Advanced cell therapy

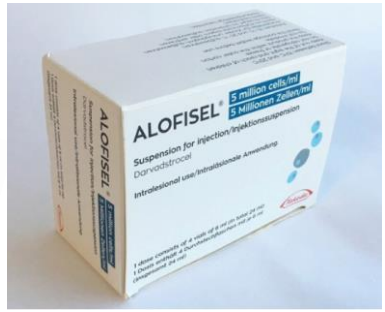
BHS Educational Session

Bart Vandekerckhove
Ghent University

Advanced Therapy Medicinal Products (ATMPs)

Gene Therapy Medicinal Products	Somatic Cell Therapy Medicinal Products	Tissue Engeneering Products

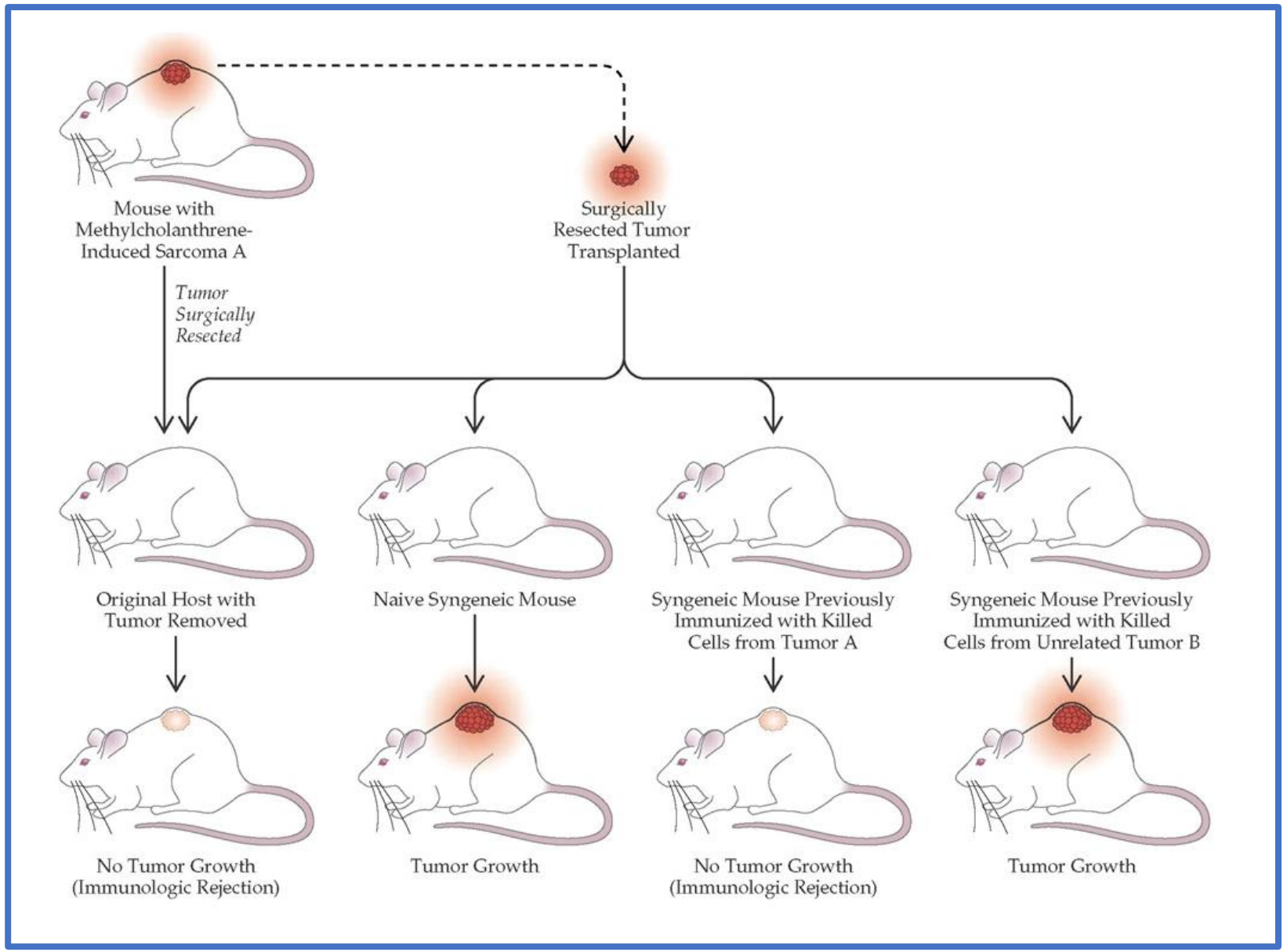
Genetically Modified Cells



HOLOCLAR®
Ex vivo expanded autologous human corneal epithelial cells containing stem cells

[Regulation (EC) No 1394/2007]

Malignant tumor can be rejected by the immune system

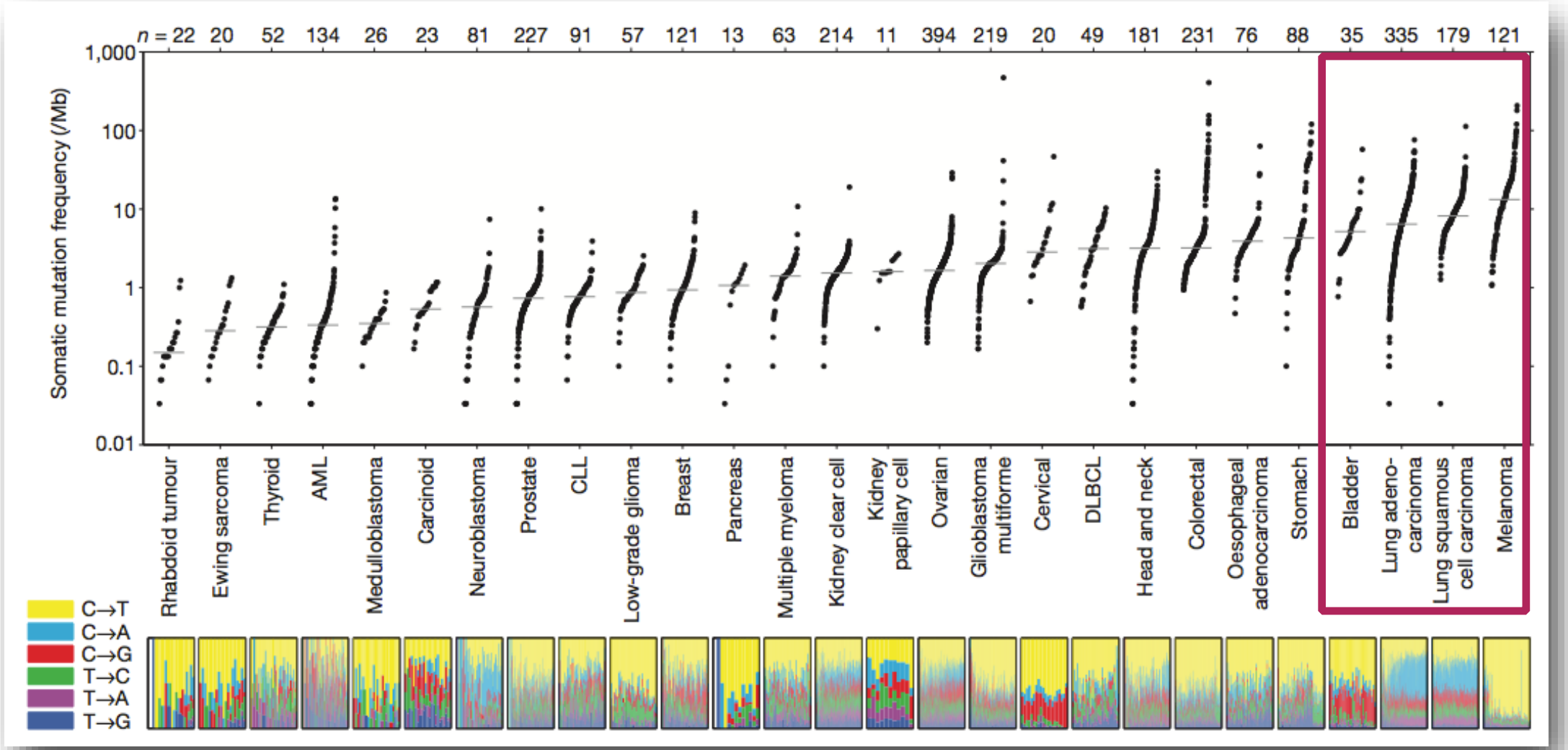


> J Natl Cancer Inst. 1957 Jun;18(6):769-78.

Immunity to methylcholanthrene-induced sarcomas

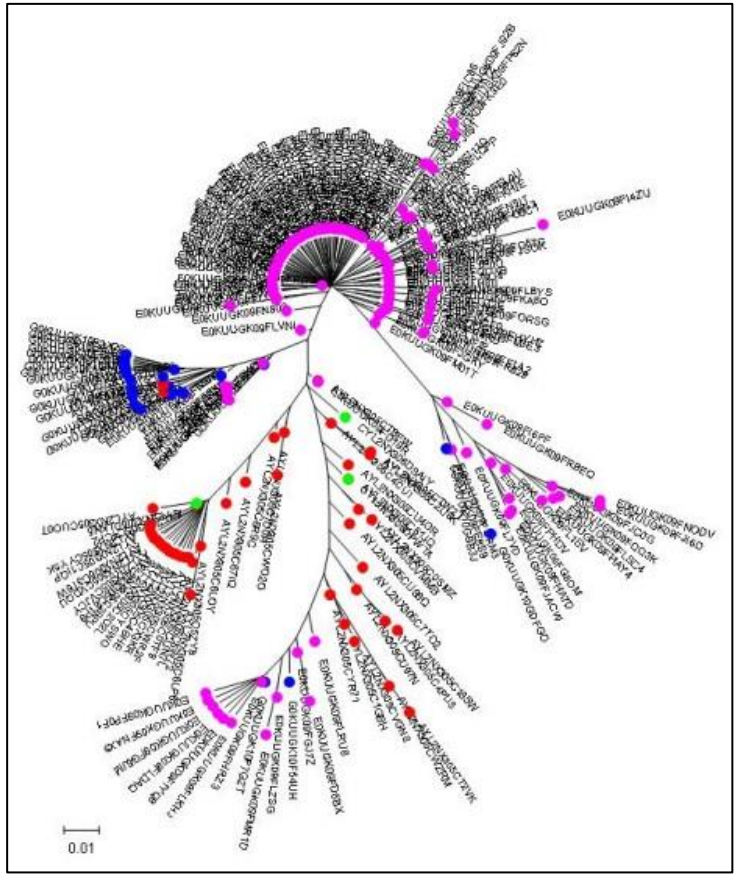
R T PREHN, J M MAIN

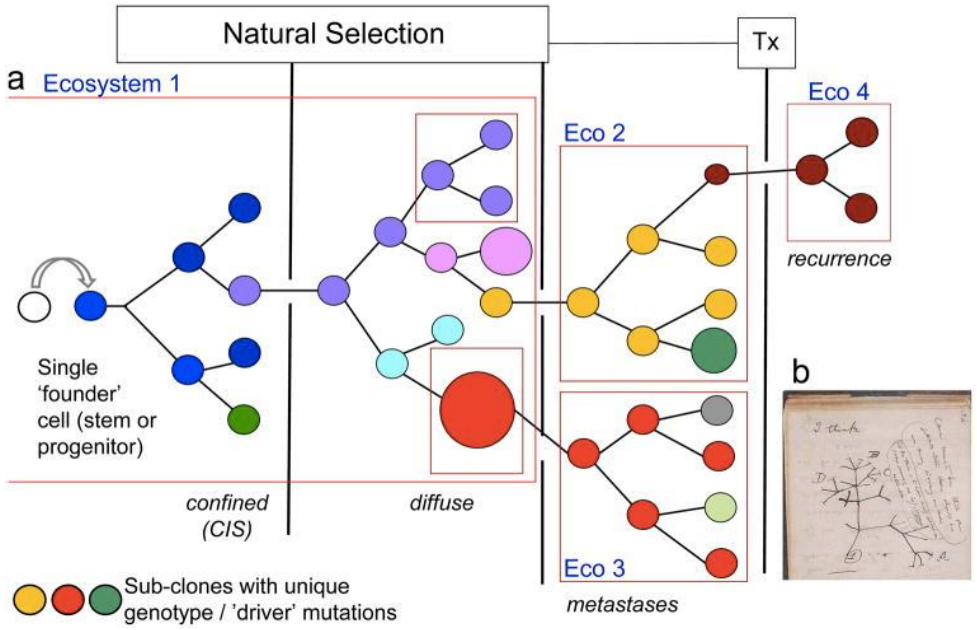
CANCER MUTATIONAL LOAD vs IMMUNOGENICITY

