Emerging Trends in Immunotherapy for Solid Tumors

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Paul G. Allen Research Center

KANSAS SOCIETY OF CLINICAL ONCOLOGY

COI: None

CME Objectives

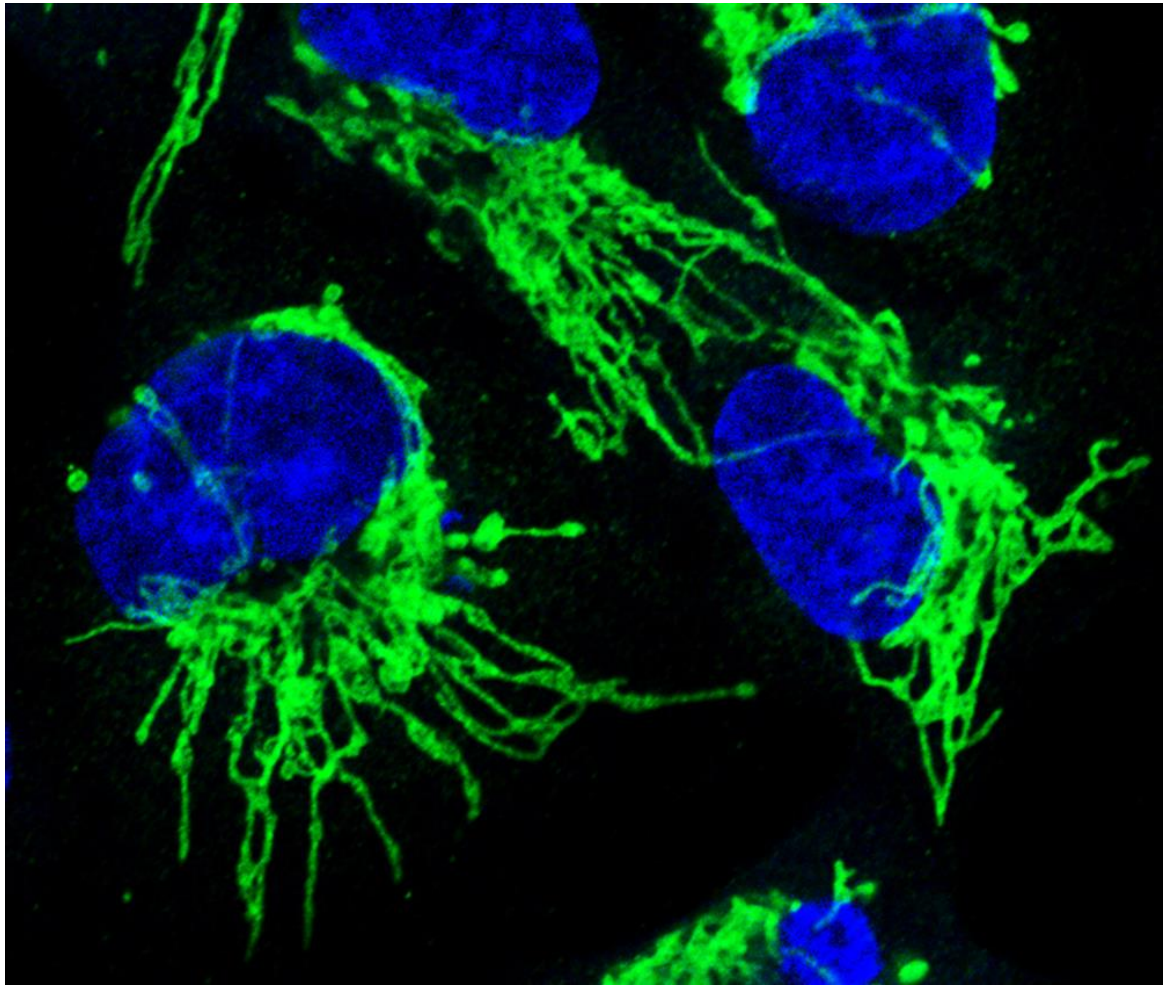
- Recognize emerging trends in solid tumor immunotherapy
- Identify common and rare immune related adverse events and resources for safe management
- Understand mechanisms of emerging bispecific therapies for solid tumor and unique toxicities

Outline

- Part 1: the checkpoint inhibitors
  - Indication & utilization
  - Toxicity management
  - How long?
  - Nutritional optimization
  - Site of care
  - New checkpoints
- Part 2: new approaches
  - Bispecifics including TCR based bispecifics
  - TIL therapy
  - Vaccine
  - TCR-T

Impact of cancer

- 1.71 million newly dx cancers in US in 2018 alone
  - 38,000 of these in Washington state
- 600,000 cancer deaths
  - 2nd leading cause of death in the US
  - 1 in 4 deaths due to cancer
- Each year, one in 200 people diagnosed
- Current lifetime risk of developing cancer in US
  - Men: 1 in 2.5 (40% lifetime risk)
  - Women: 1 in 3 (38% lifetime risk)



Data: US Cancer Statistics Public domain image: NCI.gov, author D. Kashtatus

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Solid Tumor Immunotherapy in 2023

- anti-PD1/PDL1
  - ~~7~~ 8 drugs: pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, dostarlimab, retifanlimab
  - 20+ solid tumor indications: melanoma, NSCLC, RCC, HNSCC, MCC, MSI-H, CRC (MSI-H), gastric, HCC, cervical, SCLC, cSCC, BCC, bladder, breast, dMMR, endometrial, esophageal, mesothelioma, **TMB-high**
- Other checkpoint inhibitors: anti-CTLA4, anti-LAG3
- Intralesionals/topicals: T-Vec, imiquimod, BCG, others
- Dendritic vaccine (Provenge)
- Bispecifics: tebentefusp
- (cytokines: IL2, interferon)

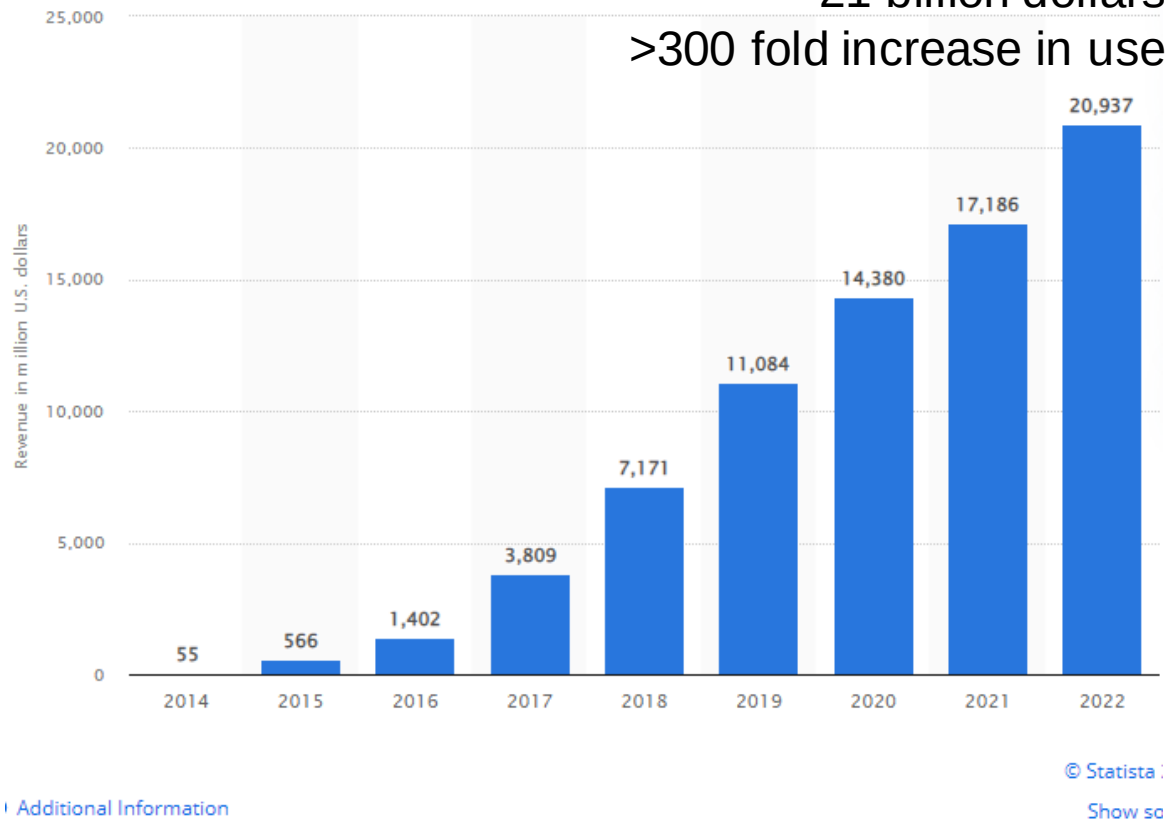
Source: CRI

Pembrolizumab annual sales: 2014-2022

Source: Statista

21 billion dollars

>300 fold increase in use



FDA-Approved anti-PD(L)1 in 2023

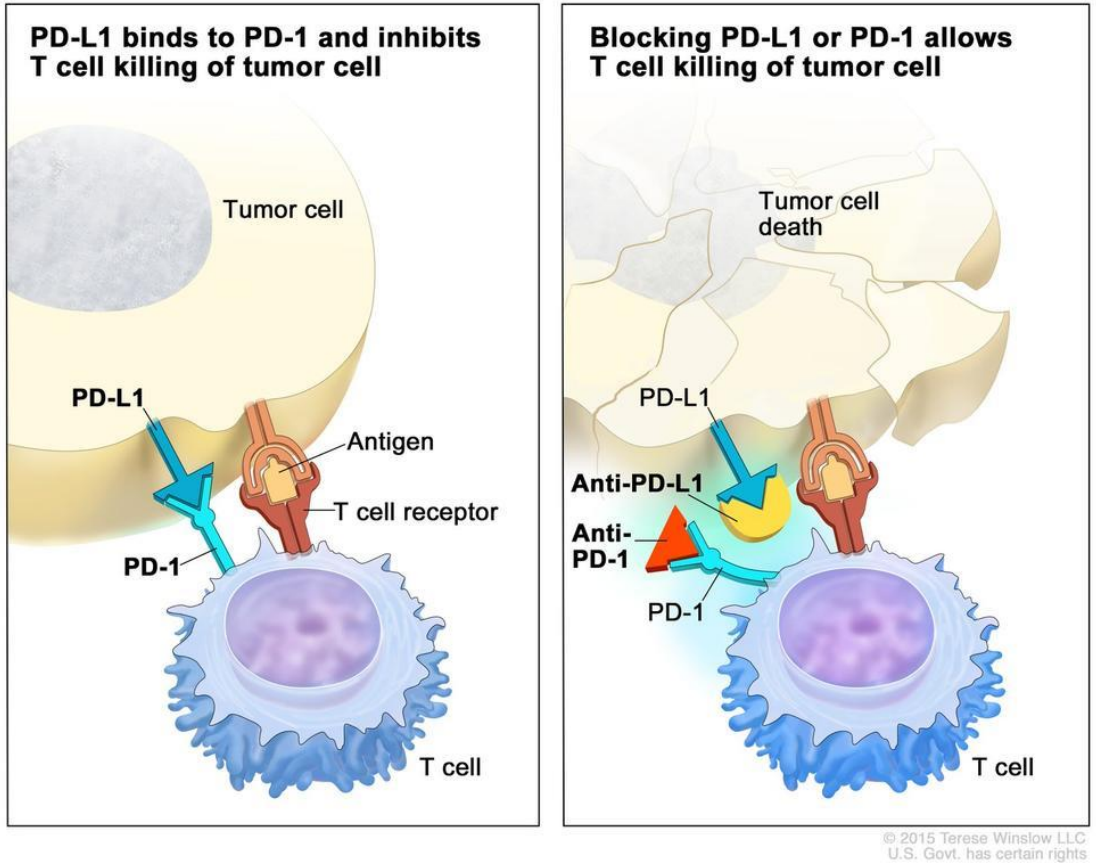
8 drugs: pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, dostarlimab, retifanlimab

