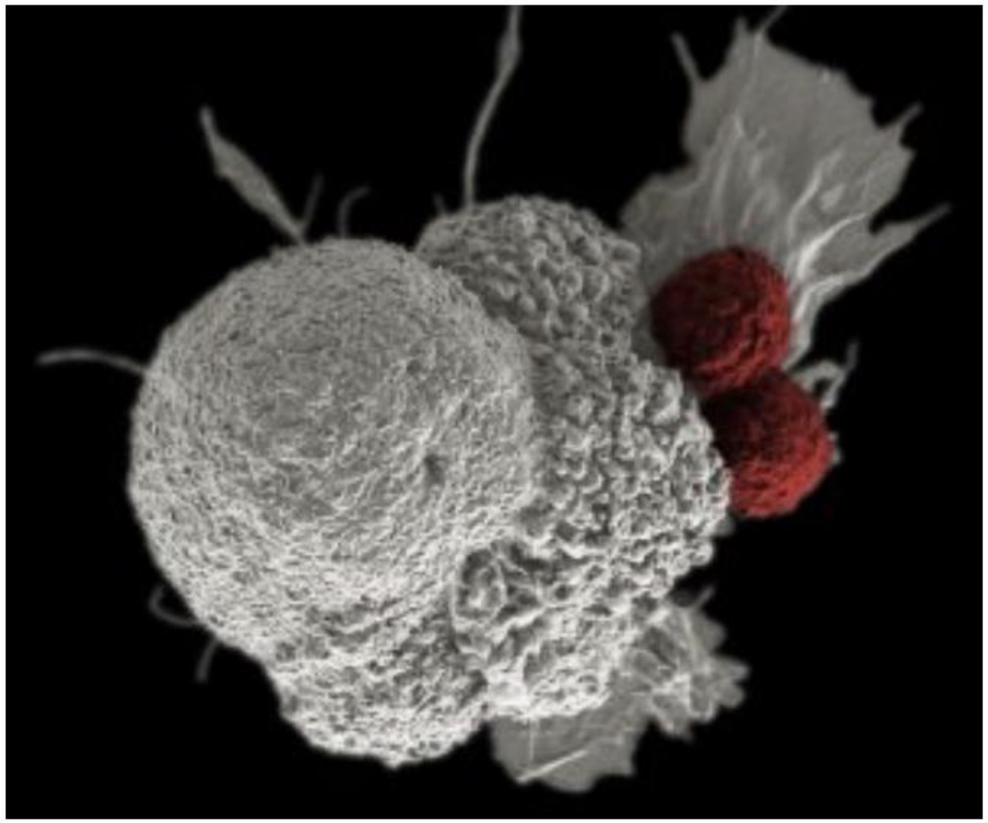
Sneak Preview to the Future—Targeted Immunotherapy (Cellular Therapy, modified antibodies and cancer vaccines)



Electron micrograph of T cells (red) attacking cancer cells (white). Source: National Cancer Institute Duncan Comprehensive Cancer Center at Baylor College of Medicine

Jared Weiss, MD

Professor of Medicine, Section Chief of Thoracic and Head/Neck Oncology

UNC Lineberger Comprehensive Cancer Center

NORTH CAROLINA Oncology Association

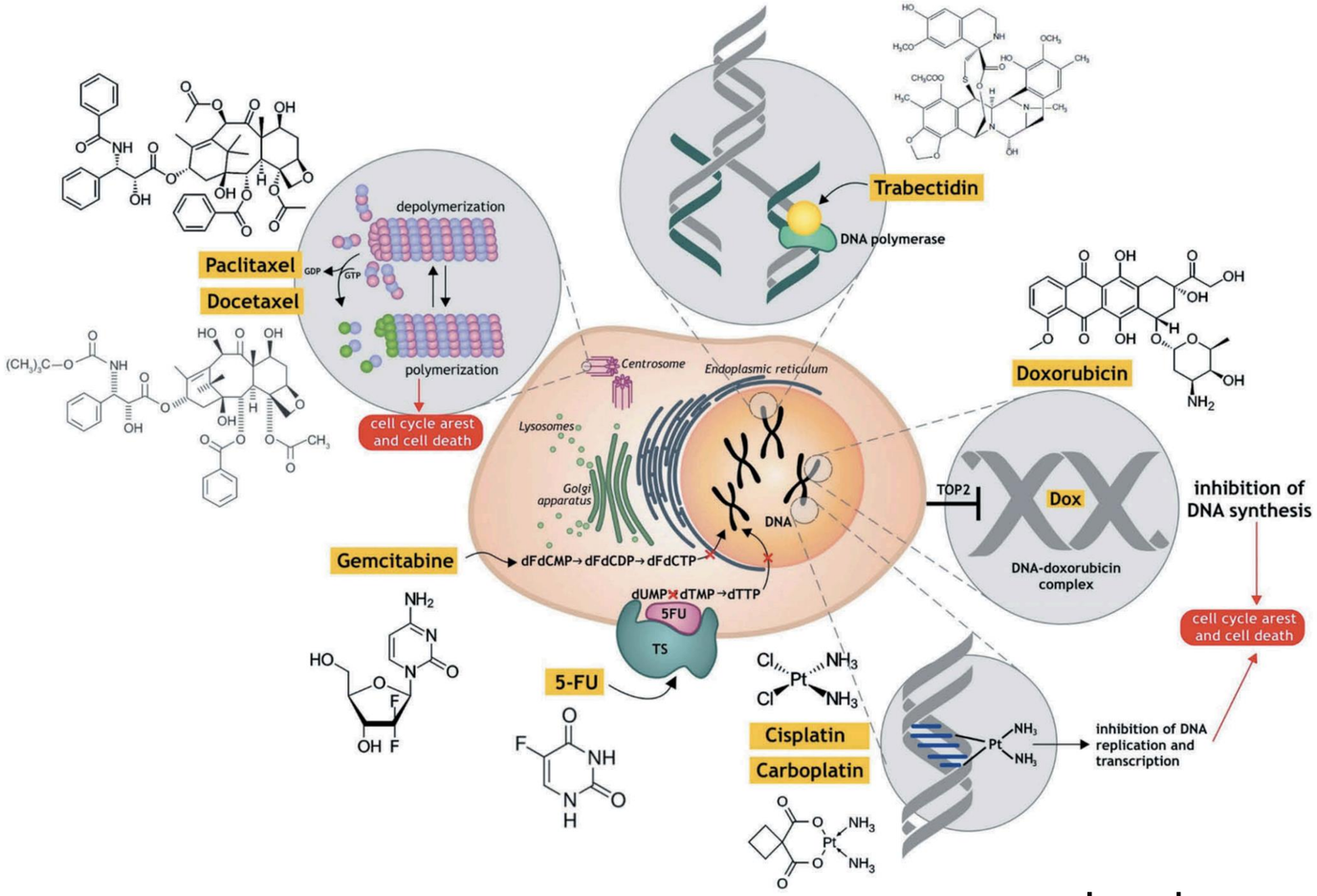
Disclosures

- Full COI can be found at https://coi.asco.org/share/QQC-WTX6/Jared%20Weiss
- Related to Content:
    - Industry: Merck (KN12), Iovance (TIL for NSCLC), Amgen (Tarlatamab SPP)
    - UNC Products: LCCC1804 (PANDA-VAC), LCCC2115-ATL (GD2 CART), LCCC2060-ATL (CSPG4 CART), NUT discovery

Introduction: What we have now

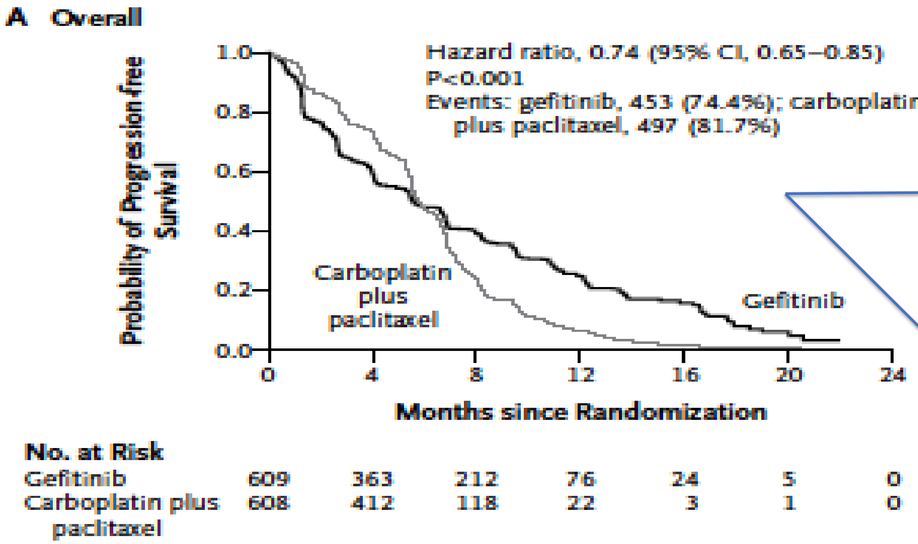
NORTH CAROLINA
Oncology Association

Chemotherapy

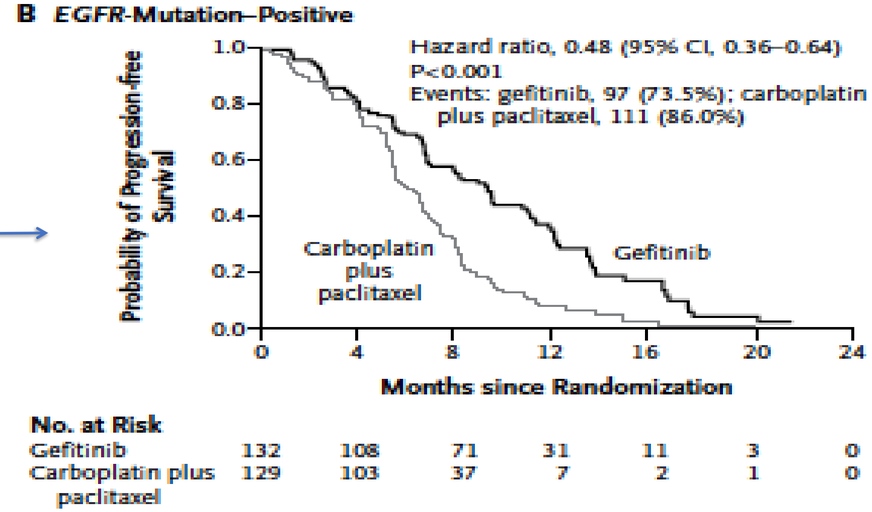


Larionova, Oncoimmunology 2019

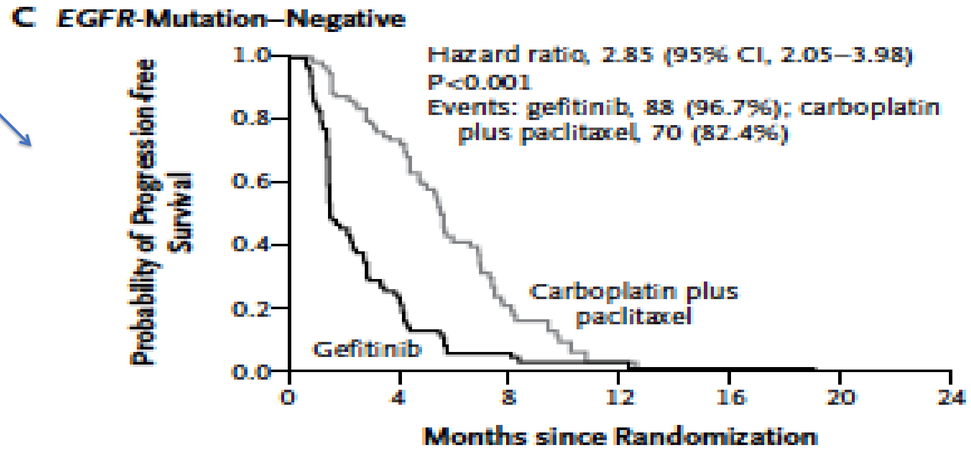
Signal Transduction Inhibitors



No. at Risk							
Gefitinib	609	363	212	76	24	5	0
Carboplatin plus paclitaxel	608	412	118	22	3	1	0



No. at Risk							
Gefitinib	132	108	71	31	11	3	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0

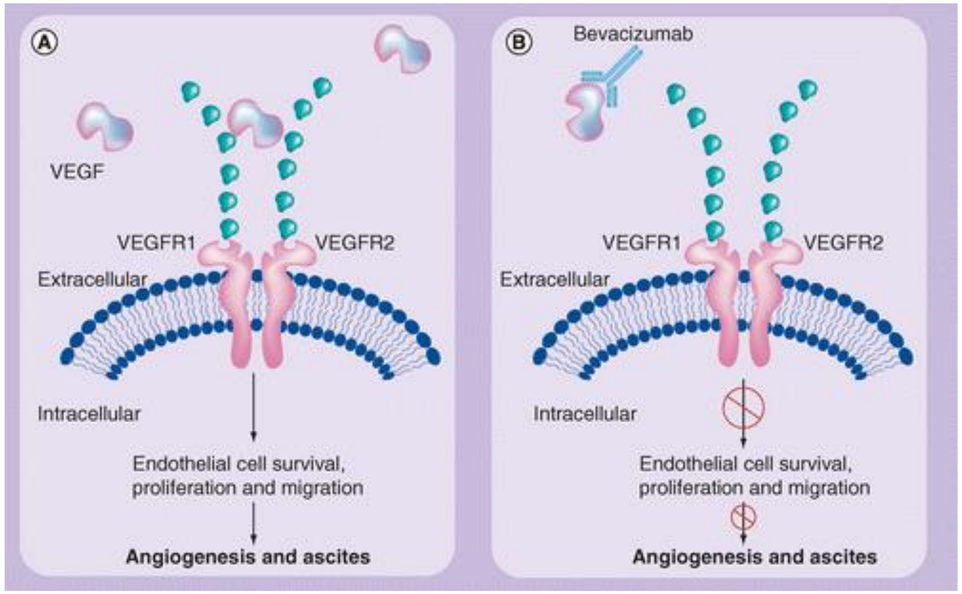


No. at Risk							
Gefitinib	91	21	4	2	1	0	0
Carboplatin plus paclitaxel	85	58	14	1	0	0	0

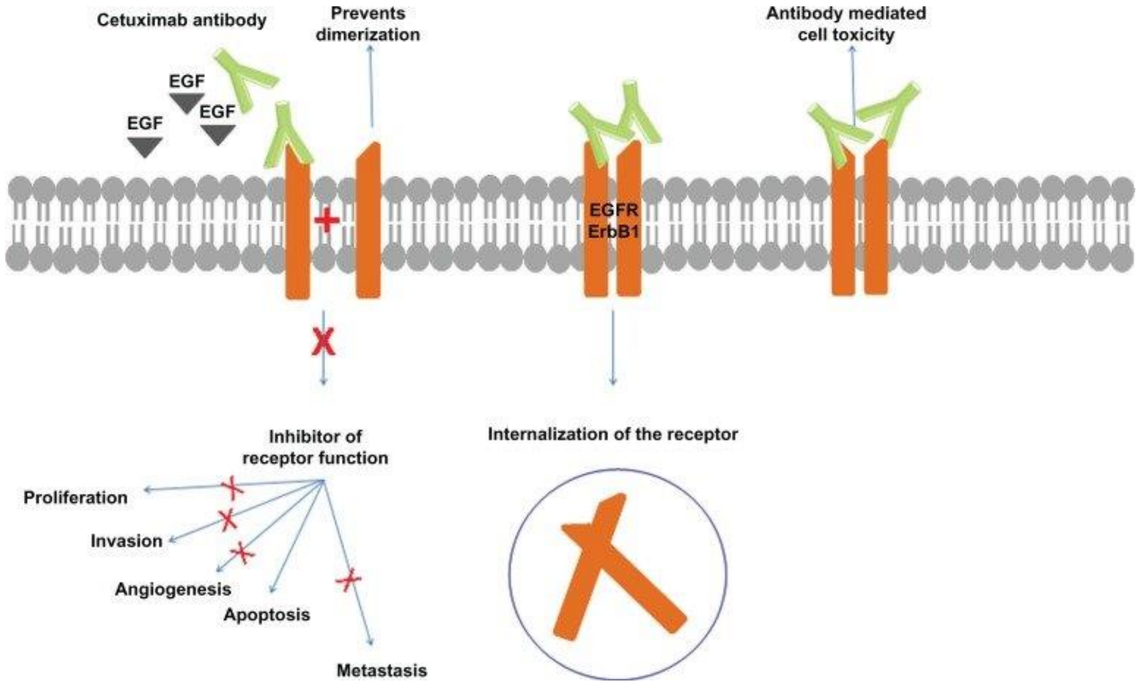
Mok, NJEM 2009

NORTH CAROLINA Oncology Association

Antibodies

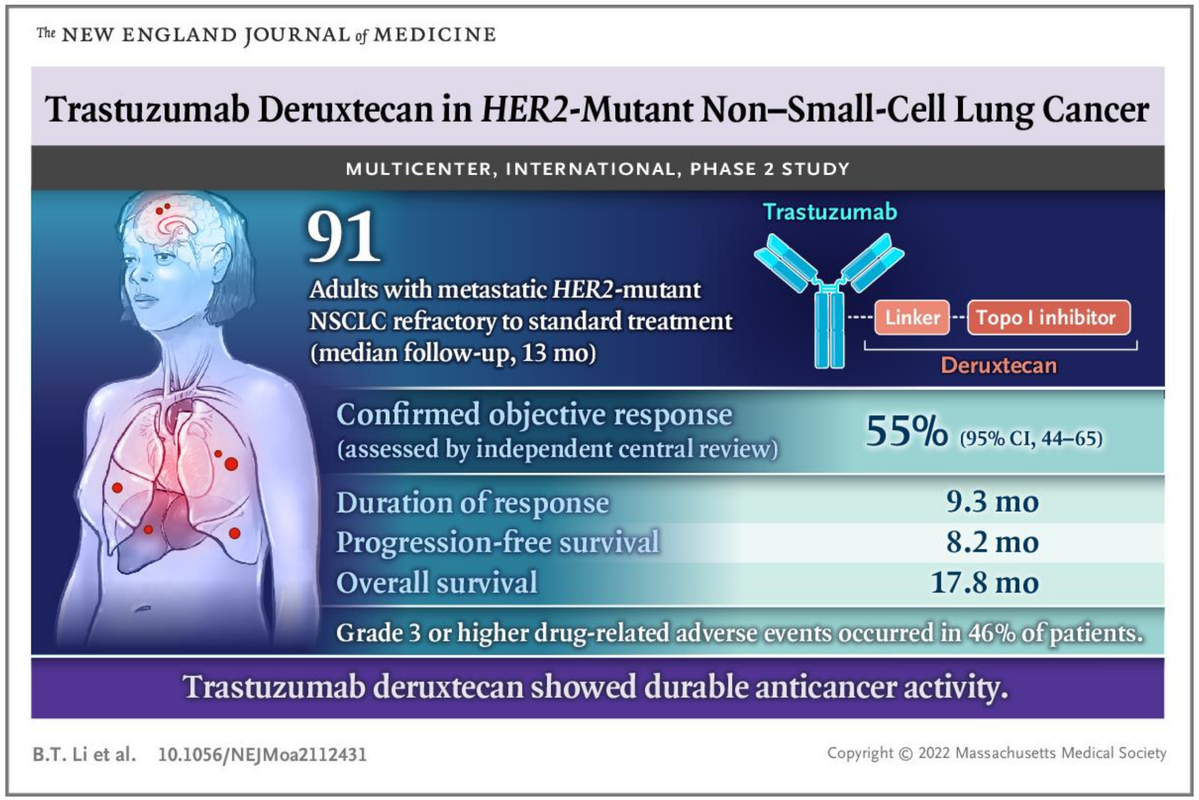


Eskander, Future Oncology 2015



Patil, Biologics: Targets and Therapy, 2012

ADCs—An advance in chemotherapy (but not targeted therapy)