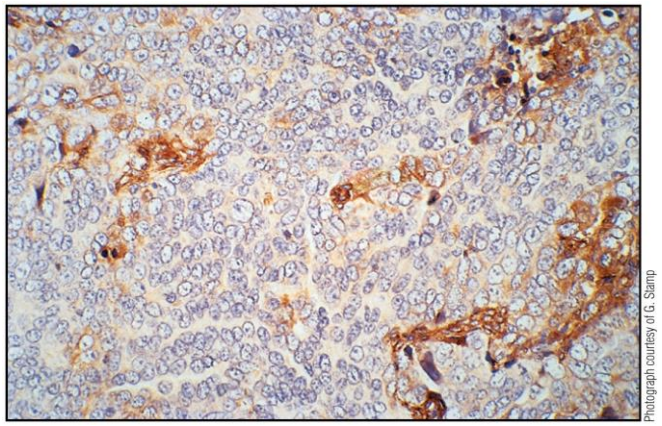


Lawrence et al, Nature, July 2013

Evidence for immune mediated killing of cancer in humans: 1. immuno-editing







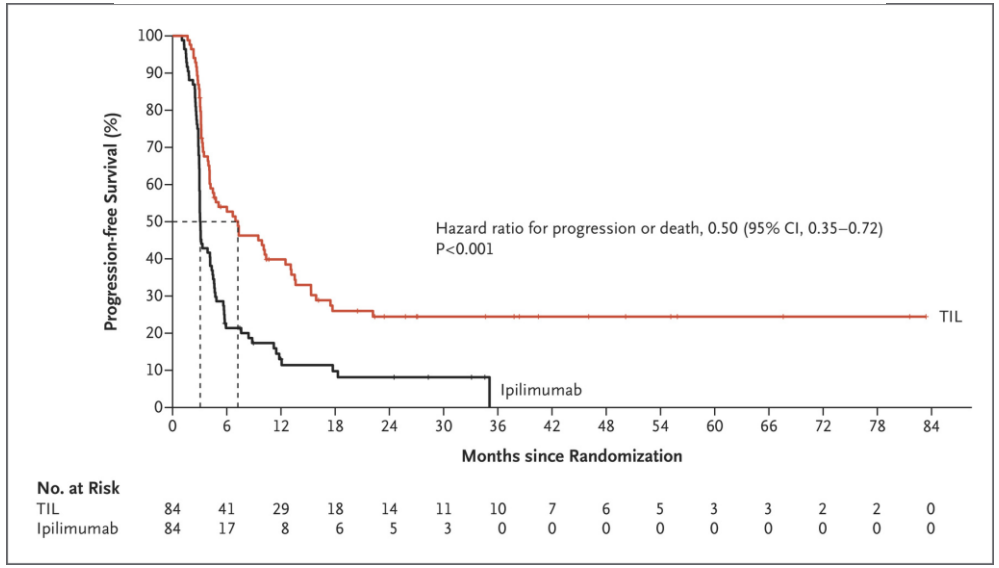
Genovese G et al. N Engl J Med 2014;371:2477-2487.

Evidence for immune mediated killing of cancer in humans : 2. tumor infiltrating lymphocytes (TIL)

CLINICAL TRIAL

Design: A phase 3, multicenter, open-label, randomized trial examined the efficacy and safety of TIL therapy, as compared with ipilimumab immunotherapy, as first- or second-line treatment in patients with advanced melanoma.

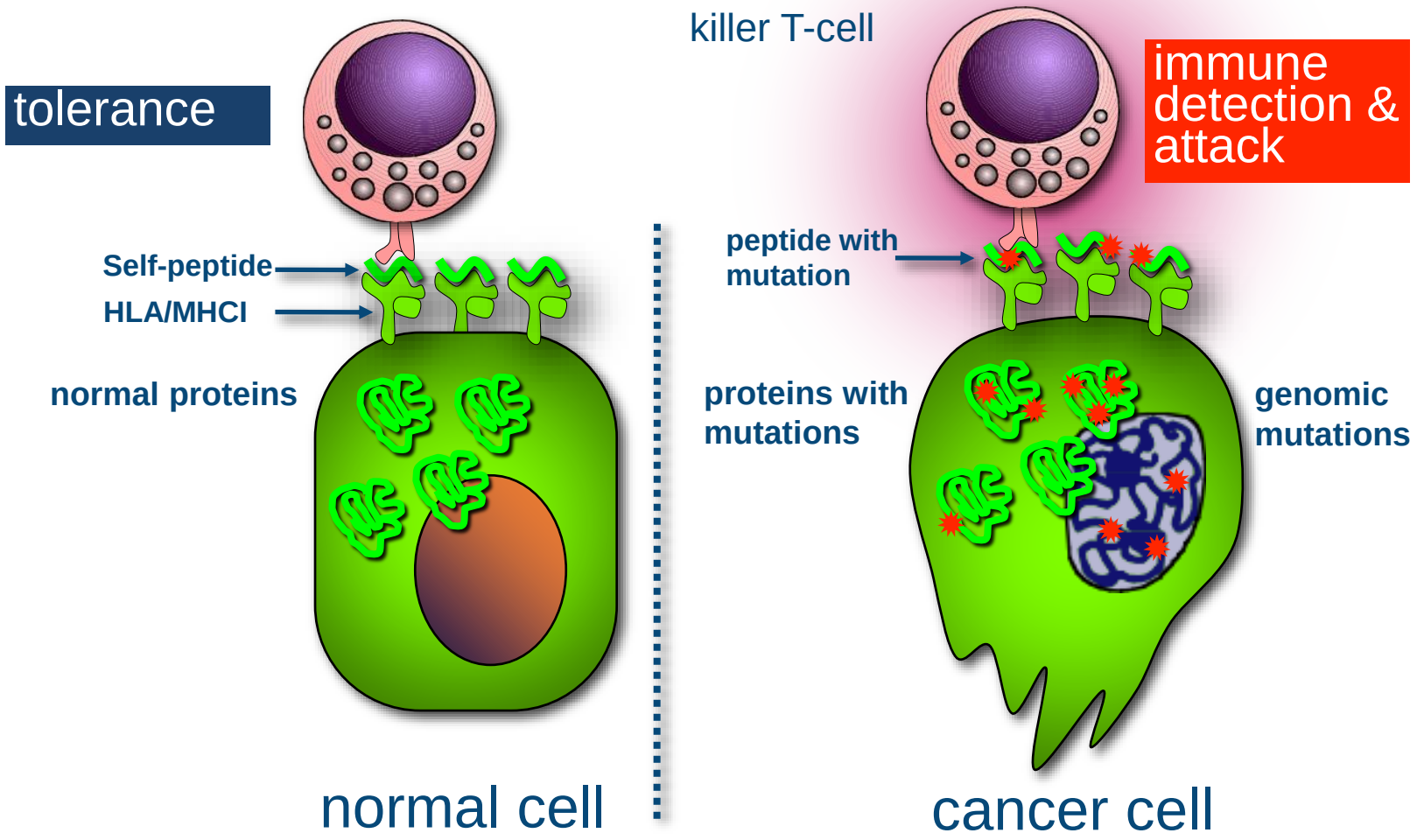
Intervention: 168 adults with histologically confirmed, unresectable or metastatic stage IIIC or IV cutaneous melanoma were assigned to receive TIL therapy or ipilimumab. In the TIL group, patients underwent metastasectomy for TIL retrieval and expansion, followed by hospitalization for administration of nonmyeloablative, lymphodepleting chemotherapy and intravenous infusion of TILs and subsequent high-dose interleukin-2. The primary end point was progression-free survival.



First controlled trial shows proof the therapeutic effect of TIL therapy, the results consistently show about a 25-30% long-term survivors compared to 5-10% with "classic" chemotherapy. Finally, because 1. the logistics of the therapy (autologous ATMP) and 2. outgrowth of TILs does not work in 100% of patients and, most important, 3. inability to generate TILs from other more common tumors that are specifically killing tumor cells, this therapy is still confined to a few expert centers. Note: TILs work in an autologous setting.

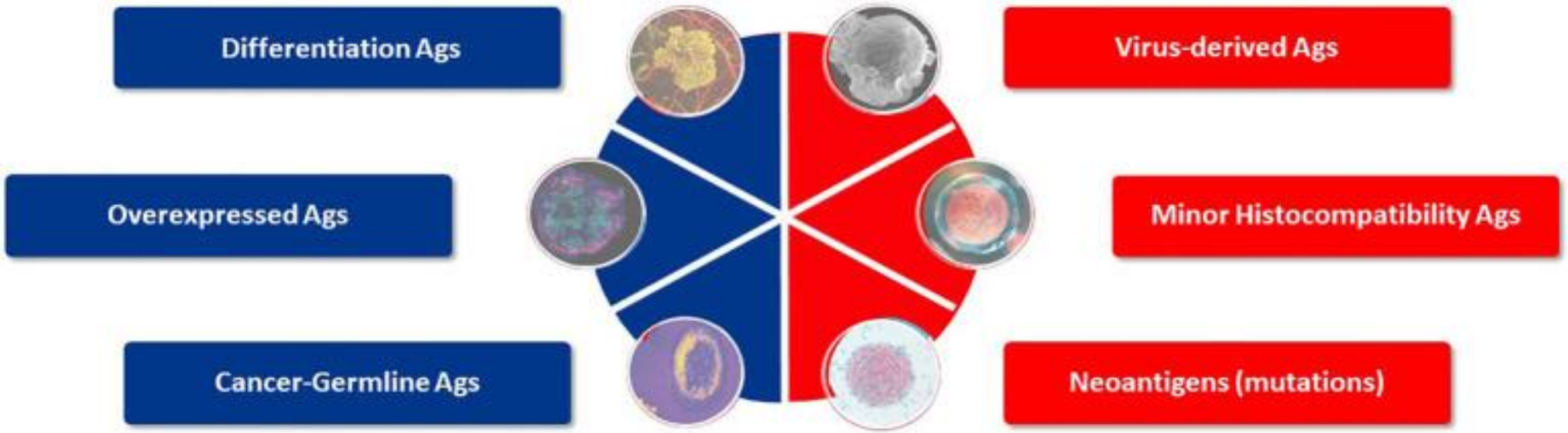
December 8, 2022
N Engl J Med 2022; 387:2113-2125

