

MULTI-STAKEHOLDER
WORKSHOP

New modalities in cancer
drug development

SESSION 4: CELLULAR THERAPIES

Cellular therapies and GMOs: What is out there and pipeline

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Attending Physician

Early Clinical Drug Development Group

Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch (VHIO, Barcelona)



MULTI-STAKEHOLDER WORKSHOP

New modalities in cancer
drug development

Disclosures:

Institutional support from Seagen Inc., SOTIO Biotech AG, Shattuck Labs, Inc., T-knife GmbH, F. Hoffmann-La Roche Ltd, Janssen Research & Development, LLC, Novartis, Affimed GmbH, Anaveon AG, BioNTech SE, BicycleTx Ltd, Epizyme, Inc., Epizyme, Inc., Regeneron Pharmaceuticals, Inc., Boehringer Ingelheim, Genmab, Pieris Pharmaceuticals, Inc., Celgene Corporation, Debiopharm International S.A., F-star Therapeutics Limited, ImCheck Therapeutics, Gilead Sciences, Inc, Sanofi-Aventis Recherche & Développement



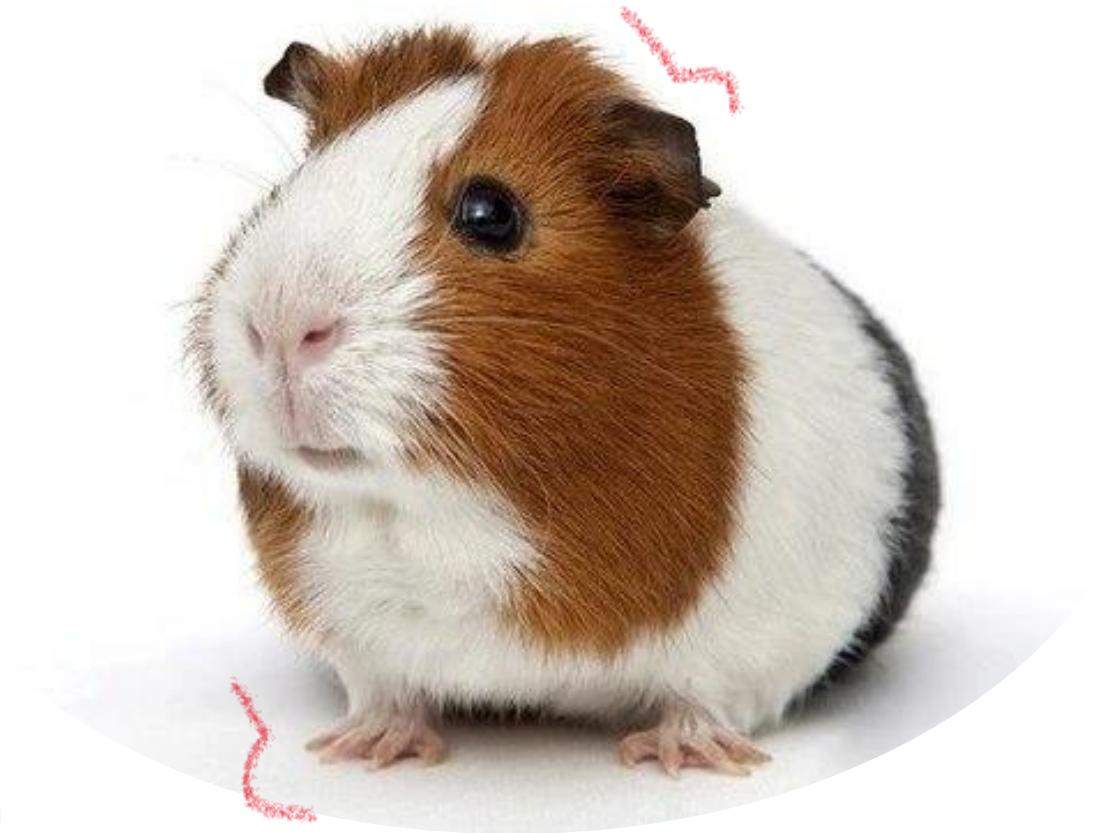
MULTI-STAKEHOLDER WORKSHOP

New modalities in cancer
drug development

Outline:

- Introduction
- Approved therapies
- Pipeline
- Future Trends and Next-Generation Approaches

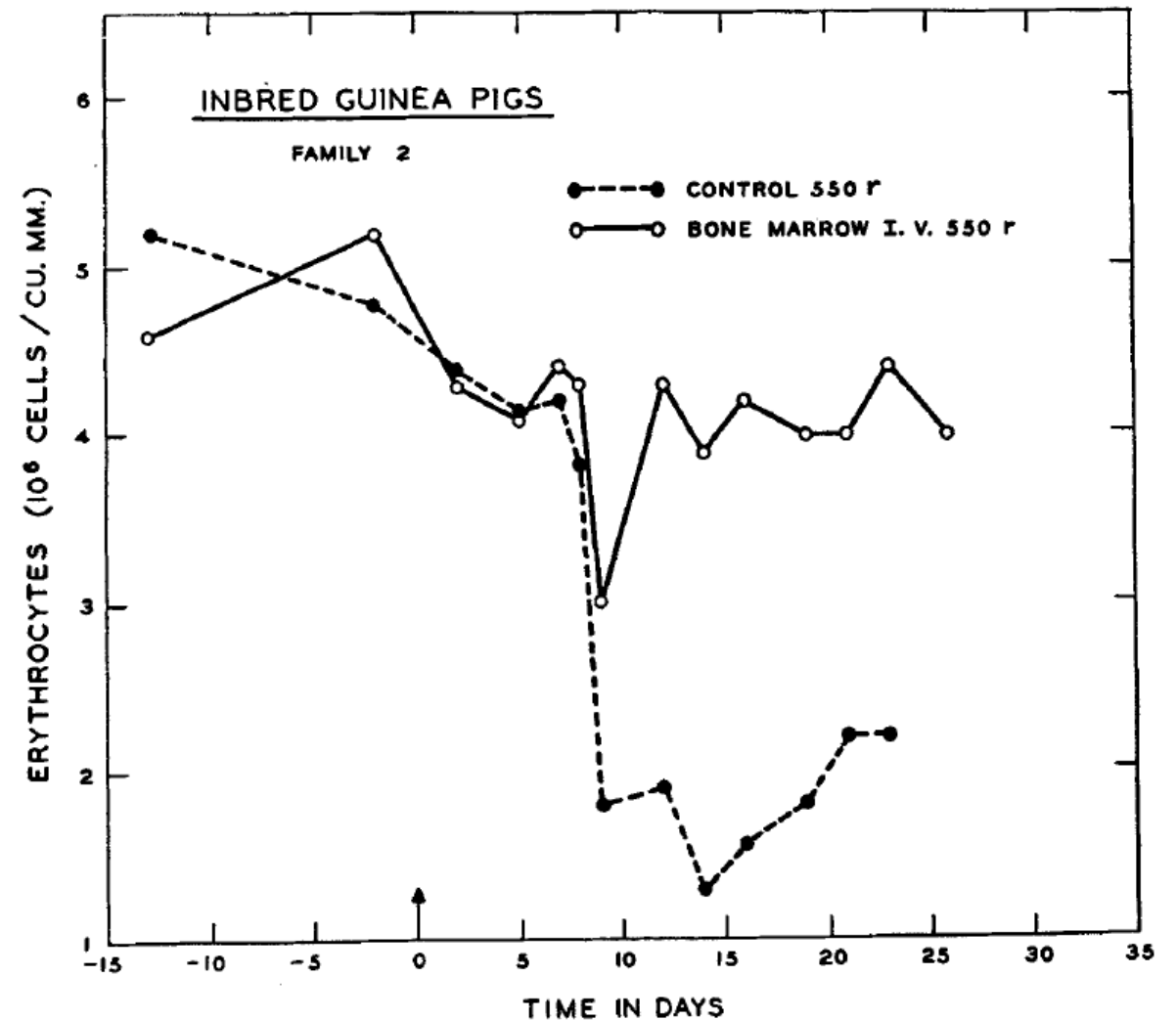




Cavia porcellus (Guinea pig)

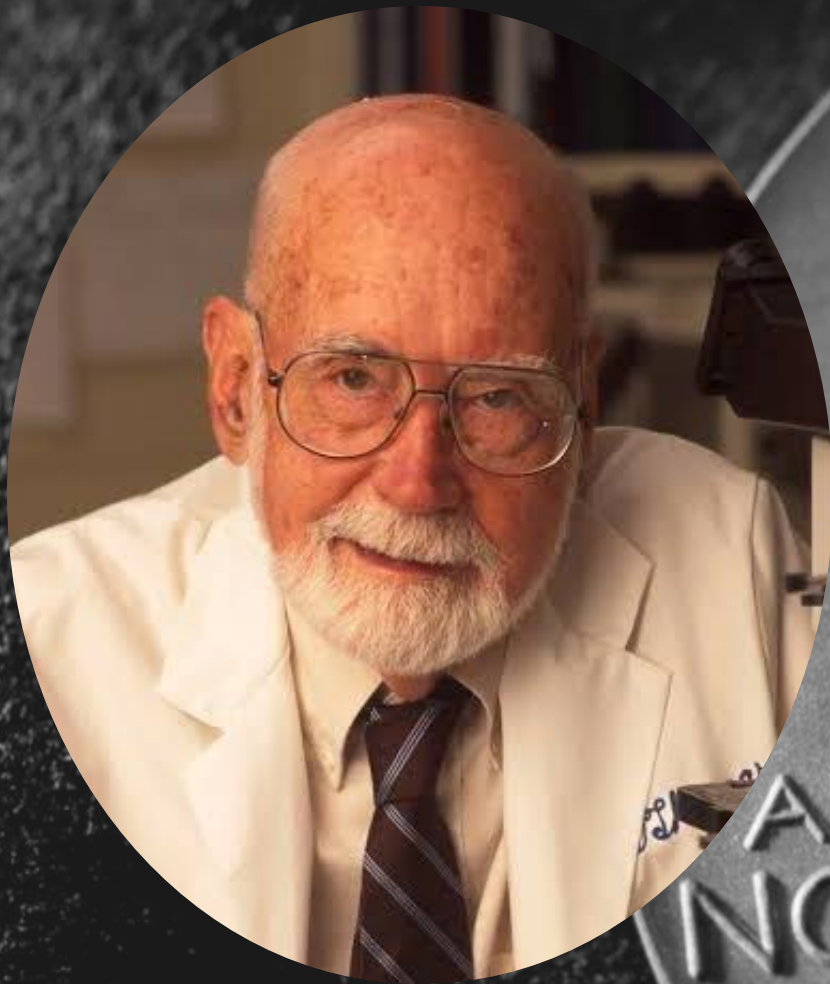


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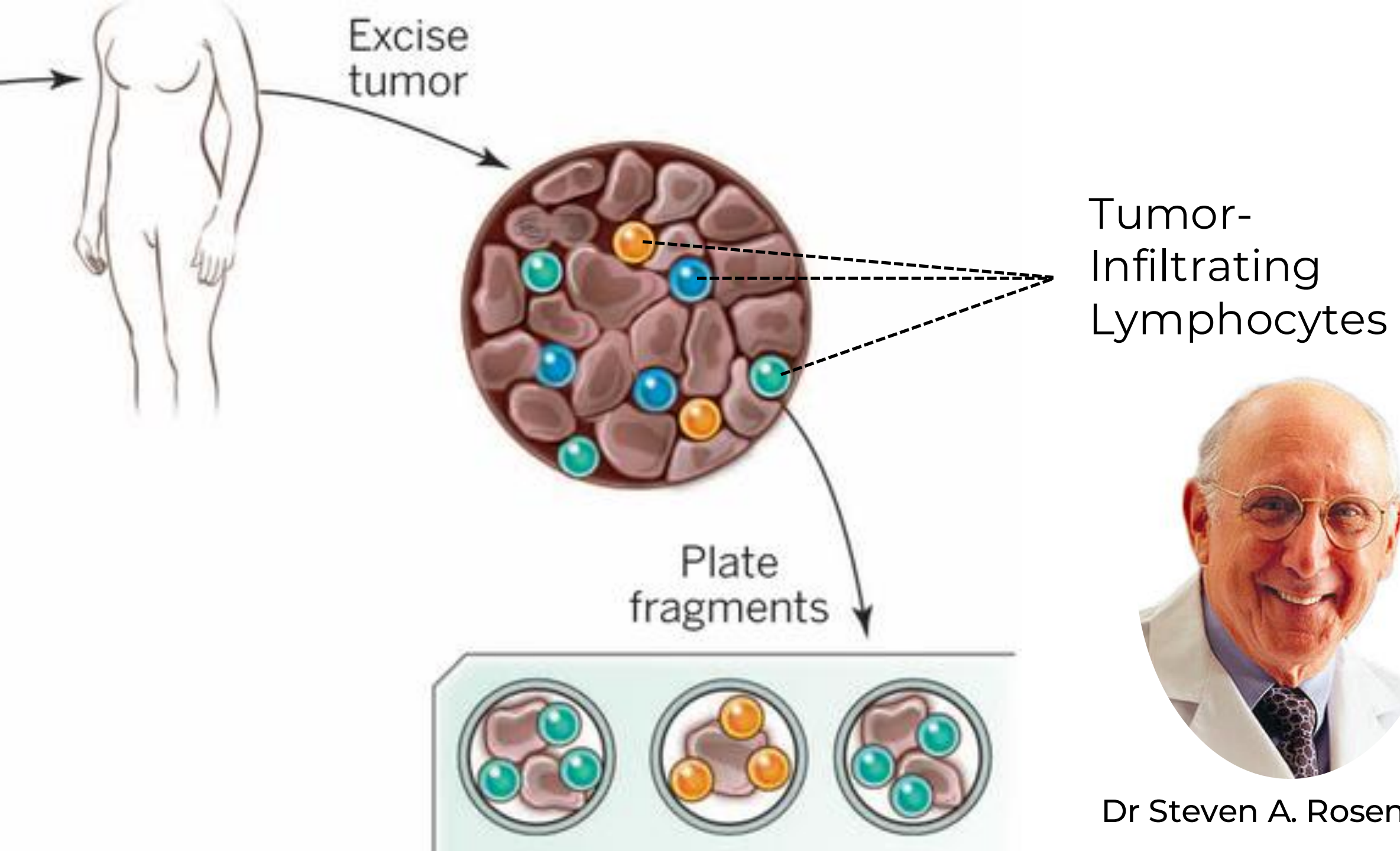
TEXT-FIGURE 2.—Erythrocyte count of guinea pigs exposed to 550 r.

Lorenz E, Uphoff D, Reid TR, Shelton E. Modification of irradiation injury on mice and guinea pigs by bone marrow injections. *J Natl Cancer Inst* 1951; 12: 197-201.



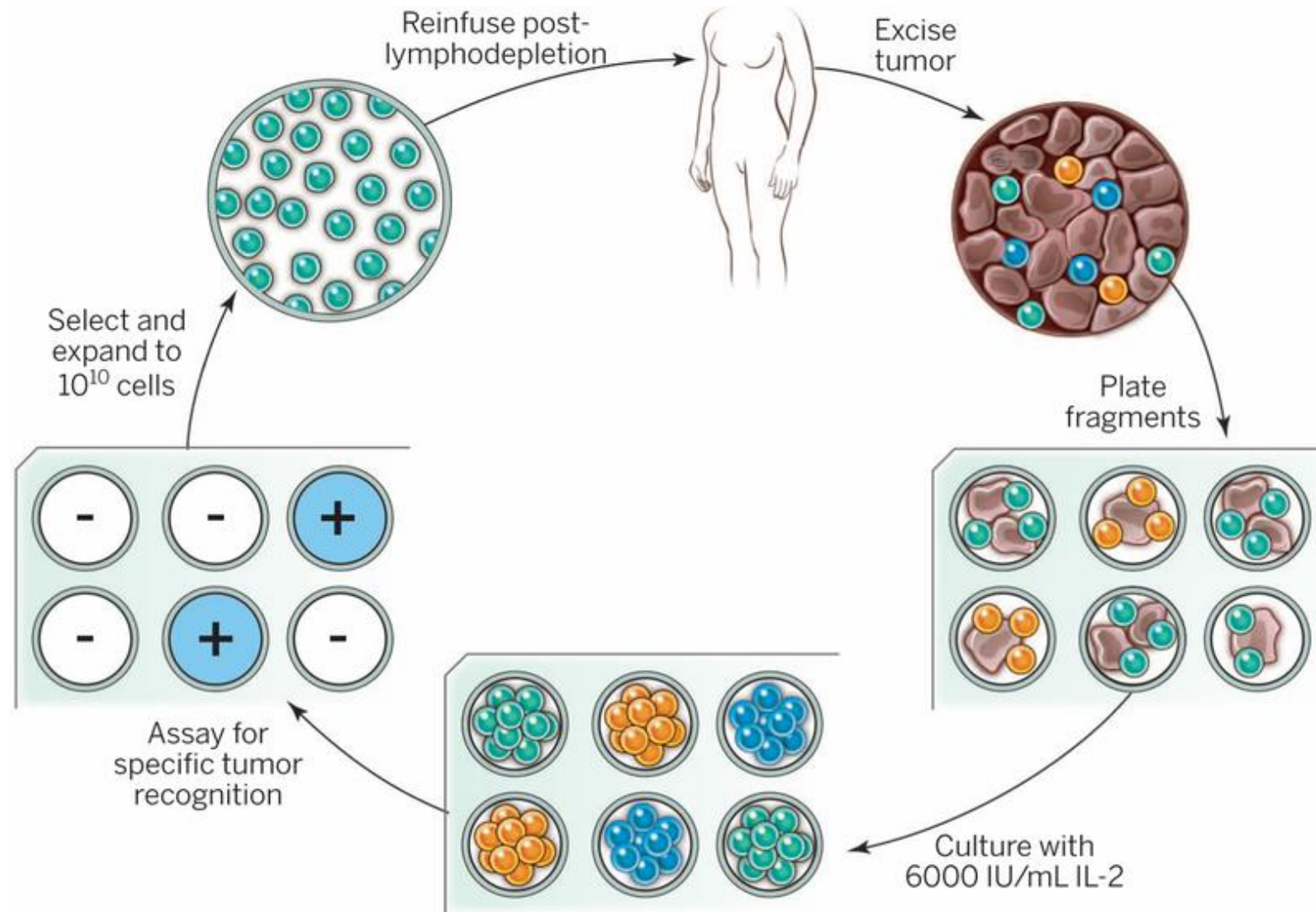
Dr. E. Donnall Thomas
1990 Physiology or Medicine



