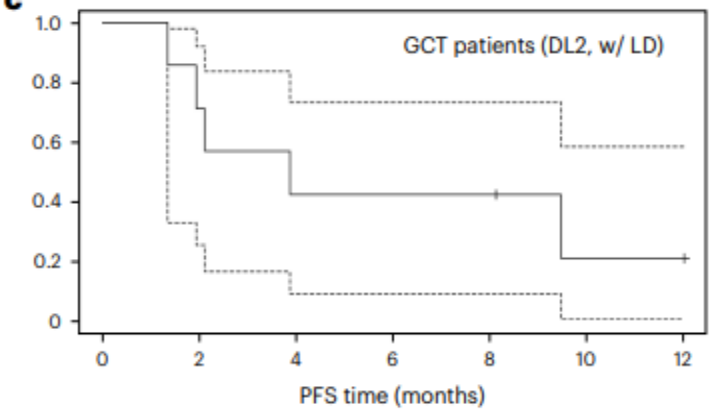
a



b

All patients	1×10^7 w/ LD	1×10^8 w/ LD	Total w/ LD	1×10^8 w/o LD	Total
n	6	13	19	2	21
ORR, %	17	46	37	0	33
DCR, %	50	85	74	0	67
GCT patients	1×10^7 w/ LD	1×10^8 w/ LD	Total w/ LD	1×10^8 w/o LD	Total
n	4	7	11	2	13
ORR, %	25	57	45	0	38
DCR, %	25	86	64	0	54
Non-GCT patients	1×10^7 w/ LD	1×10^8 w/ LD	Total w/ LD	1×10^8 w/o LD	Total
n	2	6	8	0	8
ORR, %	0	33	25	N/A	N/A
DCR, %	100	83	88	N/A	N/A

c



Role of CD70 in Immune Response and Cancer

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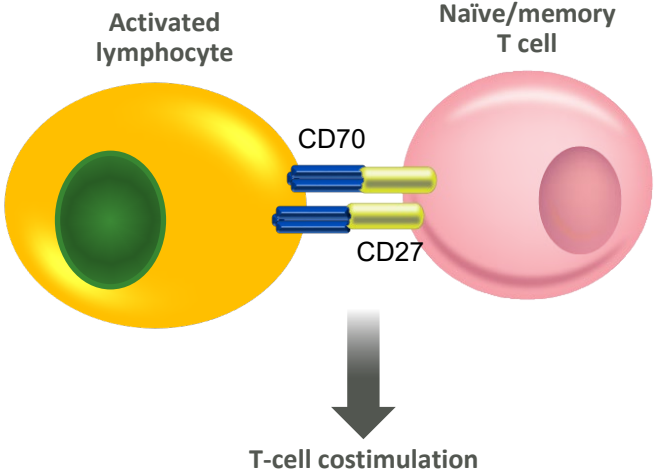
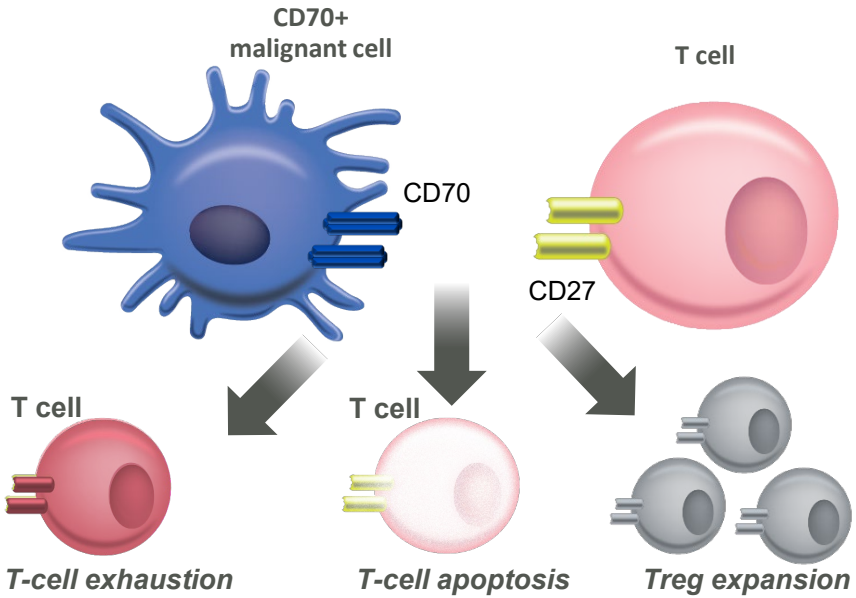
Physiological role of CD70

- Transient CD70 expression on activated lymphocytes as well as NK cells and mature dendritic cells[1]
- Controls naïve and memory T-cell activation via interaction with CD27



Role of CD70 in cancer

- High levels of CD70 expression have been detected in approximately 80% of ccRCC samples[2]
- CD70 expression is regulated by the VHL pathway; HIF activates CD70[3]
- Possible immunosuppressive role due to T-cell exhaustion, apoptosis, or Treg expansion[1]



ccRCC, clear cell renal cell carcinoma; NK, natural killer; VHL, Von Hippel-Lindau; HIF hypoxia-inducible factor; Treg, regulatory T cell

References: 1. Flieswasser T et al., *J Exp Clin Cancer Res* 2022:41:12. 2. Flieswasser T et al., *Cancers* 2019:11:1161. 3. Ruf M et al., *Clin Cancer Res* 2015:21:889-898.

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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

Samer A. Srour, MD[1], Ben Tran, MBBS, FRACP[2], John B. Haanen, MD, PhD[3], Michael Hurwitz, MD, PhD[4], Adrian Sacher, MD[5], Neeraj Agarwal, MD[6], Nizar Tannir, MD[1], L. Elizabeth Budde, MD[7], Simon Harrison MBBS, PhD, FRACP[2], Sebastian Klobuch, MD[3], Sagar S. Patel, MD[6], Mary-Lee Dequeant, PhD[8], Qiuling Ally He, PhD[8], Alissa Keegan, MD, PhD[8], Henia Dar, PhD[8], Anna Ma, PhD[8], PK Morrow, MD[8], Sumanta K Pal, MD[7]

[1] The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Peter MacCallum Cancer Centre, Melbourne, Australia; [3]Netherlands Cancer Institute, Amsterdam, Netherlands; [4]Yale School of Medicine, New Haven, CT; [5]Princess Margaret Cancer Centre, University Health Network, Toronto, Canada; [6]Huntsman Cancer Institute, University of Utah Comprehensive Cancer Center, Salt Lake City, UT; [8]CRISPR Therapeutics, Boston, MA; [7]City of Hope Comprehensive Cancer Center, Duarte, CA

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CANCER DISCOVERY

RESEARCH ARTICLE | APRIL 05 2024

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

Sumanta K. Pal ; Ben Tran ; John B.A.G. Haanen ; Michael E. Hurwitz ; Adrian Sacher ; Nizar M. Tannir ; Lihua E. Budde ; Simon J. Harrison ; Sebastian Klobuch ; Sagar S. Patel ; Luis Meza ; Mary-Lee Dequeant ; Anna Ma ; Qiuling Ally He ; Leah M. Williams ; Alissa Keegan ; Ellen B. Gurary ; Henia Dar ; Sushant Karnik ; Changan Guo ; Heidi Heath ; Rachel R. Yuen ; Phuong K. Morrow ; Neeraj Agarwal ; Samer A. Srour

+ Author & Article Information

Cancer Discov OF1–OF14.

https://doi.org/10.1158/2159-8290.CD-24-0102 **Article history**

CTX130 is an allogeneic CAR T targeting CD70

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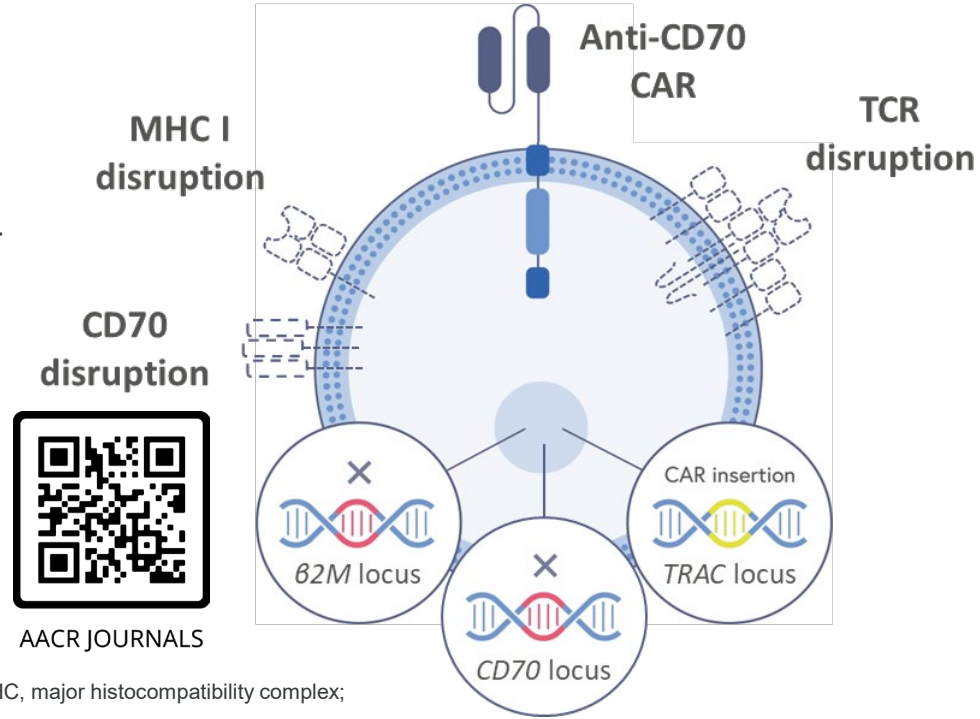
- CTX130 is an investigational allogeneic, CRISPR/Cas9 gene-edited, anti-CD70 CAR T cell therapy with TRAC, β2M, and CD70 disruptions
  - Using an AAV vector, an anti-CD70 CAR cassette is specifically inserted into the TRAC locus by homology-directed repair
- CTX130 is manufactured from T cells collected from a healthy donor, which are then selected and edited before expansion and cryopreservation for off-the-shelf availability

CTX130 Construct



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AAV, adeno-associated virus; β2M, β2-microglobulin; CAR, chimeric antigen receptor; MHC, major histocompatibility complex; TCR, T-cell receptor; TRAC, T-cell receptor alpha constant.

