Advancements in systemic therapy for patients with melanoma

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8 May 2024

NCI CCC
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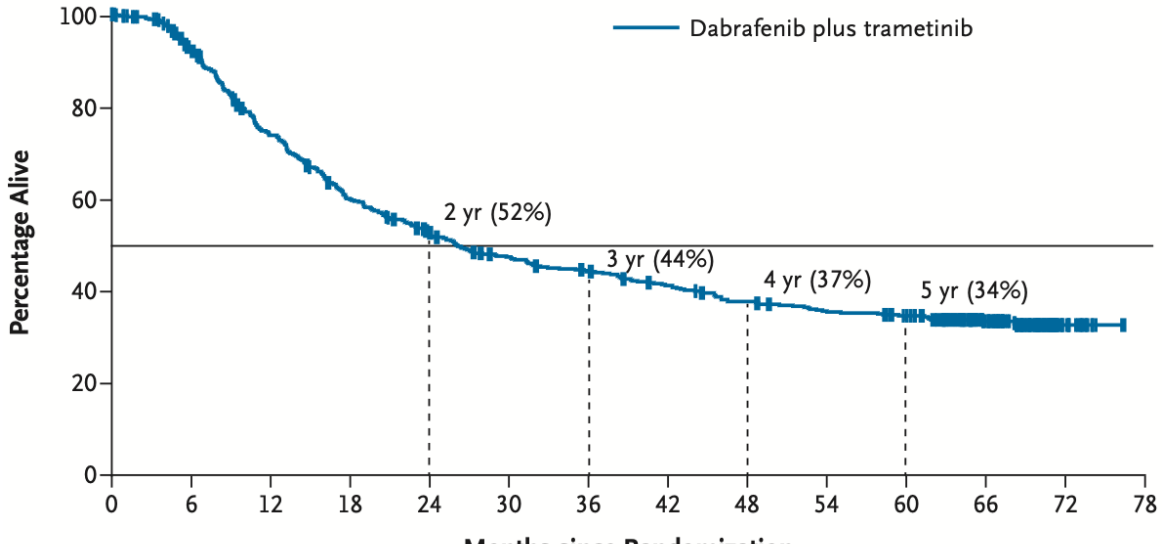
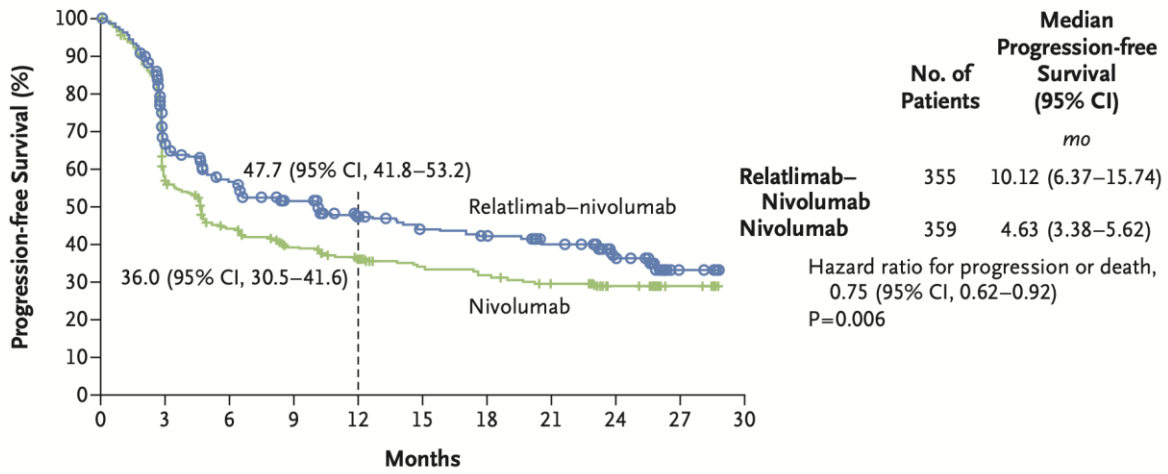
Disclosures and Objectives