CANCER MUTATIONAL LOAD vs IMMUNOGENICITY



Passive immunotherapy

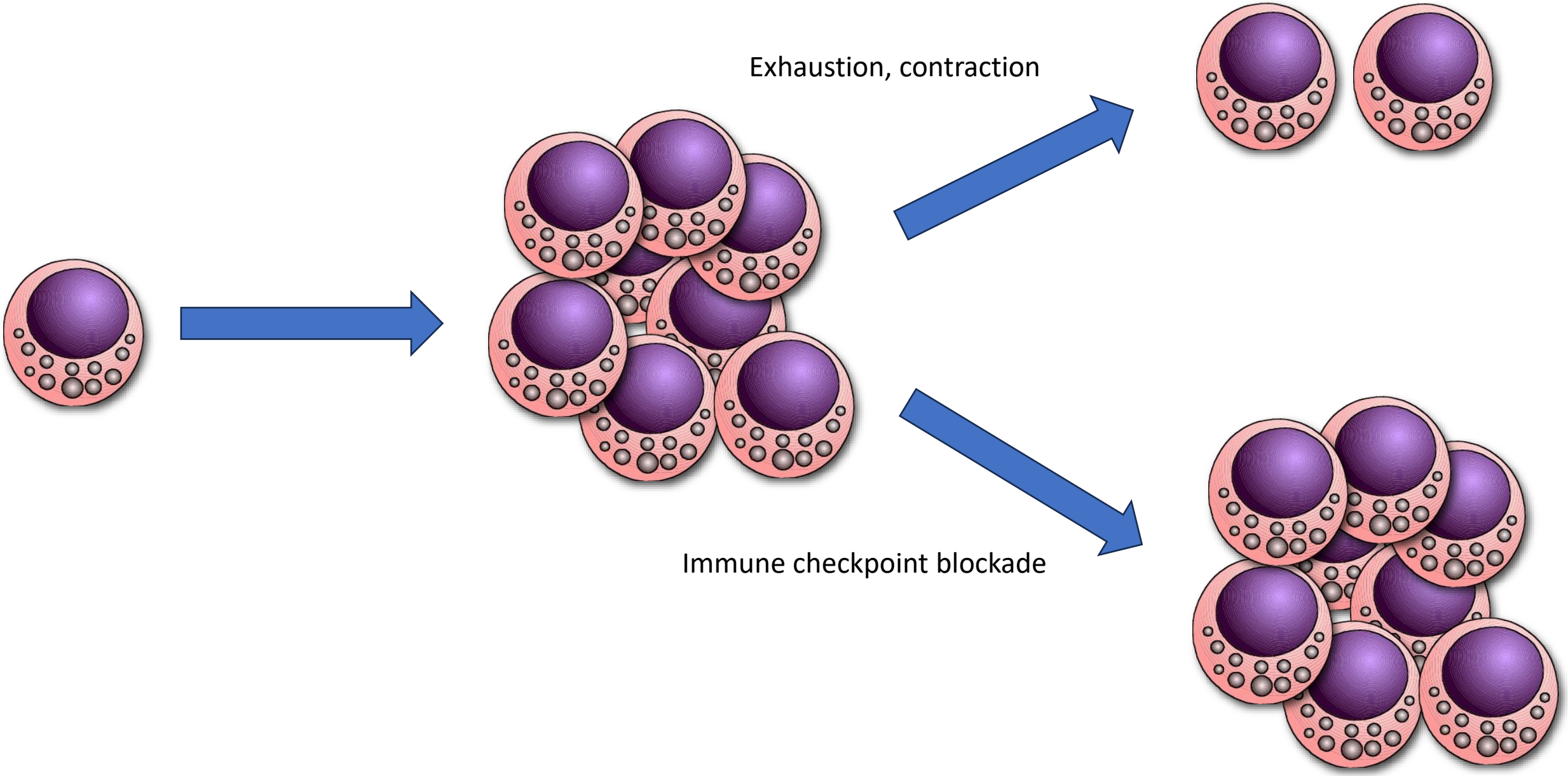
Active immunotherapy



- Autoantigens
- Tolerance

- “Foreign”
- No Tolerance

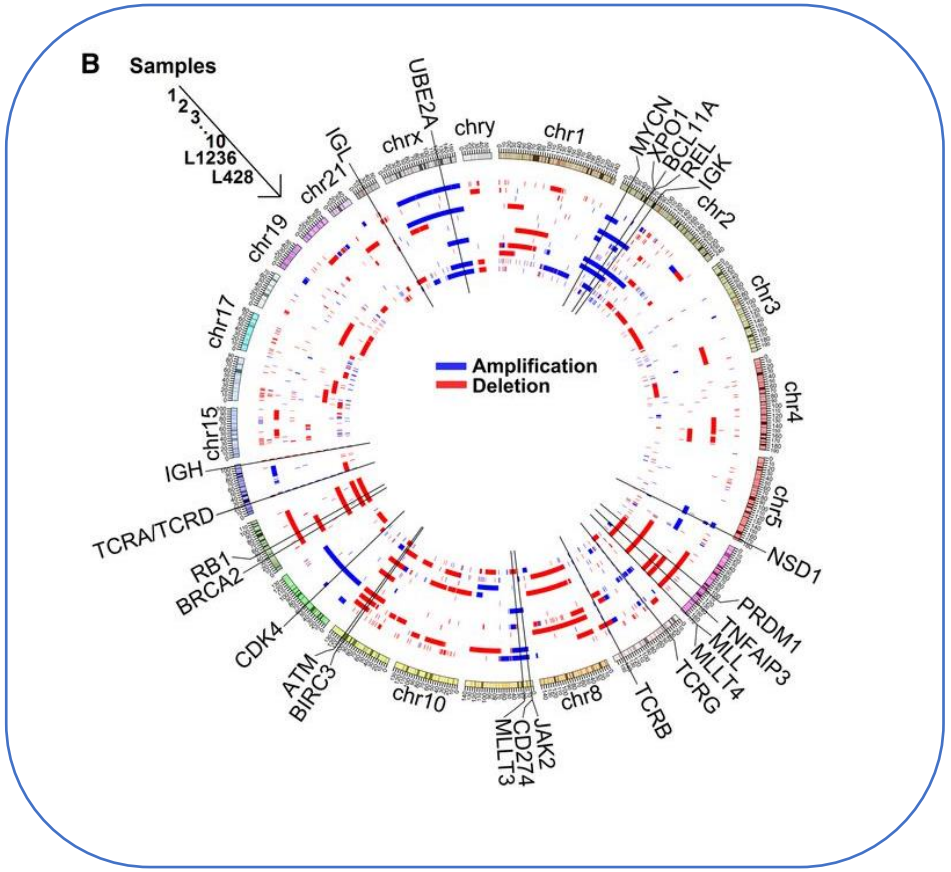
Induction and continuation of immune response

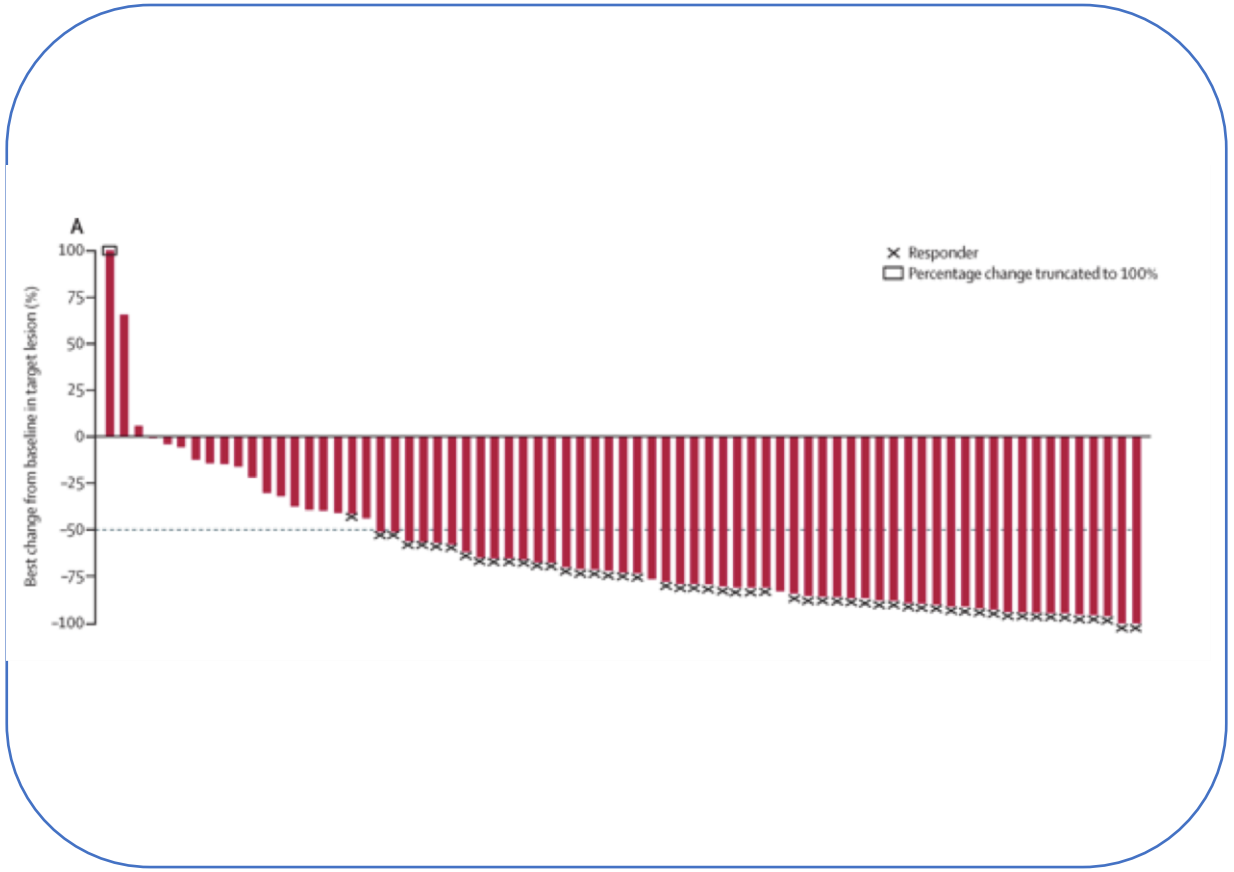


Evidence for immune mediated killing of cancer in humans : 3. immune checkpoint blockers

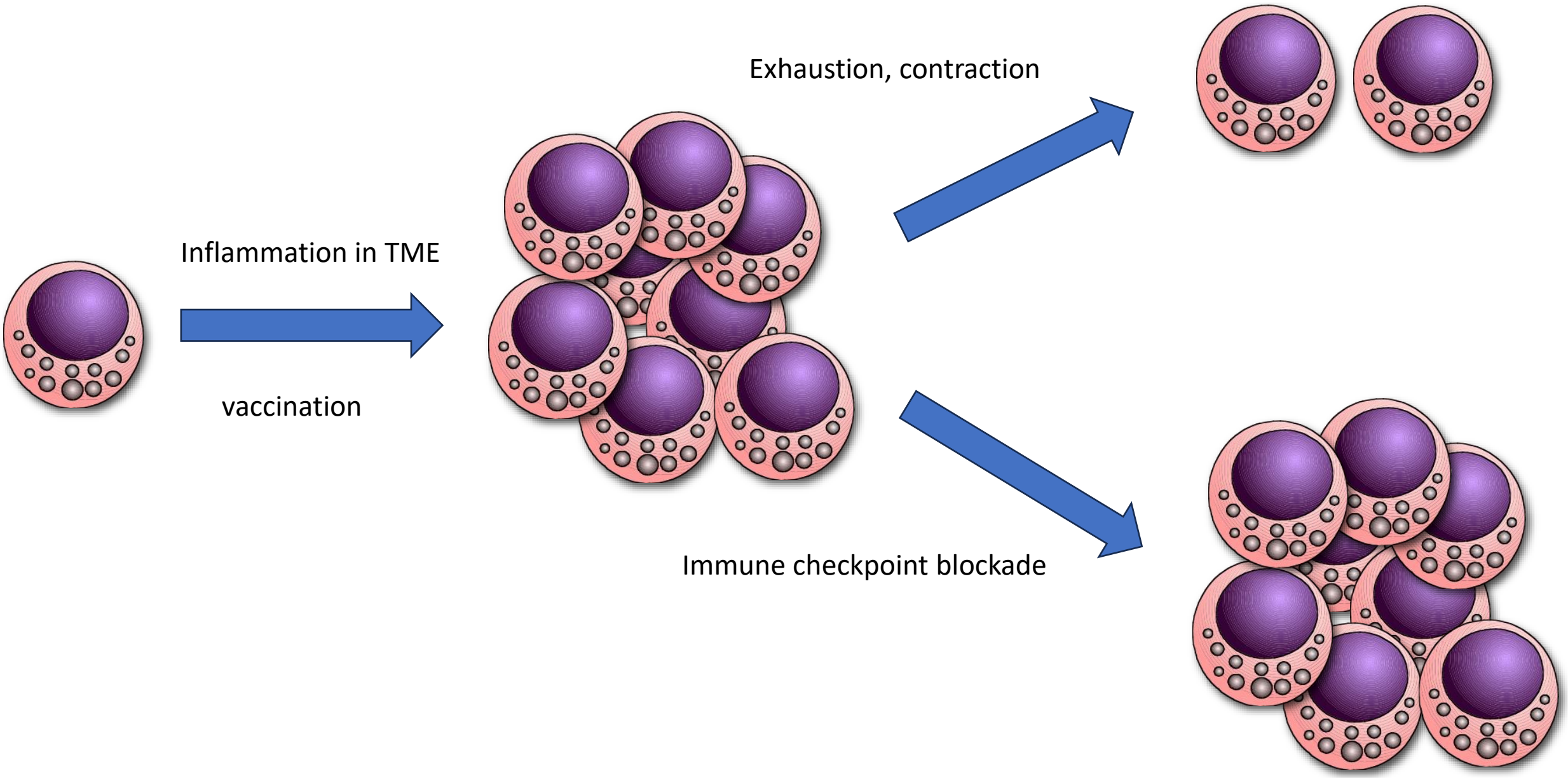
THE LANCET
Oncology
Volume 17, Issue 9, September 2016, Pages 1283-1294