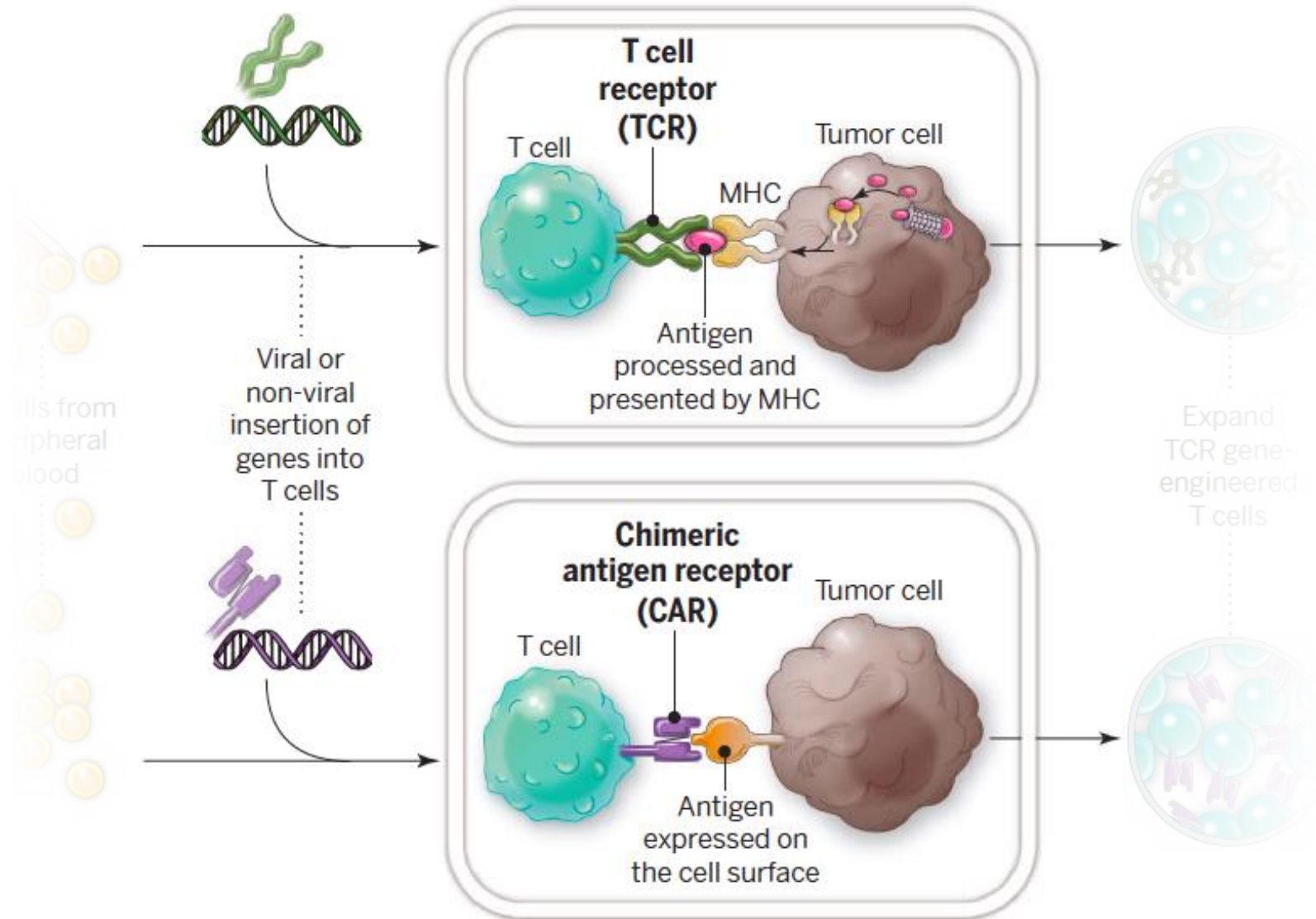


Dr Steven A. Rosenberg

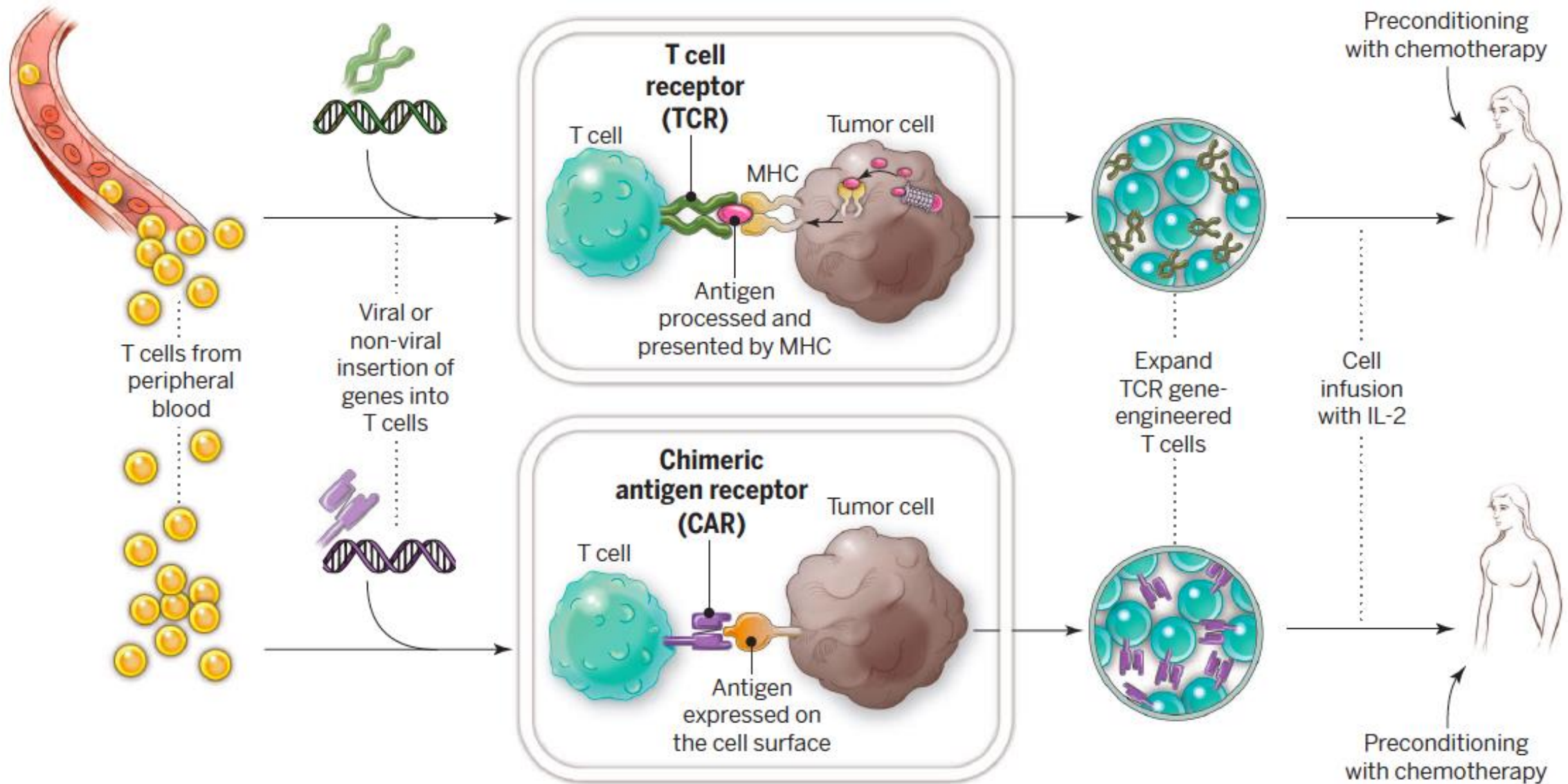
TIL



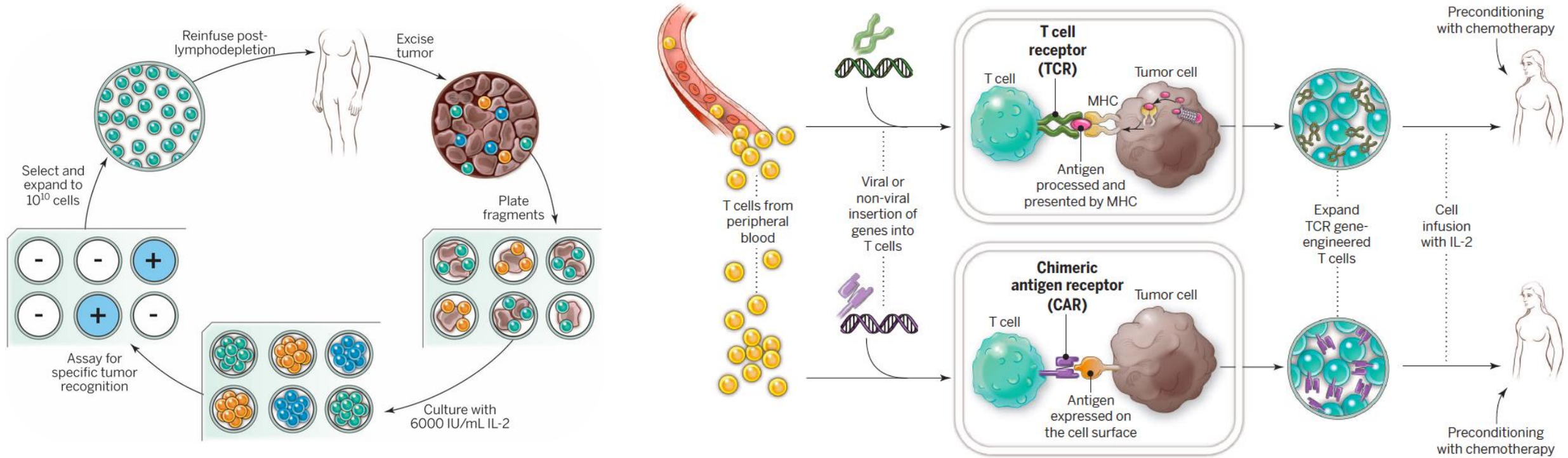
Genetically Modify Organisms



Genetically Modify Organisms



Adoptive Cell Therapy



Rosenberg, S. A., & Restifo, N. P. (2015). Adoptive cell transfer as personalized immunotherapy for human cancer. *Science (New York, N.Y.)*, 348(6230), 62–68. <https://doi.org/10.1126/science.aaa4967>



Cancer Treatment

Immunotherapy

Adoptive Cell Therapy

CD-19 and BCMA CAR-T in Hematology

TIL and TCR in Oncology

CD19- and BCMA CAR-T cells in hematology

Tisagenlecleucel
Idecabtagen vicleucel
Lisocabtagene maraleucel
Ciltacabtagene autoleucel
Axicabtagene ciloleucel
Brexucabtagene autoleucel

Aug, 2017

CD19- and BCMA CAR-T cells in hematology

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Axicabtagene ciloleucel
Brexucabtagene autoleucel

Aug, 2017

TIL therapy for melanoma

Lifileucel

Feb, 2024

CD19- and BCMA CAR-T cells in hematology

Tisagenlecleucel
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Axicabtagene ciloleucel
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Aug, 2017

TIL therapy for melanoma

Lifileucel

Feb, 2024

MAGE-A4-TCRcell for synovial sarcoma

Afamitresgene
Autoleucel

Aug, 2024



153

75% > 3 target and non-target lesions

71.2% $\geq$ 3 anatomic sites

54.2% $\uparrow$ LDH

Median of 3 previous lines:

anti-PD1/anti-PD-1l therapy	anti-PD-1 + anti-CTLA4	BRAF+MEK inhibitors
100%	53.6%	25.5%

TIL therapy for
melanoma

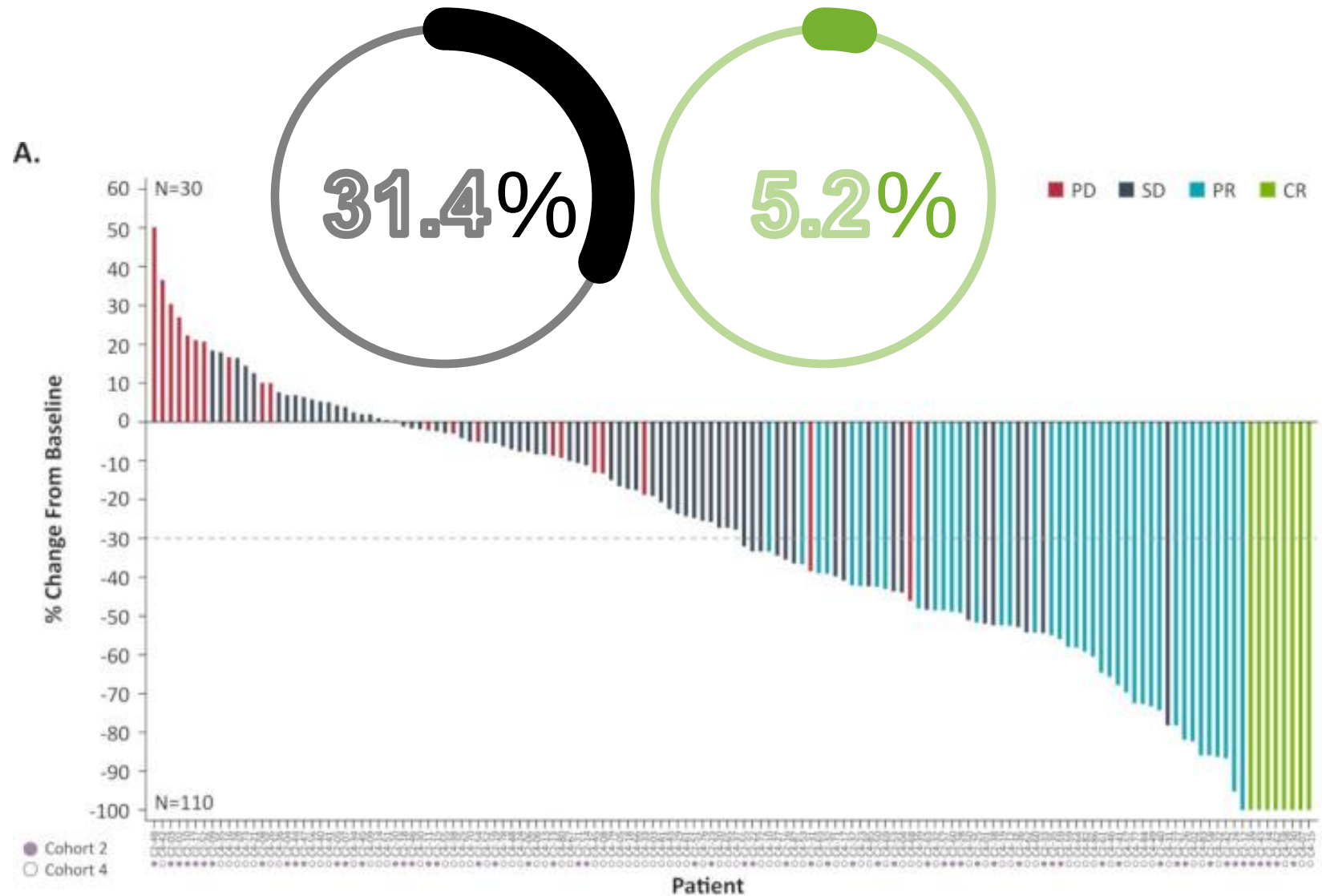
Lifileucel

Feb, 2024

TIL therapy for melanoma

Lifileucel

Feb, 2024

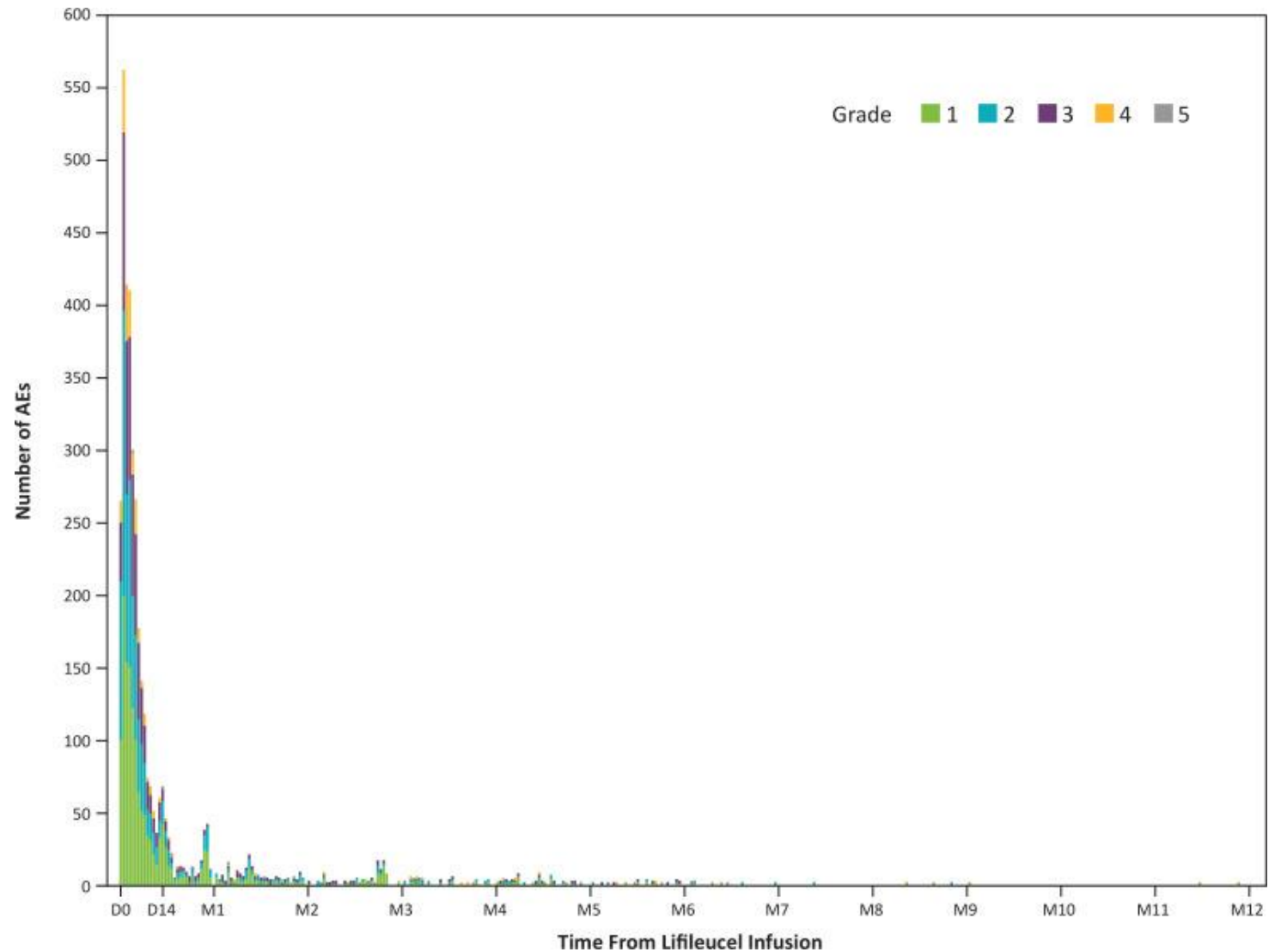


Chesney, J., Lewis, Sarnaik, A. et. al (2022). *Journal for ImmunoTherapy of Cancer*