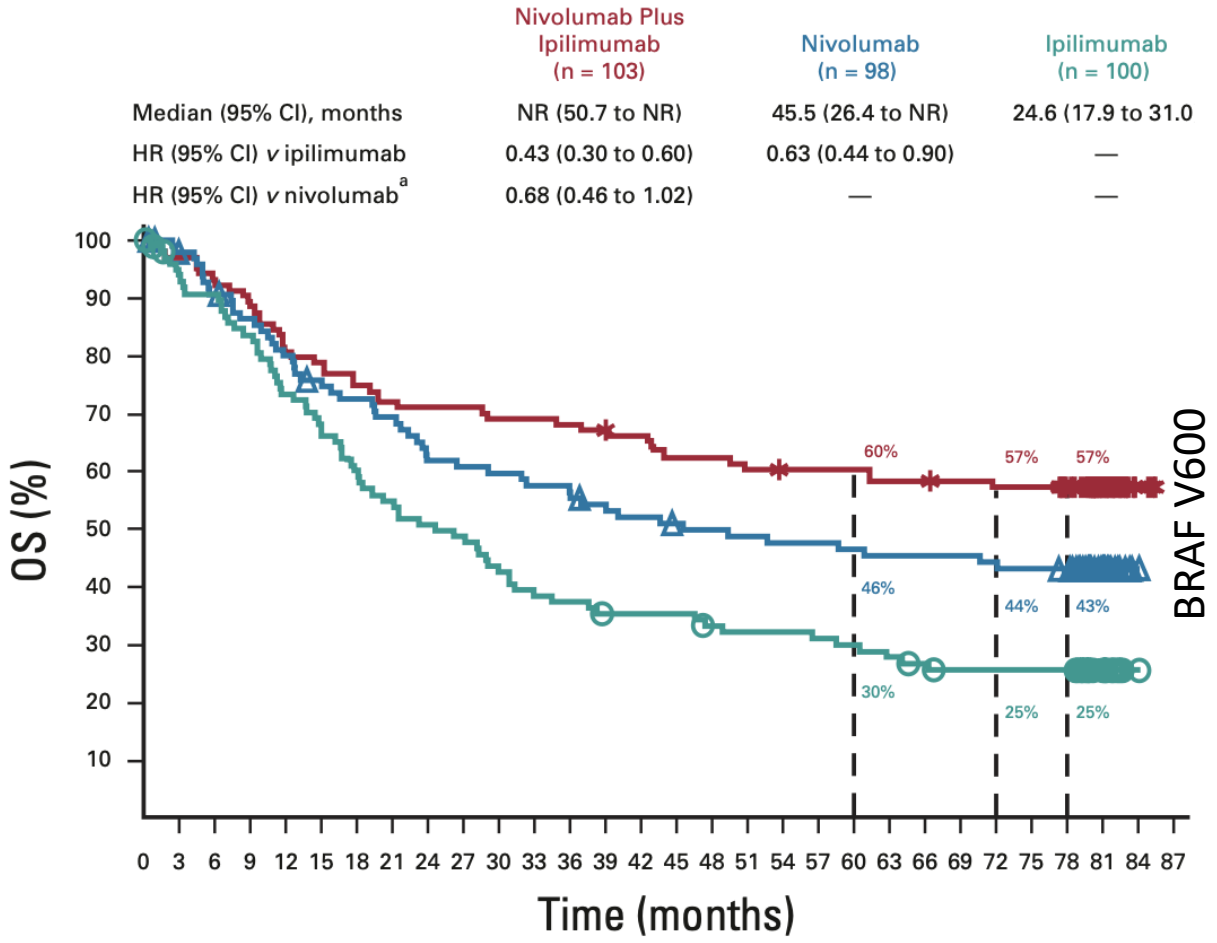
- No disclosures

- Objectives
  - **Describe current advances in systemic treatment strategies for melanoma**