Reference: Dequeant M-L, et al. CD70 knockout: A novel approach to augment CAR-T cell function. Poster presented at American Association for Cancer Research 2021. April 10-15 and May 17-21, 2021.

Patient Demographics and Baseline Characteristics

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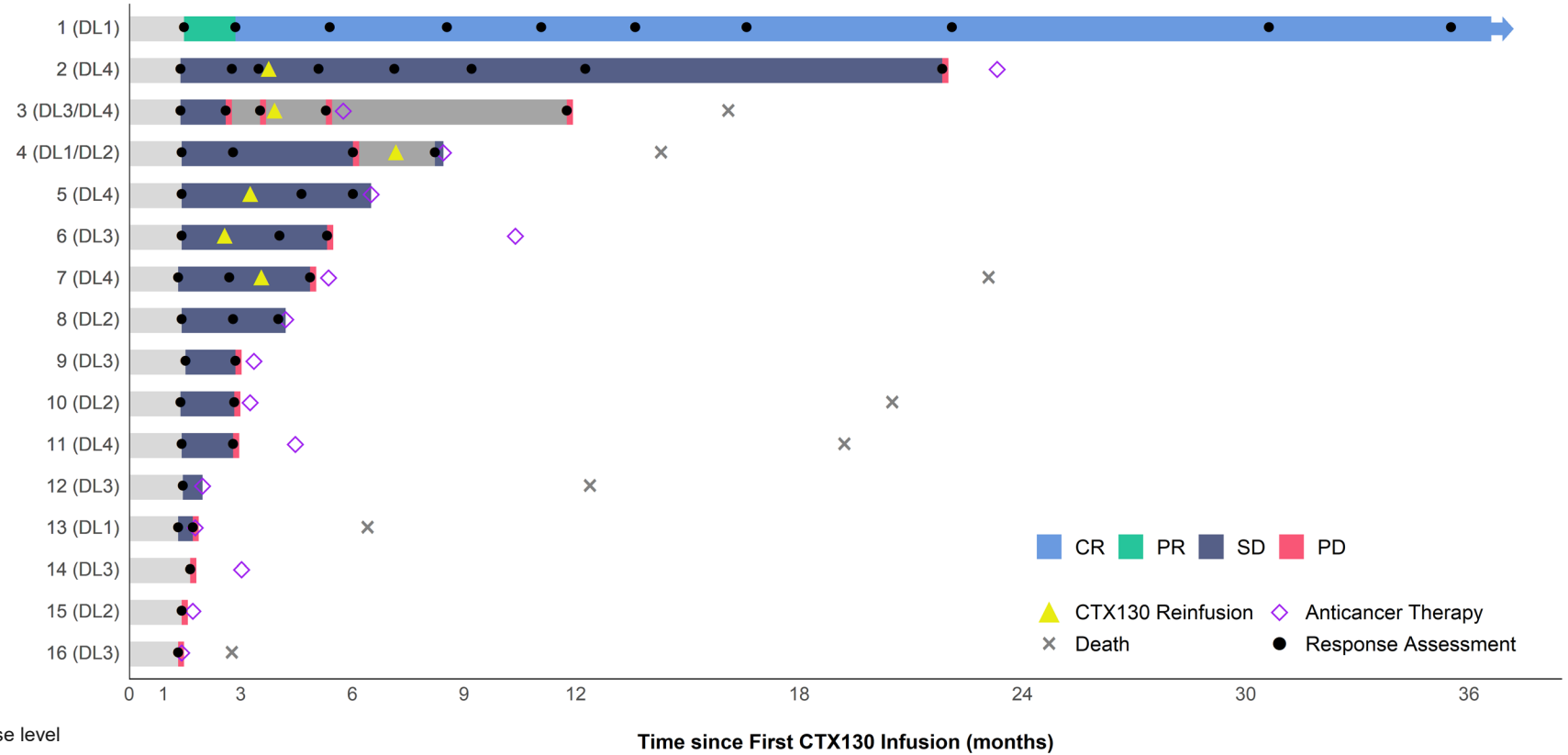
Data cutoff date: 09 OCT 2023

	DL1 3×10^7 N=3	DL2 1×10^8 N=3	DL3 3×10^8 N=6	DL4 9×10^8 N=4	Total N=16
Median age, y (range)	59 (58-64)	60 (54-65)	61 (53-73)	70 (66-77)	63 (53-77)
Male sex, n (%)	3 (100.0)	3 (100.0)	6 (100.0)	2 (50.0)	14 (87.5)
Metastatic disease, n (%)	3 (100.0)	3 (100.0)	6 (100.0)	4 (100.0)	16 (100.0)
Prior anticancer therapies, n (%)					
Systemic therapy	3 (100.0)	3 (100.0)	6 (100.0)	4 (100.0)	16 (100.0)
Radiotherapy	1 (33.3)	2 (66.7)	4 (66.7)	4 (100.0)	11 (68.8)
Surgery	3 (100.0)	3 (100.0)	5 (83.3)	4 (100.0)	15 (93.8)
Median prior lines of systemic therapy, n (range)	2 (1-3)	3 (2-4)	3 (1-5)	3 (2-6)	3 (1-6)
Median time from diagnosis, y (range)	3.4 (2.5-6.3)	2.7 (0.7-3.3)	5.1 (2.5-6.3)	10.5 (5.1-24.0)	4.9 (0.7-24.0)
IMDC category at screening, n (%)					
Favorable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intermediate	3 (100.0)	3 (100.0)	3 (50.0)	1 (25.0)	10 (62.5)
Poor	0 (0.0)	0 (0.0)	3 (50.0)	3 (75.0)	6 (37.5)
eGFR <60 mL/min/1.73 m^2, n (%)	2 (66.7)	1 (33.0)	1 (16.7)	2 (50.0)	6 (37.5)

DL, dose level; eGFR, estimated glomerular filtration rate; IHC, immunohistochemistry; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; SoD, sum of diameters.

Efficacy

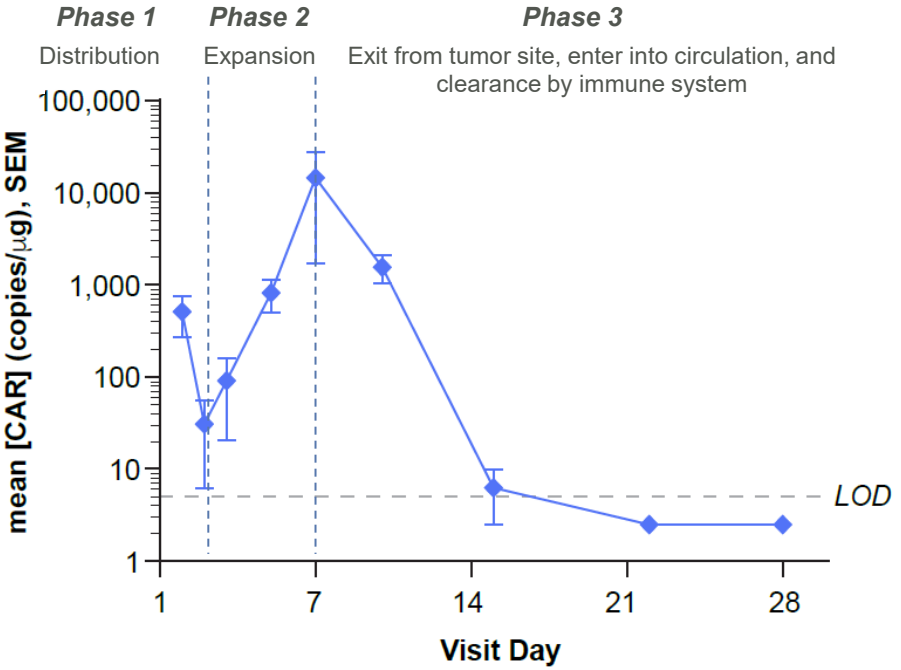
Data cutoff date: 09 OCT 2023



DL, dose level

Pharmacokinetics

CTX130 was detected after infusion then redistributed and declined to a nadir in most patients around Day 2 to Day 3 after infusion. This was followed by rapid expansion with peak concentration Day 7 to Day 15. CTX130 cells then subsequently declined and were no longer detected by Day 28



N=4 DL4 subjects, first infusions only

Preclinical efficacy of CTX131™:
a next-generation CAR T with additional potency edits