(Some) Recent anti-PD(L)1indications:

- Nivolumab adjuvant esophageal
- Pembrolizumab TMB-high
- Pembrolizumab NSCLC adjuvant
- nivolumab (+ chemo) Neoadjuvant NSCLC
- Retifanlimab Merkel cell carcinoma
- Atezolizumab ASPS
- Dostarlimab endometrial dMMR

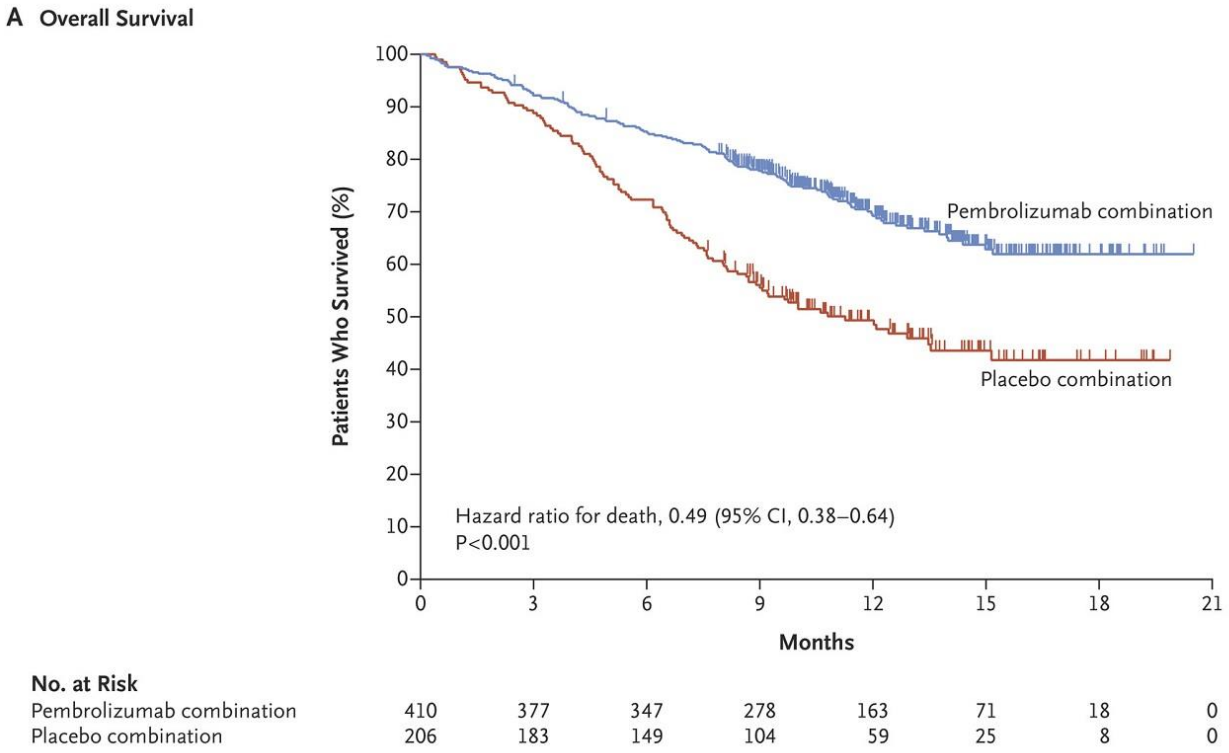
Anti-PD(L)1 indication withdrawn:

2020-2023: nivolumab (SCLC), pembrolizumab (SCLC), atezolizumab (TNBC, bladder), pembrolizumab (gastric/GEJ), nivolumab (HCC), durvalumab (bladder)

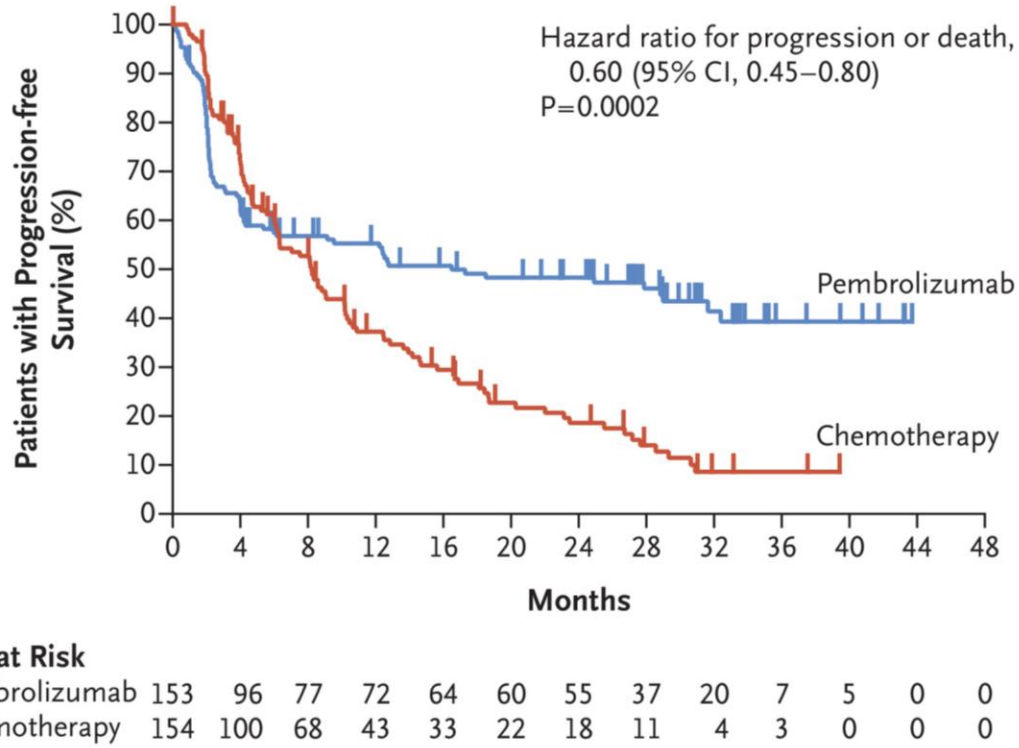


Outcomes dramatically improved with imtx across many solid tumors

NSCLC



MSI-High Colon



Keynote 189 NEJM 2018; Keynote 177 NEJM 2020

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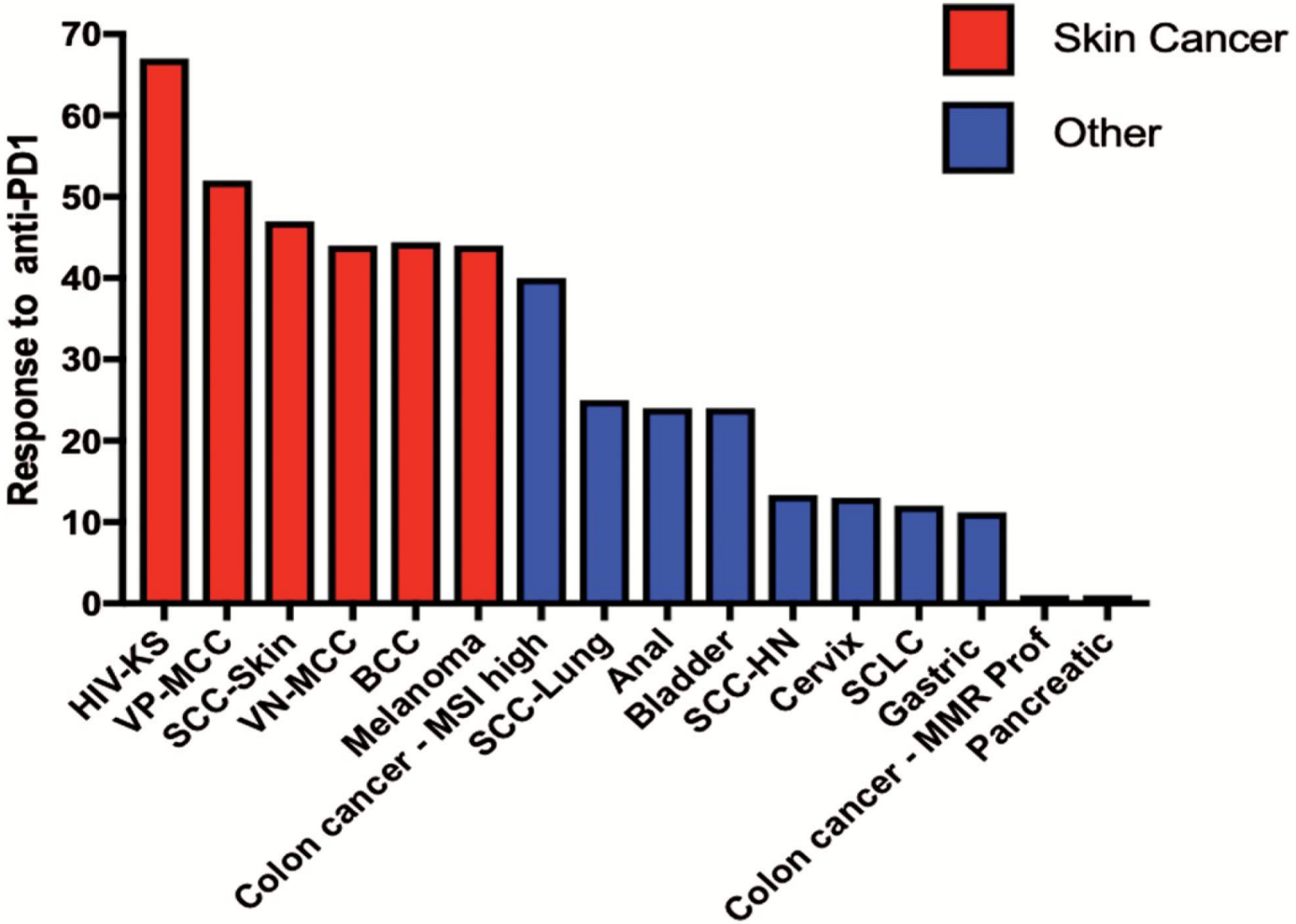
But we still have a lot of work left to do



Paulson KG et al, Int Immunol 2019

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Pembrolizumab in TMB-High cancers

- 10 mut/Mb or higher
- Foundation 1 as companion diagnostic
- "Adult or pediatric patients whose tumors have a high TMB, defined as 10 or more mutations per megabase as determined by an FDA-approved test, can be treated with pembrolizumab after disease progression following prior treatment and if they have no satisfactory alternative treatment options”

There is now an indication for comprehensive genomic profiling in essentially all patients with advanced cancer

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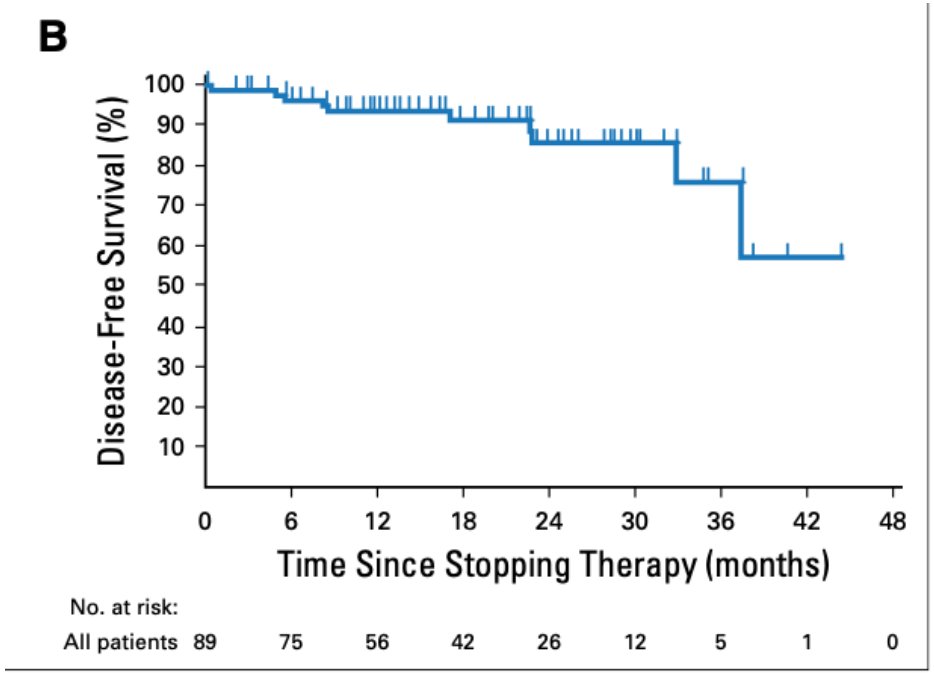
Reference: pembrolizumab FDA label

Duration of anti-PD1 IMTX – rethinking elective discontinuation

In 2018, we saw this data from CR patients with melanoma: Robert et al JCO 2018 and the field started moving towards limiting duration of therapy



Optimal Duration of Checkpoint Inhibition in Melanoma Is **No More Than 2 Years**. For patients with advanced melanoma, the concept of treating to disease progression does not always apply. Dec 25, 2018

https://ascopost.com › issues › december-25-2018 › optim...