Event	Grade 1–2	Grade 3	Grade 4	Grade 5	Overall
	number of patients (percent)				
Drug-related adverse event	46 (51)	37 (41)	4 (4)	1 (1)*	88 (97)
Drug-related adverse events with ≥20% incidence					
Nausea	58 (64)	8 (9)	0	0	66 (73)
Fatigue†	42 (46)	6 (7)	0	0	48 (53)
Alopecia	42 (46)	0	0	0	42 (46)
Vomiting	33 (36)	3 (3)	0	0	36 (40)
Neutropenia‡	15 (16)	14 (15)	3 (3)	0	32 (35)
Anemia§	21 (23)	9 (10)	0	0	30 (33)
Diarrhea	26 (29)	2 (2)	1 (1)	0	29 (32)
Decreased appetite	27 (30)	0	0	0	27 (30)
Leukopenia¶	17 (19)	4 (4)	0	0	21 (23)
Constipation	20 (22)	0	0	0	20 (22)

Our Goal is Cure

National Cancer Institute (NCI)
29,209 followers
2mo

NCI Director Dr. Sharpless highlights research findings from the 2018 ASCO meeting.

2018 ASCO® ANNUAL MEETING

DELIVERING DISCOVERIES: EXPANDING THE REACH OF PRECISION MEDICINE

Of course, we don't want to overpromise and give people, especially patients, false hope. But too many from my generation are afraid to be optimistic, too sheepish to ever use the word "cure." But that's what we want to do, *cure* our patients. We are, in fact, curing patients right now, more than ever, including those with metastatic cancer.

CAROLINA Association

A Vision On How to Cure

TARGET ANTIGEN(S)

THERAPEUTIC AGENT(S)

IMMUNOSUPPRESSION REVERSAL

- In vivo response monitoring
- Broadening antigen prediction
- Optimizing immunogenicity prediction

Checkpoint Blockade

Neoantigen Vaccines

CURE

Traditional therapies

- Vaccine &/or cell therapy?
- "Off-the-shelf" priming agent as induction?
- NeoAg-specific mAbs?

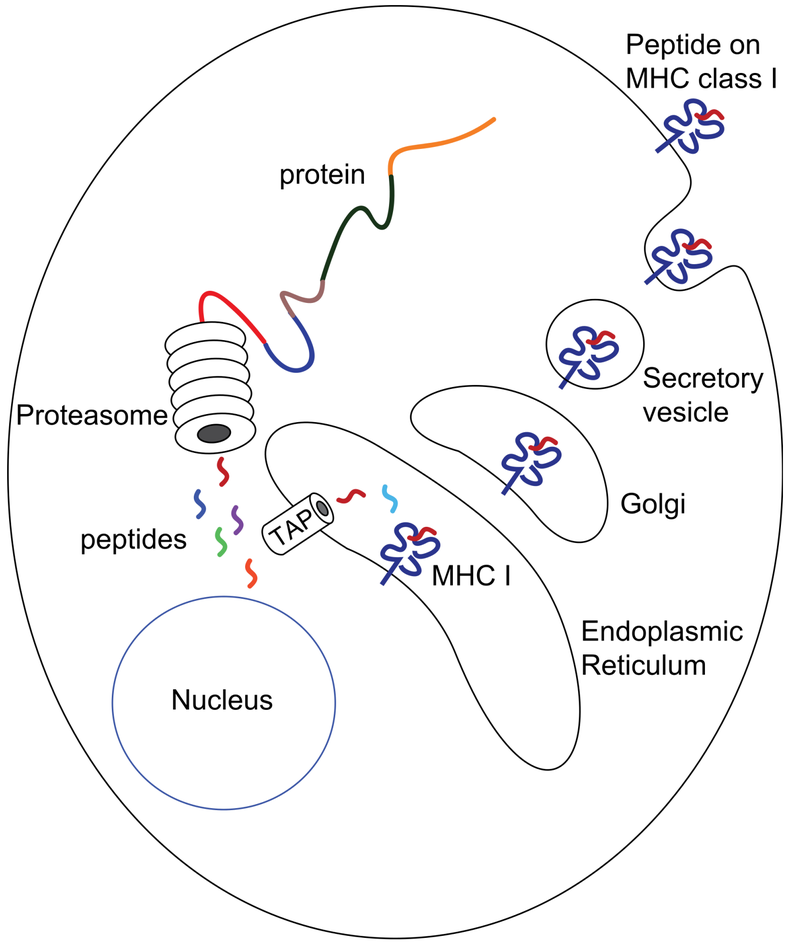
- Discover resistance mechanisms
- Overcome resistance mechanisms

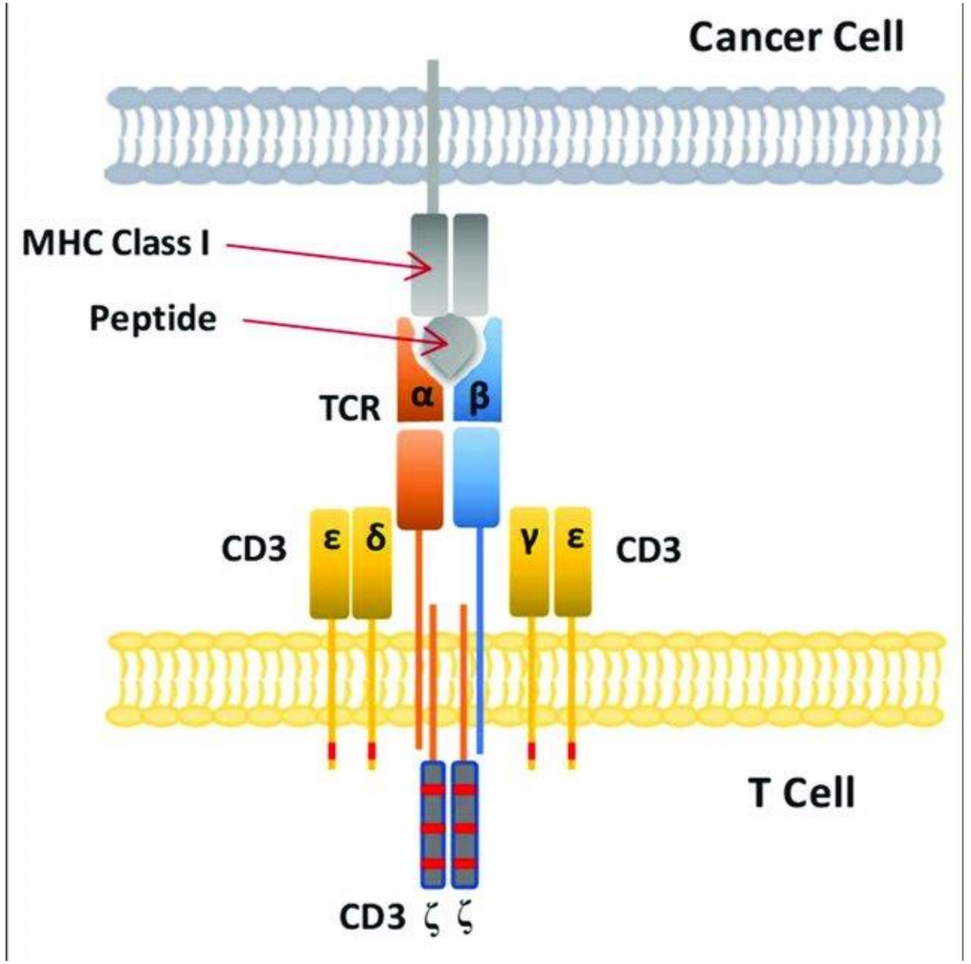
Slide Credit: Ben Vincent, PIRL. Image credits: www.wikipedia.org

PART 1 of Targeted IO: The Immunopeptidome

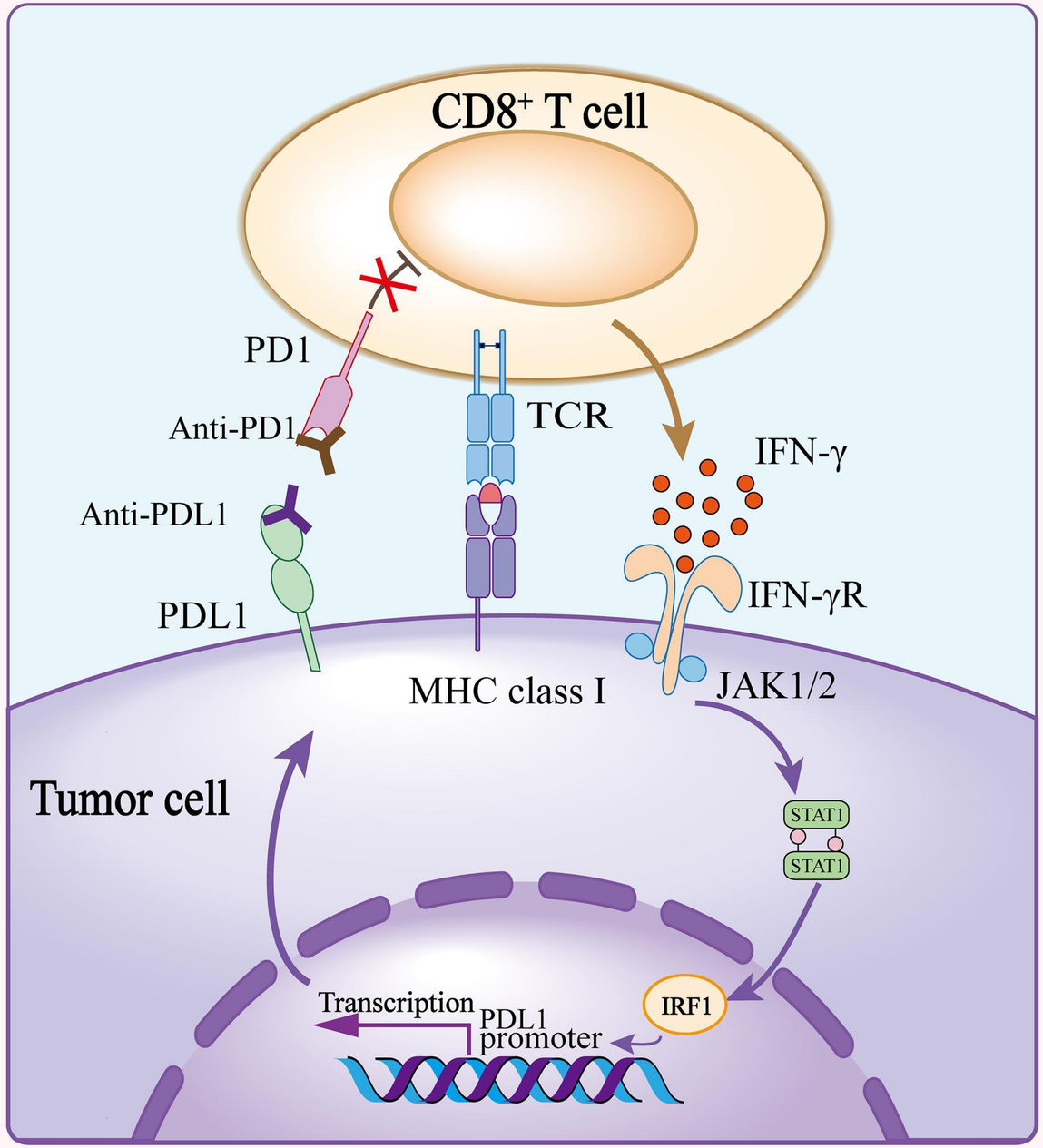
NORTH CAROLINA Oncology Association

The T Cell


Peptide on
MHC class I
protein
Proteasome
Secretory
vesicle
Golgi
peptides
TAP
MHC I
Endoplasmic
Reticulum
Nucleus