Hodgkin's Disease

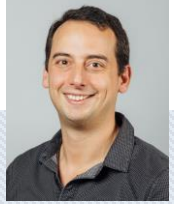


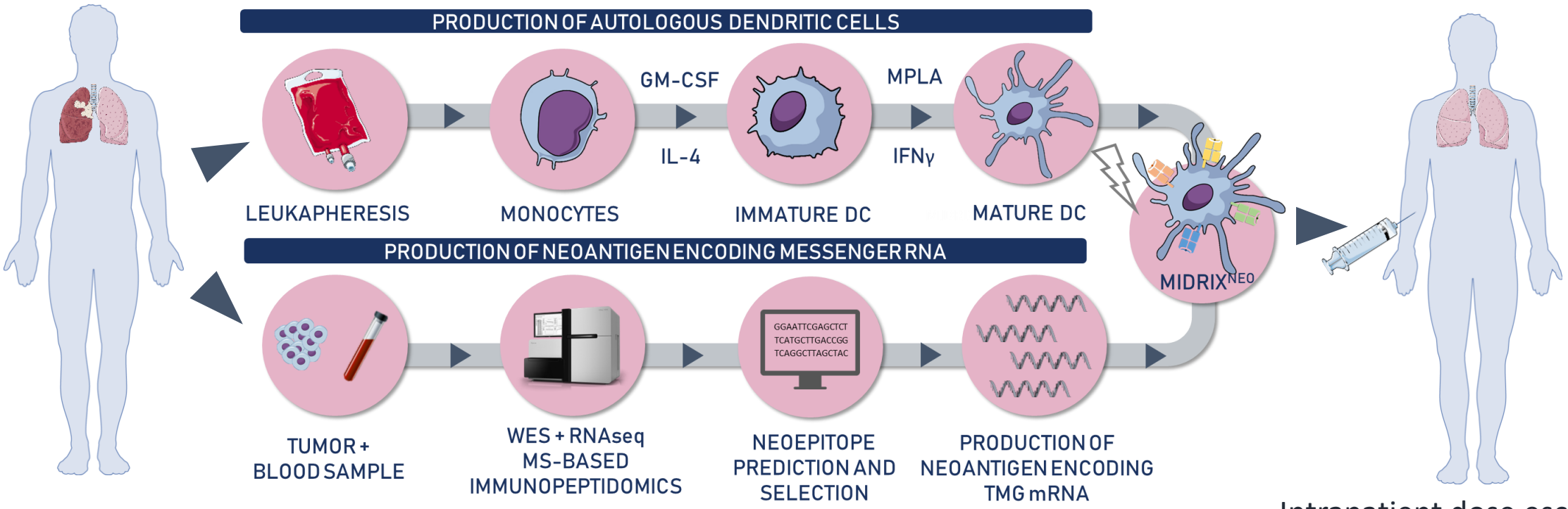


Induction and continuation of immune response



| MIDRIX^{NEO}: ATMP Design



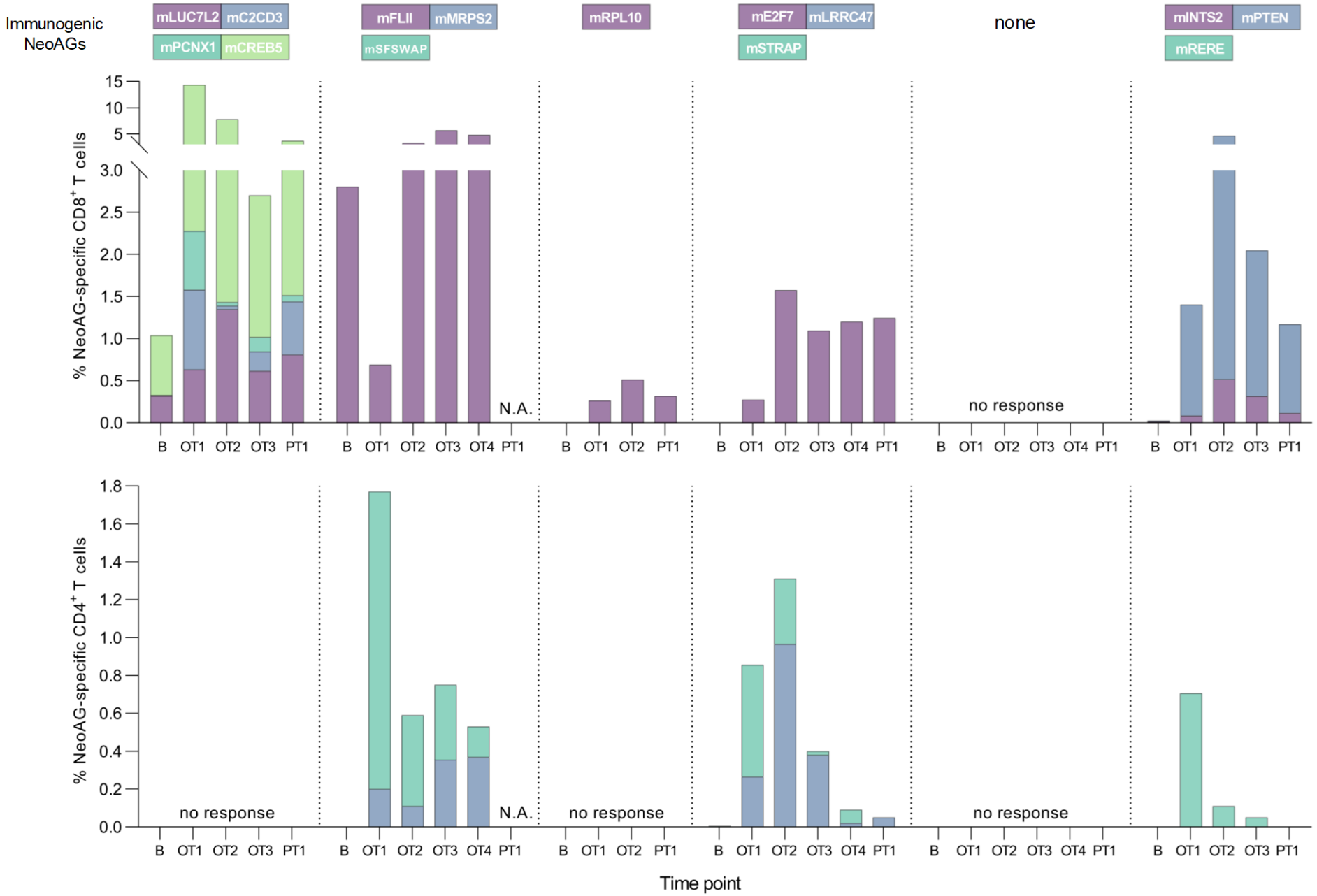



6 patients with resectable NSCLC

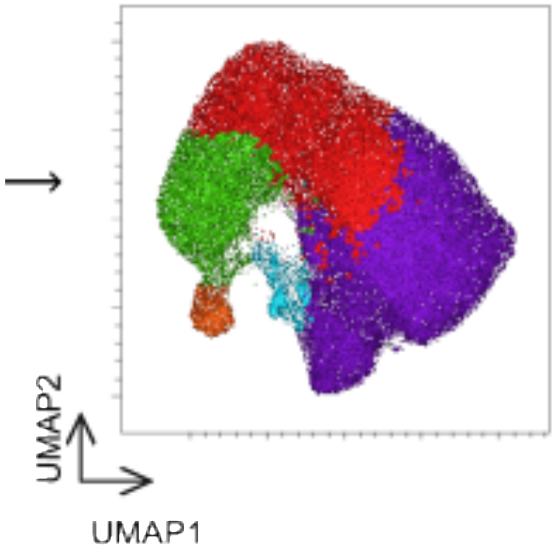
Intrapatient dose escalation
Dose 1 -> Dose 5
$10x10^6$ DC -> $100x10^6$ DC

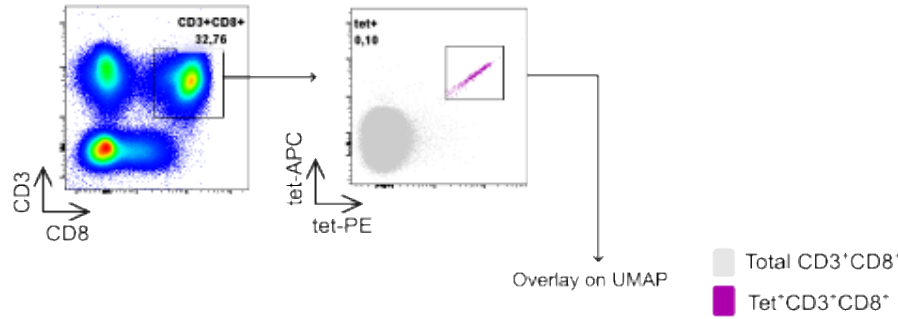
Brabants *et al.* Cytotherapy 2018

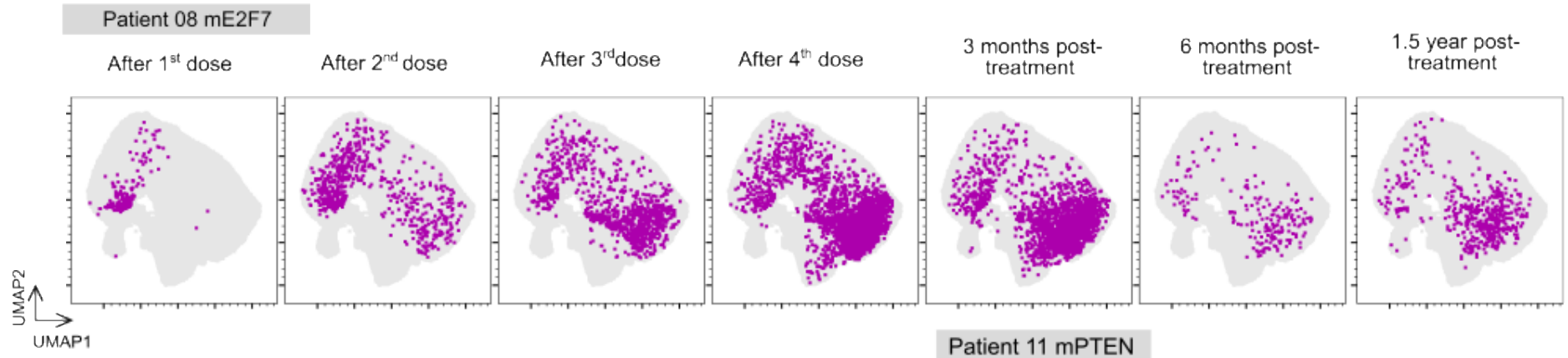
E

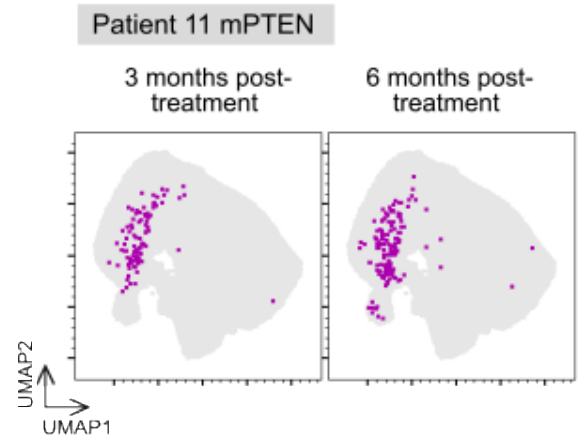


Patient ID	02	03	05	08	10	11


UMAP2
UMAP1


CD3+CD8+
32,76
CD3
CD8
tet+
0,10
tet-APC
tet-PE
Overlay on UMAP
Total CD3⁺CD8⁺
Tet⁺CD3⁺CD8⁺


Patient 08 mE2F7
After 1st dose
After 2nd dose
After 3rddose
After 4th dose
3 months post-treatment
6 months post-treatment
1.5 year post-treatment
UMAP2
UMAP1

