Transforming Oncology Care
Through Medically Integrated Collaboration

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Breaking New Ground in Melanoma: Recent Updates and Emerging Therapies

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OBJECTIVES

1. Compare and contrast previous standards of care in melanoma treatment to new management practices based on recent literature and drug approvals
2. Summarize the rationale behind neoadjuvant treatment in melanoma and the literature supporting its use
3. Analyze the impact sequencing immune-checkpoint inhibitors and BRAF/MEK inhibitors has on patient outcomes
4. Explore the novel agents nivolumab-relatlimab and lifileucel for their utility and place in melanoma therapy
5. Describe the use of circulating tumor DNA (ctDNA) testing in treatment of cutaneous melanoma

DISCLOSURES

No relevant financial relationships from the past 24 months have been identified for the following planners and faculty of this CE activity:

- Andrew Ruplin, PharmD
- Tahsin Imam, PharmD
- Ginger Blackmon, PharmD

Off-label uses of medications will be discussed

Current Outcomes in Melanoma

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Epidemiology – Cutaneous Melanoma

Over ***1.4 million*** people lived with cutaneous melanoma in the U.S. in 2021

2.1% of men and women will be diagnosed in their lifetime

Median age at diagnosis is 66 (Men: Women – 2:1)

Fair complexion, light hair, blue/green eyes tanning = higher risk

U.S. 2024 – 5th most common cancer | 1.4% of all cancer deaths

The major cause of skin cancer deaths (65 - 80%)

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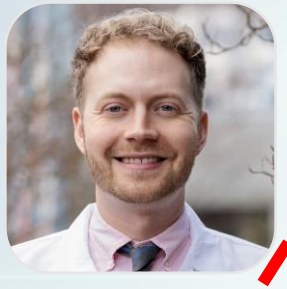
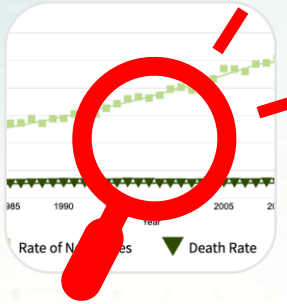
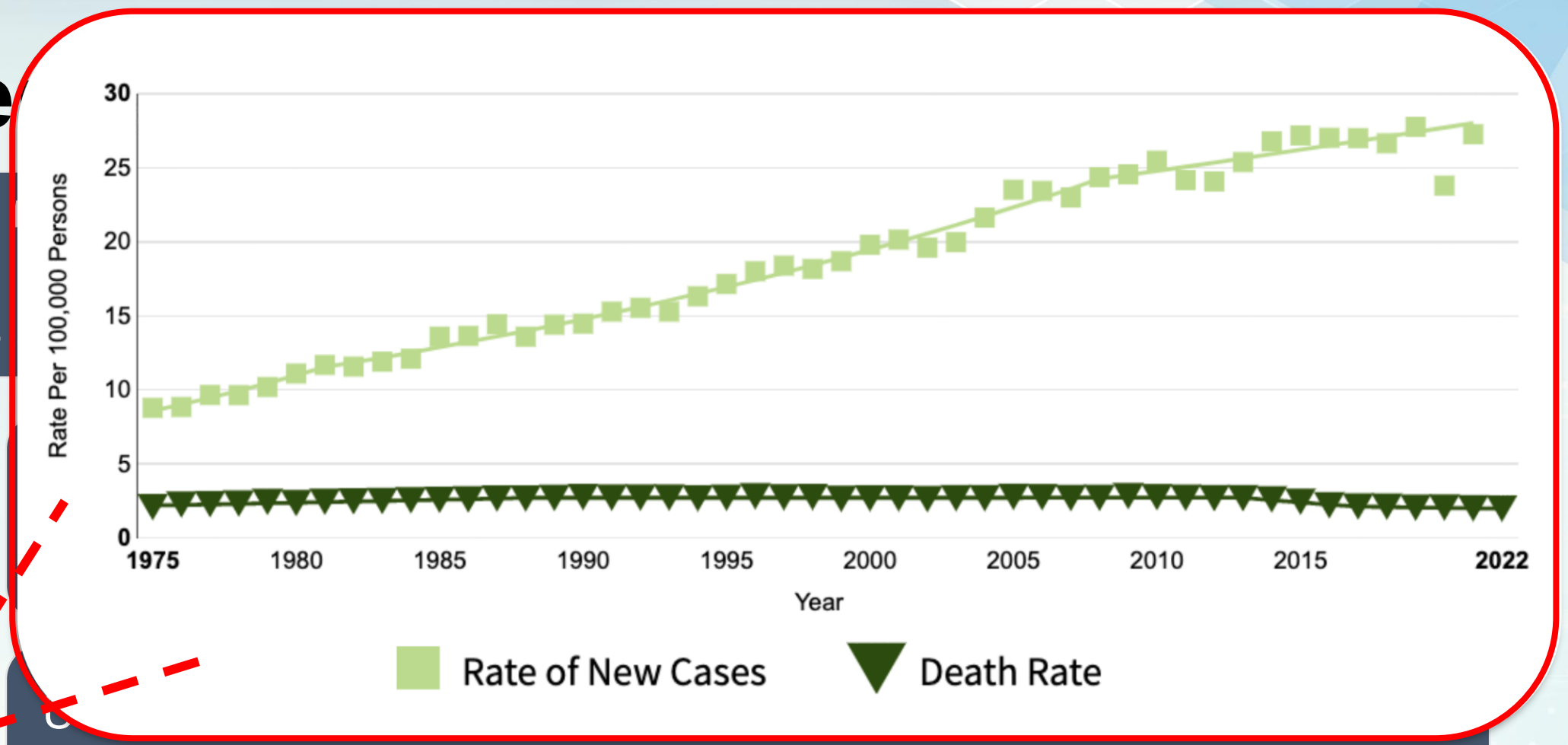
American Cancer Society. Accessed January 2, 2025. https://www.cancer.org/cancer/types/melanoma-skin-cancer.html; Med Sci (Basel). 2021;9(4):63; *National Cancer Institute*. SEER Cancer Stat Facts

Epide

Over ***1.4***
2021
2.1%







The major cause of skin cancer deaths (65 - 80%)

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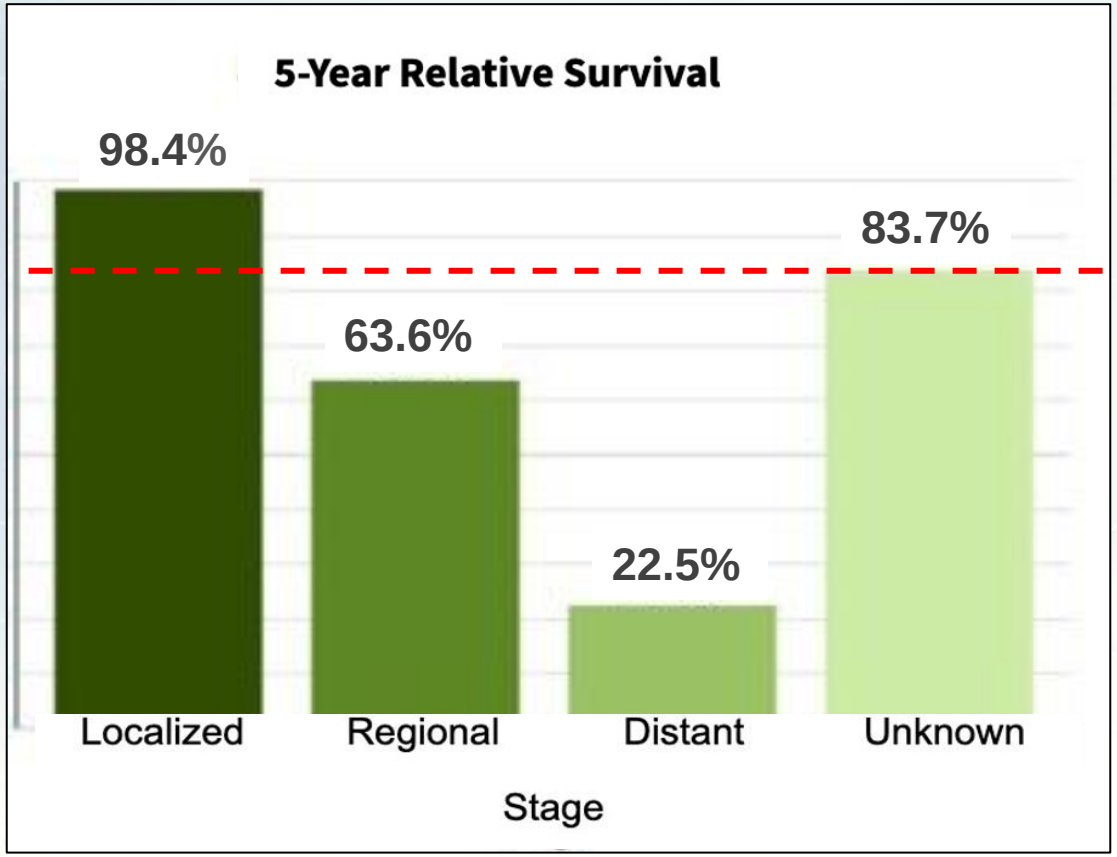
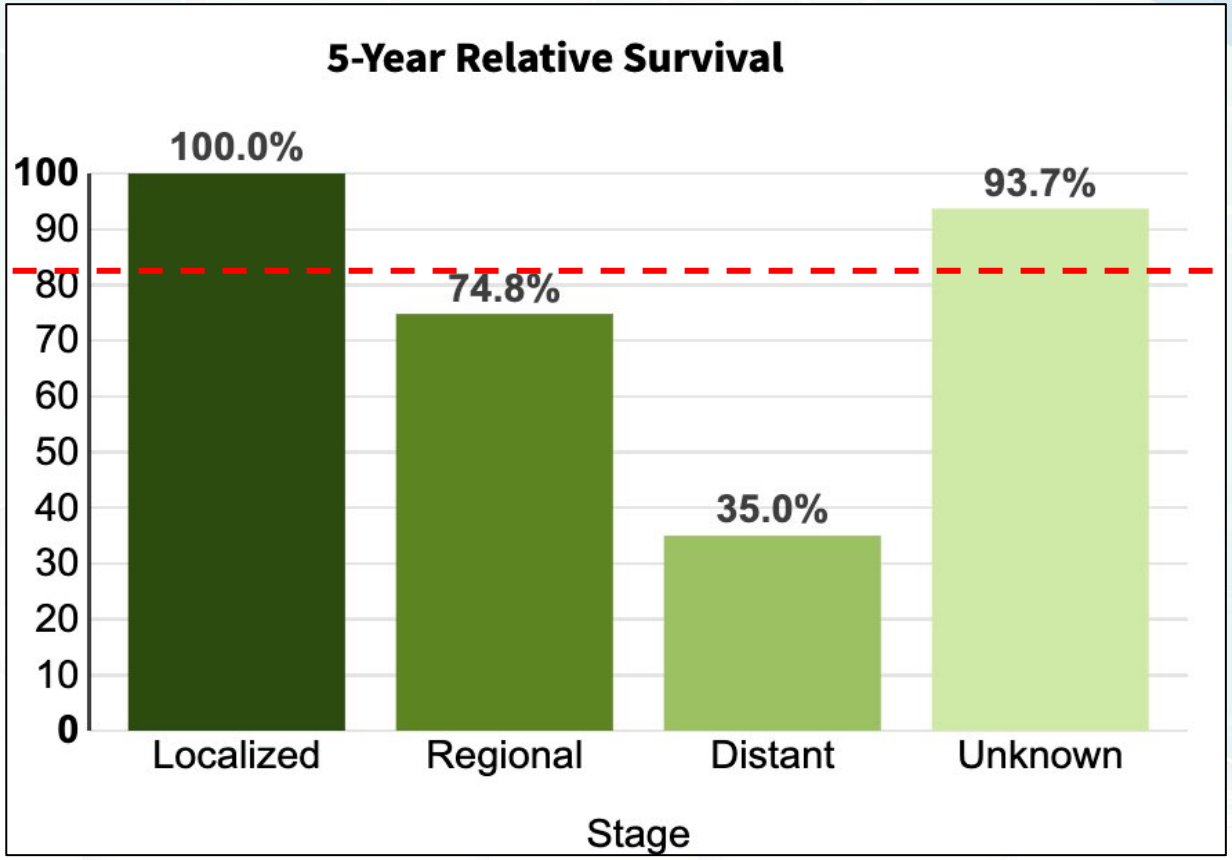
American Cancer Society. Accessed January 2, 2025. https://www.cancer.org/cancer/types/melanoma-skin-cancer.html; Med Sci (Basel). 2021;9(4):63; *National Cancer Institute*. SEER Cancer Stat Facts