Cancer Cell
MHC Class I
Peptide
TCR
α
β
CD3
ε
δ
γ
ε
CD3
T Cell
CD3 ζ ζ

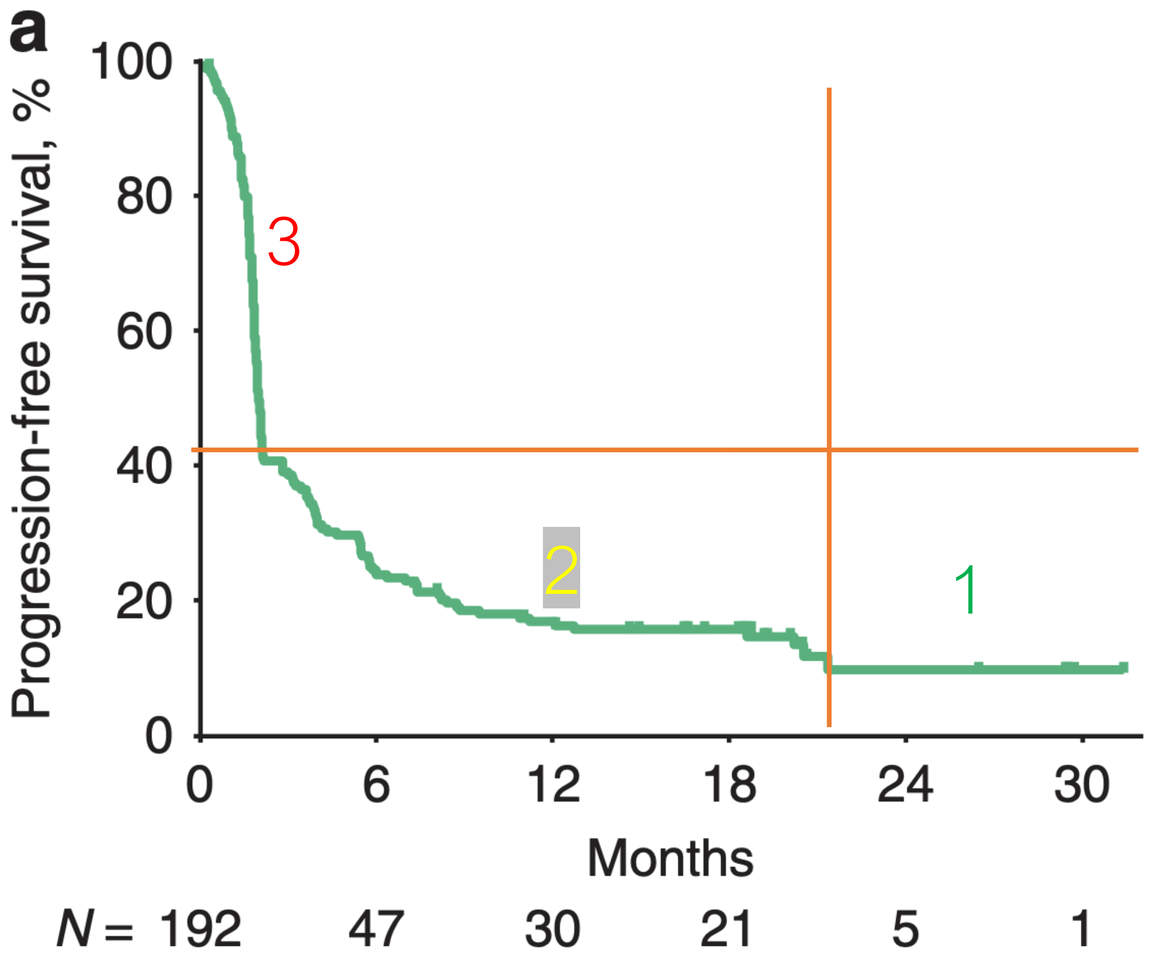
PD1 Classical MOA

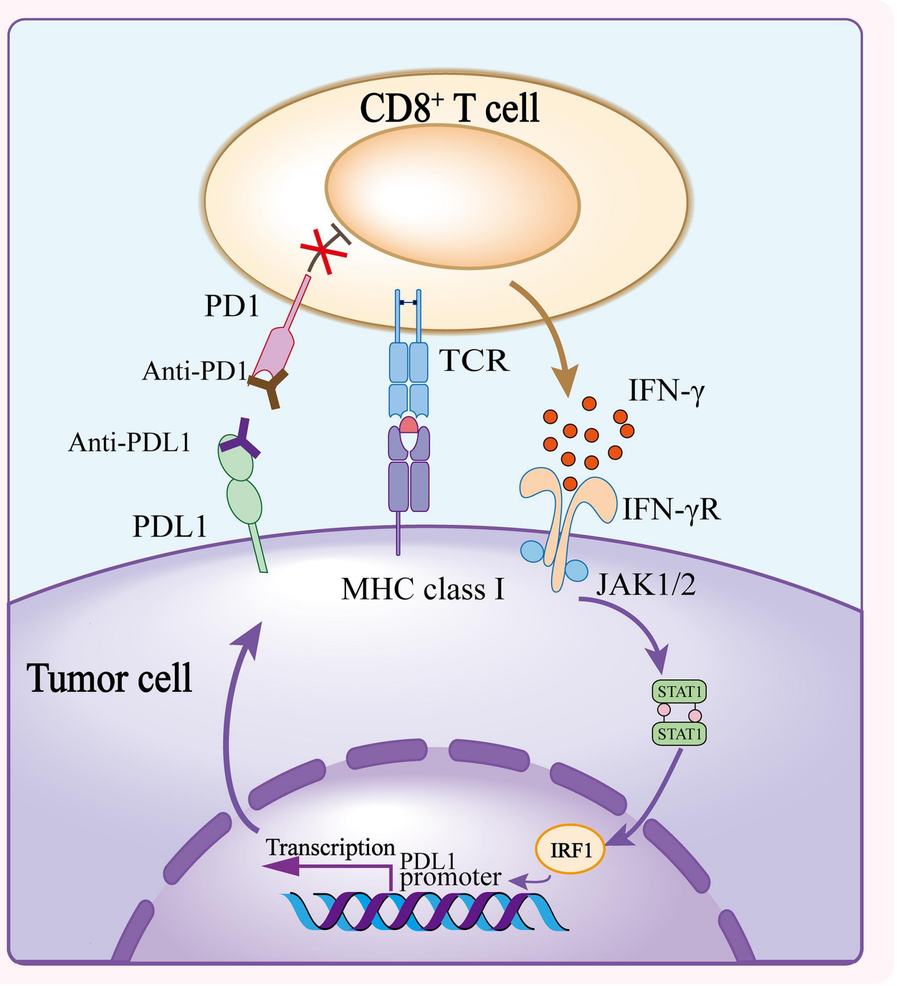


Lei, Fron. Cell Dev Biol. 2020

NORTH CAROLINA Oncology Association

PD1 Immunotherapy

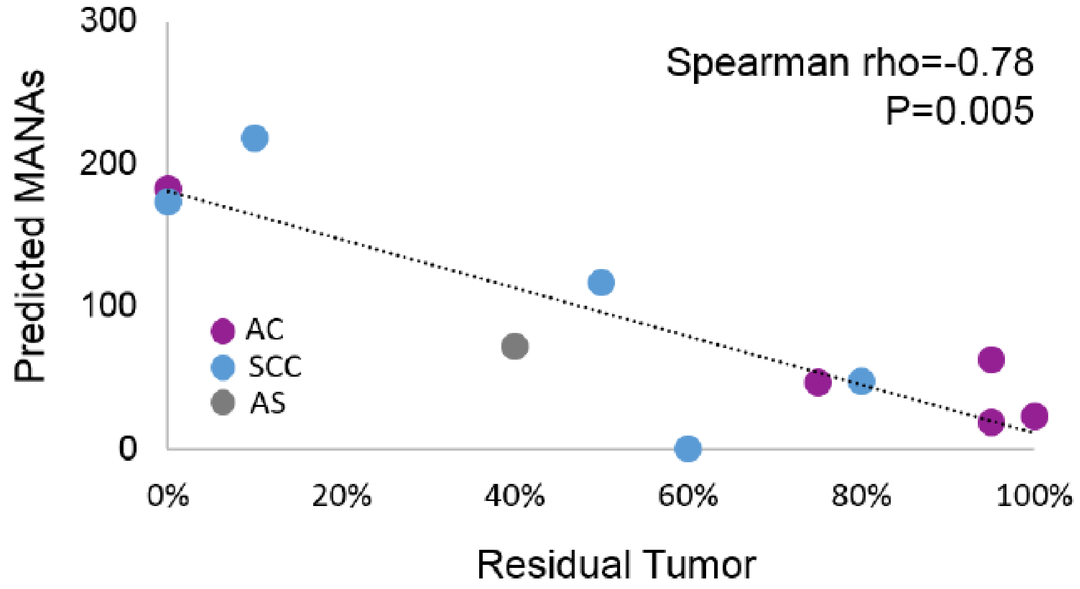


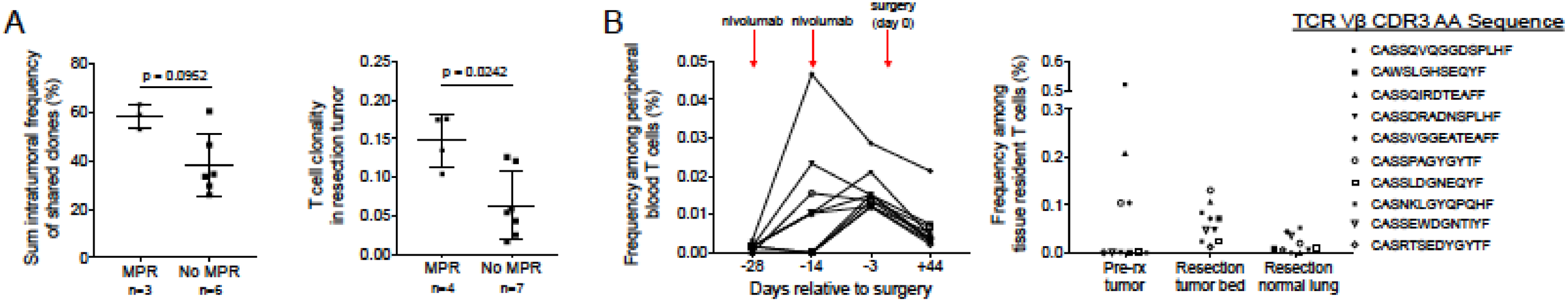


Lei, Fron. Cell Dev Biol. 2020

NORTH CAROLINA Oncology Association

PD1 MOA, Reconsidered

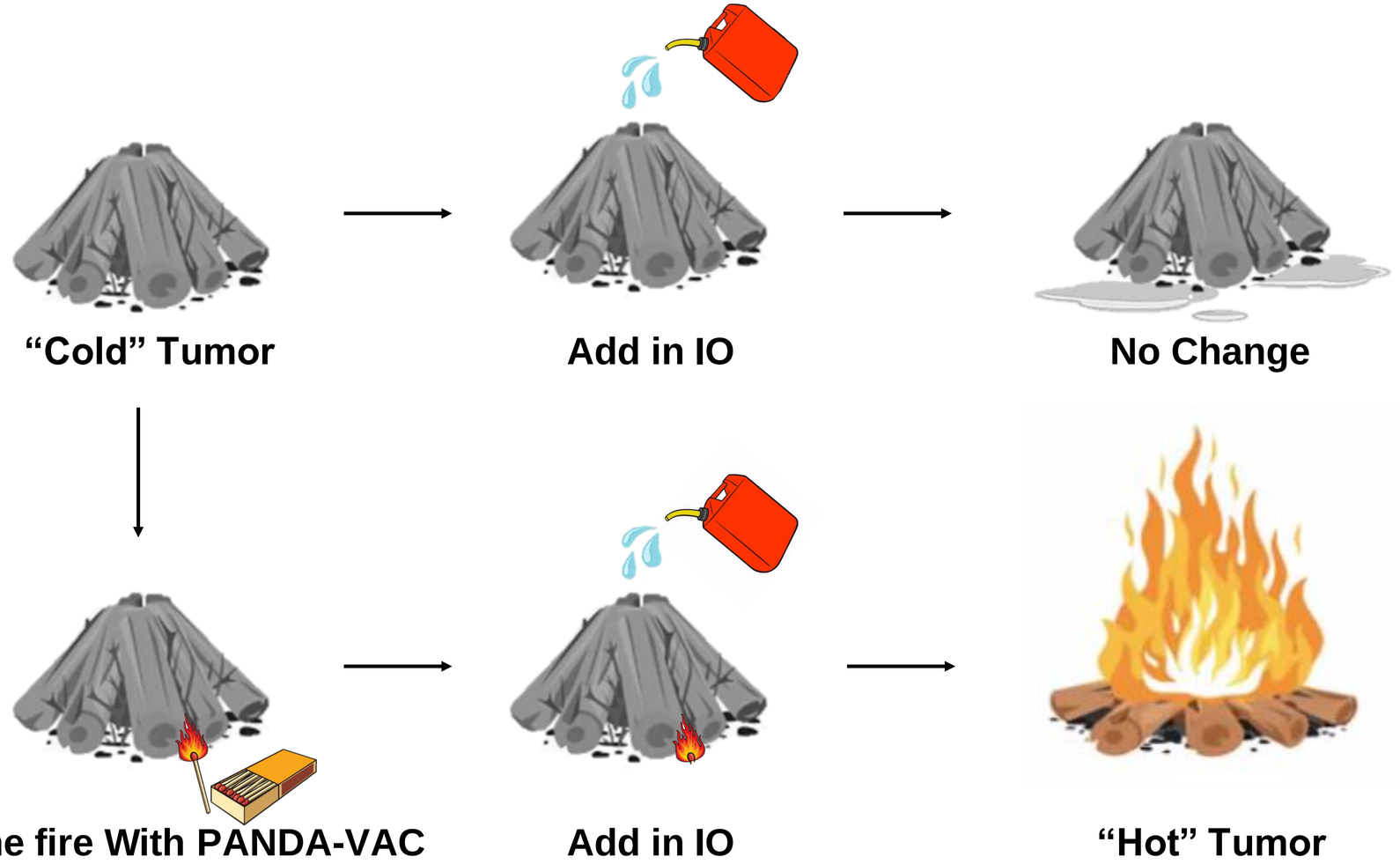




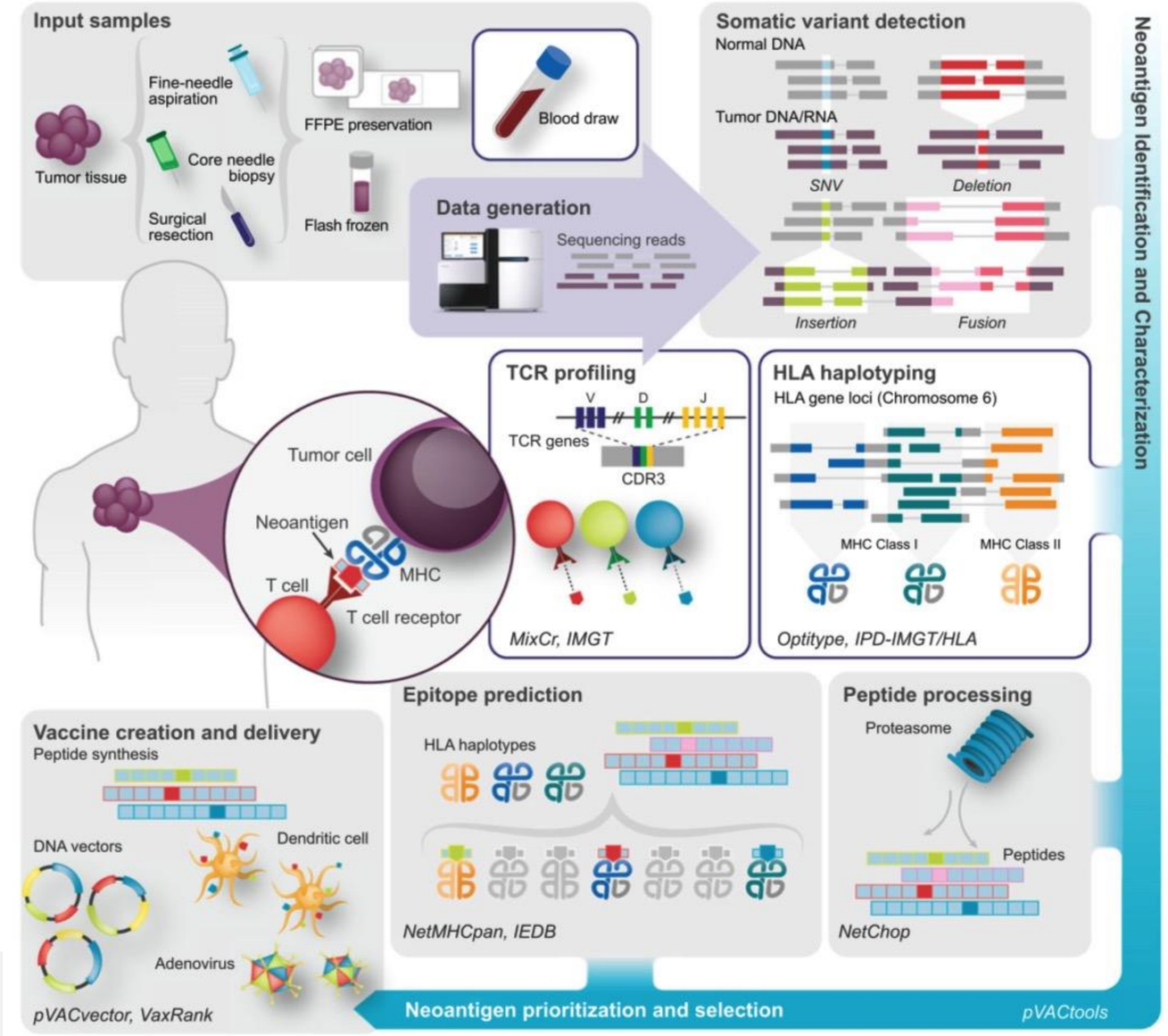
Forde, Chaft et al. NEJM 2018

NORTH CAROLINA Oncology Association

Analogy: Dramatic Immune Response as Bonfire



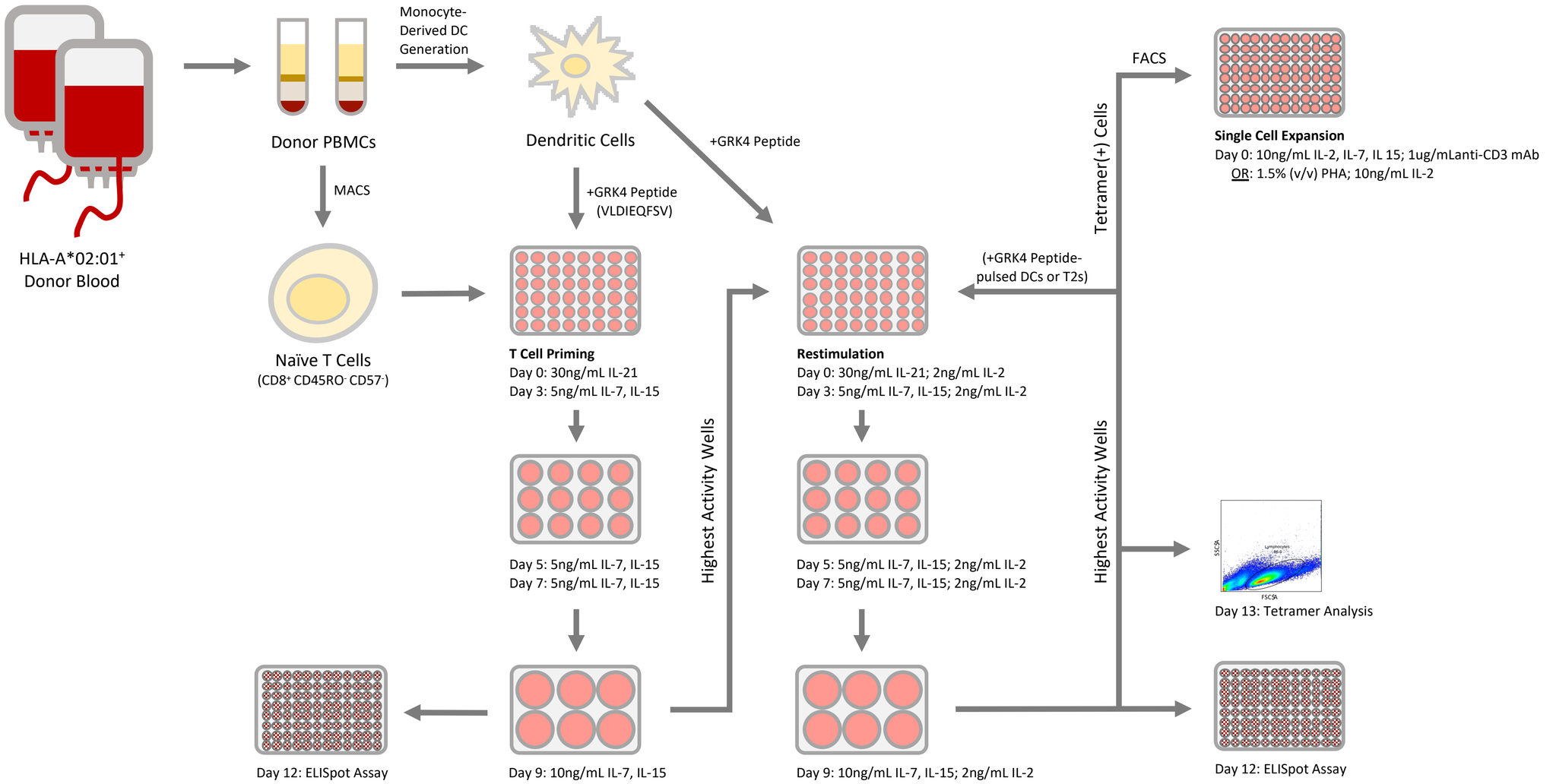
Genomics + Bioinformatics can Predict Tumor Antigens