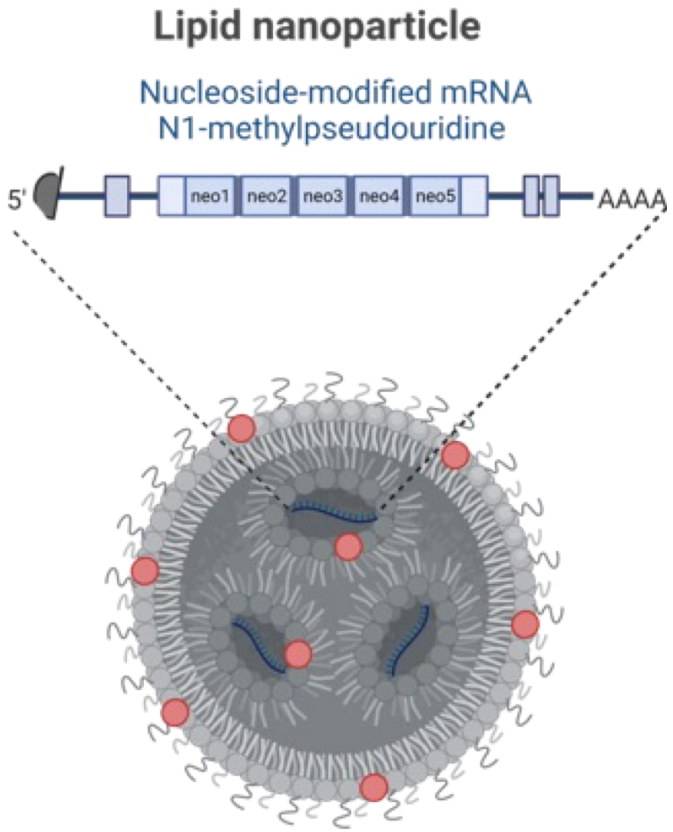

Patient 11 mPTEN
3 months post-treatment
6 months post-treatment
UMAP2
UMAP1

Evidence for immune mediated killing of cancer in humans : 4. neoantigen vaccination

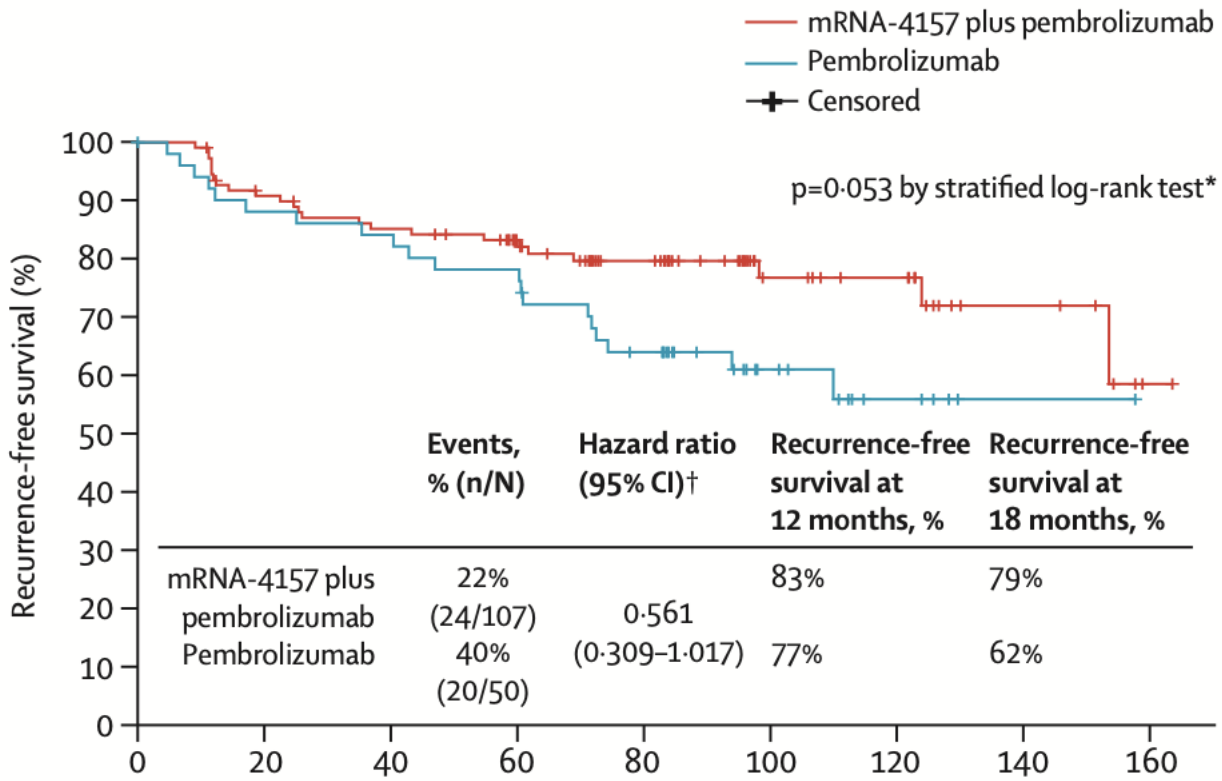
Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study

Lancet 2024.

Jeffrey S Weber, Matteo S Carlino, Adnan Khattak, Tarek Meniawy, George Ansstas, Matthew H Taylor, Kevin B Kim, Meredith McKean,



A

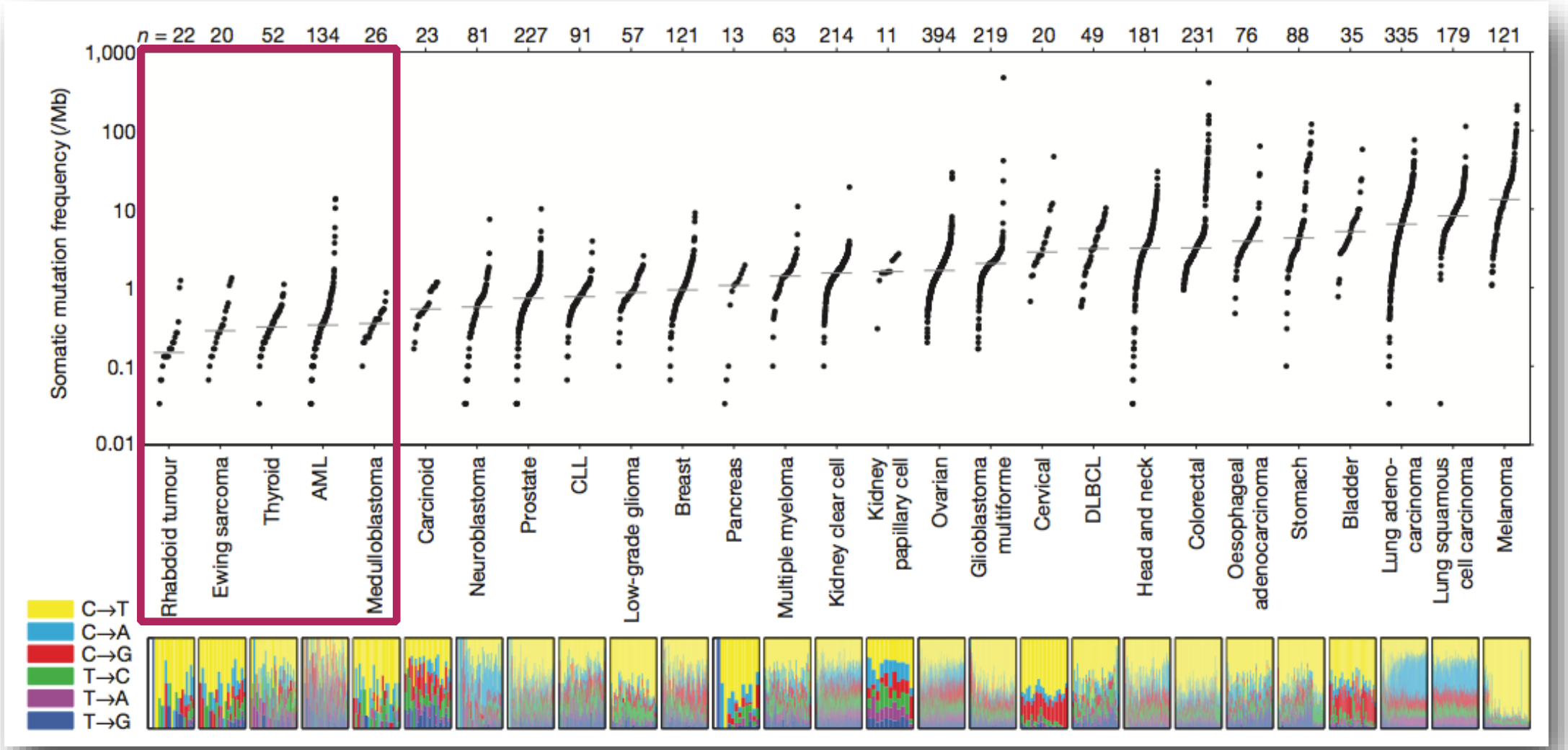


	Events, % (n/N)	Hazard ratio (95% CI)†	Recurrence-free survival at 12 months, %	Recurrence-free survival at 18 months, %
mRNA-4157 plus pembrolizumab	22% (24/107)	0·561 (0·309–1·017)	83%	79%
Pembrolizumab	40% (20/50)		77%	62%

Number at risk

mRNA-4157 plus pembrolizumab	107 (0)	92 (5)	85 (6)	73 (16)	49 (37)	24 (61)	20 (65)	8 (76)	1 (82)
Pembrolizumab	50 (0)	42 (2)	40 (2)	37 (2)	28 (4)	13 (18)	6 (24)	1 (29)	0 (30)

