Emerging Trends in Solid Tumor Immunotherapy

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Disclosure of Conflicts of Interest

Kelly Paulson MD, PhD has the following financial relationships to disclose:

- Advisory: Bristol Myers Squibb
- Research Funding (to institution): Amgen, Bristol-Myers Squibb, Iovance, Merck, Immunocore

CME Objectives

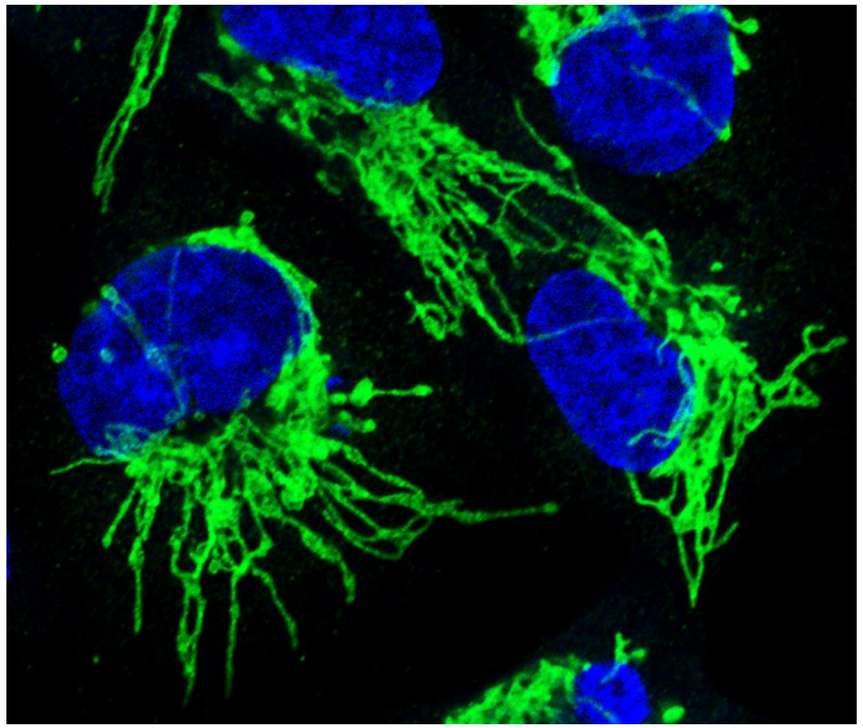
- Recognize emerging trends in solid tumor immunotherapy
- Identify common and rare immune related adverse events and resources for safe management
- Understand mechanisms of emerging bispecific therapies for solid tumor and unique toxicities
- Be aware of recent FDA approvals for cellular therapy in solid tumors

Outline

1. Checkpoint inhibitors: updates, duration, iRAE, and regulatory issues
2. Bispecific T cell engagers: who, what, how and where
3. Cellular immunotherapy for solid tumors
4. Vaccines and other approaches

Impact of Cancer

- 2,000,000 new cases/year in USA (~11,000 in New Mexico)[1]
- Lifetime risk ~40%
- 611,000 cancer deaths each year in USA (#2 after heart disease)



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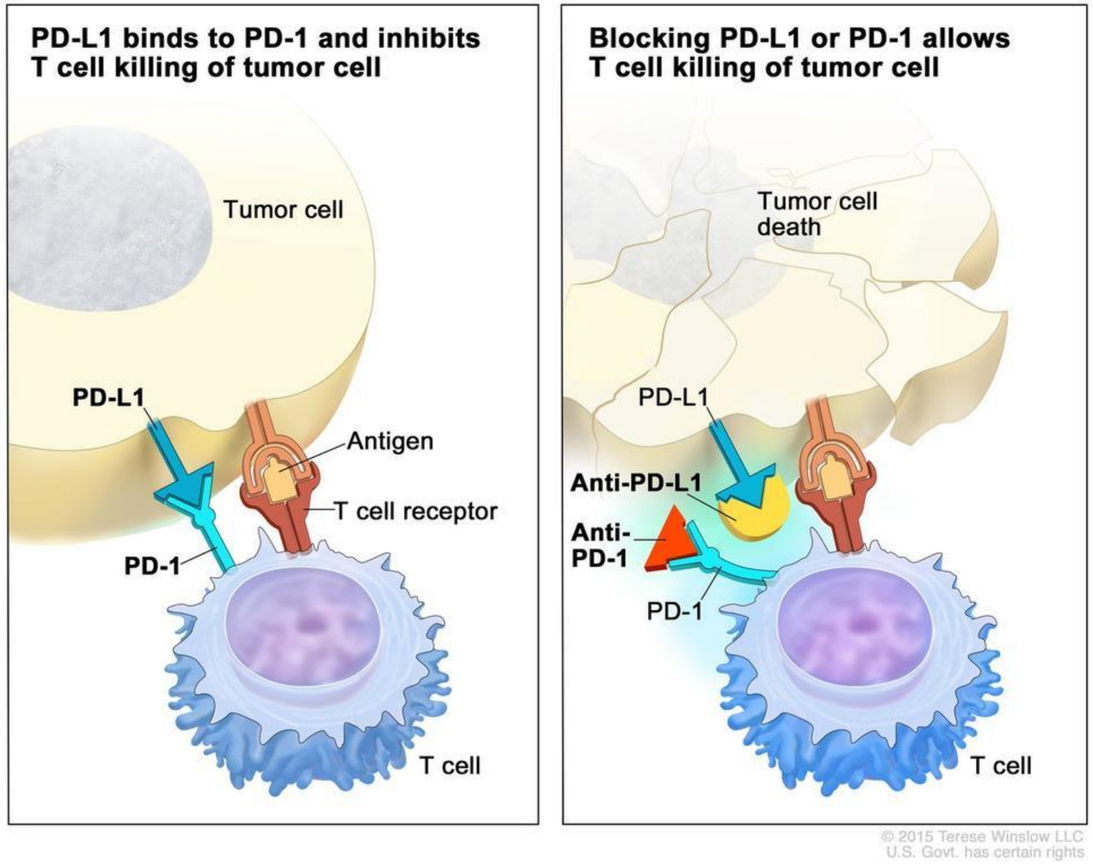
Immune Checkpoint Inhibitors (ICI)

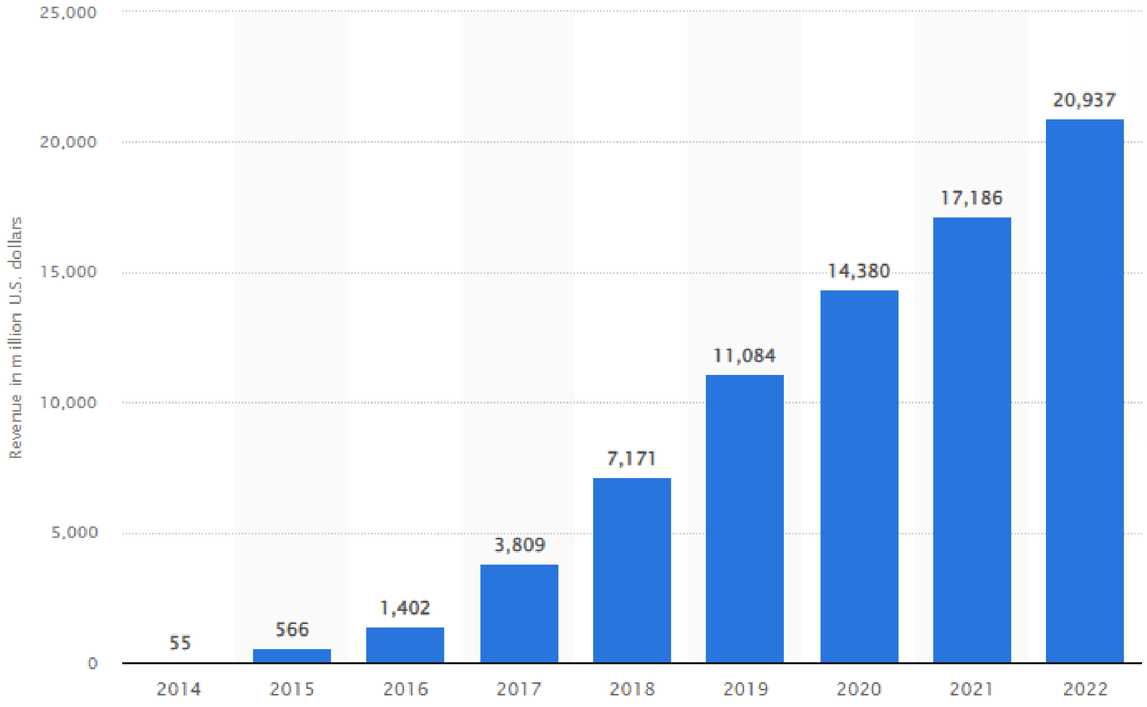


- Anti-PD-1: pembrolizumab, nivolumab, cemiplimab, dostarlimab, retifanlimab, toripalimab, tislelizumab
- Anti-PD-L1: atezolizumab, avelumab, durvalumab
- Anti-CTLA4: ipilimumab, tremelimumab
- Anti-LAG3: relatlimab