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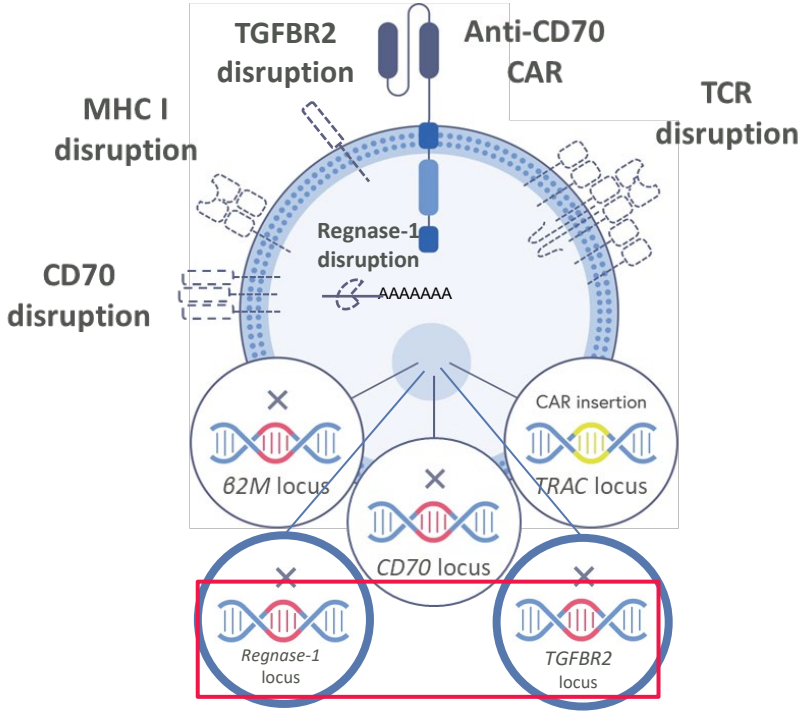
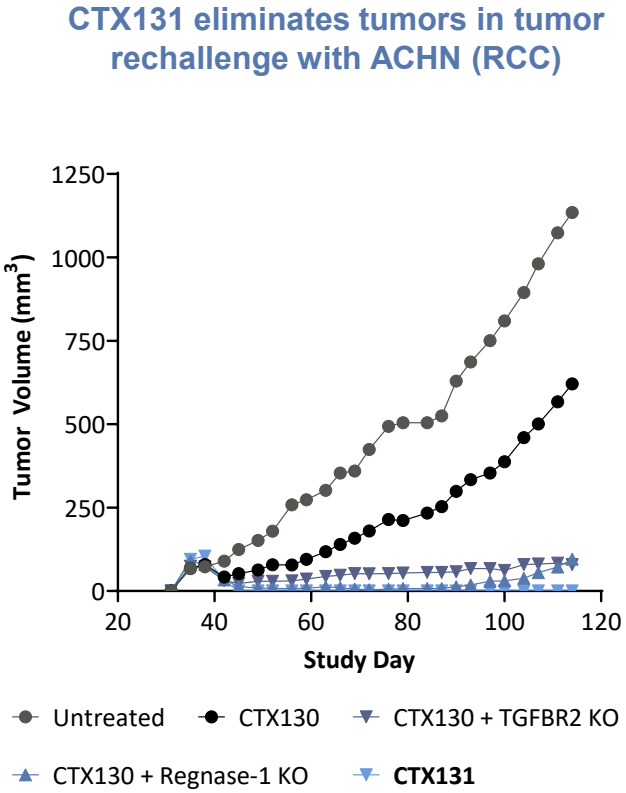
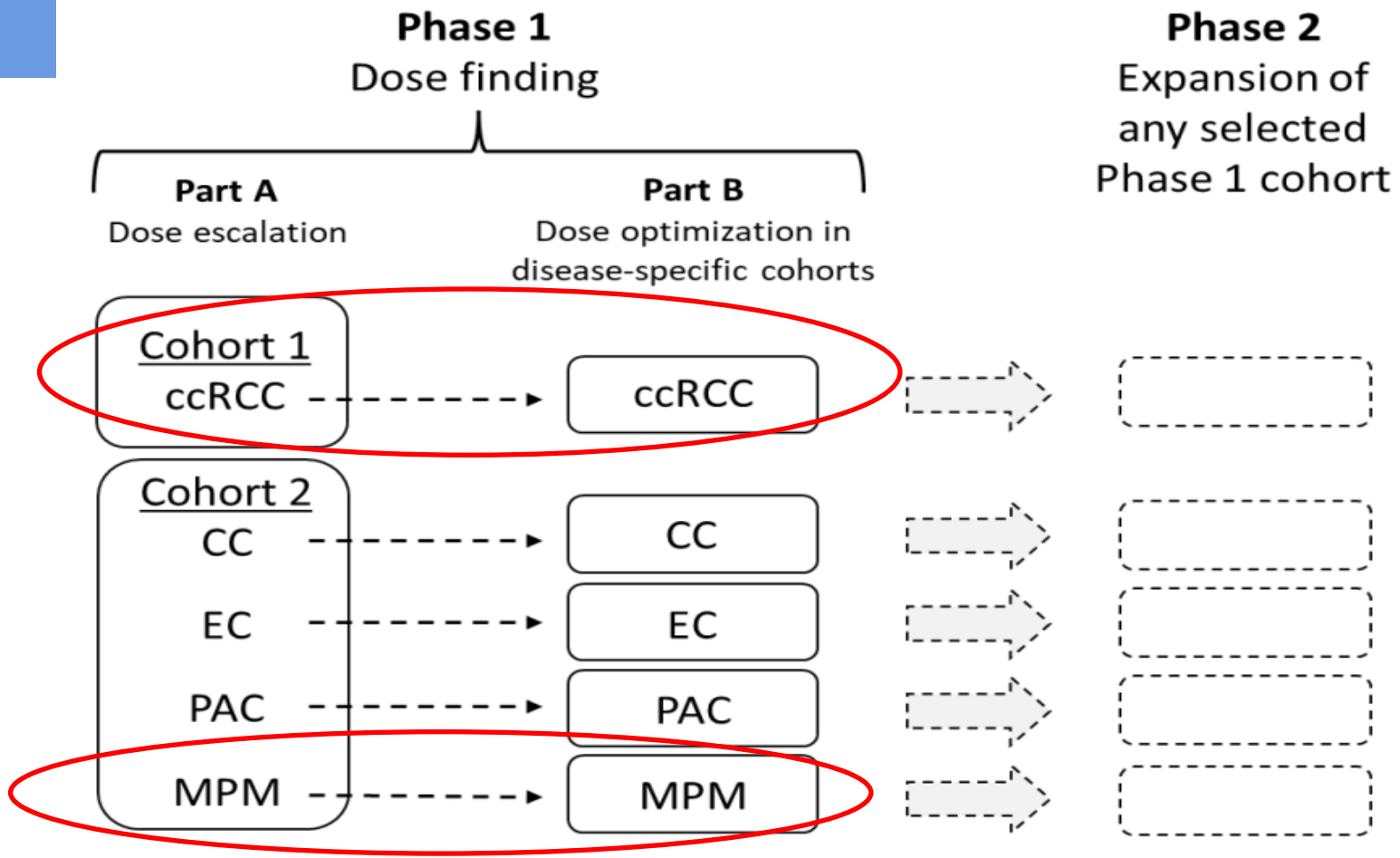




Reference: Terrett J et al., *Cancer Res* (2023) 83 (7_Supplement): ND02

Study Design for CTX131



2025 ASCO® ANNUAL MEETING

ALLO-316 in Advanced Clear Cell Renal Cell Carcinoma: Updated Results From the Phase 1 TRAVERSE Study

Samer A. Srour[1]; Jad Chahoud[2]; Alexandra Drakaki[3]; Brendan D. Curti[4]; Geoffrey T. Gibney[5]; Sumanta Pal[6]; Lily Tang[7]; Sara Charmsaz[7]; Joy Atwell[7]; Paul B. Robbins[7]; Chelsea Williams[7]; Srinivas Ghatta[7]; Christopher J. Severyn[7]; John Le Gall[7]; Nizar M. Tannir[8]; Ritesh R. Kotecha[9]

[1]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Moffitt Cancer Center, Tampa, FL, USA; [3]UCLA Health, Los Angeles, CA, USA; [4]Providence Cancer Institute, Franz Clinic, Portland, OR, USA; [5]Georgetown University Hospital, Washington, DC, USA; [6]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [7]Allogene Therapeutics, San Francisco, CA, USA; [8]Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [9]Memorial Sloan Kettering Cancer Center, New York, NY, USA

TRAVERSE: Transition from Phase 1a to Phase 1b

Total patients enrolled (N = 51)

Received at least 1 dose of LD (n = 50)

Received ALLO-316 (n = 46)

Evaluable for efficacy (n = 46)

CD70⁺ (n = 38)

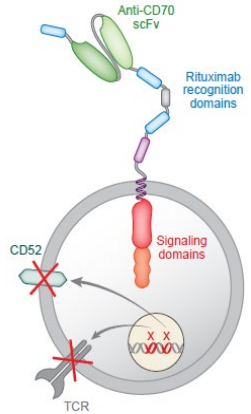
CD70⁻ (n = 5)
CD70 unknown (n = 3)

Dose level 1	Dose level 2	Dose level 3	Dose level 4
(40×10^6)	(80×10^6)	(120×10^6)	(240×10^6)
Total n = 3	Total n = 28	Total n = 6	Total n = 1
FCA n = 3	**FCA** n = 5	**FC300** n = 3	**FC300** n = 1
	FC300 n = 3	**FC500** n = 3	
	FC500 n = 20		

Phase 1b

CD70⁺ TPS ≥50%[a] (n = 16)
CD70⁺ TPS <50%[a] (n = 4)

Median follow-up:
5 months (range, 2-14)



FCA, fludarabine, cyclophosphamide, and ALLO-647 (an anti-CD52 monoclonal antibody)
FC300, fludarabine 30 mg/m² and cyclophosphamide 300 mg/m²
FC500, fludarabine 30 mg/m² and cyclophosphamide 500 mg/m²