Optimal Duration of Checkpoint Inhibition in Melanoma Is No ...

Duration of Anti-Programmed Death-1 Therapy in Advanced Melanoma: How Much of a Good Thing Is Enough?

Khushalani NI.

J Clin Oncol. 2018 Jun 10;36(17):1649-1653. doi: 10.1200/JCO.2017.76.8275. Epub 2018 Feb 1.

PMID: 29389234

https://www.nature.com › ... › comment

Are we over-treating with checkpoint inhibitors? - Nature

by S Danson · 2019 · Cited by 14 — We challenge the need for long-term treatment **duration**, using evidence from **melanoma** research, both published and in process.

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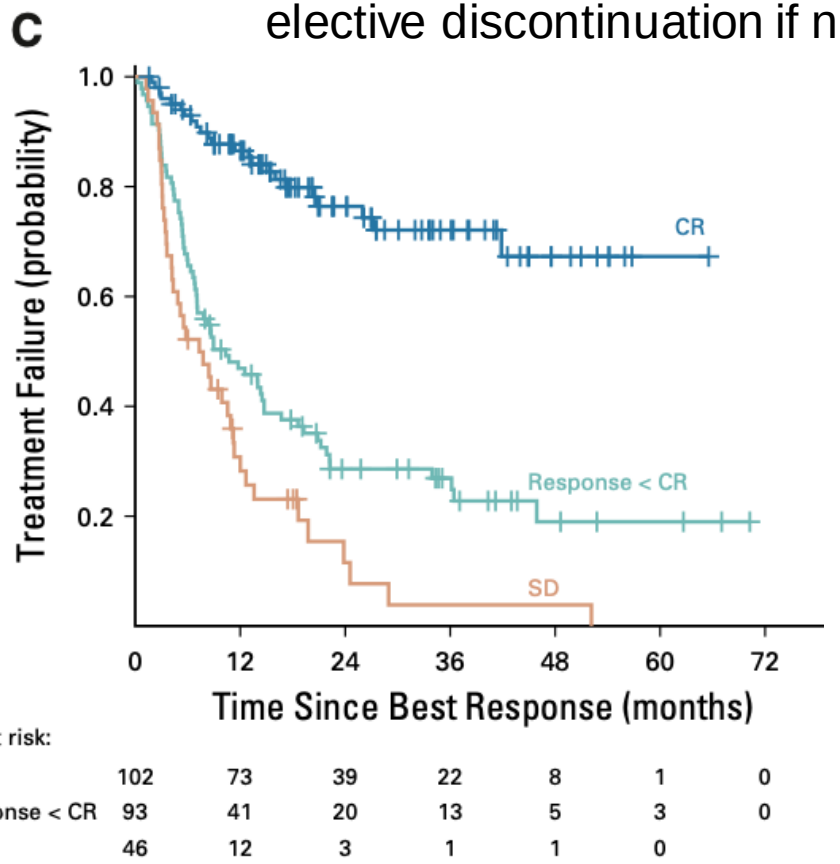
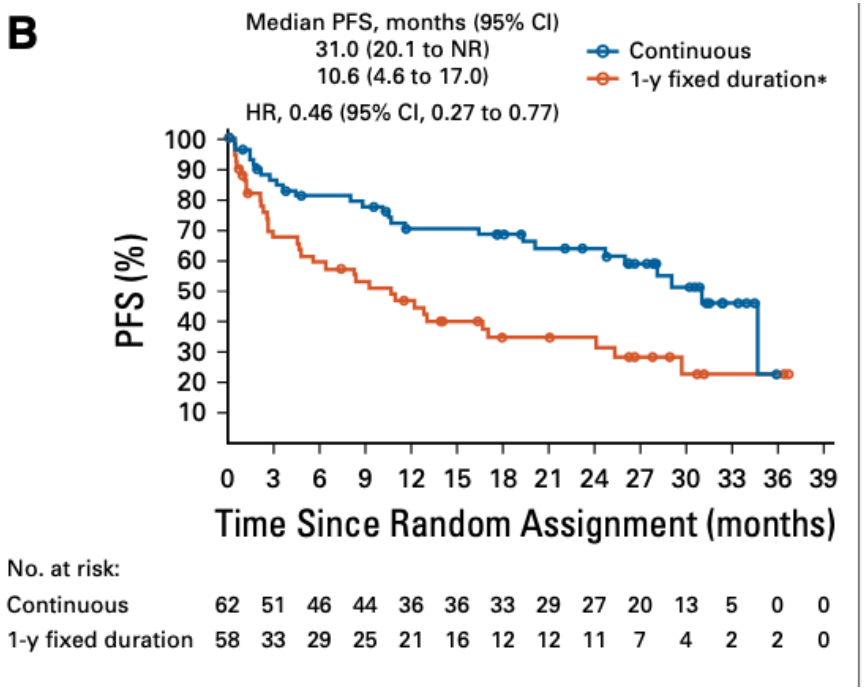
Duration of anti-PD1: new data muddy waters

Melanoma: frequent relapse after elective discontinuation if not in CR



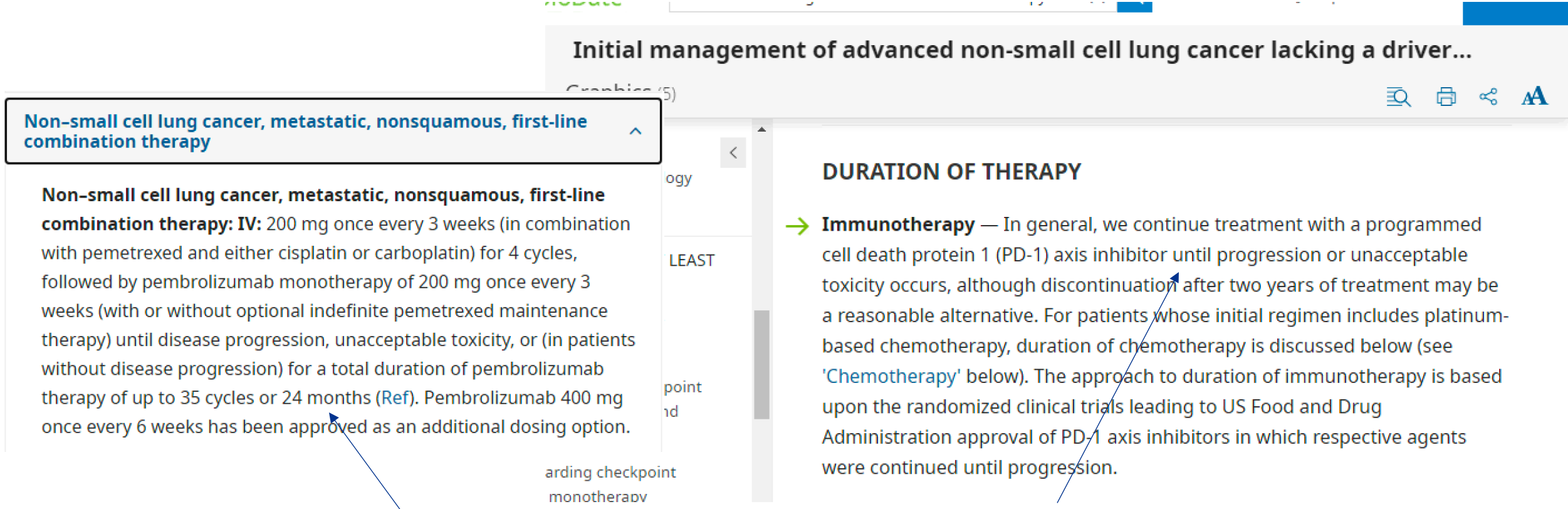
Betof Warner et al JCO 2020

NSCLC: >1 year better than 1 year anti-PD1 in RCT



Waterhouse et al JCO 2020

For many diseases we now have a mismatch: NSCLC shown as an example



FDA approval is 24 months

UpToDate suggest indefinite

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BUT: extended ICI comes with toxicity

Financial: cost of anti-PD1 = approximately $180K per year

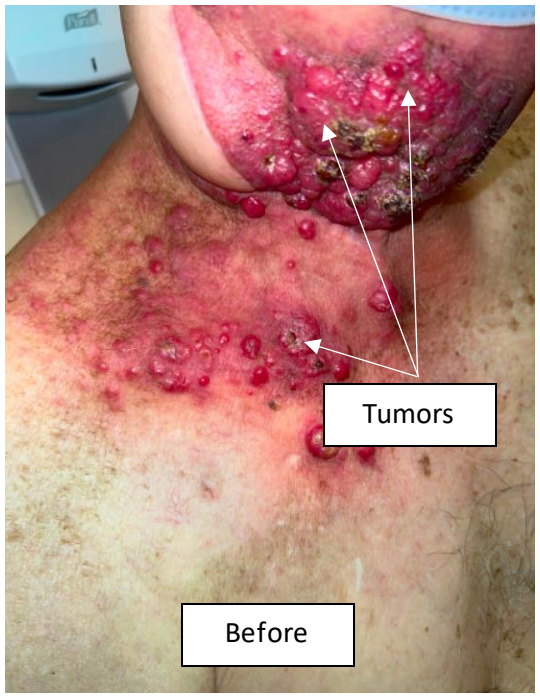
list price (keytruda.com) pembrolizumab $11,115.04 per 3 week dose dose