Five-Year Survival By Stage

2008–2014



2014–2020



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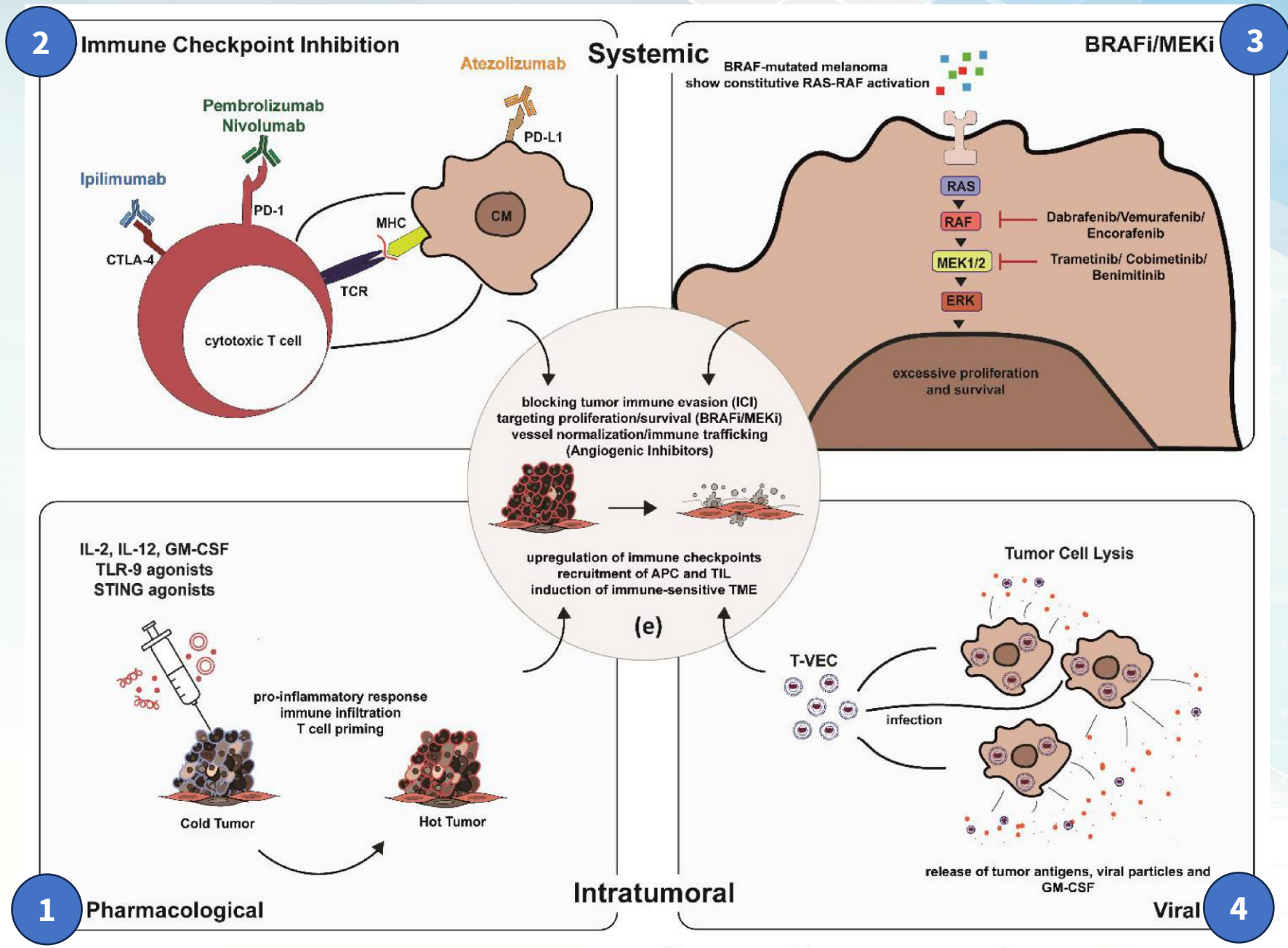
National Cancer Institute. SEER Cancer Stat Facts

Previous Standards in the Treatment of Cutaneous Melanoma

Treatment Mechanisms

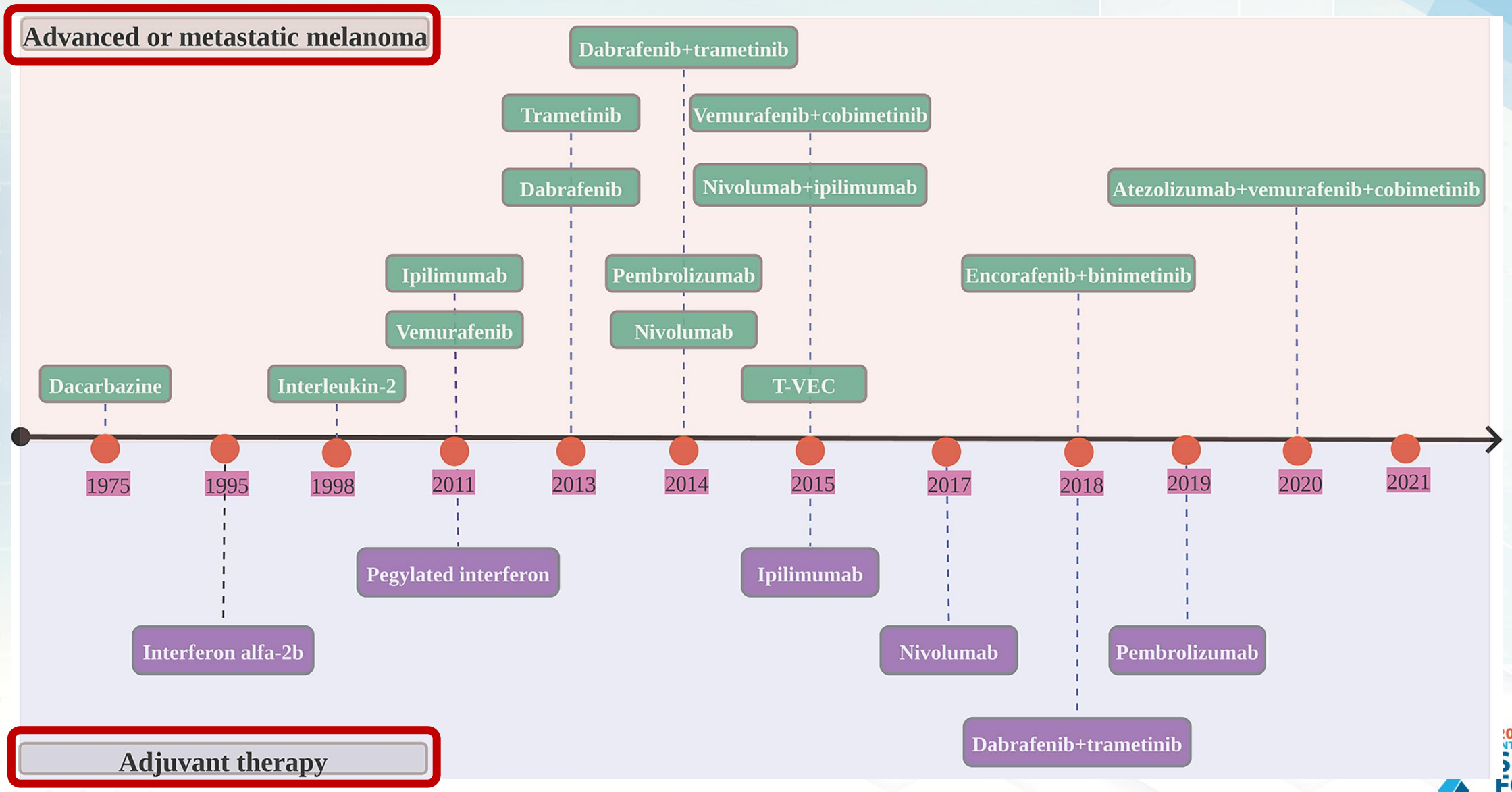
Targeting:

- Immune system
- Activating mutations



Cancers. 2021; 13(9):2090

The Timeline of Melanoma Treatment



Front Oncol. 2021;11:775100

Updates in Approaches to Treatment of Cutaneous Melanoma

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Neoadjuvant Therapy

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Establishing a Need for Neoadjuvant Therapy

- Adjuvant administration of systemic therapies including nivolumab, pembrolizumab and BRAF/MEK inhibitors (dabrafenib plus trametinib) have shown clear benefits to recurrence-free survival… but not overall survival
- About 40-50% of patients have a relapse within 3–5 years after therapeutic lymph node dissection
- Phase 1 and pre-clinical data suggest that neoadjuvant administration of immune checkpoint inhibitors is superior to adjuvant administration

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Clin Cancer Res 2023;29:3352-3361.; *Nat Med* 2018;24:1655-1661.

Off-label use

Neoadjuvant Nivolumab + Ipilimumab

Clinical stage IIIB – IIID nodal melanoma

NADINA

Phase 3, international, RCT

Resectable, macroscopic stage III cutaneous or acral melanoma
- Included: in-transit metastases

Neoadjuvant IPI 80 mg + NIVO 240 mg q3wks x2 → TLND → observation or adjuvant therapy if pPR or pNR*

TLND → adjuvant NIVO x12

Event-Free Survival

PRADO

Phase 2, multi-center, RCT

Clinical stage IIIB – IIID nodal melanoma

Neoadj IPI 1 mg/kg + NIVO 3 mg/kg q3wks x 2 → (response directed adj)
- MPR* → observation
- pPR* → TLND only
- pNR* → TLND + adjuvant systemic** therapy ± RT

- Pathologic response rate
- Ability to omit TLND in MPR
- RFS improvement in pNR

*Pathologic partial response (pPR; >10 to ≤50% viable tumor); pathologic non-response (pNR; >50% viable tumor; major pathologic response (MPR, ≤10% viable tumor))
**Adj NIVO (BRAF WT) or BRAF/MEKi (BRAFV600E/K mut) x 52 wks

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N Engl J Med. 2024;391(18):1696-1708; *Nat Med*. 2022;28(6):1178-1188

NADINA Results

Trial	**NADINA** N = 423, median 60 y.o., 65% male	
Outcome	Neoadjuvant	Adjuvant
EFS (At 12 mo)	= 83.7% (99.9% CI 73.8 - 94.8)	57.2% (99.9% CI 45.1 - 72.7)
Mean difference in survival time	8 mo (99.9% CI 4.94 - 11.05) ***HR PD, recurrence, or death*** *0.32 (99.9% CI 0.15 - 0.66)*	
PR Complete Partial Non-response	45.8 % 9.4% 25%	-
AEs Any ≥ grade 3 trAE Endocrinopathies	29.7% 30.7%	14.7% 9.9%

Limitations –

- Short follow-up (median 9.9 mo)
- IPI+NIVO before surgery experienced higher rates of serious complications (36.3%) compared to others (23.6%)

Takeaway –
Among patients with stage III macroscopic melanoma, **neoadjuvant IPI + NIVO followed by surgery and response-driven adjuvant therapy resulted in longer EFS** than surgery followed by adjuvant nivolumab

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N Engl J Med. 2024;391(18):1696-1708; *Nat Med*. 2022;28(6):1178-1188

PRADO Results

Trial	**PRADO** N = 99, median 58 y.o., 66% male	
Outcome	Neoadjuvant	
EFS	**NR** [24 mo est. 80% (95% CI, 72 - 88%)]	
pRR MPR CR	72% **61%** (49% CR) 49%	
TLND Omission in MPR based on ILN	98.3%	
RFS MPR pPR pNR	**93%** (95% CI 87 - 99) **64%** (95% CI 41 - 99) **71%** (95% CI 55 - 94) *vs. 35% in pNR from OpACIN-neo (did not use response-directed treatment)*	
AEs	ILN alone	ILN + TLND
Any ≥ grade 3 trAE Surgery-related AEs	30% (***22% in 1st 12 mo***) 46%	**84%**, p<0.001

Pathologic partial response (pPR; >10 to ≤50% viable tumor); pathologic non-response (pNR; >50% viable tumor); major pathologic response (MPR, ≤10% viable tumor)

Limitations –

- Small sample size per pathologic subgroup
- Non-randomized

Takeaway –

- **Treatment de-escalation is safe in patients with MPR on their ILN** but treatment escalation in non-responding patients improves outcomes
- **Given tolerability concerns, further research is needed** to identify which patients will do better on one of these sequences vs. the other

N Engl J Med. 2024;391(18):1696-1708; *Nat Med*. 2022;28(6):1178-1188; *Lancet Oncol*. 2019;20(7):948-960

Off-label use

Neoadjuvant Pembrolizumab - SWOG S1801 Trial

Trial Design	Patient Population	Study Arms	Primary Endpoint
Phase II, Open-label, RCT 	Resectable, stage IIIB to IVC melanoma 	**Neoadjuvant–adjuvant group** Neoadjuvant pembrolizumab (200 mg IV every 3 weeks x3) → surgery → adjuvant pembrolizumab x15 cycles every 3 weeks	Event-free survival
	Included: cutaneous, acral, and mucosal subtypes **Excluded**: brain metastases and previous receipt of immunotherapy for melanoma	**Adjuvant-only group** Surgery → adjuvant pembrolizumab x18 cycles every 3 weeks	

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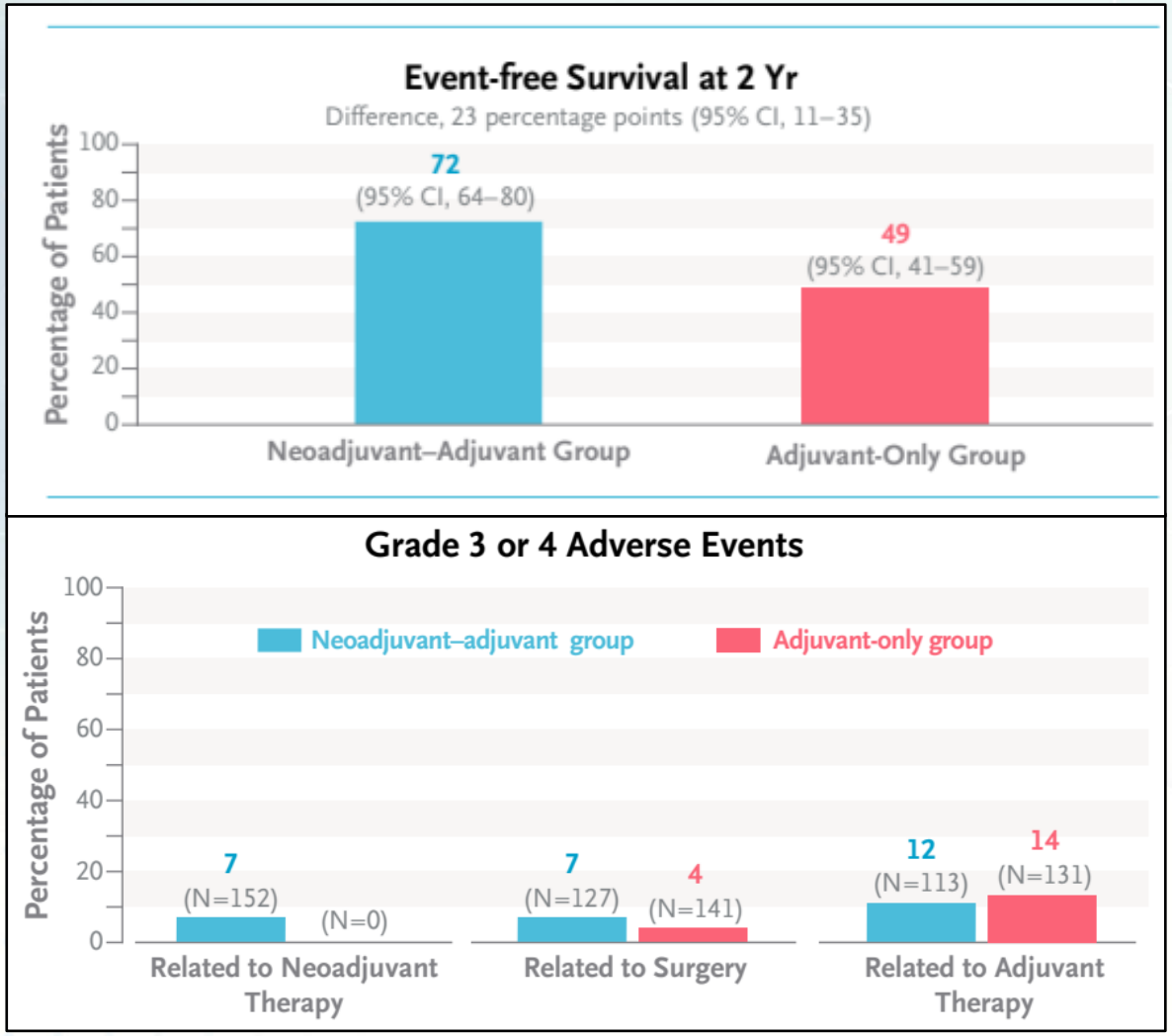
N Engl J Med. 2023;388(9):813-823