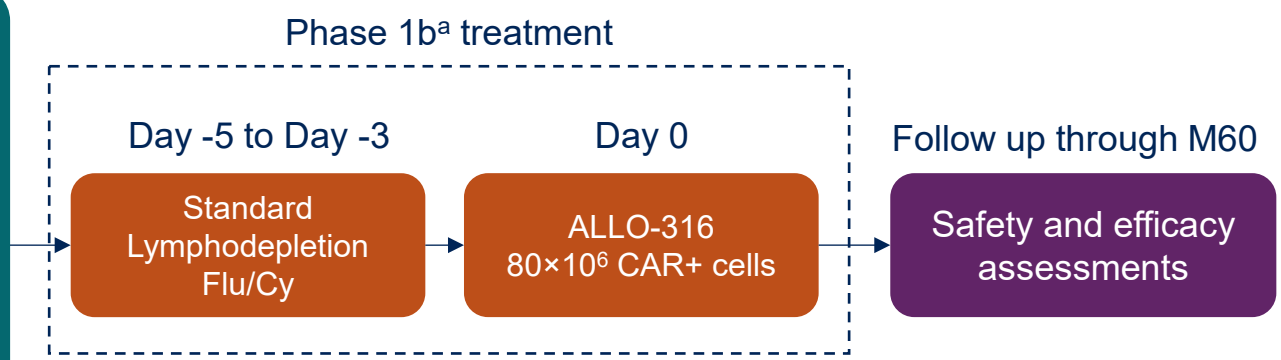
[a]IHC-based CD70 expression.
LD, lymphodepletion; TPS, Tumor Proportion Score.

PRESENTED BY: Dr. Samer A. Srour

TRAVERSE Phase 1b Study Design (NCT04696731)

Key Eligibility Criteria

- Aged ≥18 years with advanced or metastatic ccRCC
- Disease progression after PD-1 axis and VEGF targeted therapies
- CD70 positive by IHC on archival or fresh tumor tissue
- ECOG 0-1
- Adequate pulmonary, cardiac, renal, hepatic, and hematologic function



Phase 1b Endpoints

- Primary
  - TEAEs
- Secondary
  - ORR, CRR, DOR, TTR, PFS, OS, CAR T expansion kinetics

[a]Phase 1a evaluated escalating doses of both ALLO-316 and various lymphodepletion regimens in a 3+3 design.

CAR, chimeric antigen receptor; ccRCC, clear cell renal cell carcinoma; CRR, complete response rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; Flu/Cy, fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2 daily for 3 days; IHC, immunohistochemistry; M, month; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; TEAE, treatment-emergent adverse events; TTR, time to response; VEGF, vascular endothelial growth factor.

All Patients Had Multiple Treatment-Refractory Advanced or Metastatic ccRCC

Phase 1b patients received a median of 4 prior lines of therapy: 59% had received 3+ prior TKIs, 41% had received belzutifan, and 32% were quadruple class refractory to inhibition of the CTLA-4, PD-(L)1, TKI, and HIF-2α pathways

Demographics and Disease Characteristics	Phase 1b n = 22[a]	All patients N = 50
Age, median (range), years	56 (35-67)	60 (35-70)
Male sex, n (%)	20 (91)	44 (88)
ECOG PS 0, n (%)	10 (45)	27 (54)
Disease stage IV, n (%)	22 (100)	50 (100)
Prior nephrectomy, n (%)	22 (100)	45 (90)
IMDC risk at screening, n (%)		
Favorable	8 (36)	19 (38)
Intermediate	14 (64)	27 (54)
Poor	0	3 (6)
Not available	0	1 (2)
Treatment timing	**Phase 1b n = 22[a]**	**All patients N = 50**
Time from enrollment to treatment, median (range), days	4 (1-15)	4 (1-15)

Prior Treatment	Phase 1b n = 22[a]	All patients N = 50
Lines of prior therapy, median (range)	4 (1-11)	4 (1-11)
Prior therapies, n (%)		
Anti-PD-(L)1 therapy	22 (100)	50 (100)
Anti-CTLA-4 therapy	12 (55)	31 (62)
Cabozantinib	18 (82)	39 (78)
≥2 TKIs	18 (82)	32 (64)
≥3 TKIs	13 (59)	17 (34)
mTOR inhibitor	15 (68)	20 (40)
Belzutifan	9 (41)	10 (20)
Received CTLA-4 inhibitor, PD-(L)1 inhibitor, TKI, and HIF-2α inhibitor	7 (32)	8 (16)

[a]Includes 2 patients who received LD but did not receive ALLO-316.

ccRCC, clear cell renal cell carcinoma; CTLA-4, cytotoxic T-lymphocyte associated protein 4; ECOG, Eastern Cooperative Oncology Group; HIF-2α , hypoxia-inducible factor 2α; IMDC, International Metastatic RCC Database Consortium; LD, lymphodepletion; PD-1, programmed cell death protein 1; TKI, tyrosine kinase inhibitor. Data cutoff: 02-May-2025

Adverse Event Profile Consistent With Lymphodepletion and an Active CAR T Therapy

TEAEs ≥20% incidence in Phase 1b, n (%)	Phase 1b n = 22[a]		All patients N = 50	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Neutropenia	15 (68)	15 (68)	30 (60)	28 (56)
WBC decreased	15 (68)	15 (68)	28 (56)	26 (52)
Anemia	13 (59)	9 (41)	26 (52)	17 (34)
Thrombocytopenia	12 (55)	6 (27)	23 (46)	13 (26)
Nausea	8 (36)	0	25 (50)	0
ALT increased	7 (32)	2 (9)	16 (32)	7 (14)
Peripheral edema	7 (32)	0	17 (34)	0
Pyrexia	7 (32)	0	19 (38)	1 (2)
Arthralgia	6 (27)	0	13 (26)	0
AST increased	6 (27)	2 (9)	15 (30)	7 (14)
Fatigue	5 (23)	0	26 (52)	1 (2)
Headache	5 (23)	0	16 (32)	0

AEs of Special Interest, n (%)	Phase 1b n = 22[a]		All patients N = 50	
	All Grades	Grade ≥3	All Grades	Grade ≥3
CRS	15 (68)	0	31 (62)	1 (2)
Infection	10 (45)	8 (36)	29 (58)	18 (36)
IEC-HS	8 (36)	2 (9)[b]	12 (24)	3 (6)
ICANS	4 (18)	0	4 (8)	0
GVHD	0	0	0	0

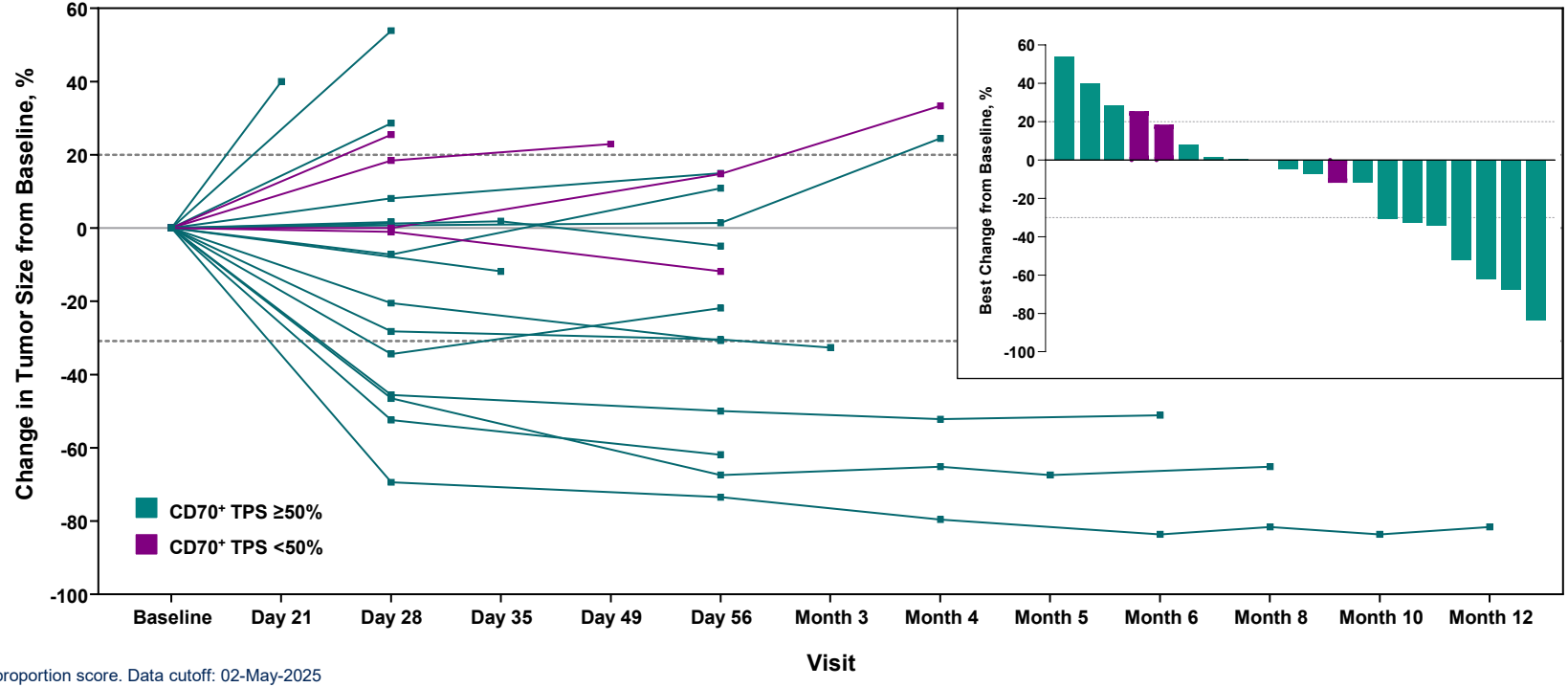
- Any-grade TEAEs occurred in 100% of Phase 1b patients, including:
  - Majority of grade ≥3 TEAEs were hematologic events
  - No treatment related grade 5 AEs

