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UNC CANCER CARE

Advances in Immunotherapy – What the Future May Hold

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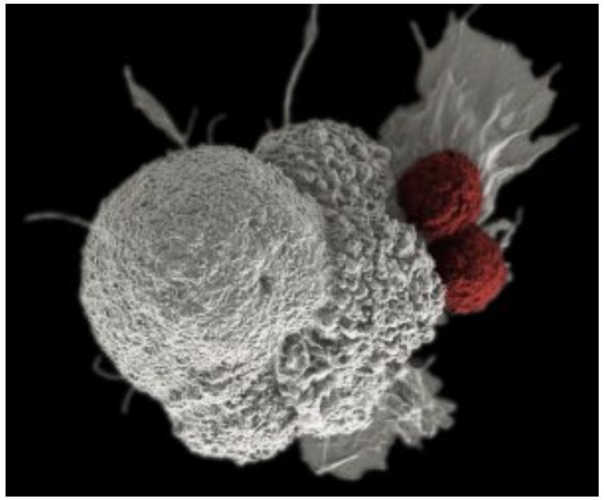


Electron micrograph of T cells (red) attacking cancer cells (white). Source: National Cancer Institute Duncan Comprehensive Cancer Center at Baylor College of Medicine

Hawaii Society of Clinical Oncology
2023 Annual Conference

October 21st, 2023

Disclosures

- Sheth: no relevant disclosures to this talk

- Full COI Disclosure: https://coi.asco.org/share/F3K-WRFQ/Siddharth%20Sheth

Great to be back in Hawaii!

Classes of Cancer Directed Therapies

Cytotoxic Chemo

- Alkylating Agents
- Antimetabolites
- Antimicrotubular Agents
- Topoisomerase Inhibitors
- Cytotoxic Antibiotics

Hormone Therapy

- Anti-estrogens
- Anti-androgens
- Peptide Hormones

Targeted Therapy

- Biologic Agents (mAbs)
- Small Molecules (TKIs)
- Antibody-Drug Conjugates

Immunotherapy

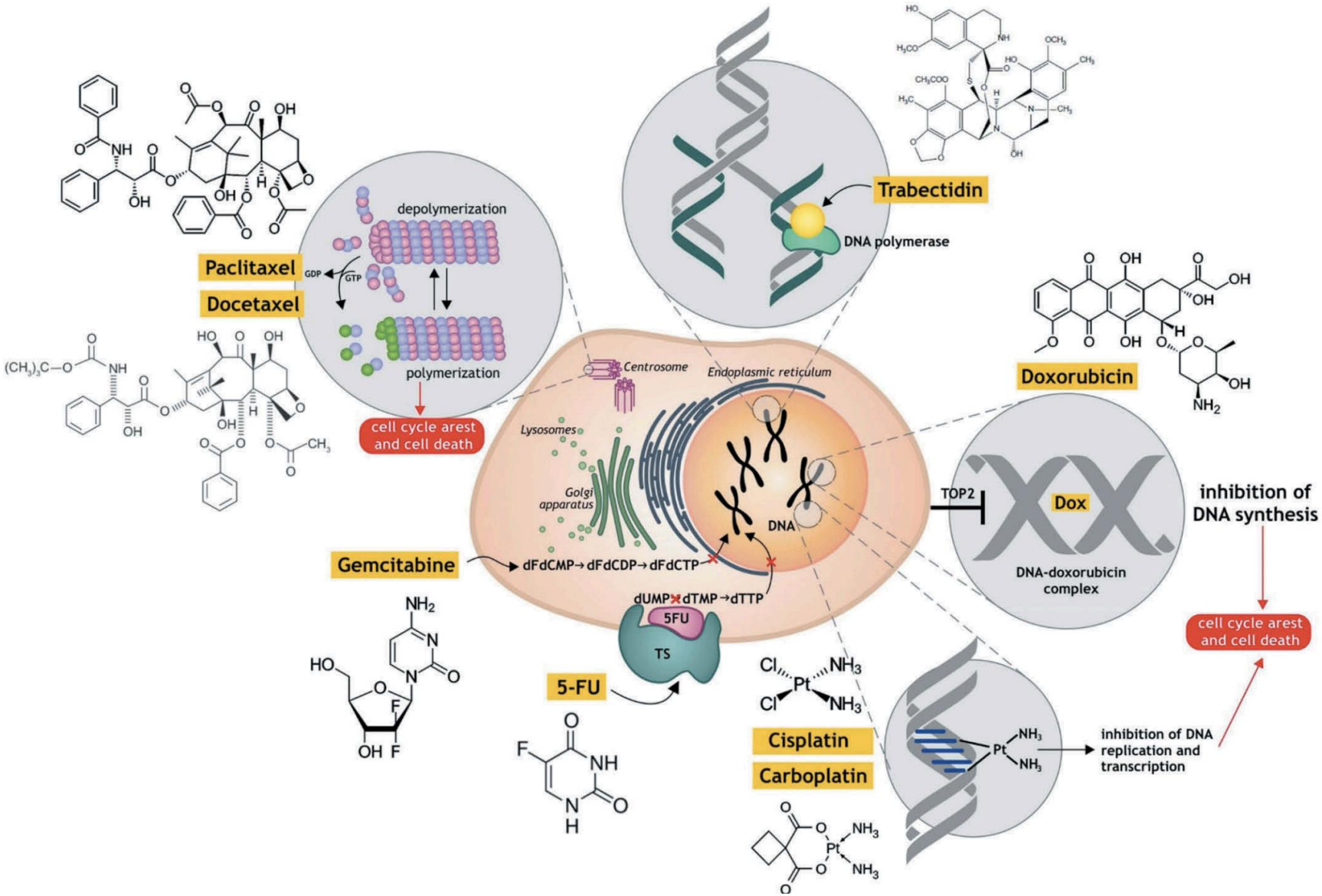
- Checkpoint Inhibitors
- Cellular Therapies
- Bi-specific T-cell Engagers
- Cytokine Therapy
- Oncolytic Viruses

Agenda

1. Past
2. Present
3. Future

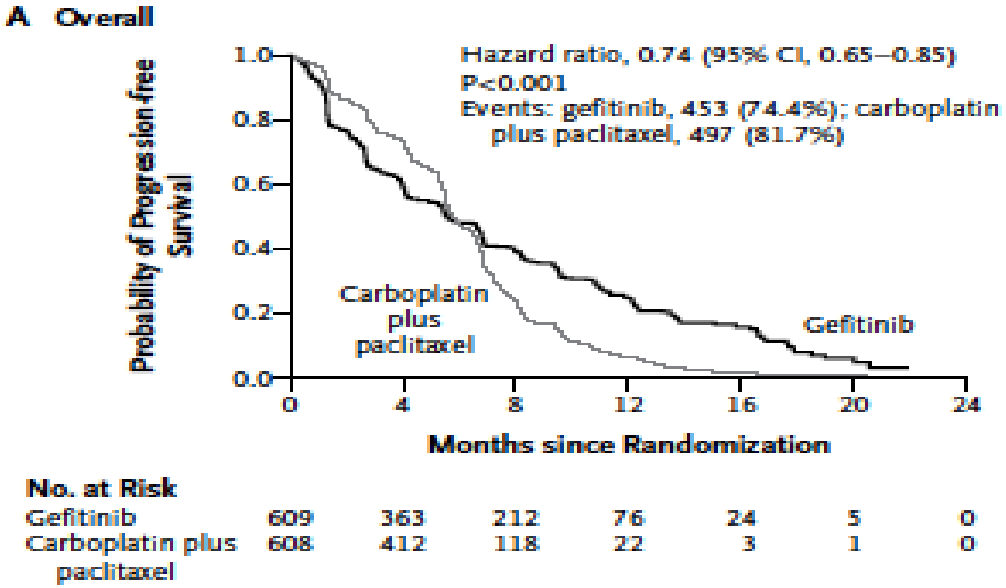
How did we get here?