CANCER MUTATIONAL LOAD vs IMMUNOGENICITY



Lawrence et al, Nature, July 2013

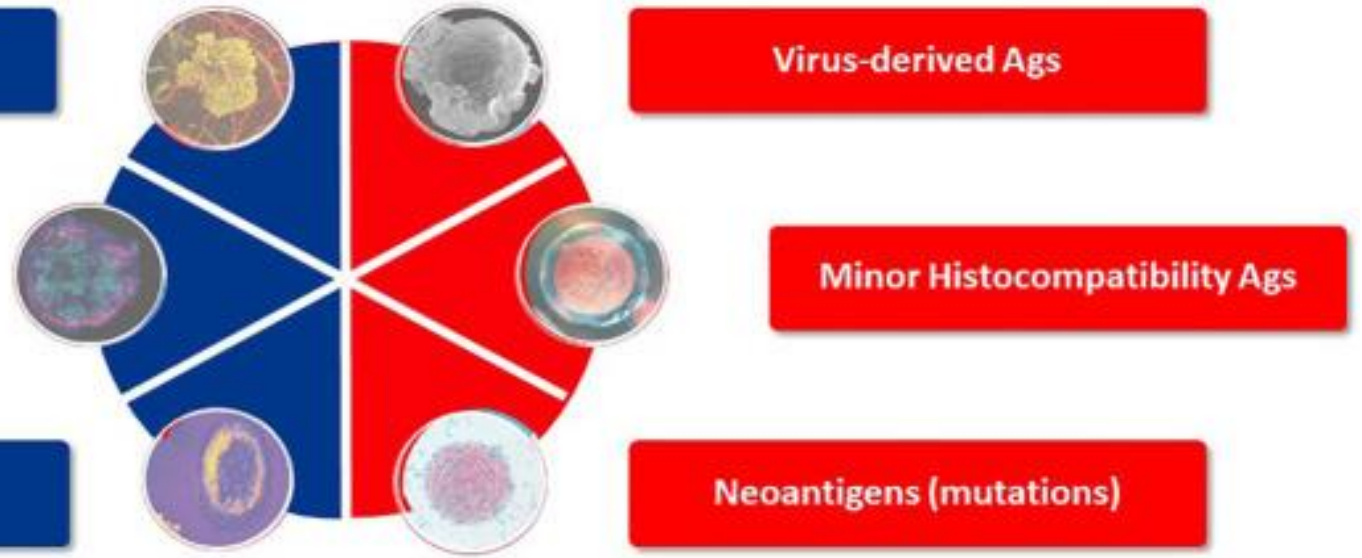
Passive immunotherapy

Active immunotherapy

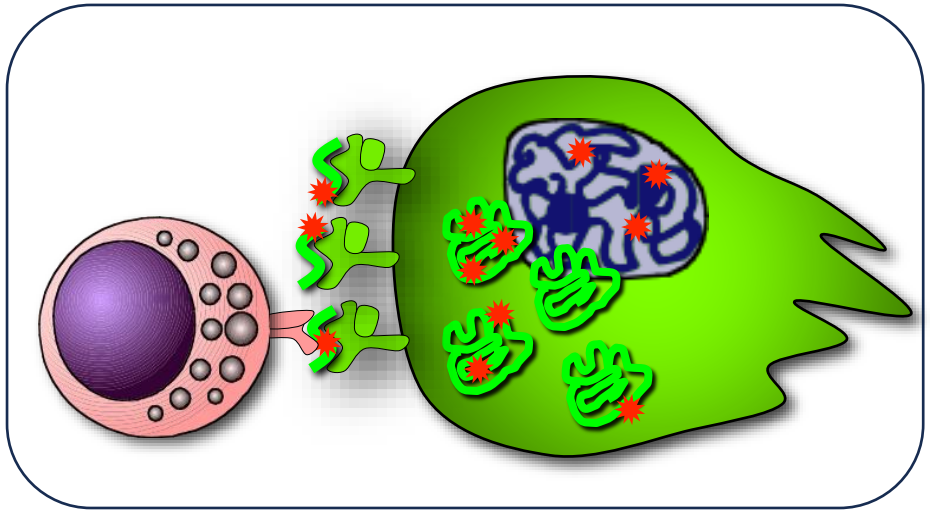
CD19, BCMA

WT1
NY-ESO-1

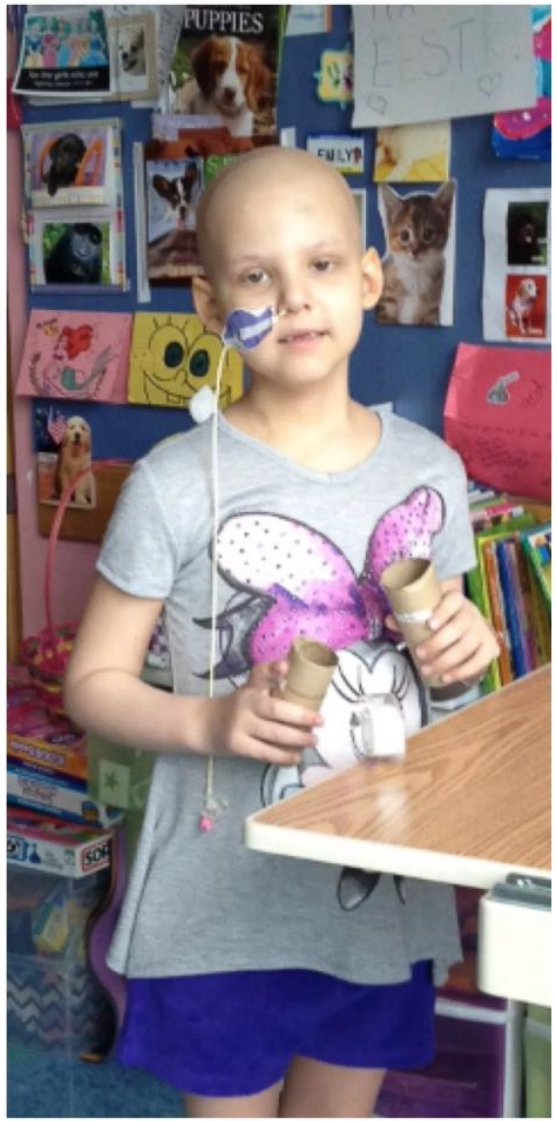
MAGE

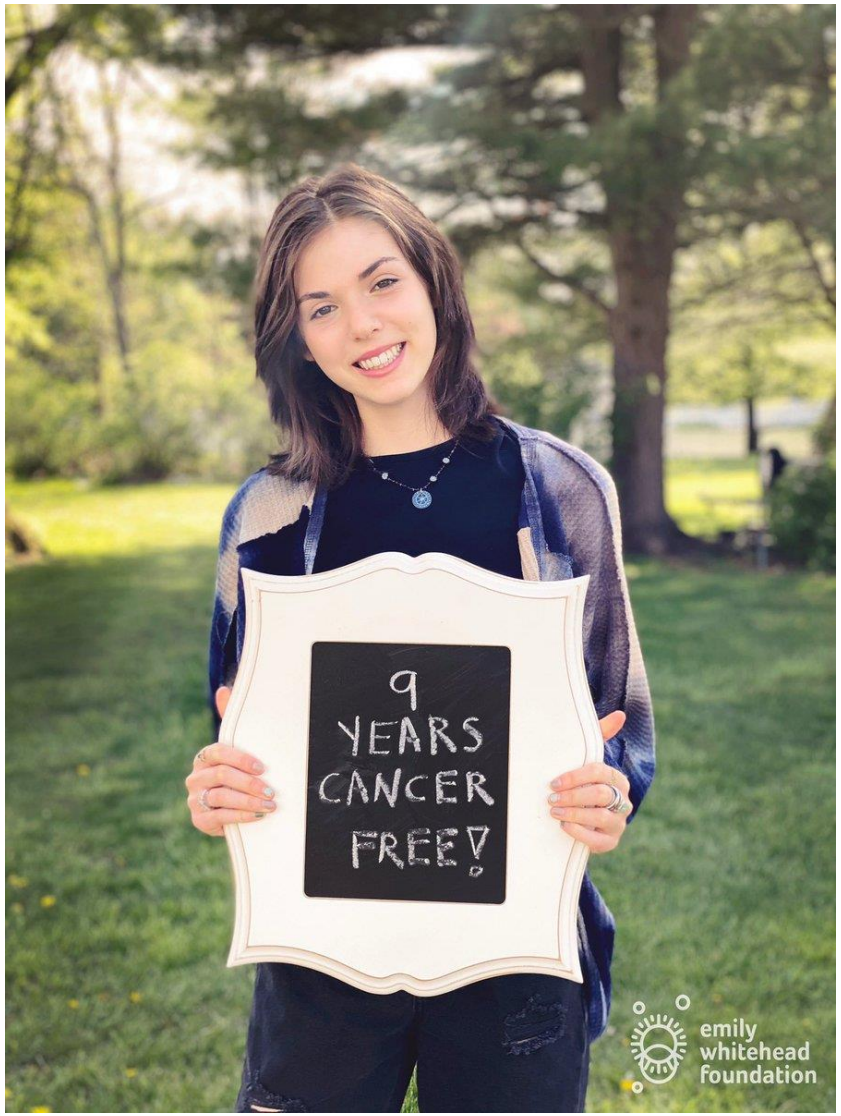


- Cytoplasm or membrane
- HLA restriction

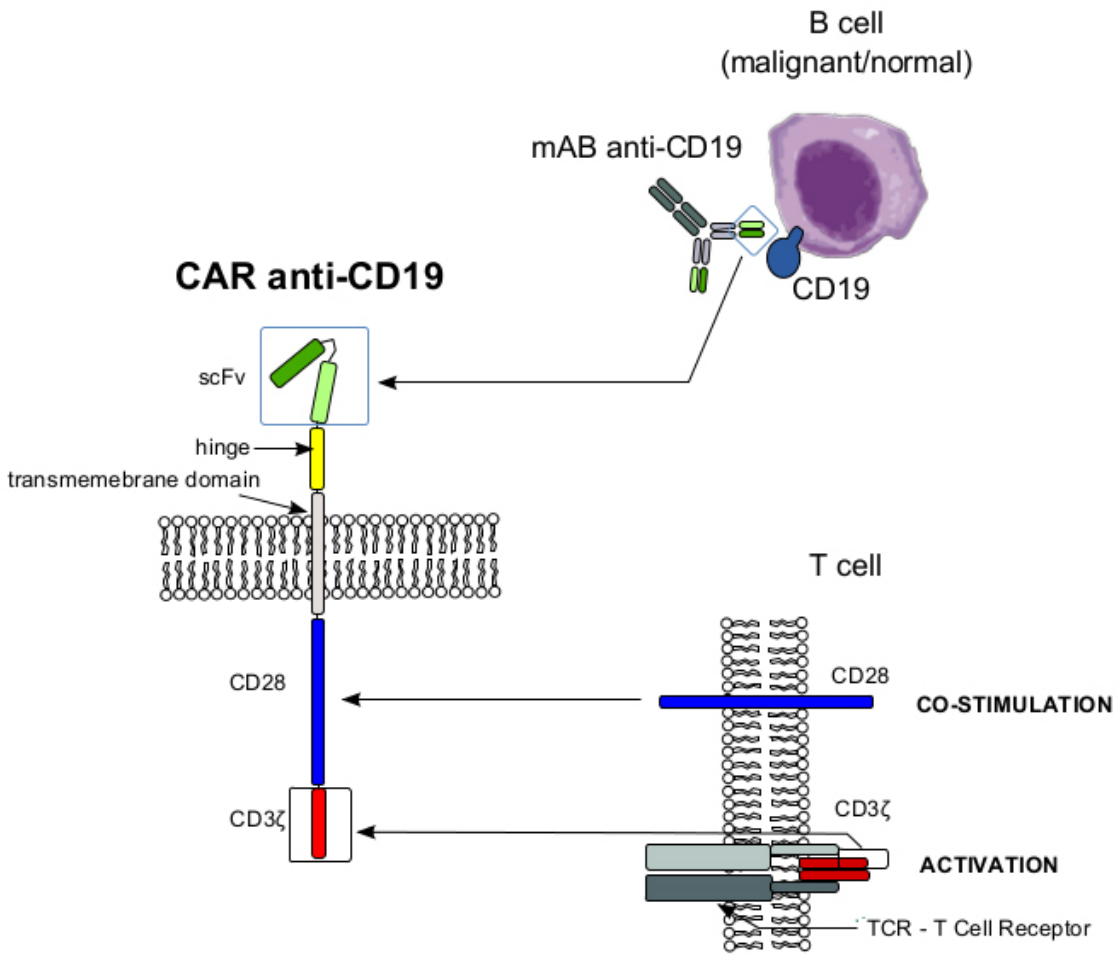


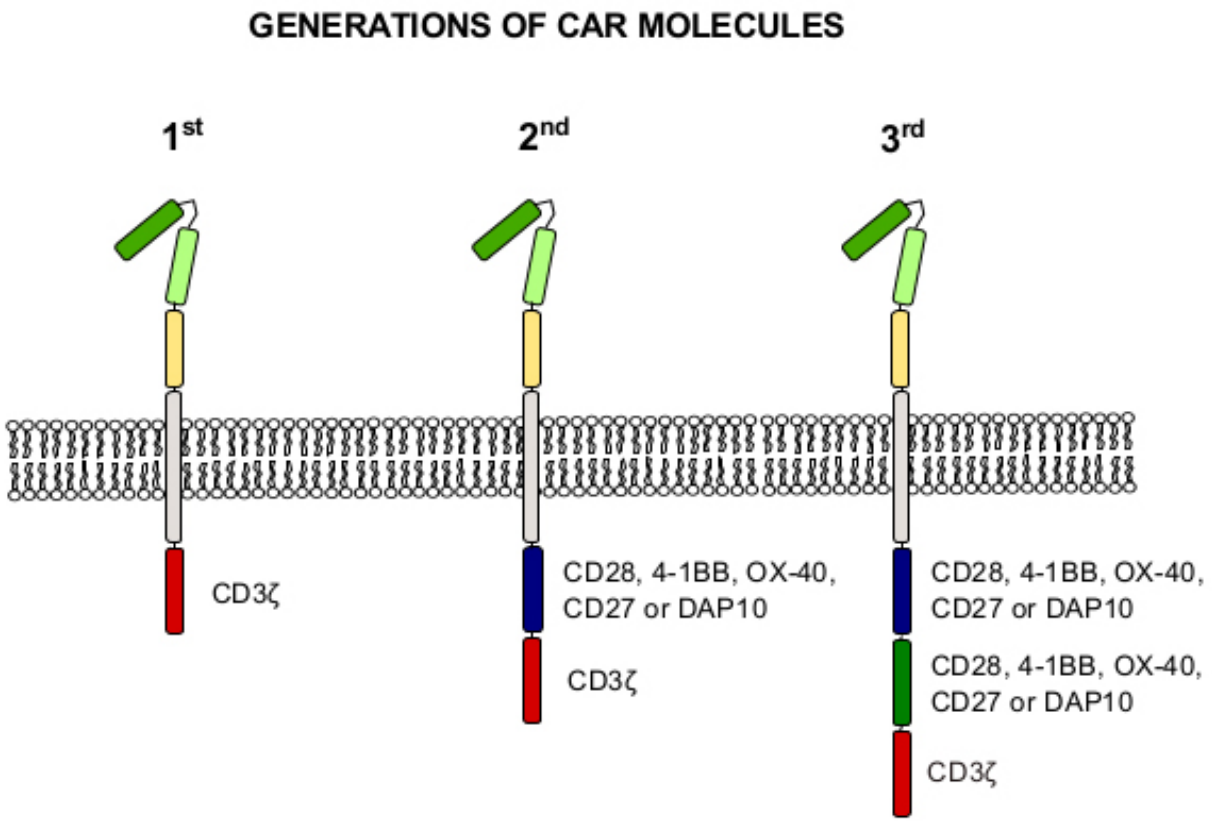
Chimeric antigen receptor T cells





Chimeric Antigen Receptors





CAR-T Cell Therapy for malignancies

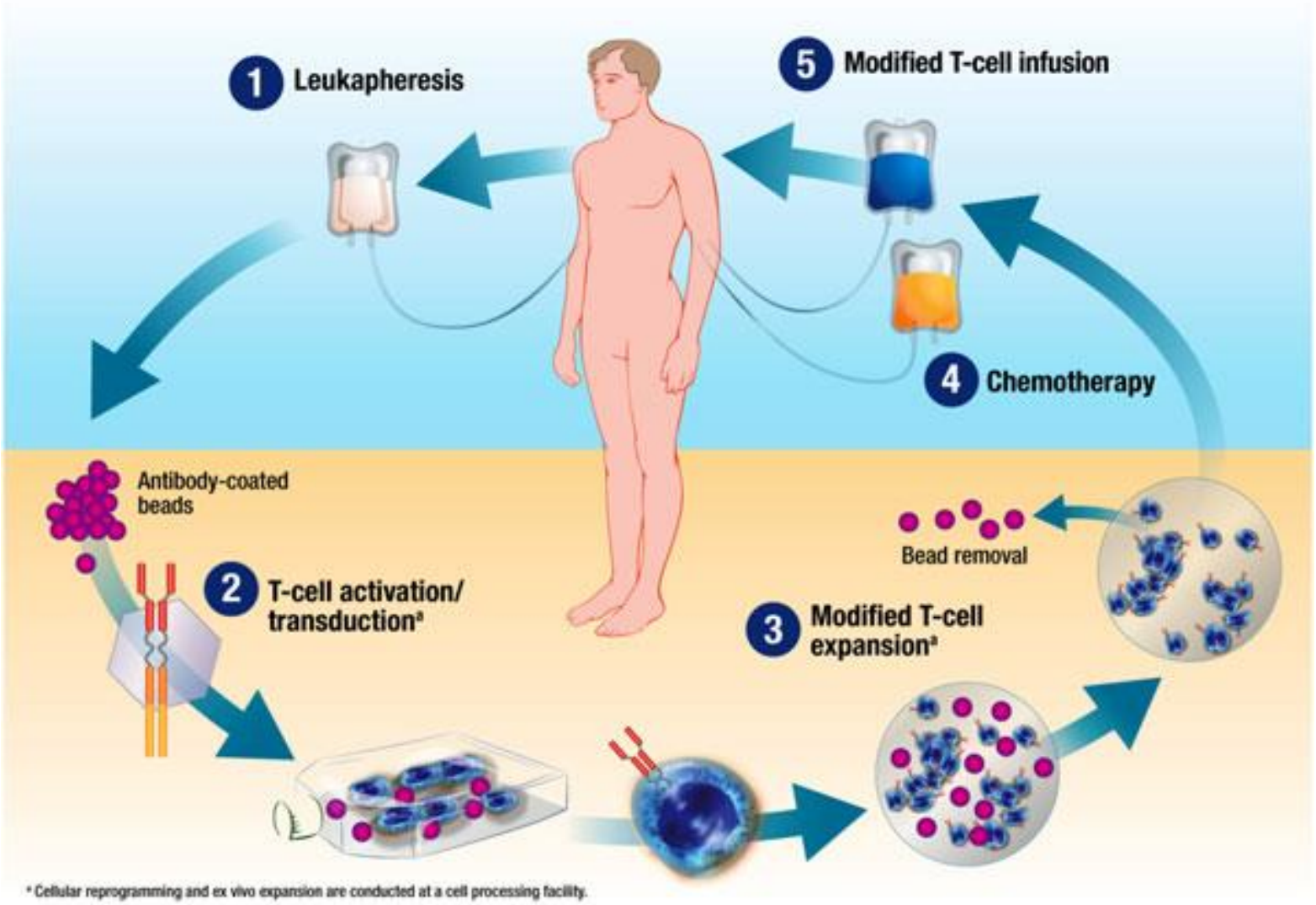


Table 1. **Summary of FDA-approved CAR-T cell product manufacturing**

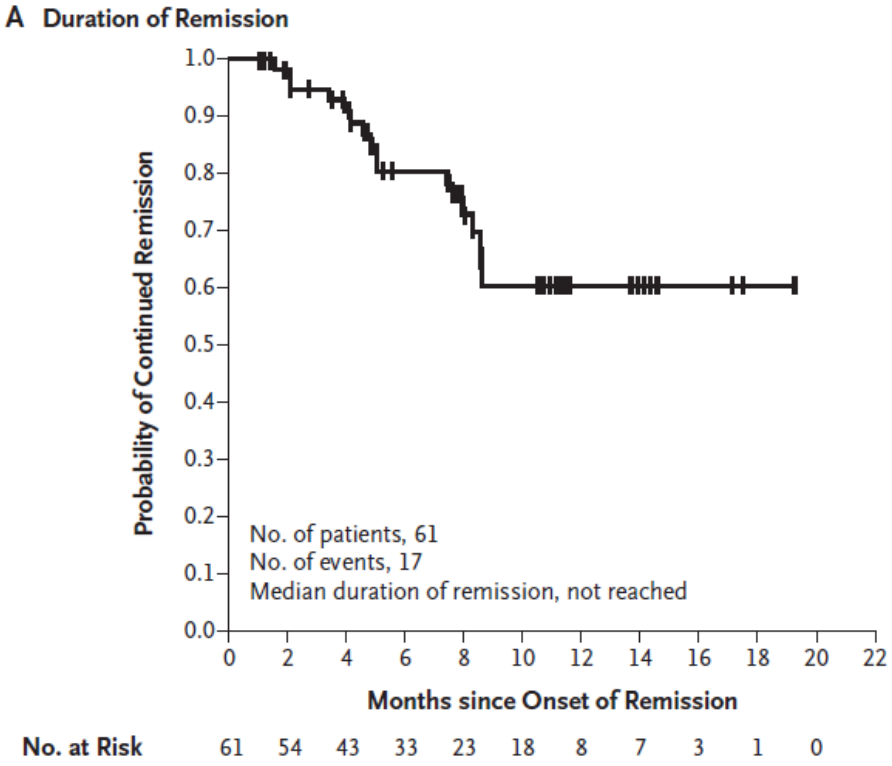
Product name	Commercial name	Cell population prior to T-cell activation	Starting leukopak storage	Transgene integration method	Final product storage	References
Tisa-cel	Kymriah	Enriched T cells	Frozen	Lentivirus	Frozen	Fowler et al. (2022), Maude et al. (2018), Schuster et al. (2019), Tyagarajan et al. (2019)