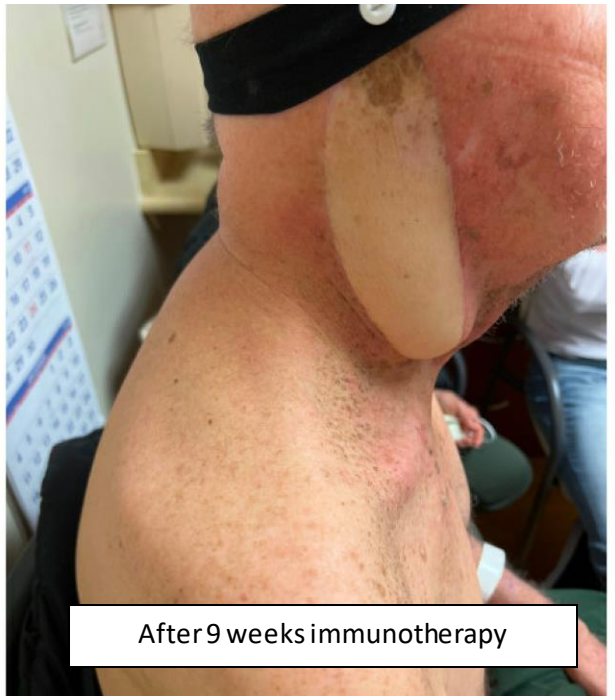
17 doses * $11k = ~180K per year

other manufacturers pricing is very similar

Physical: Late iRAEs can and do happen

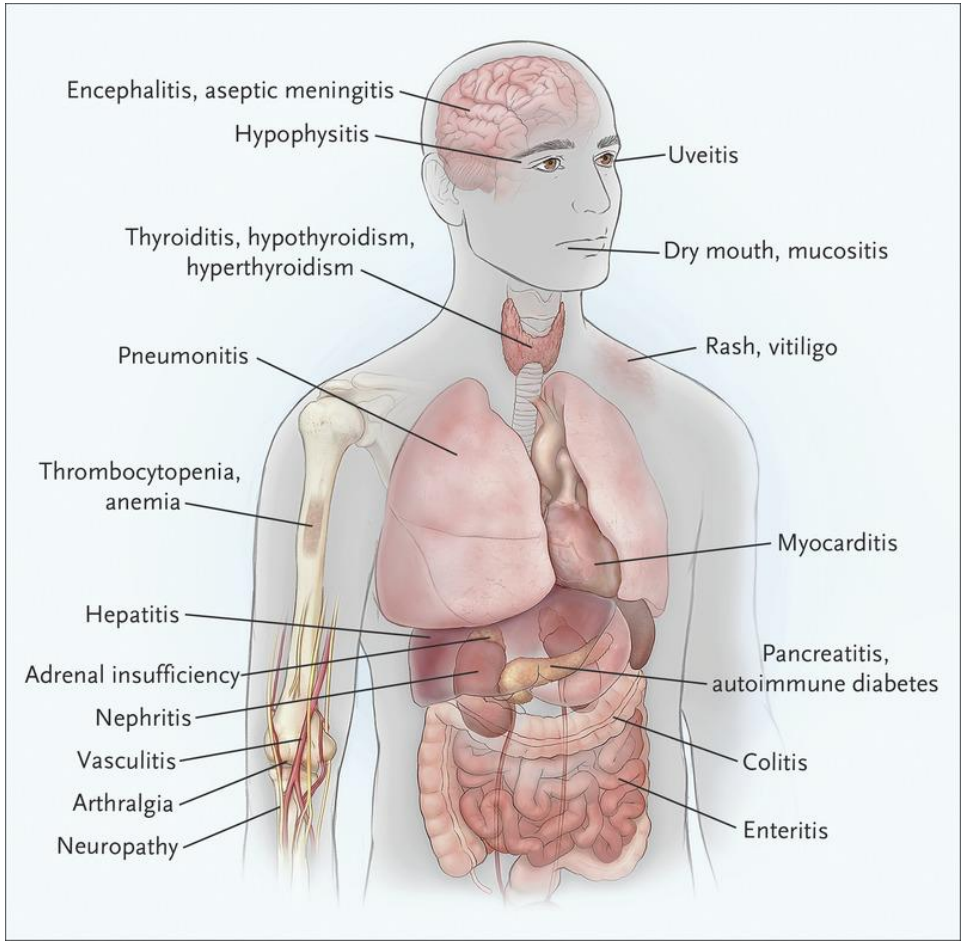
These drugs are miraculous when they work





Unpublished; image with patient's written permission

These drugs have a big problem: iRAE



1. LATE
2. NOT ON TREATMENT DAY
3. PATIENT CAN HAVE HAD NO SIDE EFFECTS

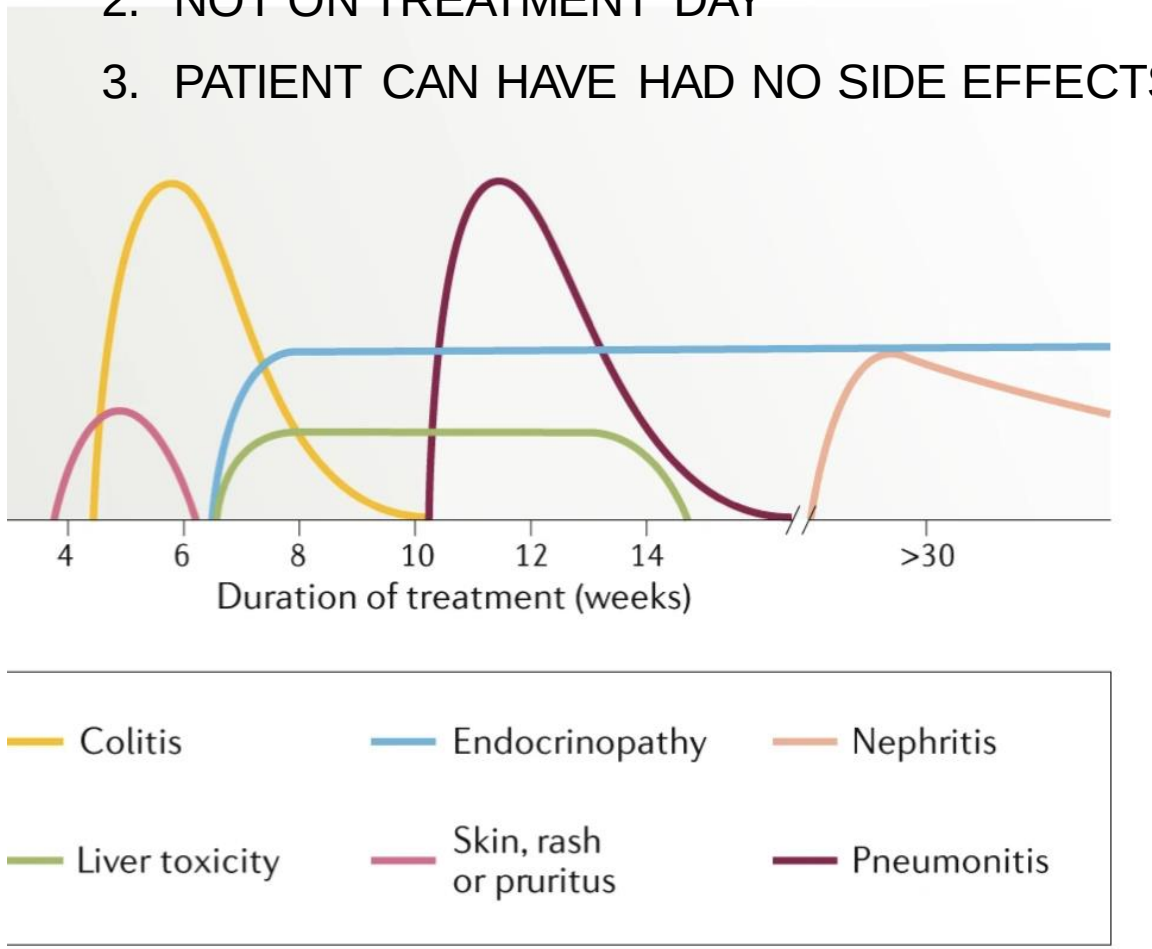


Image: NEJM. Image Martins et al Nature Reviews Clin Oncol

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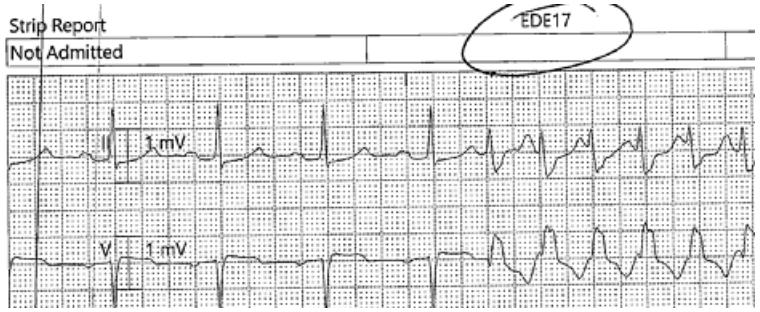
iRAEs can be VERY late ....

Qin et al ASCO 2020

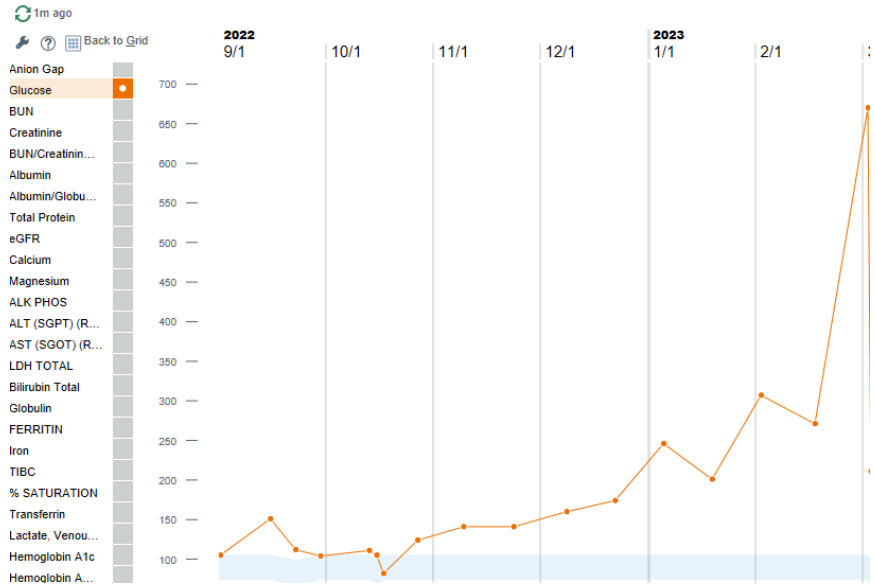
IRAE group (n)	Subtype (n)	SS	ICI DC	HP	Time to IRA (w, media [range
Cardiac (3)	Myocarditis (3)	3 (100%)	2 (67%)	1 (33%)	6 [1.5-54]
Endocrine (43)	Adrenal insufficiency (10) Autoimmune Pancreatitis /Diabetes (4) Hypophysitis (6) Thyroiditis (23)	17 (40%)	8 (19%)	8 (19%)	14.5 [1.5-130]
GI (40)	Colitis (20) Enteritis (1) Hepatitis (19)	19 (48%)	13 (33%)	7 (18%)	8 [1-107.5]
Kidney (2)	Nephritis (2)	0	0	0	14 [6.5-21]
Lung (11)	Pneumonitis (11)	10 (91%)	7 (64%)	7 (64%)	34 [1.5-127]
Musculoskeletal (11)	Inflammatory arthritis (8) PMR (3)	8 (73%)	3 (27%)	0	38 [1-127]
Skin (35)	Dermatitis (31) Mucositis (3) Conjunctivitis (1)	8 (23%)	6 (17%)	1 (3%)	7 [2-149.5]

Example acute late iRAE from recent patients

Myocarditis – 7 months



T1DM with DKA: 8 months



Retinitis resulting in 20/400 vision – 29 months

OCT Macula: Findings OD: Reason for Testing: Monitor Progression. Comparative Data: Worsening Compared to Prior Study. Retinal Thickening Consistent with Macular Edema. Parafoveal outer retinal loss, loss of RPE layer/ellipsoid zone IS/OS Junction. Foveal Thickness 351 (was 314, 320, 368) microns. **Findings OS:** Reason for Testing: Monitor Progression. Comparative Data: No Significant Change Compared to Prior Study. Parafoveal outer retinal loss, loss of RPE layer/ellipsoid zone IS/OS Junction. Foveal Thickness 277 microns.