[a]Includes 2 patients who received LD but did not receive ALLO-316. [b]One patient experienced G4 IEC-HS based on GI bleeding with subsequent improvement and 1 patient experienced G3 IEC-HS based on hypotension managed without pressors with subsequent improvement. There were no grade 5 events of IEC-HS.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; GVHD, graft versus host disease; ICANS, immune effector cell-associated neurotoxicity syndrome; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; LD, lymphodepletion; TEAE, treatment-emergent adverse event; WBC, white blood cell. Data cutoff: 02-May-2025

Tumor Responses Occur Early and Are Sustained Following a Single Infusion of ALLO-316

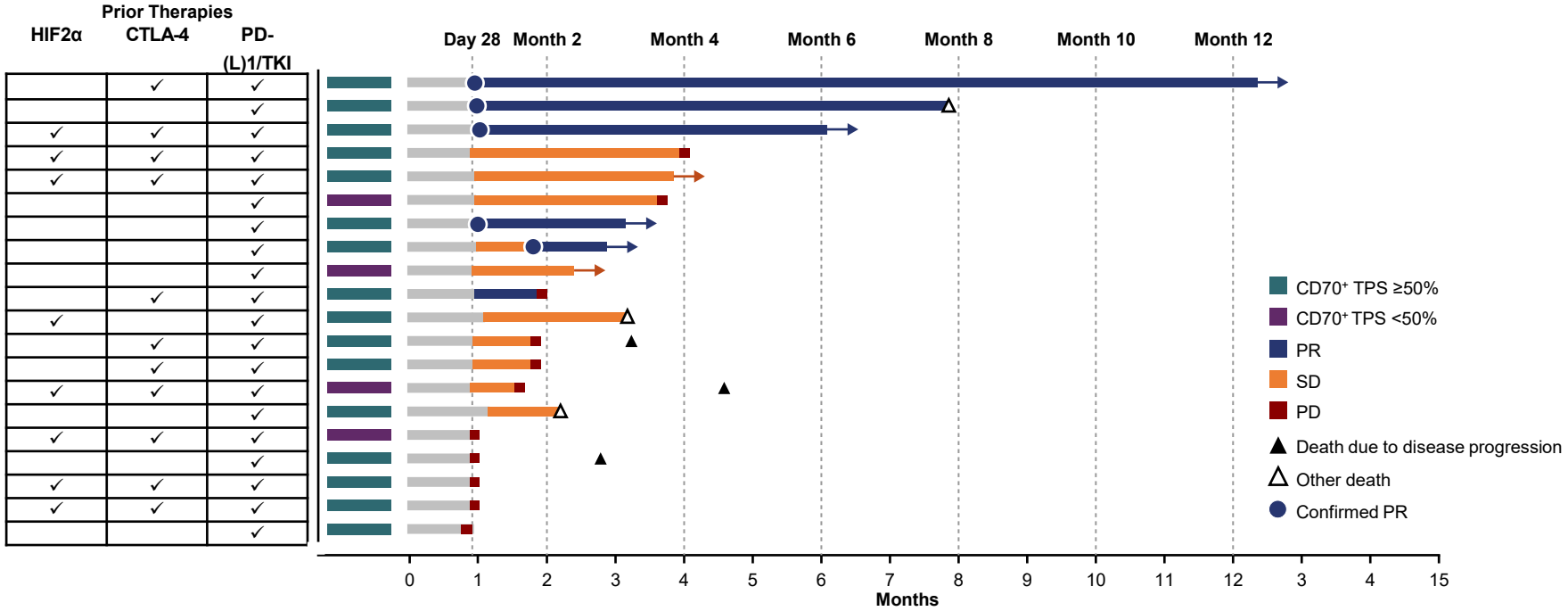
Among CD70⁺ TPS ≥50% patients, 44% (7/16) had >30% reduction in diameter of baseline target lesions



TPS, tumor proportion score. Data cutoff: 02-May-2025

High Response Rate and Ongoing Remissions

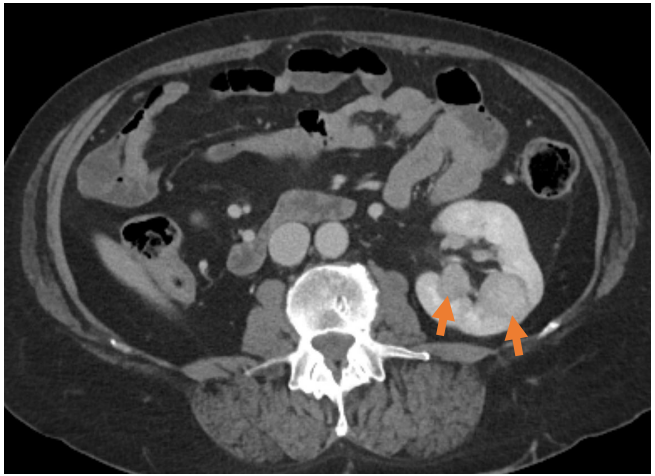
Out of 5 confirmed responders, 4 have an ongoing response; 1 has reached the 1 year mark post–ALLO-316



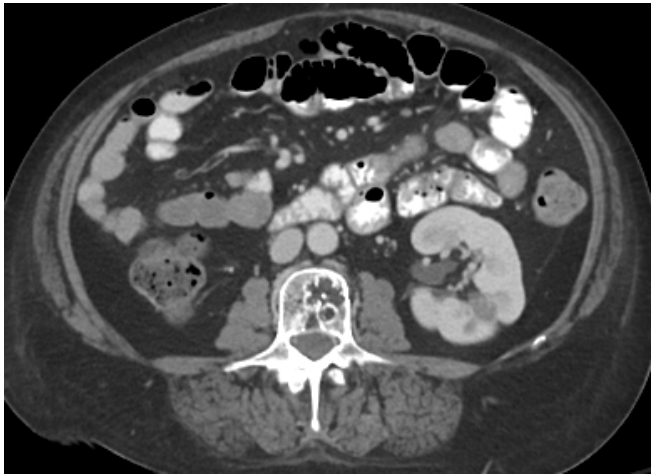
CTLA-4, cytotoxic T-lymphocyte associated protein 4; HIF-2α , hypoxia-inducible factor 2α; PD, progressive disease; PD-(L)1, programmed cell death protein/ligand 1; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score. Data cutoff: 02-May-2025

Regression of Contralateral Kidney Metastasis Following a Single Dose of ALLO-316