SWOG S1801 Results

N = 313; median 63 y.o., 65% male, 92% stage III, 93% cutaneous, 25.5% BRAF mutated



Efficacy –

- Difference in EFS favored neoadj-adj by 23% (95% CI 11 - 25, p = 0.004)
- Less than 10% of patients who received neoadjuvant therapy had PD (n = 12) that precluded surgery

Safety –

- One neoadjuvant patient had an AE that precluded surgery
- Grade 3 or 4 AEs related to adjuvant therapy were similar in the two groups and expected of ICIs

Limitations –

- Phase 2 trial
- Higher rate of early event censoring in neoadjuvant group
- Unusual event assignment rule

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N Engl J Med. 2023;388(9):813-823

Takeaway from S1801

- Despite potential limitations, **neoadjuvant + adjuvant pembrolizumab significantly improved EFS with no new toxic effects** vs. adjuvant alone in patients with resectable stage III **or IV melanoma (M1a, b, or c)***
  - **Lower grade 3 and 4 trAE rates** vs. PRADO trial [neoadjuvant anti-CTLA/anti-PD1 (IPI/NIVO) combination]
  - *Stage IV not included in neoadjuvant IPI/NIVO trials

N Engl J Med. 2023;388(9):813-823

Neoadjuvant Treatment of Melanoma

Why should it be considered?

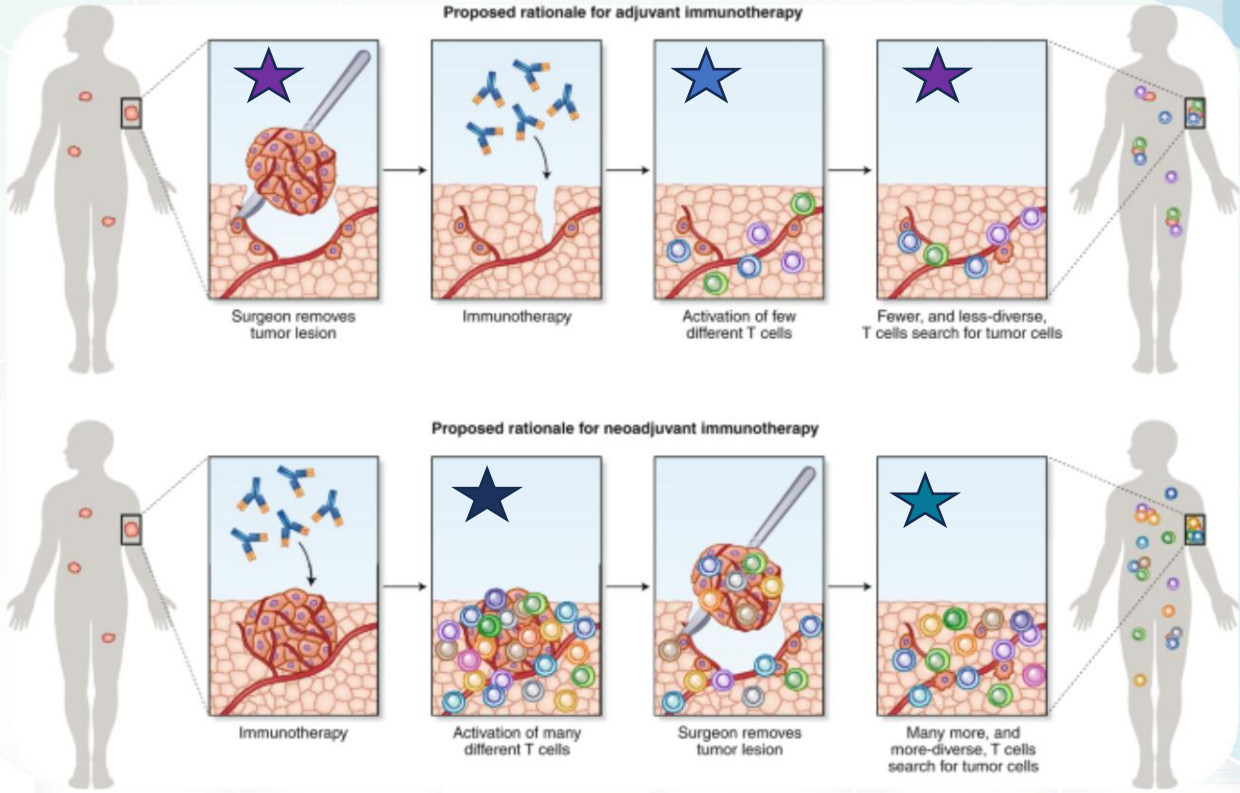
Response to PD-1 blockade requires preexisting antitumor T-cells to be in contact with cancer cells

Resecting the bulk of the tumor (along with the tumor-infiltrating lymphocytes; TIL) removes potential antitumor T-cells that would proliferate after PD-1 blockade

Neoadjuvant therapy induces an immune response from a larger population of TILs at local and distant sites

Leaving behind larger numbers of antitumor T cells

Neoadjuvant PD-1 blockade could improve clinical outcomes compared with administration of the same drug delivered postoperatively



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Nat Med. 2020;26(4):475-484

Concerns With Neoadjuvant Treatment?

Impact of Neoadjuvant Systemic Therapy on Surgical Outcomes

Benefits:

- Tailoring the extent of surgery
- Reducing morbidity
- Improved ease of surgical resection
  - ***Reported in ~50% of patients in the NeoCombi trial***
- Identifying patients with resistant disease to direct towards clinical trials of novel therapies or new drug combinations
- Reduce delay in initiating effective systemic treatment

It is noted that overall survival data is still forthcoming.

Risks:

- IrAEs may adversely influence the patient's tolerance of general anesthesia and surgery
  - High-dose steroids can impair wound-healing
- BRAF/MEKi can cause drug fevers, rash, and hypertension that could skew pre-operative assessments

Surgeon Assessment of Impact

- Actual degree of difficulty **increased** from the baseline estimate **in 4 (17%)** and **decreased in 6 (25%)** operations
- Surgery difficulty vs. usual operation:
  - Less 4 (17%)
  - Average 9 (38%)
  - More 11 (46%)

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Ann Surg Oncol. 2022;29(2):780-786; *Ann Surg Oncol*. 2022 Aug;29(8):5241-5242

Audience Response Question

Do you have experience with neoadjuvant treatment of melanoma?

a. None
b. Some or only as part of a clinical trial
c. We use this is as a standard of care treatment outside of a clinical trial

Therapy Sequencing

SECOMBIT Trial – ICI or BRAF/MEK First?

Phase II, 3-arm, randomized

Patient Population

Untreated, metastatic BRAFV600-mutant melanoma

Inclusion/ Exclusion

Included: brain mets* if no PD on MRI > 4 wks post local treatment
Excluded: severe or uncontrolled systemic disease

Study Arms

Arm A – ENCO 450 mg PO daily + BINI 45 mg PO BID until PD → IPI3 + NIVO1 q3wks x 4 → NIVO3 q2 wks until PD

Arm B – IPI/NIVO until PD → ENCO + BINI until PD

Arm C – ENCO + BINI x 8 wks → IPI + NIVO until PD → ENCO + BINI until PD

*Total N = 2 for brain mets; **Not statistically significant in difference;
***More sites of metastasis/M1c, higher LDH levels

J Clin Oncol. 2023;41(2):212-221

Results of the SECOMBIT Trial

Median 54 y.o., 57% Male, 87% ECOG 0*

Outcome1	**Arm A** (N=69) BRAF/MEKi First	**Arm B** (N=71) ICI First	**Arm C** (N=69) Sandwich
OS Median 2-yr	NR **65%** (95% CI 54 - 76)	NR **73%** (95% CI 62 - 84)	NR **69%** (95% CI 59 - 80)
	OS HR** Arm B vs A: 0.73 (95% CI 0.42 - 1.26) Arm C vs A: 0.81 (95% CI 0.48 - 1.37)		
3-yr TPFS**	41%	53%	54%
ORR IPI/NIVO	26%	45%	58%
AEs Any ≥ gr 3 trAE TrAE → DC	39% 10%	59% 9%	26% 0%

Limitations –

- Arm comparisons were exploratory analyses
- Open-label
- More high-risk patients in Arm B***

Takeaway –

- Sequential immunotherapy and targeted therapy provide clinically meaningful survival benefits for patients with BRAFV600-mutant melanoma with results **numerically favoring ICI before BRAF/MEK or the "sandwich method"**
- Further follow-up and Phase III data is needed

*Total N = 2 for brain mets; **Not statistically significant in difference; ***More sites of metastasis/M1c, higher LDH levels

J Clin Oncol. 2023;41(2):212-221

DREAMSeq – Phase III Sequencing Data for ICI and BRAF/MEK

Median 61 y.o., 63% Male, 68% ECOG 0, 60% Stage M1c

Patient Population	Study Arms	Outcomes
Treatment-naive *BRAFV600*-mutant metastatic melanoma ***Incl:*** *brain mets that were treated, stable, or too small for surgery*	**Step 1** Arm A – IPI/NIVO Arm B – Dab /Tram → PD → **Step 2** Received the alternate therapy Arm C – Dab /Tram Arm D – IPI/NIVO	**2-yr OS rate (%):** A 71.8 vs. B 51.5 (p= 0.010) **PFS (mo)** **Step 1 :** A 11.8 vs. B 8.5 (p=0.054) **Step 2:** C 9.9 vs. D 2.9 *(not powered for analysis)* **ORR (%):** C 48 vs. D 29 *(not powered for analysis)* **DOR (mo):** A NR vs. B 12.7 (p<0.001)