Richters M et al. (2019) *Genome Medicine* 11:56

NORTH CAROLINA Oncology Association

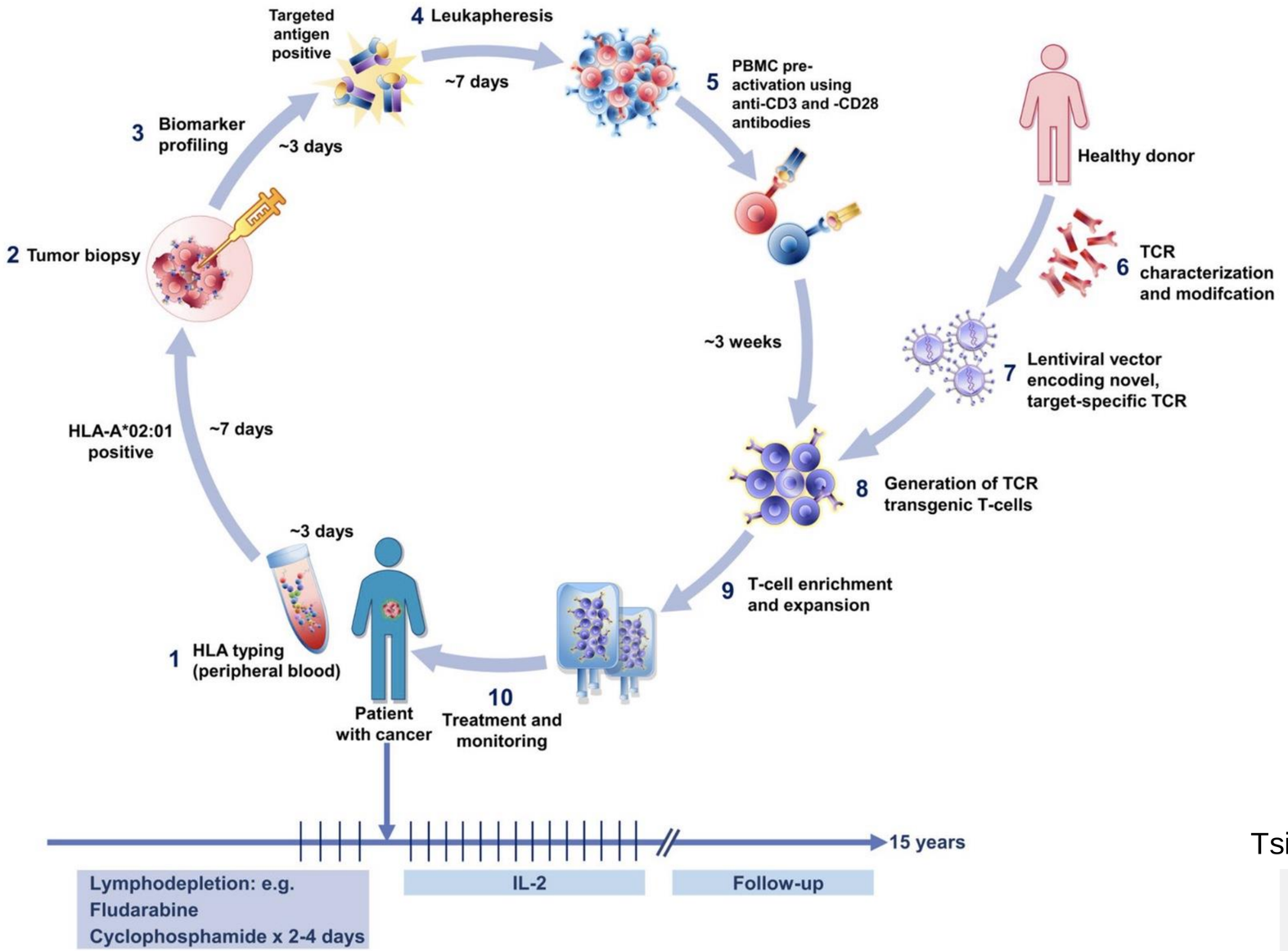
Discovering antigen specific T cell Receptors



Wölfl, Nature 2014

NORTH CAROLINA Oncology Association

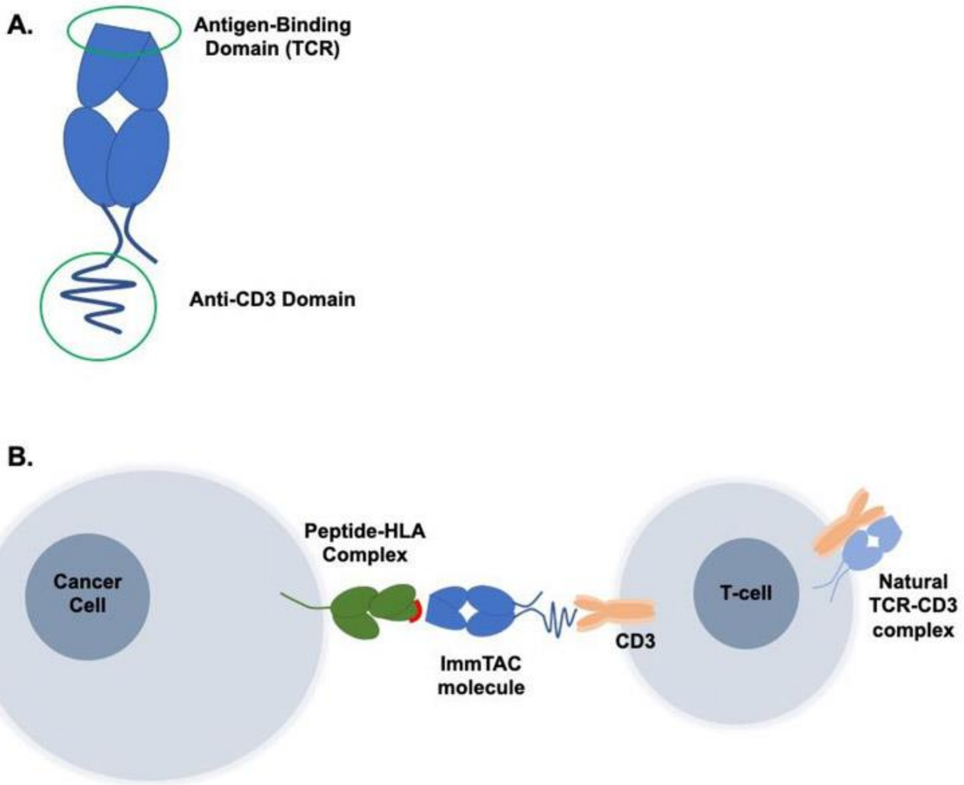
Treatment with Antigen-Specific T Cells



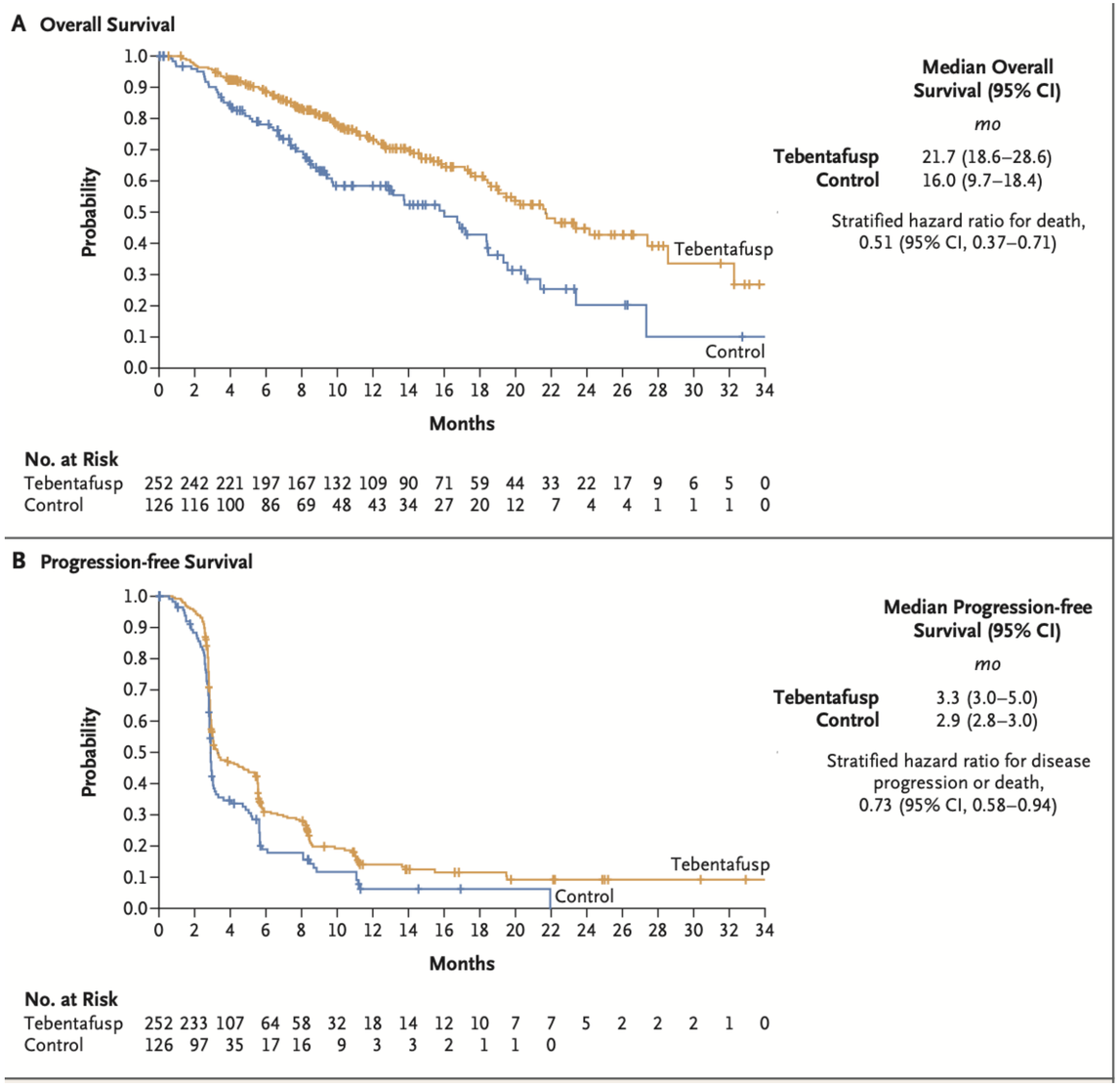
Tsimberidou et al. (2021) *J Hematol Oncol* 14:102

NORTH CAROLINA Oncology Association

Tebentafusp (Kimmtrak)