TIL therapy for melanoma

Lifileucel

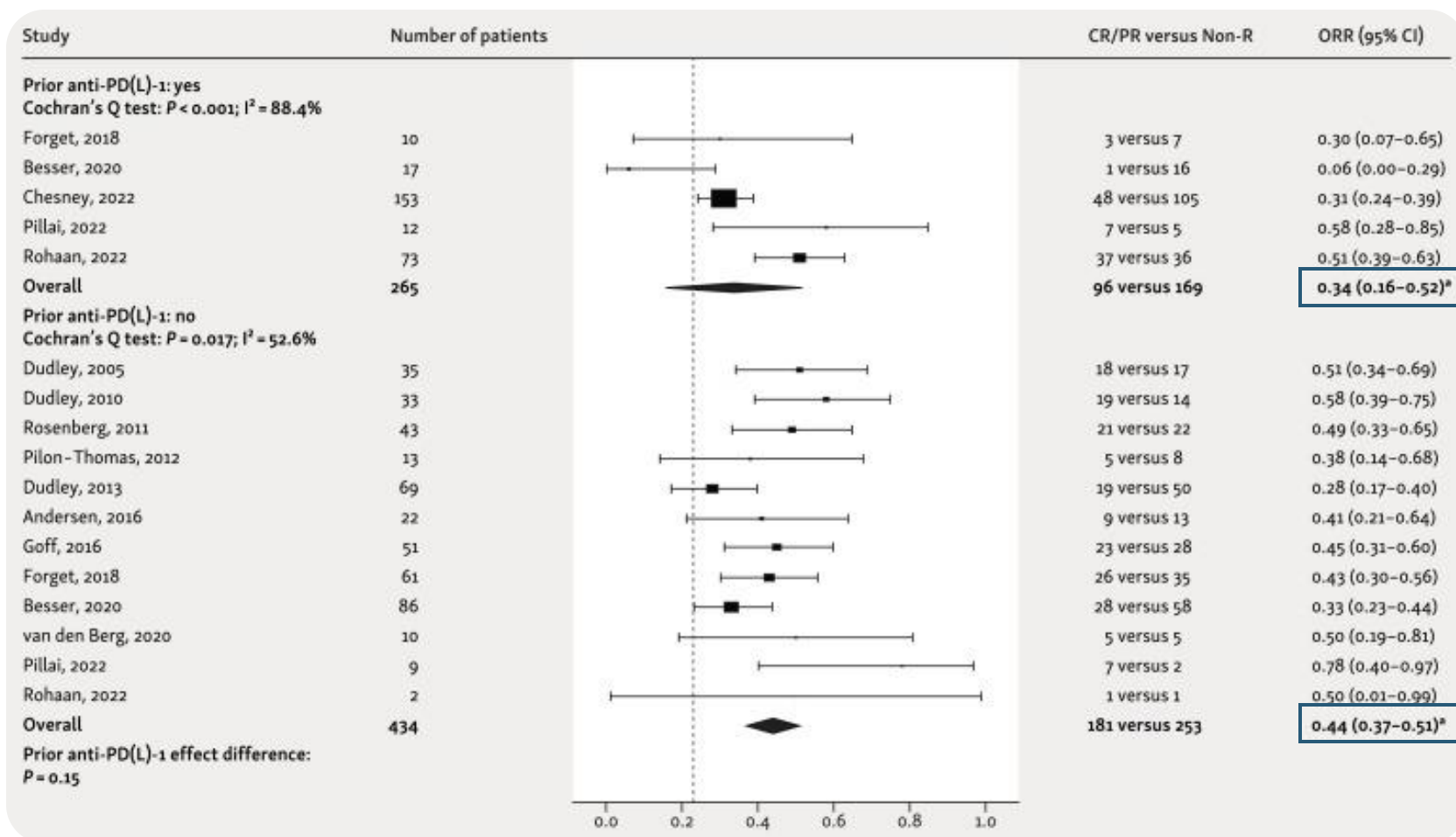
Feb, 2024



Chesney, J., Lewis, Sarnaik, A. et. al (2022). *Journal for ImmunoTherapy of Cancer*

TIL therapy for melanoma

Martín-Lluesma,
Coukos, G., et. al (2024).
Annals of Oncology

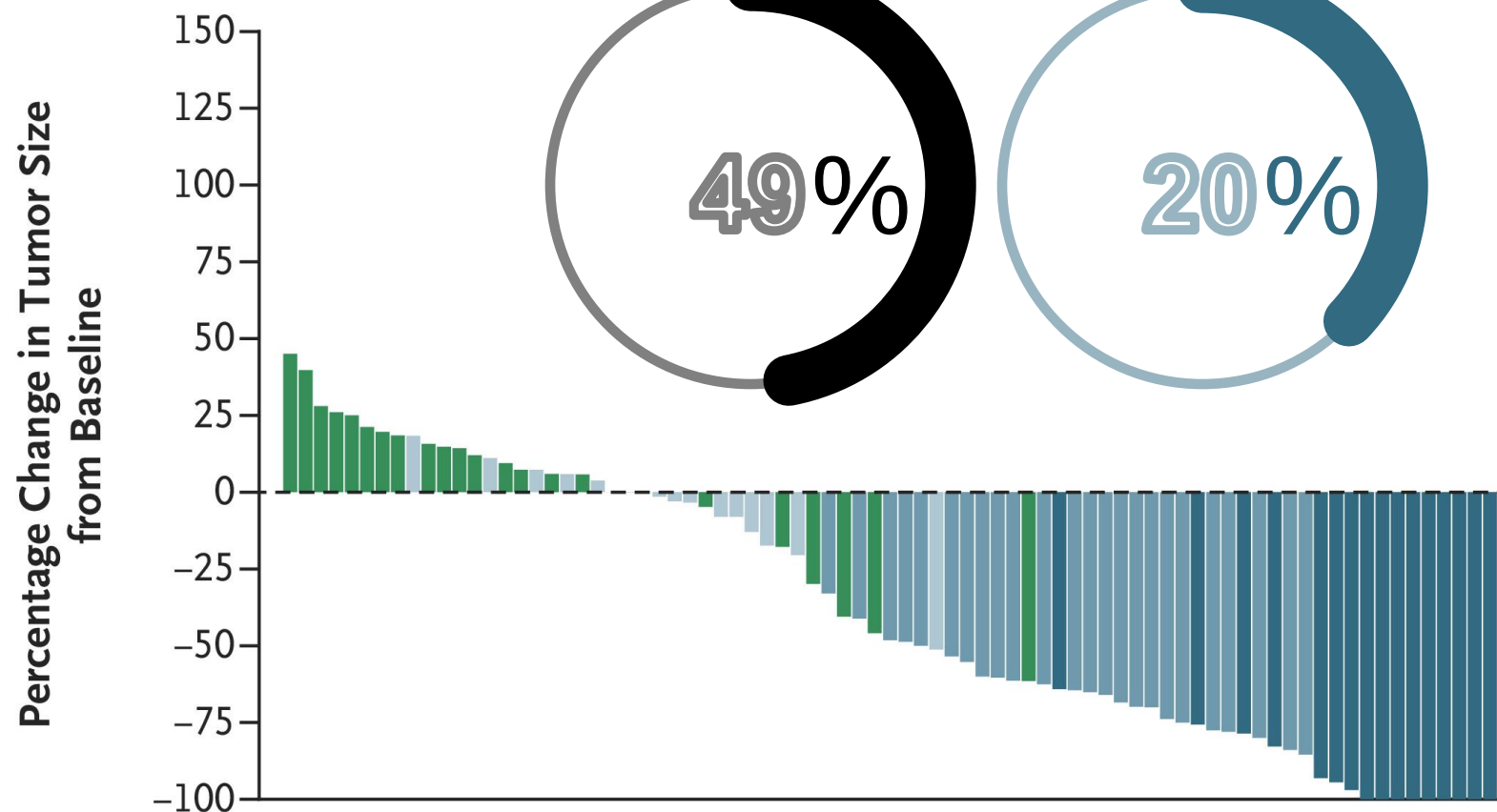


TIL therapy for melanoma

Rohaan, M. W., Haanen, J.
B. A. G. et al (2022). *New England Journal of Medicine*

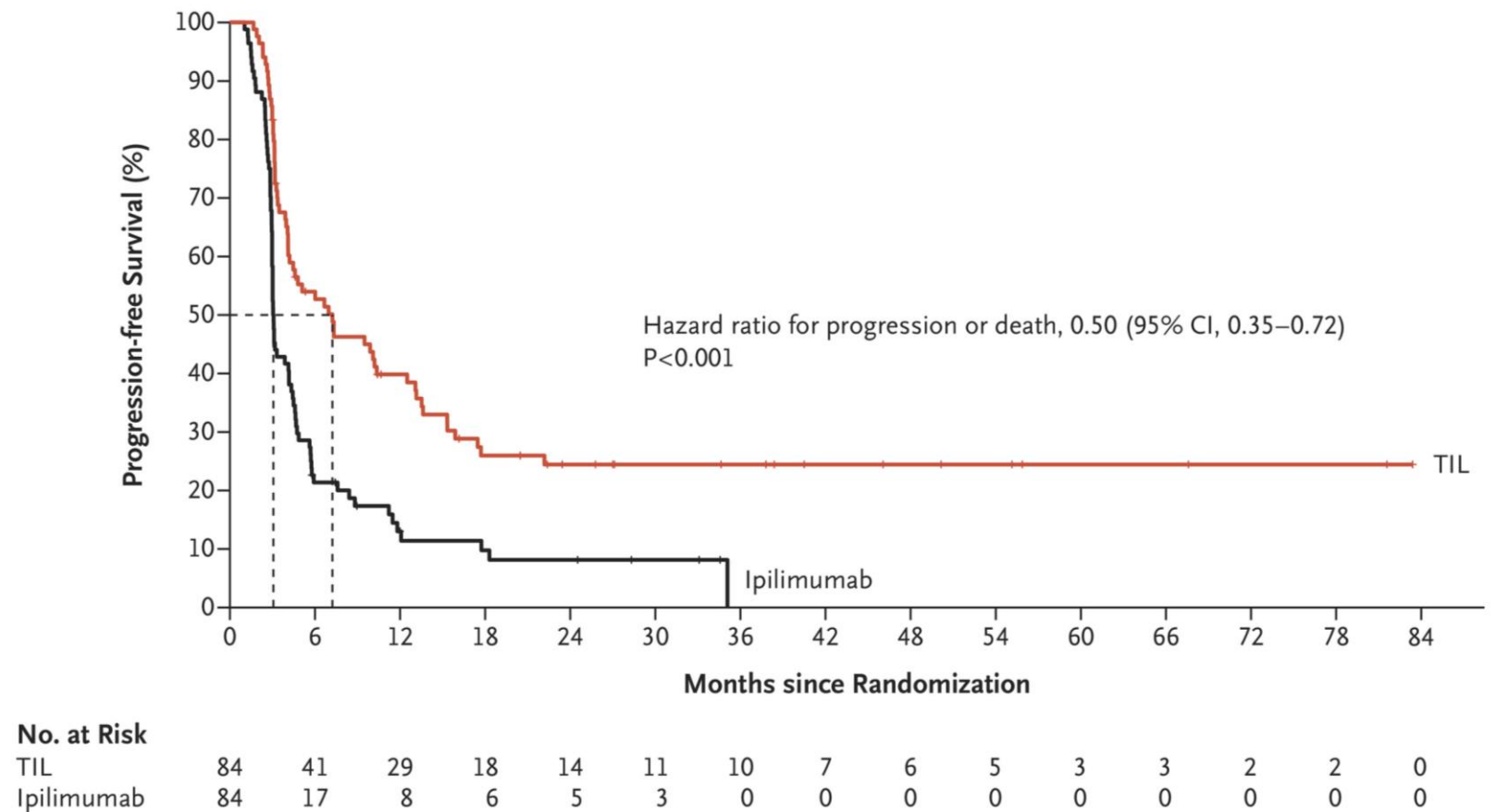
Best Overall Response: ■ Progressive disease ■ Stable disease ■ Partial response ■ Complete response

A TIL Group



TIL therapy for melanoma

Rohaani, M. W., Haanen, J. B. A. G. et al (2022). New England Journal of Medicine



TIL therapy for melanoma

Rohaan, M. W., Haanen, J. B. A. G. et al (2022). New England Journal of Medicine

 168

82% ↓ LDH (ULN)

11% NO previous lines

Types of previous lines:

Adjuvant anti-PD1	1st line anti-PD-1
24%	62%



373 pre-screened for MAGE-A4 and
HLA-A*02

105 (28%) had both at or above the
predefined level

Synovial sarcoma and myxoid round cell
liposarcoma

Median of previous lines: ≥ 4 (18 (35%))