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Or even months or years after treatment (“DIRE”)

Couey *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:165
https://doi.org/10.1186/s40425-019-0645-6

Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Delayed immune-related events (DIRE) after discontinuation of immunotherapy: diagnostic hazard of autoimmunity at a distance

Marcus A. Couey[1], R. Bryan Bell[1], Ashish A. Patel[1], Meghan C. Romba[2], Marka R. Crittenden[3], Brendan D. Curti[1], Walter J. Urba[1] and Rom S. Leidner[1*]

iRAE management

- Usually steroids
- ASCO guidelines: https://ascopubs.org/doi/10.1200/JCO.21.01440
- Can't miss: hypophysitis, myocarditis, encephalitis, T1DM, hepatitis
- General rules for restarting a checkpoint inhibitor:
  - The risk to the patient of the cancer needs to be higher than the risk to the patient of the checkpoint inhibitor
    - Toxicity well controlled
    - Do you actually need the checkpoint inhibitor?
    - Toxicity not previously life threatening (or if it was, going in with eyes wide open)

Current status re: anti-PD1 duration in 2023:

- If a patient is in CR or stable PR, PD-1 discontinuation for TOXICITY is appropriate and strong consideration should be given to reserving rechallenge for relapse
- If a patient is in CR at 2-3 years (depending on indication), ELECTIVE discontinuation is likely indicated
- If patient is NOT in CR but is responding, ELECTIVE discontinuation is not straightforward, however need to discuss with patient and also note continuation differs from FDA label
- It is reasonable to consider alternate dosing strategies/treatment schedules in our long-term survivors

Nutritional requirements for anti-PD1

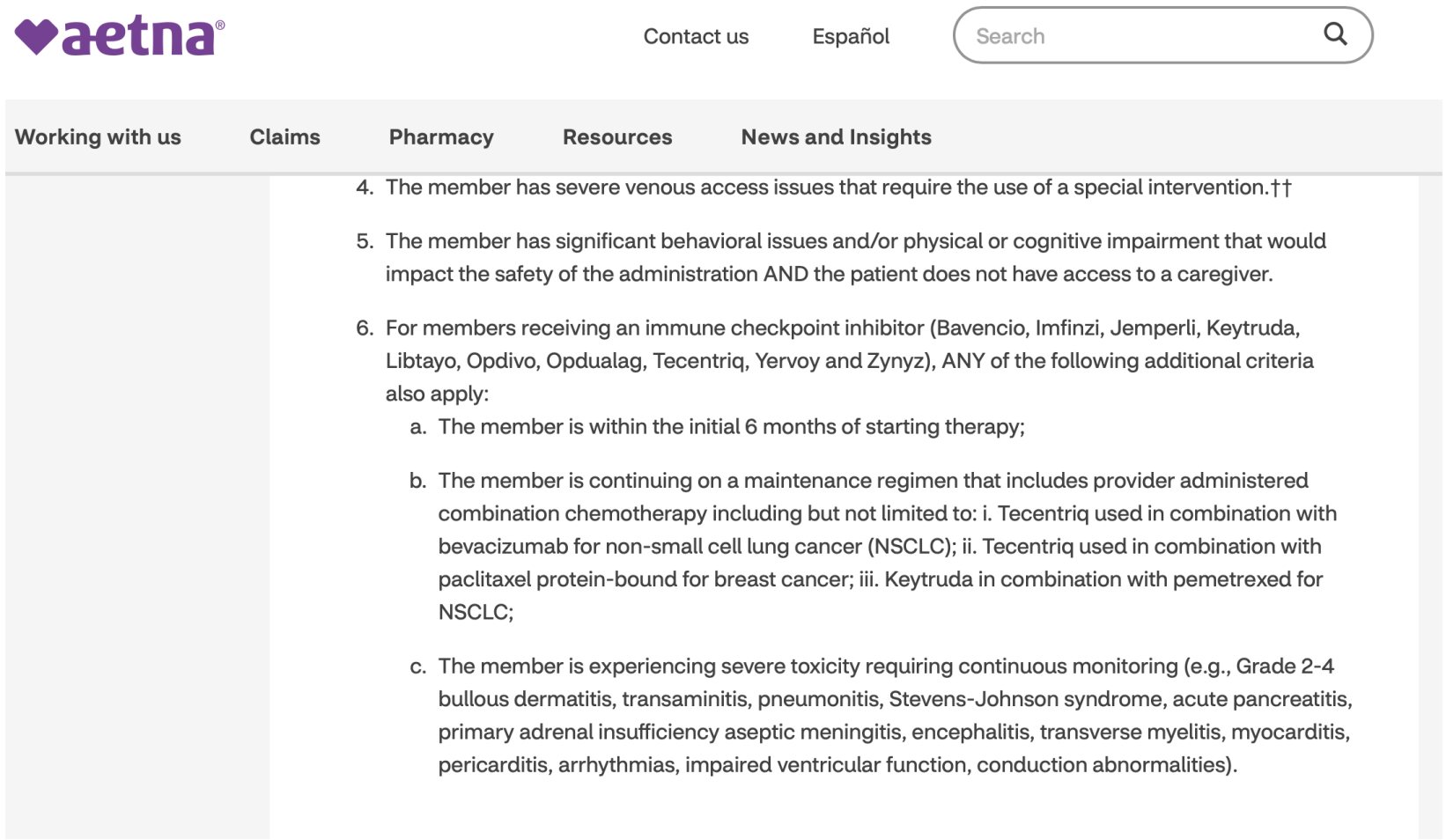
High fiber diet (Trinchieri et al Science 2021) (***vegetables!!!)***

Avoid no-sugar diets: CD8+ effector T cells eat glucose (Ma et al Immunity 2019)

Fermented and fiber foods for gut bacteria health, <u>NOT</u> probiotics!!!!

Avoid unnecessary abx (Pinato et al JAMA oncology 2019)

Site of care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4. The member has severe venous access issues that require the use of a special intervention.††
5. The member has significant behavioral issues and/or physical or cognitive impairment that would impact the safety of the administration AND the patient does not have access to a caregiver.
6. For members receiving an immune checkpoint inhibitor (Bavencio, Imfinzi, Jemperli, Keytruda, Libtayo, Opdivo, Opdualag, Tecentriq, Yervoy and Zynyz), ANY of the following additional criteria also apply:
a. The member is within the initial 6 months of starting therapy;
b. The member is continuing on a maintenance regimen that includes provider administered combination chemotherapy including but not limited to: i. Tecentriq used in combination with bevacizumab for non-small cell lung cancer (NSCLC); ii. Tecentriq used in combination with paclitaxel protein-bound for breast cancer; iii. Keytruda in combination with pemetrexed for NSCLC;
c. The member is experiencing severe toxicity requiring continuous monitoring (e.g., Grade 2-4 bullous dermatitis, transaminitis, pneumonitis, Stevens-Johnson syndrome, acute pancreatitis, primary adrenal insufficiency aseptic meningitis, encephalitis, transverse myelitis, myocarditis, pericarditis, arrhythmias, impaired ventricular function, conduction abnormalities).

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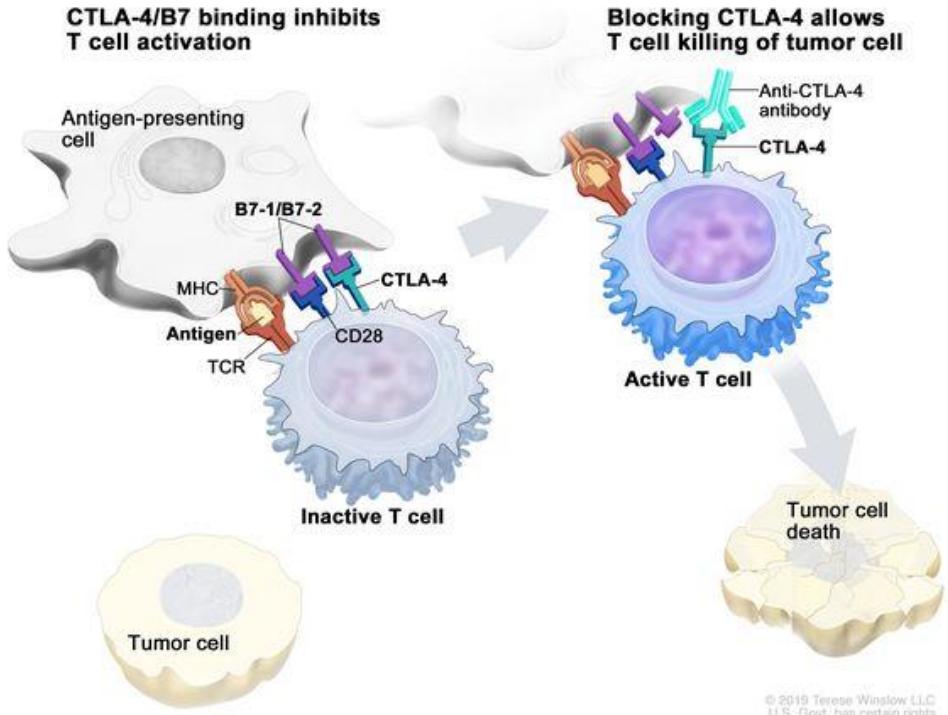
All images from Amazon.com or Walmart

Other FDA-Approved Checkpoints



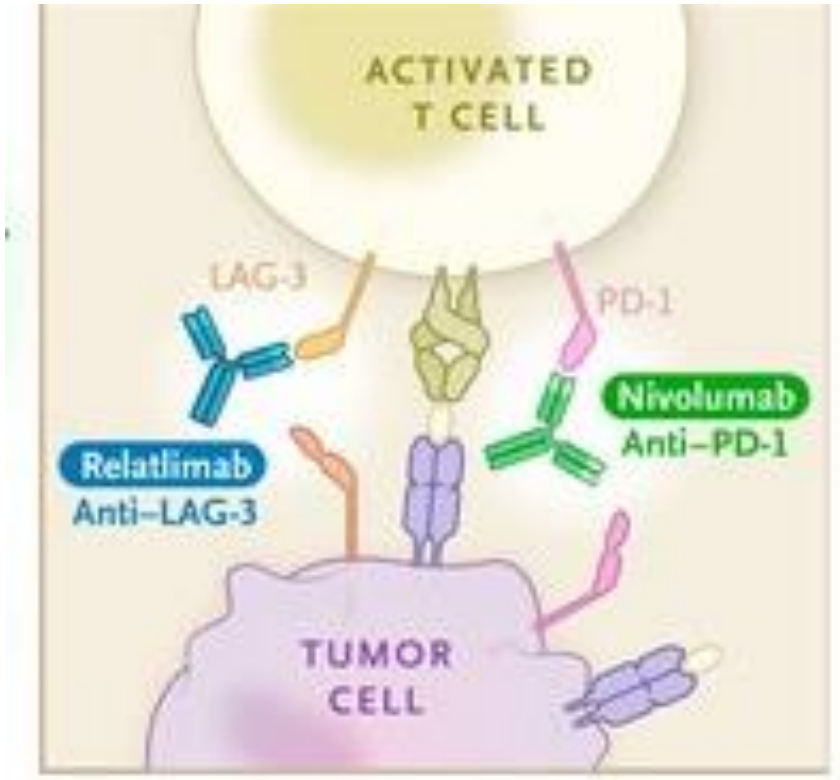


Image: NEJM

CTLA4 checkpoint
- Ipilimumab (w/nivo)
- Tremelimumab (w/durva)

NEW: LAG3
- Relatlimab (w/ nivo)

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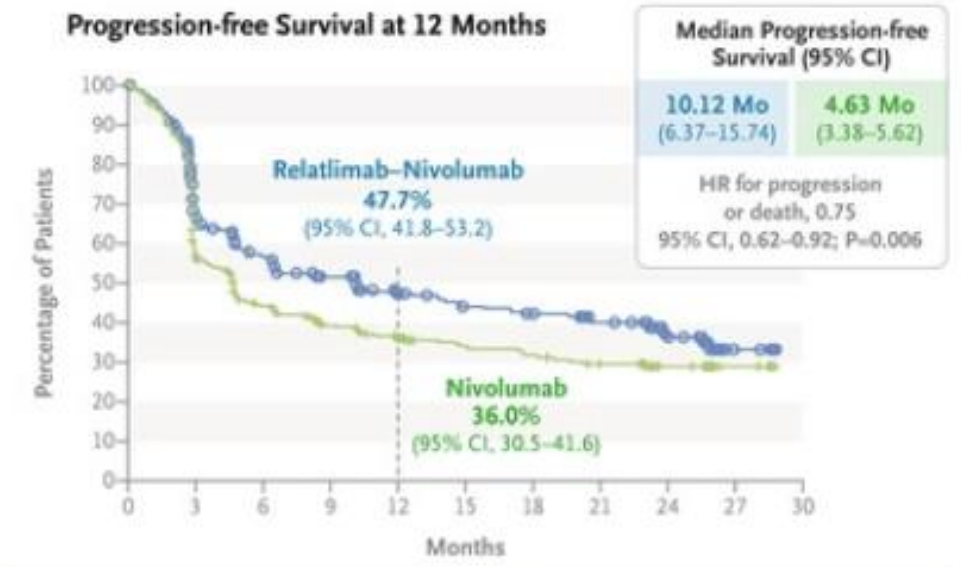
Relatlimab (+ nivo)