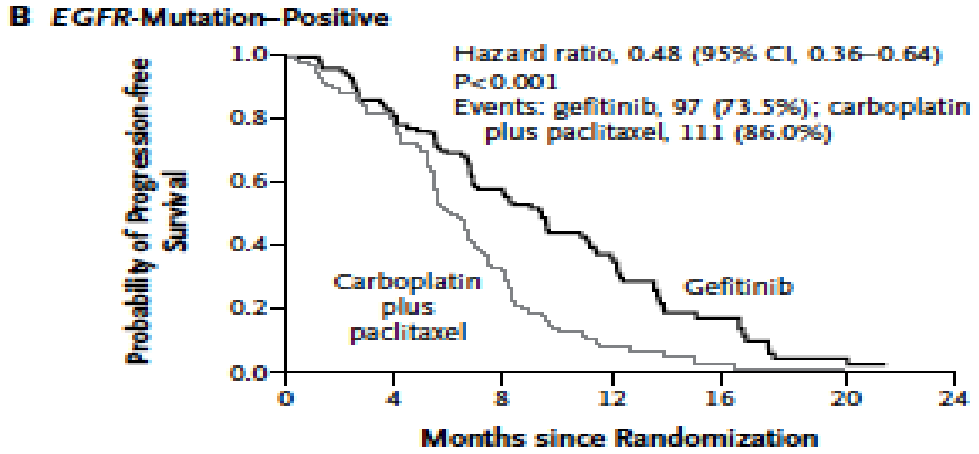
Chemotherapy

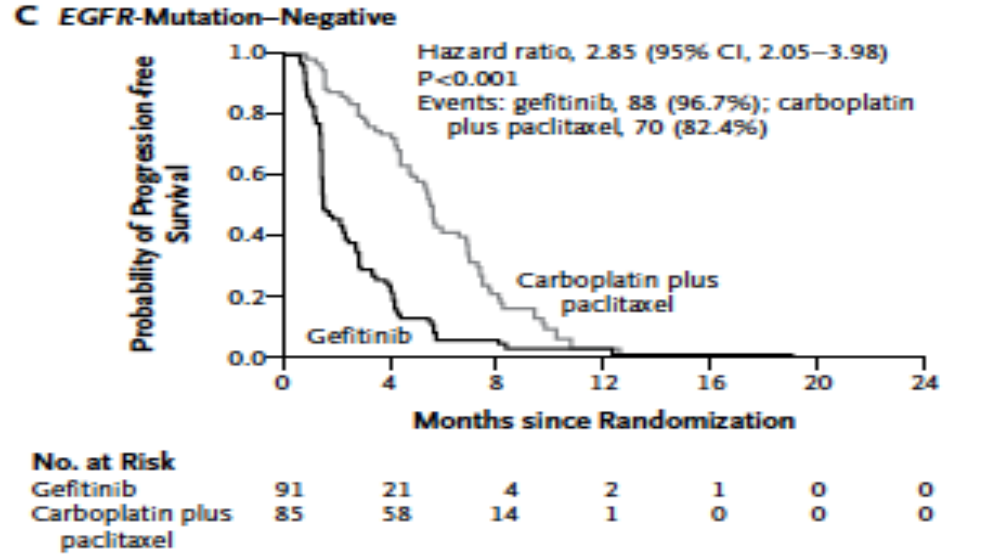


Larionova. Oncoimmunology. 2019

Targeted Therapies

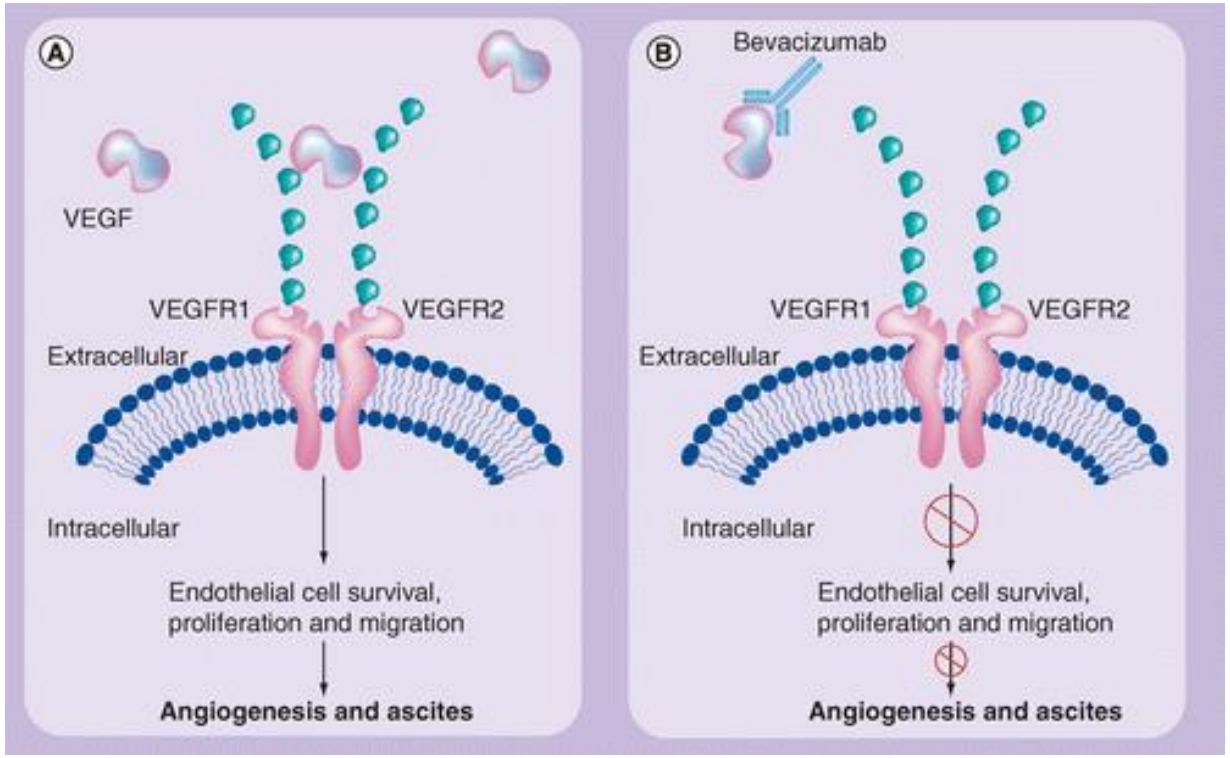


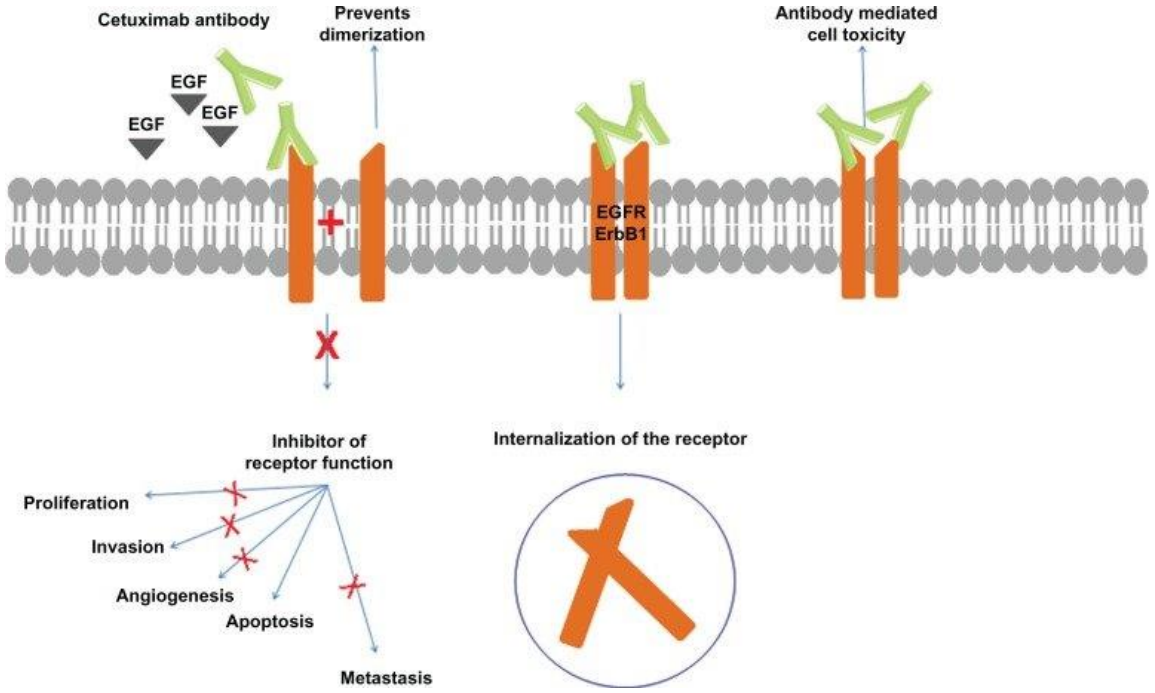




Mok. NEJM. 2009

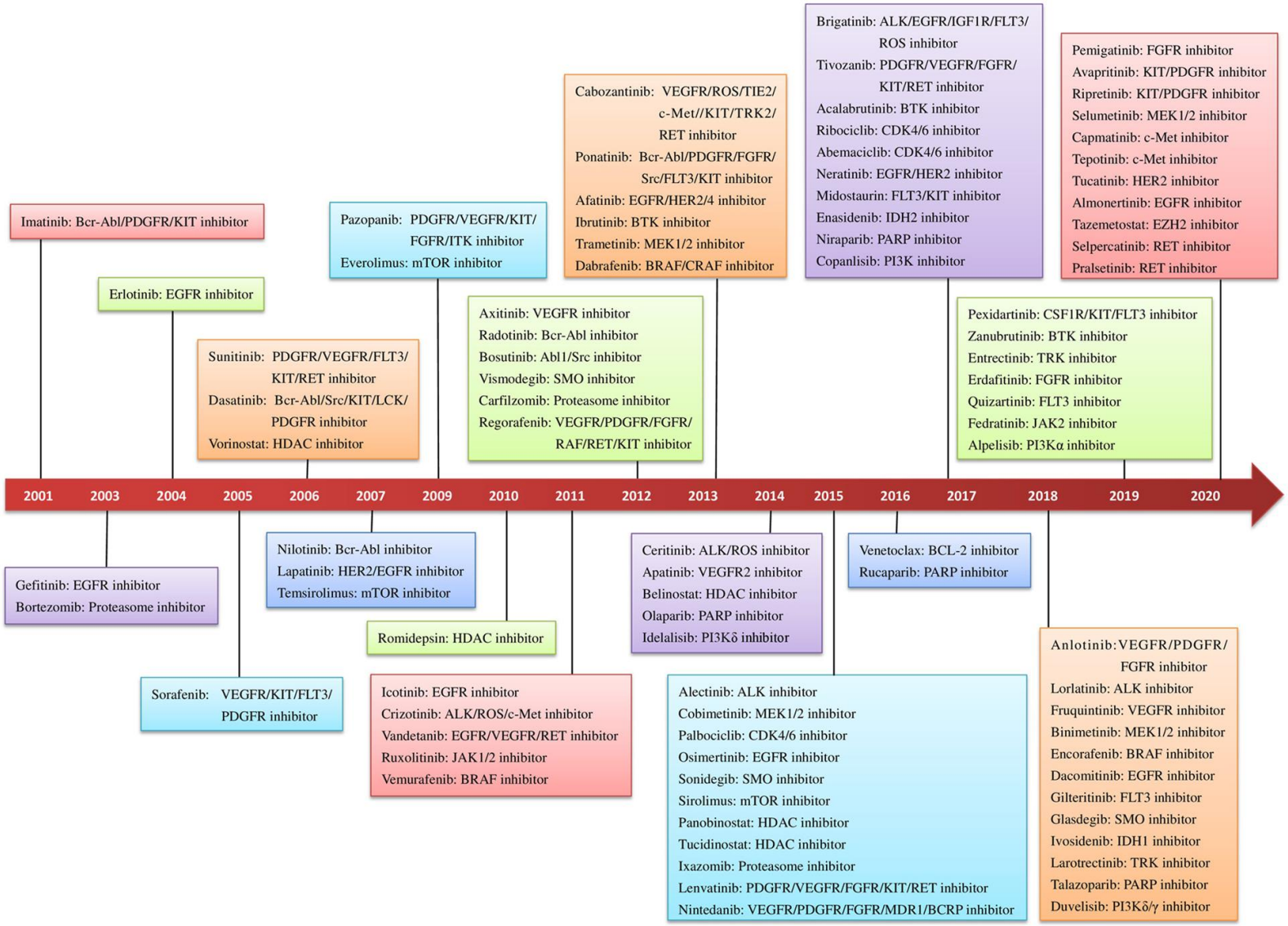
Targeted Therapies





Eskander. IJWH. 2012
Patil. Biologic Targets and Therapy. 2012

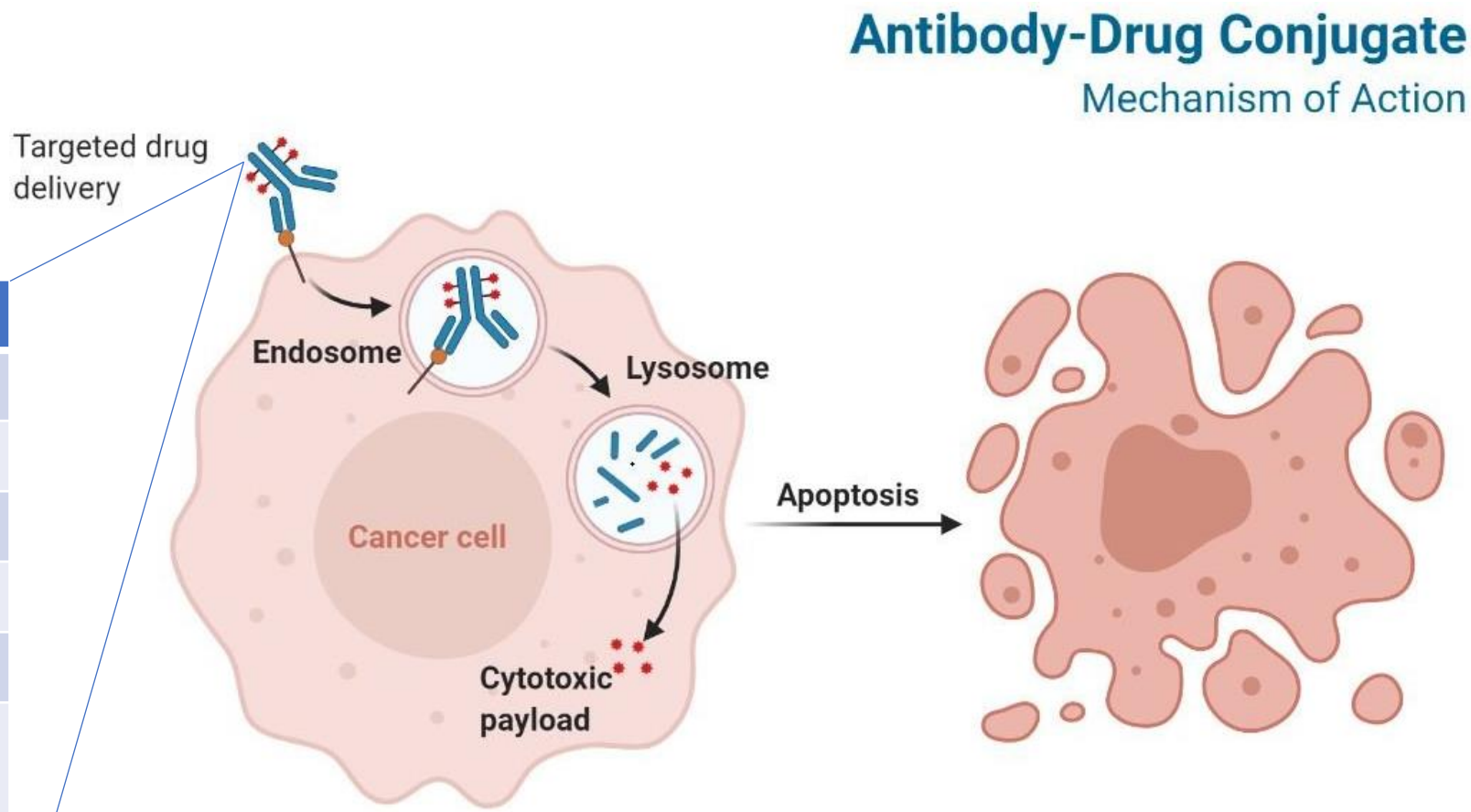
(Growing) List of FDA Approved Targeted Therapies



Zhong. Signal Transduction and Target Therapy. 2021

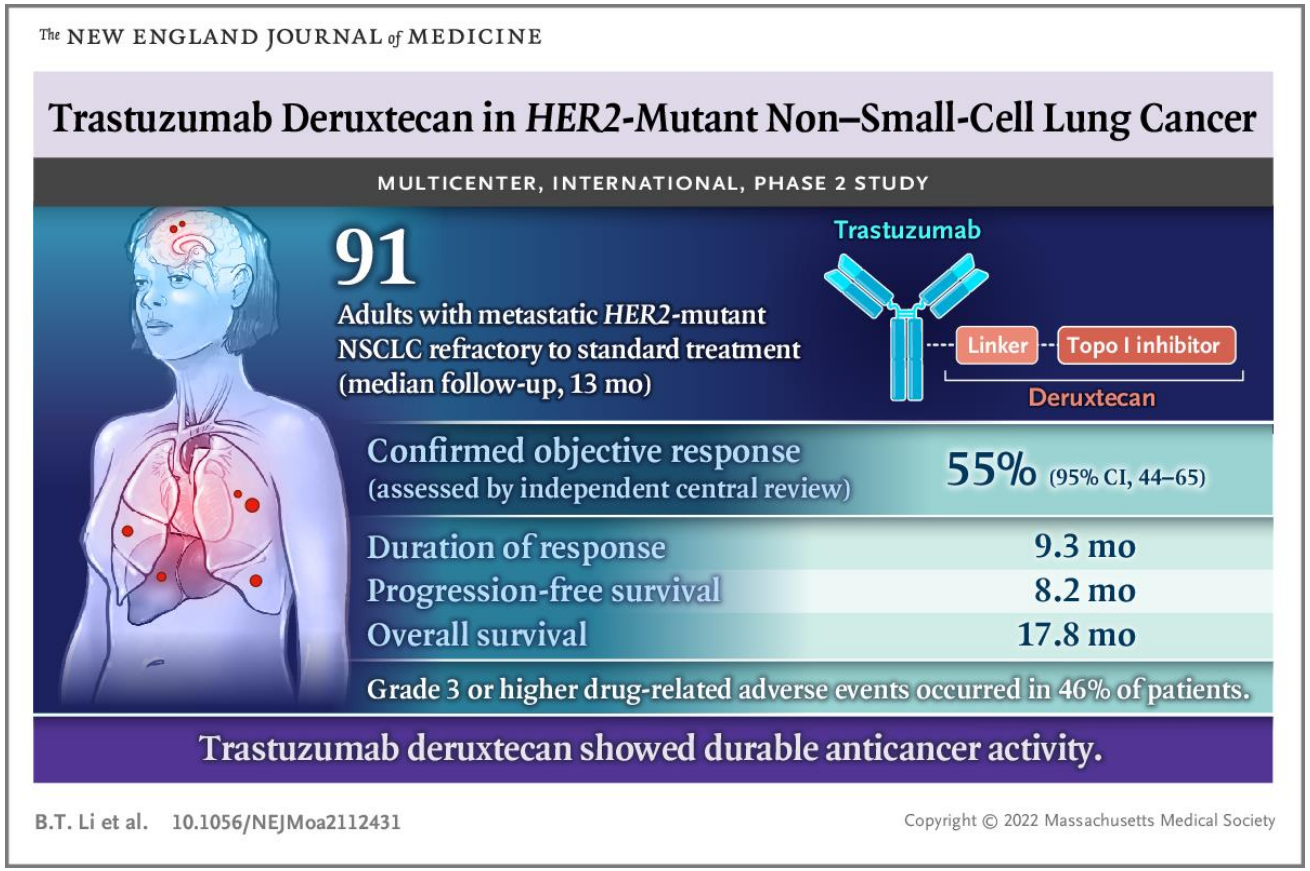
Antibody Drug Conjugates (ADCs)

Target	Drug
HER2	T-DM1 & T-Dxd
CD30	Brentuximab Vedotin
Nectin-4	Enfortumab Vedotin
BCMA	Belantamab Mafodotin
TF	Tisotumab Vedotin
CD33	Gemtuzumab Ozogamicin
CD-19	Loncastuximab Tesirine
Trop-2	Sacituzumab Govitecan



Genscript.com; 2021

ADC in NSCLC



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)

ADC are well tolerated but have real toxicities!

Cytotoxic Payload Side Effects

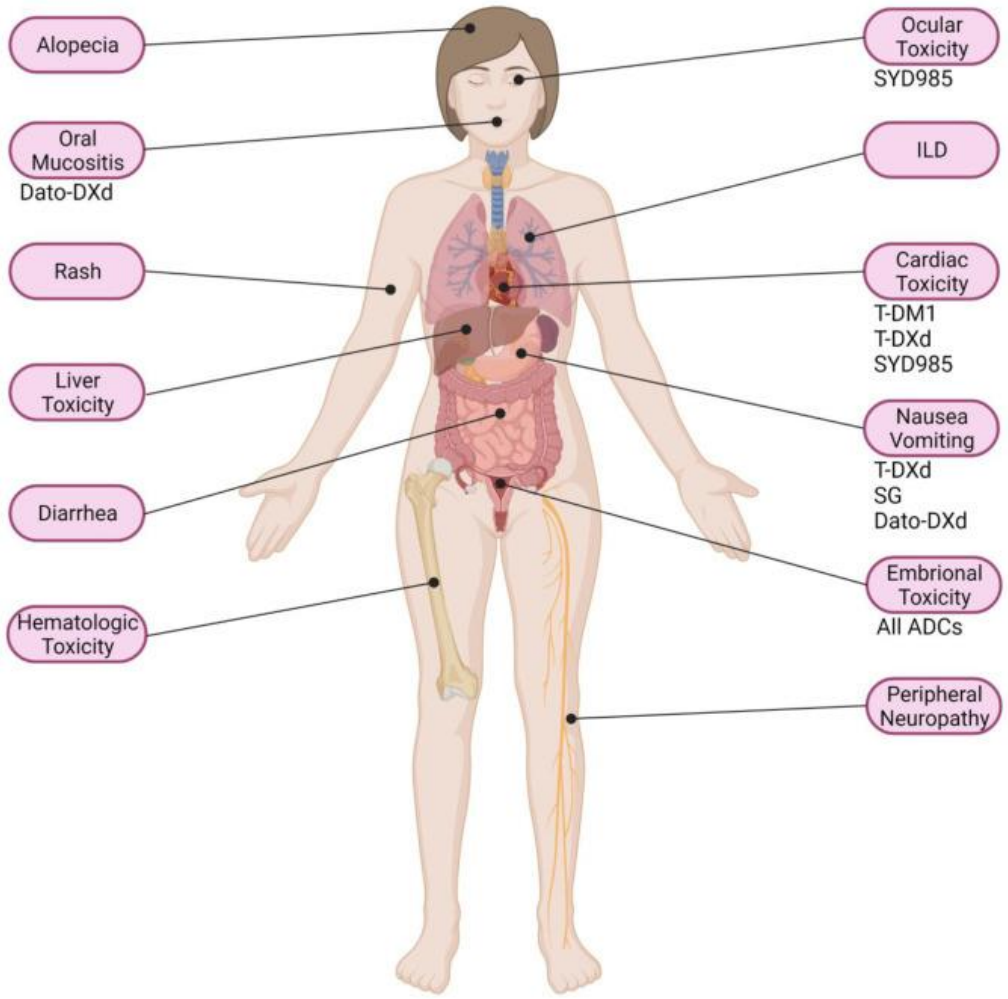
- Class effects: myelosuppression, nausea
- ADC specific effects:
  1. Vedotin: peripheral neuropathy
  2. Deruxtecan: pulmonary toxicity
  3. Ozogamycin: hepatotoxicity (VOD/SOS)

Antibody Side Effects

- Generally, well tolerated
- Class effects: infusion-related reactions
- Trastuzumab: Cardiotoxicity

Linker Effects:

- Unclear direct effects
- Alters release kinetics of cytotoxic payload
- Cleavable & non-cleavable linkers



Khongorzul P, et al., *Mol Cancer Res.* 2020 Jan;18(1):3-19.