Safety –

- Any ≥ grade 3 trAE:
  A 59.5%, **B** 53.1%,
  C 53.8%, **D** 50% (NSS)
- Numerically more grade 4 AEs in arm A

Limitations –

- Did not include sandwich method
- Only 52% reached crossover

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J Clin Oncol. 2023;41(2):186-197

Takeaway – ICI Before BRAF/MEKi

The sequence of therapy commencing with **nivolumab/ipilimumab → BRAF/MEKi** is associated with greater survival and **should be the preferred sequence for the majority of patients**

- **Caveats:** BRAFV600 + in visceral crisis or with symptomatic brain metastases → **BRAF/MEK for rapid onset**; CI to ICI

From *Phase III data* – 18% of deaths in ICI group occurred within 10 months* suggesting the following as alternatives to the sandwich method –

A) A lower threshold for switching to 2nd-line therapy

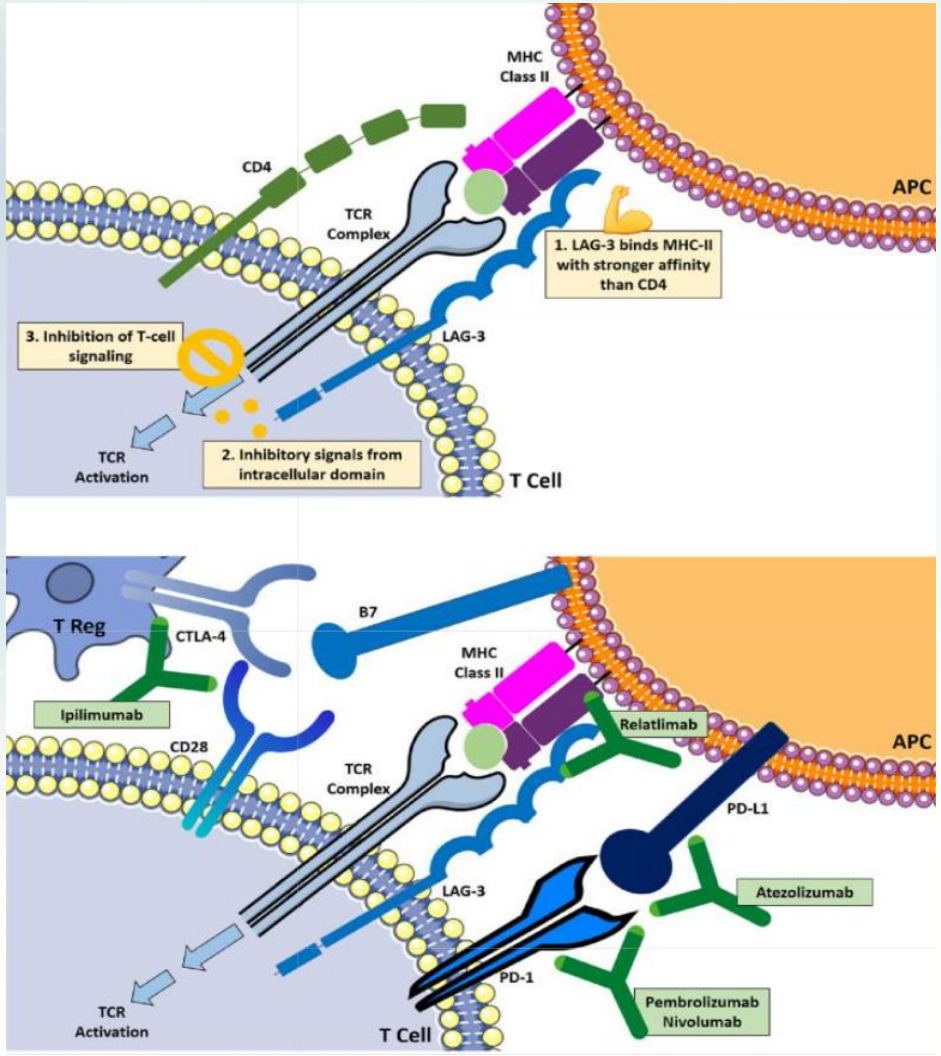
B) Using ctDNA to identify those who would most benefit from earlier BRAF/MEKi might improve outcomes

*Population notable for having relatively more aggressive disease and receiving less therapy (median one cycle) than study population as a whole

J Clin Oncol. 2023;41(2):186-197

Novel Agents

Nivolumab-Relatlimab – addition of LAG3 inhibition to PD-1 blockade



Why LAG-3?

- A co-inhibitory receptor that suppresses T-cell activation and cytokine secretion
- Aberrant expression of LAG-3 was identified in melanoma – associated with:
  - Evasion of tumor cells from the immune system
  - More aggressive disease
  - Protection to melanoma cells
  - Prevention of tumor cell apoptosis

Nivolumab-relatlimab

- Dual genetic knockout of both LAG-3 and PD-1, in murine melanoma models, resulted in delayed growth of the tumor and increased survival of mice
- Original approval 2022

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Ther Adv Med Oncol. 2023;15:17588359231186027; *Cancer Res*. 2012;72(4):917-927

RELATIVITY-047 Trial

Phase III, global, double-blind, randomized trial

01 Patient Population

Previously untreated metastatic or unresectable melanoma

Excl: active, untreated brain mets

02 Study Arms

Nivolumab 480 mg + relatlimab 160 mg) IV q4wks

vs.

Nivolumab (NIVO) 480 mg IV alone q4wks

Both until PD

03 Outcomes (Nivo-Rel vs. NIVO)

Med. PFS: 10.1 vs. 4.6 mo (HR 0.75, 95% CI 0.62 - 0.92)

Med. OS: NR (95% CI 34.2 mo - NR) vs. 34.10 mo (95% CI 25.2 mo - NR)

ORR: 43 vs. 33%

04 Safety (Nivo-Rel vs. NIVO)

Any ≥ grade 3 trAE: 18.9% vs. 9.7%

Led to treatment DC: 14.6% vs. 6.7%

Nivo-rel common irAEs: thyroiditis (18.0), rash (9.3%), diarrhea/colitis (6.8%)

N = 714, Median 63 y.o., 58% Male, 67% ECOG 0

Indirect Comparison to IPI/NIVO (Checkmate-067)

- **PFS** HR 1.08 (95% CI 0.88 - 1.33])
- **ORR** OR, 0.91 (95% CI 0.73 - 1.14)
- **OS** HR, 0.94 (95% CI 0.75 - 1.19)

- **Grade 3-4 TRAEs** 23% vs. 61%
- **Any-grade TRAEs leading to DC** 17% vs. 41%

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N Engl J Med. 2022;386(1):24-34; *NEJM Evid*. 2023;2(4):EVIDoa2200239; *J Clin Oncol*. 2024;42(33):3926-3934

Takeaways for Nivolumab-Relatlimab

- Dual immune checkpoint blockade with **nivolumab-relatlimab** is associated with **greater survival** than nivolumab monotherapy **regardless of LAG3 expression**
- Cross-trial analyses suggest **similar efficacy of nivolumab-relatlimab to IPI/NIVO with improved safety outcomes** in metastatic cutaneous melanoma
  - A noted **exception** being in patients with **brain mets – for which nivolumab-relatlimab lacks data**
- Current FDA approval is for unresectable or metastatic melanoma

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N Engl J Med. 2022;386(1):24-34; *NEJM Evid*. 2023;2(4):EVIDoa2200239; *J Clin Oncol*. 2024;42(33):3926-3934