Explosive growth in ICI usage

- Pembrolizumab now #1 340B drug
- ICI approximately ¼ of medicare hospital drug costs
- >20 solid tumor indications, now ~ 50% of solid tumor patients getting systemic tx will receive

Annual Pembrolizumab Sales (2014-2022)



Key recent ICI approvals/shifts 2022-2024

- Lung: adjuvant durvalumab for limited stage SCLC after chemoradiation
- Bladder/urothelial: enfortumab vedotin + pembrolizumab for 1L metastatic
- Melanoma: stage 2: adjuvant therapy (pembrolizumab or nivolumab) for 2B+, stage 3: neoadjuvant/adjuvant, stage 4: dual immunotherapy clear winner (either relatlimab-nivolumab or ipilimumab-nivolumab)
- cSCC: neoadjuvant cemiplimab
- Endometrial: dostarlimab or pembrolizumab w/1st line chemo

ICI are miraculous when they work

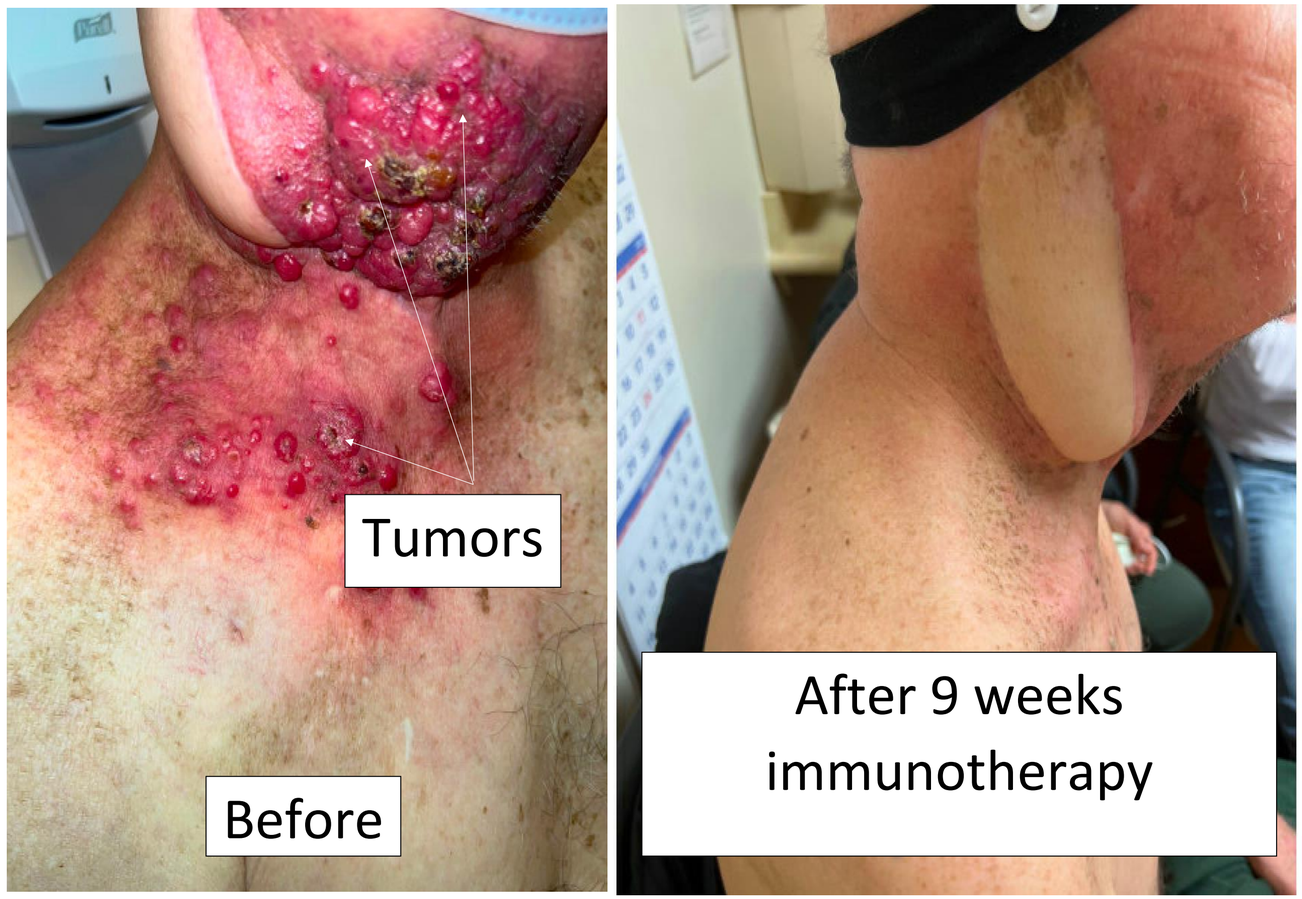
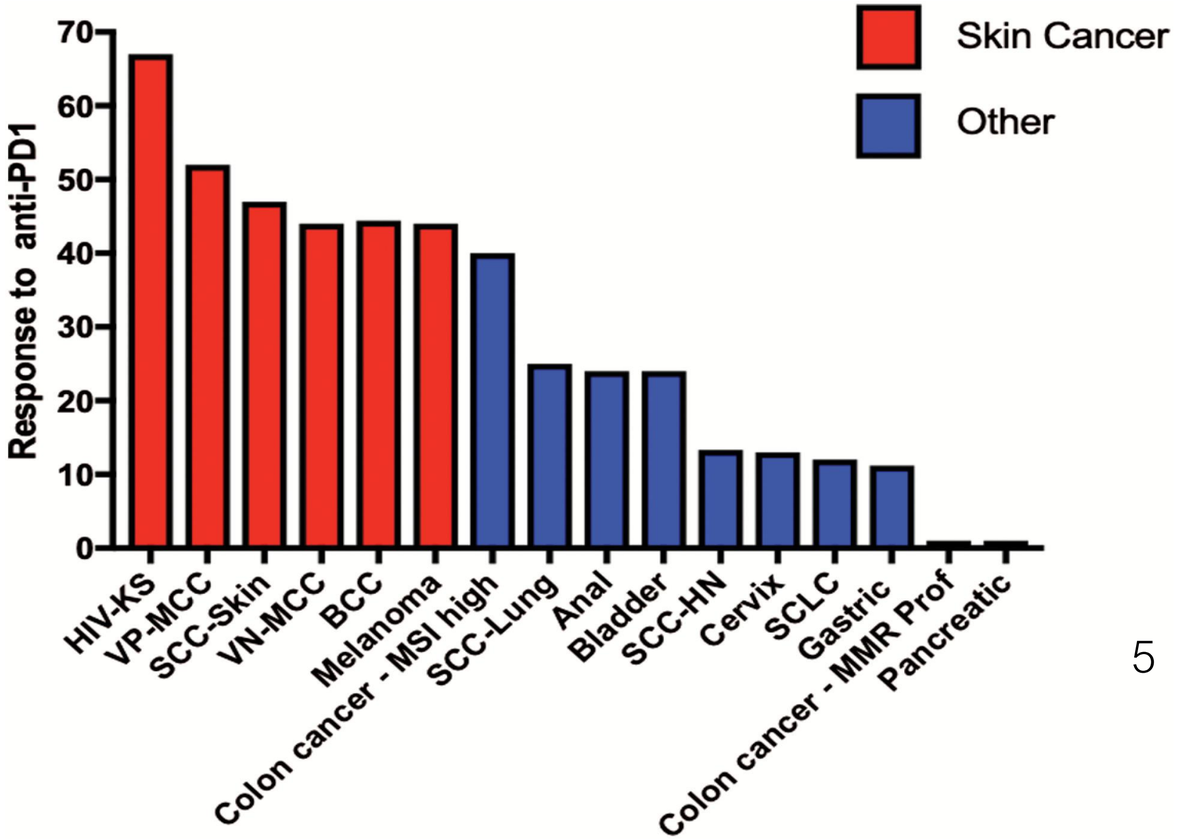