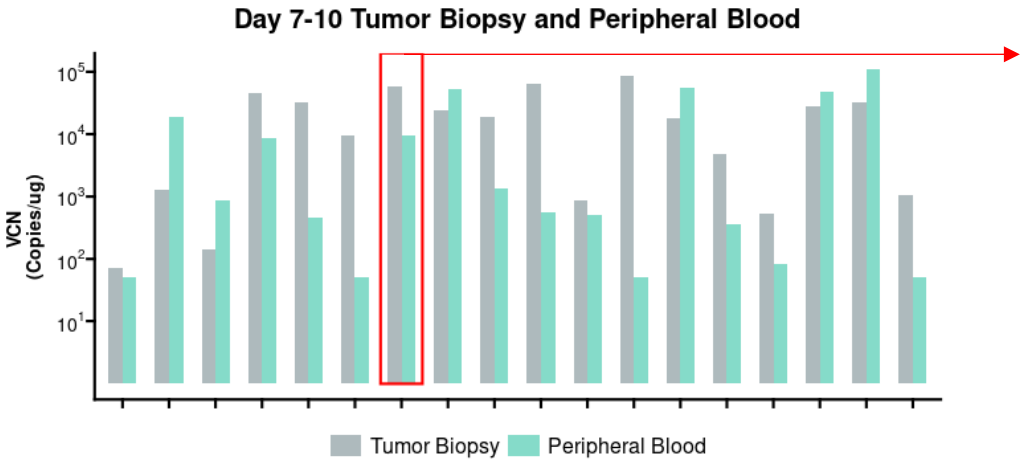
Baseline



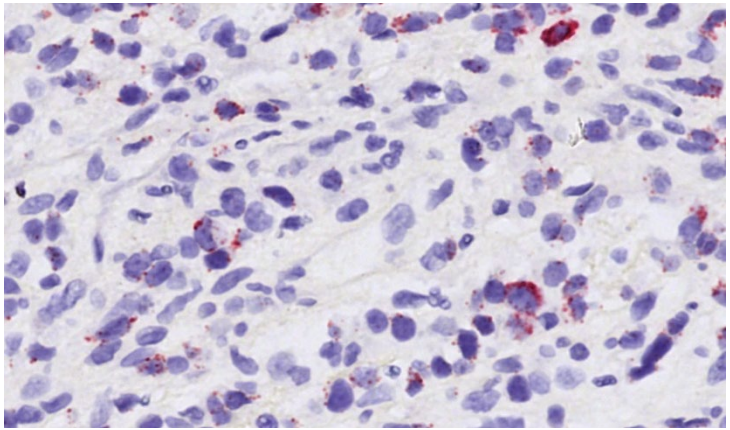
After 1 month



Marked Tumor Infiltration by ALLO-316 Seen in Paired Tumor/Blood Samples



CAR Vector Copy Number (VCN) by PCR



CAR T cell chromogenic RNA *in situ* hybridization

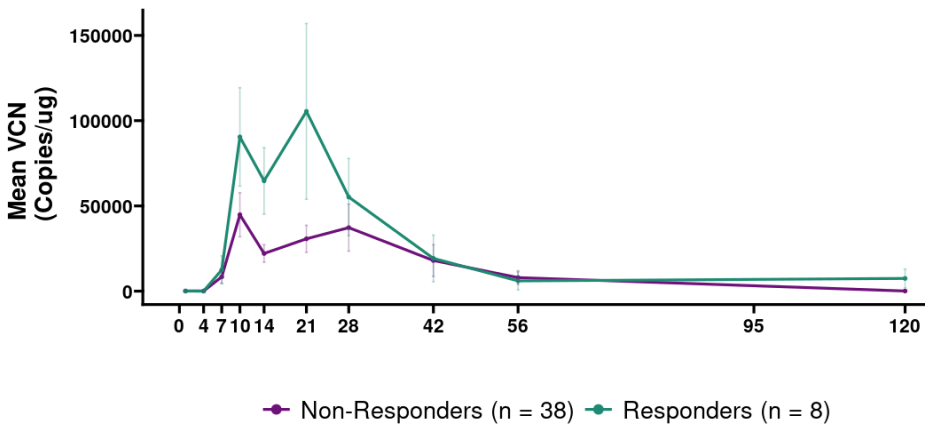
- Homing and infiltration of ALLO-316 CAR T cells into tumor was demonstrated by two independent methods: VCN (PCR) and chromogenic RNA *in situ* hybridization assay using a probe against CAR transcripts
- The high VCN levels observed in the tumor samples demonstrated the extensive infiltration of ALLO-316

CAR, chimeric antigen receptor; PCR, polymerase chain reaction; RNA, ribonucleic acid. Data cutoff: 02-May-2025

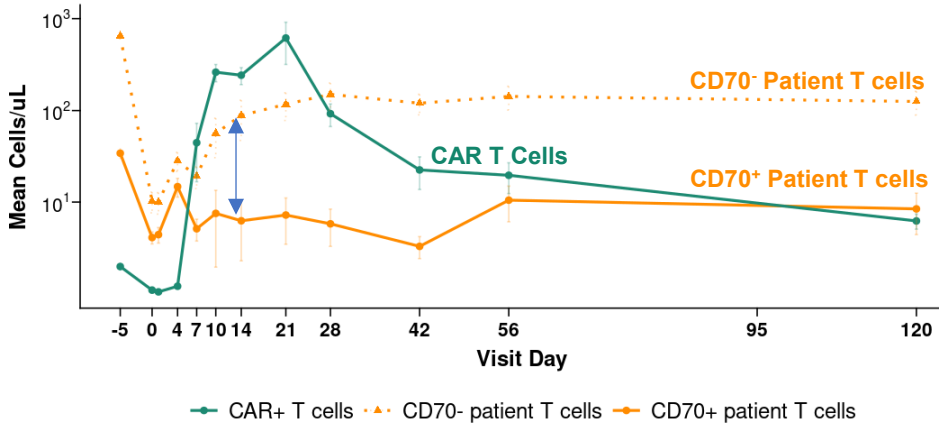
Responders Had Robust Expansion and Persistence of CAR T Cells

CD70⁻ patient T cells quickly rebounded while CD70⁺ patient T cells remained low until ALLO-316 CAR T contraction (Dagger® Effect)

VCN Over Time by Best Overall Response



CD70⁺ Host T Cells are eliminated by ALLO-316



CAR, chimeric antigen receptor; VCN, vector copy number. Data cutoff: 02-May-2025

Thyroid Cancer and ICAM-1

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ICAM-1 directed chimeric antigen receptor (CAR) T-Cells (AIC100) in patients with advanced thyroid cancers: Clinical and translational data from the phase 1 study

Samer A. Srour, MD[1], Jochen H. Lorch[2], Mark E. Zafereo[1], Victoria Meucci Villaflor[3], Yan Xing,[3] , Sonal Gupta[4], Mimi I-Nan Hu[1], Ramona Dadu[1], Adam Lin[2], Yang Lu[1], Melissa Cushing[5], Scott Avecilla[5], Theresa Scognamiglio[5], Moonsoo Jin[6], Janusz Puc[4], Tripti Gaur[4], Stacey Ukrainskyj[4], Sebastian Alexander Mayer[5], Koen Van Besien[7], Maria E. Cabanillas[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Northwestern University, Chicago, IL; [3]City of Hope National Medical Center, Duarte, CA; [4]AffyImmune Therapeutics, Natick, MA; [5]Weill Cornell Medical College, New York, NY; [6]Houston Methodist, Houston, TX; [7]UH Seidman Cancer Center, Cleveland, OH

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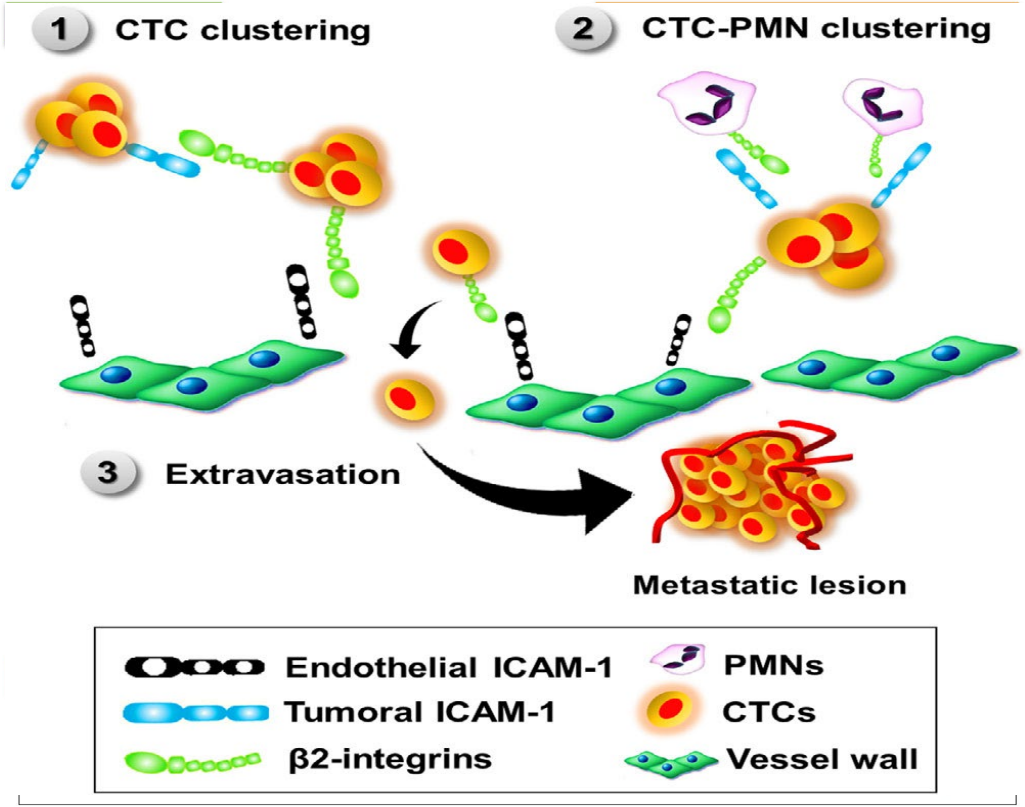
Background

ICAM-1 function in tissue homeostasis and disease

- Is a member of the immunoglobulin superfamily
- A cell surface glycoprotein and an adhesion receptor
- Upregulated by cytokines
- Overexpressed in several tumors

