Advances in the Evolving Treatment Landscape of Melanoma and Non-Melanoma Skin Cancer

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NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

UC San Diego
Moores Cancer Center

Learning Objectives

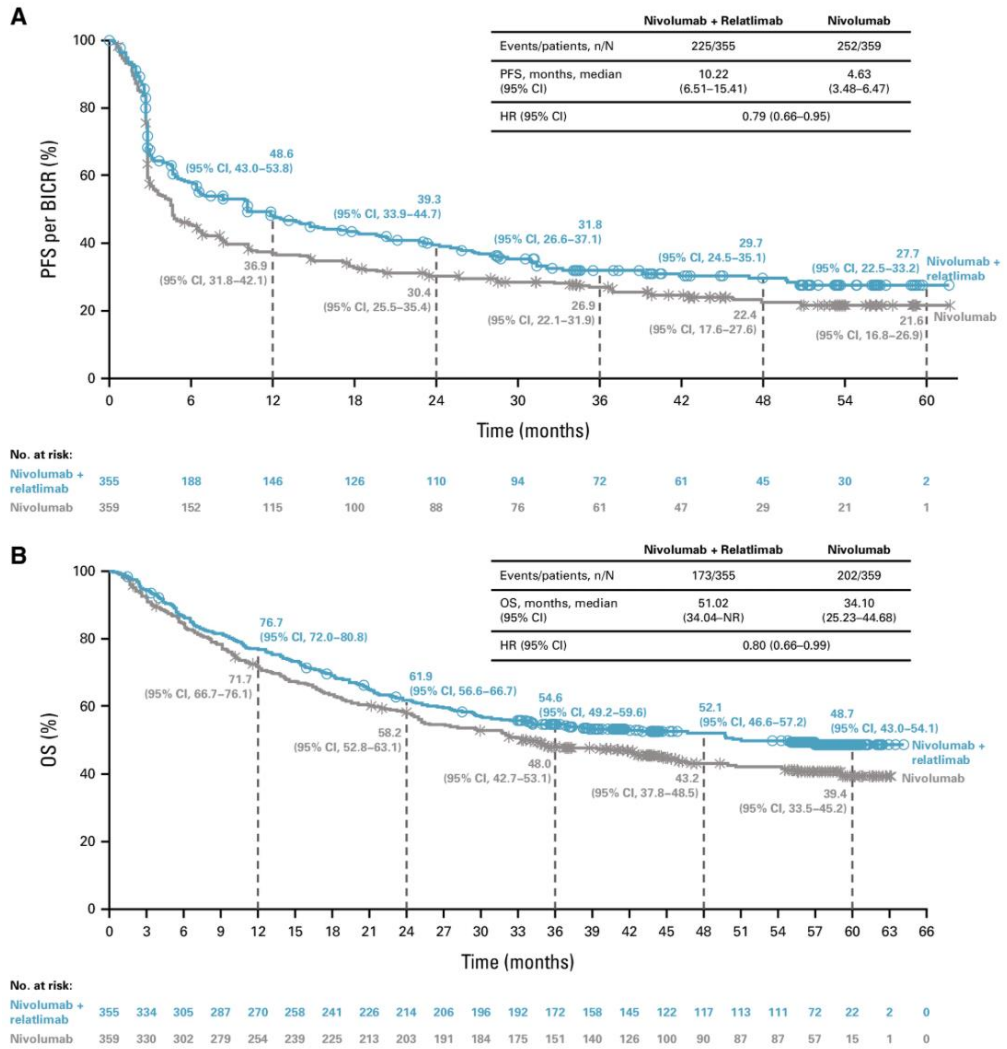
- Discuss some current clinical trials for unmet needs in melanoma and non-melanoma skin cancer.
- Be able to identifying appropriate patients for tumor-infiltrating lymphocyte therapy in melanoma.
- Understand the role of neoadjuvant therapy for patients with non-melanoma skin cancer.