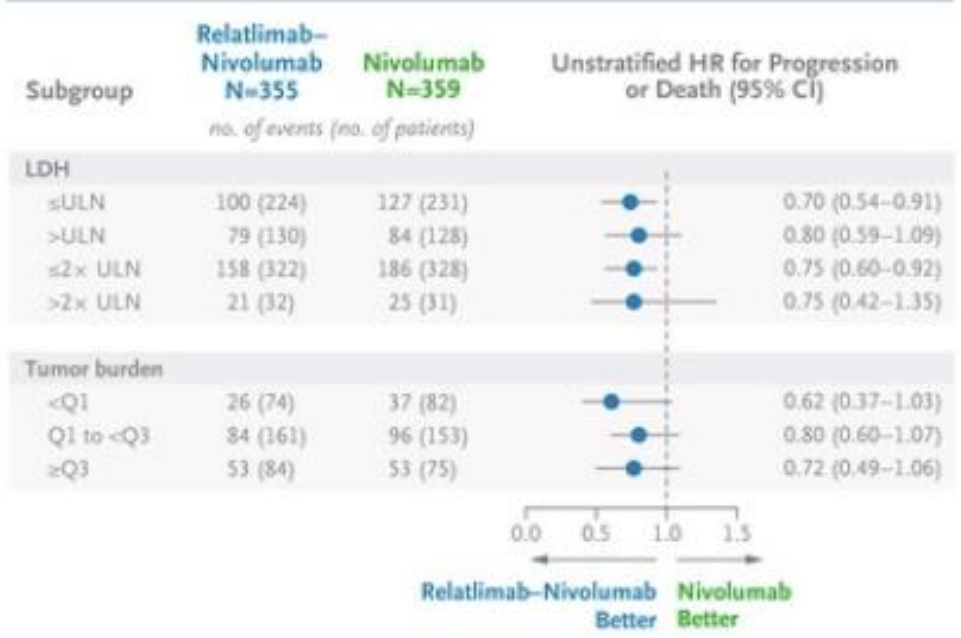
Lower reported toxicity rates than ipilimumab (+ nivo)

Improves PFS & likely OS compared to nivolumab (Tawbi et al ASCO 2023)

Who it is good for: low burden melanoma pts who you are worried about ipilimumab toxicity

Who it is less ideal for: progression after PD-1 monotherapy, brain mets, young fit pt





RELATIVITY: NEJM 2022

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Outline

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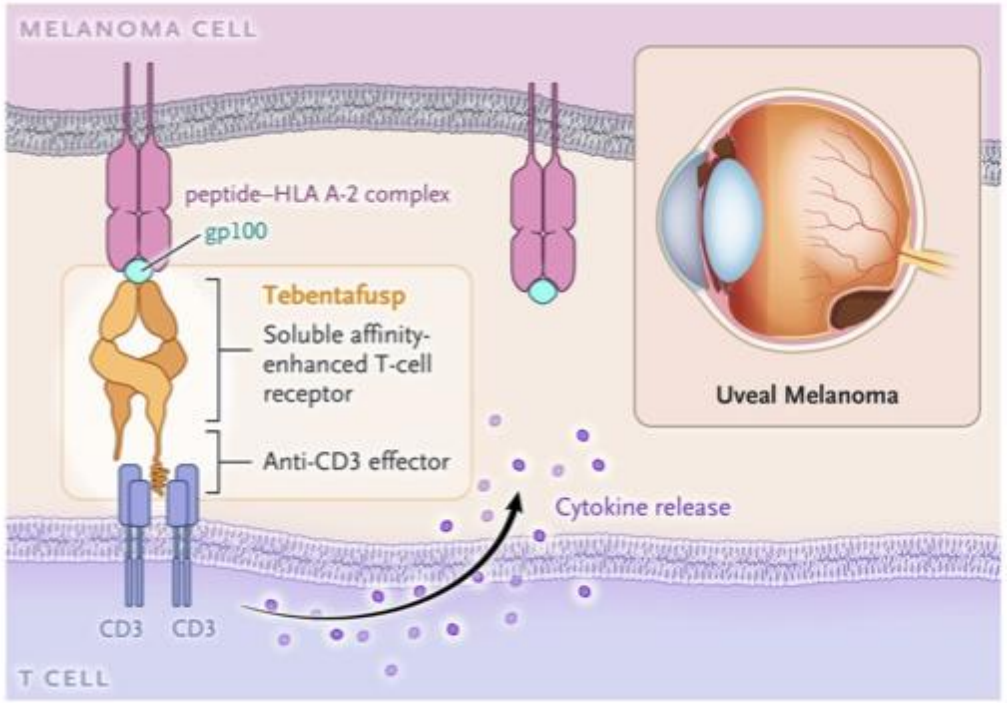
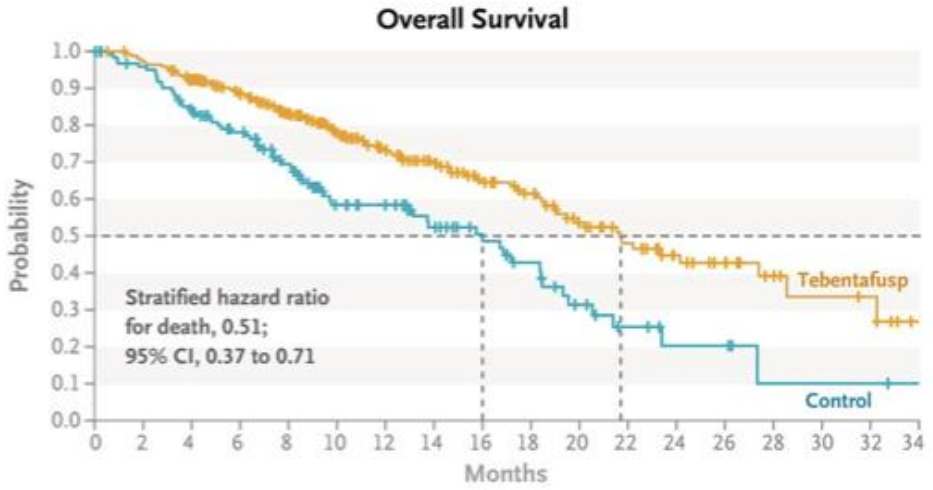
Uveal melanoma: tebentafusp TCR-CD3





1-Year Survival		
Tebentafusp Group	73%	95% CI, 66 to 79
Control Group	59%	95% CI, 48 to 67

Images: Nathan et al NEJM 2021

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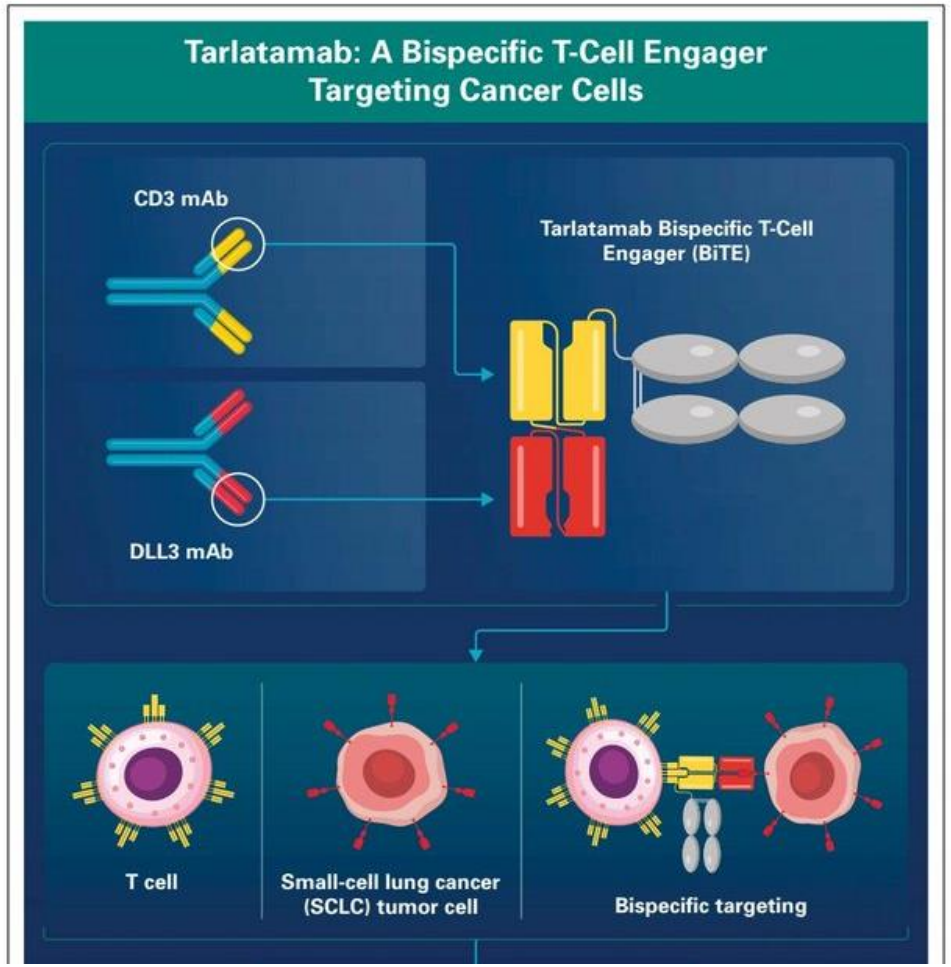
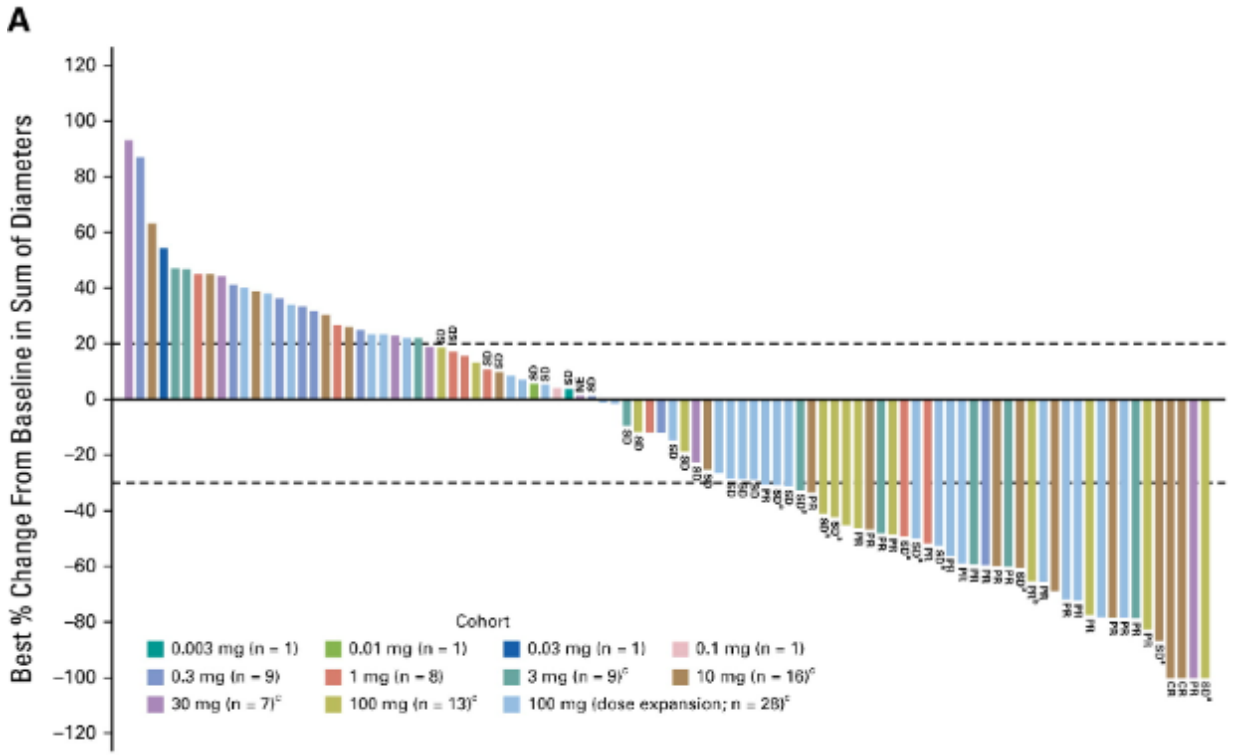
Small cell lung cancer: tarlatamab (investigational)