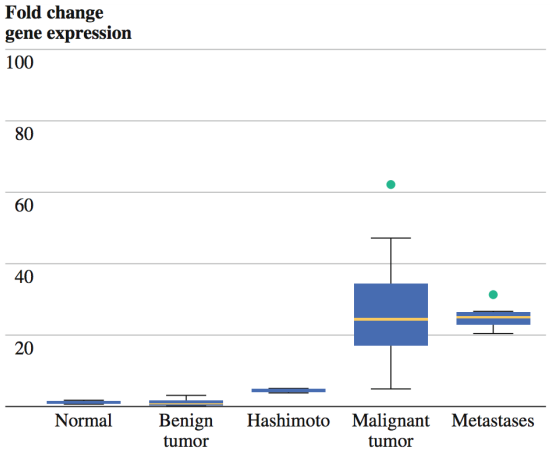


Bui *et al*; Journal of Leukocyte Bio 2020

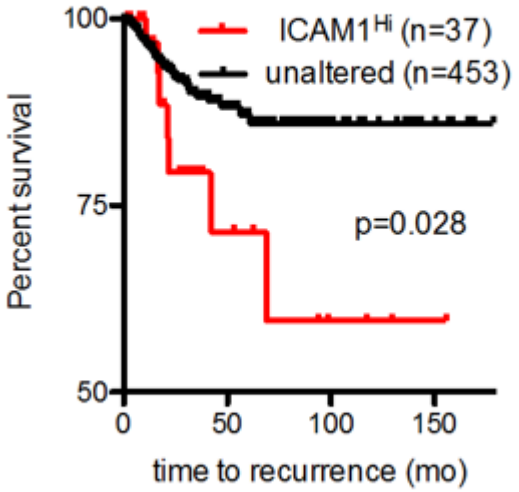
ICAM-1 as a Thyroid Cancer Target

- Highly expressed in ATC and PDTC
- Low levels in healthy tissues

ICAM-1 Expression in Human Thyroid Samples



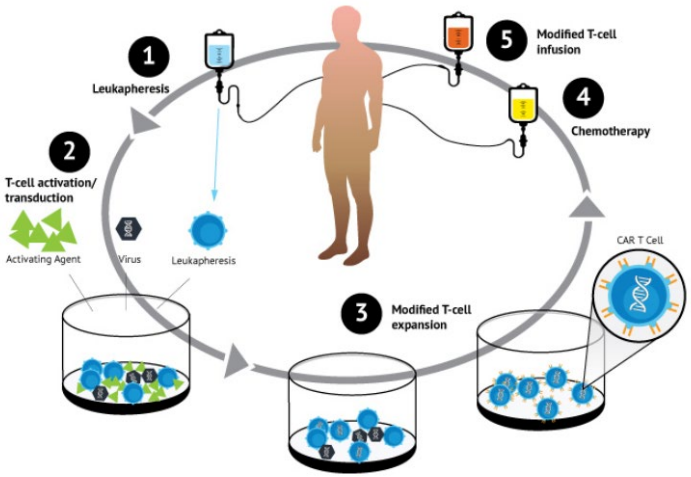
ICAM-1 Associated with Poor Prognosis

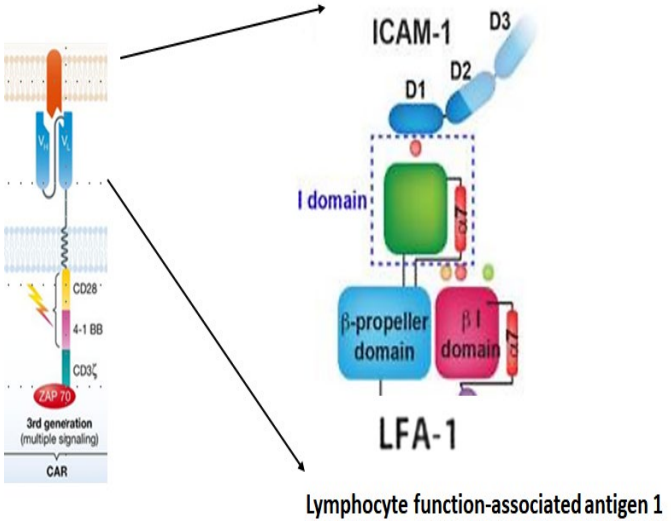


Buitrago et al. Ann Surg Oncol. 19:973–980, 2012

AIC100 – An Autologous CAR T-Cell Product Targeting ICAM-1

Autologous CAR T Therapy





Baseline Patient and Disease Characteristics

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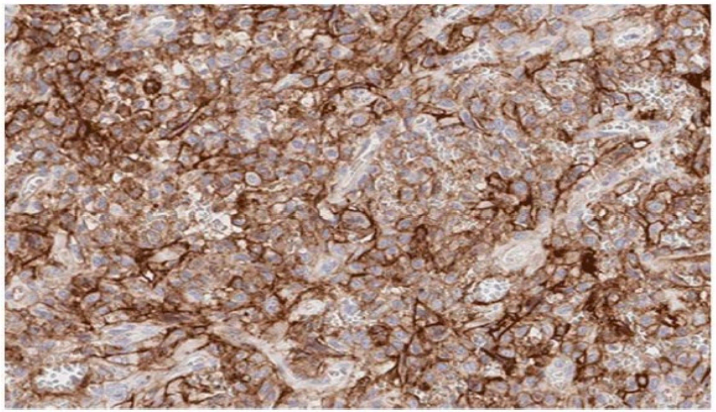
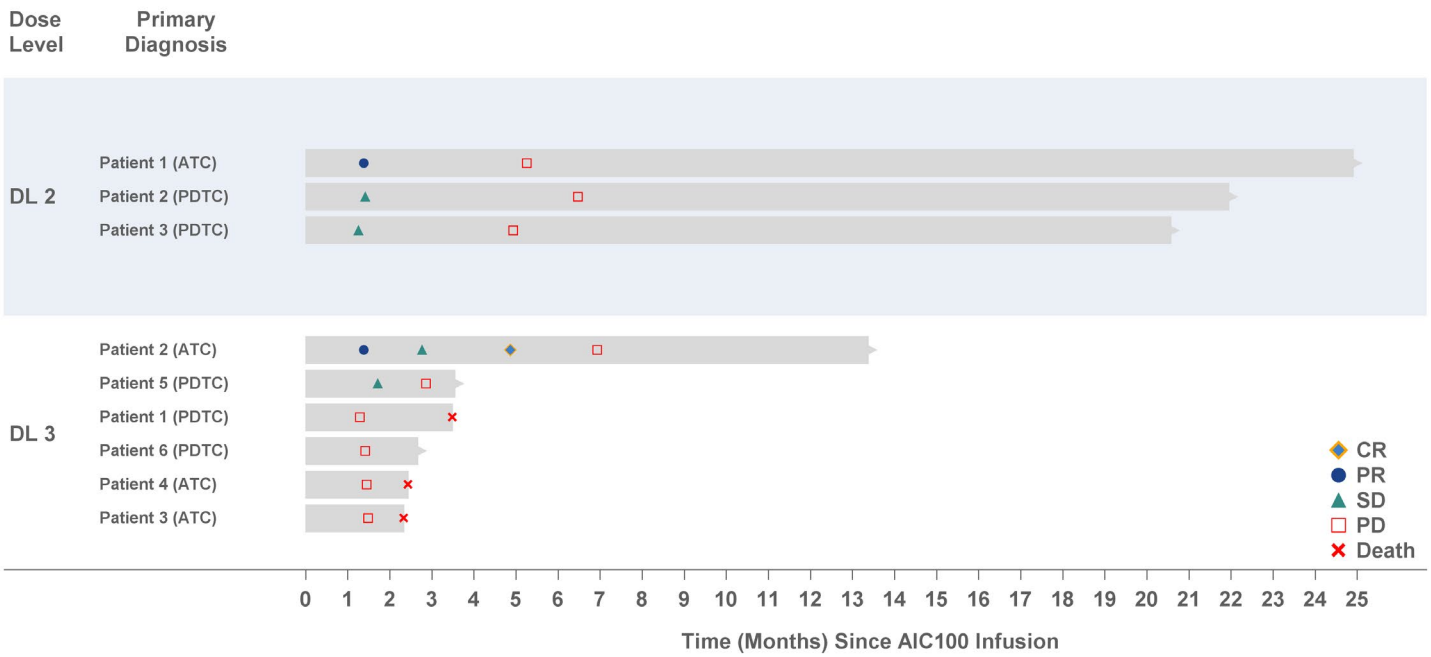
Characteristic	All Patients (N=15)
Median age (range), years	59 (47, 69)
Gender: male/female (%)	11/4 (73/27)
ECOG PS: 0/1 (%)	5/10 (33/67)
Disease Histology, n (%)	
ATC	8 (53)
PDTC	7 (47)
Disease stage at screening, n (%)	
Stage III	1 (7)
Stage IV	14 (93)
Median lines of prior therapy (range)	2 (1-4)
• ATC	2 (1-4)
• PDTC	3 (1-3)
Median time since original diagnosis (range), months	
• ATC	18.7 (1, 114)
• PDTC	54.6 (39, 111)
BRAF Mutation Status for ATC patients, n=8 (%)	
• Mutated	4 (50%)
• Wild	4 (50%)
Median time from apheresis (enrollment) to LD in days (range)	
• ATC	29 (17-51)
• PDTC	40 (23-61)

- Prescreening by IHC testing (archived or fresh biopsy) for ICAM-1 was mandated at the start of the study
  - ✓ All patients (ATC and PDTC) tested positive for ICAM-1 at screening
  - ✓ Median ICAM-1 expression treated patients (n=15) was 35% (range, 7.5-80%)



Data cutoff: Dec 12, 2024

Duration of Response and Survival



Data cutoff: December 12th, 2024. , reflects investigator-reported survival for efficacy-evaluable patients; subsequent anticancer therapies not shown.

Case Presentation #1

- A 68 year-old female patient with metastatic ATC who failed multiple lines of therapy
- 80% ICAM-1 expression
- DL2, achieved PR
- DOTATATE PET activity correlated with CAR T-cell activity and tumor response

Transient DOTATATE PET-CT activity associated with AIC100 expansion and resolution with subsequent tumor regression

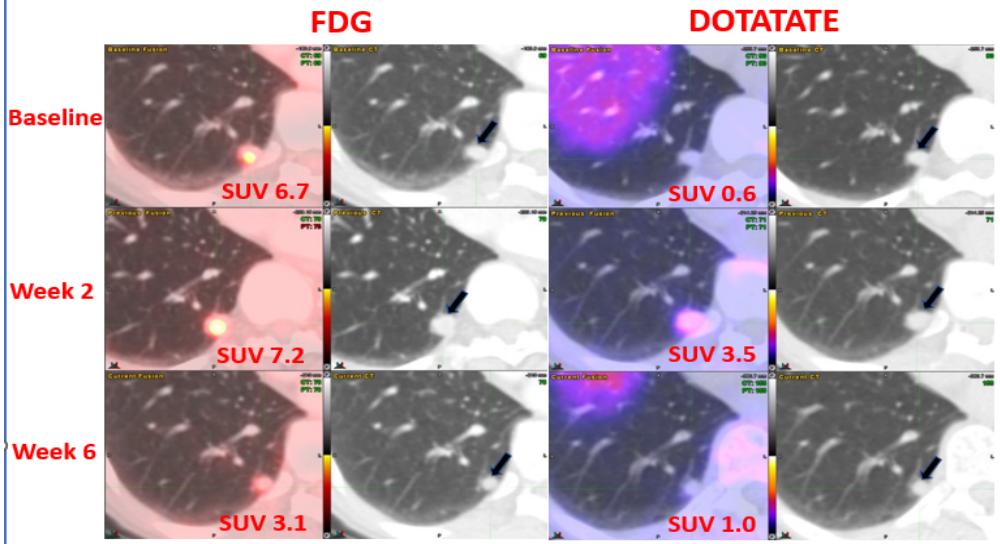


Figure 3 FDG and DOTATATE PET/CT imaging of patient #4. Scans are done 24 hour apart, FDG first followed by DOTATATE. One of the representative lesions is shown for illustration. At baseline, the lesion is FDG active but no DOTATAE activity. At 2 weeks, the lesion shows DOTATATE uptake consistent with CAR T-cell infiltration. At 6 weeks, DOTATATE activity subsided upon response with significant improvement in FDG activity