Disclosures

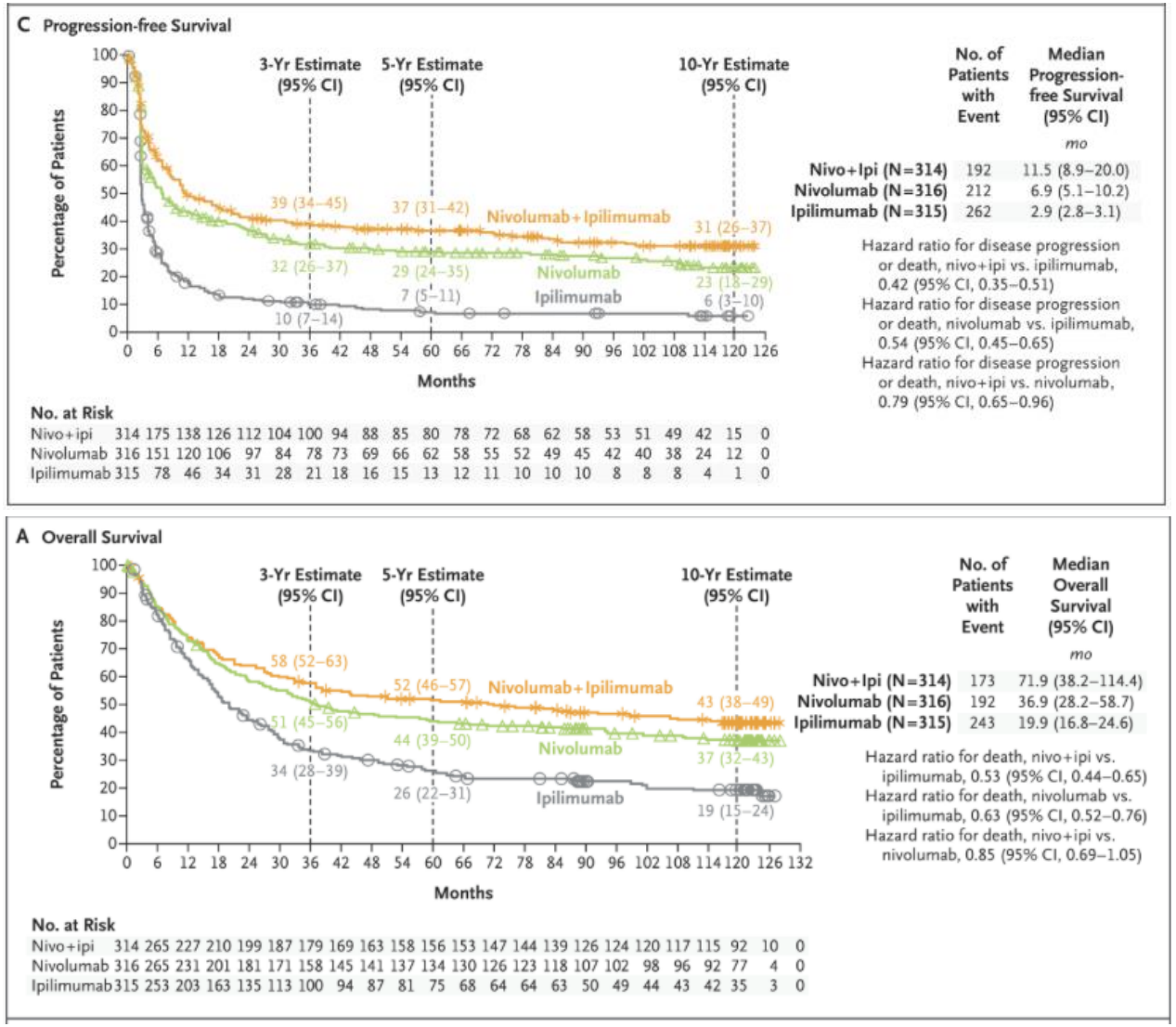
- None

- Local investigator on clinical trials
- Professor of medicine UC San Diego
- Staff physician VAMC San Diego

Frontline Unresectable Melanoma



Tawbi JCO 2024



Wolchok NEJM 2024

Many Open Fundamental Questions

- Can we identify patients better?
- How long to treat?
- Which is the best frontline therapy?