Challenges with our mainstream therapies

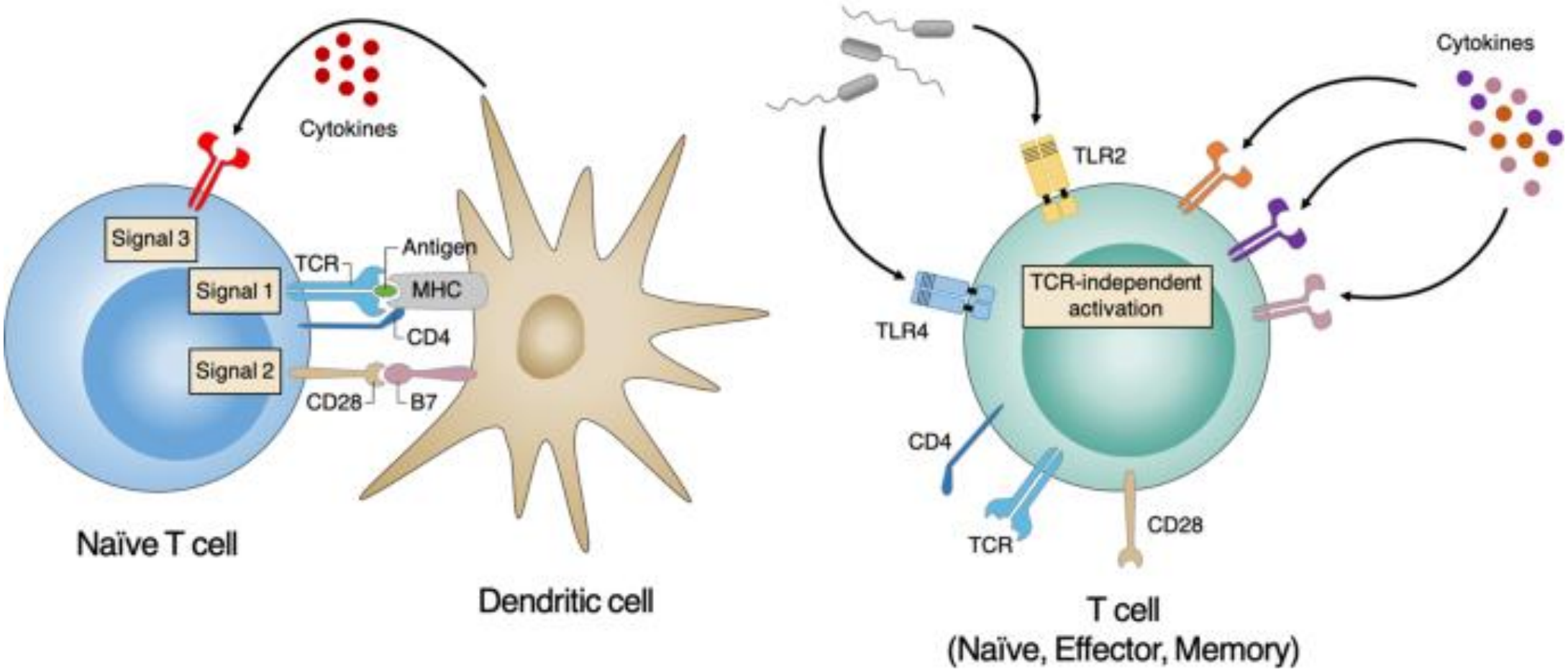
#1 Often response rates are modest and may not confer a survival benefit

#2 Drug resistance

#3 Lack of biomarkers for optimal patient selection

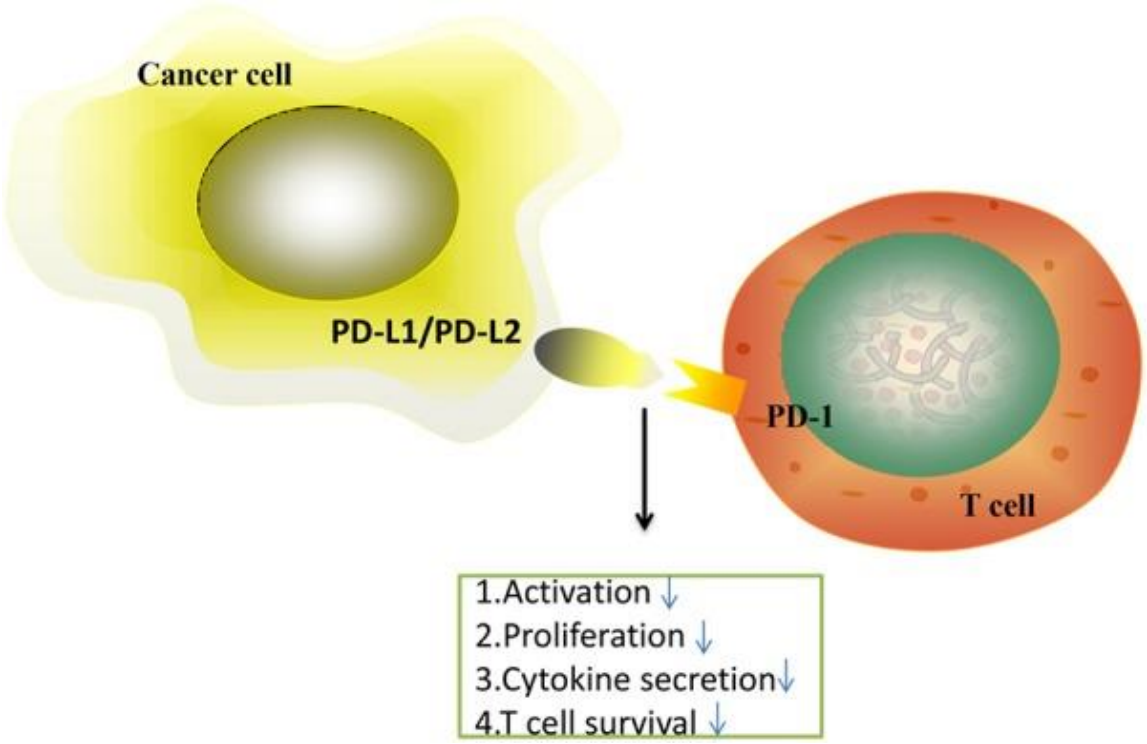
The Present

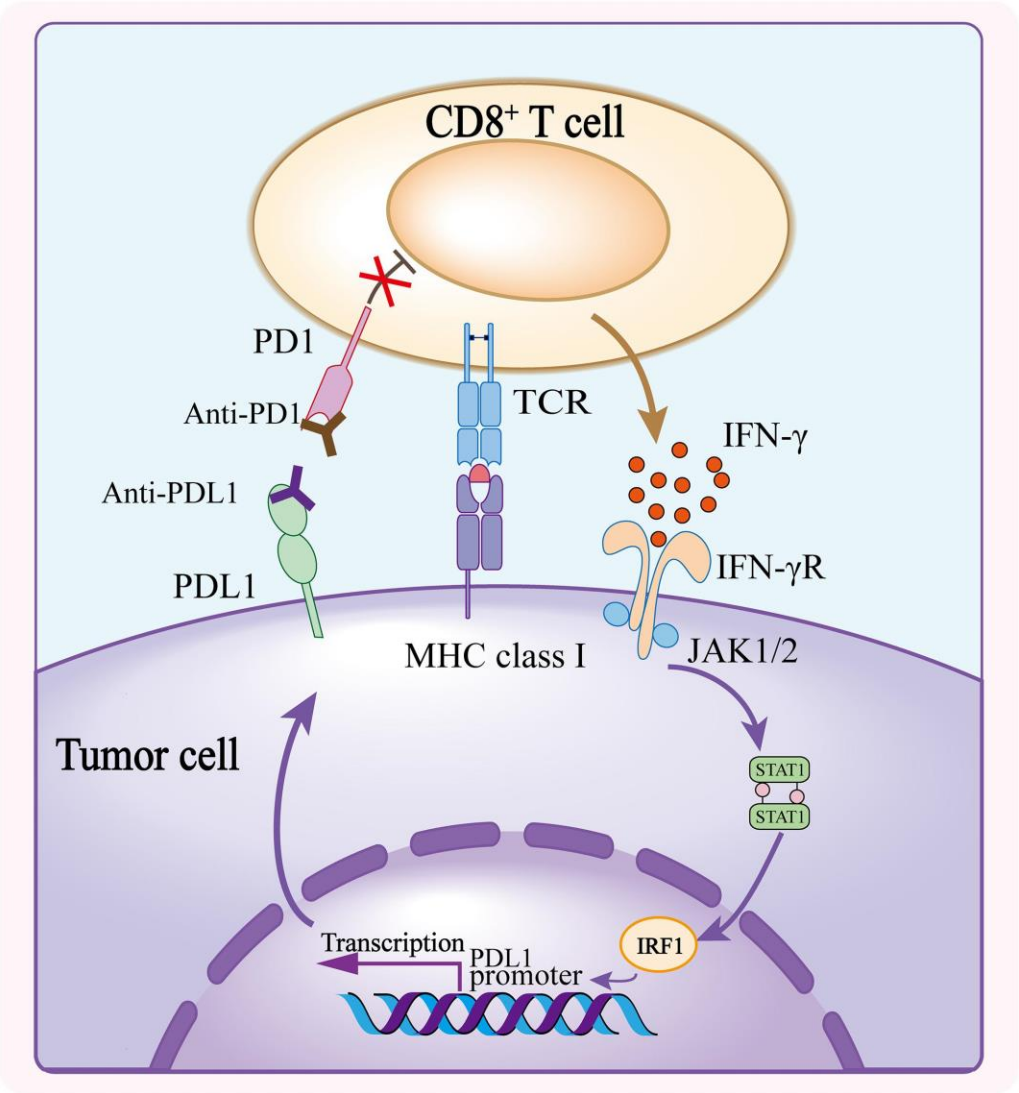
The T Cell



Lee. Nature EMM. 2020

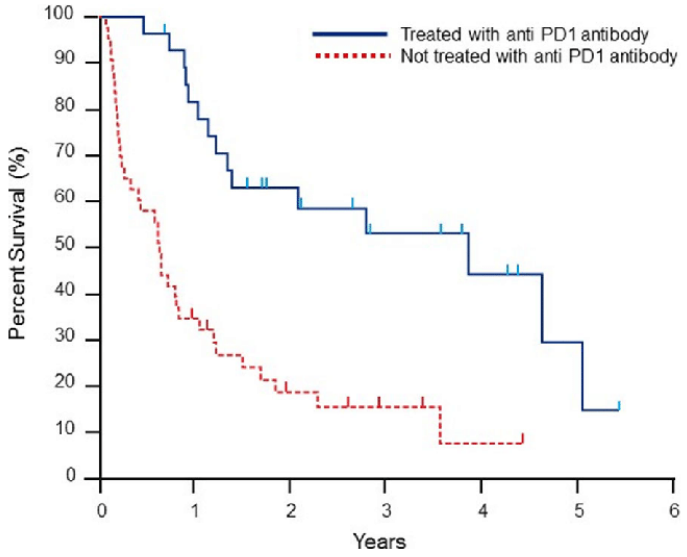
PD1 Mechanism of Action

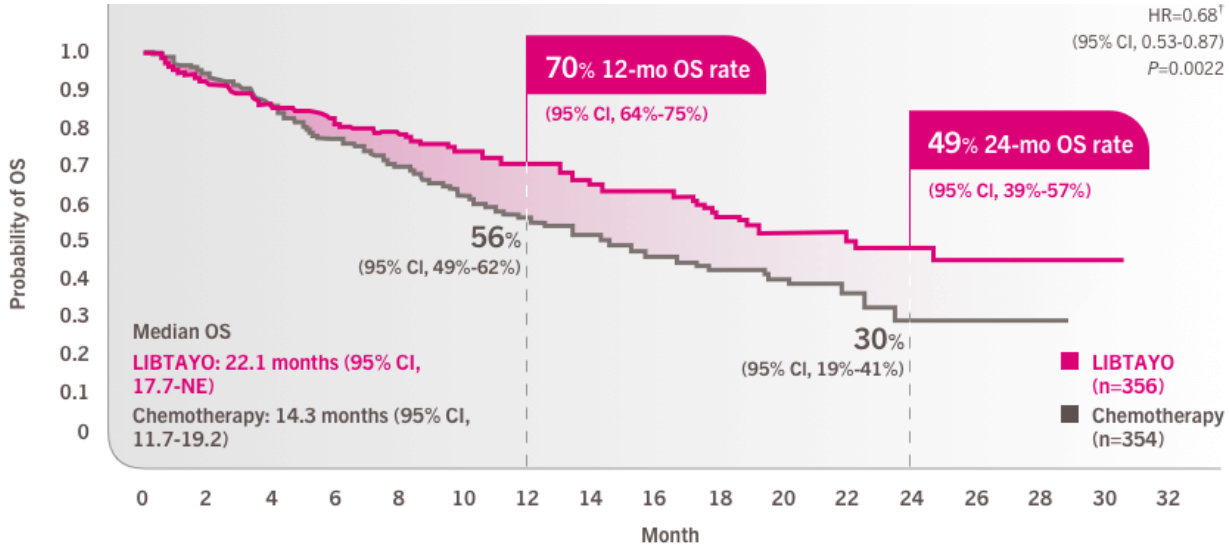


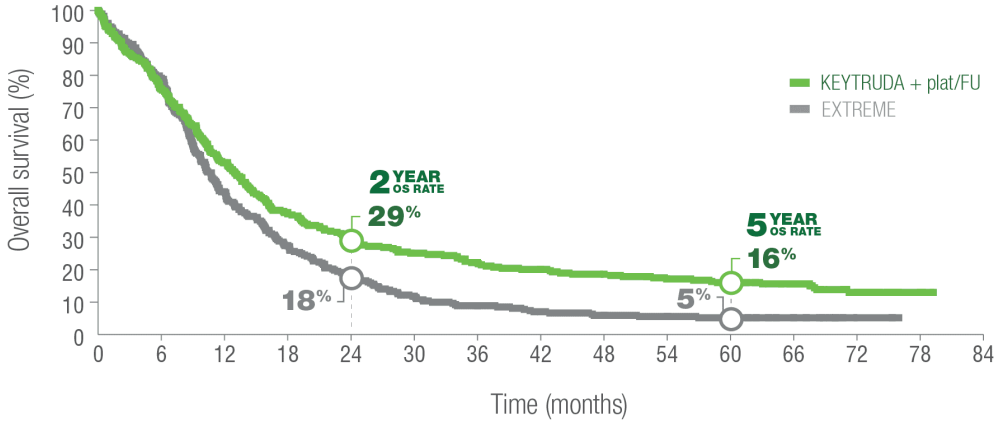


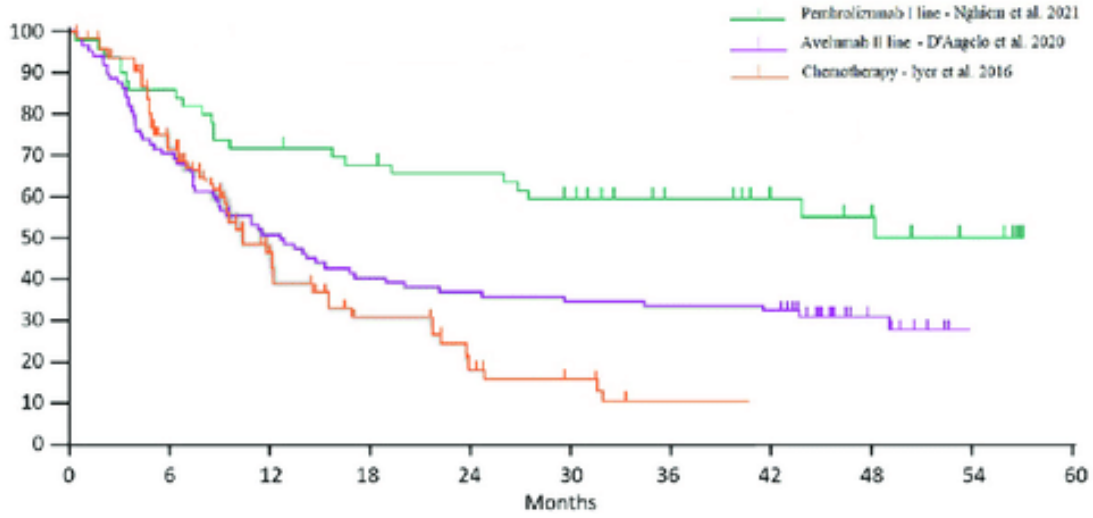
Lei. Frontiers Cell Dev Biol. 2020

Clinical Benefit with PD1/PDL1 therapy is real and significant!