Current frontline treatments for advanced melanoma



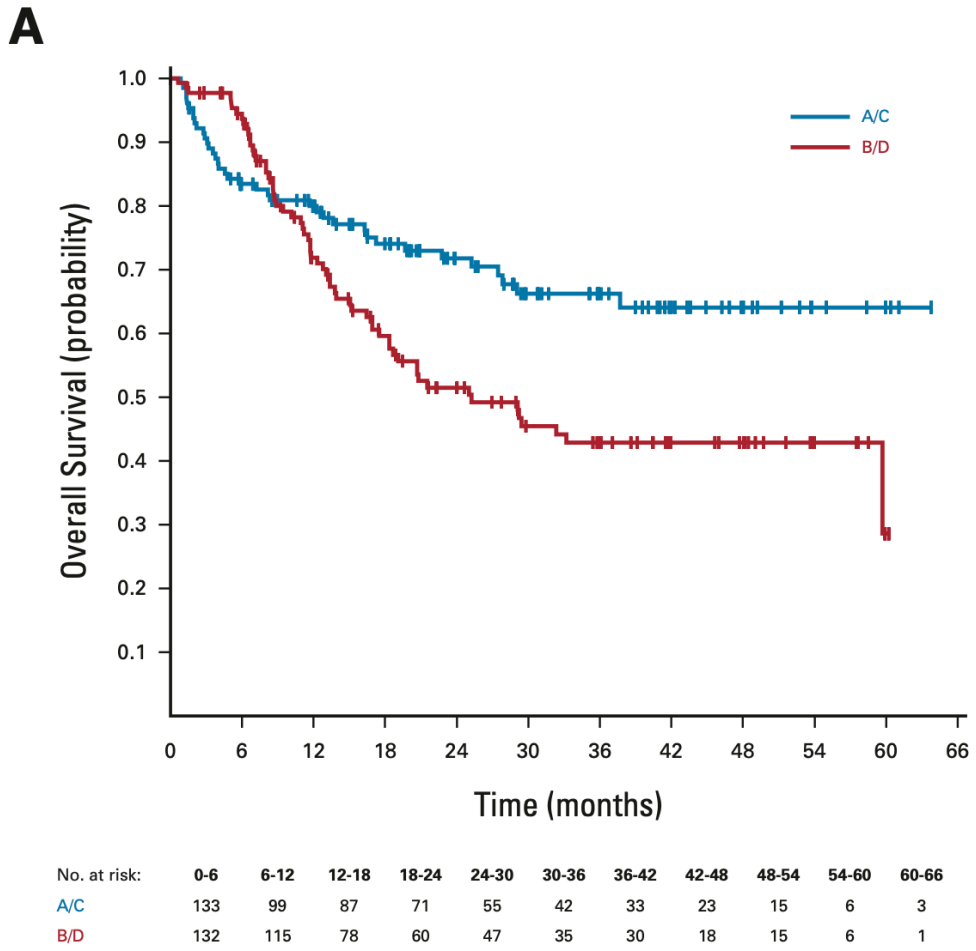




Robert NEJM 2019 Tawbi NEJN 2022 Wolchok JCO 2021

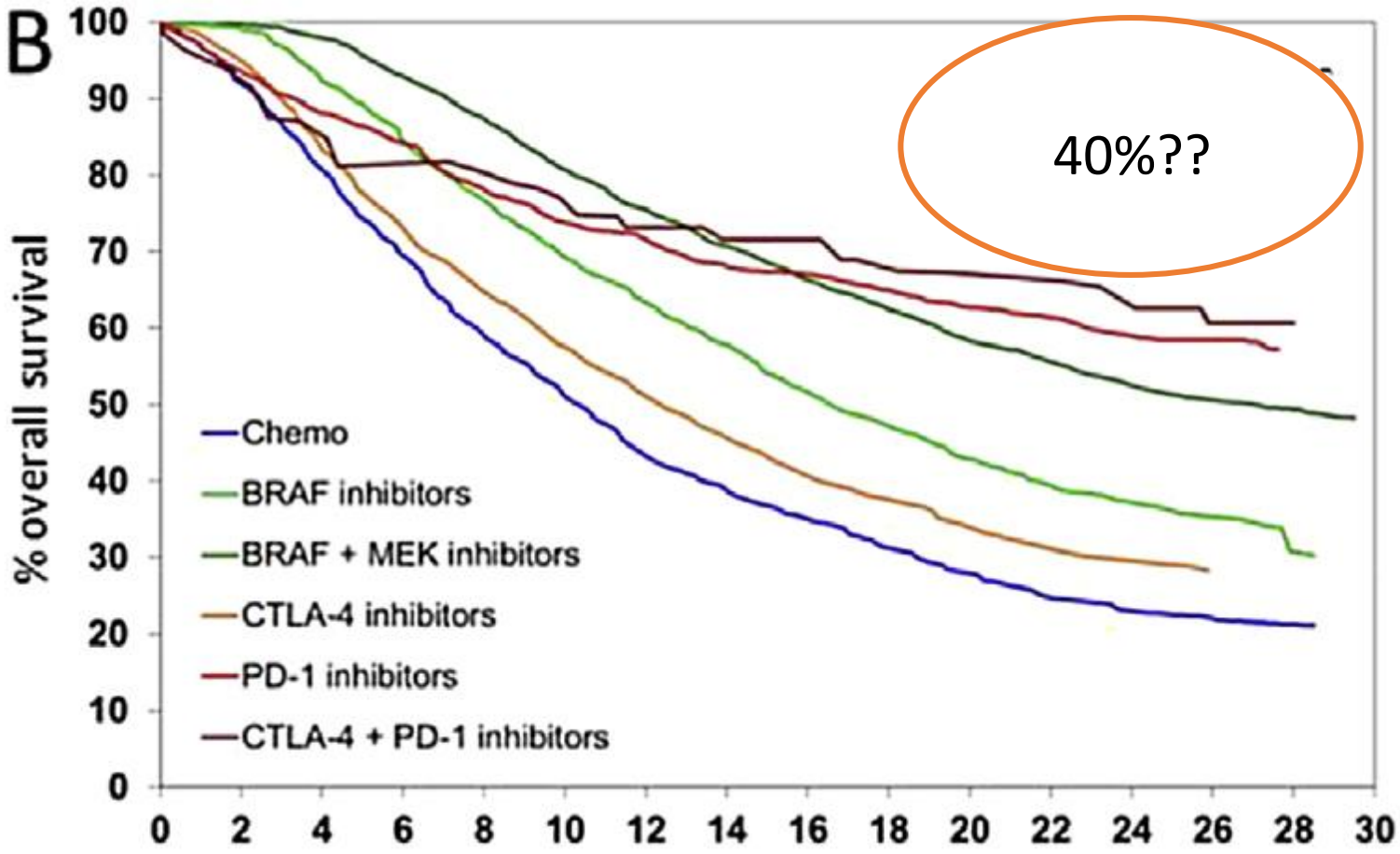
How to choose which therapy to start?