- **What to do after progression on first-line therapy?**

Beyond First-line

First-line	Subsequent	Approximate RR	References
CTLA4/PD1	PD1/LAG-3	10%	Acierto JCO 2023
	TILs	30%	Chesney JITC 2022
PD1/Lag3	CTLA4/PD1	10%	NEJM editorial 2022
	TILs	30%	Chesney JITC 2022
PD1	CTLA4/PD1	30%	Olson JCO 2021
	Lag3/PD1	10%	Acierto JCO 2023
	TILs	30%	Chesney JITC 2022

Many holes in the data above which is why I list approximate RRs

Adoptive Transfer of Autologous T cells with IL-2

Immunotherapy of Patients With Advanced Cancer Using Tumor-Infiltrating Lymphocytes and Recombinant Interleukin-2: A Pilot Study

By Suzanne L. Topalian, Diane Solomon, Frederick P. Avis, Alfred E. Chang, Deborah L. Freerksen, W. Marston Linehan, Michael T. Lotze, Cary N. Robertson, Claudia A. Seipp, Paul Simon, Colleen G. Simpson, and Steven A. Rosenberg

Clinical investigations using the adoptive transfer of lymphokine-activated killer (LAK) cells and recombinant interleukin-2 (rIL-2) to treat patients with advanced cancer have yielded encouraging results. We have thus sought ways to enhance the effectiveness of adoptive immunotherapy while minimizing its toxic side effects. Murine experiments have identified tumor-infiltrating lymphocytes (TIL) as killer cells more effective than LAK cells and less dependent on adjunctive systemically administered IL-2 to mediate antitumor effects. Accordingly, we performed a pilot protocol to investigate the feasibility and practicality of administering IL-2–expanded TIL to humans with metastatic cancers. Twelve patients, including six with melanoma, four with renal cell carcinoma, one with breast carcinoma, and one with colon carcinoma, were treated with varying doses and combinations of TIL (8.0×10^9 to 2.3×10^{11} cells per patient), IL-2 (10,000 to 100,000 U/kg three times daily to dose-limiting toxicity), and cyclophosphamide (CPM) (up to 50 mg/kg). Two partial responses (PR) to therapy were observed: pulmonary and mediastinal masses regressed in a patient with melanoma, and a lymph node mass regressed in a patient with renal cell carcinoma. One additional patient with breast cancer experienced a partial regression of disease in lymph nodal and cutaneous sites with complete elimination of malignant cells from a pleural effusion, although cutaneous disease recurred at 4 weeks. The toxicities of therapy were similar to those ascribed to IL-2; no toxic effects were directly attributable to TIL infusions. In five of six melanoma patients, TIL demonstrated lytic activity specific for the autologous tumor target in short-term chromium-release assays, distinct from the nonspecific lytic activity characteristic of LAK cells. This study represents an initial attempt to identify and use lymphocyte subsets with enhanced tumoricidal capacity in the adoptive immunotherapy of human malignancies.

J Clin Oncol 6:839-853.

PAN AMERICAN ALLERGY SOCIETY

The 1989 training course and seminar will be held in San Antonio, Tex., March 8–12.

Contact Betty Kahler at the Society, 411 E. College, Fredericksburg, TX 78624; or call (409) 297-5636.

CHICAGO SCHOOL OF MEDICINE

The following programs will be held: "The Psychiatric Interview" (Chicago, March 10–12); "New Techniques in ENT" (Vail, Colo., March 19–25); and "Advances in Gynecology" (Chicago, March 31–April 2).

Contact Univ. of Chicago, Ctr. for Cont. Medical Educ., 5841 S. Maryland, Box 139, Chicago, IL 60637; or call (312) 702-1056.

MIDWEST CENTER FOR OCCUPATIONAL HEALTH AND SAFETY

The following courses will be offered in St. Paul, Minn.: "10th Annual Occupational Medicine Update" (March 10) and "Comprehensive Industrial Hygiene Review" (March 13–17, April 10–14, and Aug. 14–18).