MAGE-A4-TCRcell
for synovial
sarcoma

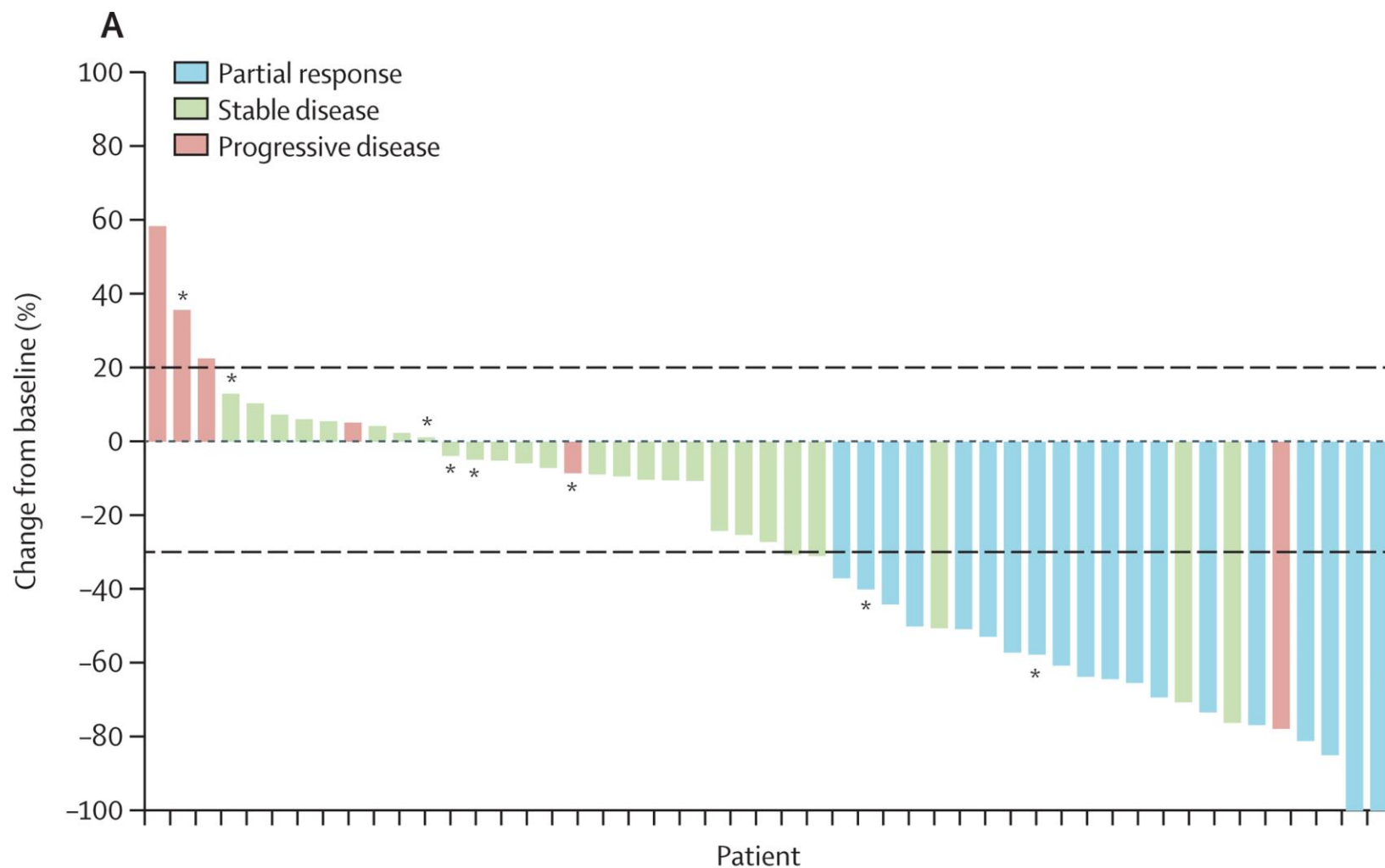
Afamitresgene
Autoleucel

Aug, 2024

MAGE-A4-TCRcell for synovial sarcoma

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Autoleucel

Aug, 2024

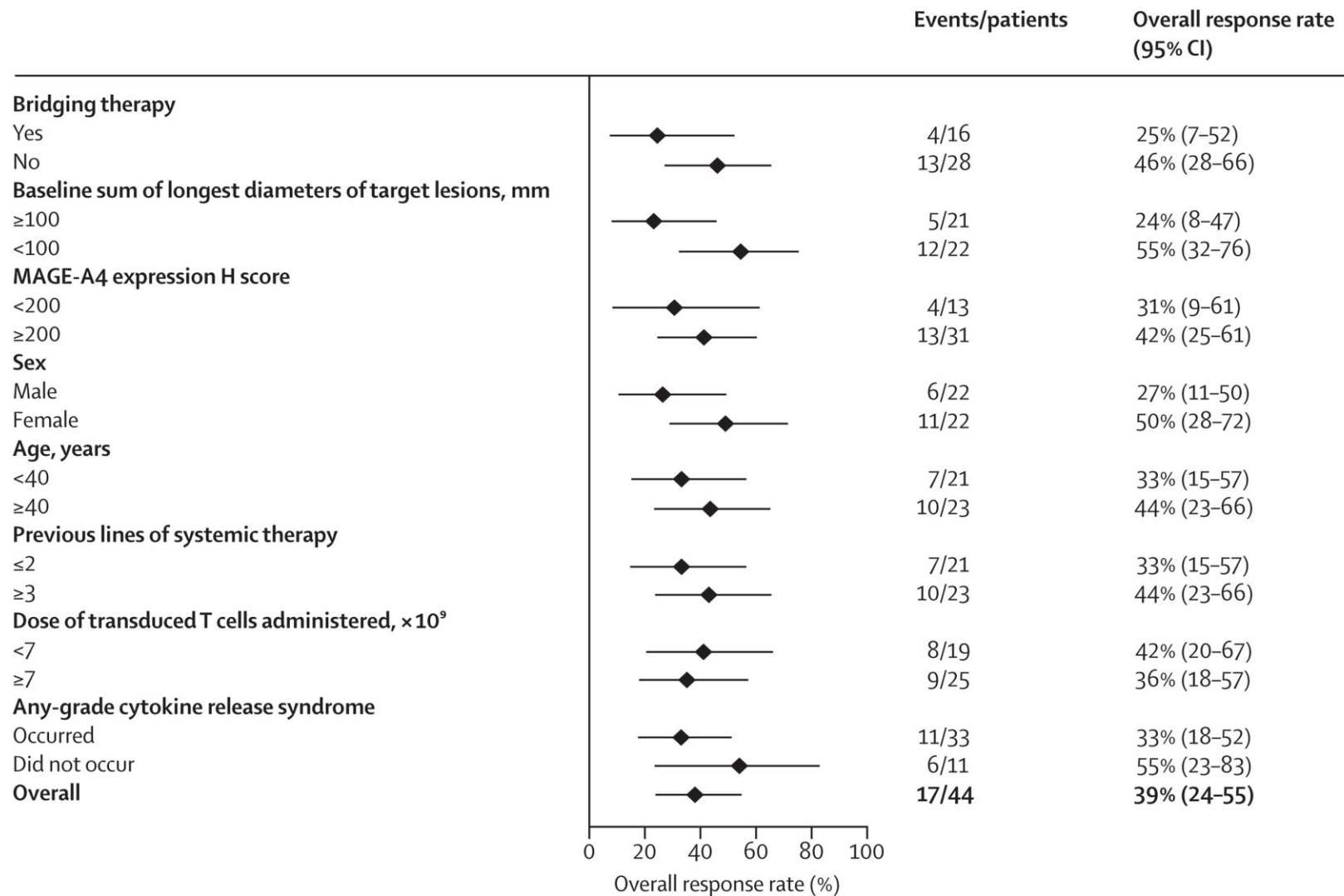


MAGE-A4-TCRcell for synovial sarcoma

Afamitresgene
Autoleucel

Aug, 2024

C



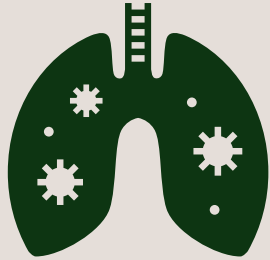




Pipeline in Oncology

TIL therapy for
other tumor types

Promising targets
of TCR and CAR-T therapy

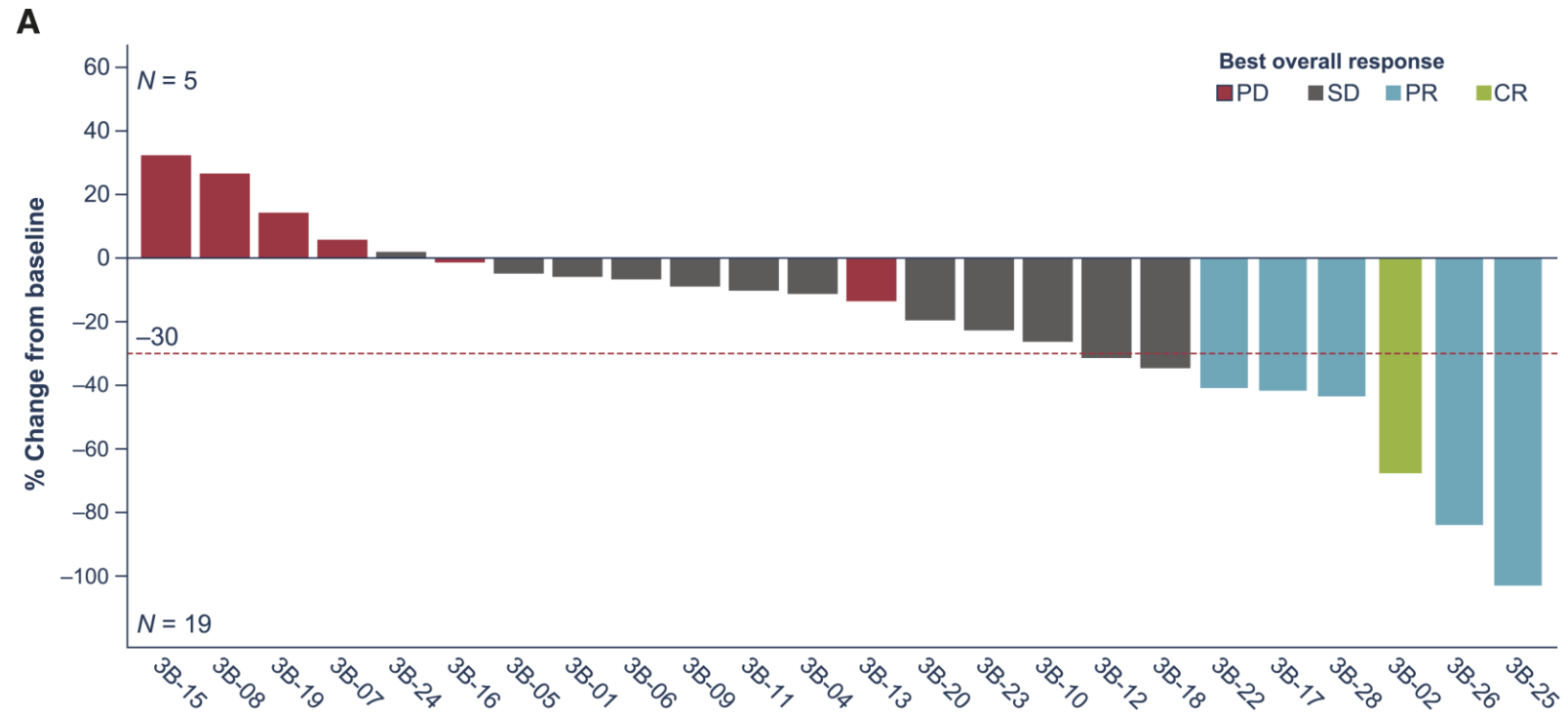


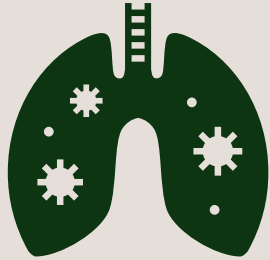
TIL



Lifileucel, an Autologous Tumor-Infiltrating Lymphocyte Monotherapy, in Patients with Advanced Non-Small Cell Lung Cancer Resistant to Immune Checkpoint Inhibitors.

Schoenfeld, A. J., He, K. et. al (2024). Cancer Discovery.



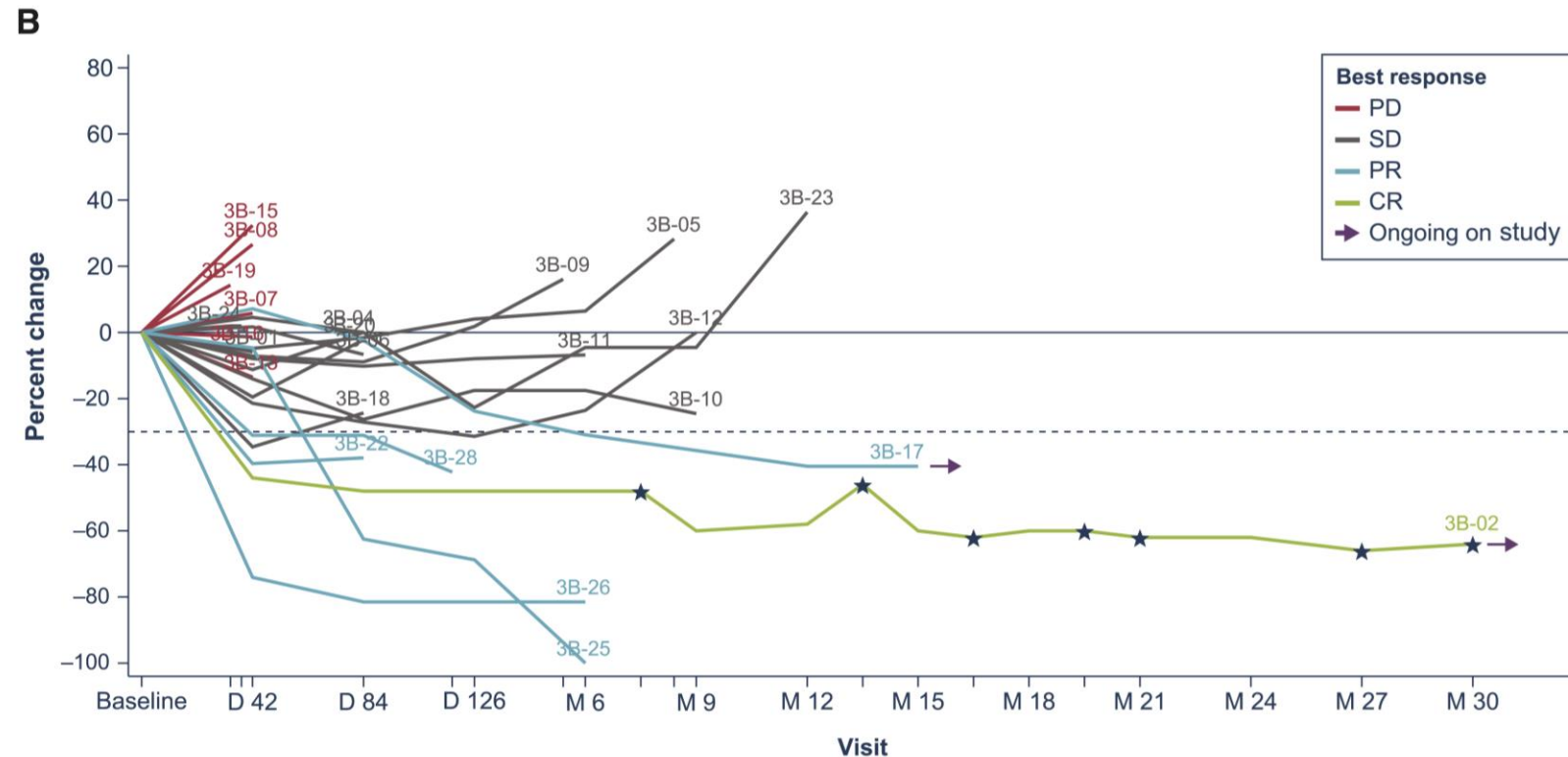


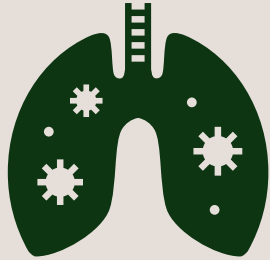
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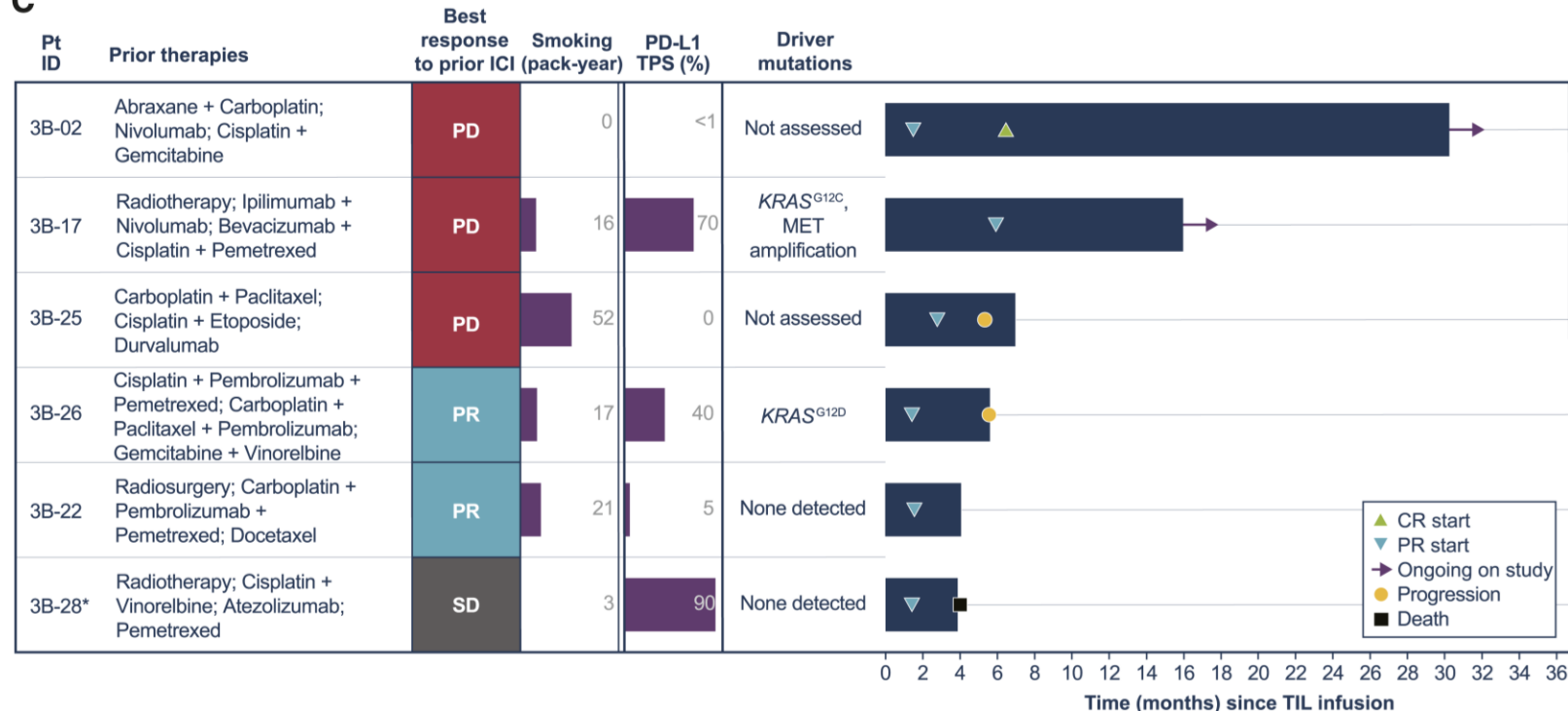
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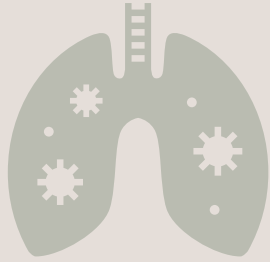


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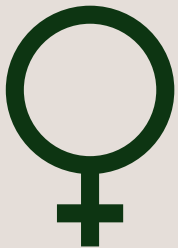
Schoenfeld, A. J., He, K. et. al (2024). Cancer Discovery.