Image with patient permission

Despite ICI growth, we still do not know:

- Who will benefit
- Optimal duration
- Long term AE risk
- Best site of care

Ongoing unmet need for better immunotherapy

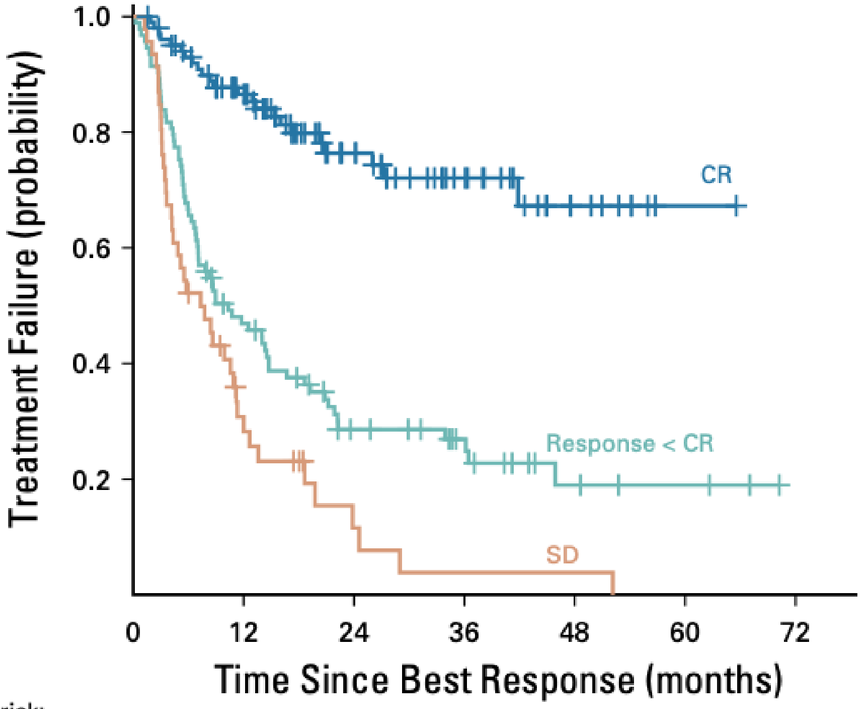


Nutrition for cancer immunotherapy

- High fiber diet: vegetable eating associated with ~15% better ORR [6]
- Promote gut bacteria diversity: avoid unnecessary antibiotics and avoid probiotics both of which diminish IMTX outcomes [6,7]

Among responders, optimal duration unclear

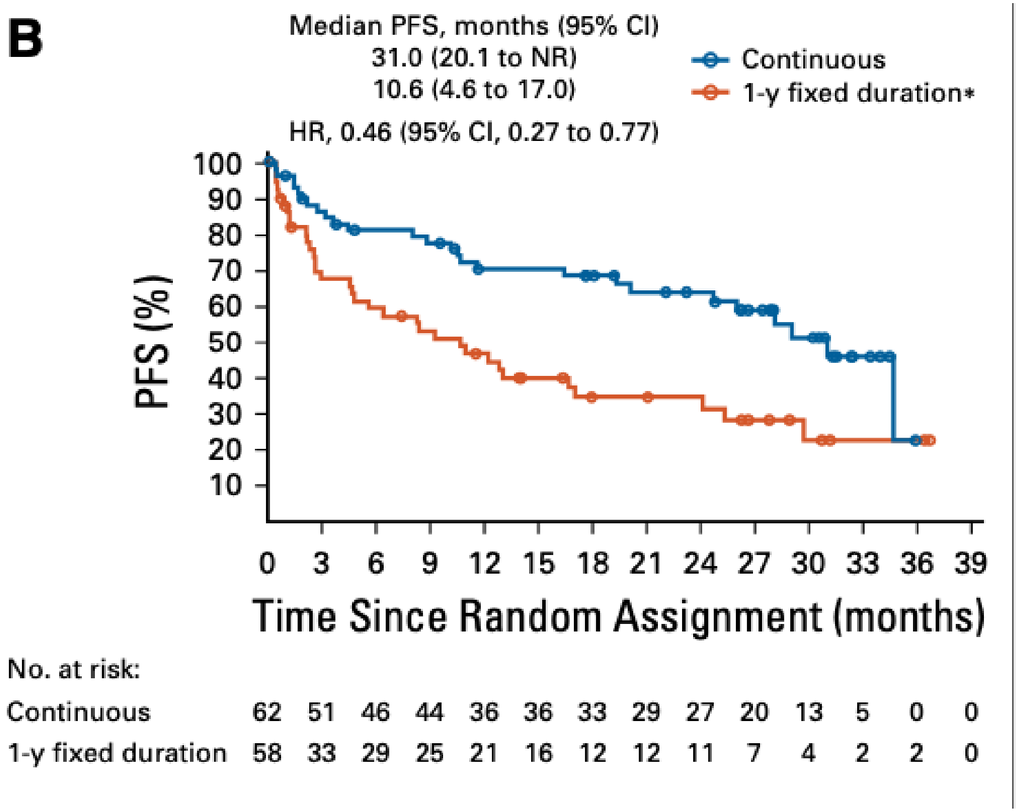
Melanoma



No. at risk:

CR	102	73	39	22	8	1	0
Response < CR	93	41	20	13	5	3	0
SD	46	12	3	1	1	0	

Non-small cell lung cancer



No. at risk:

Continuous	62	51	46	44	36	36	33	29	27	20	13	5	0	0
1-y fixed duration	58	33	29	25	21	16	12	12	11	7	4	2	2	0

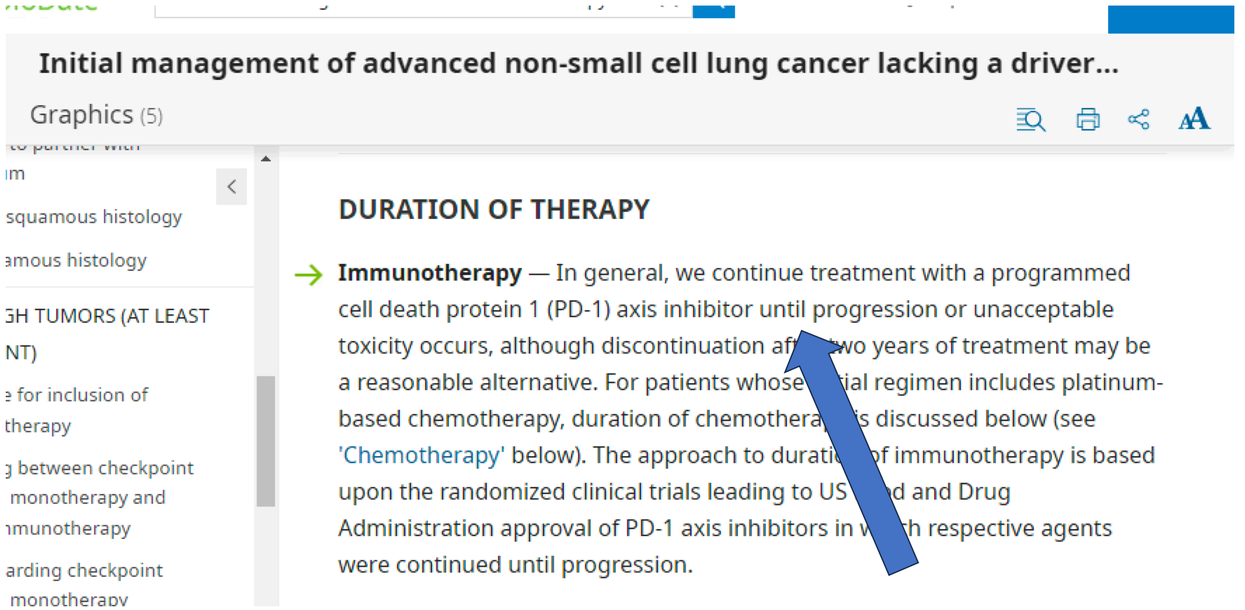
8,9

For many diseases, a mismatch (eg. NSCLC)