Contact Ruth K. McIntyre, MCOHS, St. Paul–Ramsey Medical Ctr., 640 Jackson St., St. Paul, MN 55101; or call (612) 221-3992.

SPECIAL REPORT

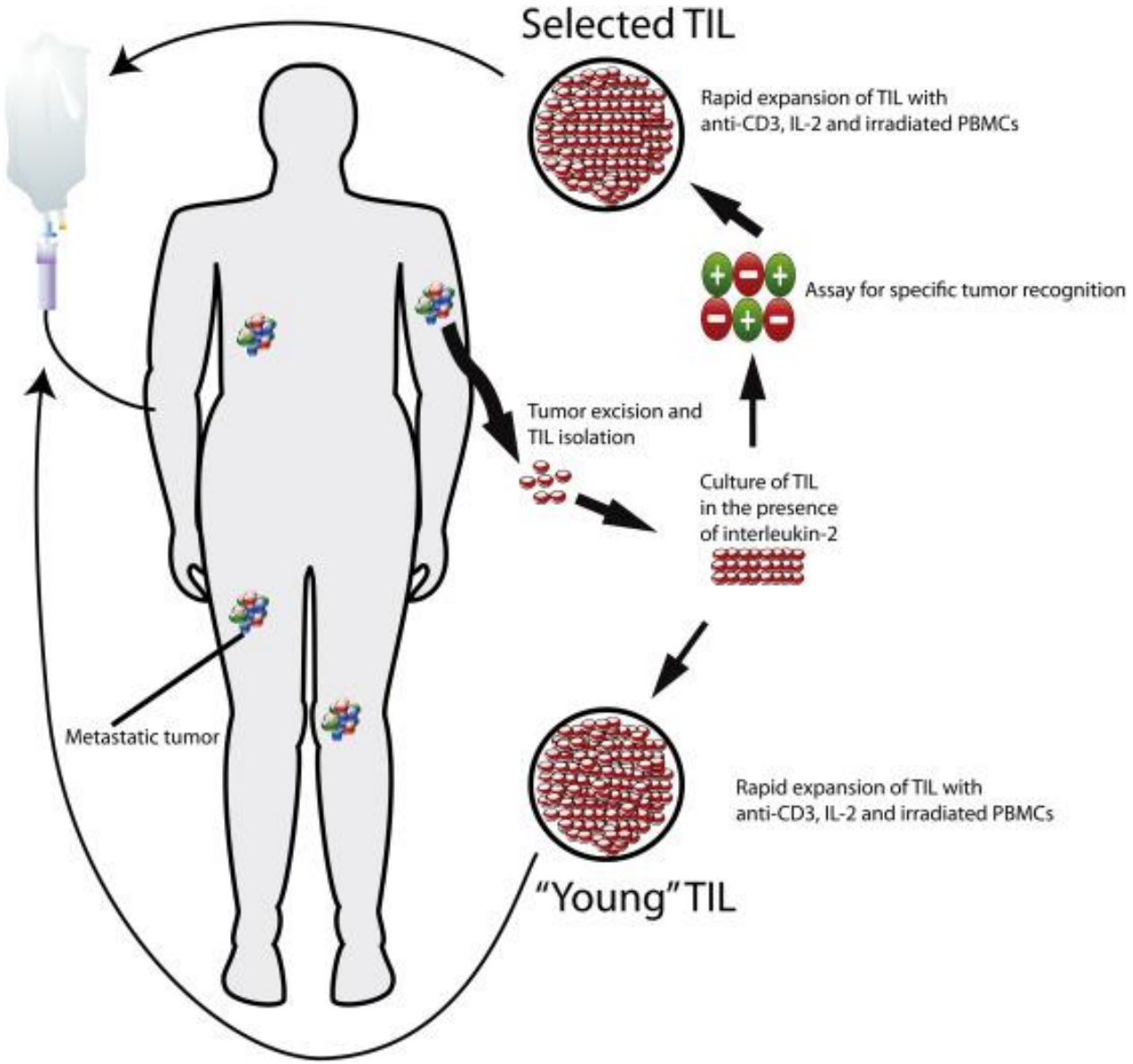
USE OF TUMOR-INFILTRATING LYMPHOCYTES AND INTERLEUKIN-2 IN THE IMMUNOTHERAPY OF PATIENTS WITH METASTATIC MELANOMA