Axi-cel	Yescarta	PBMCs (from Ficoll gradient enrichment)	Fresh	Retrovirus	Frozen	Jacobson et al. (2022), Locke et al. (2022), Roberts et al. (2018)
Brexu-cel	Tecartus	CD19-depleted and CD4/CD8-enriched T cells	Fresh	Retrovirus	Frozen	Mian and Hill (2021), Wang et al. (2020)
Liso-cel	Breyanzi	CD4 and CD8 T cells separately	Not reported	Lentivirus	Frozen	Kamdar et al. (2022), Sehgal et al. (2022), Teoh and Brown (2022)
Idecabtagene vicleucel	Abecma	PBMCs	Not reported	Lentivirus	Frozen	Al Hadidi et al. (2023), Hansen et al. (2023), Raje et al. (2019)
Ciltacabtagene autoleucel	Carvykti	Enriched T cells	Frozen	Lentivirus	Frozen	Berdeja et al. (2021); Committee for Medicinal Products for Human Use (2022); San-Miguel et al. (2023)

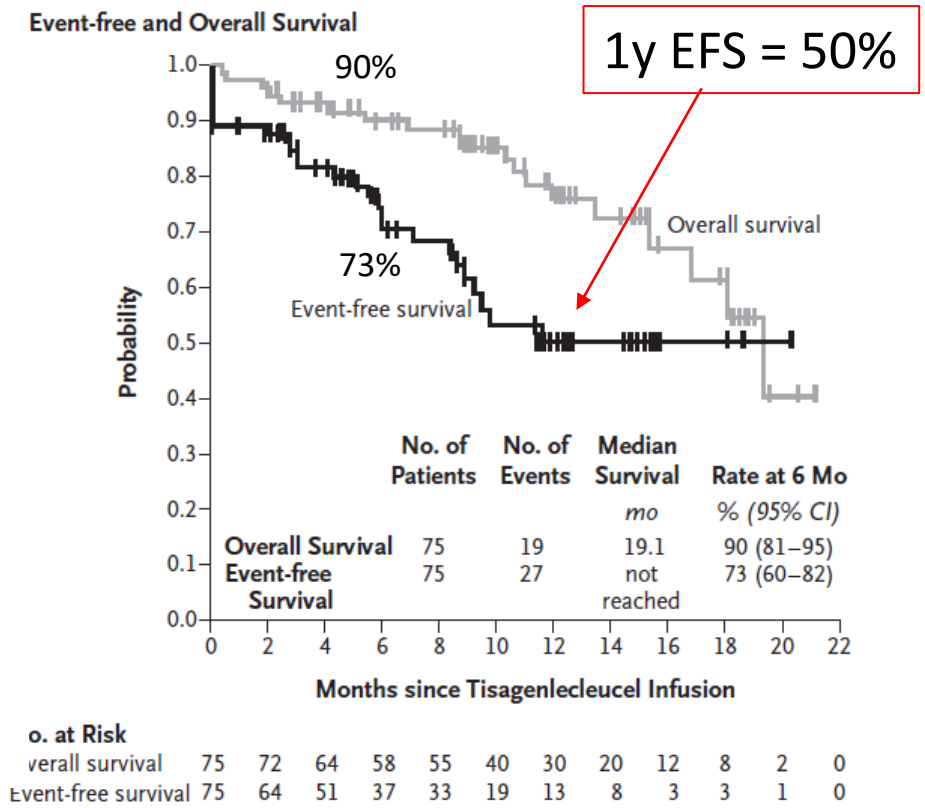
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Me C.H. June, B.L. Levine, P. Wood, T. Taran, K. Sen, D. Lebwohl, M.A. Puls