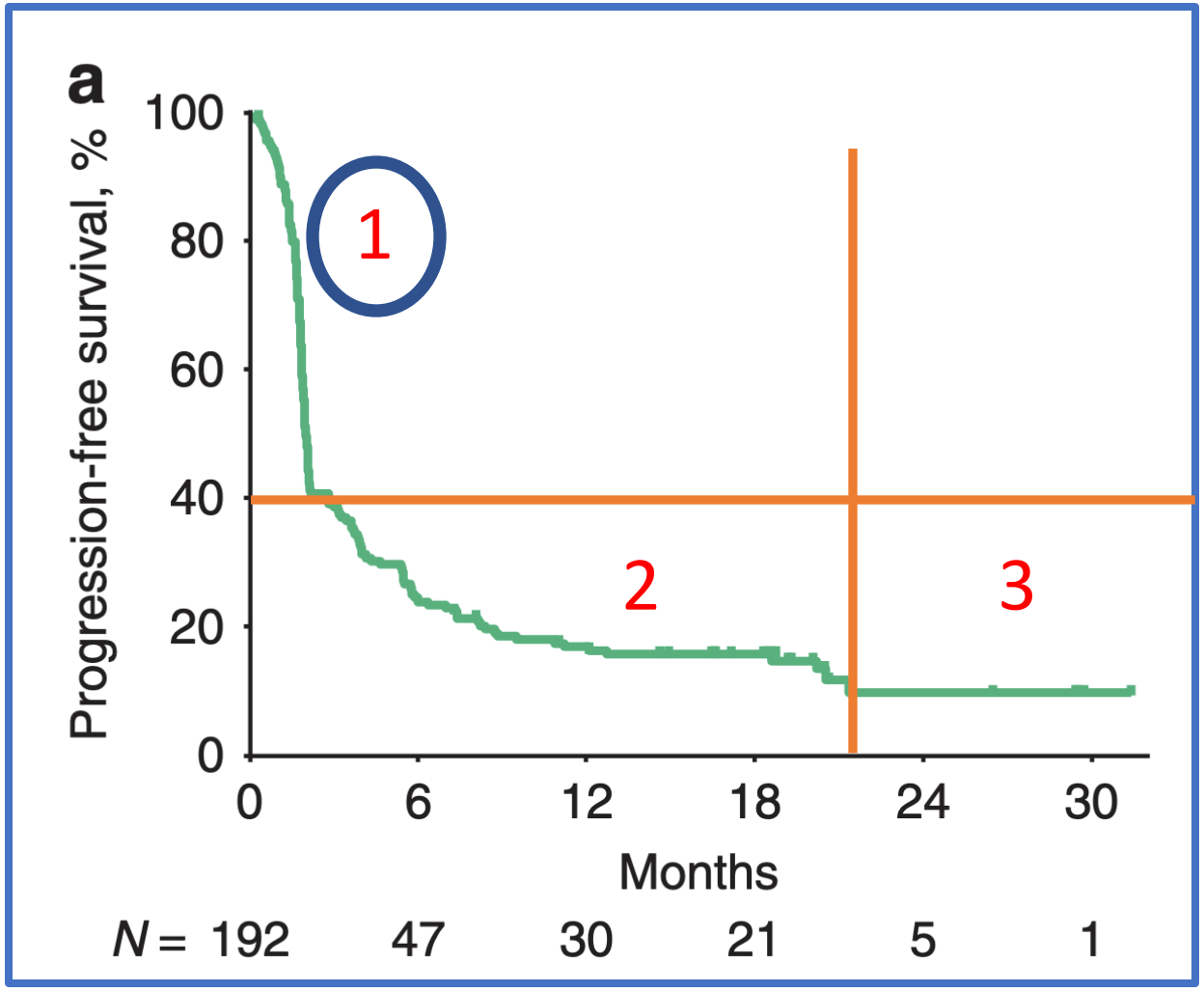




Gogishvili. Nature Medicine. 2022
Burtness. Lancet. 2010

Tanda. Frontiers. 2021
Vosoughi. BMC Cancer. 2018

What we don't talk enough about…



Zhu. Frontiers Oncology. 2022

Bonfire Analogy: Enhancing Immune Response

“Cold” Tumor

Add in IO

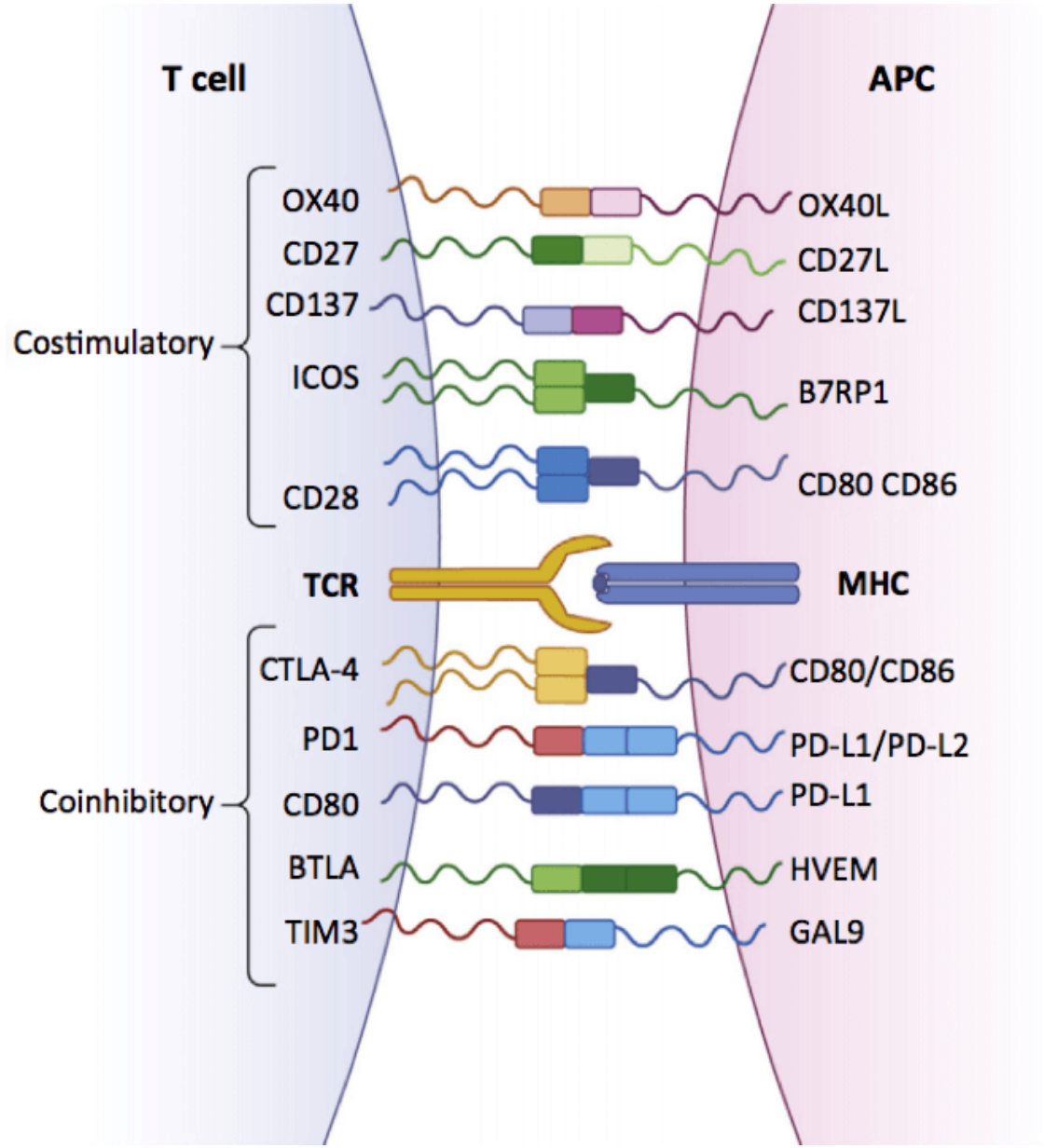
No Change

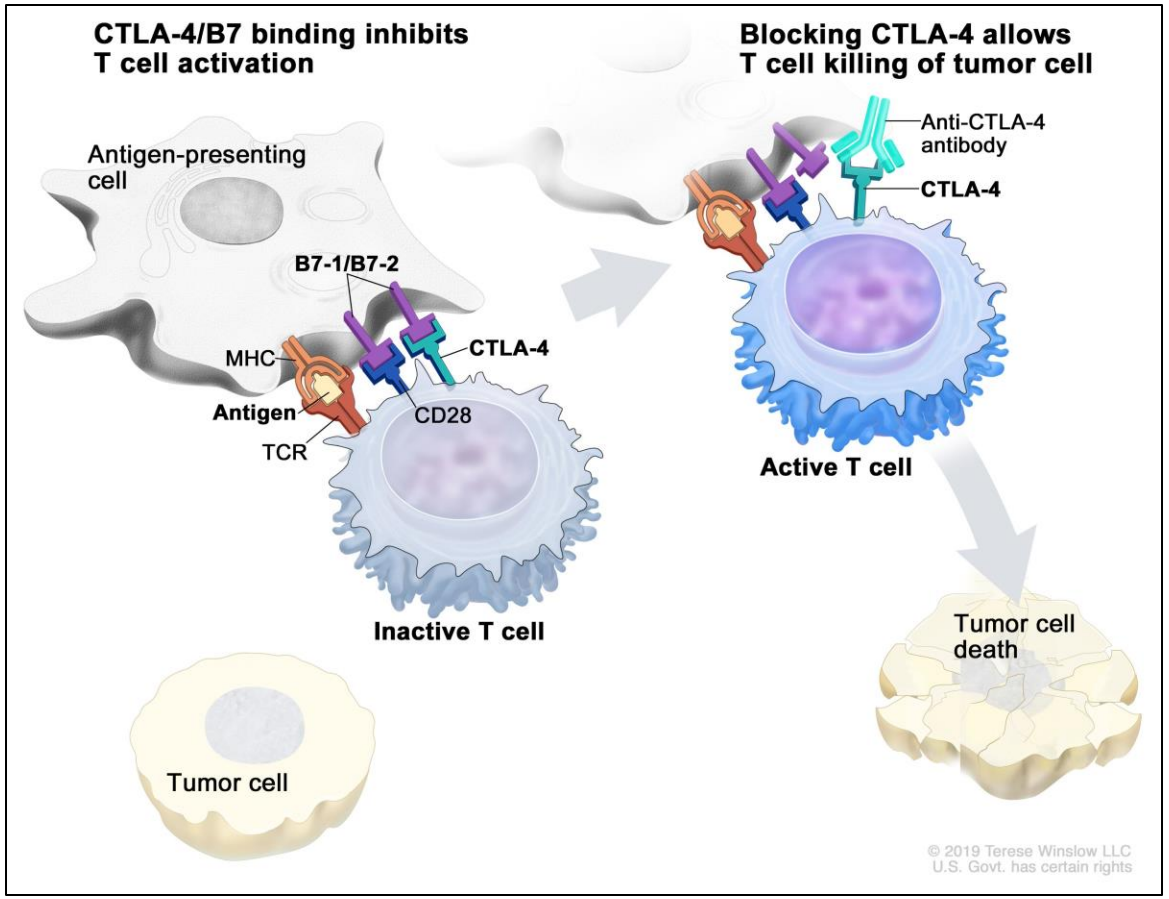
Light the fire with an “Adjuvant”

Add in IO

“Hot” Tumor

Combination Immunotherapies





Pico de Coana. Cell Press. 2015
PDQ Melanoma Treatment. 2016

Perhaps we don't give up on the old-timers yet…

- Neoadjuvant therapy in HNSCC is controversial
- Not SOC
- Intense research interest, particularly incorporating PD1 therapies

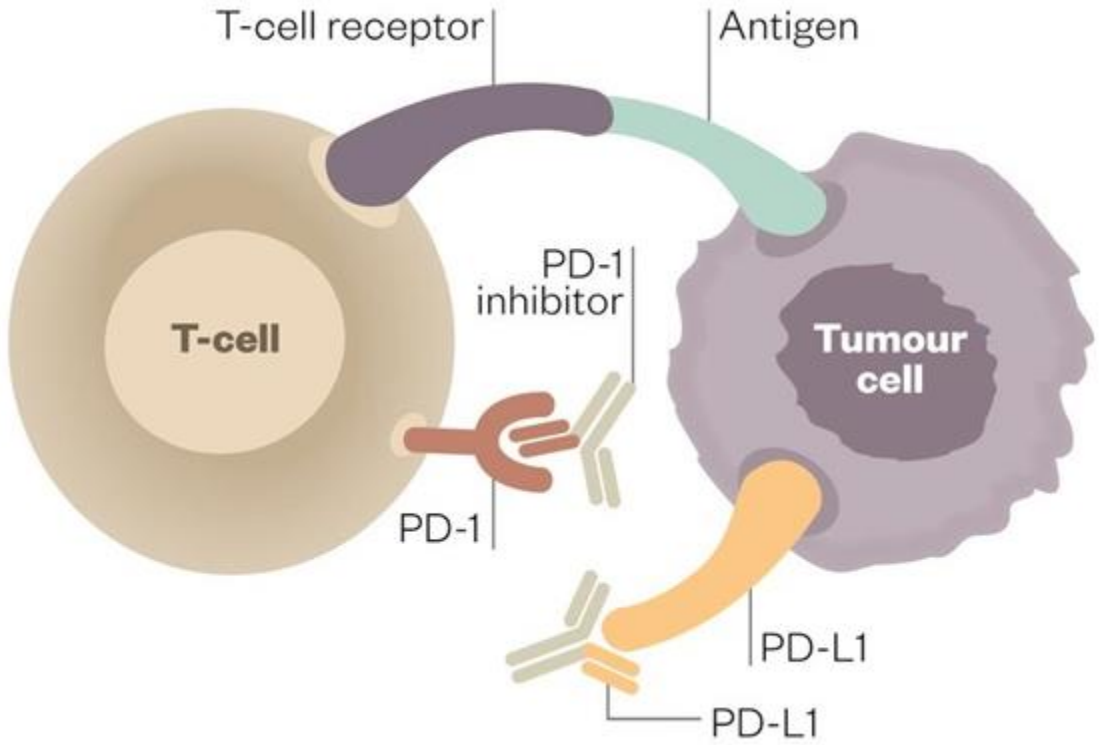
MPR=major pathologic response; pCR=complete pathologic response

Agent/s	MPR/pCR
PD1	~14%

Combination Therapies

Dual-Checkpoint Blockade
Checkmate 067
Ipilimumab + Nivolumab

Chemoimmunotherapy
Keynote 189
Carboplatin + Pemetrexed + Pembrolizumab



Immunotherapy + VEGF
Keynote 426
Pembrolizumab + Axitinib

PD-L1 + BRAF/MEK
Dabrafenib + Trametinib + Spartalizumab

Espie. Front. Immunol. 2022

The Future is here…

Disclaimer

I am not an expert in…

1. Immunology
2. Bioinformatics
3. Cellular therapy
4. Genetics
5. Virology

However, it is critically important that we become familiar with emerging therapies because your patients will be asking about these treatments.

Focus on novel immunotherapies

Cytotoxic Chemo

- Alkylating Agents
- Antimetabolites
- Antimicrotubular Agents
- Topoisomerase Inhibitors
- Cytotoxic Antibiotics

Hormone Therapy

- Anti-estrogens
- Anti-androgens
- Peptide Hormones

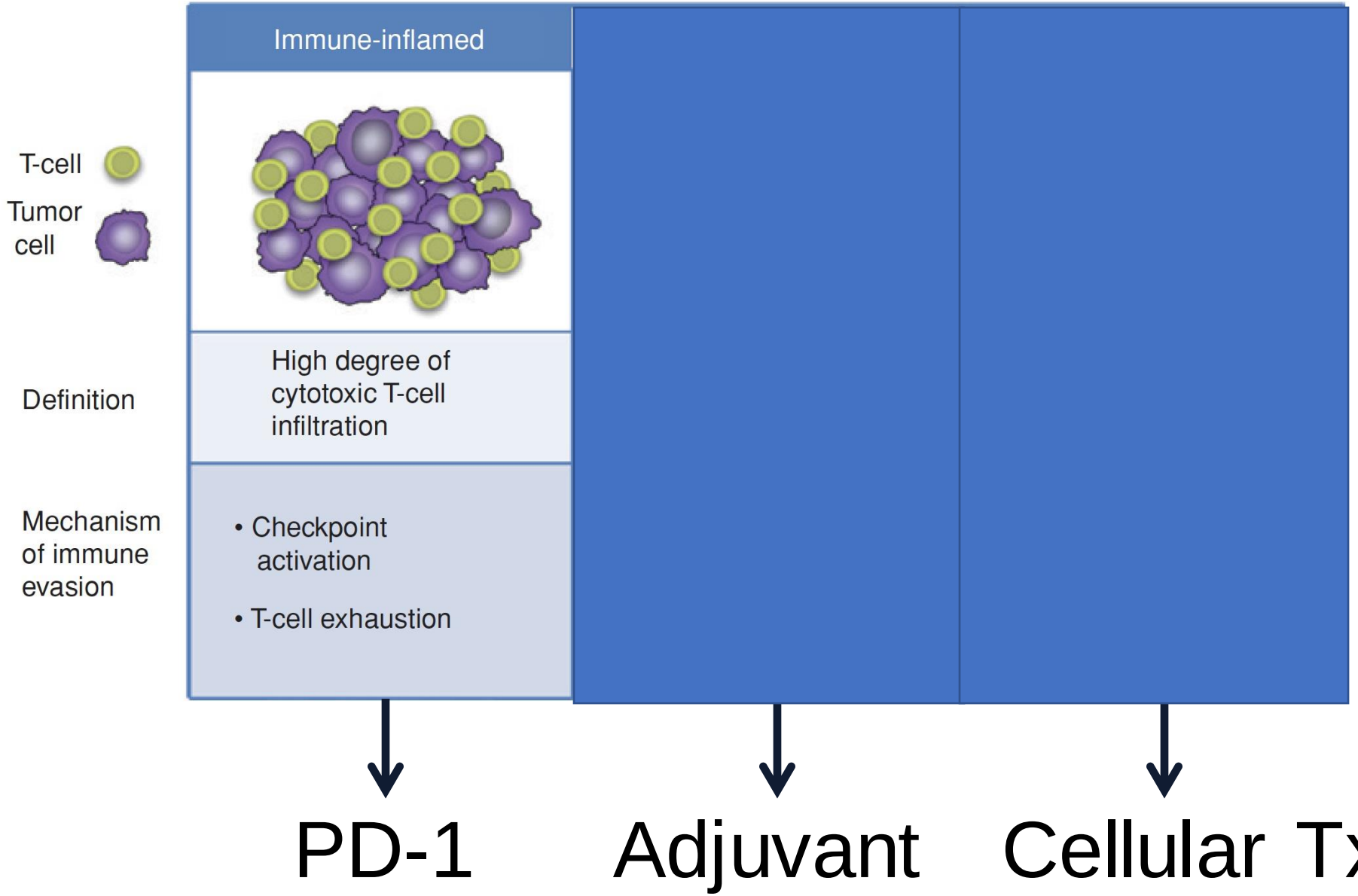
Targeted Therapy

- Biologic Agents (mAbs)
- Small Molecules (TKIs)
- Antibody-Drug Conjugates

Immunotherapy

- Checkpoint Inhibitors
- Cellular Therapies
- Bi-specific T-cell Engagers
- Cytokine Therapy
- Oncolytic Viruses