Chen, Exp Rev Anticancer Ther 2023

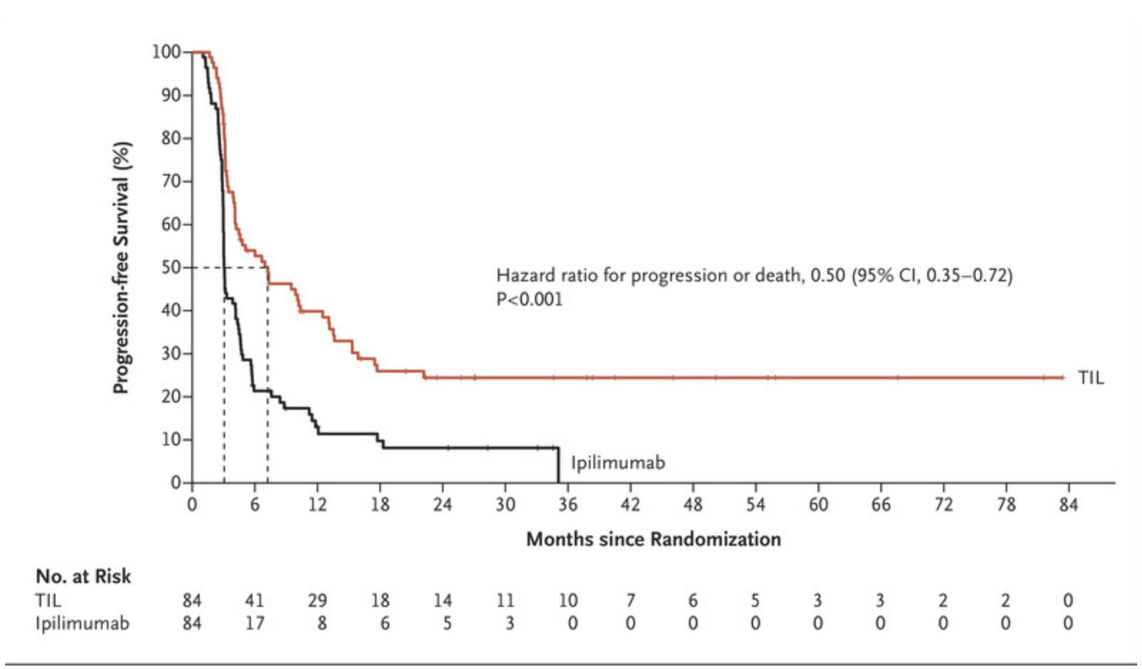


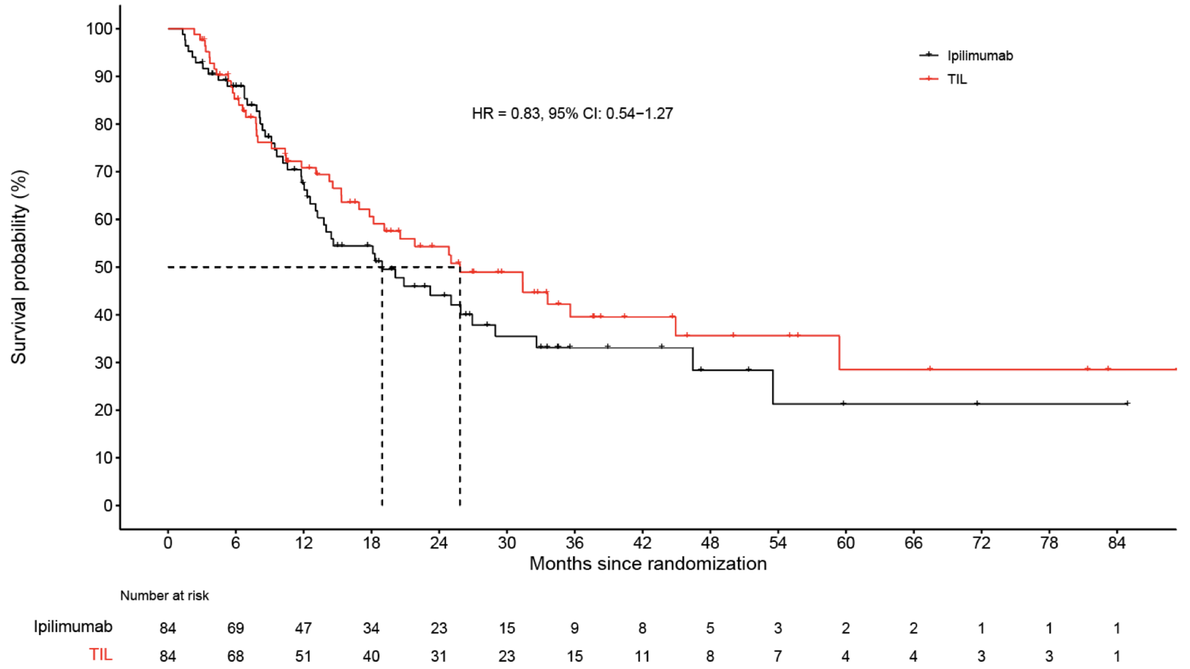
Nathan, NEJM 2021

TILs

1. Tissue Procurement
2. Flu/Cy lymphodepletion
3. Infusion of TIL
4. HD IL-2

TILs

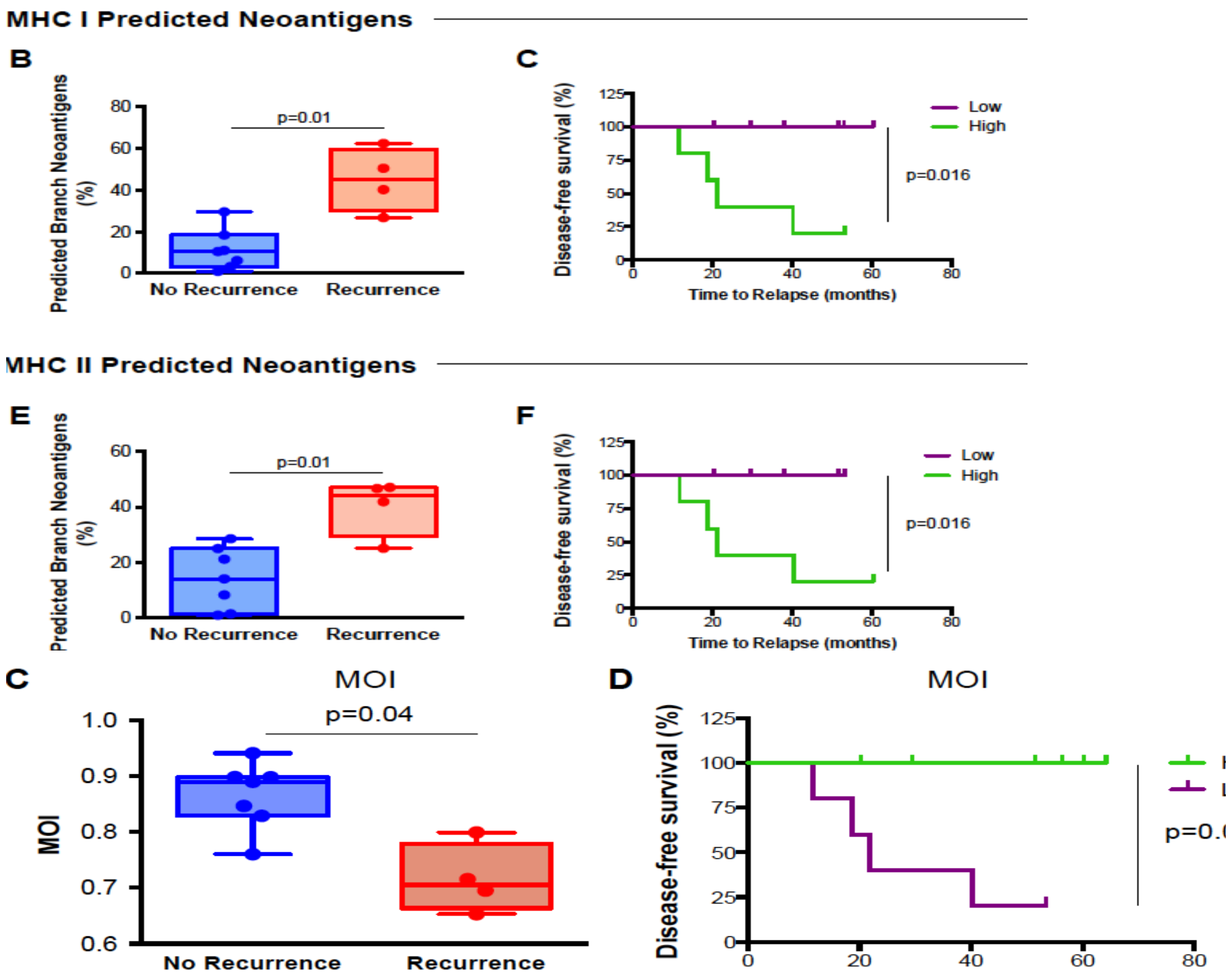


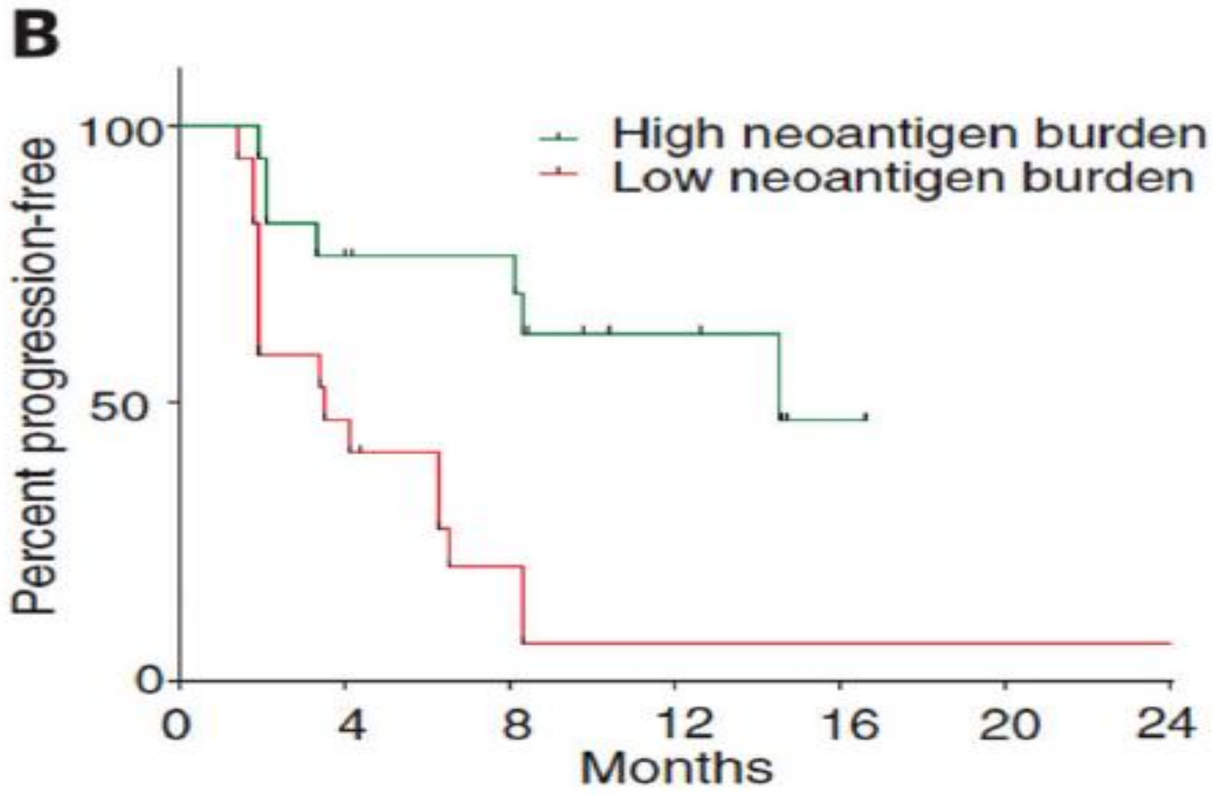


Rohaan, NEJM 2022

NORTH CAROLINA Oncology Association

Rationale for Personalized Cancer Vaccines



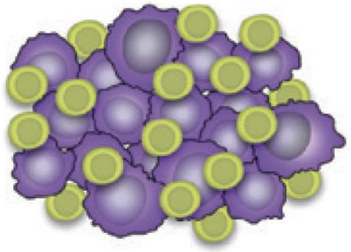
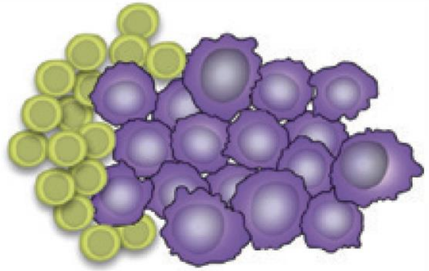
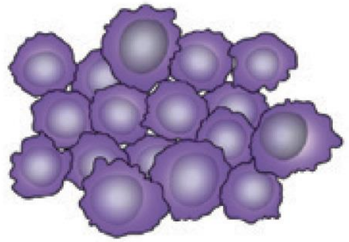


(Reuben, Cancer Discovery 2017)

Rizvi, Science 2015

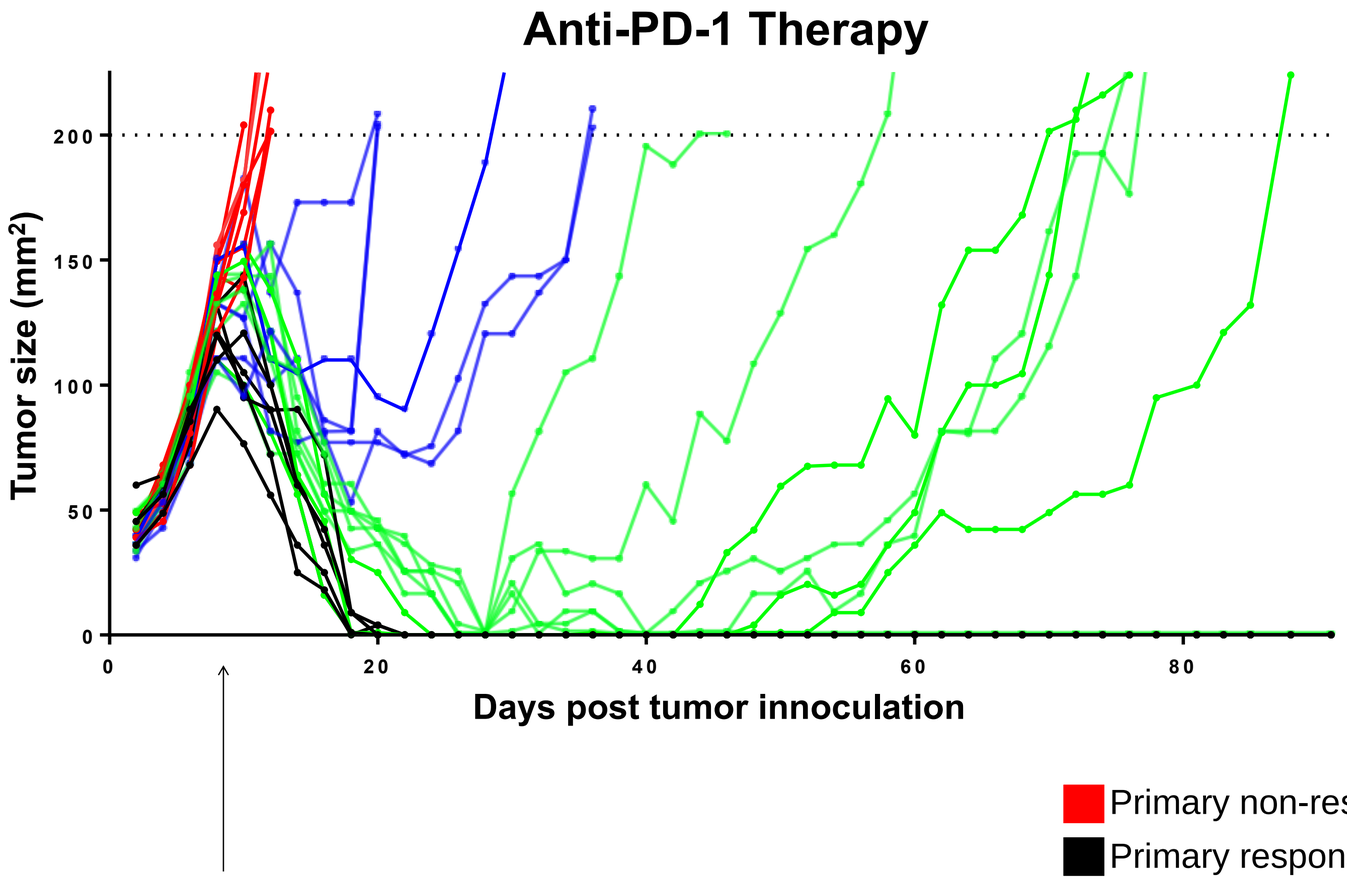
NORTH CAROLINA Oncology Association

Rationale for Personalized Cancer Vaccines

	Immune-inflamed	Immune-excluded	Immune-desert
T-cell / Tumor cell			
Definition	High degree of cytotoxic T-cell infiltration	Presence of T cells at invasive margin; absent in tumor bed	Absence of T cells within tumor and at margins
Mechanism of immune evasion	• Checkpoint activation • T-cell exhaustion	• Stromal barriers • Aberrant vasculature • Lack of chemokines • Oncogenic pathways • Hypoxia	• Insufficient priming • Defects in antigen presentation • Lack of antigen
	↓	↓	↓
	αPD-1	Adjuvant	Vaccine

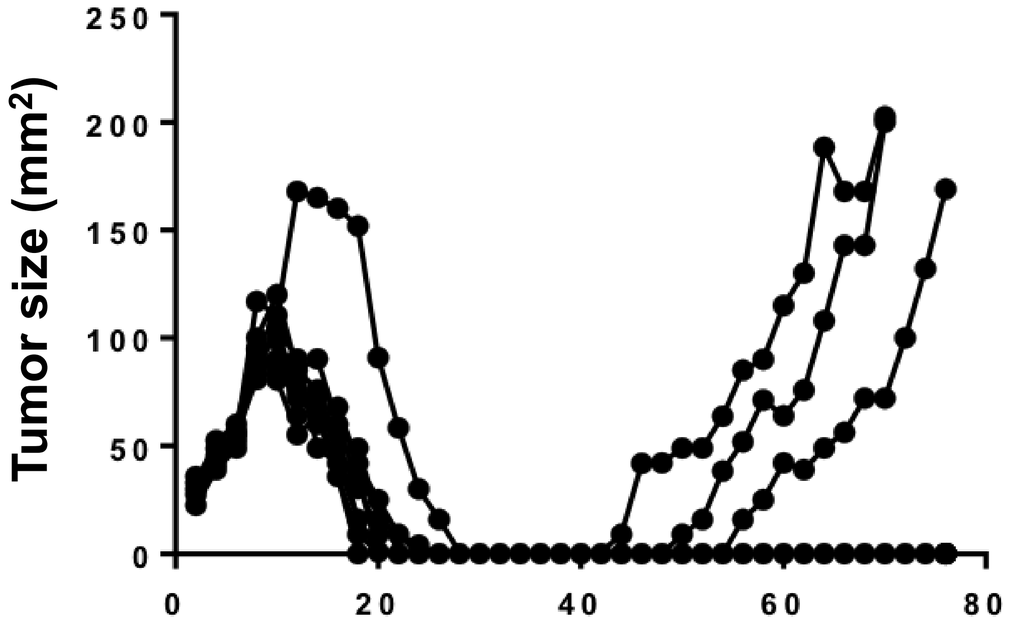
Anandappa et al. (2020) *Cancer Discovery*