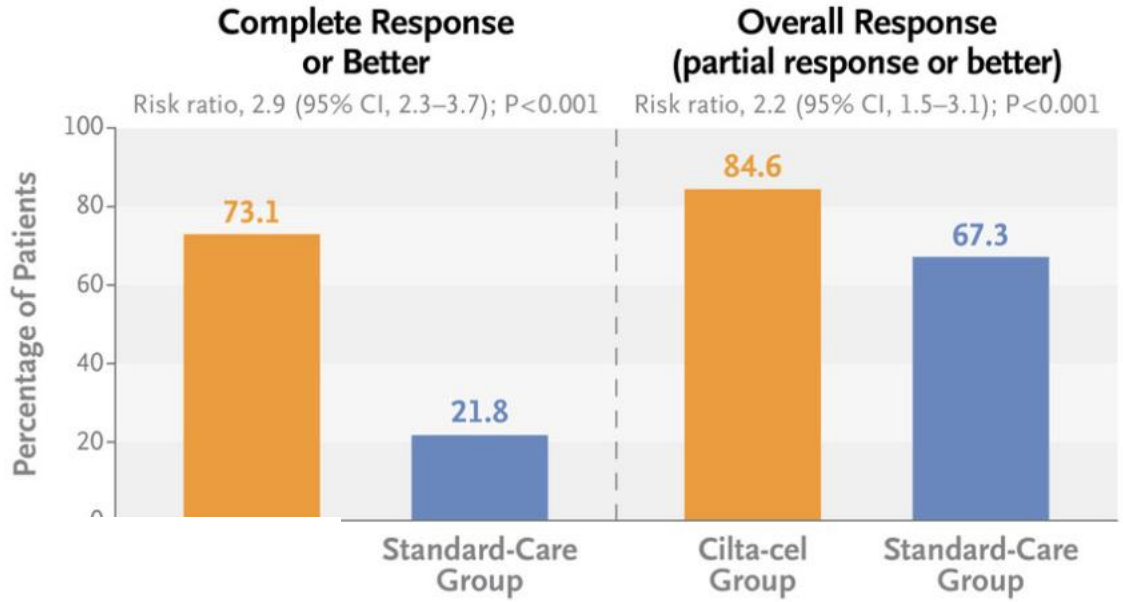


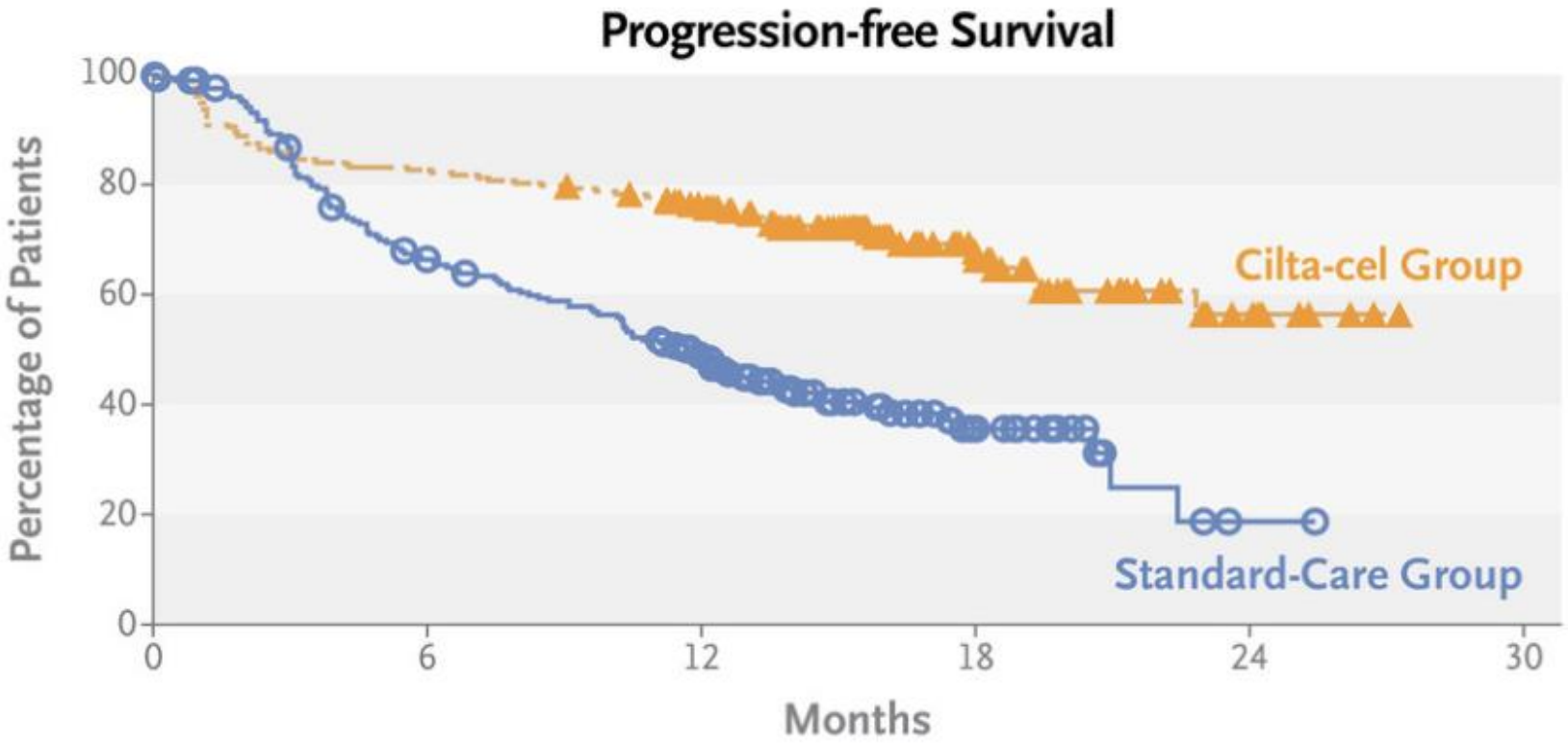


ORIGINAL ARTICLE

Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

Jesús San-Miguel, M.D., Ph.D., Binod Dhakal, M.D., Kwee Yong, Ph.D., Andrew Spencer, M.D., Sébastien Anguille, M.D., Ph.D., María-Victoria Mateos, M.D., Ph.D., Carlos Fernández de Larrea, M.D., Ph.D., Joaquín Martínez-López, M.D., Philippe Moreau, M.D., Ph.D., Cyrille Touzeau, M.D., Xavier Leleu, M.D., Irit Avivi, M.D., et al.





Immune therapy : CAR-T

Side effects (acute)

- CRS
- ICANS
- Infections
- cytopenias

Side effects (chronic)

- B cell depletion
- Hypogamma
- Cytopenias
- Infections

Durable remissions

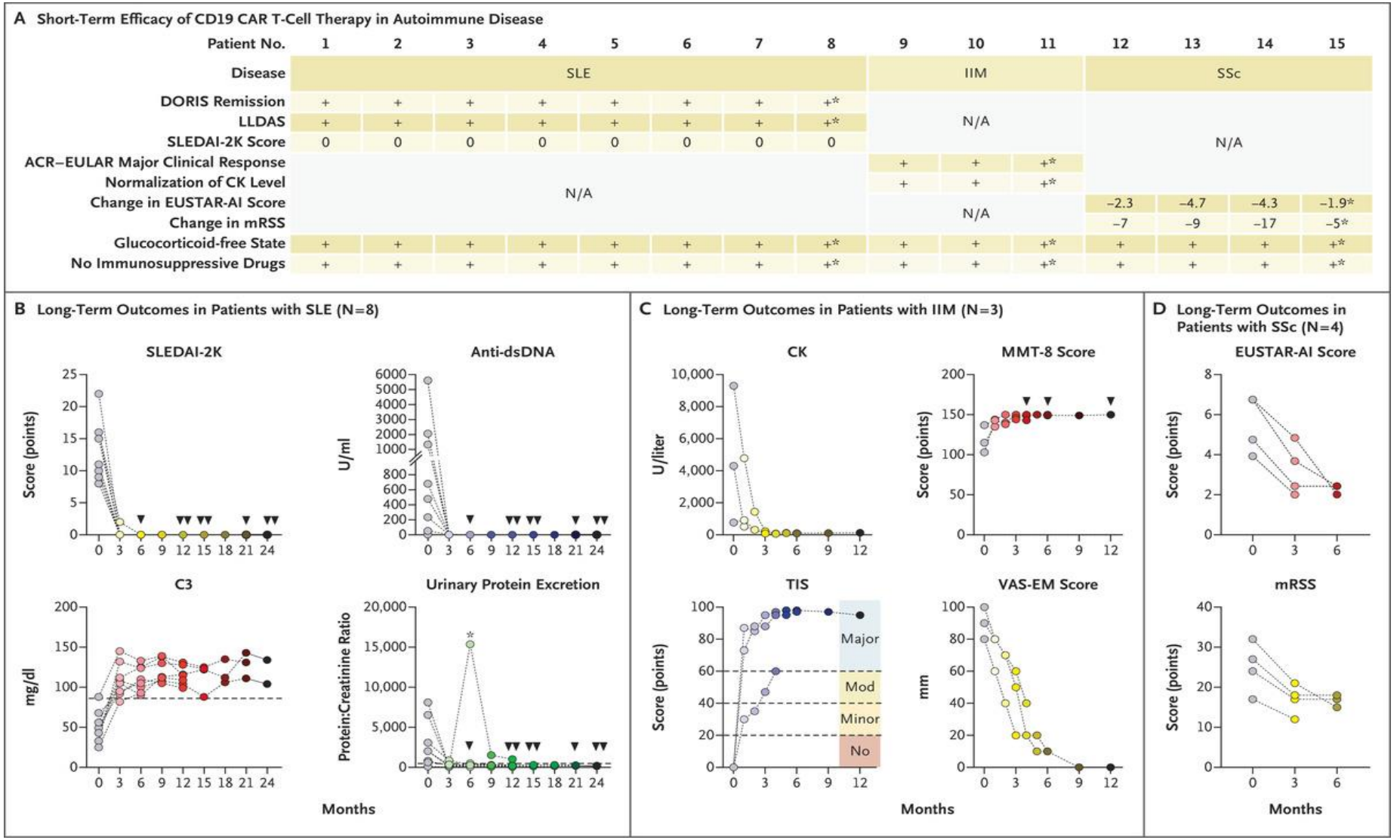
- Depth of initial reponse
- Malignancy type
  - Potential cure for pediatric B-ALL and B cell lymphoma (adult)
  - Relapse even after MRD - CR is frequent in adult ALL en MM
- Tumour burden
- CAR-T levels
- Target antigen expression

CAR-T future optimizations

- Exclusion of Treg, CD4-CD8 ratio
- Short culture to enrich for Tscm
- Point-of-care production
- Bispecific CAR-T
- “humanized” CAR
- Treatment earlier in disease process
- Combine with ICB, cytokines

- (Off the shelf) allogenic CAR-T
- Conditional CAR
- Super CAR-T cells
  - Overexpression: c-jun,..
  - knock-out: PD-1,..

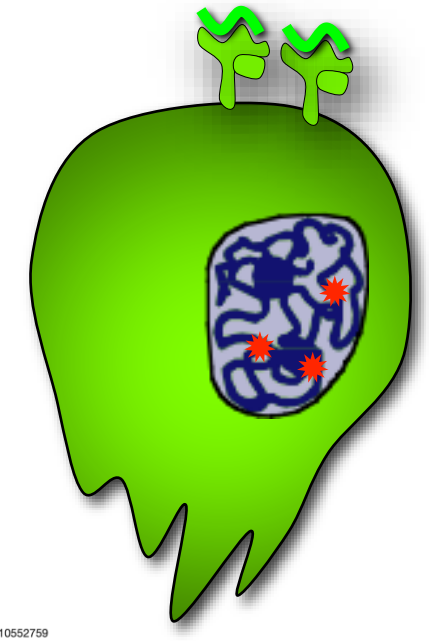
CAR-T Cell Therapy for Autoimmune diseases

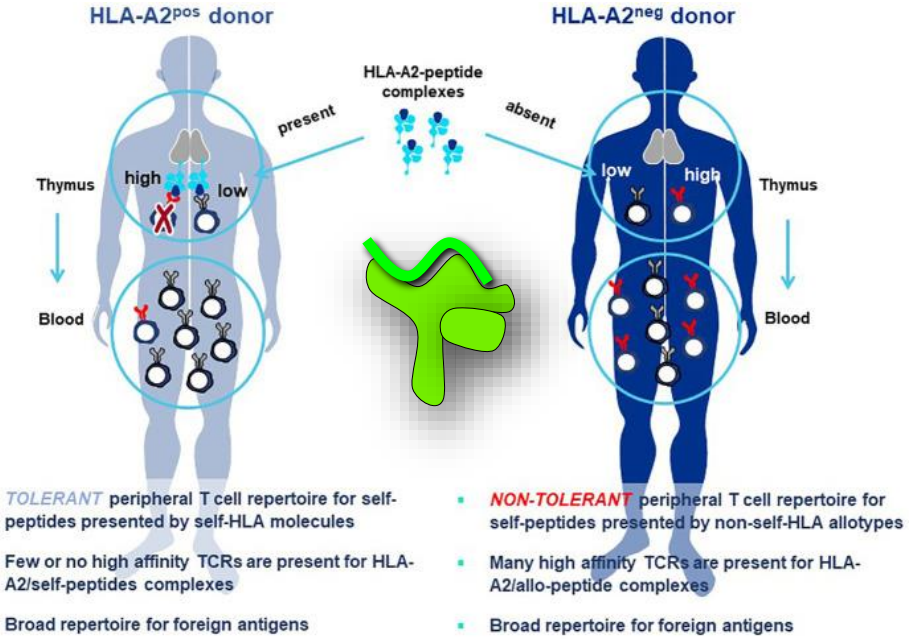


Müller et al. N Engl J Med 2024;390:687-700.

Targeting intracellular autoantigens (WT1 for AML)

AML blasts (x donors) → HLA Ligandome WT1 → Isolation of HLA-peptide+ T cells (healthy donor) → Generate WT1 specific TCR transgenic T cells





Front Oncol. 2023; 13: 1216829. PMCID: PMC10552759
Published online 2023 Sep 21. doi: 10.3389/fonc.2023.1216829 PMID: 37810959

Evolution by innovation as a driving force to improve TCR-T therapies

Dolores J. Schendel[&1,2,*]

Advanced cell therapy

Thank you!

Bart Vandekerckhove
Ghent University