Paz-Ares et al JCO 2023

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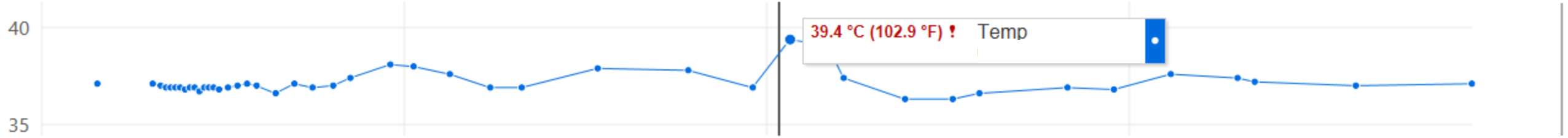
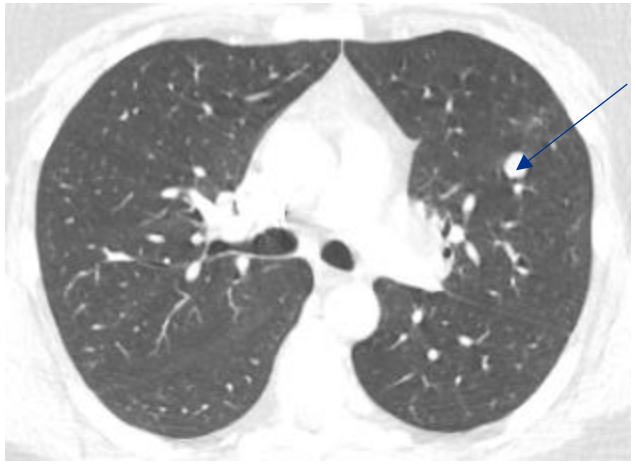
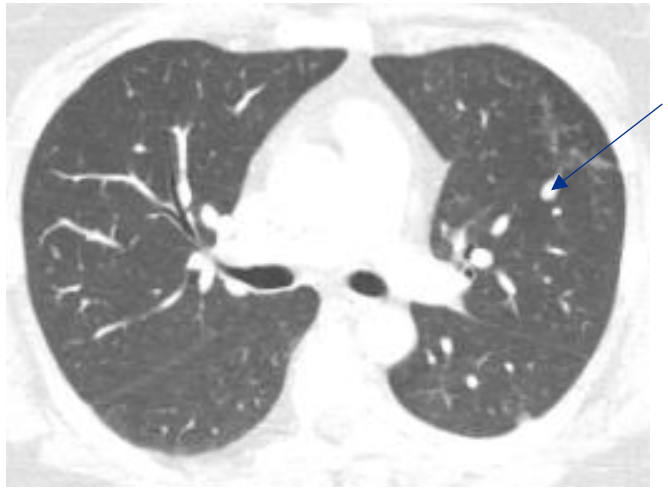
CRS happens but responses can be deep & durable







Unpublished data

TIL therapy: lifileucel T (investigational)

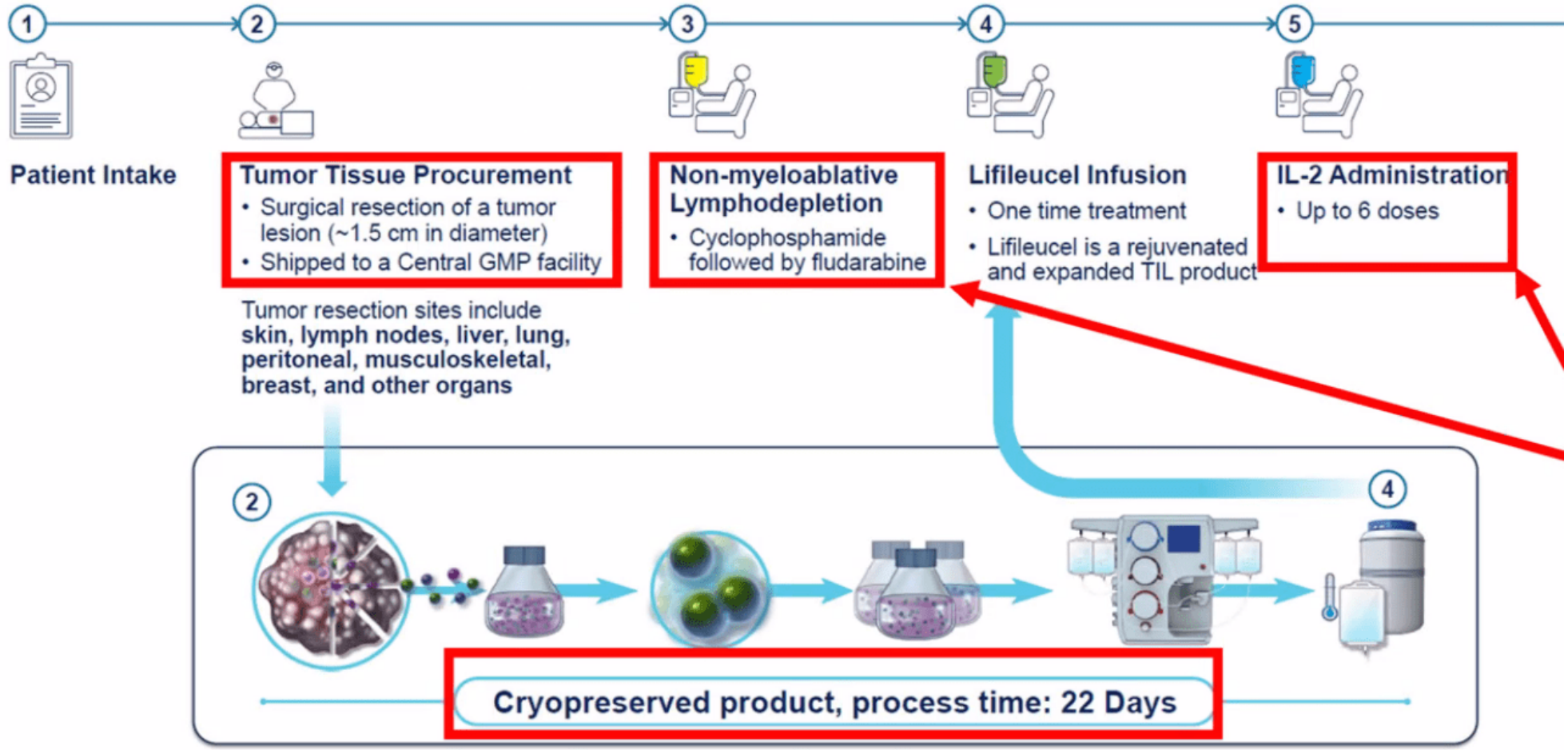


Image: Cancer connect

TIL therapy: lifileucel T (investigational)

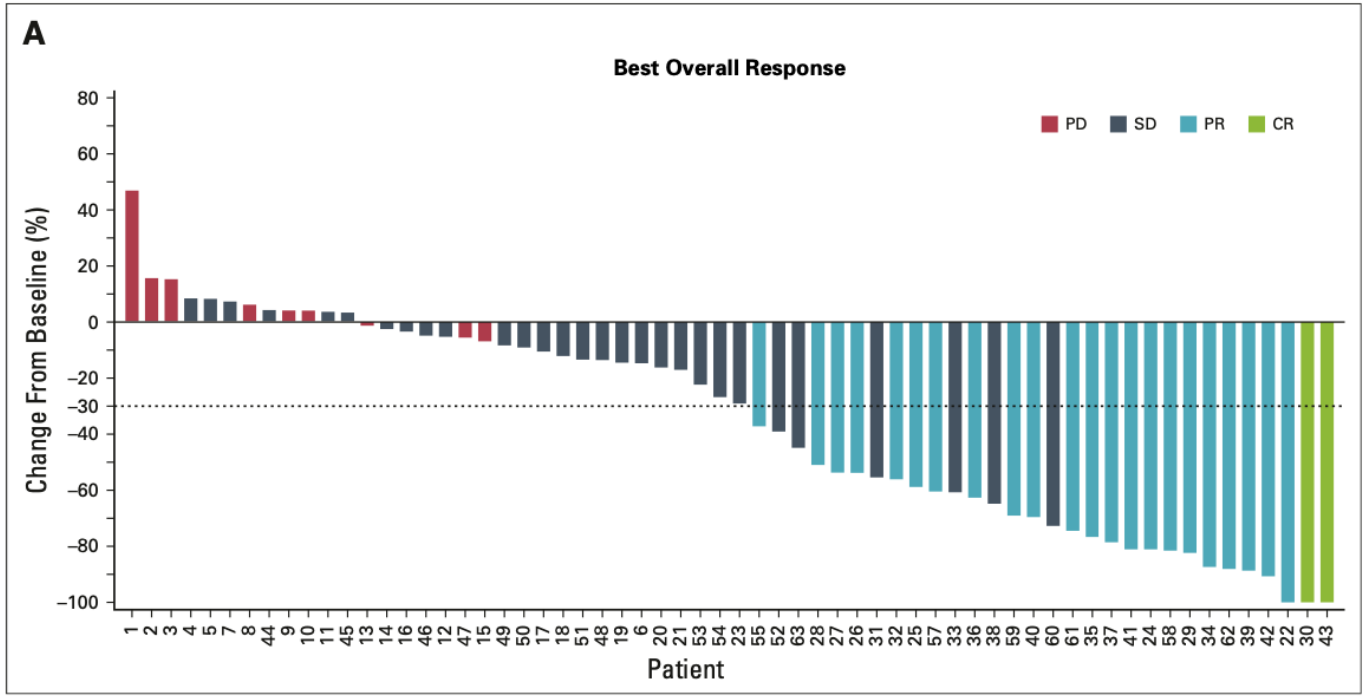
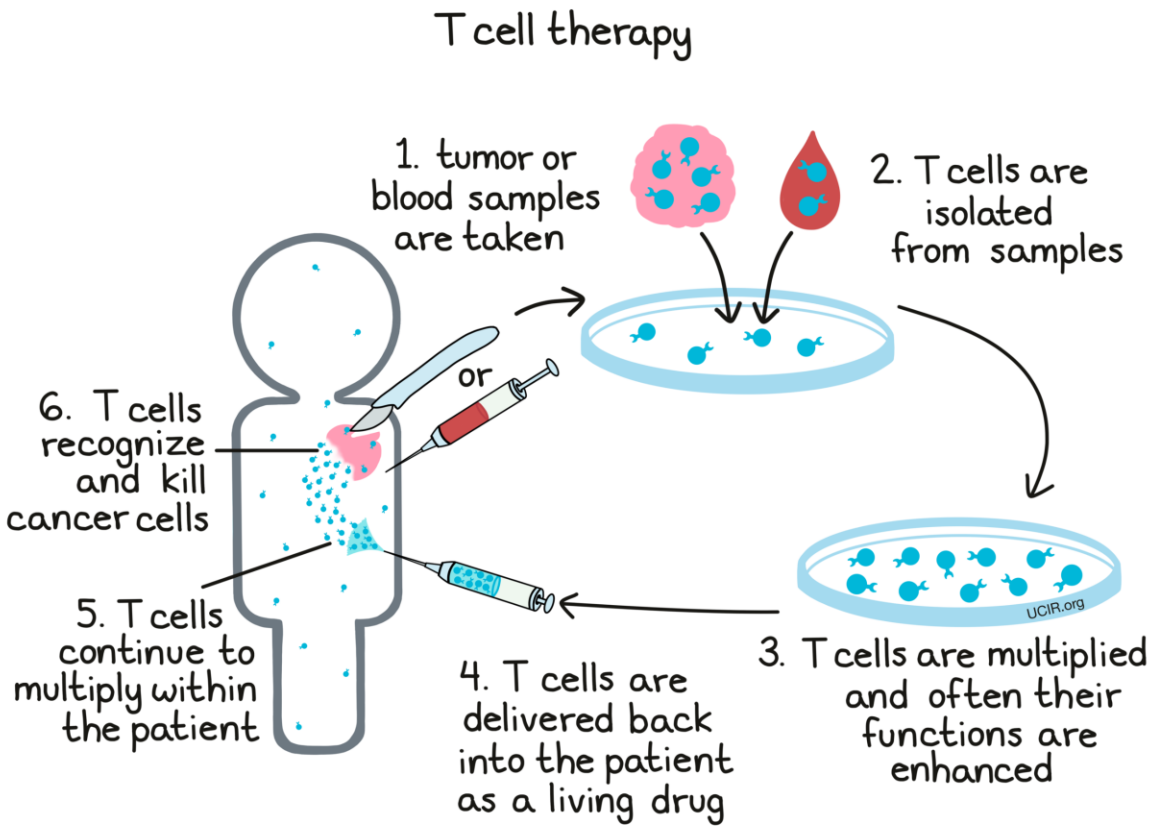