Non–small cell lung cancer, metastatic, nonsquamous, first-line combination therapy

Non–small cell lung cancer, metastatic, nonsquamous, first-line combination therapy: IV: 200 mg once every 3 weeks (in combination with pemetrexed and either cisplatin or carboplatin) for 4 cycles, followed by pembrolizumab monotherapy of 200 mg once every 3 weeks (with or without optional indefinite pemetrexed maintenance therapy) until disease progression, unacceptable toxicity, or (in patients without disease progression) for a total duration of pembrolizumab therapy of up to 35 cycles or 24 months (Ref). Pembrolizumab 400 mg once every 6 weeks has been appro as an additional dosing option.

FDA approval is 24 months



UpToDate suggest indefinite

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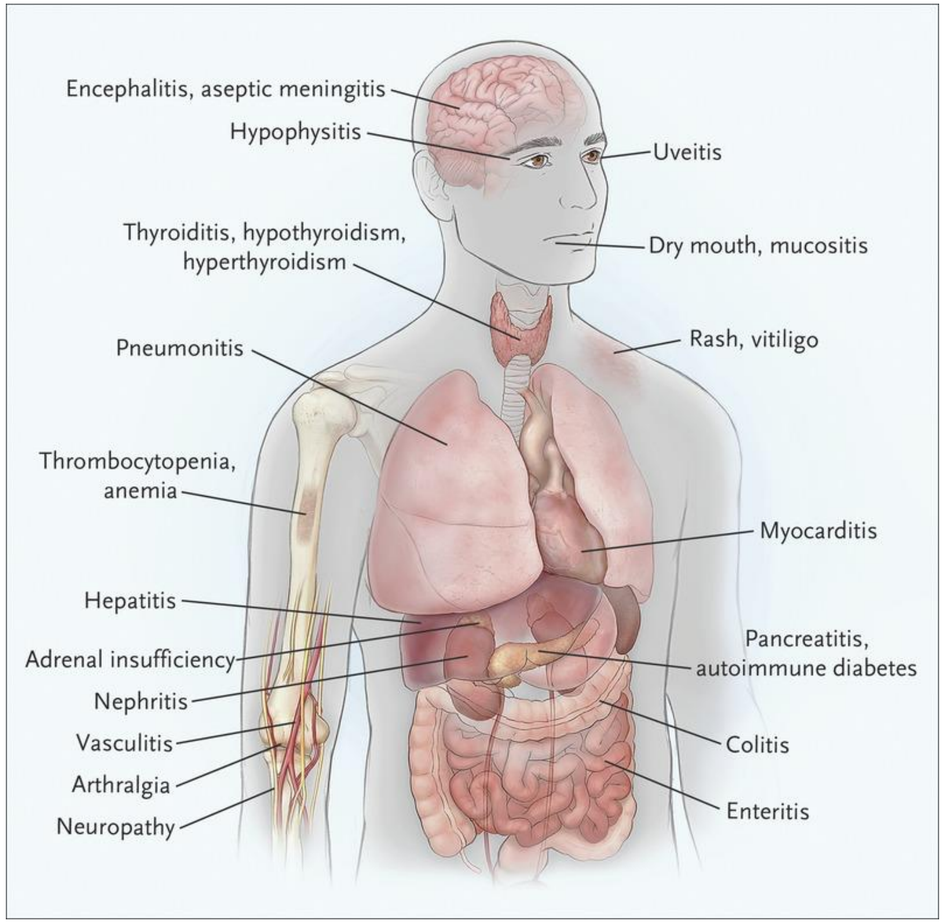
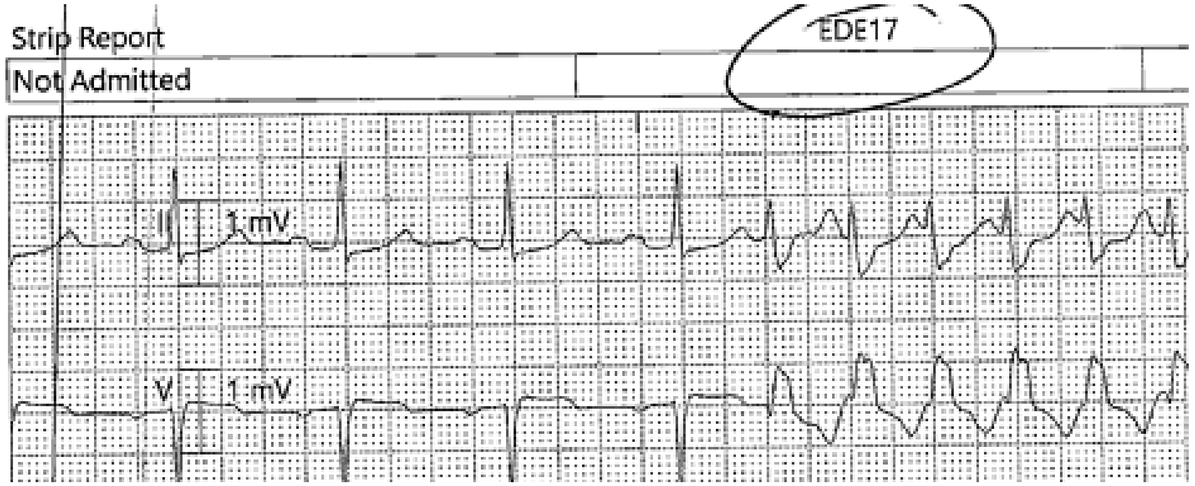
BUT with extended ICI, toxicity can and does happen



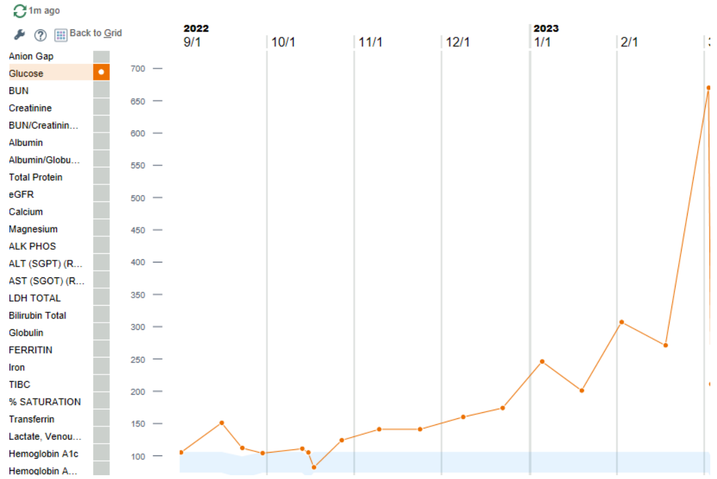
- iRAE = immune related adverse events
- Does NOT follow usual pattern of med toxicity
  - unpredictable and often acute onset
  - not on treatment day or specific timing
  - any organ system
  - can mimic other disease processes
- DIRE = delayed immune related events – **up to 2 years after IMTX given**

Example late iRAE from my 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.

iRAE management

- Usually steroids
- ASCO guidelines: https://ascopubs.org/doi/10.1200/JCO.21.01440
- Can't miss: hypophysitis, myocarditis/MMM, encephalitis, T1DM, hepatitis
- General rules for restarting a checkpoint inhibitor:
  - risk of cancer needs to be higher than risk of ICI
    -> do you actually need the ICI right now?
  - toxicity well controlled
  - toxicity not life threatening (except rare circumstances)

Site of Care Concerns – Role for NMSCO?