- Genomics
  - Driver mutation
  - TMB/histology
- Patient characteristics
  - Burden of disease, pace of disease
  - Location of disease
  - General health, immune status
    - Autoimmune disease
    - Immune suppression
- Goal of therapy



Atkins JCO 2022

Evasion and Adaptive Resistance



S Ugurel Eur J of Cancer 2017

Lifileucel

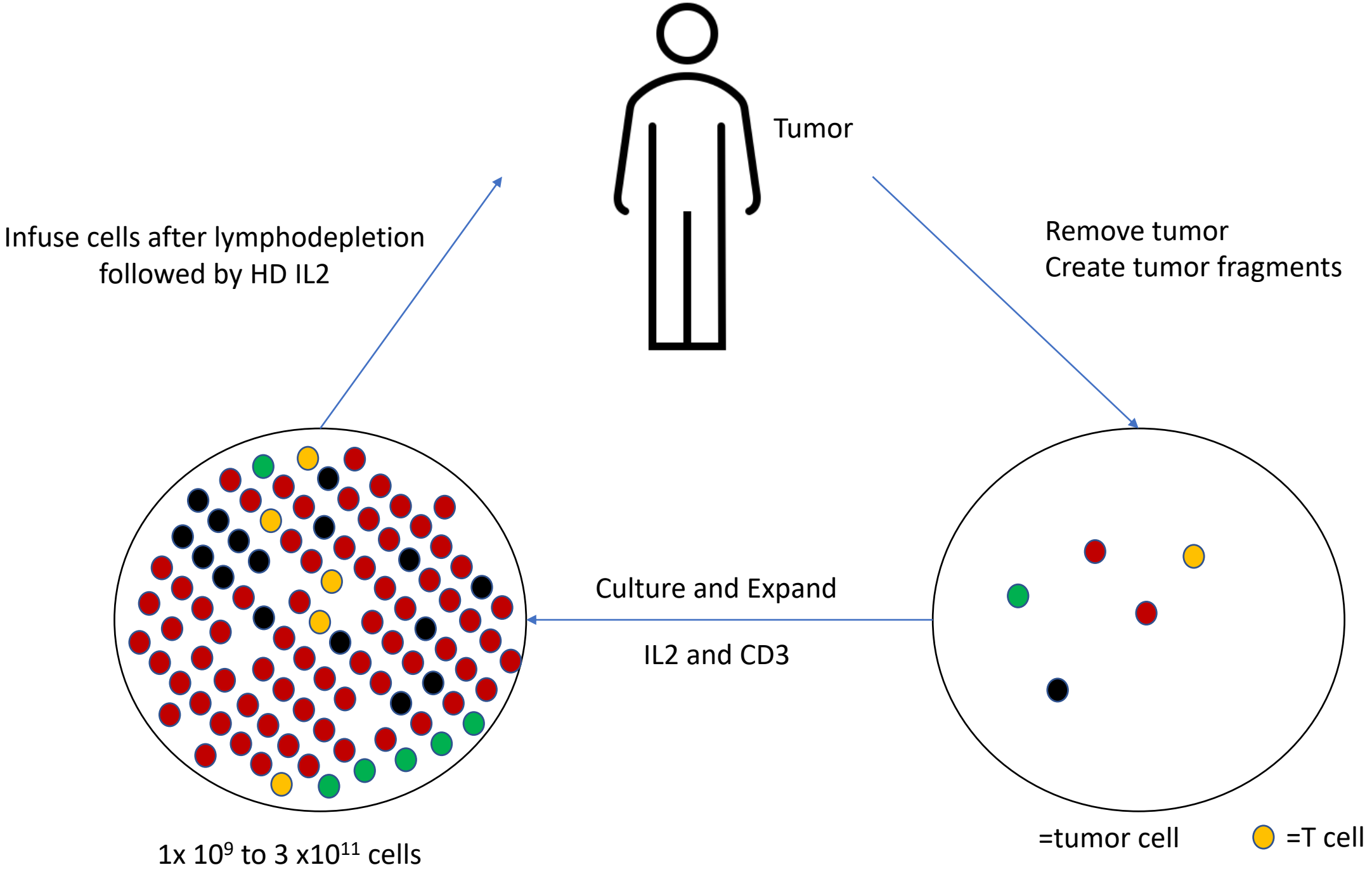
- Indication for adults with unresectable or metastatic melanoma who had previously ben treated with PD-1 inhibitor and , if BRAF-positive, a BRAF inhibitor with or without MEK

- Therapy
  - Isolate TILs and expanding ex vivo
  - Nonmyeloablative lymphodepletion to promote engraftment
  - High-dose IL2 for up to 6 doses following infusion of cells

TILs= Tumor Infiltrating Lymphocytes

Lifileucel PI 2024

Rosenberg NEJM 1988


Tumor
Infuse cells after lymphodepletion
followed by HD IL2
Remove tumor
Create tumor fragments
Culture and Expand
IL2 and CD3
1x 10^9 to 3 x10^11 cells
=tumor cell
=T cell