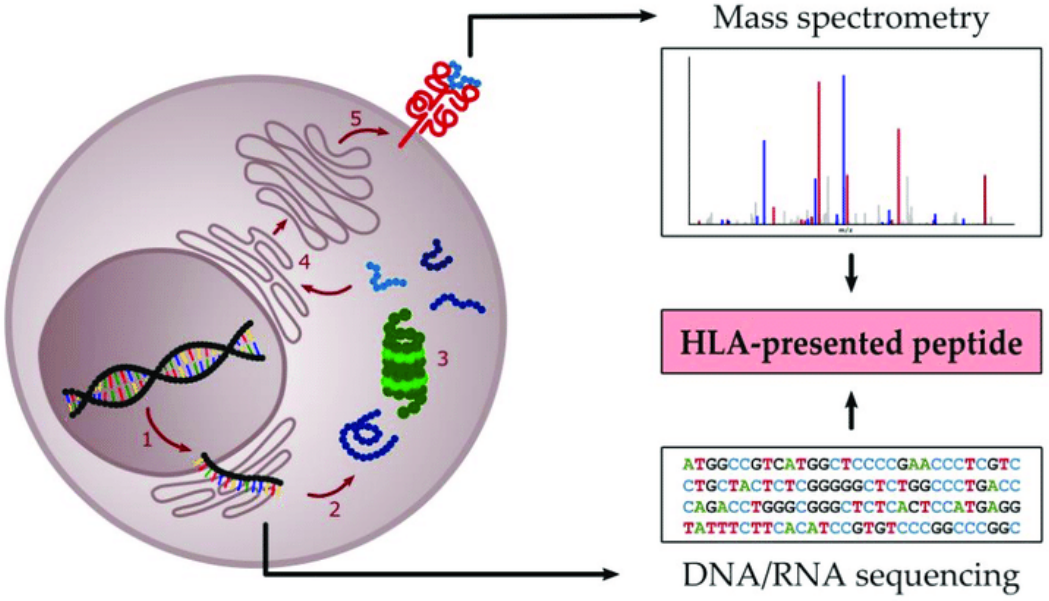
Where new IO-based therapies may have biggest impact



Cellular therapies fall into 1 of 2 categories based on their target

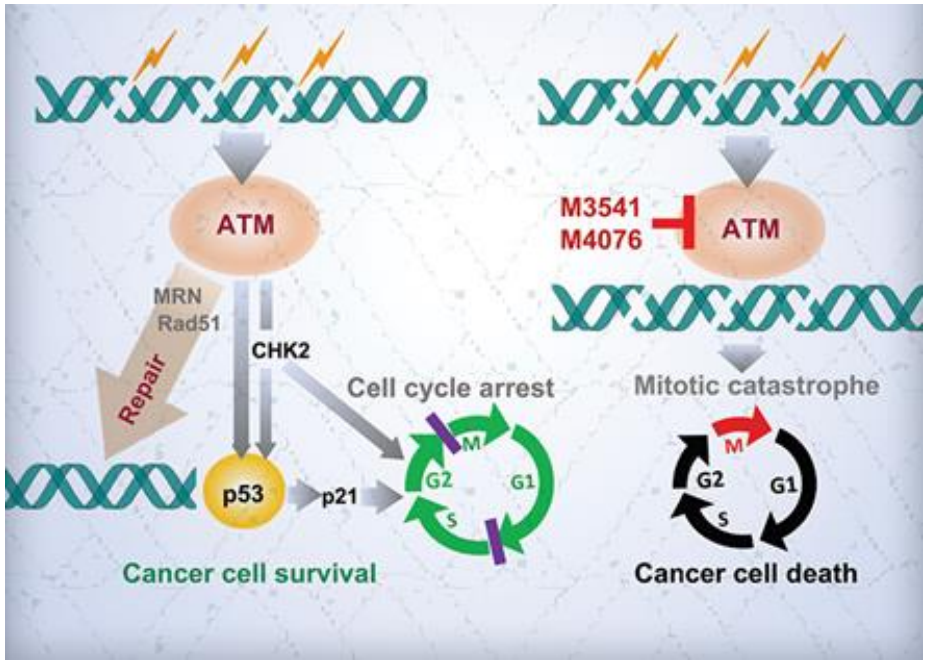
Immunopeptidome

- Set of peptides present by tumor cells
- Actioned by T-cells



Surfaceome

- Set of antigens on the surface of the cancer cell
- Actioned by antibodies and antibody constructs



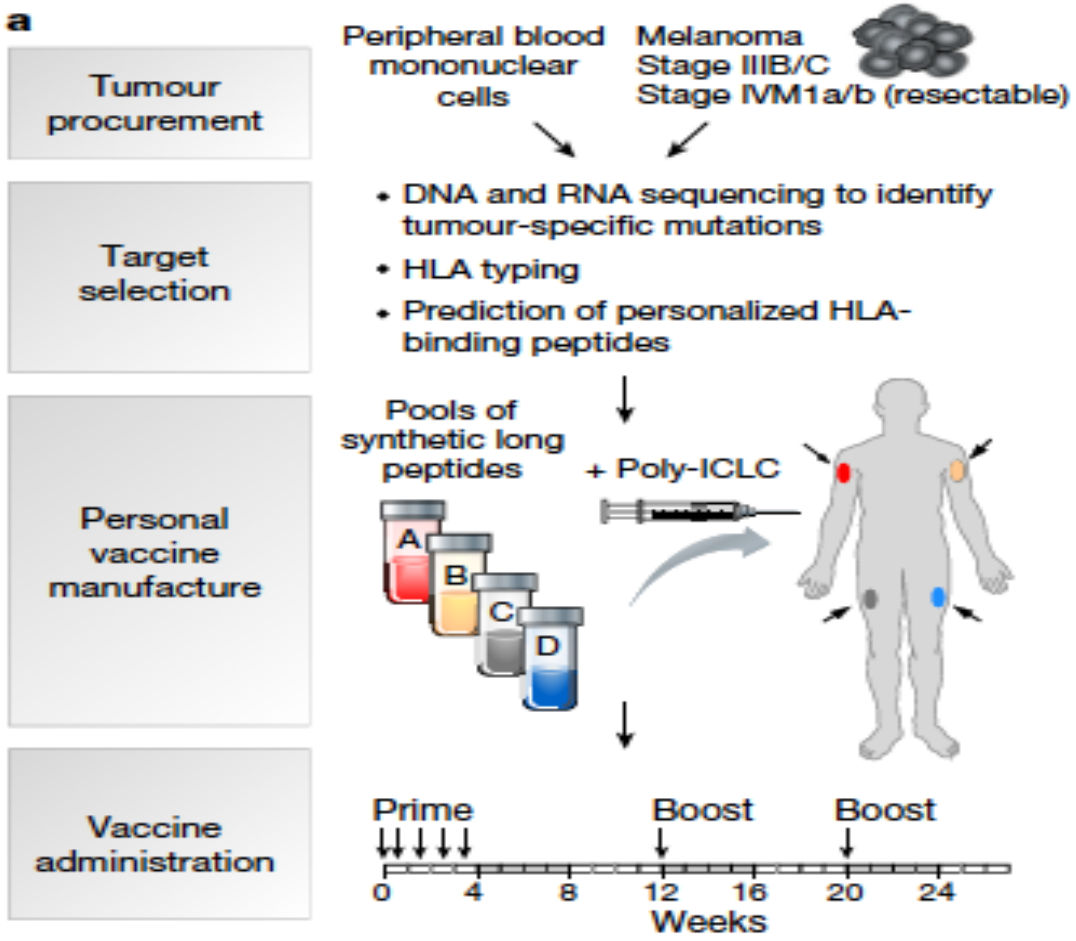
Bauer. Intern J Mol Sciences. 2019
Wang. Molecular Cancer Therapeutics. 2022

The Immunopeptidome

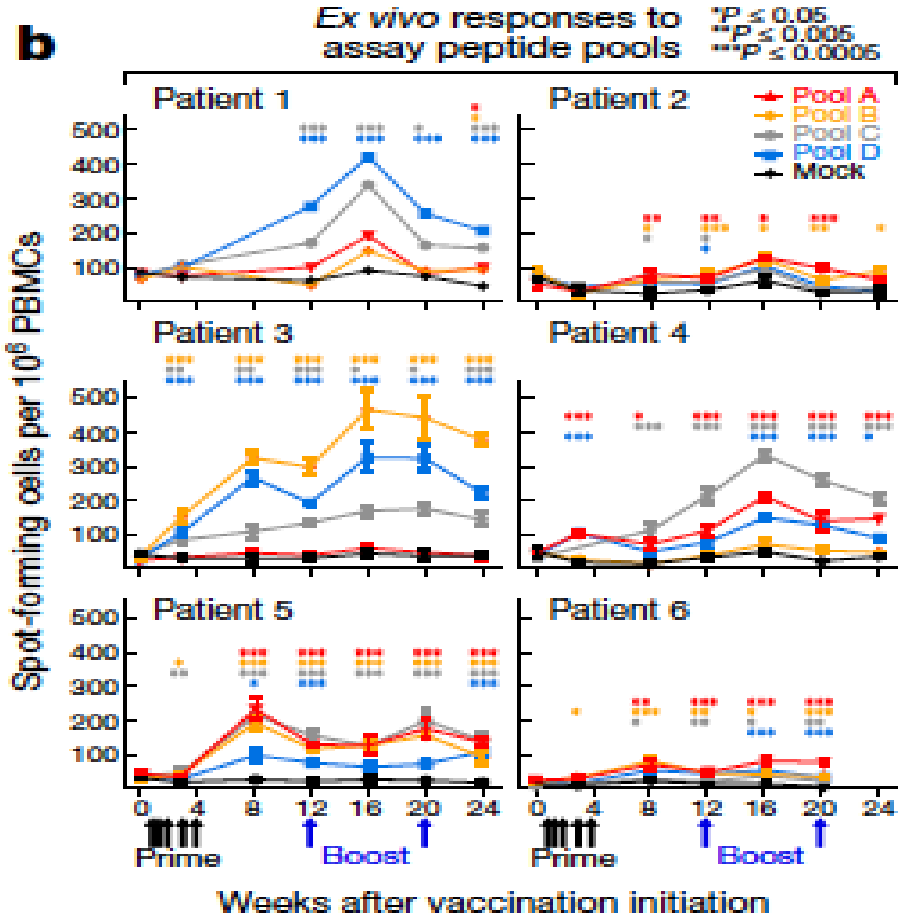
1. Vaccines
2. TCR

Vaccines

- Vaccines directed against specific tumor antigens
- Prime *de-novo* immune responses
- Earliest efforts in Melanoma



- T-cell responses were robust, durable, and polyfunctional



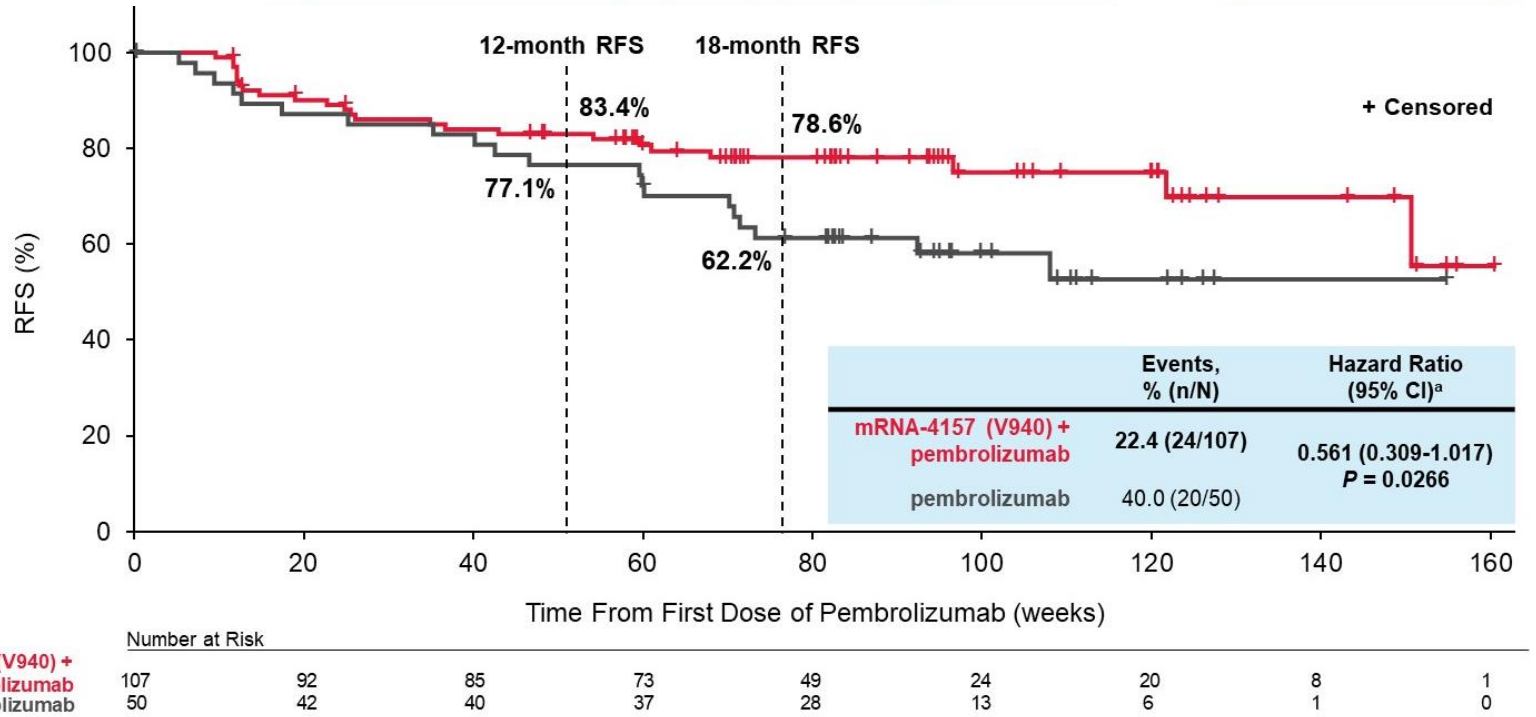
Rivzi. Science. 2015

mRNA-4157

- 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]