C



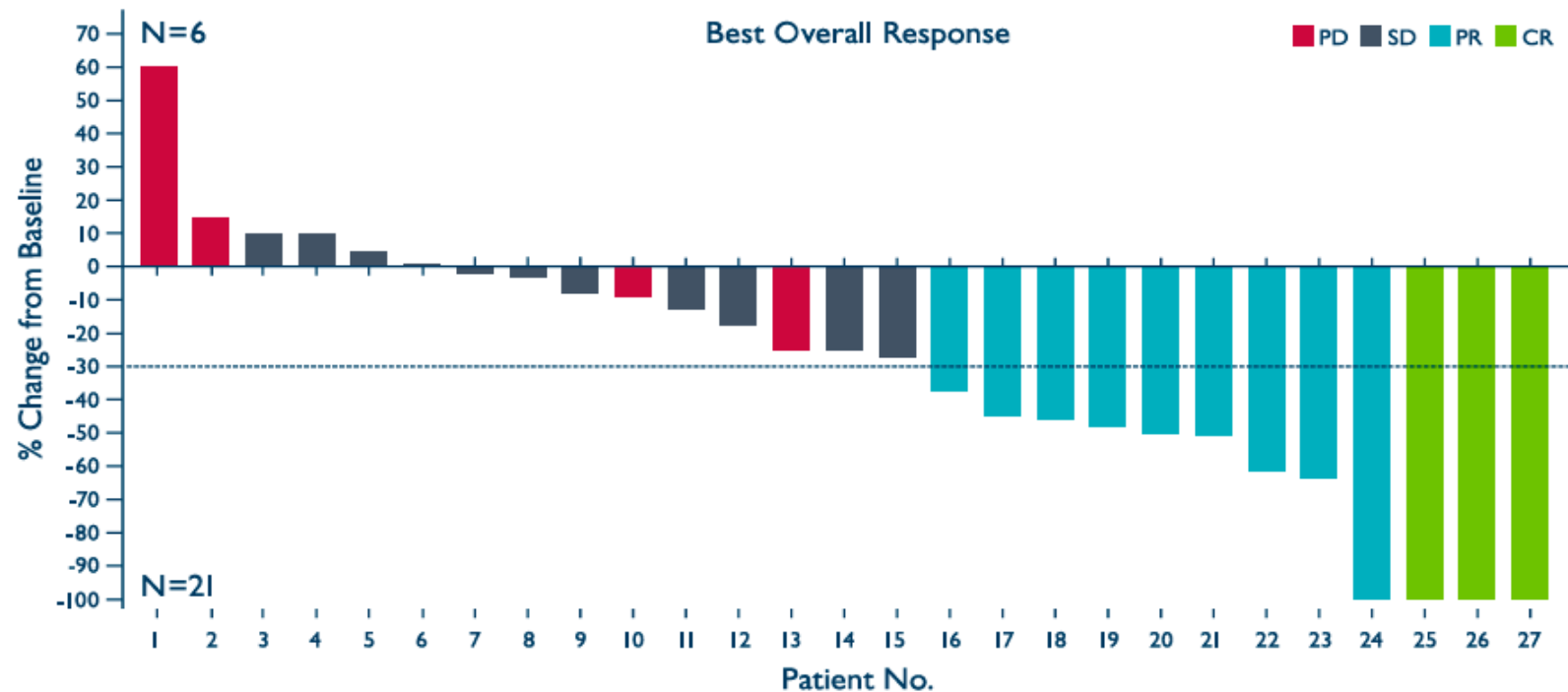


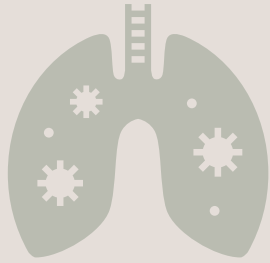
TIL



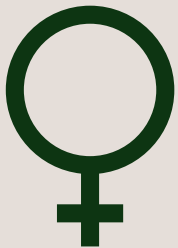
Safety & efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma.

Amir A. Jazaeri, Bradley J. Monk et. al (2019). ASCO.



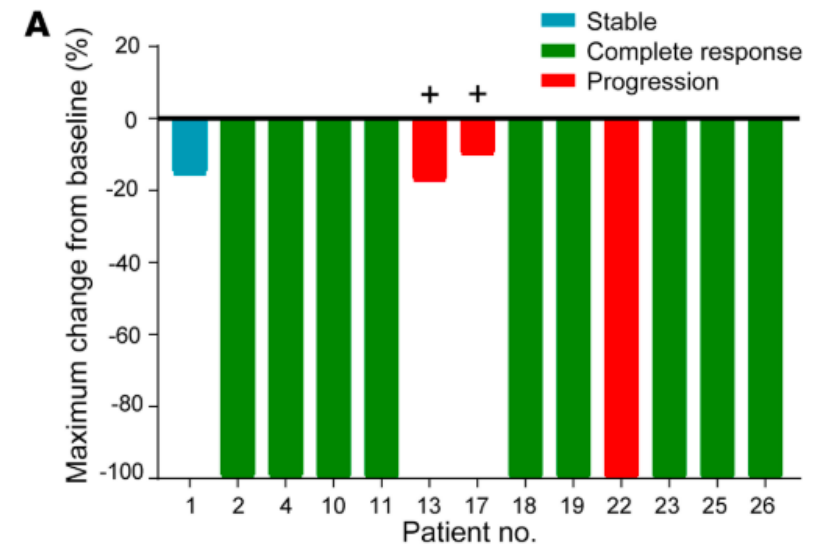
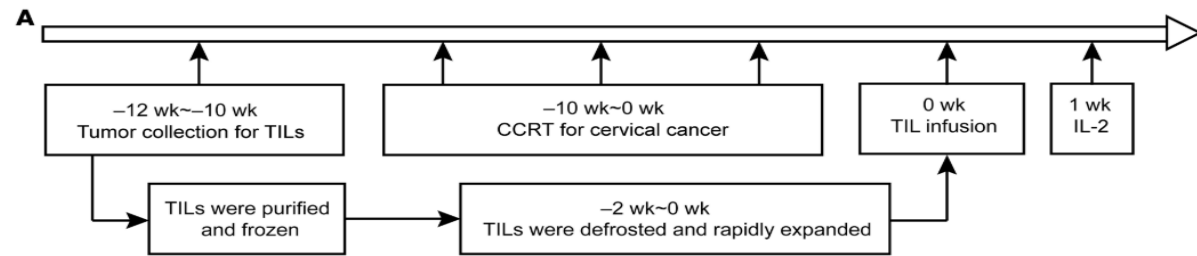


TIL



Phase I study of adjuvant immunotherapy with autologous tumor-infiltrating lymphocytes in locally advanced cervical cancer

He Huang, Jiang Li et. al (2019). The Journal of Clinical Investigation .



CAR-T

	Qi et al. (2024)	Hegde et al. (2024)	Qi et al. (2024)	Del Bufalo et al. (2023)	Mackensen et al. (2023)	Haas et al. (2019)	O'Rourke et al. (2018)
Tumor entity	GI cancers	Advanced sarcoma	CRC	Neuroblas toma	CLDN6+ solid tumors	MSLN+ solid tumors (2019)	Glioblas toma
Number of patients	98	13 in 14 enrollme nts	19	27	22 (ongoing)	15	10
CAR target	CLDN18.2	HER2	GUCY2C	GD2	CLDN6	MSLN	EGFRvIII
Overall response	38.8%	50%	26.3% (38.5%)	63%	67%	-	-
Lymphod epletion	flu + cyc + nabp/ gem	flu only or flu + cyc	flu + cyc	flu + cyc	flu + cyc	cyc	-

CAR-T

Claudin-18.2

Qi et al. (2024)		Hegde et al. (2024)	Qi et al. (2024)	Del Bufalo et al. (2023)	Mackensen et al. (2023)	Haas et al. (2019)	O'Rourke et al. (2018)
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Lymphodepletion	flu + cyc + nabp/gem	flu only or flu + cyc	flu + cyc	flu + cyc	flu + cyc	cyc	-

CAR-T

Human Epidermal Growth Factor Receptor 2

	Qi et al. (2024)	Hegde et al. (2024)	Qi et al. (2024)	Del Bufalo et al. (2023)	Mackensen et al. (2023)	Haas et al. (2019)	O'Rourke et al. (2018)
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CAR-T

Guanylate cyclase 2C

	Qi et al. (2024)	Hegde et al. (2024)	Qi et al. (2024)	Del Bufalo et al. (2023)	Mackensen et al. (2023)	Haas et al. (2019)	O'Rourke et al. (2018)
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CAR-T

Disialoganglioside GD2

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CAR-T

Claudin-6

	Qi et al. (2024)	Hegde et al. (2024)	Qi et al. (2024)	Del Bufalo et al. (2023)	Mackensen et al. (2023)	Haas et al. (2019)	O'Rourke et al. (2018)
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CAR-T

Mesothelin

	Qi et al. (2024)	Hegde et al. (2024)	Qi et al. (2024)	Del Bufalo et al. (2023)	Mackensen et al. (2023)	Haas et al. (2019)	O'Rourke et al. (2018)
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CAR-T

Epidermal Growth Factor Receptor vIII

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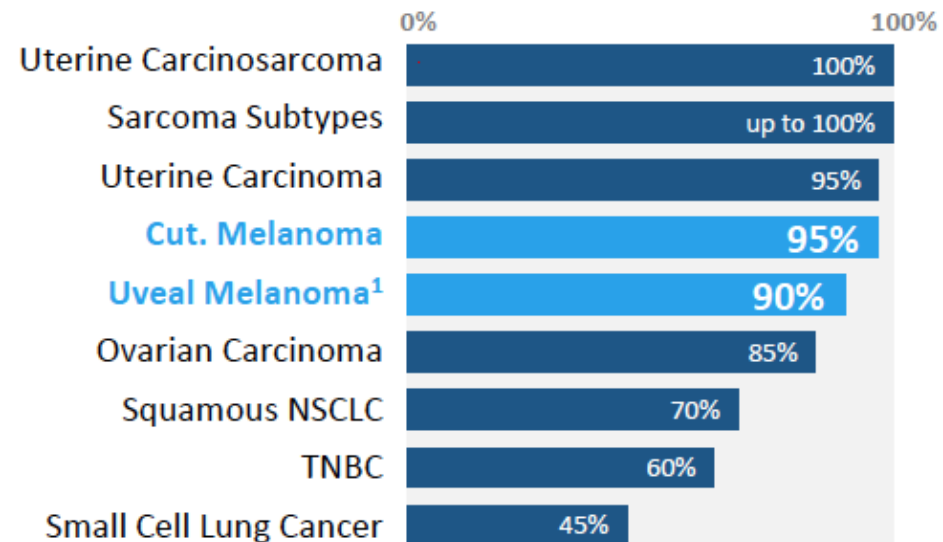
CAR-T

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TCR

ACTengine IMA203 TCR-T Targeting PRAME Shows Deep and Durable Anti-Tumor Activity in Heavily Pretreated Solid Cancer Patients

Martin Wermke, Cedrik M. Britten et al. Society of Melanoma Research Congress on October 11, 2024

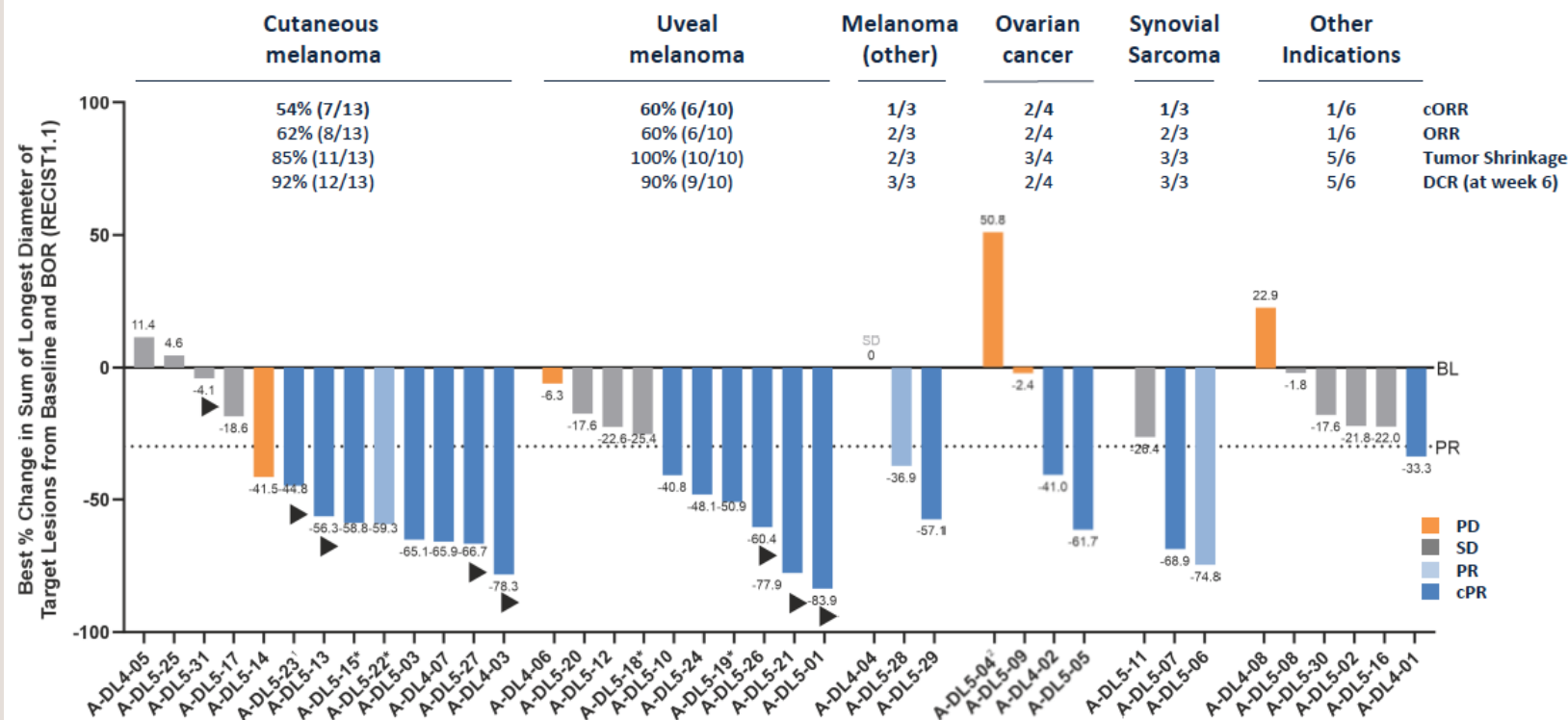


Target prevalence based on TCGA (SCLC: in-house) RNAseq data combined with proprietary mass spec-guided RNA expression threshold;
¹ Uveal melanoma target prevalence based on IMADetect qPCR testing of screening biopsies from 61 trial patients.

TCR

ACTengine IMA203 TCR-T Targeting PRAME Shows Deep and Durable Anti-Tumor Activity in Heavily Pretreated Solid Cancer Patients

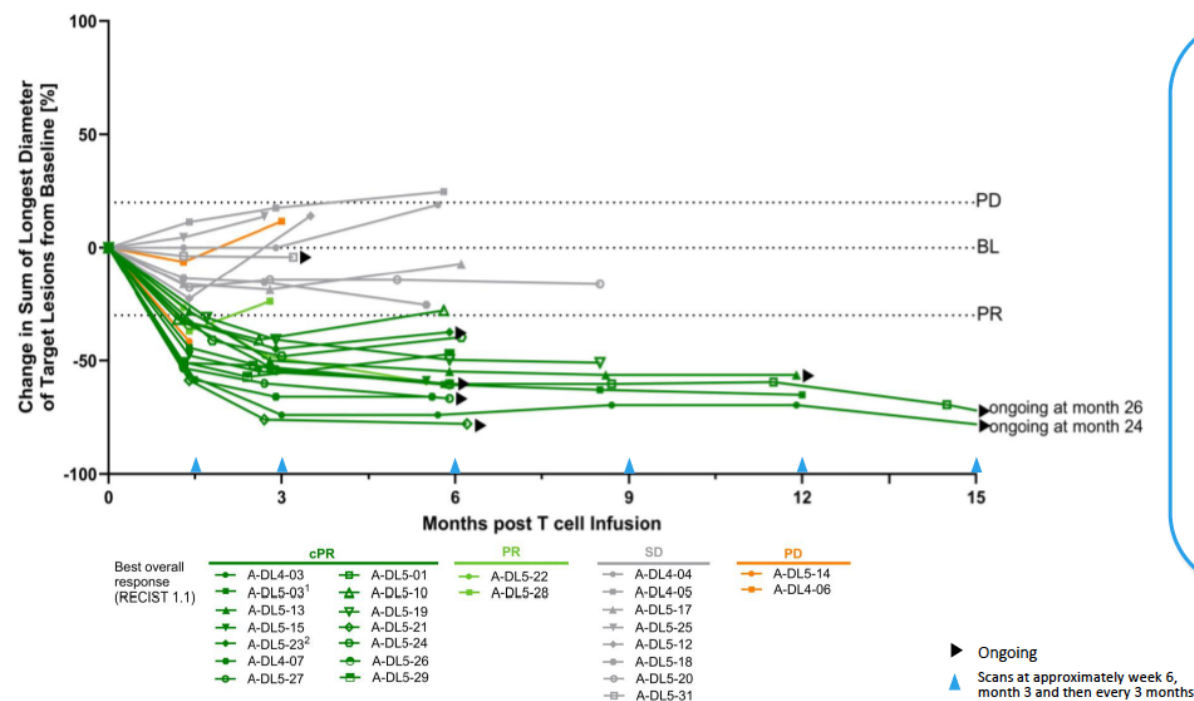
Martin Wermke, Cedrik M. Britten et al. Society of Melanoma Research Congress on October 11, 2024



TCR

ACTengine IMA203 TCR-T Targeting PRAME Shows Deep and Durable Anti-Tumor Activity in Heavily Pretreated Solid Cancer Patients

Martin Wermke, Cedrik M. Britten et al. Society of
Melanoma Research Congress on October 11, 2024



cORR 54% (14/26)

median DOR	12.1 months
(min, max)	(4.2, 25.5+ months)
mFU	9.3 months

7/14 confirmed responses ongoing

median PFS	6.0 months
(min, max)	(0.3+, 26.8+ months)

median OS	Not reached
(min, max)	(0.3+, 26.8+ months)
mFU	8.6 months

ORR 62% (16/26)

Tumor shrinkage** 88% (23/26)

DCR (at week 6) 92% (24/26)





Future trends and Next-Generation approaches

- + Combinations
- 🎯 Neoantigen selection
- 🛡️ Armoring
- 🧬 Genetic modification
- 🦠 Alternative cells

+ Combinations

A multicenter phase 2 trial of lifileucel plus pembrolizumab in patients with checkpoint inhibitor-naïve metastatic NSCLC: updated results