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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).

Putting it all together – how much is the right amount?

- In 2024, not yet clear consensus
- Neoadjuvant/adjuvant have specified duration; adjuvant imtx after CR from likely unnecessary but data still emerging
- For metastatic disease

-> if patient is SD or better and is having toxicity, stop or pause

-> if patient is at CR and is without toxicity, stop after 2-3 years

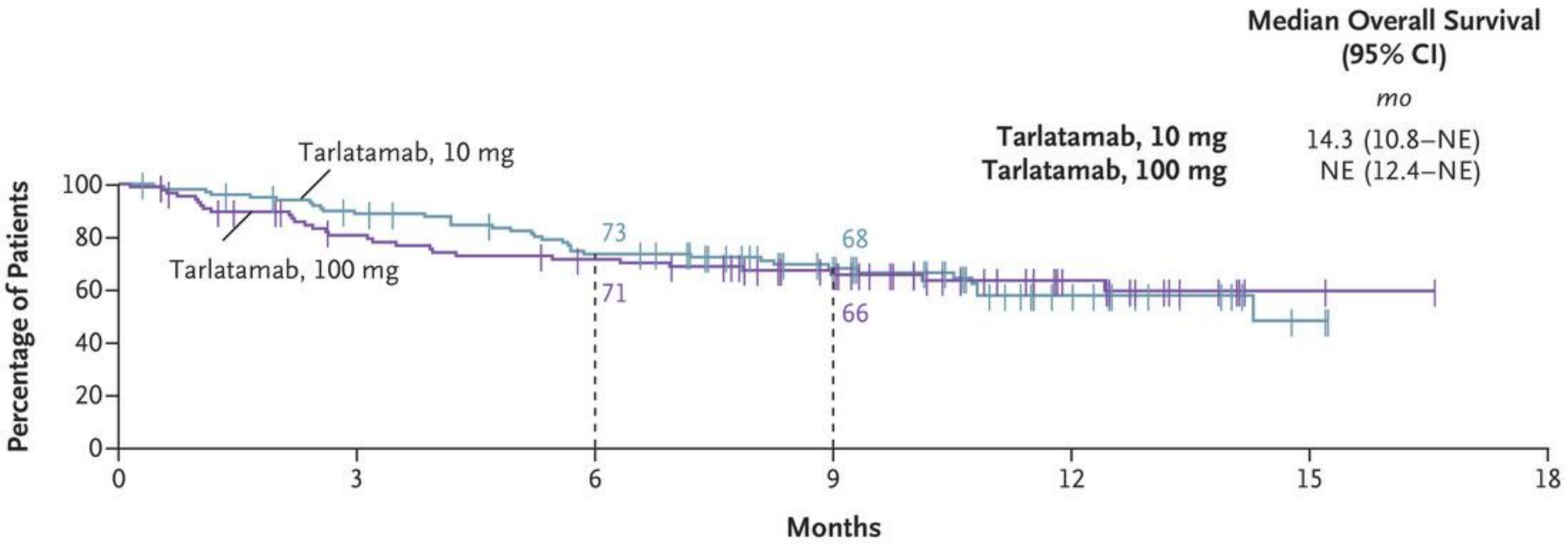
-> consider surgery or SRS to render pt dz free if single site dz

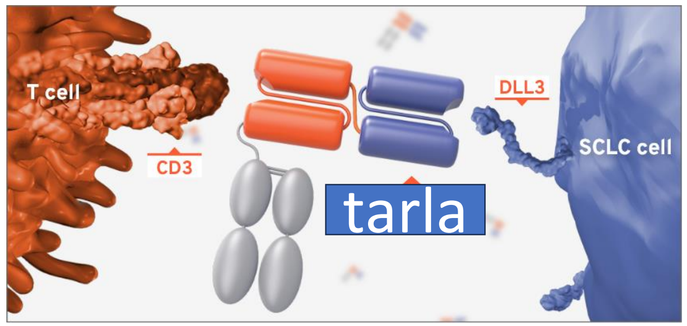
-> if patient is PR or SD and is at 2-3 years, stopping needs to be discussion with patient because recurrence risk is high; continuation is reasonable in this context but shared decision making required

- More data needed as well as more tools like ctDNA

Part 2: Other approaches

Bispecific T cell engager: tarlatamab 2L+ small cell lung cancer





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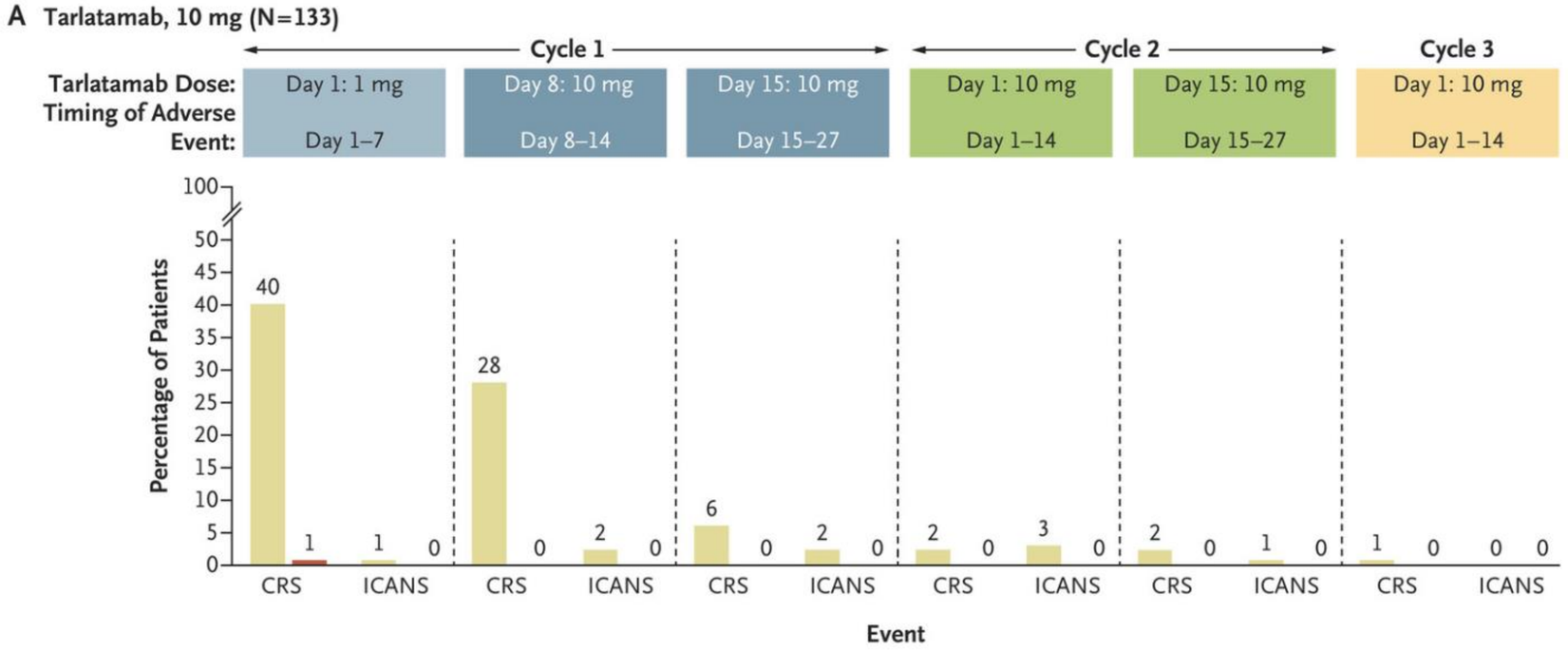
Tarlatamab toxicity – CRS, usually mild, dysgeusia



- CRS = cytokine release syndrome
- Fevers, hypotension, edema, hypoxia
- Onset ~18 hrs