Adoptive Cell Therapy in Melanoma

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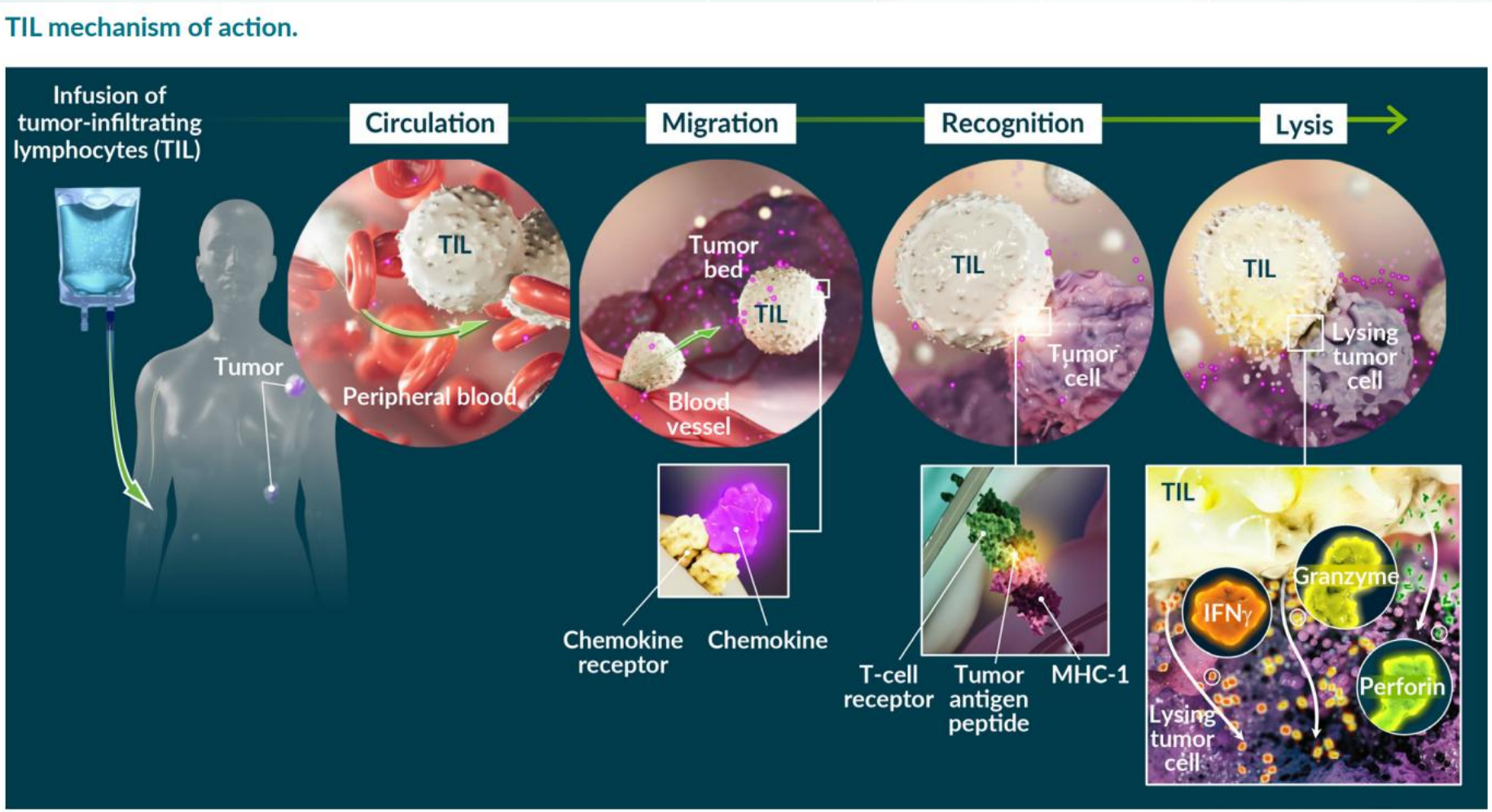
Audience Response Question

Is your center offering lifileucel to treat melanoma?

a. Yes
b. No
c. I don’t know

Lifileucel – A Re-emerging Mechanism in a Solid but Unfamiliar Space

Tumor-infiltrating Lymphocytes (TIL)



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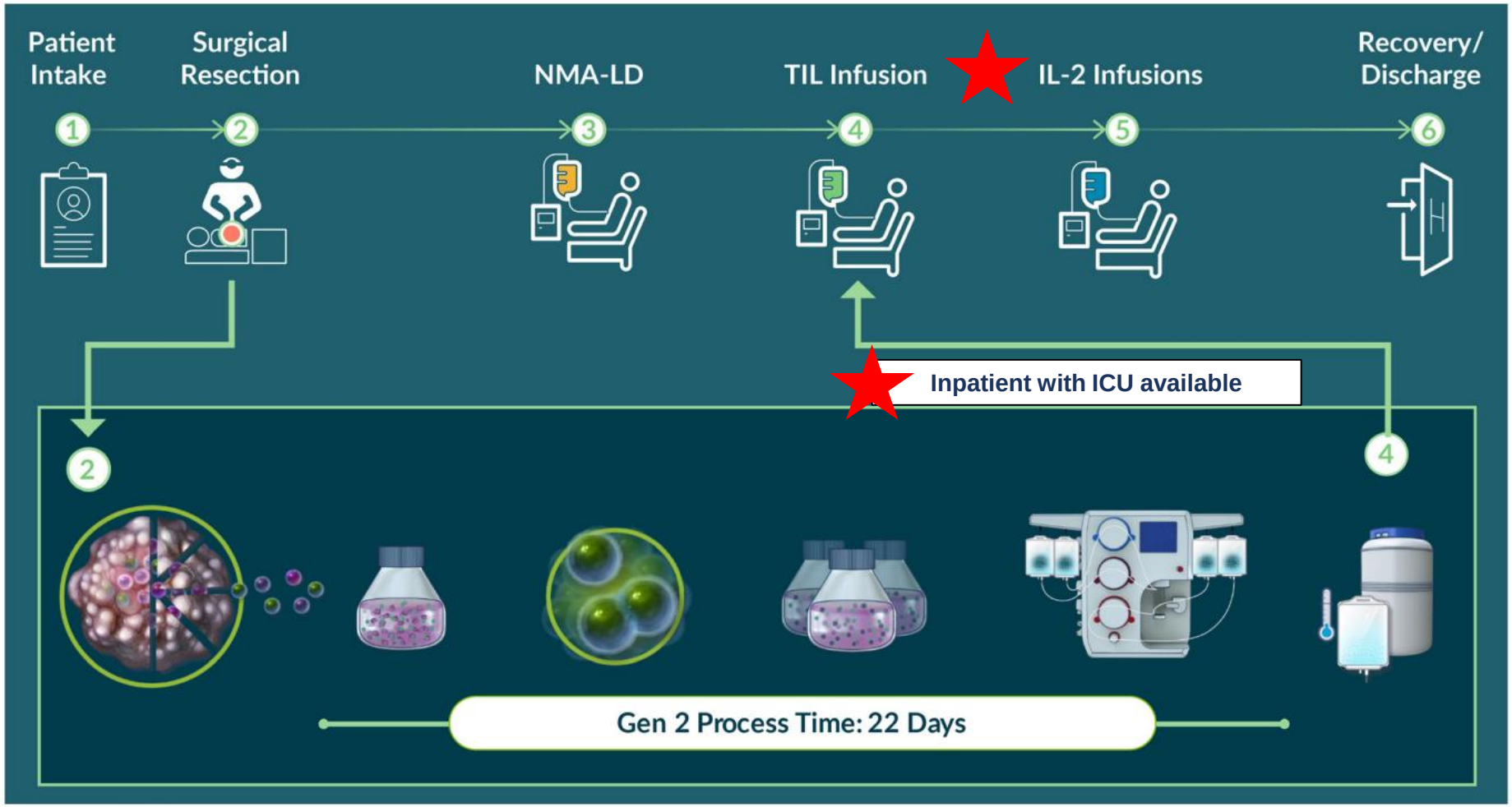
Cell & Gene Therapy Insights. 2020;6(6):855-863

Manufacturing and Administration



- **NMA-LD** = non-myeloablative lymphodepletion
  - Cyclophosphamide 60 mg/kg IV daily x 2 days (with mesna) followed by fludarabine 25 mg/m^2 daily x 5 days
- **Lifileucel**
  - Need onsite storage in vapor phase of liquid nitrogen
  - Premeds: APAP + diphenhydramine
  - 4 x 100-125 ml bags – wait to thaw next bag until prior is safely/completely administered
  - Administer within 3 hrs of thawing
    - Infusion rate 1 mL/min for initial 5 min → 5-10 mL/min

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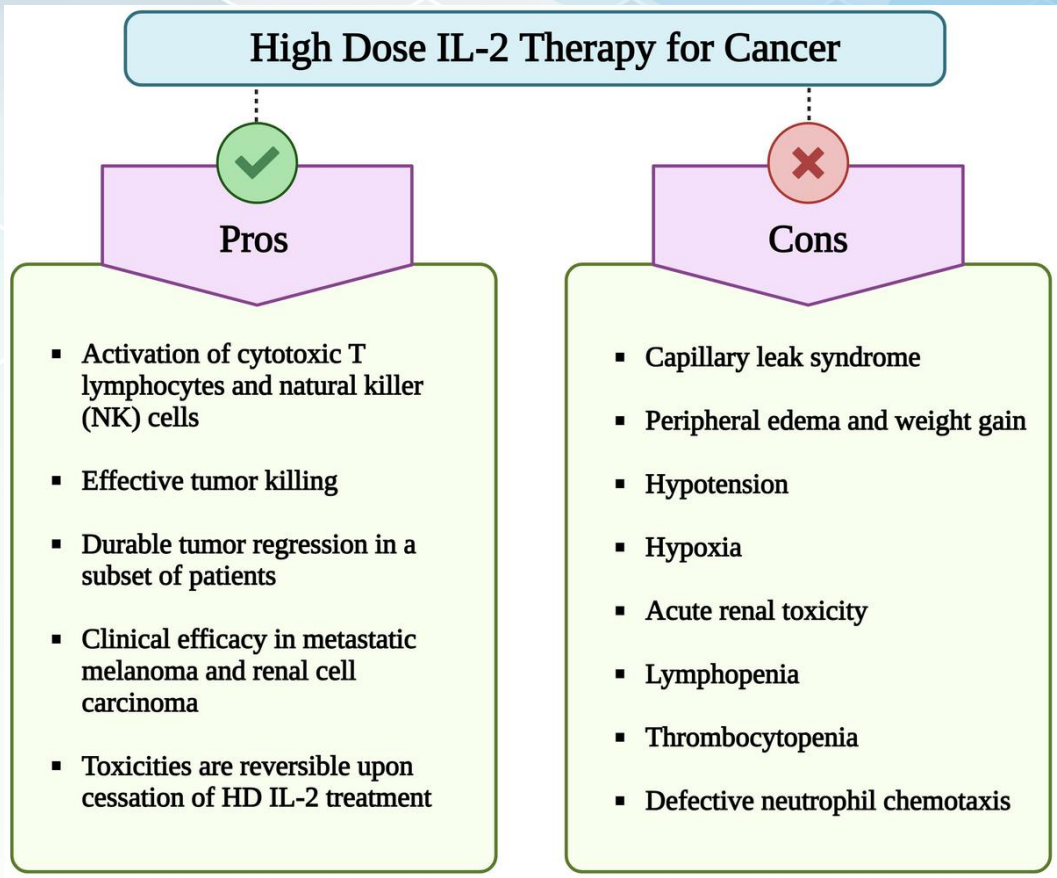
Cell & Gene Therapy Insights. 2020;6(6):855-863

An IL-2 Review

- **Interleukin-2** – a cytokine that promotes activation, proliferation, and anti-tumor cytolytic activity of WBCs
- High dose IL-2 = *a historical cornerstone in melanoma management*
  - 600,000 IU/kg IV every 8 h for ***up to 14 consecutive doses*** over 5 days
- With lifileucel – ***up to 6 doses*** of IL-2 (600,000 IU/kg) 3-24 hrs post-TIL, over 3 days
  - For cell expansion support
  - Majority received 6 doses in the landmark trial



Required ICU admission

"Inpatient setting with available ICU under supervision of physician experienced in the use of anticancer agents."