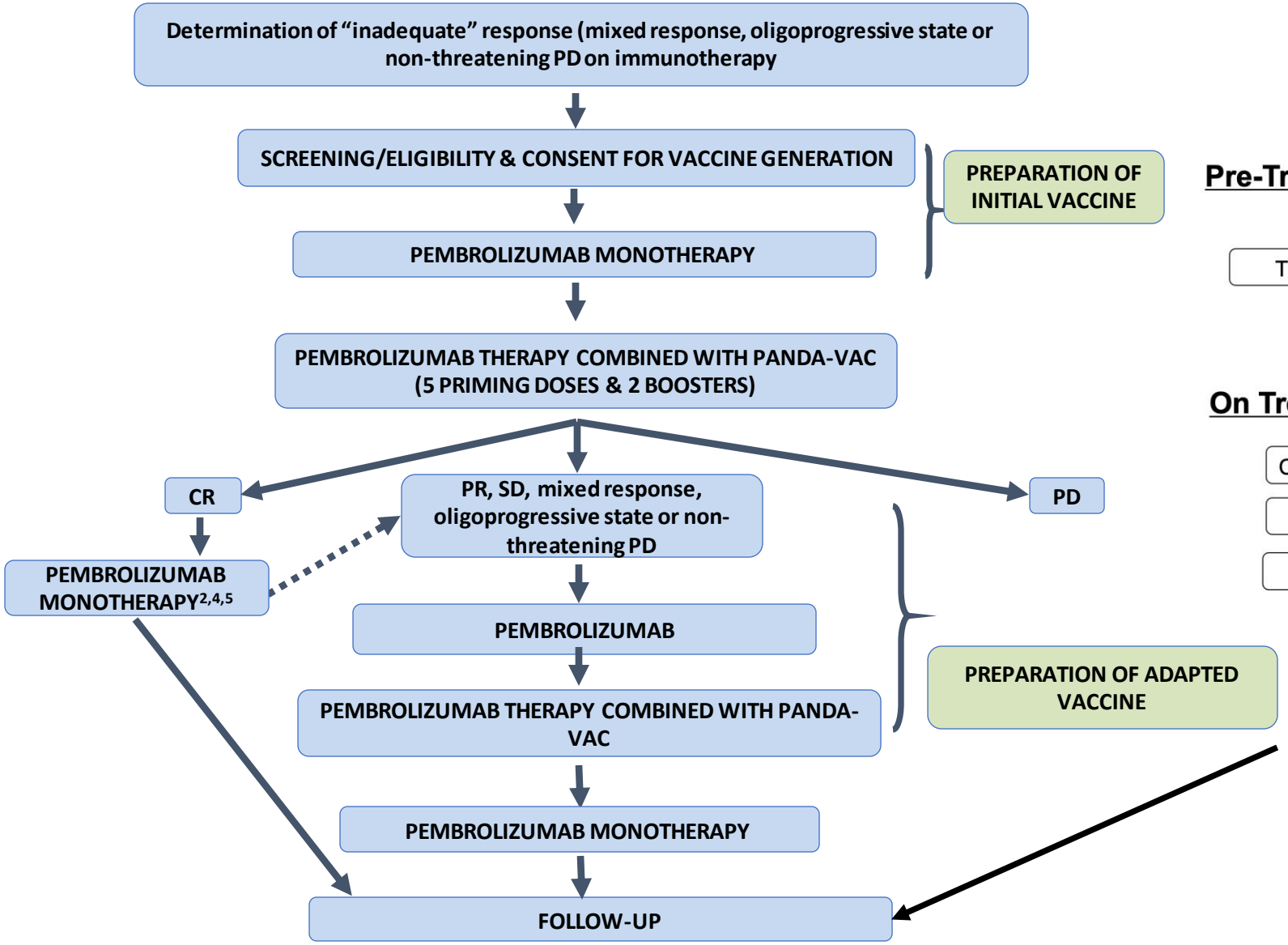
Key eligib

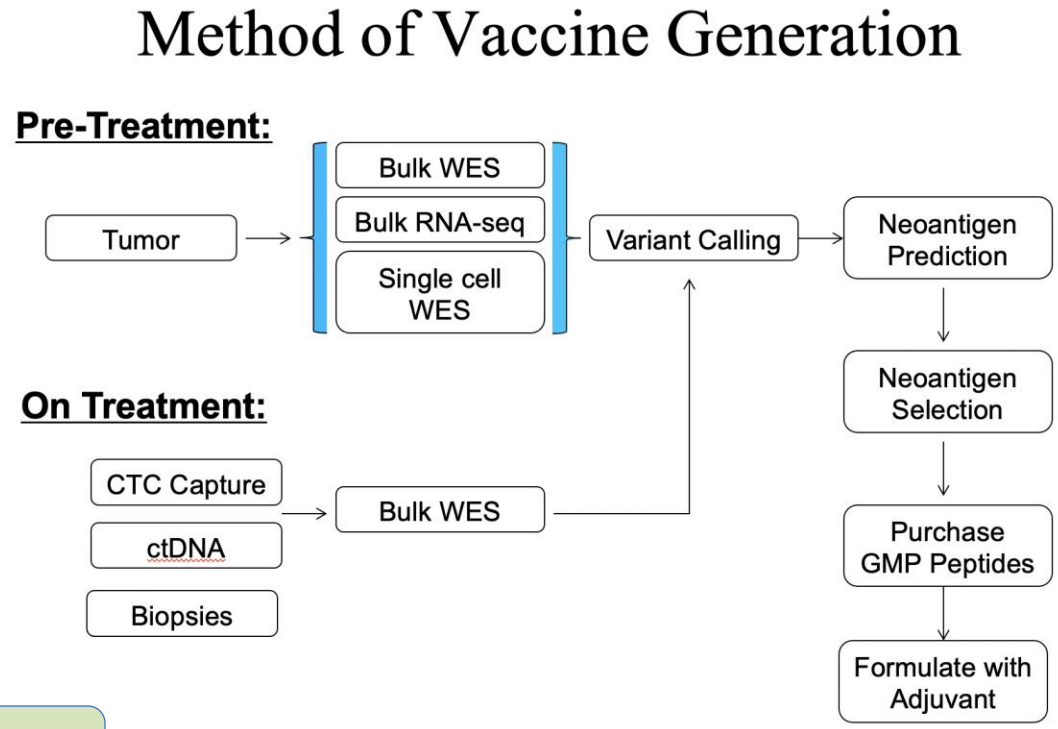
- Resected
  IIIC, IIID, c
  cutaneous
- Complete
  within 13 v
  first pembr
- Disease-fr
- ECOG PS
- Tissue ava



Rivzi. Science. 2015

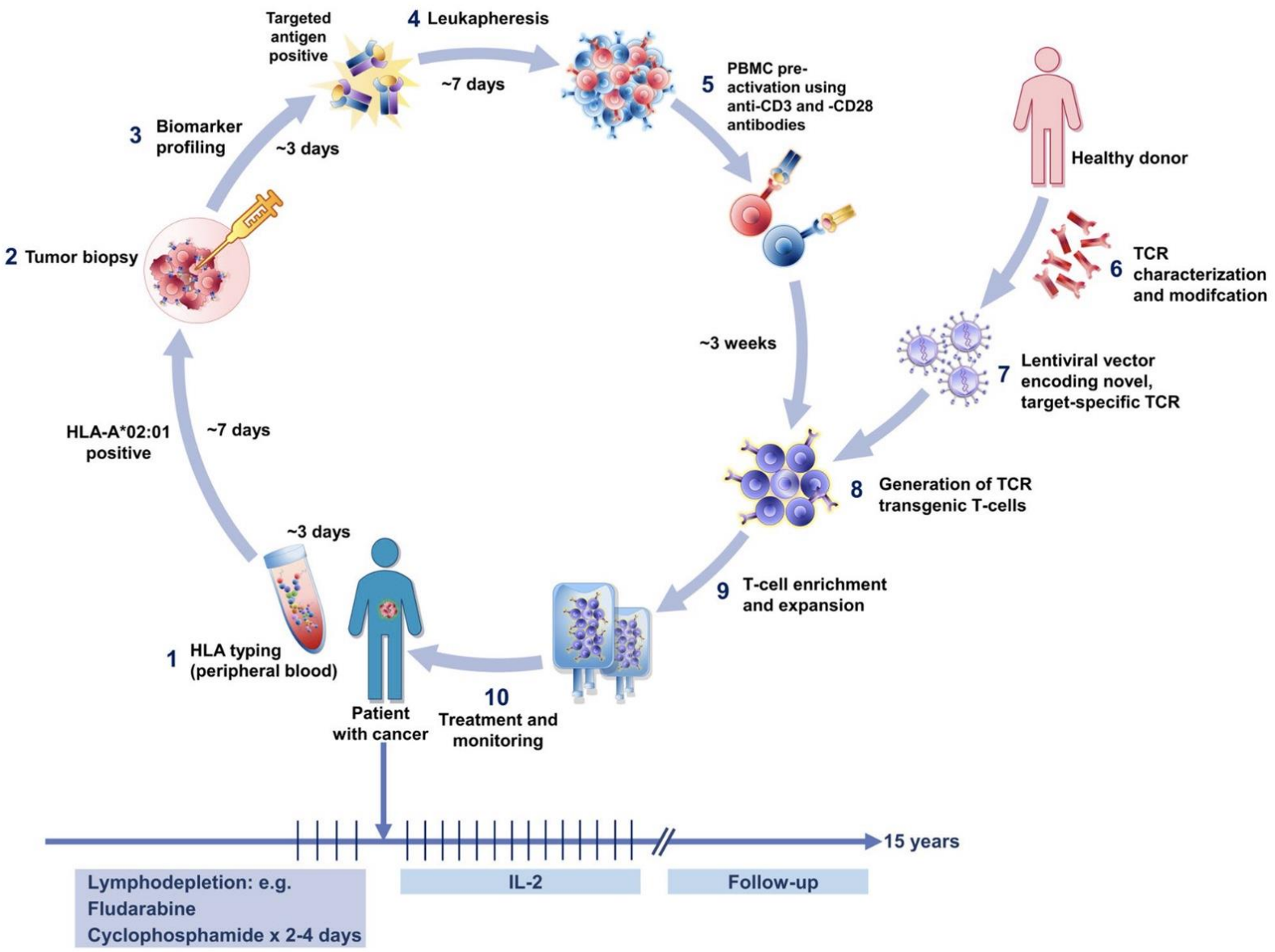
PANDA-VAC





Slide Courtesy of Jared Weiss (UNC)

T cell Receptor (TCR)