Of Mice and Men

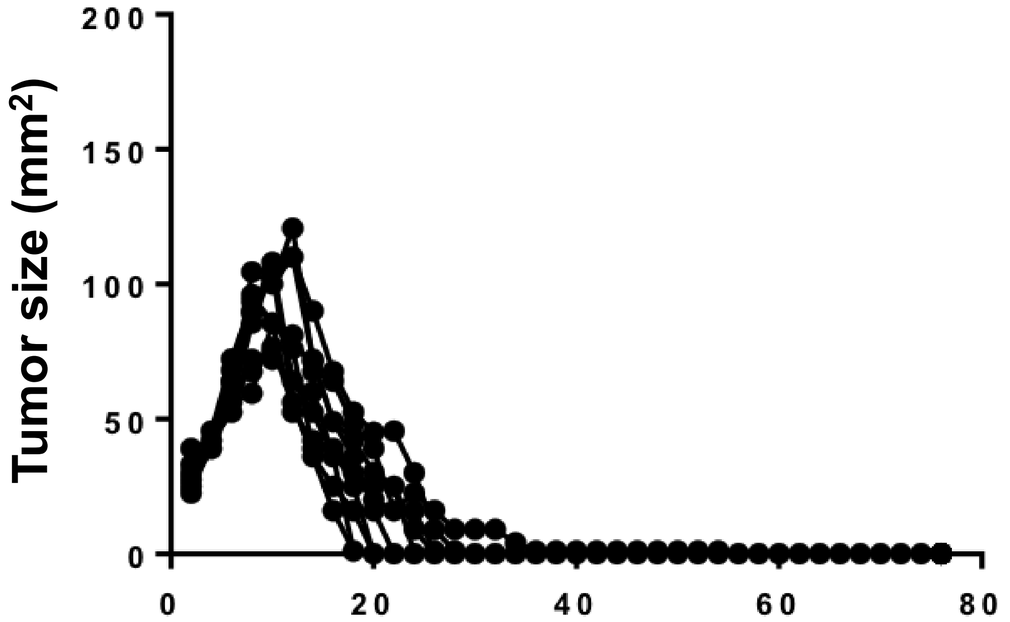


It Cured the Mice…

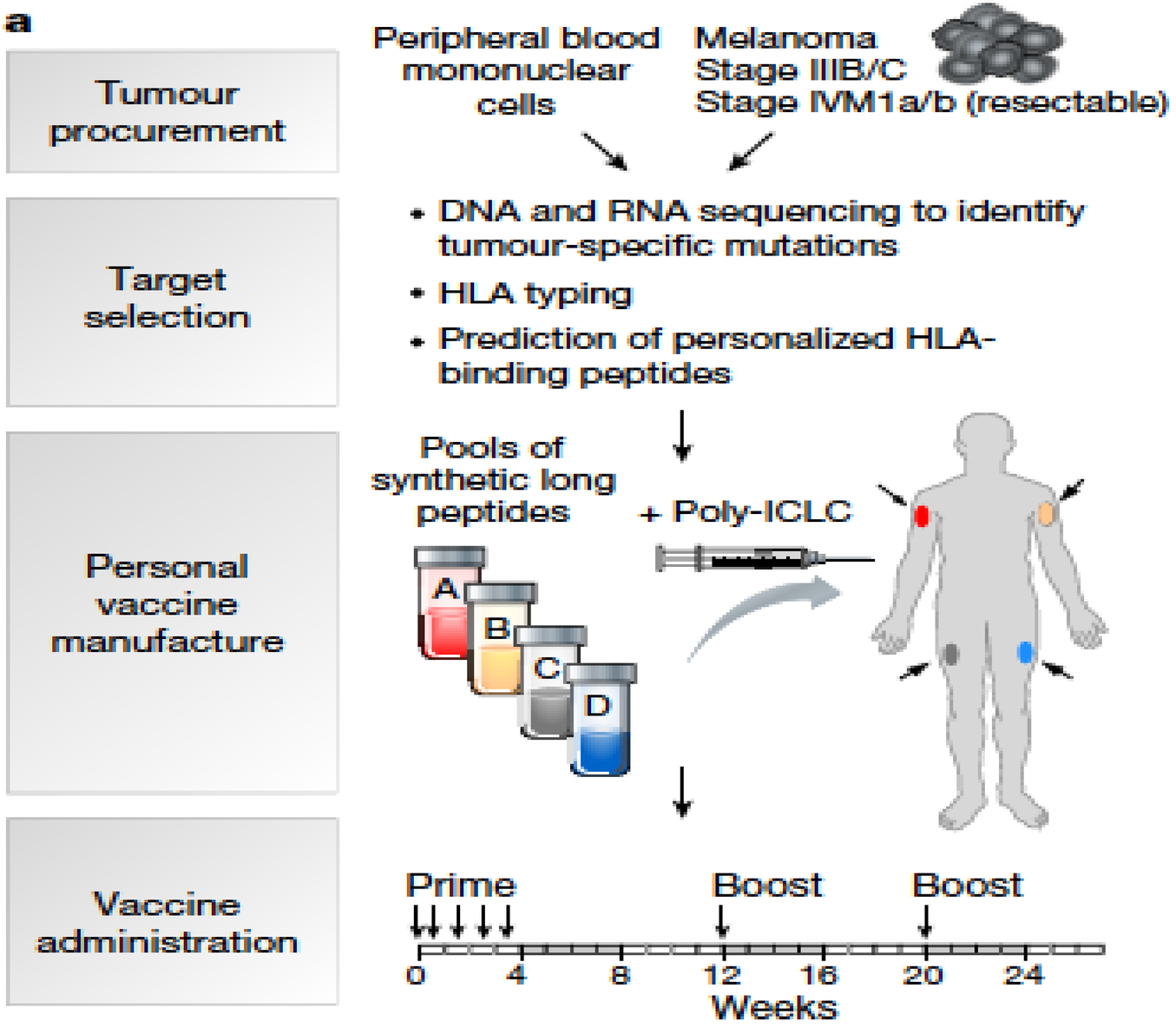
A. Anti-PD-1 + NeoAg



B. Anti-PD-1 + NeoAg + Adjuvant

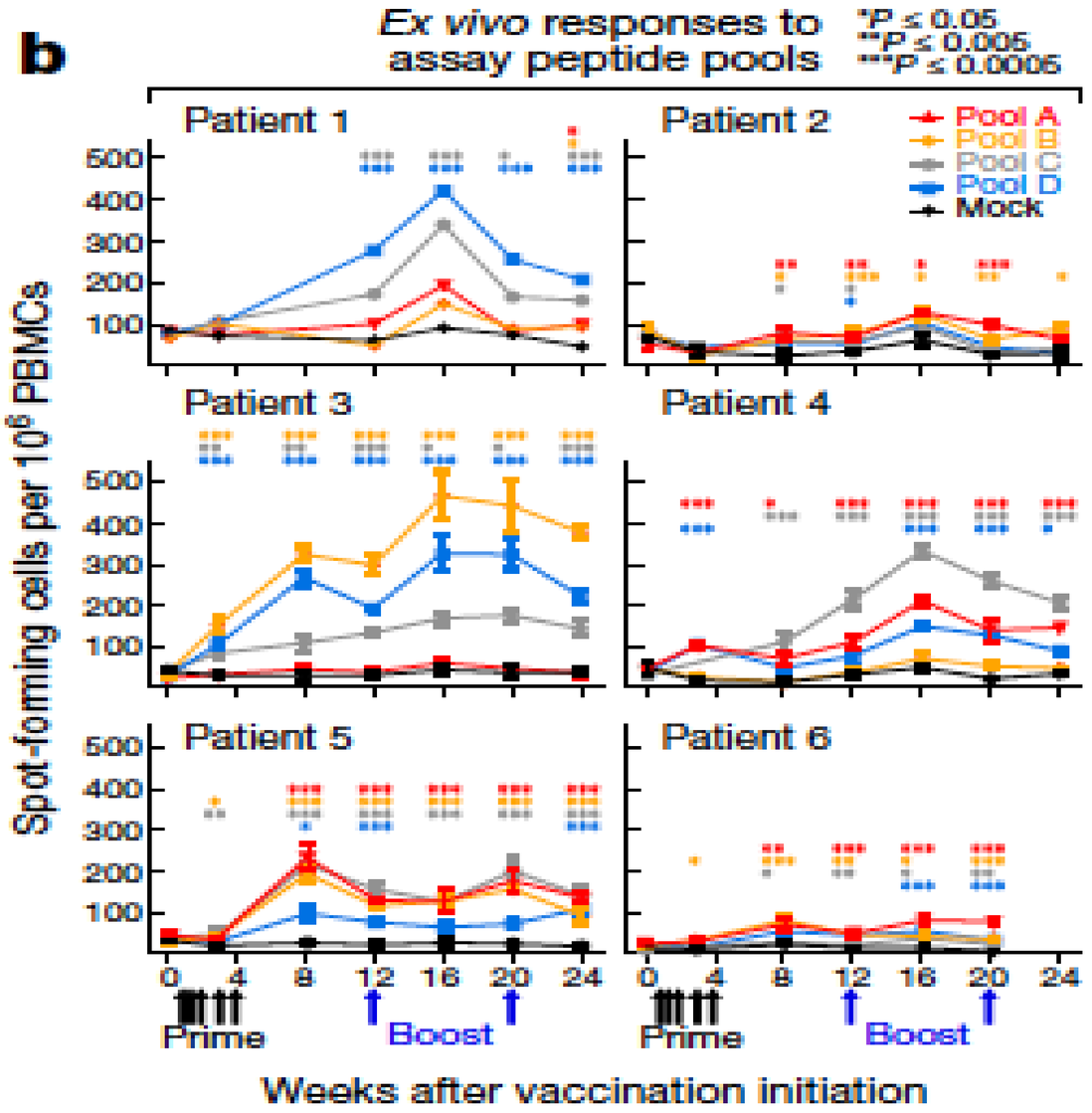


Early Effort in Melanoma



Ott, Nature 2017

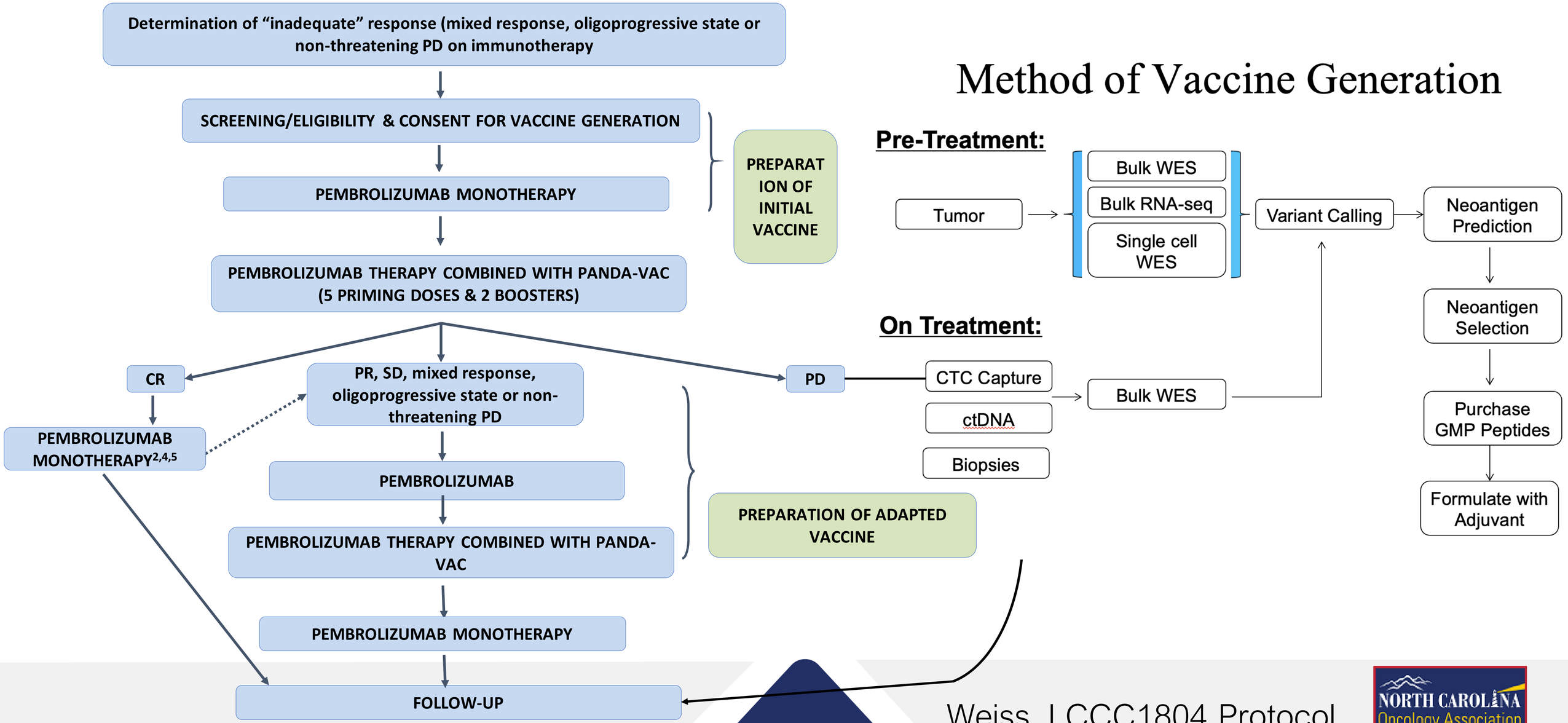
There were T Cell Reponses



Ott, Nature 2017

NORTH CAROLINA Oncology Association

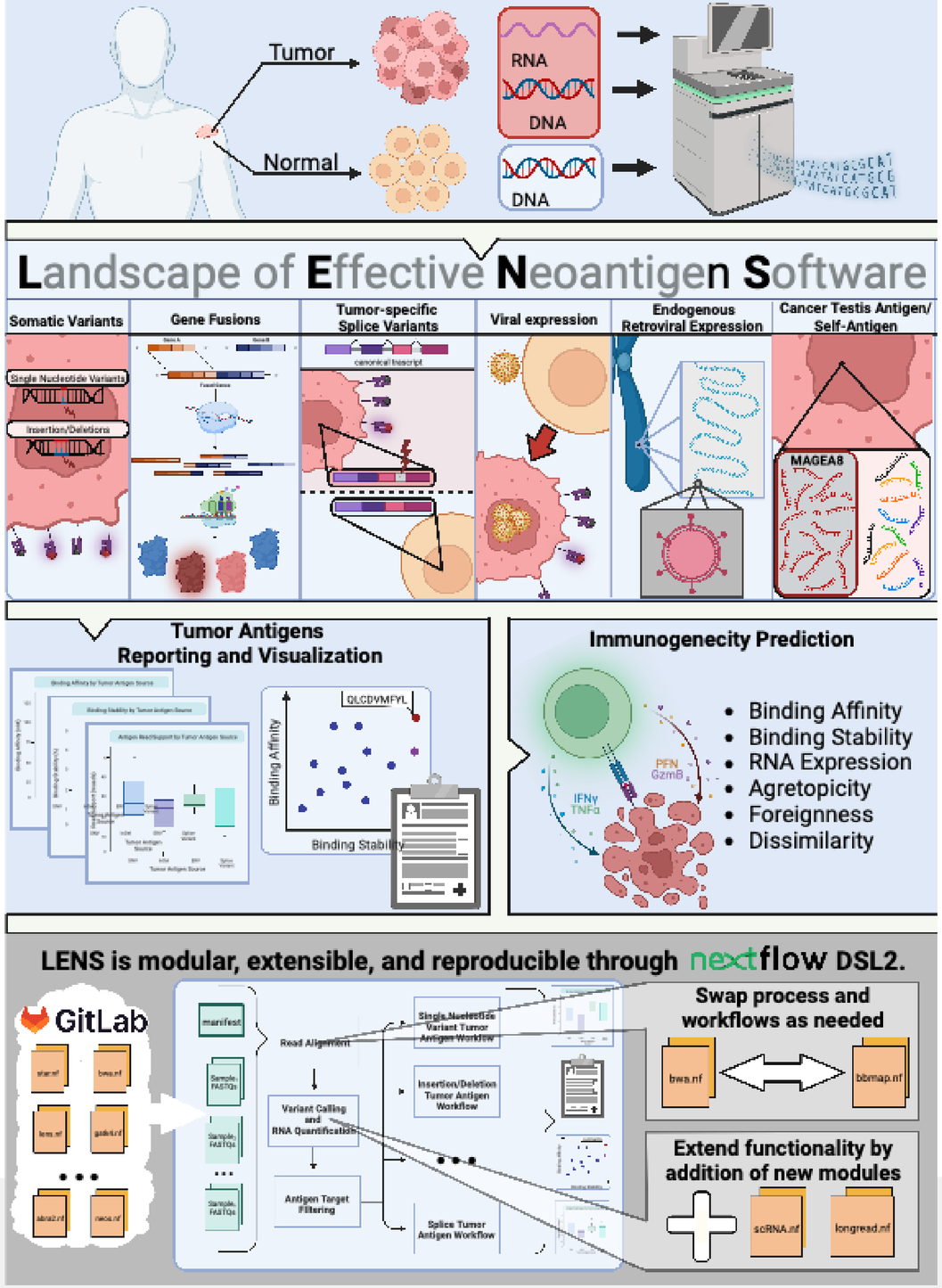
PANDA-VAC



Weiss, LCCC1804 Protocol

NORTH CAROLINA Oncology Association

LENS

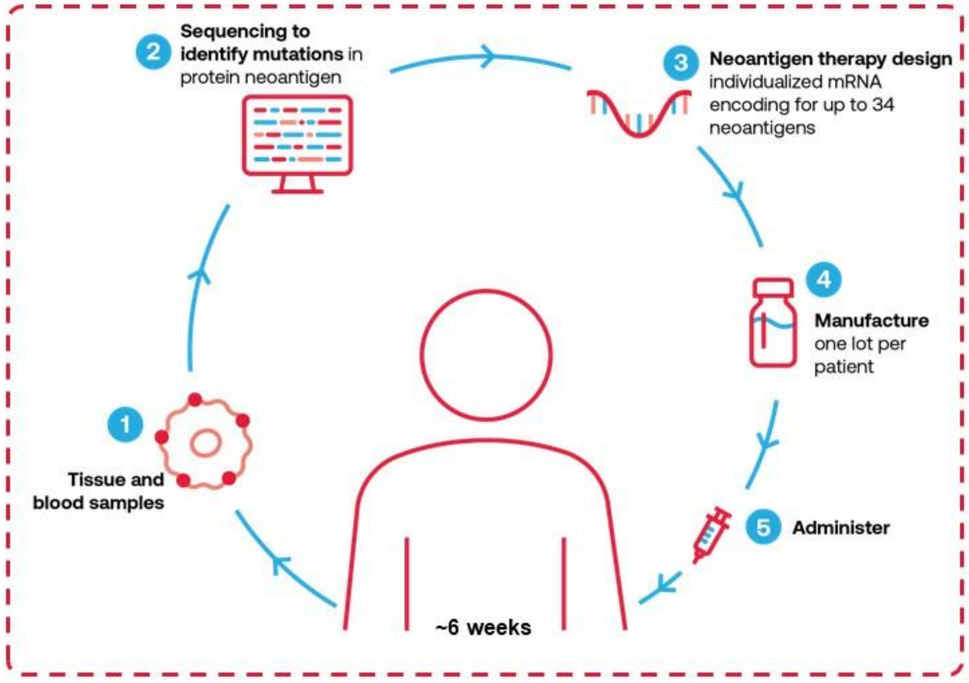


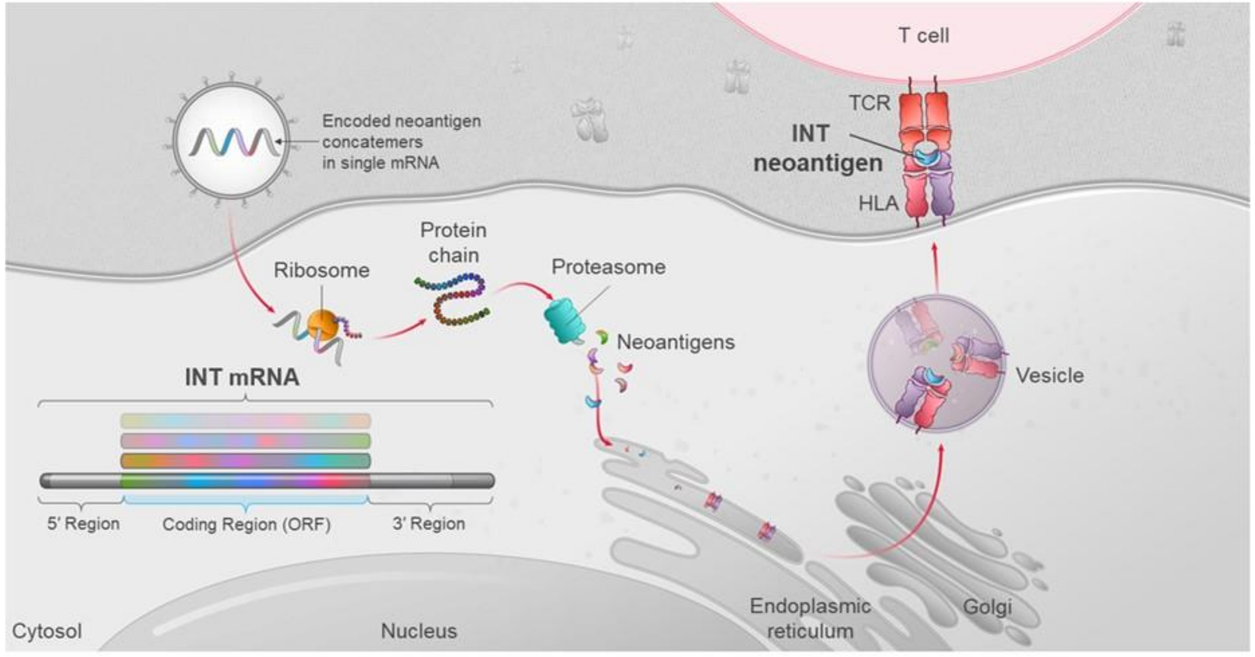
Vensko et al (2023) *BioRxiv*

NORTH CAROLINA Oncology Association

mRNA-4157 (V940) Mechanism of Action

- mRNA-4157 (V940) is **an individualized neoantigen therapy** designed to target an individual patient's unique tumor mutations and encodes up to 34 neoantigens[1,2]
- Therapies targeting neoantigens can increase endogenous **neoantigen T-cell responses and induce epitope spreading** to novel antigens with the ability **to drive antitumor responses** and **maintain memory** with cytolytic properties, potentially **producing long-term disease control** for patients[3-7]