TIL Background

URNAL OF MEDICINE Dec. 22, 1988

SPECIAL REPORT

USE OF TUMOR-INFILTRATING LYMPHOCYTES AND INTERLEUKIN-2 IN THE IMMUNOTHERAPY OF PATIENTS WITH METASTATIC MELANOMA

A Preliminary Report

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Douglas Schwartzentruber, M.D.,
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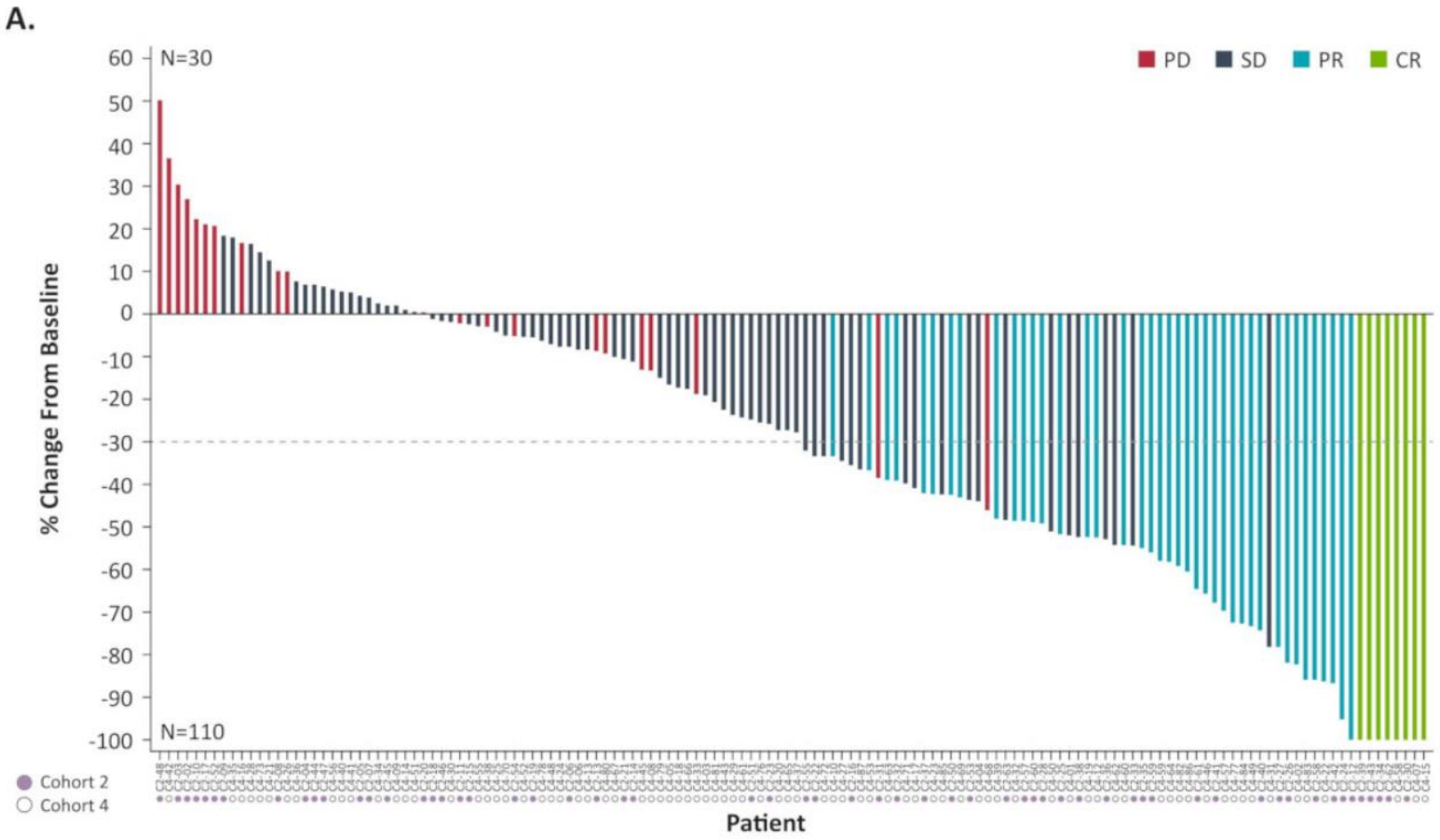
Abstract Lymphocytes extracted from freshly resected melanomas can be expanded in vitro and can often mediate specific lysis of autologous tumor cells but not allogeneic tumor or autologous normal cells. We treated 20 patients with metastatic melanoma by means of adoptive transfer of these tumor-infiltrating lymphocytes and interleukin-2, after the patients had received a single intravenous dose of cyclophosphamide. Objective regression of the cancer was observed in 9 of 15 patients (60 percent) who had not previously been treated with interleukin-2 and in 2 of 5 patients (40 percent) in whom previous therapy with interleukin-2 had failed. Regression of cancer occurred in the lungs, liver, bone, skin, and subcutaneous sites and lasted from 2 to more than 13 months. Toxic effects of interleukin-2 occurred, although the treatment course was short (five days); these side effects were reversible.