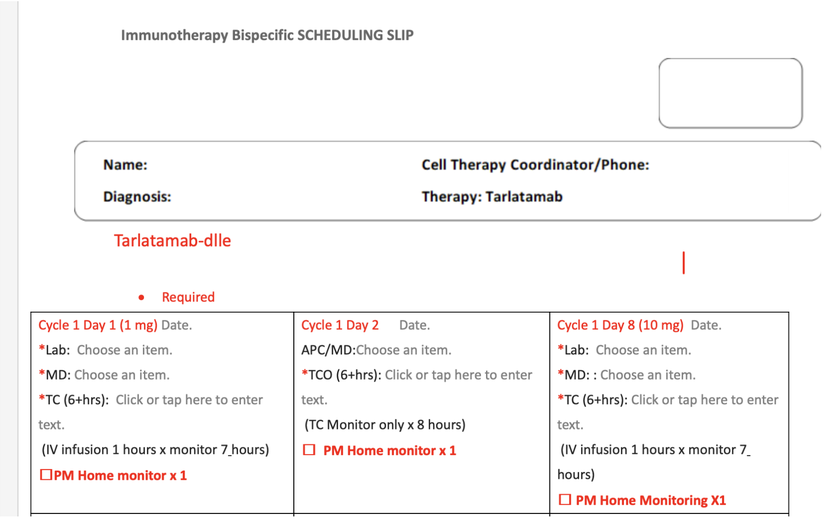
Tarlatamab outpatient administration

- FDA label: “monitor patients from the start of the tarlatamab infusion for 22 to 24 hours on C1D1 and C1D8 in an appropriate healthcare setting”
- Significant sustainability implications to inpatient
- Serious CRS risk is low
- If outpatient admin (actually, helpful for all):

  -> BP cuff, pulse ox, caregiver, phone!

  -> admission prioritization

  -> **dexamethasone pills at home**



Immunotherapy Bispecific SCHEDULING SLIP

Name: **Cell Therapy Coordinator/Phone:**

Diagnosis: **Therapy: Tarlatamab**

Tarlatamab-dlle

- Required

Cycle 1 Day 1 (1 mg) Date.	Cycle 1 Day 2 Date.	Cycle 1 Day 8 (10 mg) Date.
*Lab: Choose an item.	APC/MD:Choose an item.	*Lab: Choose an item.
*MD: Choose an item.	*TCO (6+hrs): Click or tap here to enter text.	*MD: : Choose an item.
*TC (6+hrs): Click or tap here to enter text.	(TC Monitor only x 8 hours)	*TC (6+hrs): Click or tap here to enter text.
(IV infusion 1 hours x monitor 7 hours)	☐ PM Home monitor x 1	(IV infusion 1 hours x monitor 7 hours)
☐PM Home monitor x 1		☐ PM Home Monitoring X1

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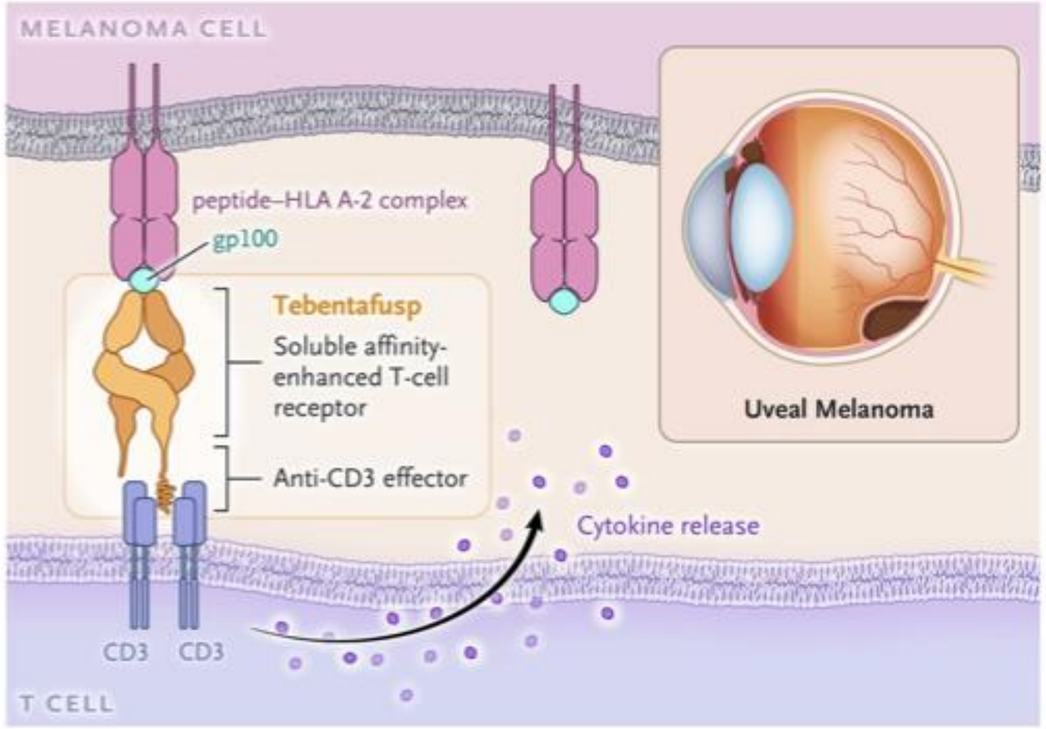
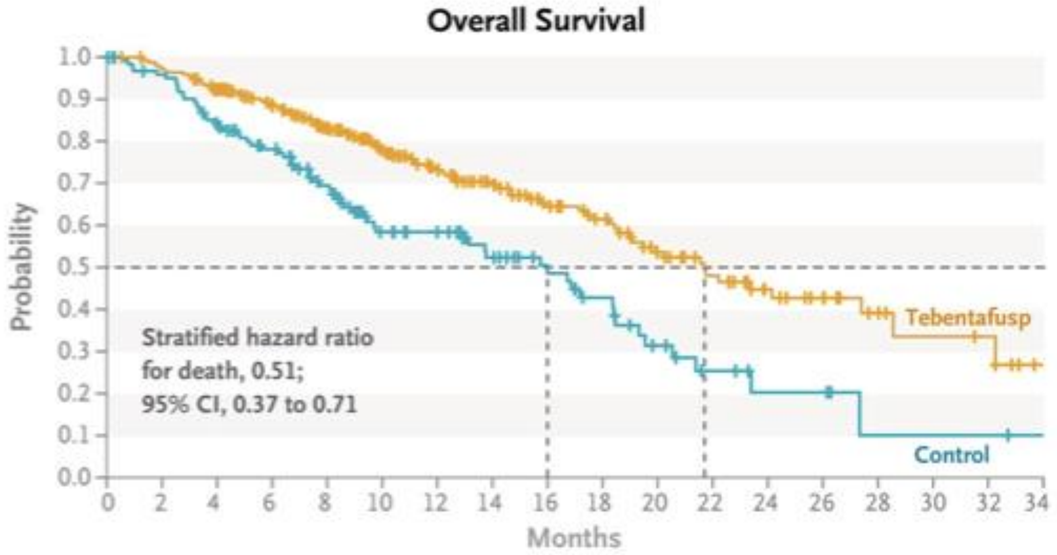
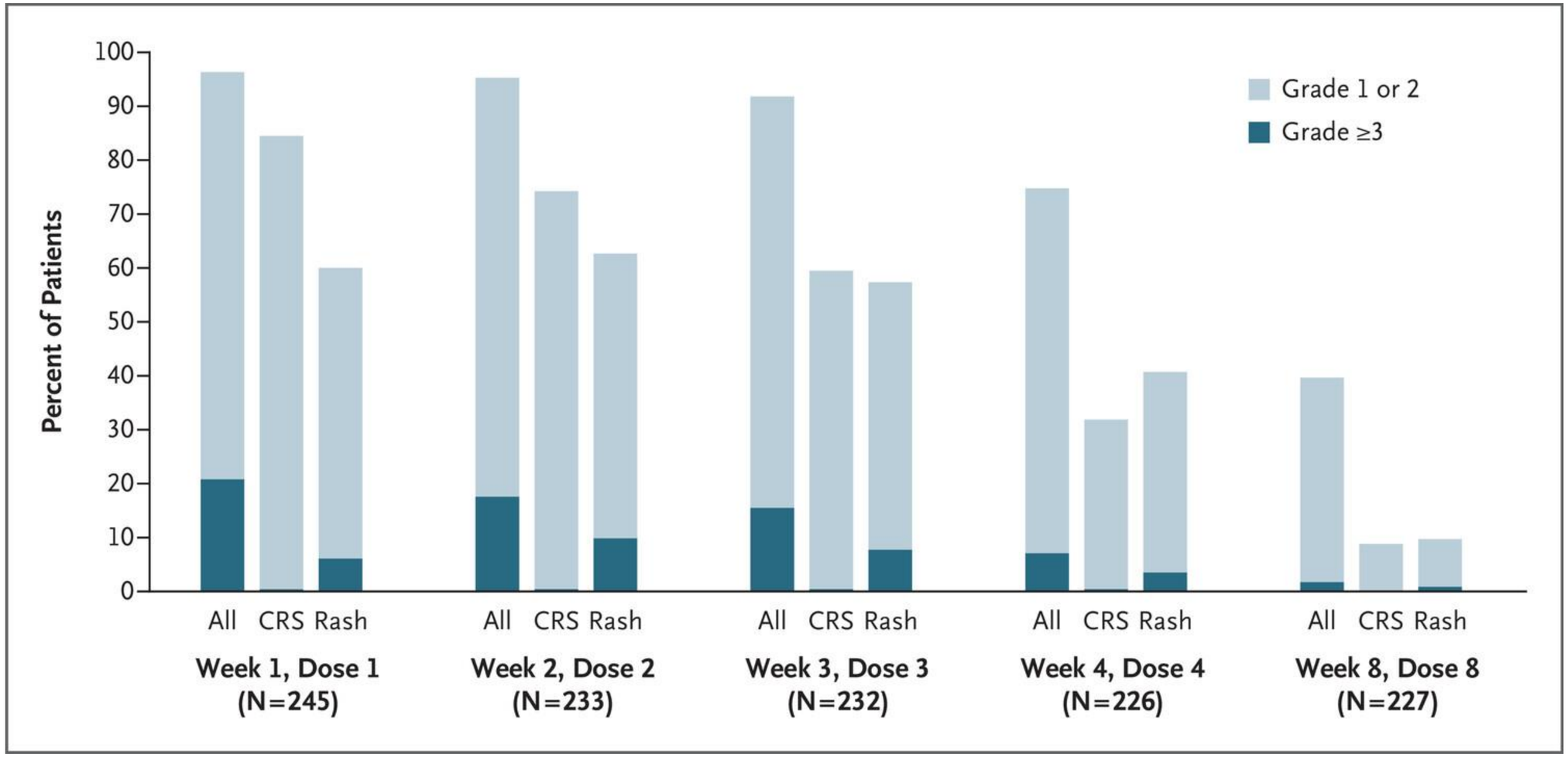
Bispecific T cell engager – tebentefusp for uveal melanoma