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Front. Immunol. 15:1433989

Supportive Care for Patients Receiving Lifileucel

PJP + HSV prophylaxis for 6 months and 1 year, respectively

TMP-SMX (or alternative) and acyclovir/valacyclovir

Antifungal prophylaxis until count recovery

Recommended to keep patients inpatient until count recovery

Filgrastim (GCSF) per institutional standard

Plan to stay within 2 hours of where you received lifileucel for several weeks post-discharge

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Cell & Gene Therapy Insights. 2020;6(6):855-863

Treatment and Supportive Care with Lifileucel

Day	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5+
Therapy													
Cyclophosphamide 60 mg/kg	X	X											
Fludarabine 25 mg/m^2			X	X	X	X	X						
TIL								X					
Interleukin-2[1]								X[1]	X	X	X	X	
Filgrastim 5 mcg/kg/day[2]									X	X	X	X	X[2]
Co-trimoxazole 480 mg[3]								X	X	X	X	X	X[3]
Fluconazole 100 mg PO[4]								X	X	X	X	X	X[4]
Valacyclovir 500 mg twice daily PO or Acyclovir 250 mg twice daily IV[5]								X	X	X	X	X	X[5]

1. Initiate within 24 hours after cell infusion
2. Continue until neutrophils count > 1 x 109 /L X 3 days or > 5 x 10^9 /L.
3. The TMP/SMX schedule should be adjusted to QD 3 times per week (Monday, Wednesday, Friday) and continue for at least 6 months and until CD4 > 200 X 10^6 /L
4. Continue until ANC > 1 x 10^9 /L
5. Continue until Day +100 and until patient no longer neutropenic

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N Engl J Med. 2022;387(23):2113-2125.

Lifileucel Landmark Phase II and III Trials

Population: advanced (stage IIIc or IV) melanoma that progressed on at least one prior systemic therapy (PD-1 and if BRAF V600 mutation-positive, a BRAF or BRAF/MEK inhibitor

Single Arm: Lifileucel

Med. follow-up: 27.6 mo.
ORR: 31.4%
Med. DOR: NR 95% CI: 8.3 mo. – NR
Med. time from infusion to best response: 1.5 mo. (range 1.3 – 29.6)

Any trAE: 100%
Grade 3/4 trAEs ≥30%: thrombocytopenia (76.9%), anemia (50%), febrile neutropenia (41.7%)
**Highest incidence within first 2 weeks post-infusion*

4-year analysis –

- The 1-, 2-, 3-, and 4-year OS rate was 54%, 34%, 28%, and 22%
- Clinically meaningful 4-year OS rates across all patterns of response (range, 37.2%–68.2%)

Compared to Ipilimumab:

- Phase 3, open-label trial
- Patients with unresectable stage IIIC or IV melanoma

Outcome	Lifileucel	Ipilimumab
PFS (mo, 95% CI)	7.2 (4.2 - 13.1)	3.1 (3.0 - 4.3)

- HR PD or death: 0.50 (95% CI 0.35 - 0.72)
- Any ≥ grade 3 trAE – Lifileucel 100%* vs. IPI 57%

Takeaway:

- In pretreated patients with advanced melanoma with a high tumor burden, responses were durable and AEs transient
  - These findings **support the potential of lifileucel to fulfill a large unmet medical need for novel therapeutic options distinct from ICI** in patients with advanced melanoma, but one must **take the burden of treatment into consideration**

*Mainly due to chemotherapy-related myelosuppression

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J Immunother Cancer. 2022;10(12):e005755; *Annals of Oncology* (2023) 20 (suppl_1): 100589-100589; *N Engl J Med*. 2022;387(23):2113-2125.

Current Role of Lifileucel

- Lifileucel is currently approved for:
  - Unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor
    - ➢ This is an accelerated approval (first approval February 2024)
    - ➢ Only 9 patients in the phase III trial were treatment-naïve
- Our center's experience:
  - High interest from patients
  - Patients getting lifileucel are cared for by our Bezos Family Immunotherapy Clinic
  - Due to the time it takes to set up TIL therapy, some patients receive a "bridging therapy"
  - Patients need to remain somewhat local after therapy

Circulating Tumor DNA (ctDNA) Monitoring for Melanoma

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QUESTION

Does your center use circulating tumor DNA in any cancers? In melanoma?

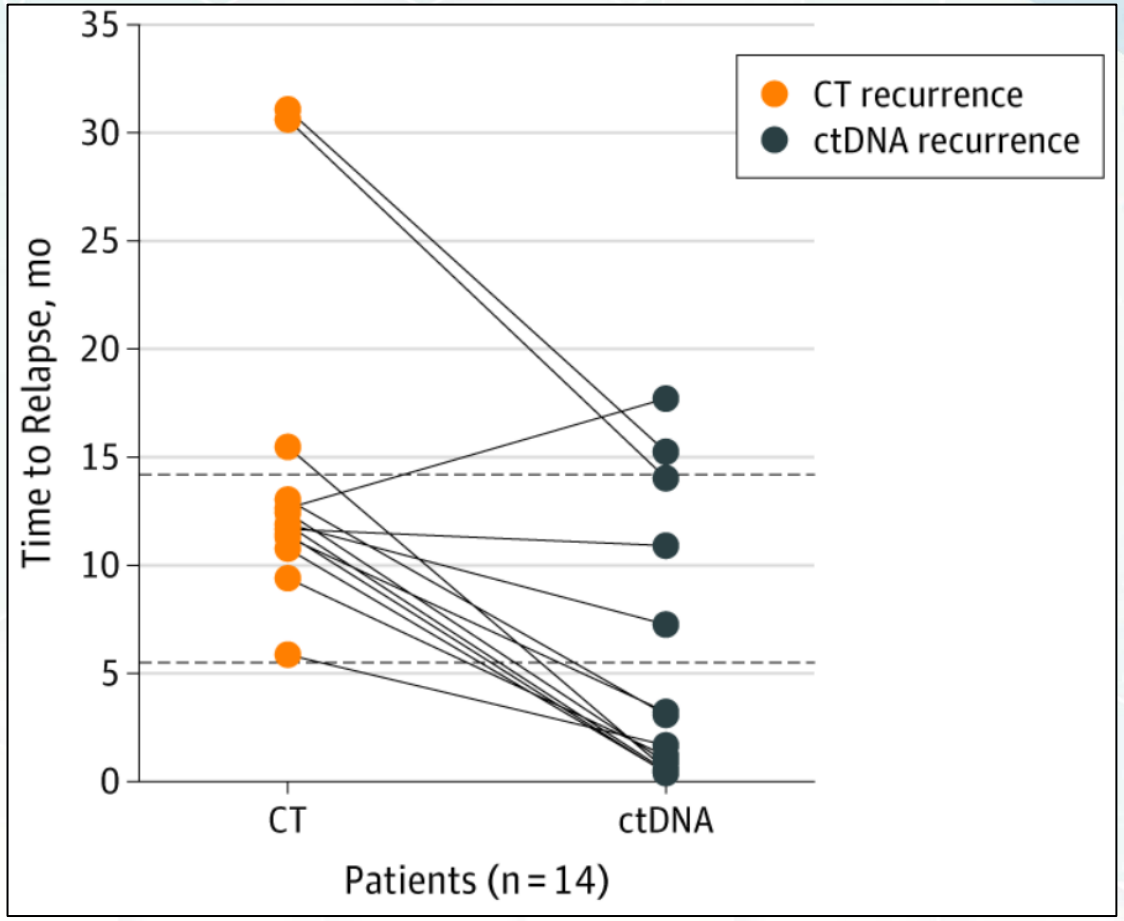
a. We do not use ctDNA at all to my knowledge
b. We use ctDNA in other cancers but not melanoma
c. We use ctDNA in as many cancers as we can

What is Circulating Tumor DNA (ctDNA)?

- Circulating tumor DNA (ctDNA) is a newer blood-based biomarker for cancer in multiple solid tumor types
  - Dead cells release DNA into the bloodstream, which can be identified
    - If a cancer harbors mutations distinguishable from healthy cells' DNA, maybe we can track the presence/absence or trajectory of cancer treatment and response in a patient
    - Nonspecific biomarkers exist for multiple cancers, but may be abnormal for reasons other than growth of cancer
    - Melanoma currently has no prognostic biomarkers to guide therapy decisions
      - Lactate dehydrogenase levels are included in AJCC TNM staging of M1 disease

Implications for ctDNA in Practice

- In colon cancer, the detection of ctDNA 30 days after surgery suggests a **7x** increased risk of relapse/recurrence than those without ctDNA detected
- ctDNA detects relapse faster than computed tomography (CT)



14.2 months (range, 5.9-31.1 months)

5.5 months (range, 0.4-17.7 months)

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Reinert et al. *JAMA Oncol*, 2019; 5(8):1124-1131. Bratman SV et al, *Nature Cancer*, 2020; 873-881.