It appears that in patients with metastatic melanoma, this experimental treatment regimen can produce higher response rates than those achieved with interleukin-2 administered alone or with lymphokine-activated killer cells. It is too early to determine whether this new form of immunotherapy can improve survival, but further trials seem warranted.



JITC 2022 Chesney

TIL Background

Table 3 TEAEs occurring in ≥30% of the patients (Safety Analysis Set (N=156))*

Preferred term, n (%)	Any grade	Grade 3/4
Thrombocytopenia	129 (82.7)	120 (76.9)
Chills	117 (75.0)	8 (5.1)
Anemia	97 (62.2)	78 (50.0)
Fever	81 (51.9)	17 (10.9)
Neutropenia†	66 (42.3)	45 (28.8)
Febrile neutropenia	65 (41.7)	65 (41.7)
Hypophosphatemia	58 (37.2)	41 (26.3)
Leukopenia†	54 (34.6)	42 (26.9)
Hypotension	52 (33.3)	17 (10.9)
Fatigue	51 (32.7)	6 (3.8)
Lymphopenia†	49 (31.4)	38 (24.4)
Diarrhea	48 (30.8)	2 (1.3)

*Other relevant events: Grade 3/4 TEAEs commonly observed with cellular therapies or IL-2 included immune effector cell-associated neurotoxicity syndrome and cytokine release syndrome (investigator-assessed, no confirmatory serum cytokine levels measured) in one patient, and capillary leak syndrome (due to IL-2) in seven patients. Grade 3/4 uveitis was reported in three patients.
†All patients had grade 4 laboratory abnormality per the Common Terminology Criteria for Adverse Events V.4.03 for leukopenia, neutropenia, and lymphopenia during the treatment-emergent period. Only clinically significant laboratory abnormalities as per investigators were reported as adverse events.
IL-2, interleukin-2; TEAE, treatment-emergent adverse event.

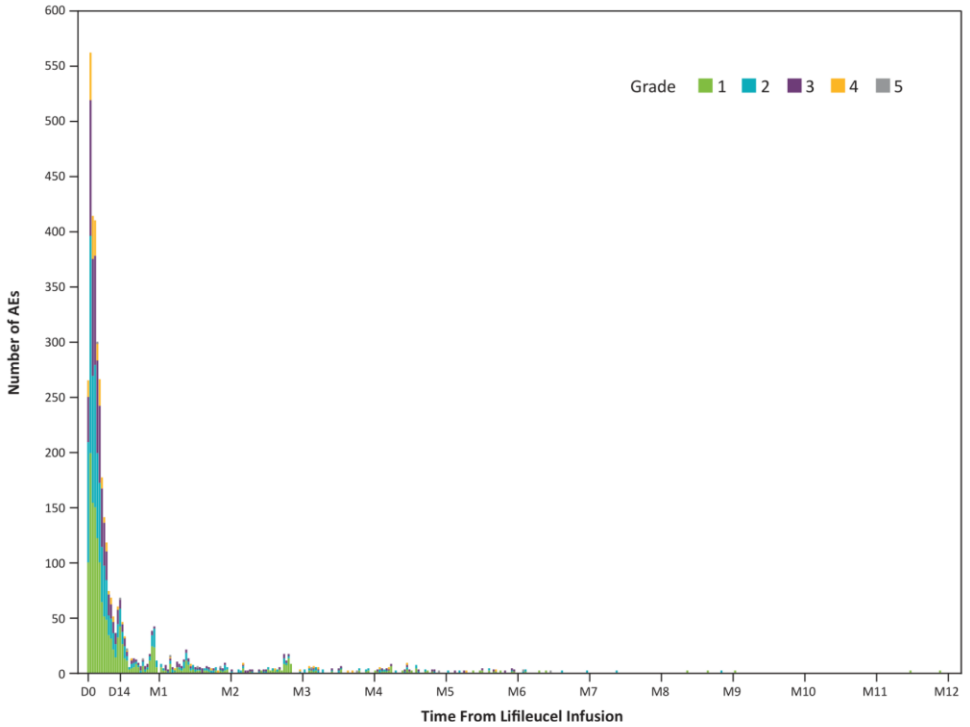


Figure 3 Incidence of AEs over time (Safety Analysis Set).* All occurrences of AEs were counted if a patient experienced a new onset of the same AE at different time points. If multiple records were reported on the electronic case report form because of toxicity grade decrease of the same AE that had not been resolved, then the event was counted once with the highest grade reported. *Fourteen events were reported after month 12 (grade 1, n=6; grade 2, n=6; grade 3, n=1, grade 5, n=1). AE, adverse event; D, day; M, month.