Benjamin C Creelan, Adam Schoenfeld et. al (2024). SITC

Figure 1. Treatment Schema

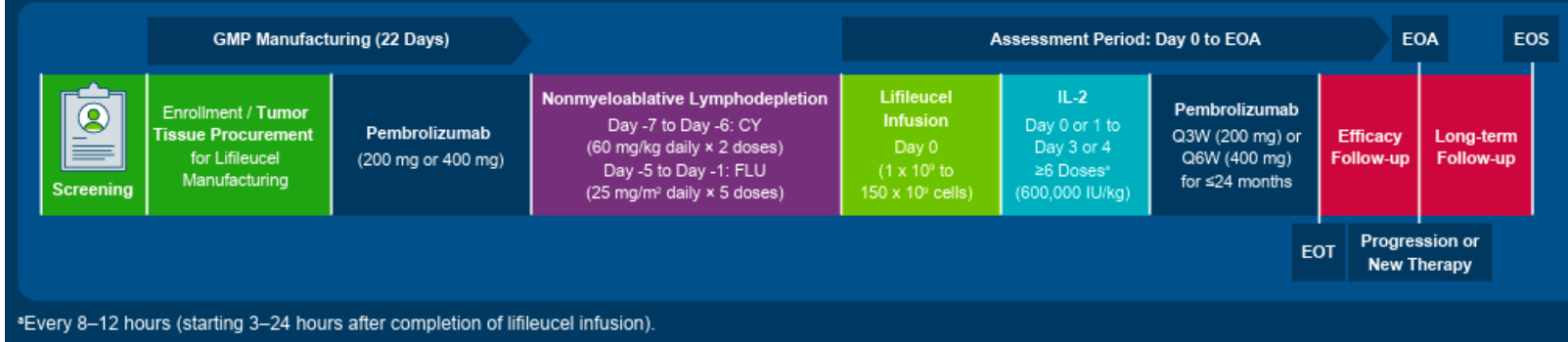
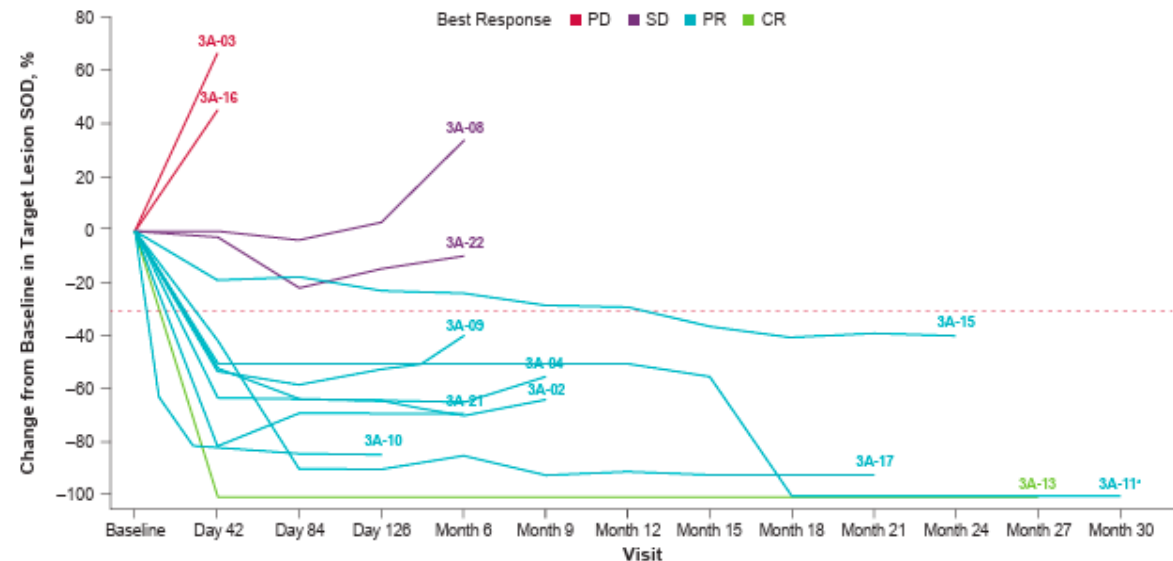


Figure 3. Percentage Change from Baseline in Target Lesion SOD Over Time in the EGFR-wt Subgroup



+ Combinations

Efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, and pembrolizumab in patients with immune checkpoint inhibitor-naïve unresectable or metastatic melanoma: updated results from IOV-COM-202 cohort 1A

Sajeve Thomas, Patriok Terheyden et al (2024) SMR

Figure 1. Treatment Schema

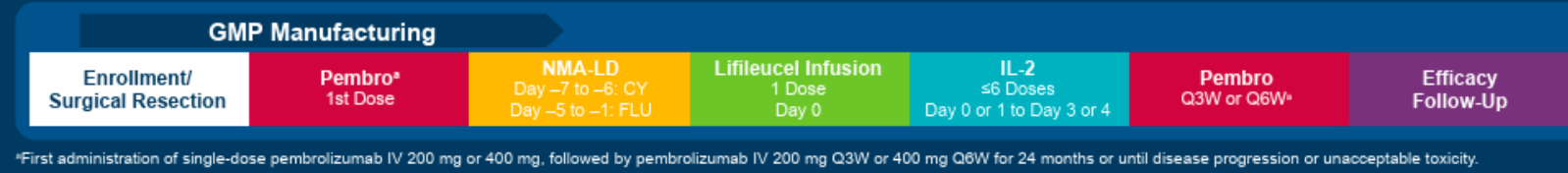
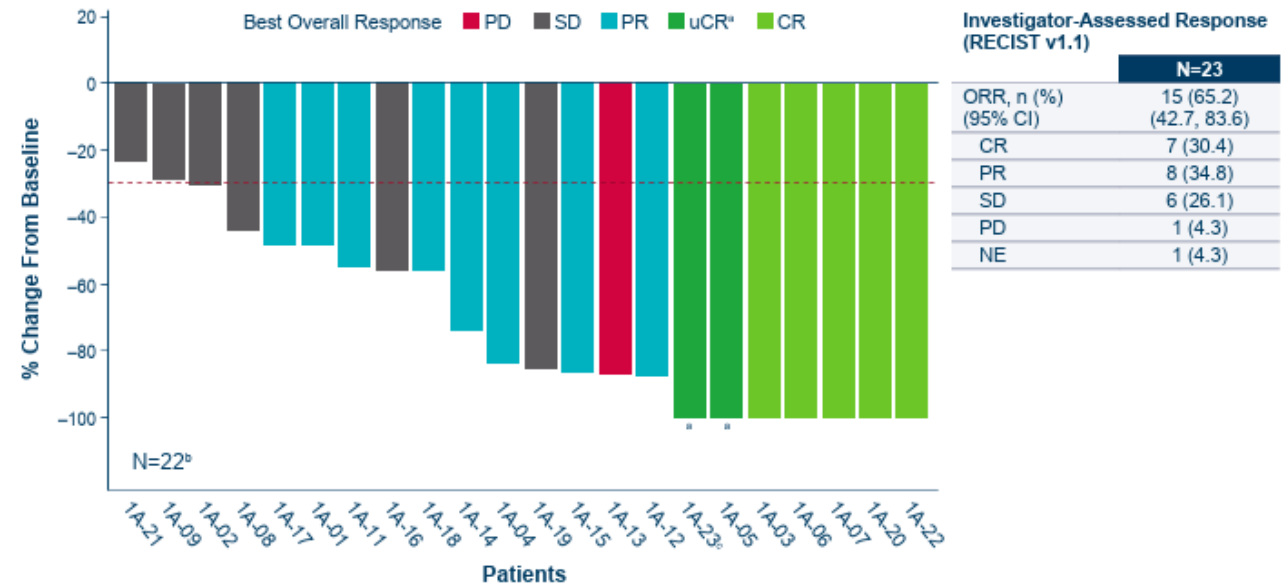


Figure 2. Best Percentage Change From Baseline in Target Lesion SOD



^aThe two uCRs have been confirmed post-data cut. ^bOne patient without a postdose tumor response assessment was not included. ^cTarget lesion lymph node at baseline decreased by 50% is no longer pathological, and thus is shown here as -100% representing uCR.

+ Combinations

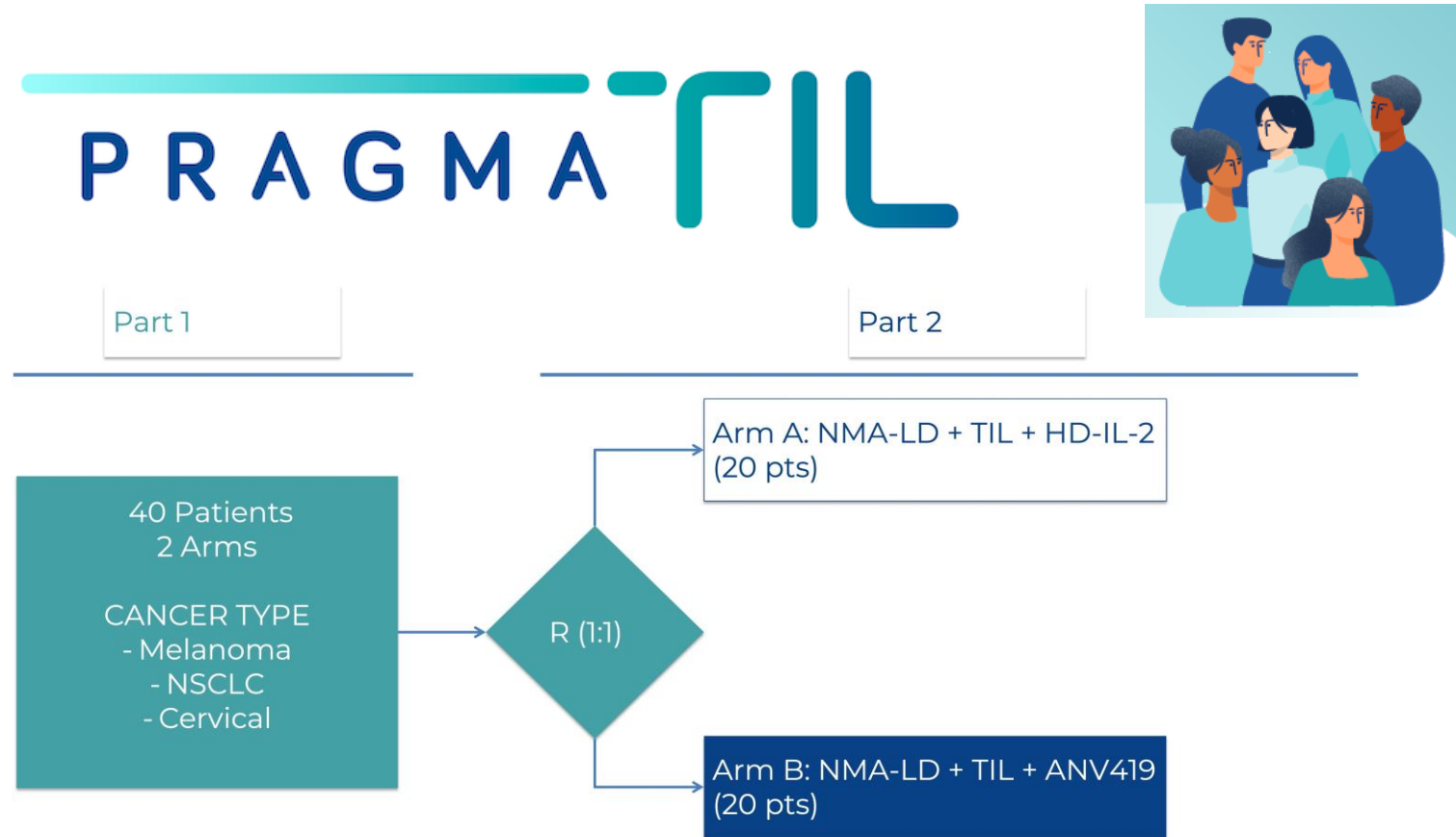


Participant organization name	Country
Vall d'Hebron Institute of Oncology (VHIO)	ES
Nederlands Kanker Instituut-Antoni van Leeuwenhoek ziekenhuis (NKI)	NL
Region Hovestaden – Herlev Hospital (REGIONH)	DK
Region Stockholm – Karolinska University Hospital (RS)	SW
Sheba Medical Center (SHEBA)	IS
Institut Gustave Roussy (IGR)	FR
Asphalion SL (ASPH)	ES
Innovandum Health SL (IH)	ES
Barcelona Health (BCNH)	ES
Fundación Bancaria La Caixa (LCF)	ES
Seintelles – Citoyens et recherche (SEINT)	FR
UNICANCER	FR



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+ Combinations



To evaluate whether TIL-ACT using the **IL-2 analog ANV419** compared to TIL-ACT using HD-IL-2:

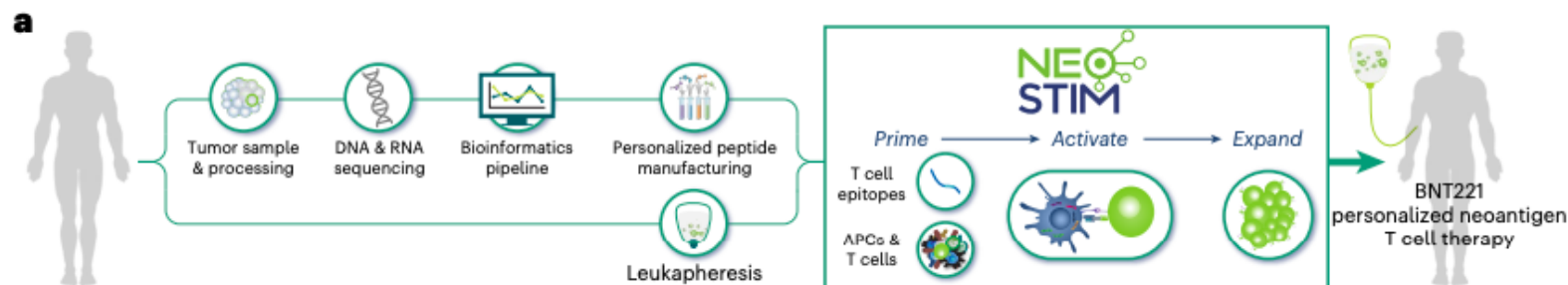
- 1) Reduces the mean number of predefined grade ≥ 3 relevant adverse events related to interleukin
- 2) Improves patient-reported outcomes (PROs)



Neoantigen selection

Personalized, autologous neoantigen-specific T cell therapy in metastatic melanoma: a phase 1 trial

Jessica S. W. Borgers, Marit M. van Buuren et al. (2025)
Nature Medicine

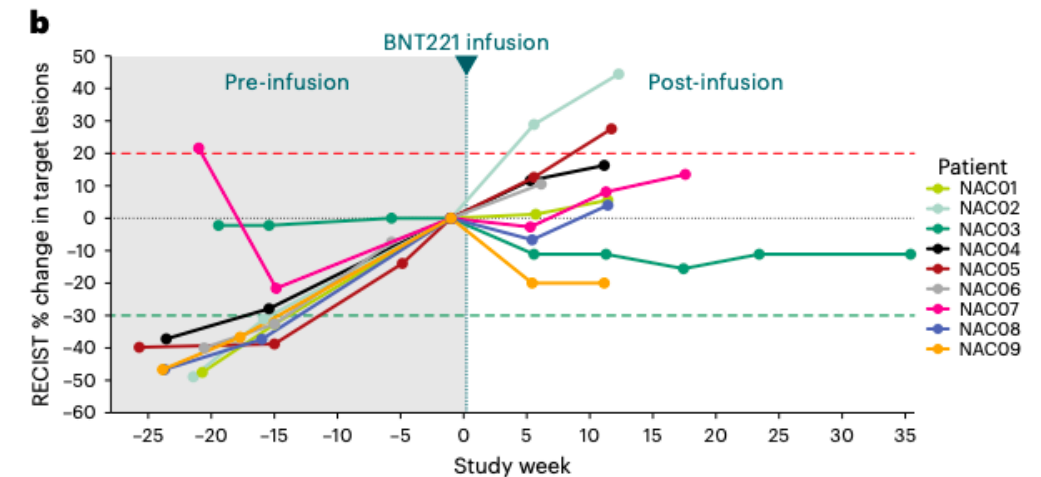
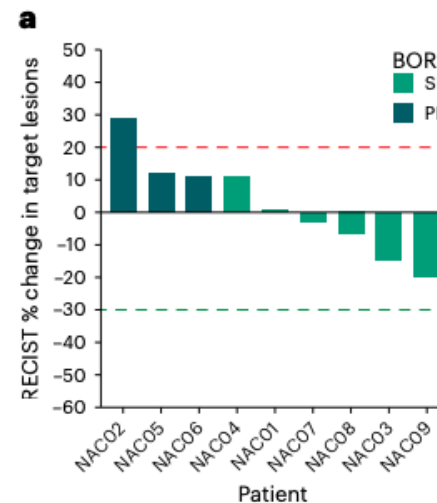
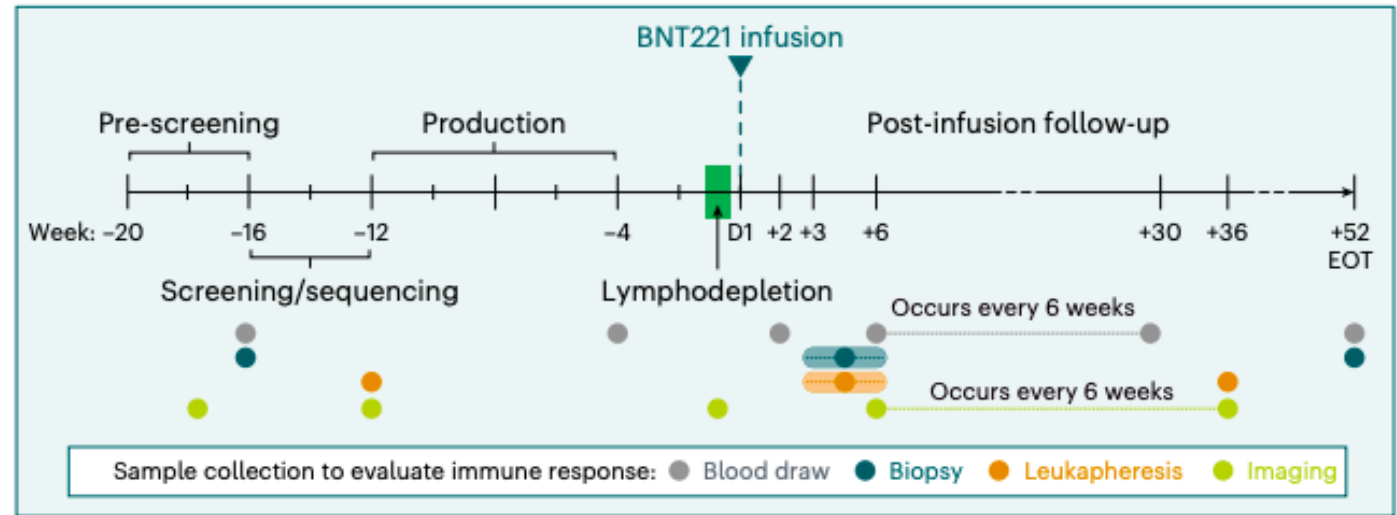