Case Presentation #2

- A 58 year-old male patient with metastatic ATC (PDTC with anaplastic features) who failed multiple lines of therapy
- 20% ICAM-1 expression
- DL3, achieved CR over time

FDG and Dotatate PET avidity associated with Complete Metabolic Response (CMR) and CAR T cell Trafficking into Tumor Lesion

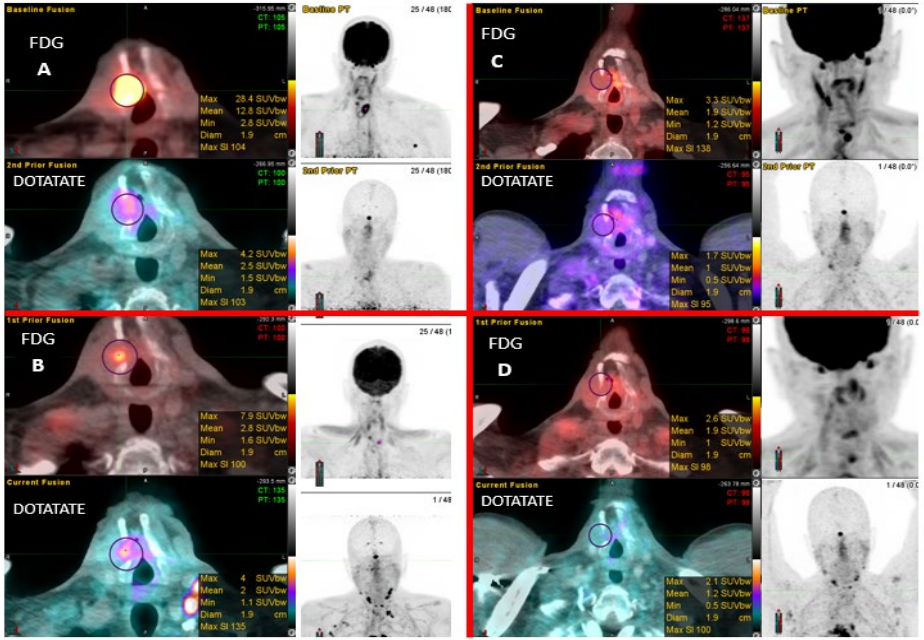


Figure 3 Baseline before infusion (A), and 2 weeks (B), 6 weeks (C) and 3 months (D) after AIC100

Peripheral blood CAR T-cell expansion by ddPCR was observed in all tested patients

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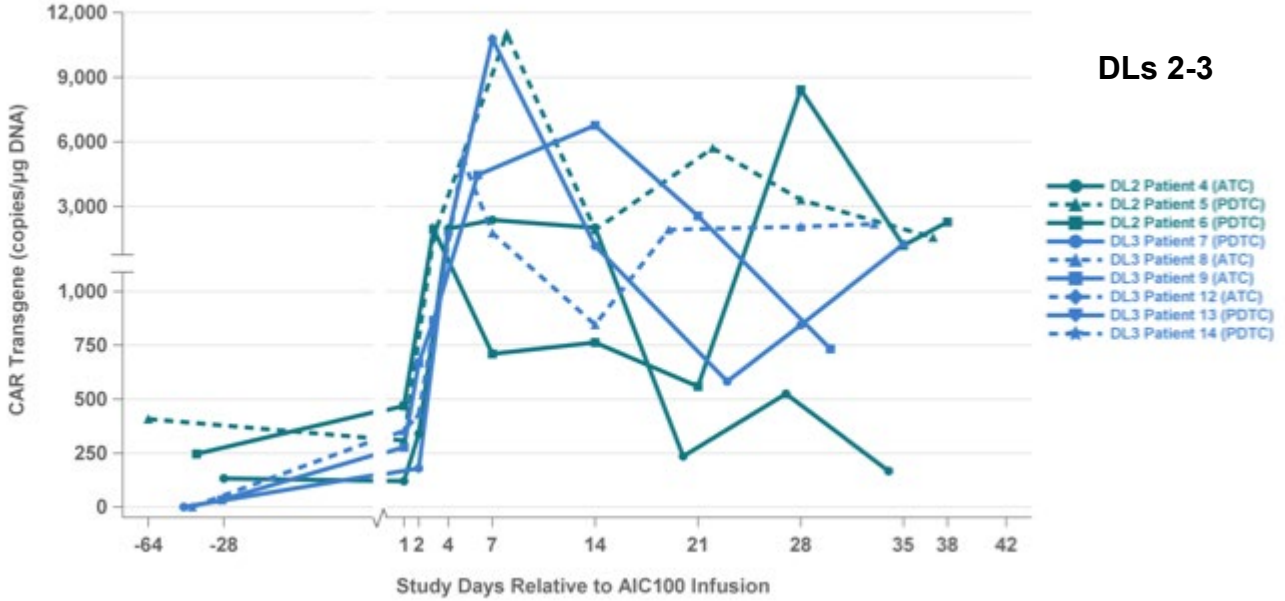

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Safety and Efficacy of HLA-G-Targeted CAR T Cells (IVS-3001) in Patients with Advanced HLA-G-Positive Solid Tumors: Clinical Trial in Progress

Samer A. Srour[1], Nizar Tannir[2], Amir Jazaeri[3], Matthew Campbell[2], Yago Nieto[1], Cara Haymaker[4], Ying Yuan[5], Israa Salih[6], Yali Yang[6], Valerie Doppler[3], Julie Garibal[3], Marie Escande[3], Qi Melissa Yang[6], Jake A. Kushner[3], Jane Koo[7], Serdar Gurses[6], David Hong[6], Siqing Fu[6], Funda Meric-Bernstam[6], Aung Naing[6]

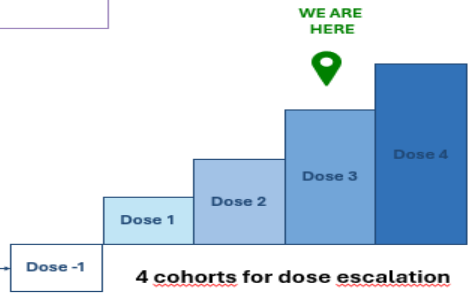
[1]The University of Texas MD Anderson Cancer Center, Department of Stem Cell Transplantation and Cellular Therapy; [2]The University of Texas MD Anderson Cancer Center, Department of Genitourinary Medical Oncology; [3]The University of Texas MD Anderson Cancer Center, Department of Gynecologic Oncology and Reproductive Medicine; [4]The University of Texas MD Anderson Cancer Center, Department of Translational Molecular pathology; [5]The University of Texas MD Anderson Cancer Center, Department of Biostatistics; [6]The University of Texas MD Anderson Cancer Center, Department of Investigational Cancer Therapeutics; [7]CTMC; [8]Invectys Inc.

PHASE 1 – Dose Escalation

- Evaluate **safety and RP2D** in solid tumors

- **Bayesian optimal interval (BOIN) design**
- At least **3 patients per dose** level
- DLT evaluation period is **28 days**

1 **de-escalation cohort** (dose minus 1) in case of toxicity observed at the first dose level tested



4 cohorts for dose escalation

PHASE 2a – Dose Expansion

Evaluate **clinical efficacy** at the RP2D on tumor shrinkage (**ORR by RECIST 1.1**)

Initial Phase (up to 3 cohorts)		Expansion Phase (up to 3 cohorts)
COHORT 1: 1st indication HLA-G+ (n=14)	If ≥ 1 response, Enroll up to additional 16	COHORT 1 : 1st indication HLA-G+ (n≤16)
COHORT 2: 2nd indication HLA-G+ (n=14)	If ≥ 1 response, Enroll up to additional 16	COHORT 2 : 2nd indication HLA-G+ (n≤16)
COHORT 3: « biomarker driven » Other HLA-G+ refractory/relapsed solid tumors (n=14)	If ≥ 1 response, Enroll up to additional 16	COHORT 3: « biomarker driven » Other HLA-G+ refractory/relapsed solid tumors (n ≤ 16)

If no responses among the first 14 subjects (within initial cohorts) are observed, no further subjects will be enrolled

Closing Remarks and Future Directions

- Immunotherapy has revolutionized the landscape of treatment options for solid tumors
  - ✓ Small proportion of patients achieve durable responses
- Cellular therapy for solid tumors is expanding in scope and complexity
  - ✓Remarkable advances in more recent years
- Overcoming the challenges to advance the field
  - ✓ Identifying the right tumor specific antigen
  - ✓ Improve T-cell trafficking to overcome the hostile TME

Acknowledgements

- To all our patients and their wonderful caring families and caregivers!

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Thank You

Questions & Discussion