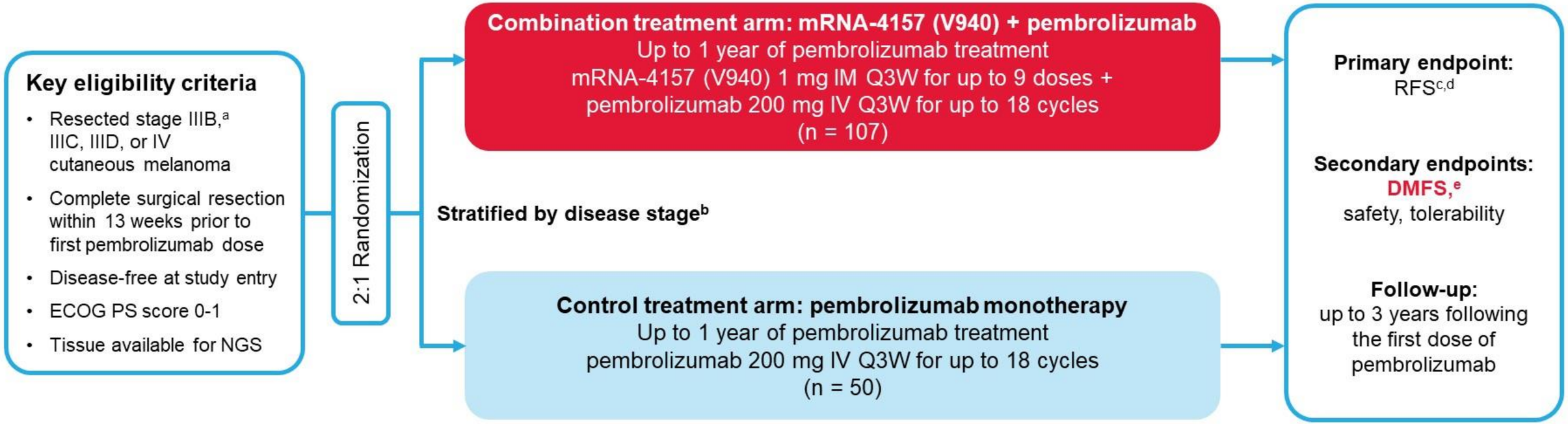
HLA, human leukocyte antigen; INT, individualized neoantigen therapy; ORF, open reading frame.

1. Burris HA, et al. *J Clin Oncol*. 2019;37(suppl 15). Abstract 2523. 2. Zhong S, et al. *Cancer Res*. 80(suppl 16). Abstract 6539. 3. Wirth TC, Kühnel F. *Front Immunol*. 2017;8:1848. 4. Ott PA, et al. *Nature*. 2017;547:217-221. 5. Hu Z, et al. *Nat Med*. 2021;27:515-525. 6. Ott PA, et al. *Cell*. 2020;183:347-362. 7. Palmer CD, et al. *Nat Med*. 2022;28:1619-1629.

PRESENTED BY: Adnan Khattak, MBBS, FRACP, PhD

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

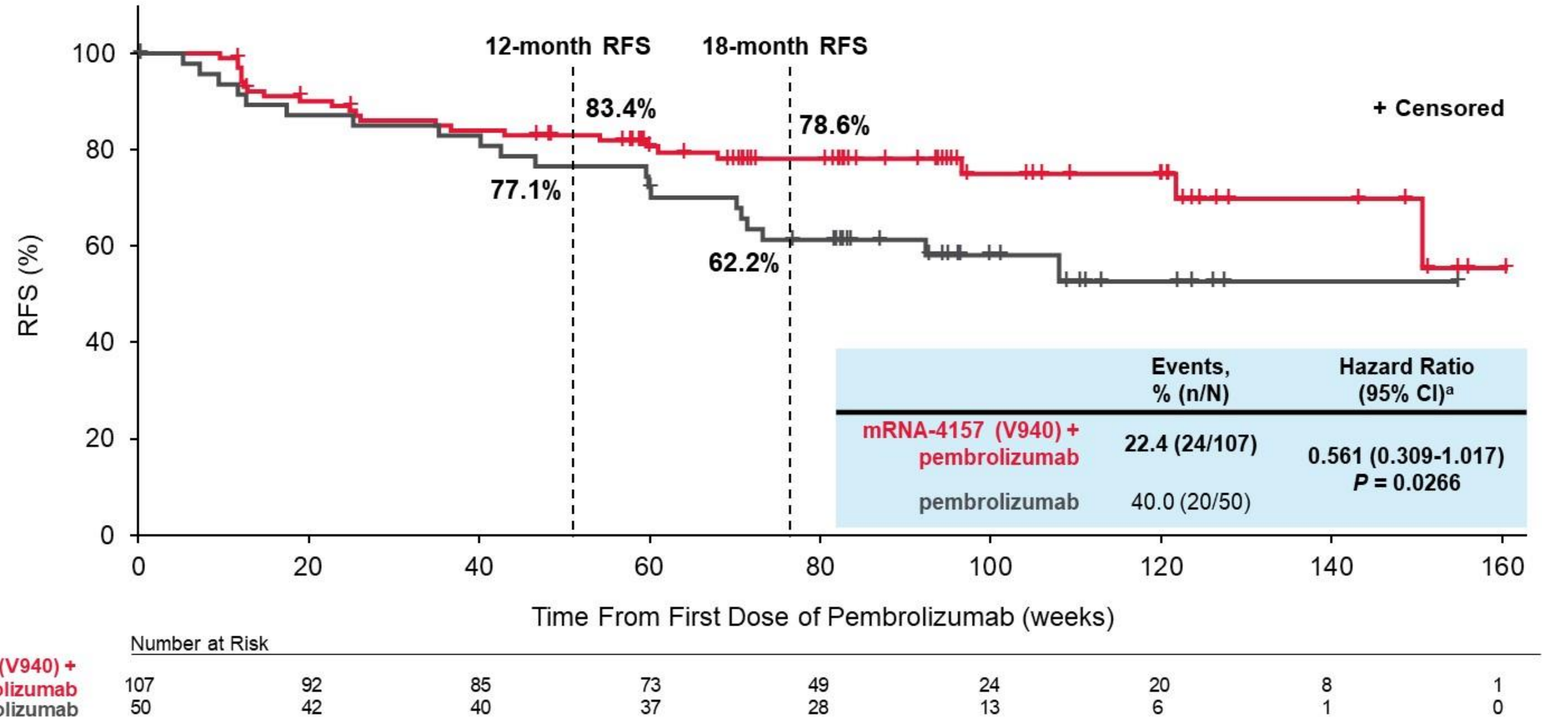
Randomized, phase 2, open-label study in adjuvant resected melanoma patients at high risk of recurrence



Designed with 80% power to detect an HR of 0.5 with ≥40 RFS events (with a 1-sided alpha of 0.1)
DMFS analysis was prespecified for testing following positive RFS in the ITT population[f]
Median follow-up[g]: 23 months for mRNA-4157 (V940) + pembrolizumab
24 months for pembrolizumab monotherapy

[a]Patients with stage IIIB disease were eligible only if relapse occurred within 3 months of prior surgery of curative intent. [b]According to the 8th edition of the American Joint Committee on Cancer Staging Manual. [c]The primary endpoint was investigator-assessed RFS (defined as the time from first dose of pembrolizumab until the date of first recurrence [local, regional, or distant metastasis], a new primary melanoma, or death from any cause) in the intention-to-treat population. [d]The primary analysis for RFS was specified to occur after all patients completed ≥12 months on study and ≥40 RFS events were observed. Descriptive analysis was specified to occur when ≥51 RFS events were observed. [e]Investigator-assessed DMFS was defined as the time from first dose of pembrolizumab until the date of first distant recurrence or death from any cause. [f]The stratified log-rank test was used for comparison. [g]Time of database cutoff was November 14, 2022.

Primary Efficacy Endpoint: RFS[1]



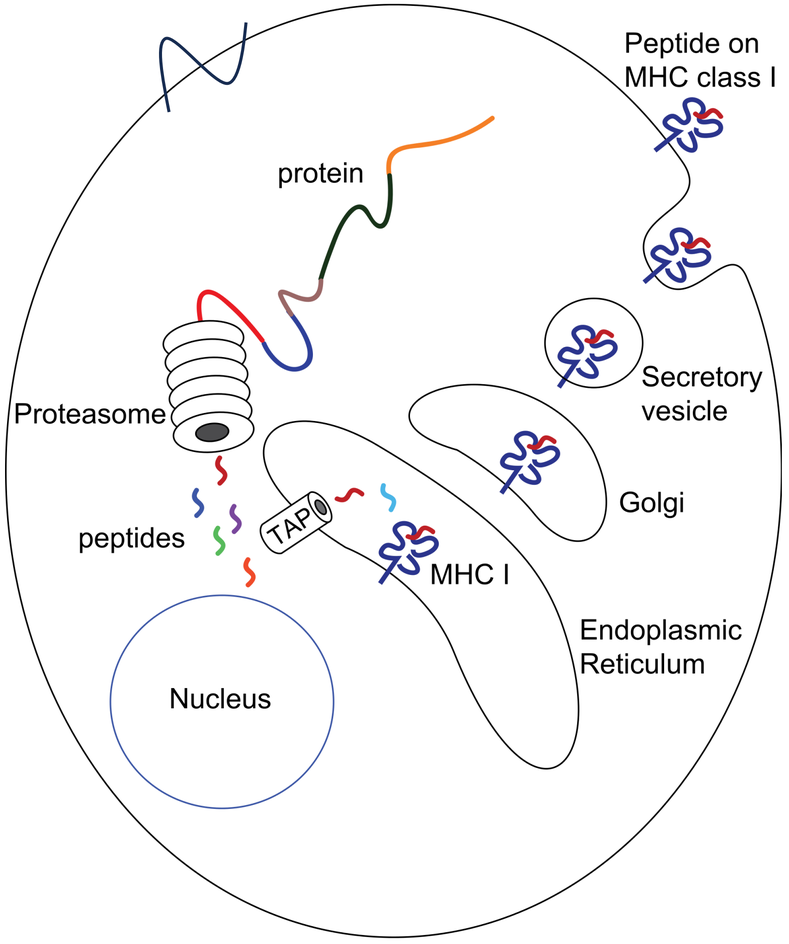
[a]The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. The *P* value is based on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

1. Khattak A, et al. Presented at the American Association for Cancer Research® (AACR) Annual Meeting; April 14-19, 2023; Orlando, FL, USA. Oral presentation CT001.

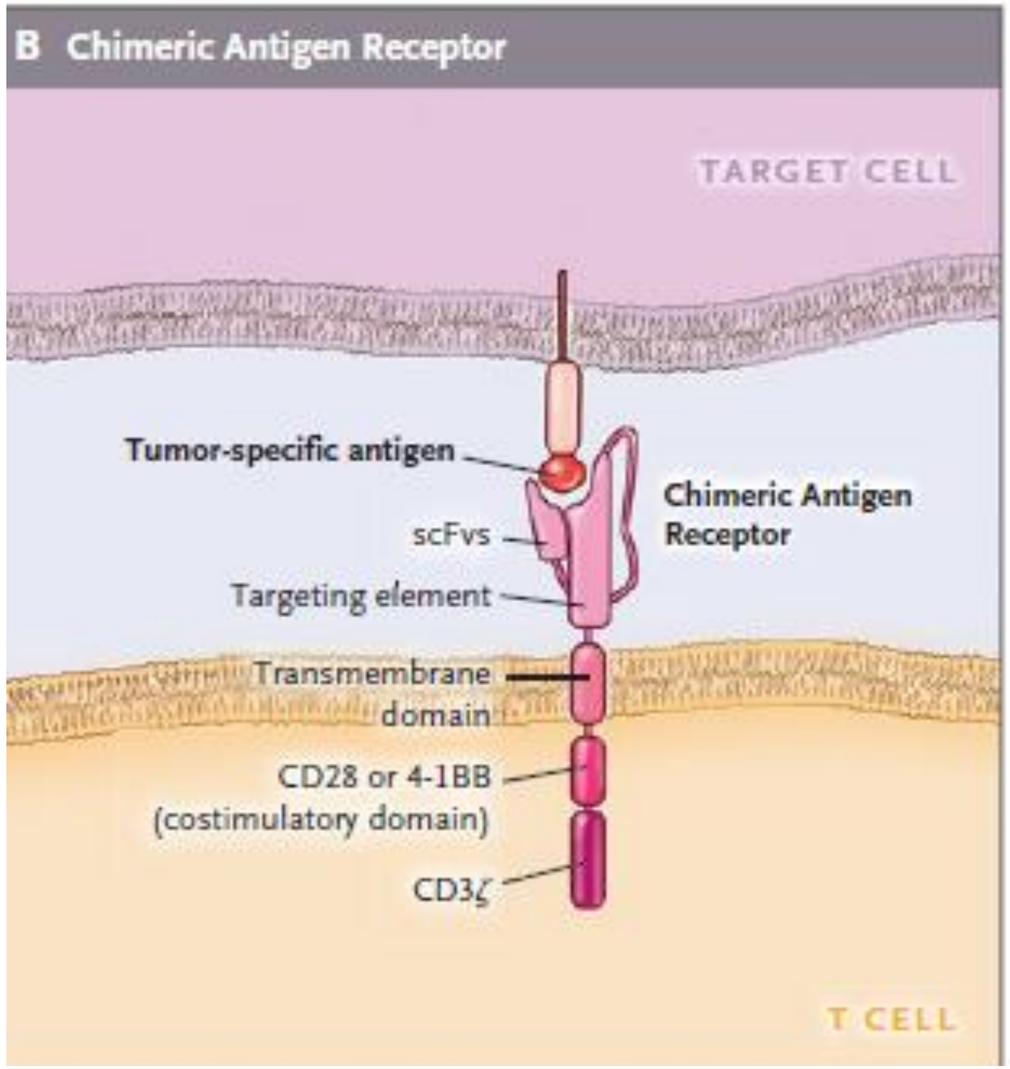
PART 2 of Targeted IO: The Surfaceome

NORTH CAROLINA
Oncology Association

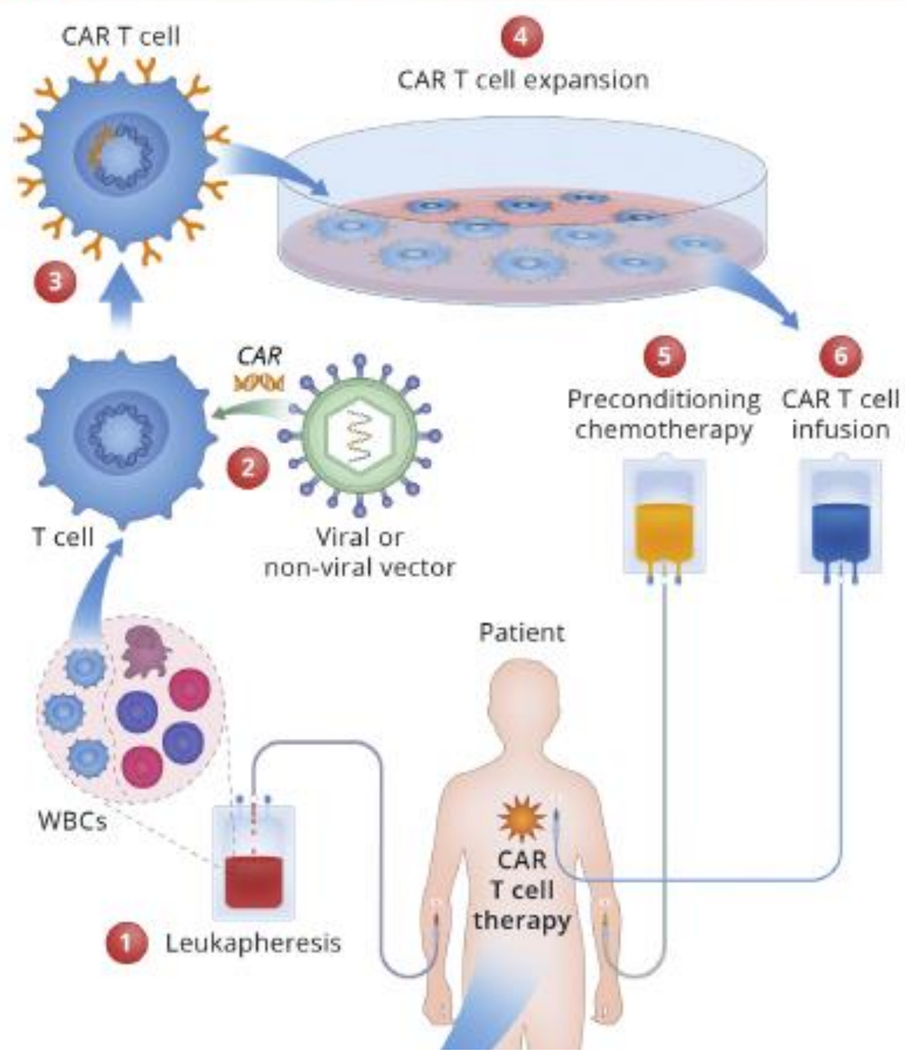
Limitations of the (unmodified) T Cell



Chimeric Antigen Receptor T-cell therapy (CAR T)