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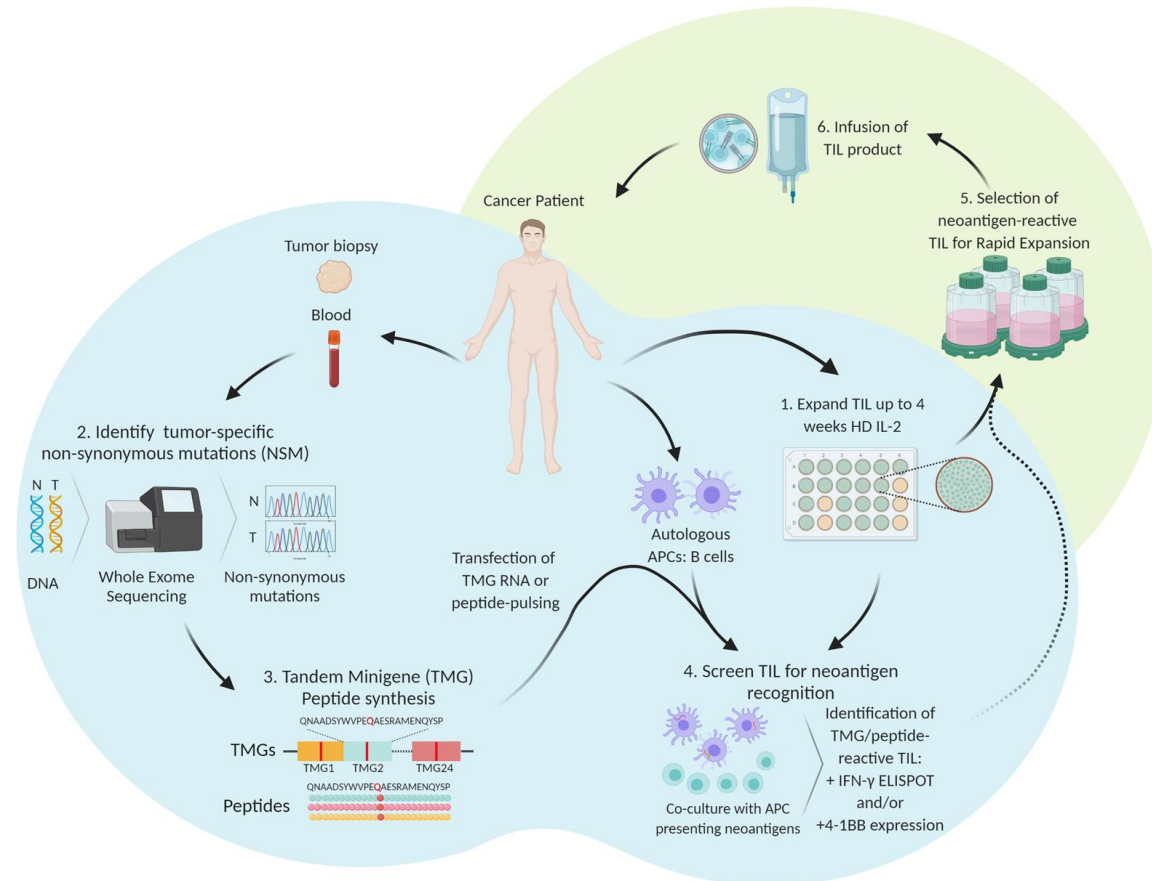




Neoantigen selection

An investigator-initiated phase I study to assess the safety and tolerability of ex vivo next-generation neoantigen-selected tumor-infiltrating lymphocyte (TIL) therapy in advanced immune checkpoint blockade (ICB) resistant solid tumors (NEXTGENTIL-ACT)

Vladimir Galvao, Elena Garraida et al. (2023) ESMO

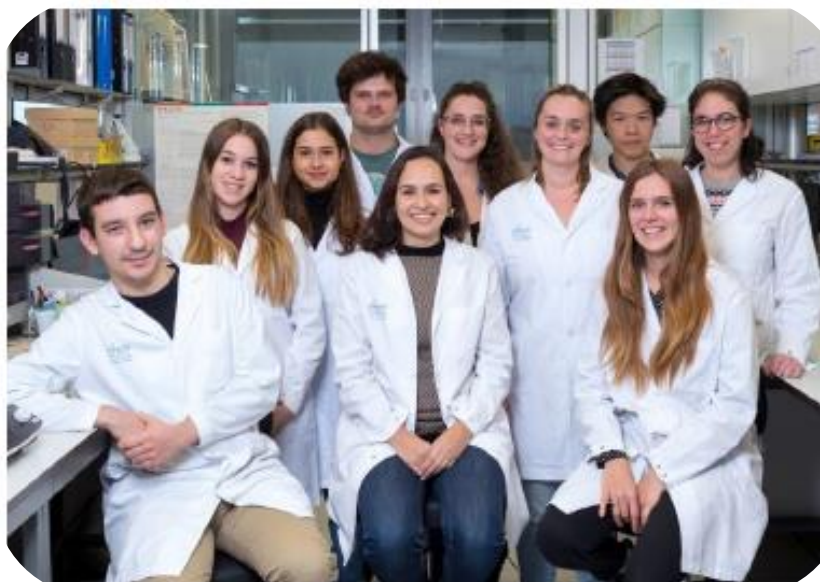




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Vall d'Hebron
Institute of Oncology

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de Salud
Carlos III

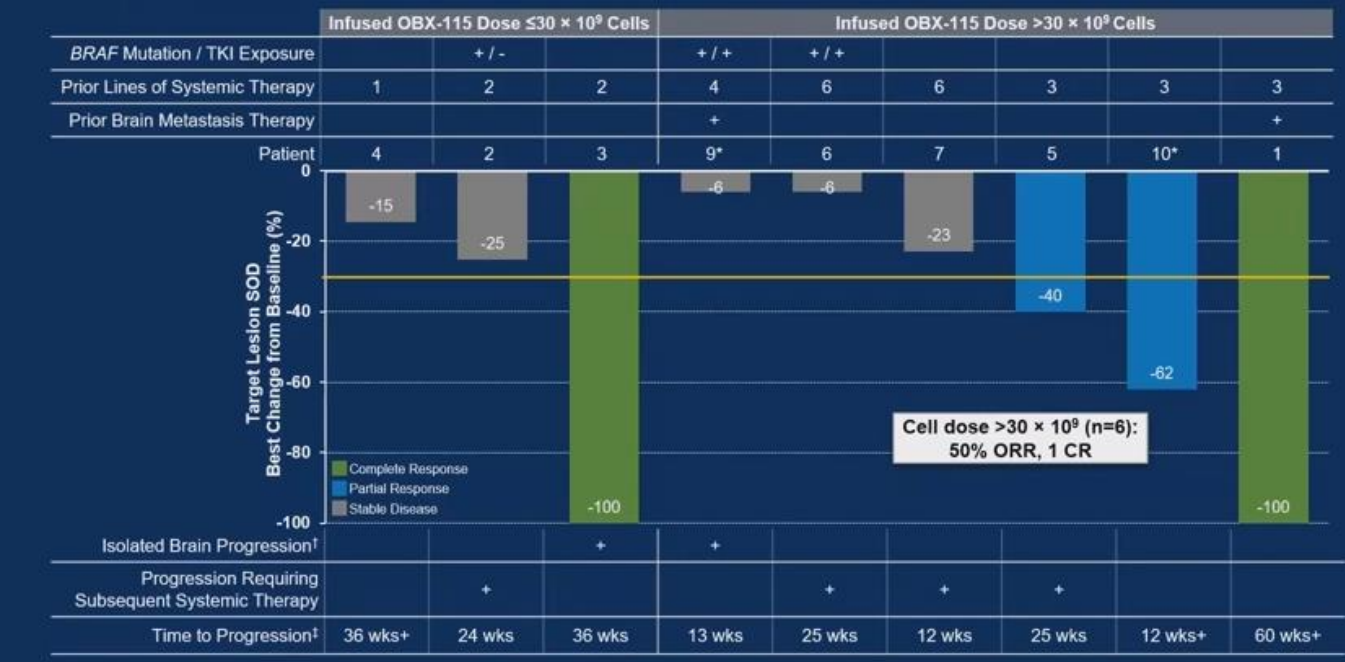
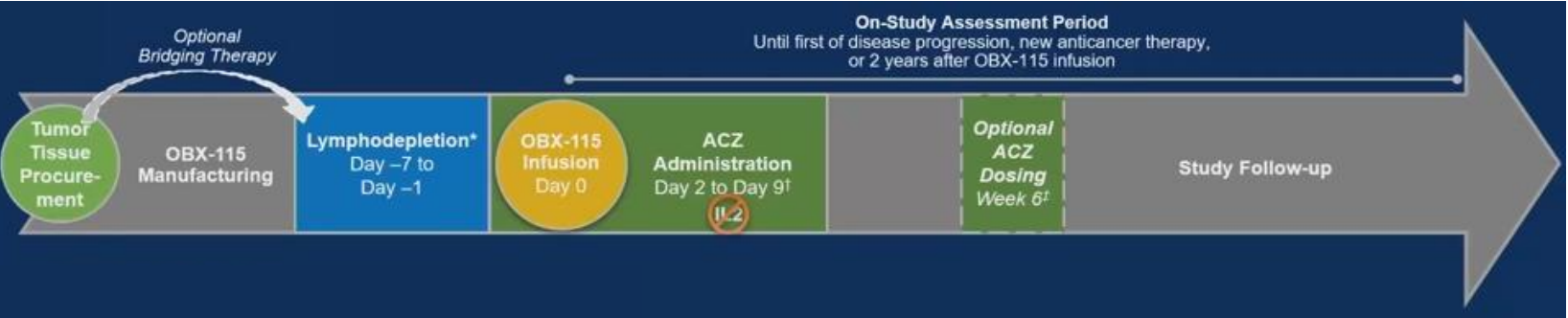
Fundación
BBVA

OBX-115, an interleukin 2 (IL2)-sparing engineered tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with immune checkpoint inhibitor (ICI)-resistant unresectable or metastatic melanoma (membrane-bound IL-15)

Rodabe N Amaria, Parameswaran Hari et al. (2024) ASCO



Armoring



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Armoring

Nonhematologic TEAE,* n (%)	All Patients (N=10)		
	All Grades	Grade 3	Grade 4+
Increased alanine aminotransferase	4 (40.0)	1 (10.0)	0
Abdominal pain†	1 (10.0)	1 (10.0)	0
Syncope	1 (10.0)	1 (10.0)	0

- Hematologic AEs were consistent with known lymphodepletion safety profile
- Eight patients experienced rash / pruritus (all Grade 1–2)
- Uveitis / iritis (all Grade 1–2) in 4 patients, 1 of whom reported optic neuritis (Grade 3) that has resolved

A phase I single-arm, open-label trial of engineering tumor-infiltrating lymphocytes with membrane-bound IL-7 for recurrent ovarian cancer

Jing Guo, Zhongping Cheng, et al. (2024) ASCO

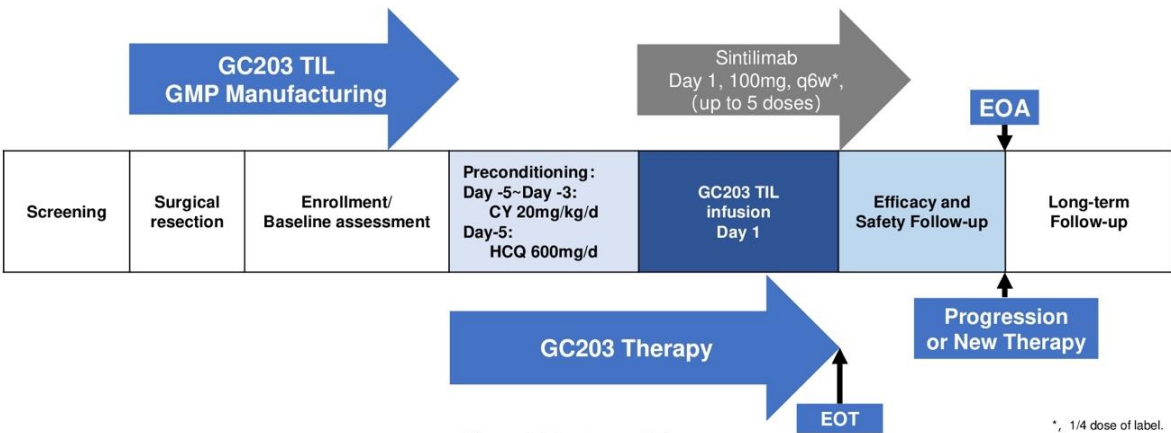


Figure 3. Treatment Schema

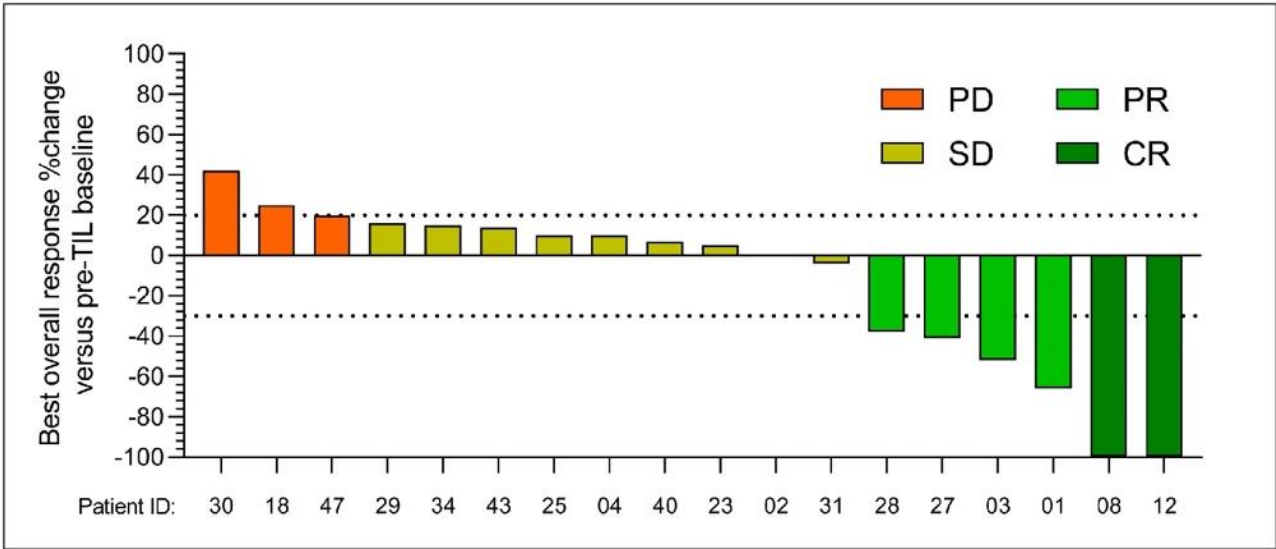


Figure 6. Best Percentage Change From Baseline in Target Lesion SOD

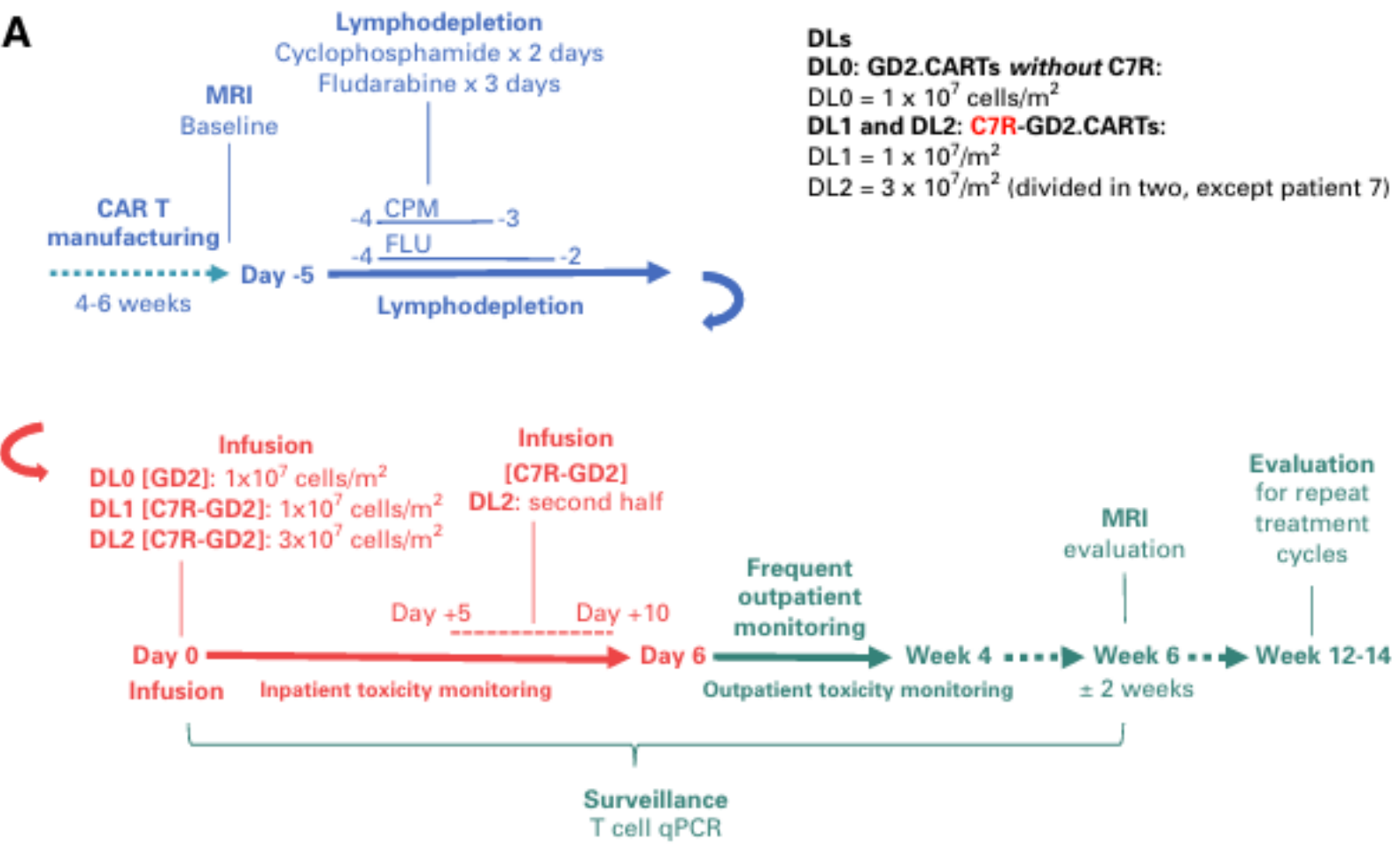
Phase I Trial of GD2.CARTCells Augmented With Constitutive Interleukin-7 Receptor for Treatment of High-Grade Pediatric CNS Tumors