25 patients did not receive lifileucel for patient-related reasons (PD (n=9, 4.8%), death (n=5, 2.6%), AE (n=3, 1.6%), new anticancer treatment (n=2, 1.1%), withdrawal of consent (n=1, 0.5%), withdrawal by patient (n=1, 0.5%), and other reason (n=4, 2.1%)), whereas lifileucel was not available for infusion for 8 patients (4.2%).

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TIL Background

Table 2 Efficacy outcomes by IRC assessment for Cohorts 2, 4, and pooled Cohorts 2 and 4 (Full Analysis Set)

Response (RECIST V.1.1)*	Cohort 2 (n=66)	Cohort 4 (n=87)	Pooled Cohorts 2+4 (N=153)
ORR, n (%)	23 (34.8)	25 (28.7)	48 (31.4)
(95% CI)	(23.5 to 47.6)	(19.5 to 39.4)	(24.1 to 39.4)
Best overall response, n (%)			
CR	5 (7.6)	3 (3.4)	8 (5.2)
PR	18 (27.3)	22 (25.3)	40 (26.1)
SD	24 (36.4)	47 (54.0)	71 (46.4)
Non-CR/non-PD†	1 (1.5)	0	1 (0.7)
PD	15 (22.7)	12 (13.8)	27 (17.6)
Non-evaluable‡	3 (4.5)	3 (3.4)	6 (3.9)
Median DOR,§ months (range)	NR (1.4+ to 45.0+)¶	10.4 (1.4+ to 26.3+)	NR (1.4+ to 45.0+)
Median study follow-up,** months	36.6	23.5	27.6

*Objective response refers to patients with the best overall response of CR and PR. 95% CI for ORR was calculated using the Clopper-Pearson exact test.
†Patient did not have measurable target lesions by IRC and had best overall response of non-CR/non-PD per IRC assessment.
‡Six patients were non-evaluable for response (five due to early death; one due to new anticancer therapy).
§Based on responders and using Kaplan-Meier product-limit estimates.
¶Note: + refers to censored.
**Based on the reverse Kaplan-Meier method.
CR, complete response; DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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TIL Background

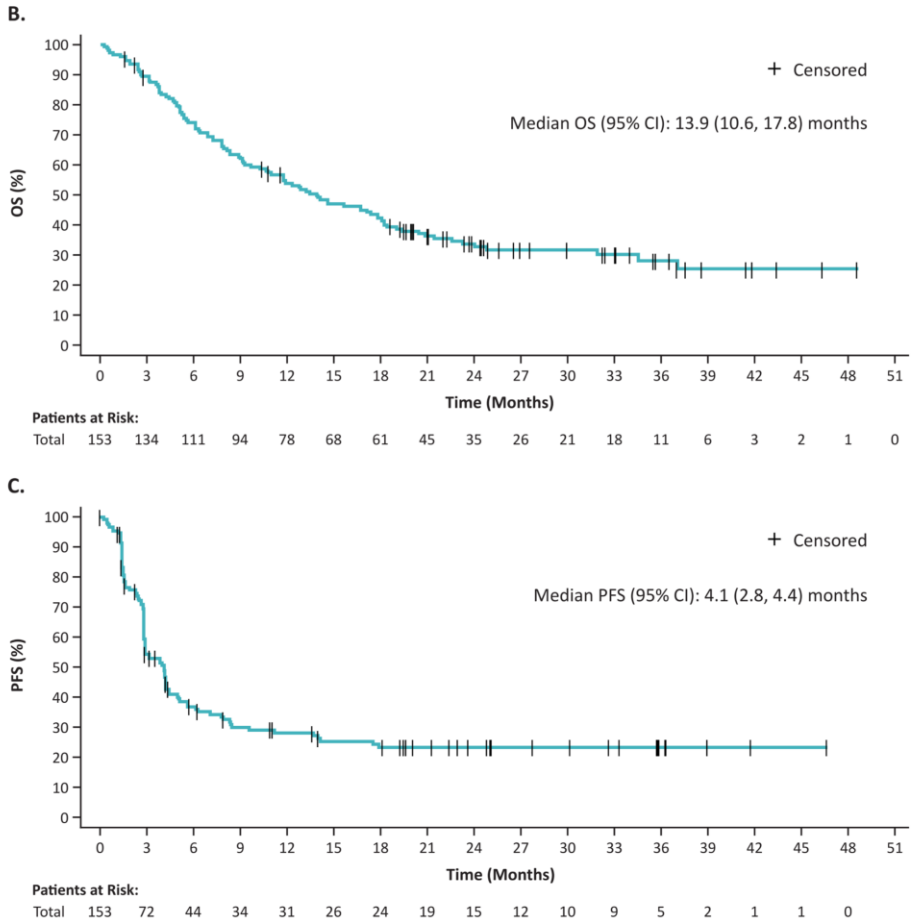

Figure 2 DOR in confirmed responders (PRor better) by IRC assessment per Response Evaluation Criteria in Solid Tumors V.1.1 (A), OS (B), and PFS (C) for pooled Cohorts 2 and 4. DOR, duration of response; IRC, independent review committee, NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response.