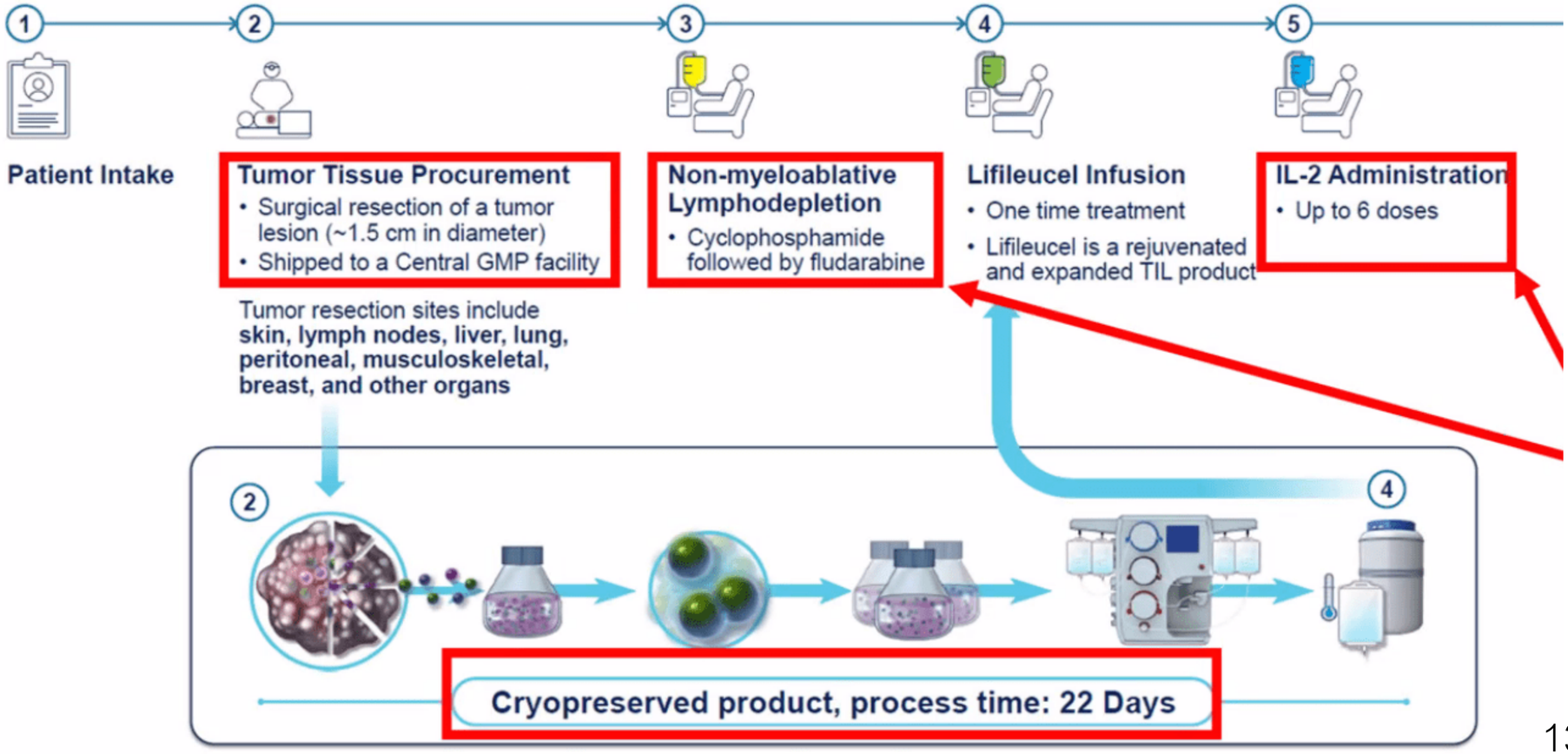


1-Year Survival		
Tebentafusp Group	73%	95% CI, 66 to 79
Control Group	59%	95% CI, 48 to 67

Tebentefusp toxicity – substantial CRS, cutaneous



Adoptive cellular therapy – Lifeleucel TIL for melanoma (2L+)