Frank Y. Lin, Bilal Omer et al. (2024) JCO



Armoring

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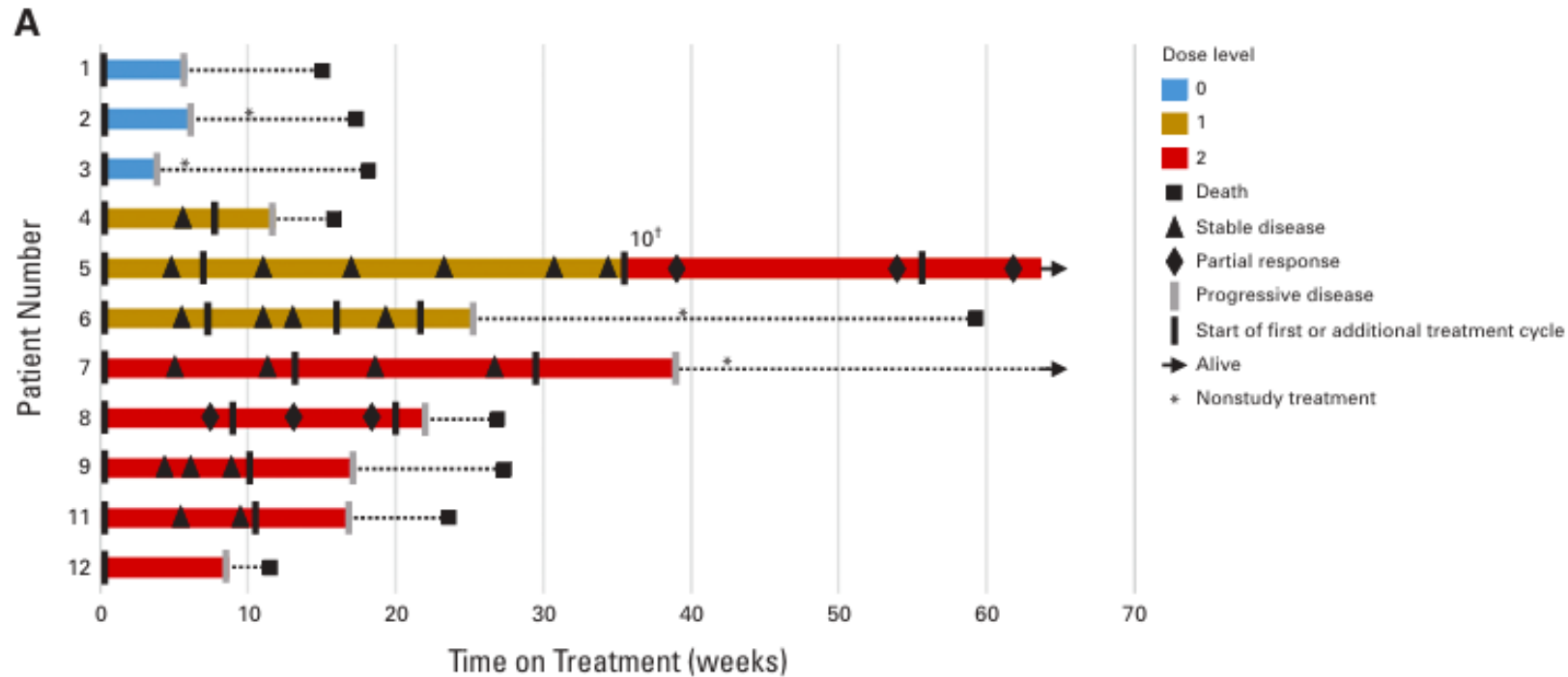


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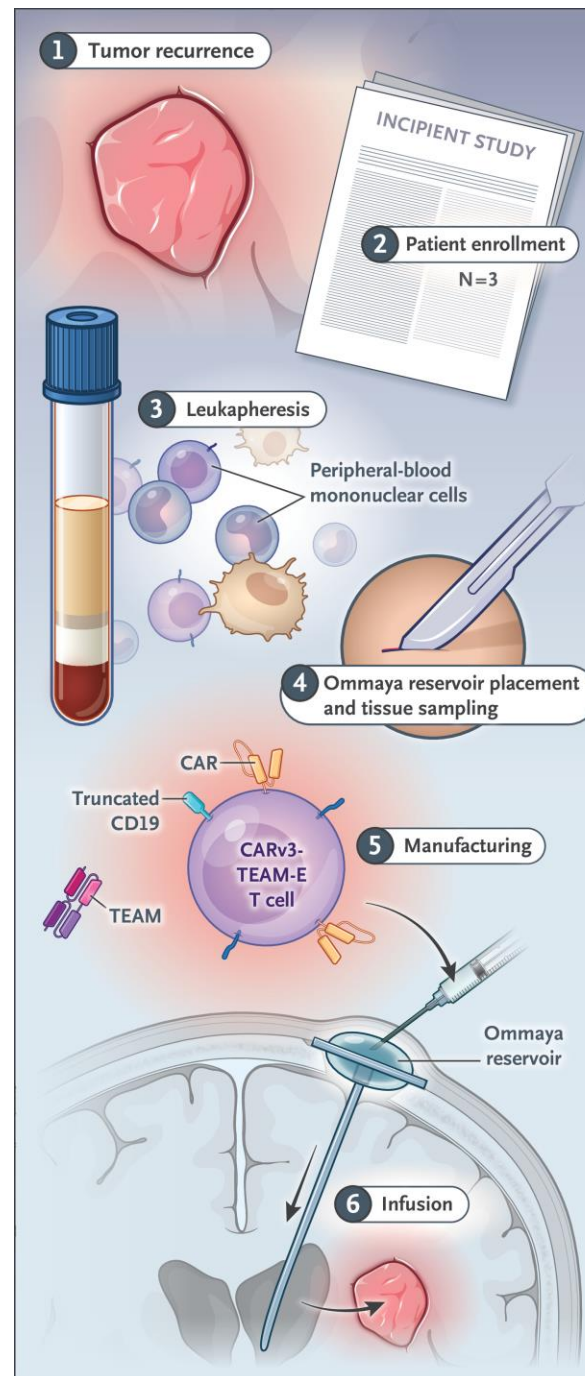


Intraventricular CARv3-TEAM-E T Cells in Recurrent Glioblastoma

Bryan D. Choi, Marcela V. Maus et al. (2024) NEJM

CAR-T - EGFRvIII + T-cell-engaging antibody molecule (TEAM) against wild-type EGFR

Safety run-in cohort: 3 patients (ORR: 100%)



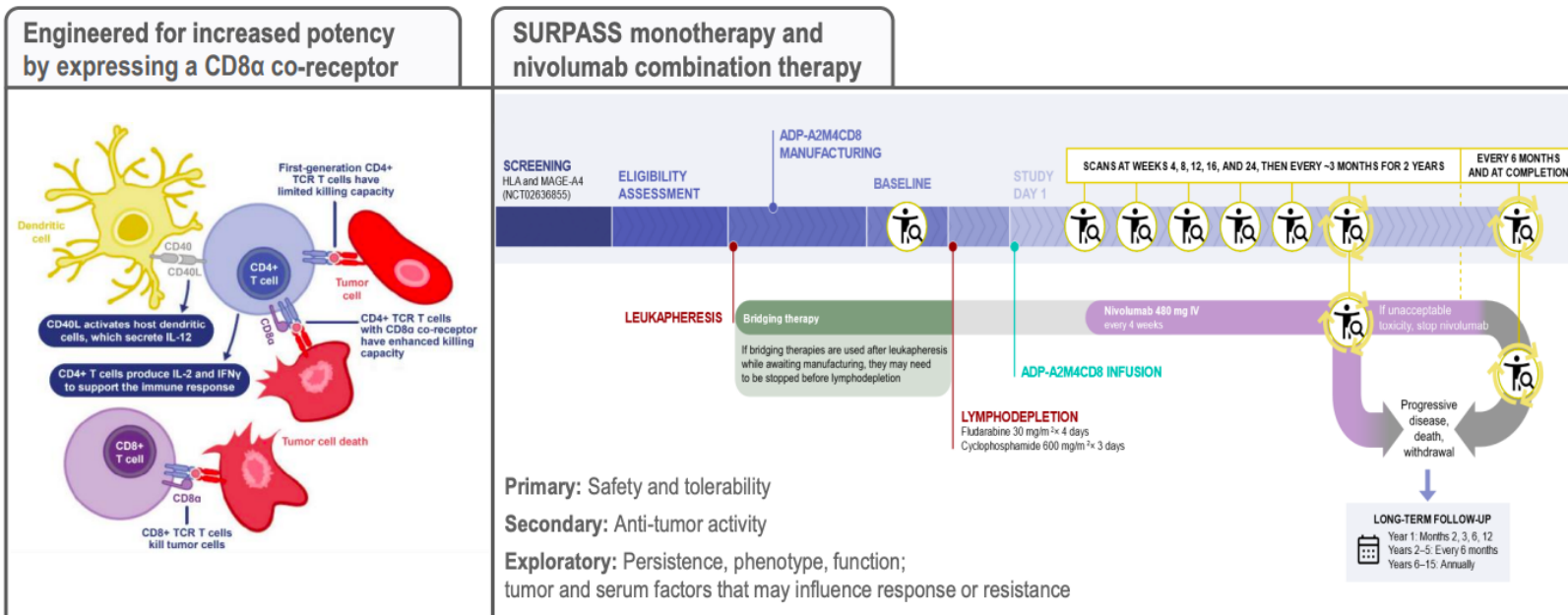
Armoring

Clinical and translational data from the phase I SURPASS trial of ADP-A2M4CD8 T cell receptor (TCR) T cell therapy alone or combined with nivolumab in solid tumors

V. Moreno Garcia, D.S. Hong et al. (2023) ESMO



Armoring

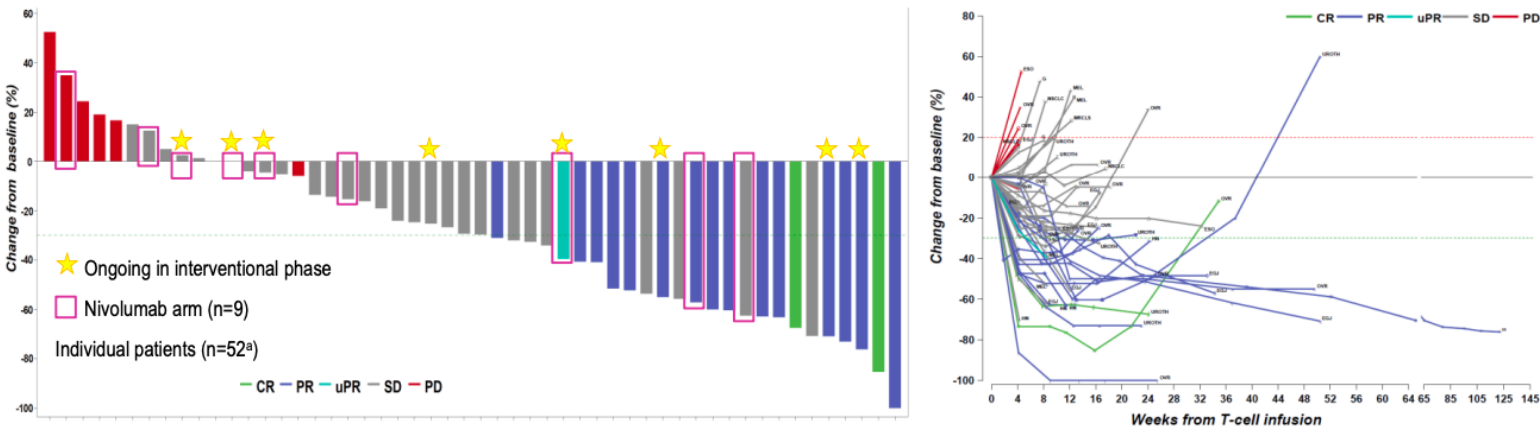


Clinical and translational data from the phase I SURPASS trial of ADP-A2M4CD8 T cell receptor (TCR) T cell therapy alone or combined with nivolumab in solid tumors

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Group	Overall response rate, n (%); 95% CI	Duration of response, weeks
Monotherapy (n=46)	16 (34.8); 21.4–50.3	Median: 21 (95% CI: 12–38)
Nivolumab arm (n=10)	1 (10.0); 0.3–44.5	30

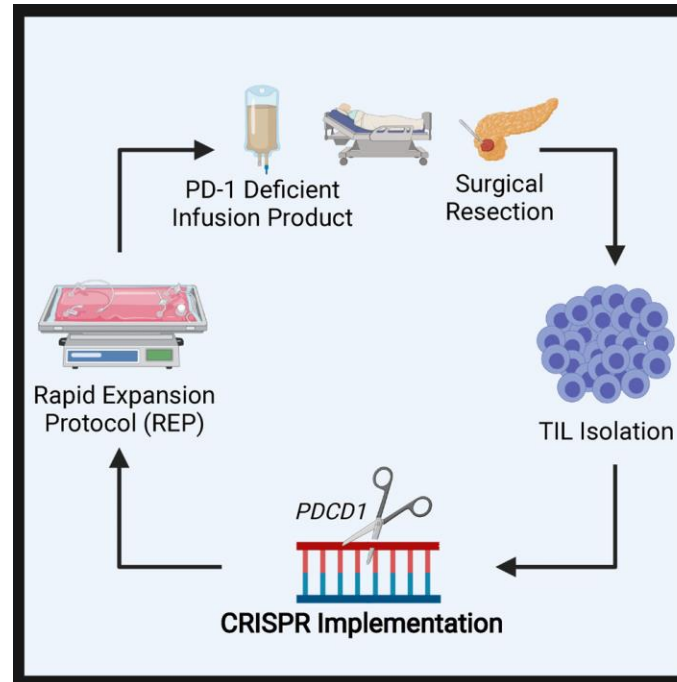


Genetic modification

T-cell Therapy with CRISPR PD1-edited Tumor Infiltrating Lymphocytes for Patients with Metastatic Melanoma (CRISPR-TIL). NCT06783270

Inge Marie Svane et al. Herlev Hospital

First patient treated in 2025!



*Chamberlain, C. A., Met, Ö.
Et al. (2022). Molecular
Therapy - Oncolytics
Inge Marie Svane et al.
Herlev Hospital*



Alternative cells

Donor Natural Killer Cells, Cyclophosphamide, and Etoposide in Treating Children and Young Adults With Relapsed or Refractory Solid Tumors. NCT03420963

Demetrios Petropoulos, M.D. Anderson Cancer Center

Advantages of NK cells:

- ✓ do not require TCR-HLA interactions for cell killing
- ✓ very little effect on healthy tissues
- ✓ multiple mechanisms to kill tumor cells
 - release of perforins and granzymes
 - antibody-dependent cellular cytotoxicity
 - death receptor-mediated pathways
 - production of cytokines and chemokines that recruit antigen presenting cells

MULTI-STAKEHOLDER WORKSHOP

New modalities in cancer
drug development

Conclusions:

- ✓ Approval of TIL therapy (Lifileucel) for metastatic melanoma and TCR-T therapy (Afamitresgene autoleucel) for MAGE-A4+/HLA*02+ synovial sarcoma marks a new era in cancer immunotherapy — cell therapies for solid tumors.
- ✓ TILs emerges as a new standard-of-care in melanoma (NSCLC and cervical carcinomas to be confirmed)
- ✓ Encouraging data for CAR-T targeting: CLDN18.2, CLDN6, HER2, EGFRvIII, GD2, among others.
- ✓ New strategies: CPI combinations, alternatives to HD-IL-2, selection of best TILs, cell armoring, co-secretion of T-cell engagers, genetic modifications
- ✓ Expanding use of NK cell therapies in solid tumors.

MULTI-STAKEHOLDER WORKSHOP

New modalities in cancer
drug development

Aknowledgments:

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- Oriol Miralles
- Study Nurses
- Study Coordinators

VHIO Investigators

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- Pere Barba – UTAH Director. Hematology
- Paolo Nuciforo's Team - Molecular Oncology Pathology Lab

VHIO Projects office

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- Susana Muñoz
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Others

- Patients
- Families
- Funding Entities

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European Union's Horizon Europe
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MULTI-STAKEHOLDER WORKSHOP

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Aknowledgments:

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