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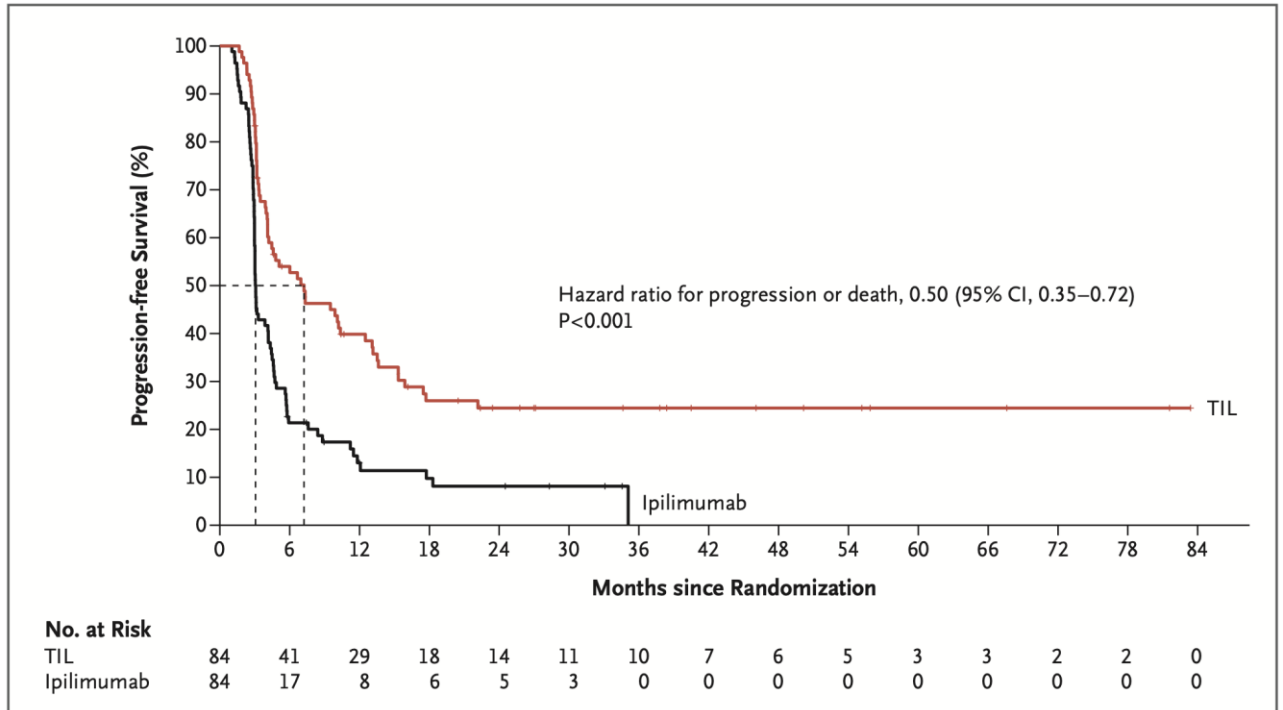

Figure 1. Progression-free Survival.

Progression-free survival assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, is shown for all patients who were randomly assigned to receive tumor-infiltrating lymphocyte (TIL) therapy or ipilimumab (the intention-to-treat population). The patients were stratified according to *BRAF* V600–mutation status, line of treatment, and treatment center. Hazard ratios were estimated with the use of the stratified Cox regression model. The P value was calculated with the use of the stratified log-rank test with a two-sided 95% confidence interval. Tick marks indicate censored data..

NEJM 2022 Rohaan

Challenges with TILs

- Complexity
  - Multi-step
  - Points of failure
- Limited treatment centers
  - About 30 in the US to start
  - Capacity of manufacturer
  - Selection process
- Toxicity
  - SIRS, neutropenia, pulmonary
  - Death
  - Long-term immunologic changes?
- Cost
- Unique components
  - Nonmyeloablative chemo
  - HD IL2
  - Cell infusions
- Patient Selection
  - PS
  - Pace, location of disease

Warner JITC 2024

Patient Selection

- Anticipated tolerance to conditioning and IL2
- Pace of disease
- Brain metastasis
- Bowel metastasis
- Renal function (GFR >40mL/min)
- Cardiac function
  - EF >45%
  - Ischemia evaluation if suspected and treat
- Pulmonary function
  - Spirometry should be performed in these patients and diffusing lung capacity for carbon monoxide (DLCO) should be measured
  - Patients with moderate to severe impairment, that is, DLCO<50%or <40%,
- Recovered from prior therapy
- Prednisone of 10mg or less

Warner JITC 2024

Systemic therapy in Melanoma

- Choice of first-line therapy balances patient and treatment characteristics with no “one size fits all”
- Immune therapy should be favored when choosing between targeted and immune checkpoints due to likely survival advantage
- Tumor infiltrating lymphocytes are appropriate to consider in a select group of patients

- Clinical trials remain appropriate for all stages of disease therapy

Thank you

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