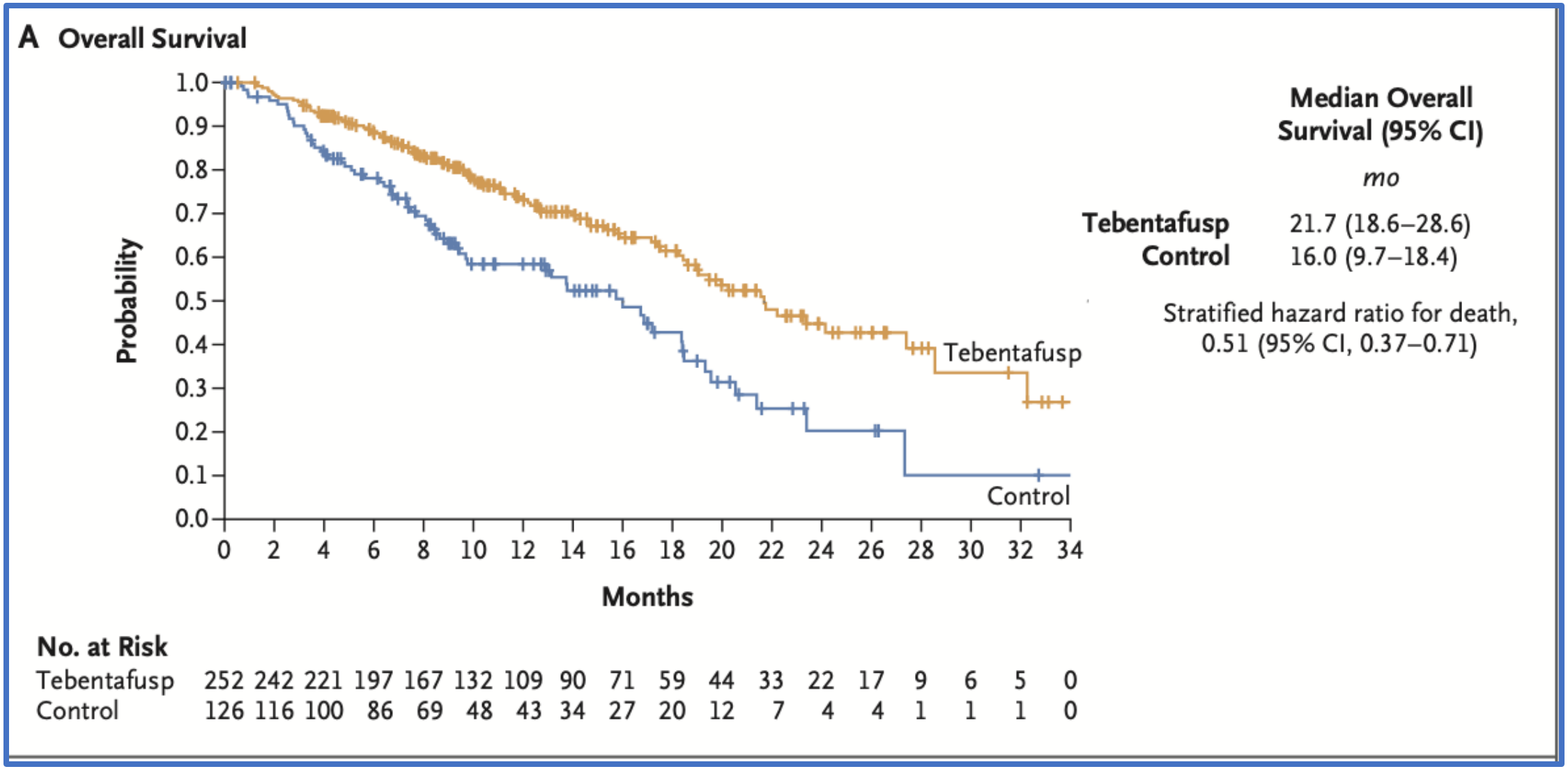


Challenges

- Product manufacturing
- Patient selection
- Preparation with lymphodepletion

Tsimberidou. J Hematology & Oncology. 2021

Tebentafusp



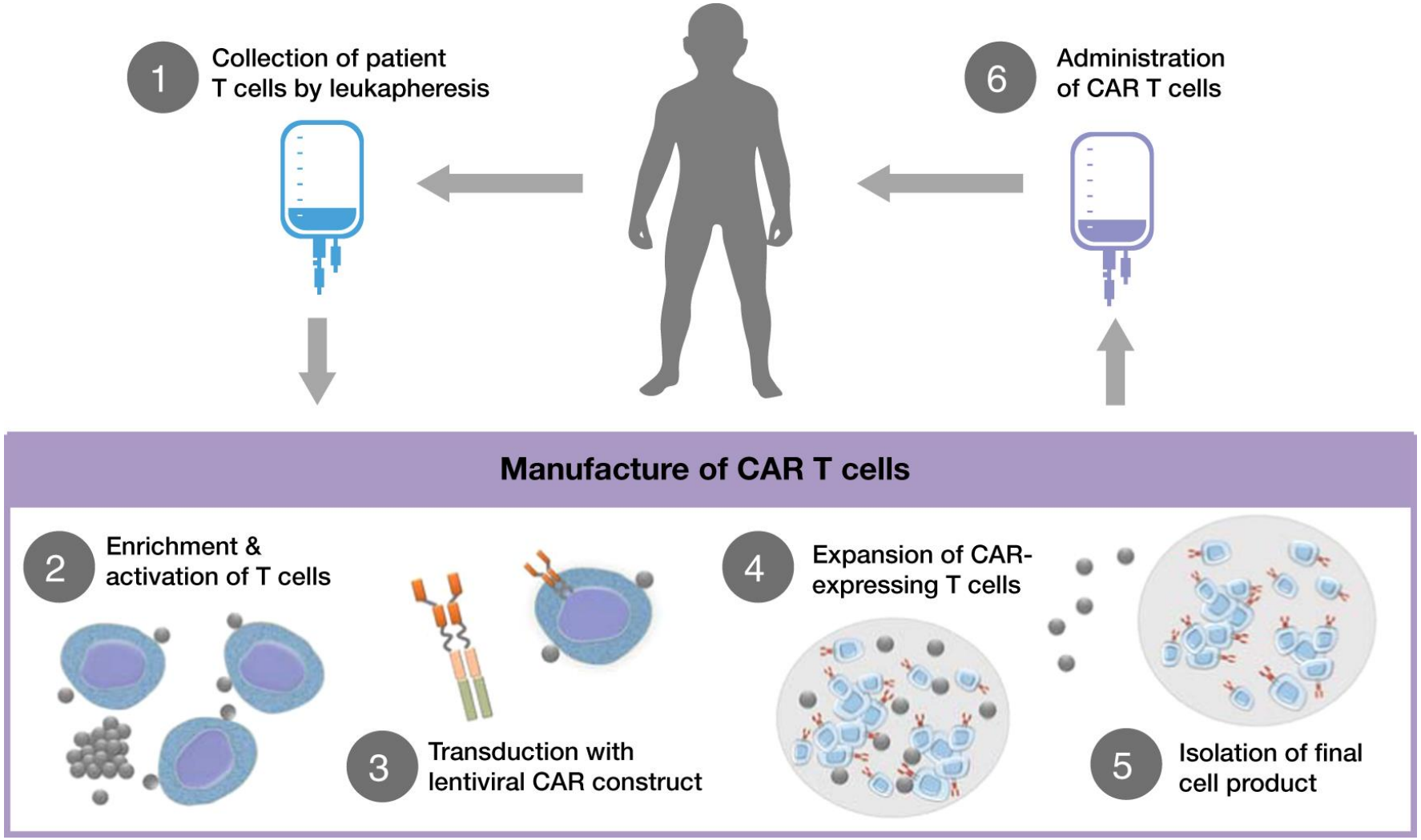
FDA Approval in Uveal Melanoma in 2022

Natham NEJM 2021

The Surfaceome

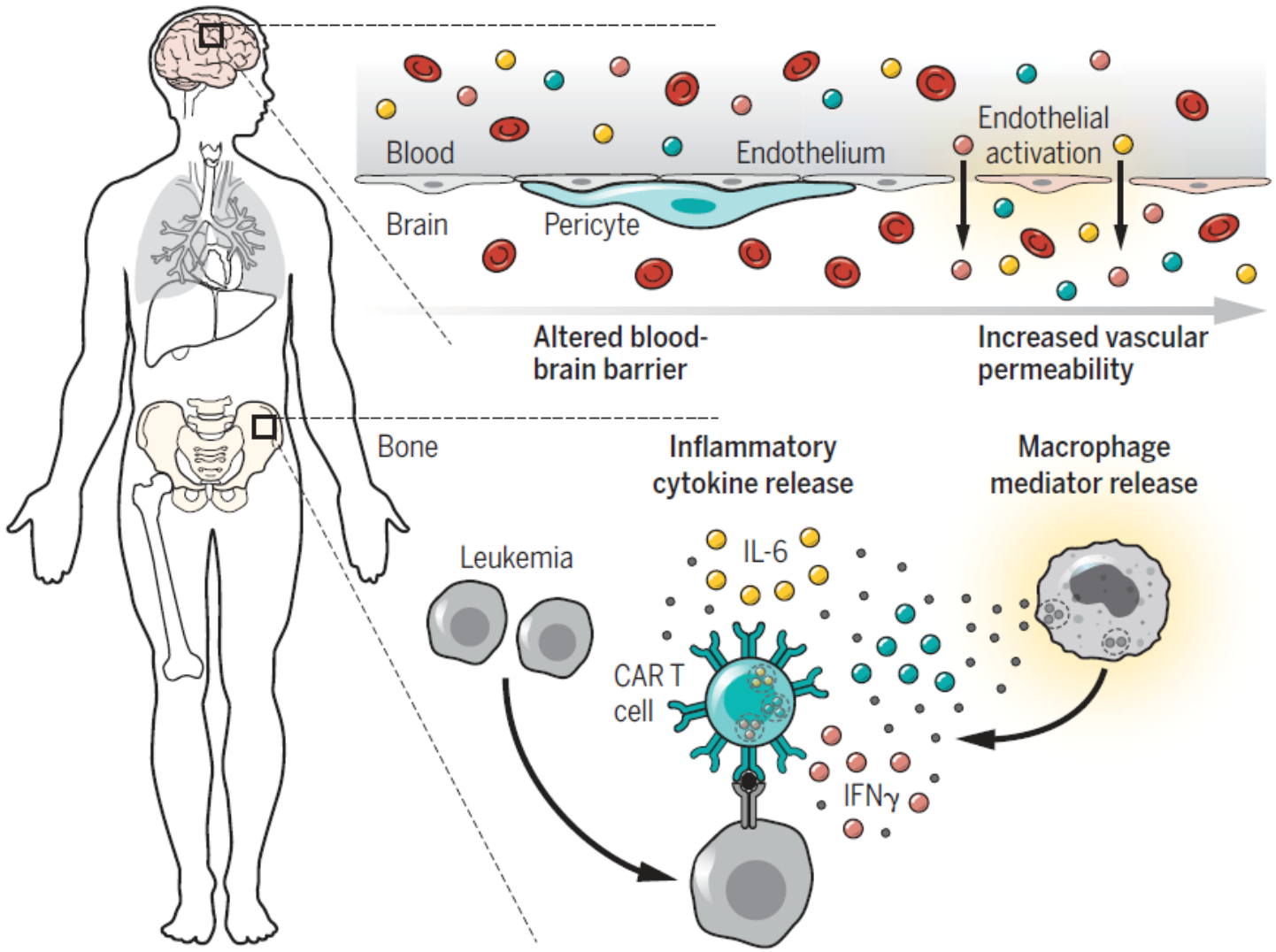
1. CAR-T
2. BiTE

CAR-T



NCI. Cancers.gov. 2020

CAR-T Side Effects



Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

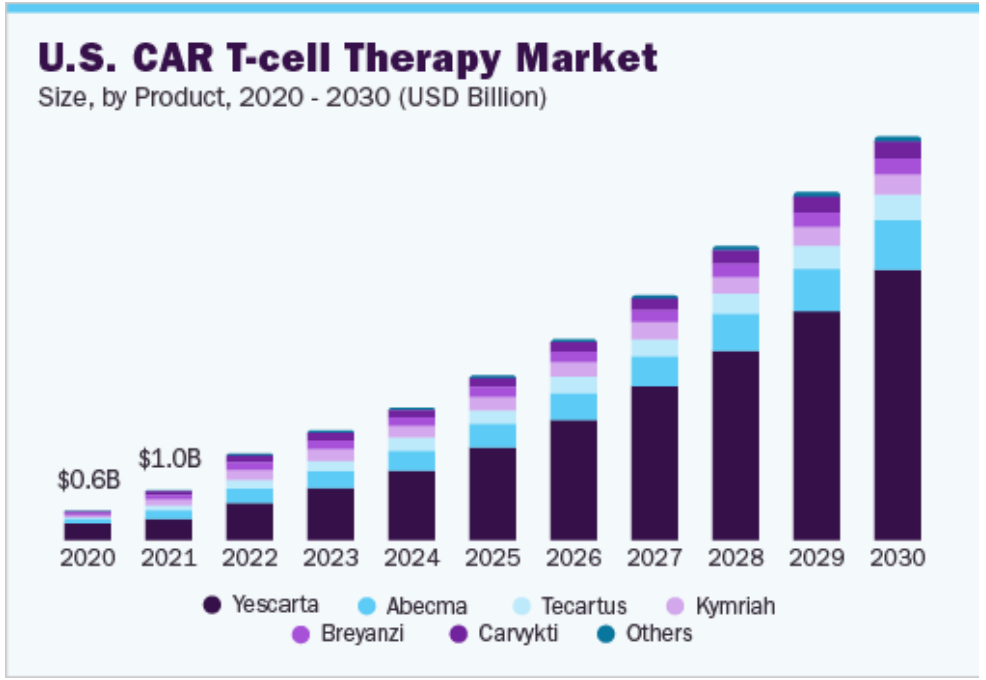
Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

Gupta. AJKD. 2019

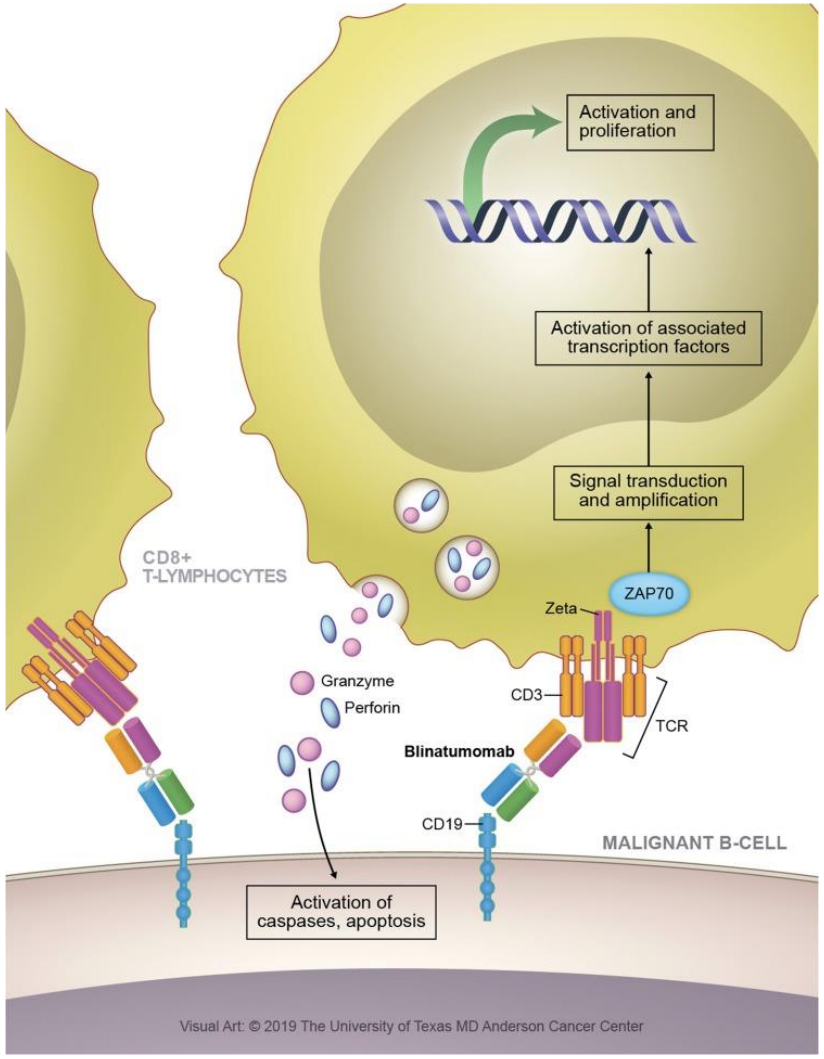
Approved CAR-T Cell Therapies

FDA-Approved CAR T-Cell Therapies

Generic Name	Brand Name	Target Antigen	Targeted Disease	Patient Population
Tisagenlecleucel	Kymriah	CD19	B-cell acute lymphoblastic leukemia (ALL)	Children and young adults with refractory or relapsed B-cell ALL
			B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Axicabtagene ciloleucel	Yescarta	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
			Follicular lymphoma	Adults with relapsed or refractory follicular lymphoma
Brexucabtagene autoleucel	Tecartus	CD19	Mantle cell lymphoma (MCL)	Adults with relapsed or refractory MCL
			B-cell acute lymphoblastic leukemia (ALL)	Adults with refractory or relapsed B-cell ALL
Lisocabtagene maraleucel	Breyanzi	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Idecabtagene vicleucel	Abecma	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma
Ciltacabtagene autoleucel	Carvykti	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma

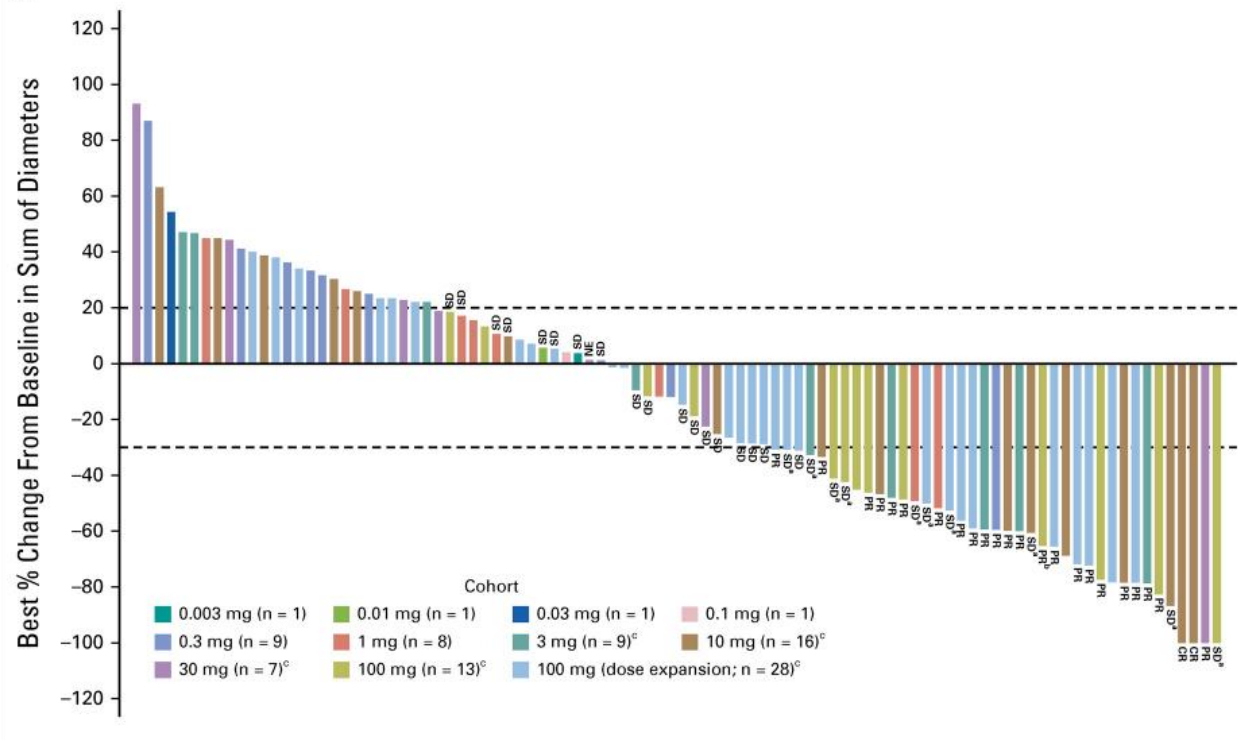


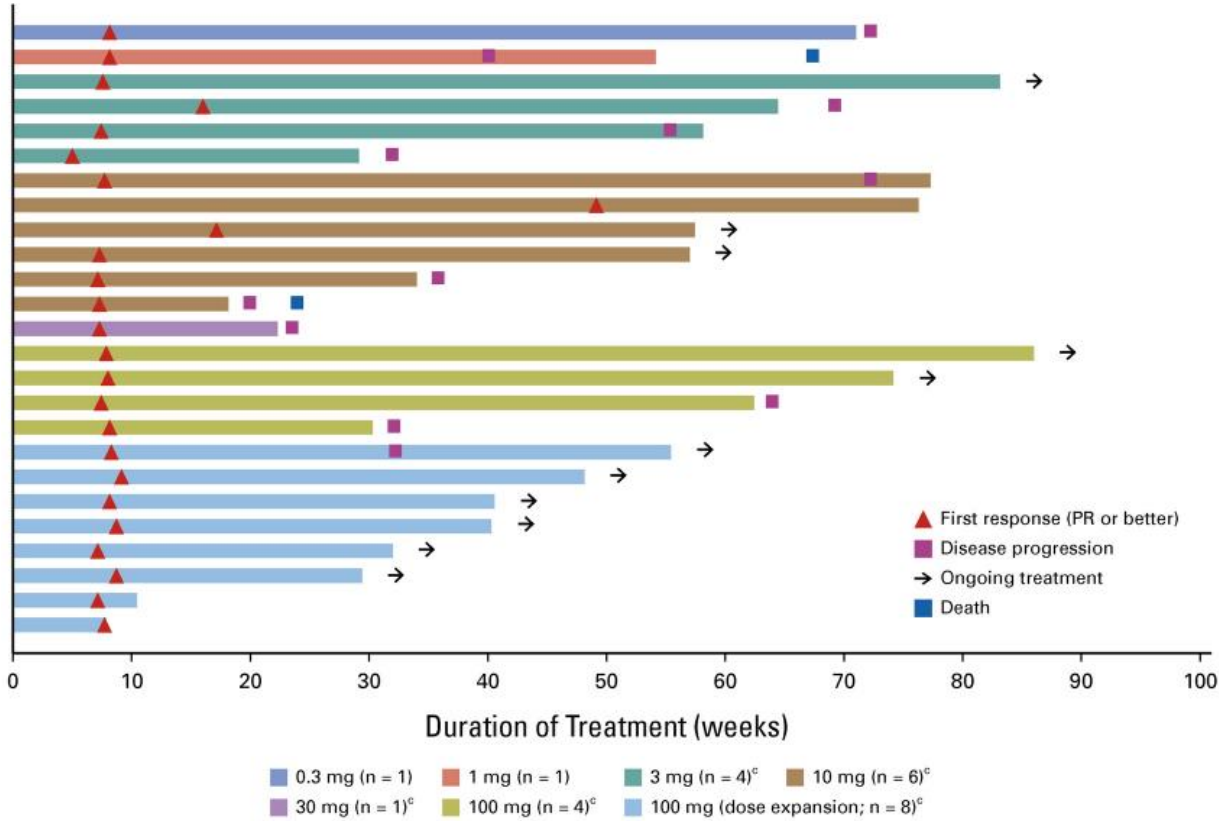
Bispecific T cell Engager (BiTE)



Tarlatamab

- MOA: BiTE
- AE's: CRS in 52%, G3 in 1%; Neurologic in 70%, 1% G3
- RR: 23%; >30% at higher doses