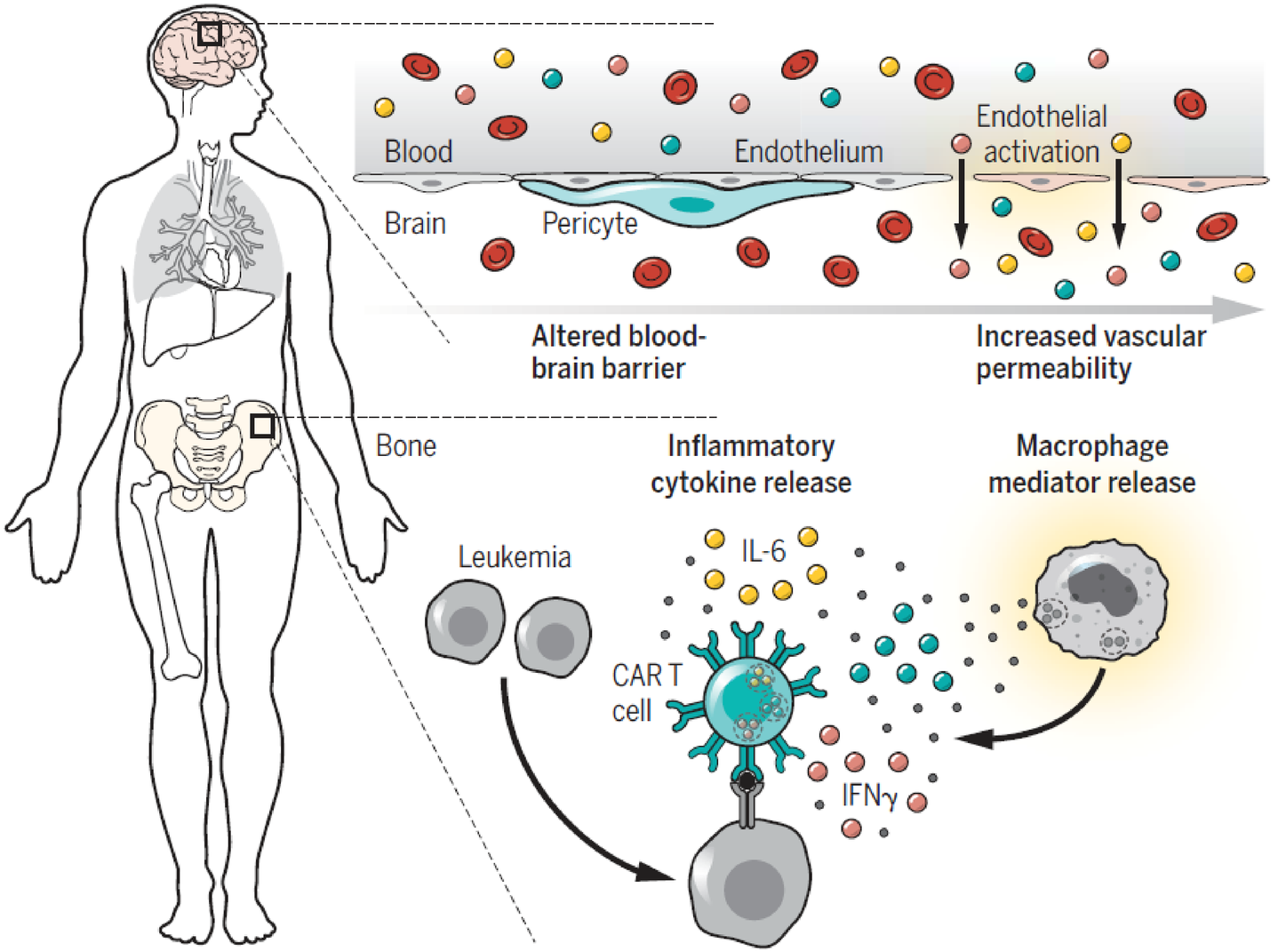
June and Sandelain, NEJM 2018



Ganatra et al – JACC 2019

NORTH CAROLINA Oncology Association

CAR-T Side Effects



Neurotoxicity

Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability

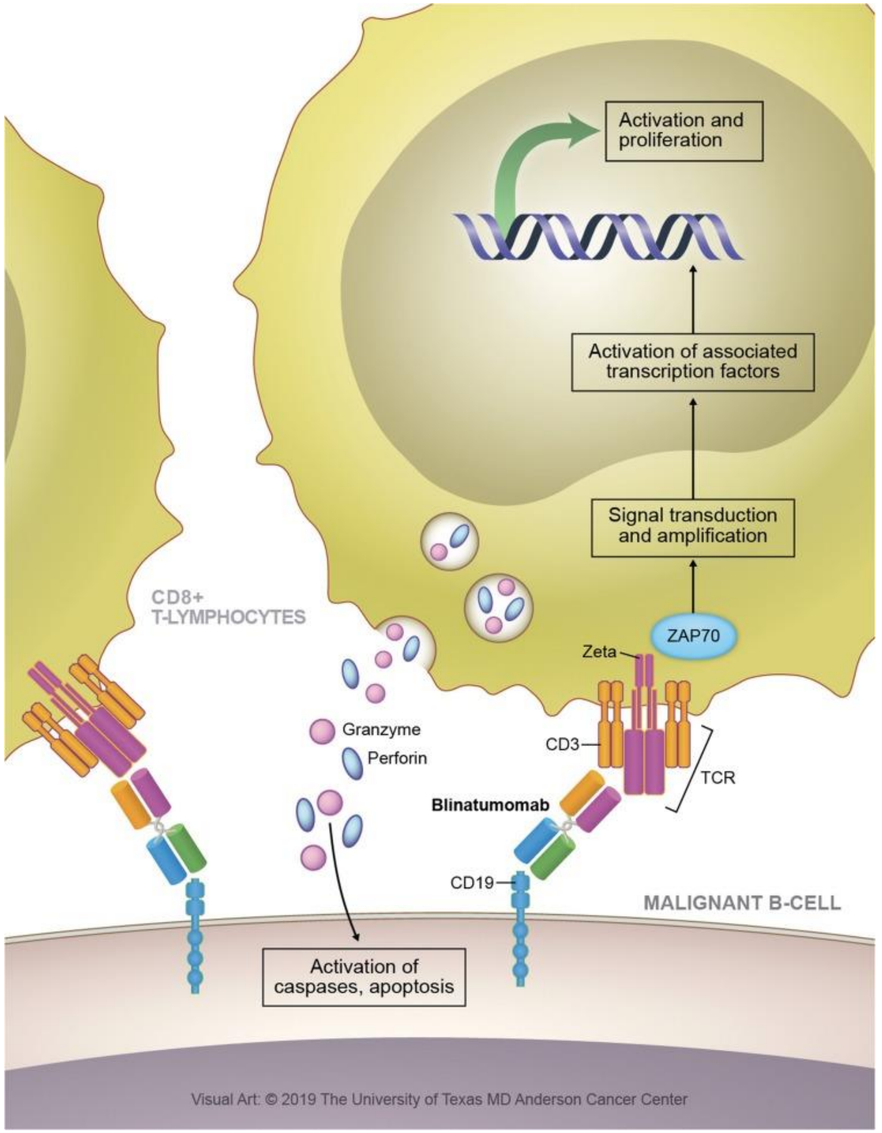
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction

AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

June et al., Science 2018

Modified Antibodies As Targeted Immunotherapy—The BiTe

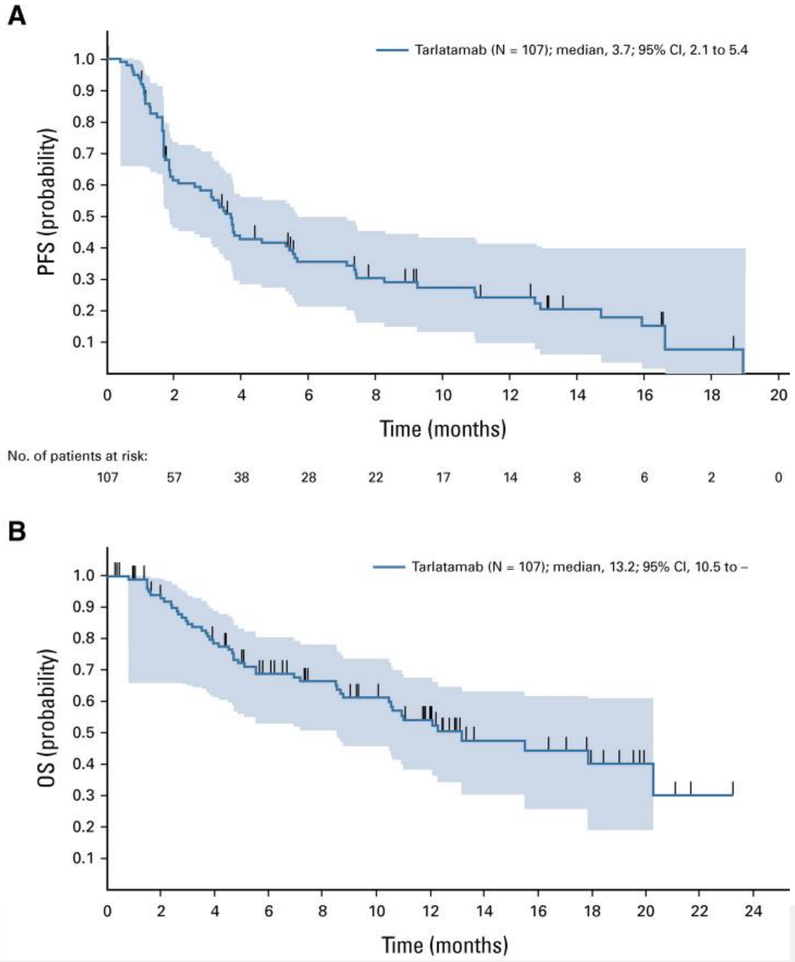


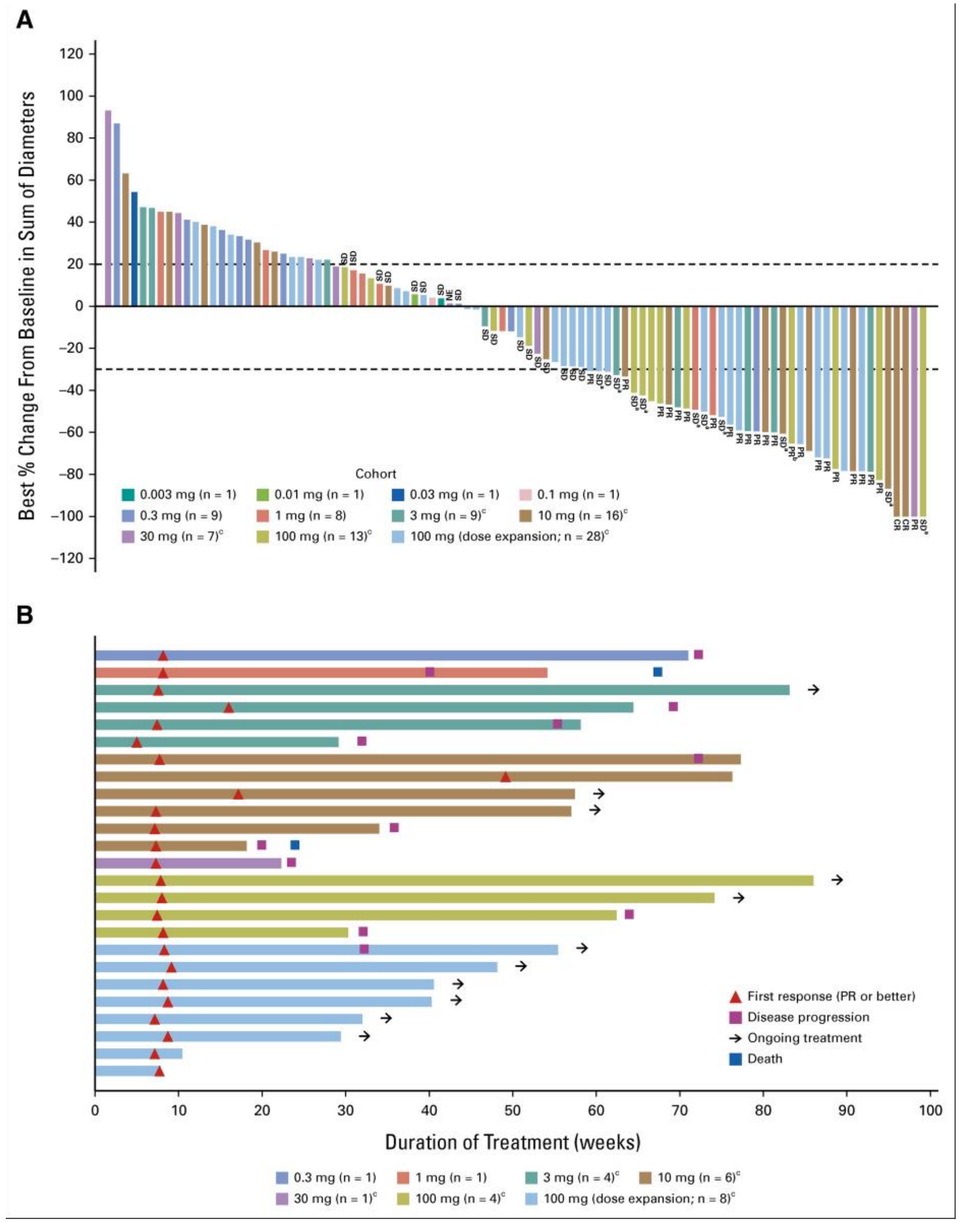
Franquiz, Biologics 2020

NORTH CAROLINA Oncology Association

Tarlatamab

- MOA: BITE
- Tox: CRS in 52%, G3 in 1%; Neurologic in 70%, 1% G3
- RR: 23%, but 30%+ at higher doses





Paz-Ares JCO 2023

NORTH CAROLINA Oncology Association

Conclusions

- Immunotherapy, beyond checkpoint inhibitors, appears promising widely for solid tumors.
- The immunopeptidome is the set of peptides present by tumor cells. These can be actioned by T cells, including:
  - TCR and related products (Tebentafusp already approved)
  - T-cell vaccines (Such as PANDA-Vac). Vaccines are polyfunctional.
- The surfaceome is the set antigens on the surface of the cancer cell. These can be actioned by antibodies and anti-body constructs including:
  - CAR-T
  - CAR-M
  - BiTE
- TILs are likely to be FDA approved for melanoma than lung cancer soon. They do not require genomics/bioinformatic predictions, but do require surgery, flu/cy, and HD IL-2. They are polyfunctional.

Personalized Immunotherapy Research Lab

The Personalized Immunotherapy Research Lab (PIRL) is a multi-investigator research group at the University of North Carolina's School of Medicine, whose members bring together expertise in **immunology**, **genomics**, **oncology**, and **machine learning**. We work on developing cancer immunotherapies that use a patient's immune system to attack specific mutations from their cancer.

The goal of our research is to use experimental insights and novel computational tools to start new investigator-initiated early phase clinical trials at UNC, the first of which is PANDA-VAC. We are also committed to *open science* through building open source research software, making experimental data unconditionally available, and disseminating results quickly through blog posts and preprints.

Principal Investigators

Dr. Benjamin Vincent, MD

Bio | Scholar

Dr. Alex Rubinsteyn, PhD

Bio | Scholar | GitHub | ORCID | Twitter

Dr. Jared Weiss, MD

Bio | Scholar

NORTH CAROLINA Oncology Association

https://pirl.unc.edu/rese

Questions?

NORTH CAROLINA Oncology Association