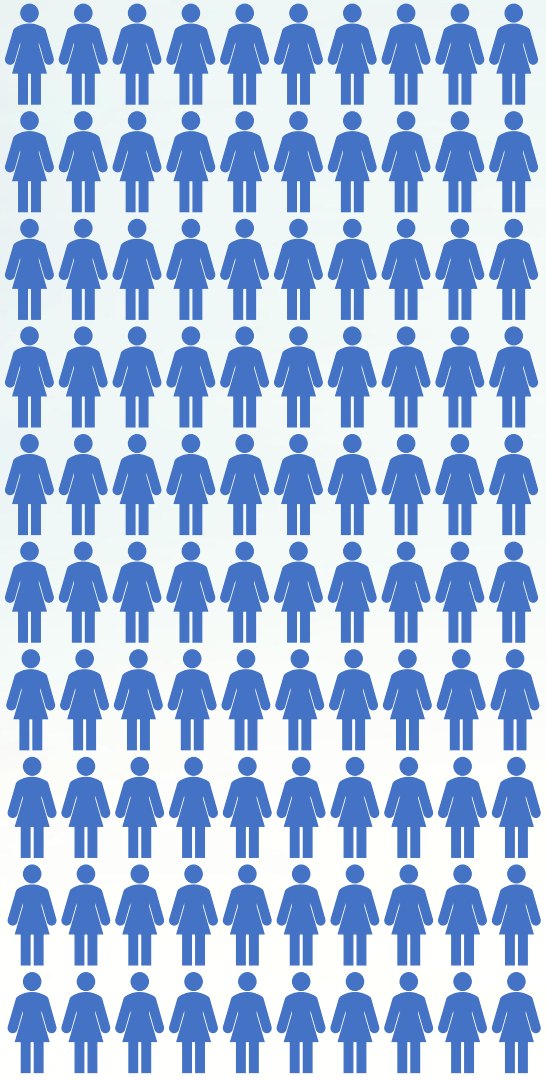
How ctDNA Could Improve Melanoma Care?

- For patients who have completed surgery:
  - ✓ Detection of ctDNA may identify patients at higher risk of recurrence who could possibly benefit from more aggressive treatments (such as immunotherapy) to reduce risk of recurrence
  - ✓ Absence of ctDNA may identify patients at lower risk of recurrence who may not benefit as much from additional treatments
  - ✓ Potential for more personalized, tailored care
- For patients with metastatic disease:
  - ✓ ctDNA may complement imaging to help us determine if a given treatment is having the intended effect

Clinical Scenario

- For many patients with melanoma, surgery is a potentially curative procedure
- Cancer stage provides prognostic information
  - Recurrence rates for patients with stage I melanoma can be as low as 1-2%
  - However, recurrence rates after surgery for patients with stage IIID melanomas can be as high as 80%
    - Distant metastatic melanoma still shows 5-year survival rates <50%
- Among patients within a given stage, we currently do not have the precision to predict who will have melanoma recurrence and who will not
  - Thus, we may offer adjuvant systemic therapy to anyone who is at least a certain stage

At the time after surgery,…



100 patients
none of whom
have detectable
melanoma

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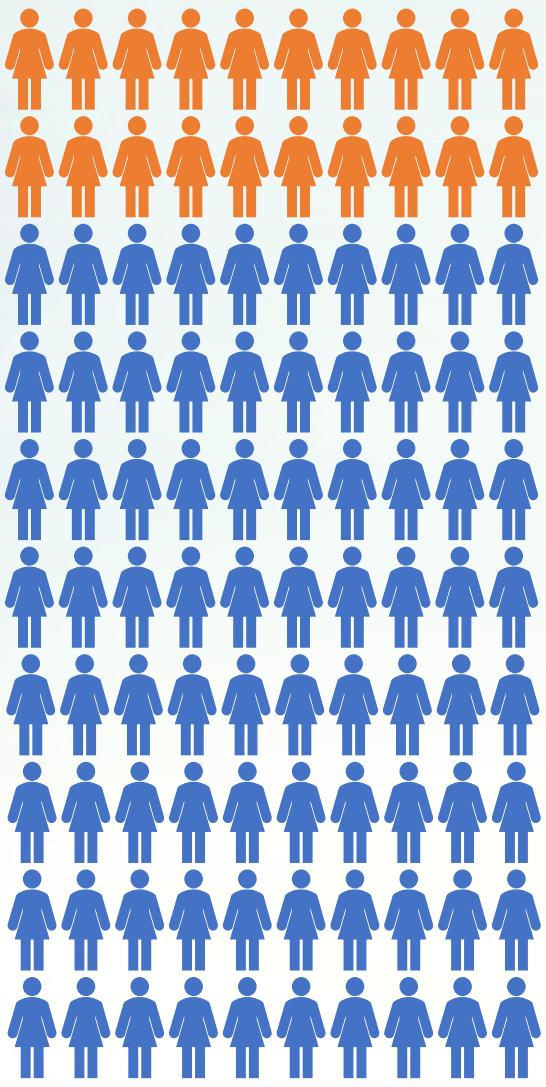
Five years after surgery,…



~20 patients will have a recurrence. These patients may benefit from more treatment

~80 patients won’t have recurrence and were cured with surgery alone. Additional treatment after surgery could cause harmful side effects when the melanoma was never going to recur

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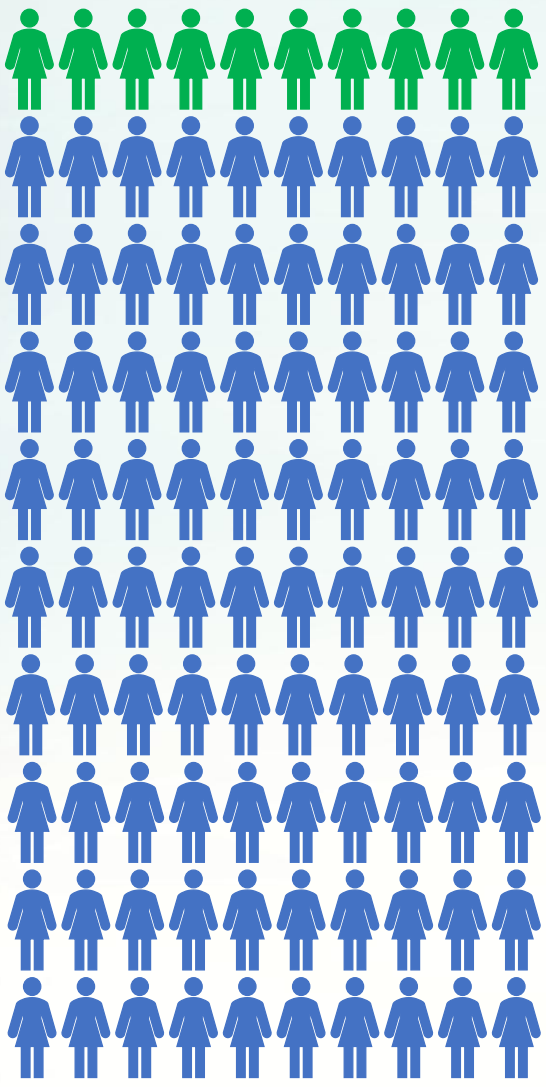
What a ctDNA test may be able to do after surgery…



10 patients with +ctDNA. These patients could strongly consider more treatment after surgery

90 patients without +ctDNA. They are less likely to have a recurrence. More treatment may or may not be considered

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ctDNA levels may be prognostic

- Low baseline levels of ctDNA are predictive of better effectiveness of immunotherapy in patients with metastatic melanoma (vs high baseline levels)
- Decreasing ctDNA levels while on immunotherapy are associated with longer survival for patients with metastatic melanoma
- ctDNA status 4 weeks (positive or negative) after treatment initiation predicts duration of response to BRAF/MEK inhibitor therapy (7.1 months +ctDNA vs 12.9 months undetectable ctDNA)

Marsavela G, et al. *Clin Cancer Res,* 2020, 26(22):5926-5933.
Lee JH, et al. *Ann. Oncol.*, 2017, 28(5):1130-1136.
Syeda et al. *Lancet Oncol.*, 2021, 22:370-380.

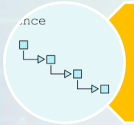
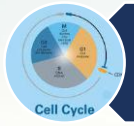
Final Thoughts

- ctDNA is an emerging technology that could help us to better personalize and tailor melanoma therapy in the future
- The presence of detectable ctDNA after surgery may allow us to more clearly identify patients at risk of recurrence and tailor treatment
- Trends in ctDNA levels may be useful when considering treatment options for patients with metastatic melanoma
- This is not yet ready or recommended by major guidelines for routine use, but is an active area of ongoing research

Ongoing Studies & Future Directions

Off-label use

Ongoing Studies & Future Directions

- ¾ Triple and quadruple therapy
-  Further sequencing data
-  Neoadjuvant BRAF/MEKi or nivolumab-relatlimab
-  Lifileucel in first-line metastatic treatment?
-  Continued search to modify the immune system to fight cancer
-  Efficacy of additional targeted therapies (CDK 4/6i)

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SUMMARY

Neoadjuvant immune checkpoint blockade improves clinical outcomes compared to adjuvant administration - without significant impact on surgical outcomes

- Due to a larger population of TILs leaving behind more antitumor T cells

The sequence of therapy commencing with nivolumab/ipilimumab followed by BRAF/MEKi is associated with greater survival

- This should probably be the preferred sequence for patients (recall caveats)

Novel anti-cancer mechanisms like those with nivolumab-relatlimab and TILs are improving outcomes in advanced melanoma

- As evidenced by FDA approvals of nivolumab/relatlimab and lifileucel in the metastatic setting

Lifileucel is a potentially powerful therapy, but hospitals need to be appropriately equipped to care for patients receiving it.

- Given the need for comprehensive management of logistics and supportive care

QUESTION & ANSWER

Breaking New Ground in Melanoma: Recent Updates and Emerging Therapies

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CE CODES