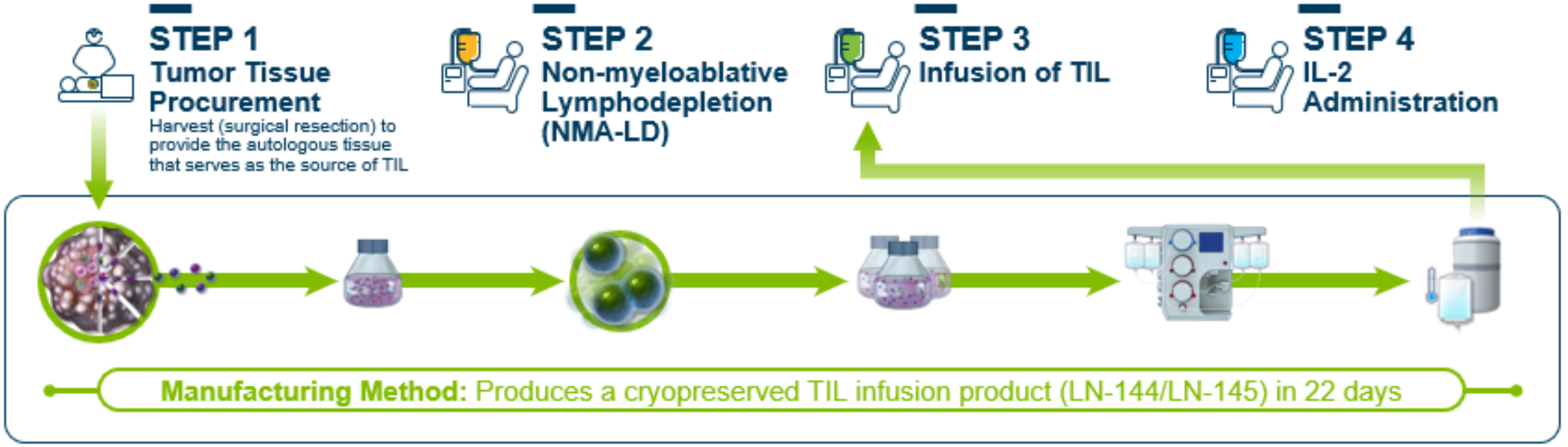


Paz-Ares JCO 2023

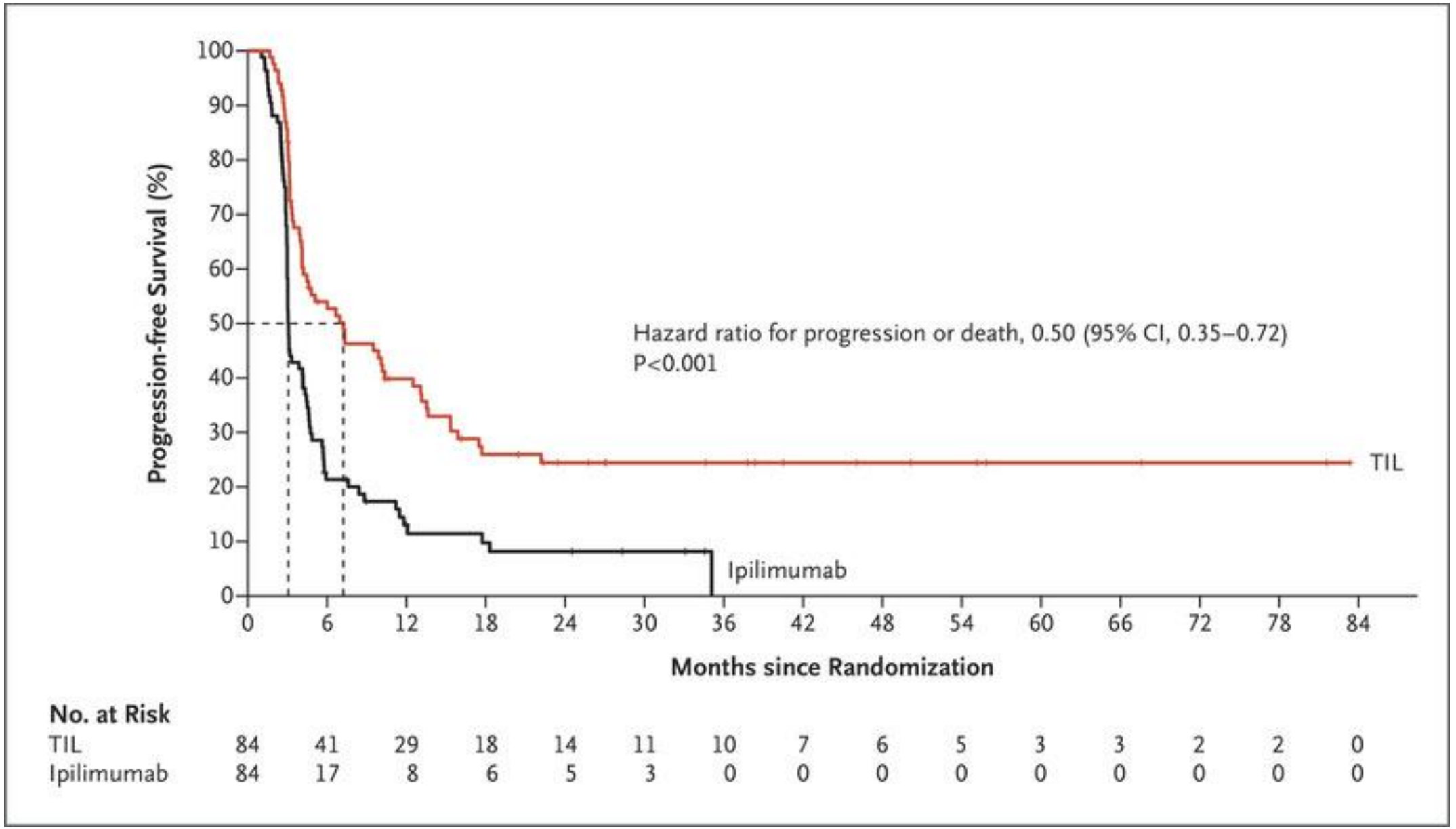
TCR vs CAR-T

	Modified TCR expressed on T-cells, NK cells, and other cells	**CAR expressed on T-cells, NK cells, and other cells**
Constructs	Native or minimally engineered native TCR delivered via biologic vector	Artificial receptor complex delivered by a biologic vector
Targets	MHC peptides derived from intracellular proteins	Surface proteins and glycans
Manufacturing	Ex vivo gene transfer into autologous T-cells or NK cells, "personalized" for each patient	Ex vivo gene transfer into autologous T-cells or NK cells, "personalized" for each patient
Mechanism of action	Binds and kills target cells leading to limited clonal expansion of T-cells	Binds and kills target cells leading to extensive clonal expansion of T-cells
Dosing	Single or limited doses	Single or limited doses
Availability	Experimental basis only	Experimental and commercially available products
Unique facets	Small patient populations for any single construct	Limited number of suitable potential targets
Safety	Modest cytokine release syndrome due to limited proliferation	Extensive cytokine release syndrome due to extensive cell proliferation
Mechanism of resistance	Loss of target, loss of IFNγ signaling	Loss of target, loss of IFNγ signaling

TILs

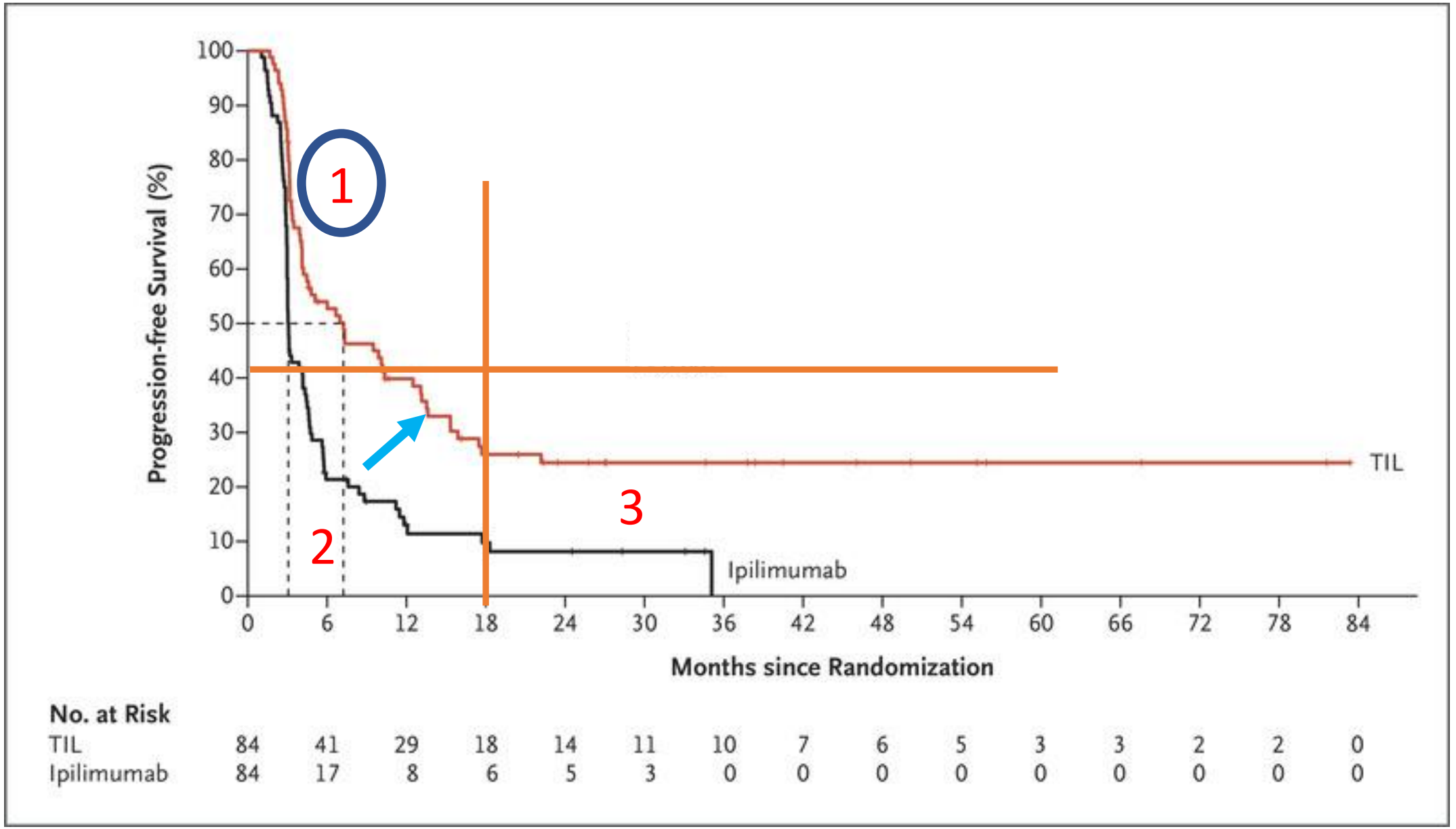

STEP 1
Tumor Tissue Procurement
Harvest (surgical resection) to provide the autologous tissue that serves as the source of TIL
STEP 2
Non-myeloablative Lymphodepletion (NMA-LD)
STEP 3
Infusion of TIL
STEP 4
IL-2 Administration
Manufacturing Method: Produces a cryopreserved TIL infusion product (LN-144/LN-145) in 22 days

TIL vs. Ipi in Metastatic Melanoma



Rohaan. NEJM. 2022

The curves look better but not great…



Rohaan. NEJM. 2022

Our goal is cure.

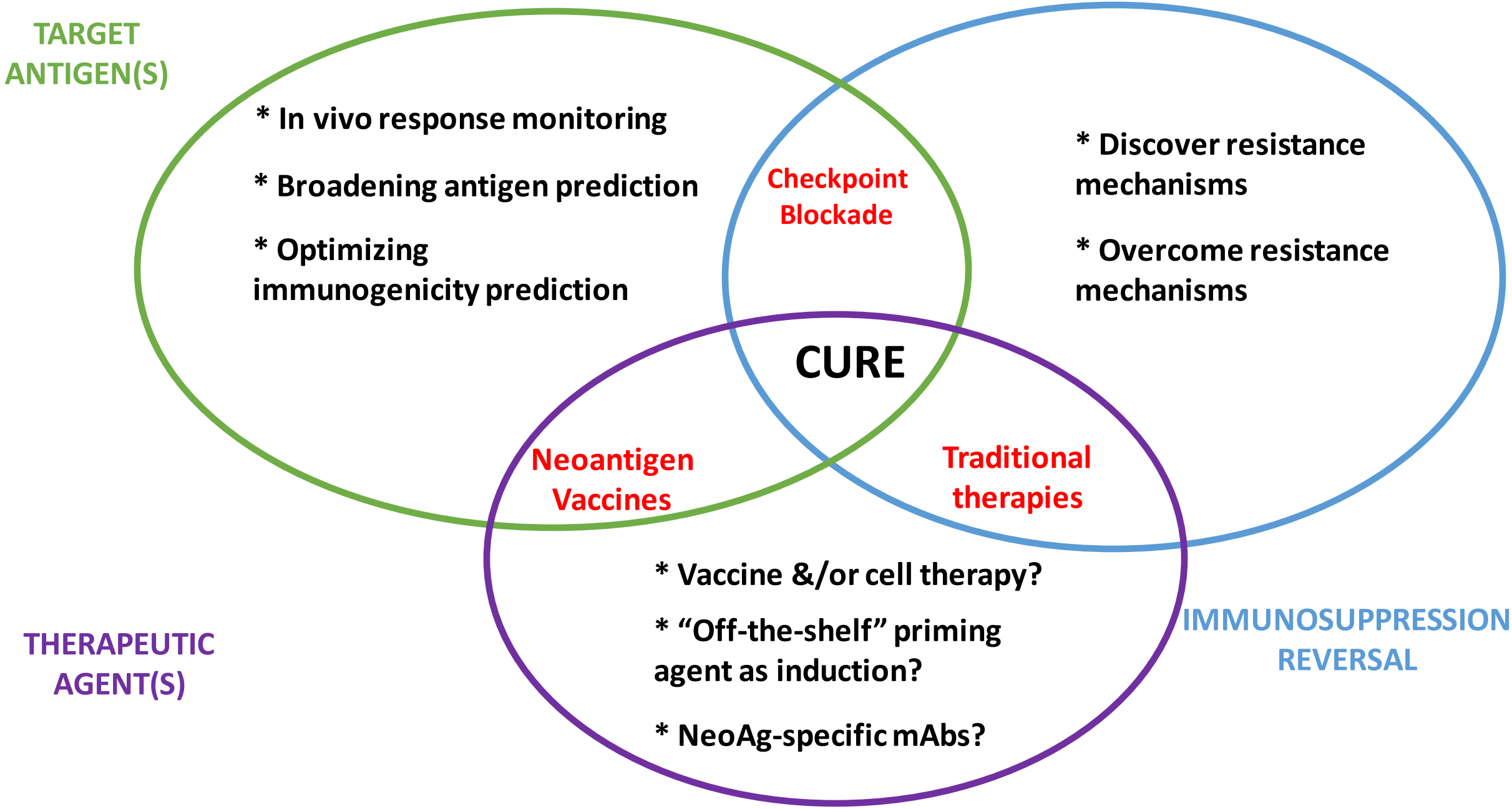
2018 ASCO®
ANNUAL MEETING
DELIVERING DISCOVERIES: EXPANDING THE REACH OF PRECISION MEDICINE

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

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

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.

A Vision on How to Cure



Cellular Therapies in Community Oncology??

BRINGING CAR T-CELL THERAPIES TO COMMUNITY ONCOLOGY

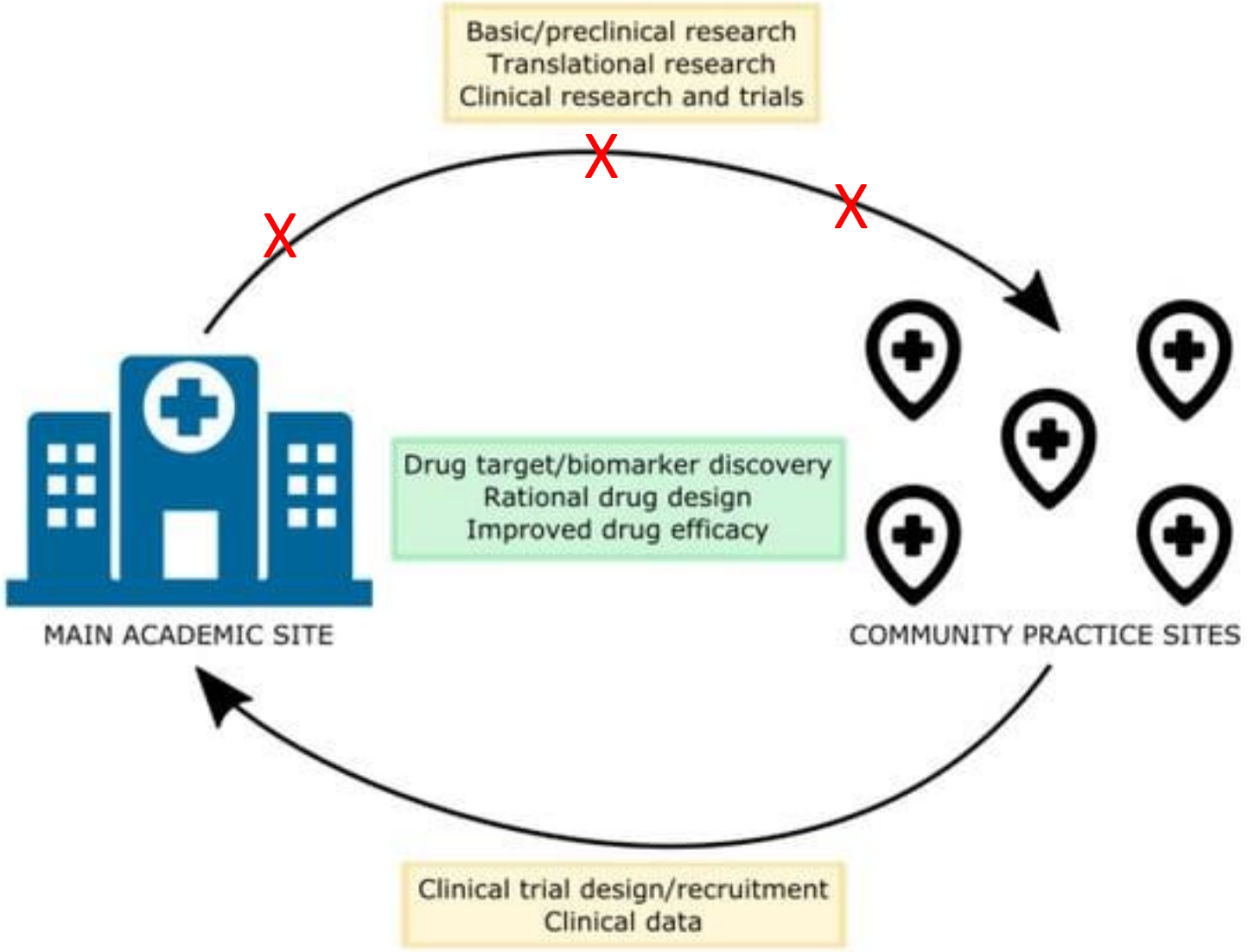
The delivery of CAR T-cell therapy requires workforce and infrastructure not necessitated by more traditional cancer therapies, such as chemotherapy and radiation. While sustained remission and improved survival for patients with hematologic malignancies has led to a growing interest in CAR T-cell therapy among community cancer providers, there is a wariness among lesser-resourced programs and practices to take steps to offer CAR T-cell therapy. Smaller community cancer programs have expressed a preference for referring patients who are candidates for CAR T-cell therapy to larger cancer programs and academic medical centers, due to unfamiliarity with the therapy; inadequate reimbursement for steep costs; insufficient infrastructure; and the potential for unfamiliar life-threatening toxicities in patients.

In a series of surveys in 2016 and 2017, of nearly 400 US community oncologists/hematologists and practice administrators representing a diverse mix of practice types and geographic regions, 64% said the biggest barrier they face to successfully implementing CAR T-cell therapy is the logistics involved in administering treatment and patient follow-up.

ACCC, with support by Bristol Myers Squibb, Janssen Oncology, and Legend Biotech, is helping community cancer programs and practices of all sizes gain the education they need to offer CAR T-cell therapy, sharing effective practices on overcoming logistical and financial hurdles, and highlighting tips on the operational infrastructure (eg, care coordination and patient support) required for a successful program.

For more information on this program, please contact the ACCC Provider Education department.

Cellular Therapies in Community Oncology



~~Summary~~ Bold Statements

1. We will continue to see rapid advances in immunotherapy, particularly in solid oncology

2. Our “older” agents continue to have a purpose and will be a part of the solution (*not replaced*) to achieve more cures

3. Newer therapies will become mainstream, outpatient, “off-the-shelf”, community based in the not-too-distant future

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