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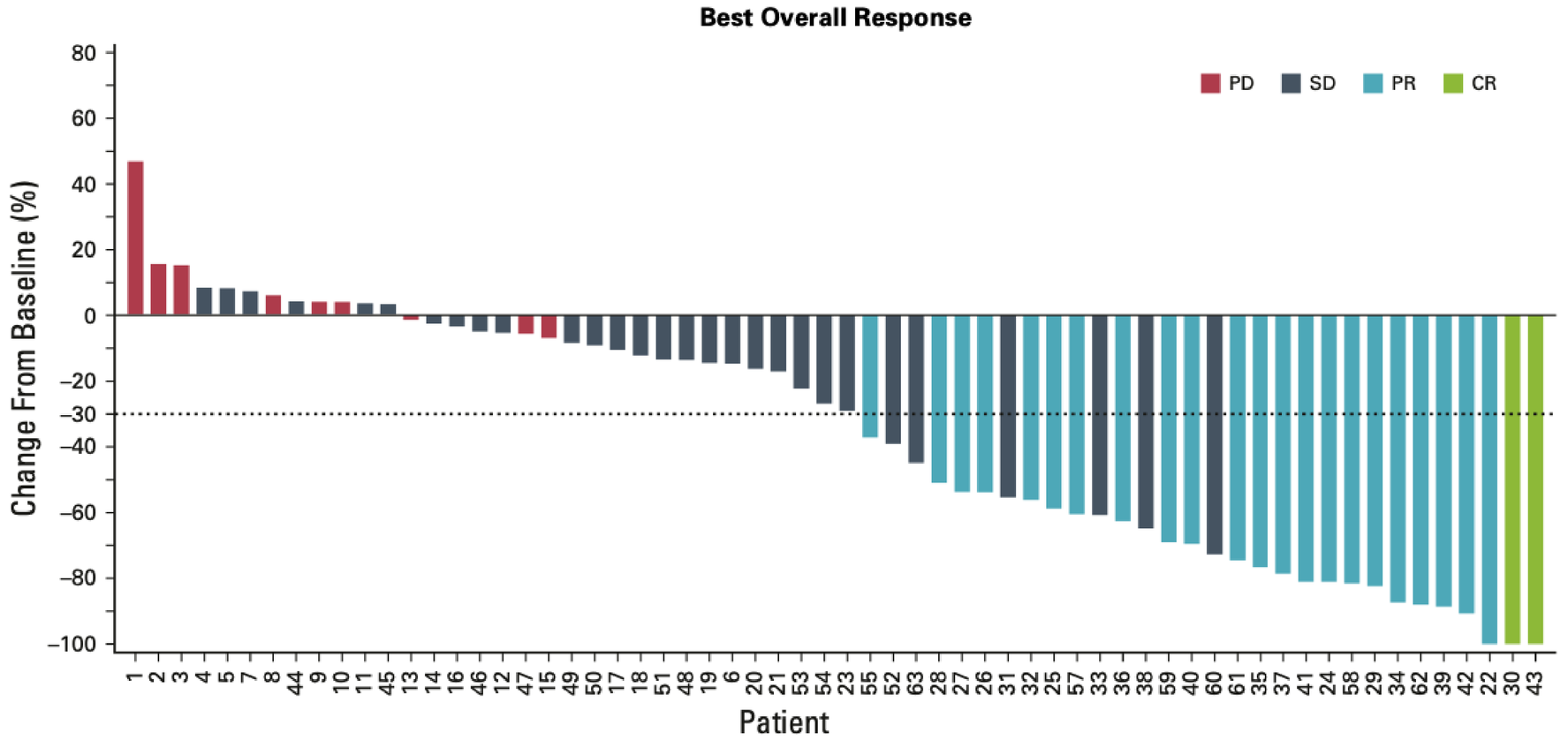


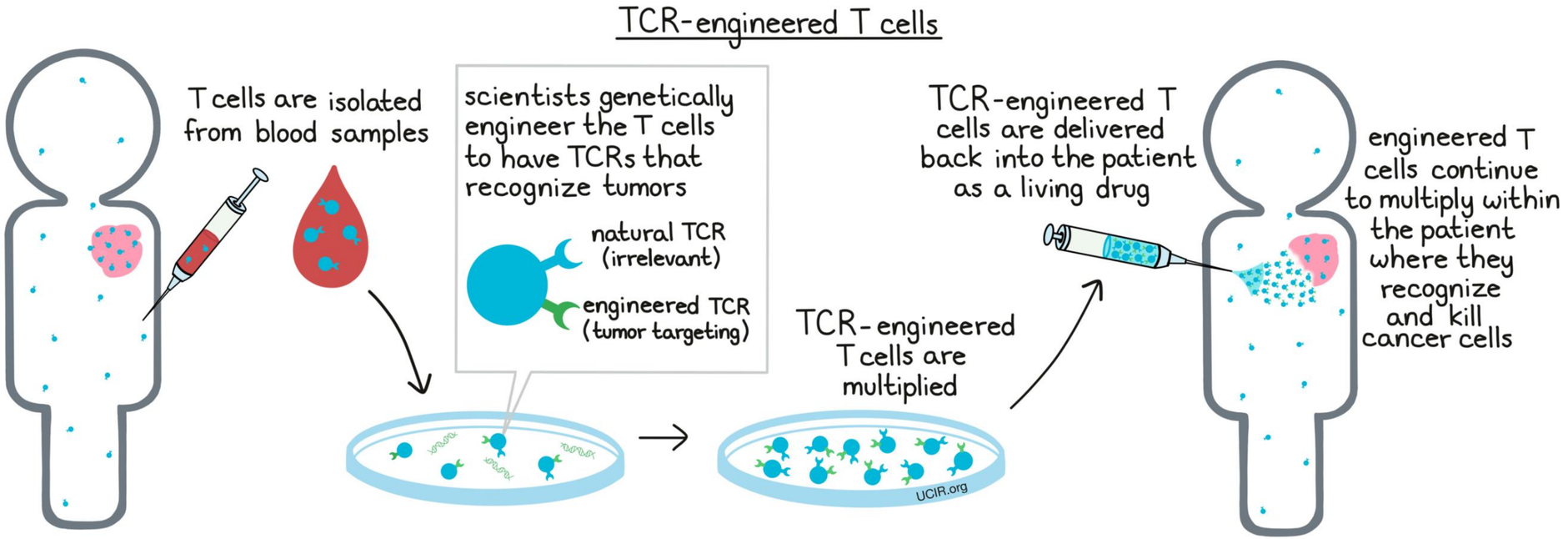
Key considerations compared to other IEC therapy

- Melanoma specific considerations:
  -> not many good bridging options (refer to TIL when starting BRAF/MEKi)
  -> get an access point in (port-a-cath)
  -> pts need chemo education

- TIL vs CAR-T
  -> surgical harvest/careful coordination
  -> IL-2 management is NOT the same as CRS management and needs lots of inpatient education
  -> LONG hospital stays. Very much not outpatient.

Afamicel for Synovial Sarcoma

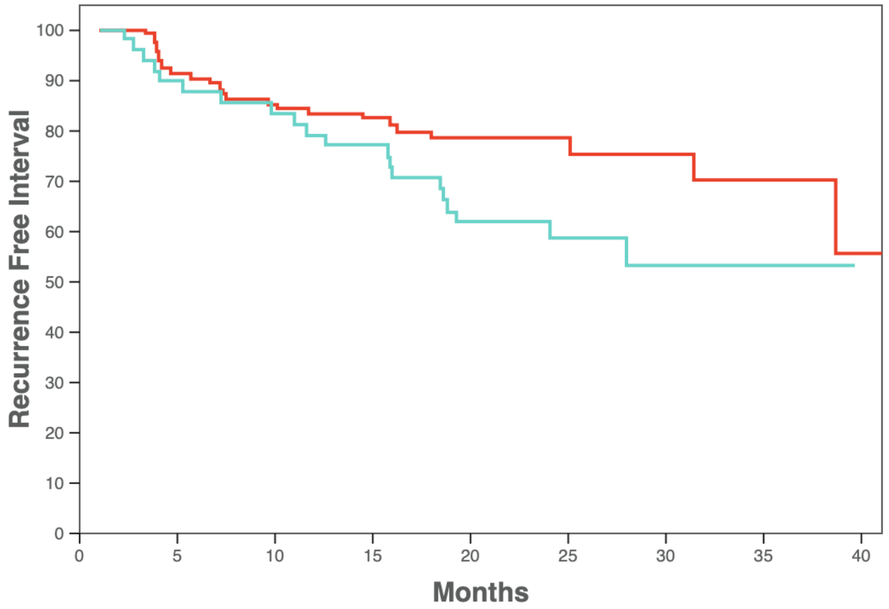
- TCR-T (must be HLA matched); 1st in class
- More similar to CAR-T in administration
- Specialized centers; rare indication
- 2nd generation being tested in large trials for ovarian ca



Vaccine (investigational)

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

Khattak et al AACR 2023

AACR 2023 (14-03-2023)

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Questions