A Preliminary Report

STEVEN A. ROSENBERG, M.D., PH.D., BEVERLY S. PACKARD, PH.D., PAUL M. AEBERSOLD, PH.D., DIANE SOLOMON, M.D., SUZANNE L. TOPALIAN, M.D., STEPHEN T. TOY, PH.D., PAUL SIMON, PH.D., MICHAEL T. LOTZE, M.D., JAMES C. YANG, M.D., CLAUDIA A. SEIPP, R.N., COLLEEN SIMPSON, R.N., CHARLES CARTER, STEVEN BOCK, M.D., DOUGLAS SCHWARTZENTRUBER, M.D., JOHN P. WEI, M.D., AND DONALD E. WHITE, M.S.

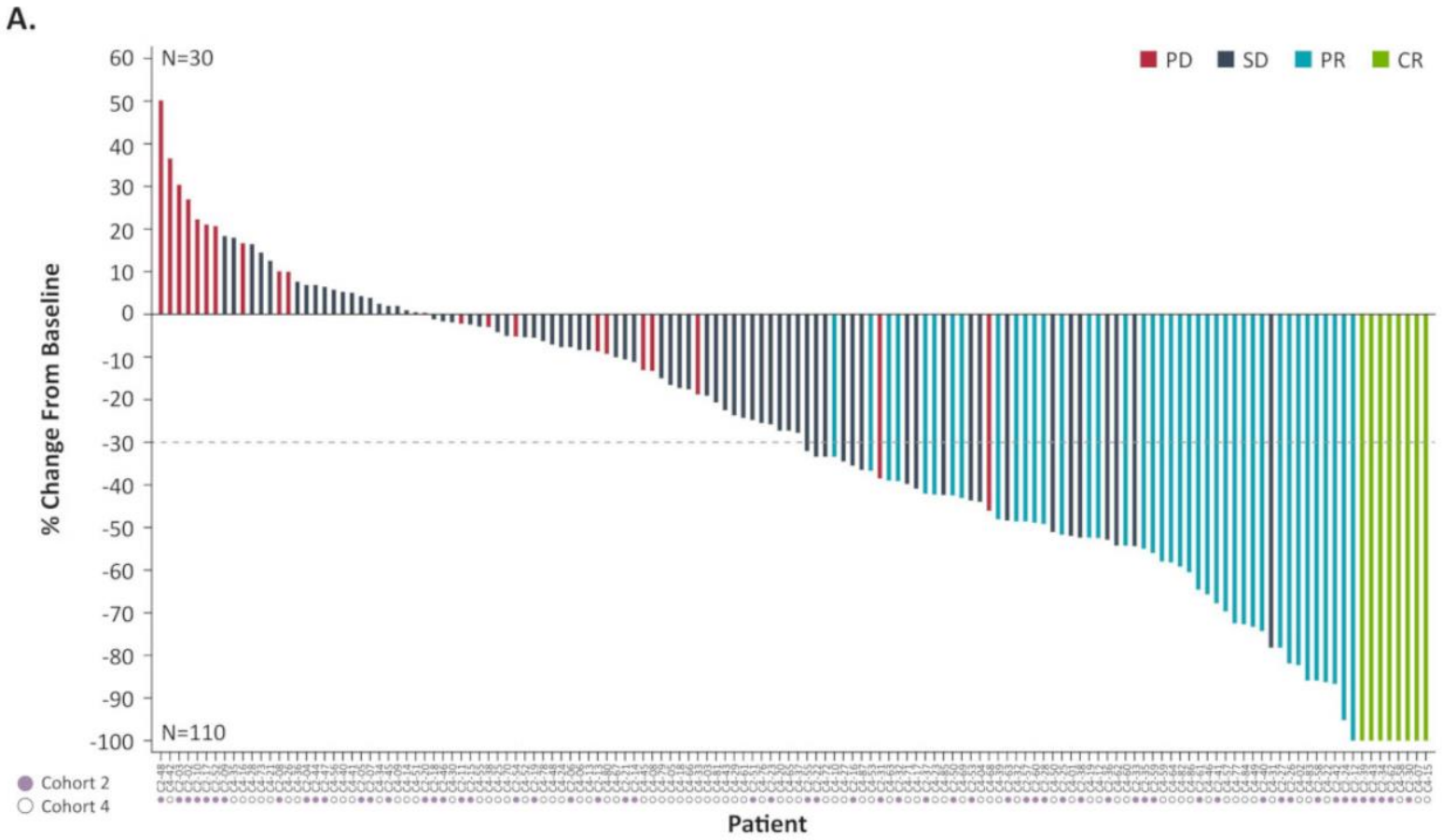
Background TILs

- Tumors are resected
- Fragments are cultured with interleukin-2 (IL-2)
  - Tumor-infiltrating lymphocytes exit the tumor
  - Hyperstimulated and expanded