FIG 1. Change in tumor burden of target lesions, response by subgroup, and response assessment in individual patients. (A) Waterfall plot depicting BOR as assessed by investigator and the best change from baseline in the SOD of the target lesions (per RECIST v1.1 criteria) in the FAS. A change of −100% from baseline is presented for CR assessment that includes lymph node lesions that resolved to < 10 mm. The horizontal dashed line indicates a 30% reduction in the tumor burden in the target lesions. Twelve patients had an increase in the SOD of the target lesions, whereas 50 patients had a decrease in the SOD of the target lesions. Thirty patients (two CR, 22 PR, and six SD) had > 30% reduction in the SOD of the target lesions. Three patients had no post-TIL assessments because of early death. One patient had no post-TIL assessment because of start of new anticancer therapy before day 42. (continued on next page)

Sarnaik et al JCO 2021

Engineered T cell based cellular immunotherapy



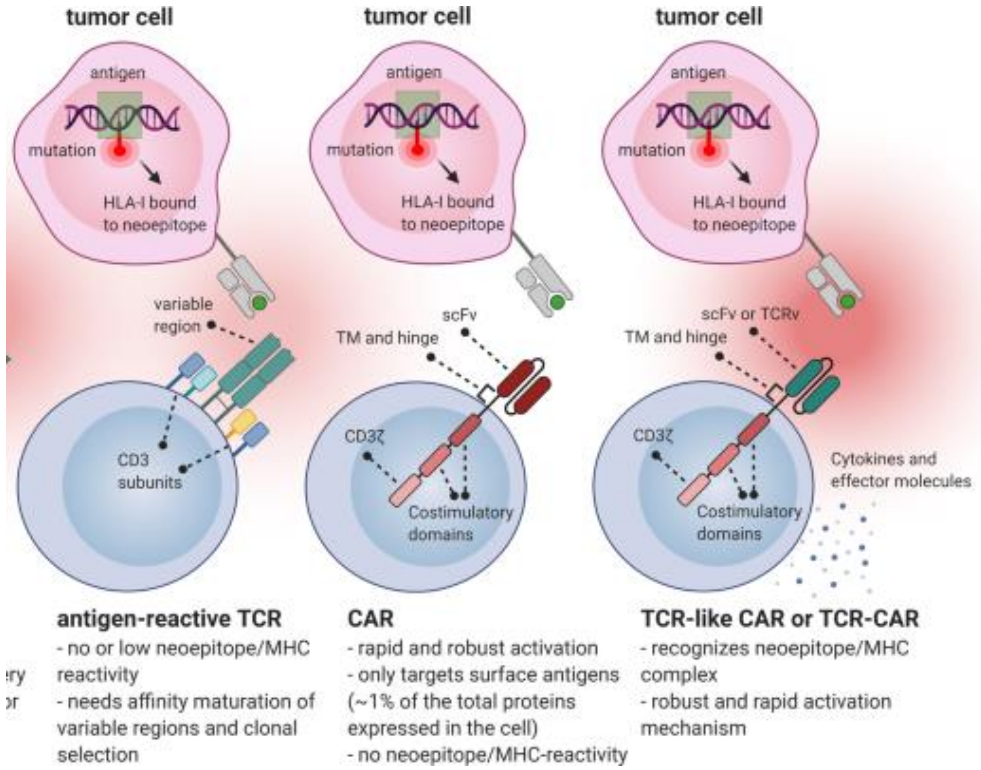


Image: Cancer Immunotherapy Research. Figure: Nature

What about the melanoma vaccine?

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Session CTPL01 - Harnessing the Immune System in the Clinic

CT001 - A personalized cancer vaccine, mRNA-4157, combined with pembrolizumab versus pembrolizumab in patients with resected high-risk melanoma: Efficacy and safety results from the randomized, open-label Phase 2 mRNA-4157-P201/Keynote-942 trial

April 16, 2023, 12:45 PM - 1:00 PM | Chapin Theater - Convention Center

Presenter/Authors

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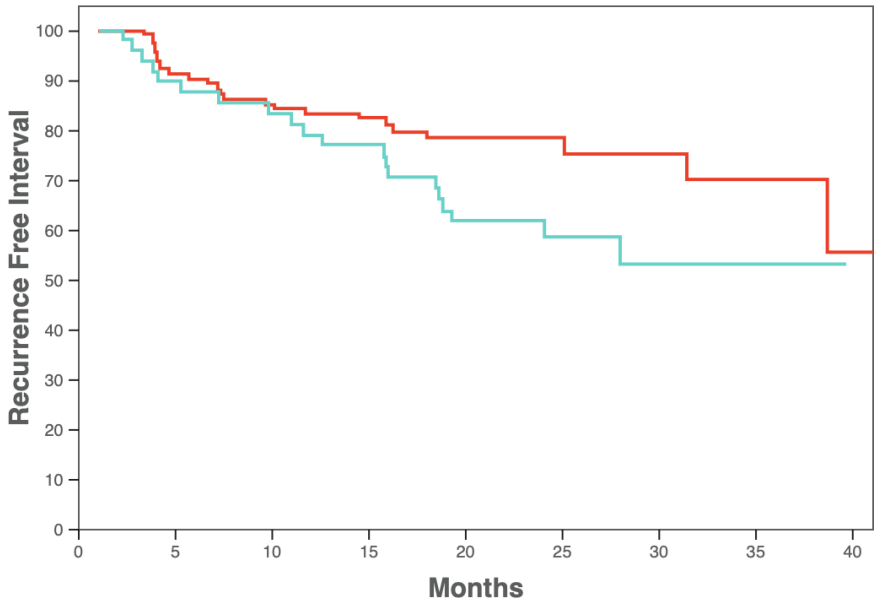
What about the melanoma vaccine?

Keynote-942 - An Efficacy Study of Adjuvant Treatment With the Personalized Cancer Vaccine mRNA-4157 and Pembrolizumab in Participants With High-Risk Melanoma (KEYNOTE-942)

Recurrence-free survival



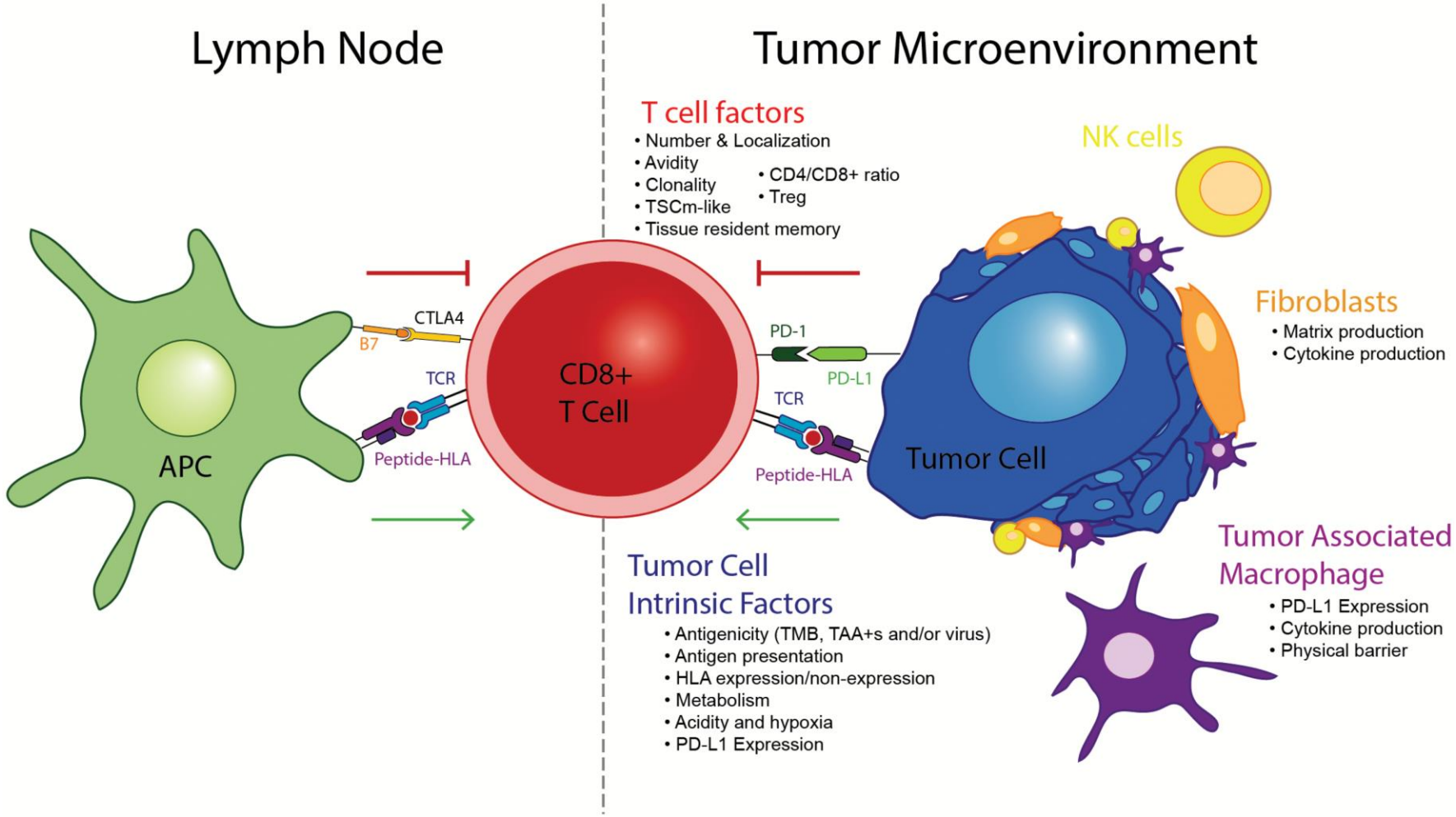
Curves	N
mRNA-4157 (V940) + Pembrolizumab	107
Pembrolizumab	50

	HR (95% CI)	P-value
mRNA-4157 (V940) + Pembrolizumab vs Pembrolizumab	0.56 (0.31 - 1.02)	0.0266

AACR 2023 (14-03-2023)

Khattak et al AACR 2023

IMTX Response Mechanisms Complex



Providence SWEDISH

Paulson KG et al Int Immuno 2019

Thank you!

KASCO/ACCC team

Dr. Jay Lopez & WSMOS team

Dr. Sara Jo Grethlein

Doug Kieper, Lauren Garvey, Dr. Chuck Drescher, Dr. Hank Kaplan & Paul G Allen Research Center Team

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Dr. Bin Xie, Dr. Min Park, & Melanoma team at SCI

Oncology RNs!!!

Surgical and dermatology and radiology and palliative care colleagues

Collaborators

Patients & family members

Questions?