- Patients undergo nonmyeloablative lymphodepletion
- Tumor-infiltrating lymphocytes are expanded and infused back into the patient
- IL-2 to tolerance



MH Geukes Foppen Mol Onc 2015

TIL Background



JITC 2022 Chesney

TIL Background

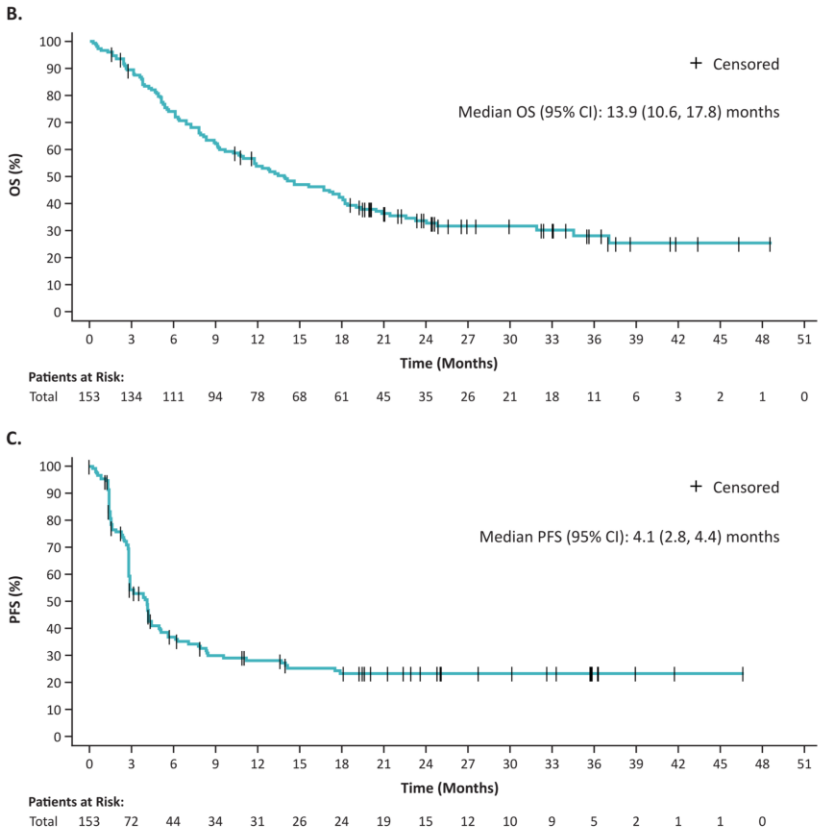


Figure 2 DOR in confirmed responders (PRor better) by IRC assessment per Response Evaluation Criteria in Solid Tumors V.1.1 (A), OS (B), and PFS (C) for pooled Cohorts 2 and 4. DOR, duration of response; IRC, independent review committee, NR, not reached; OS, overall survival; PFS, progression-free survival;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

JITC 2022 Chesney

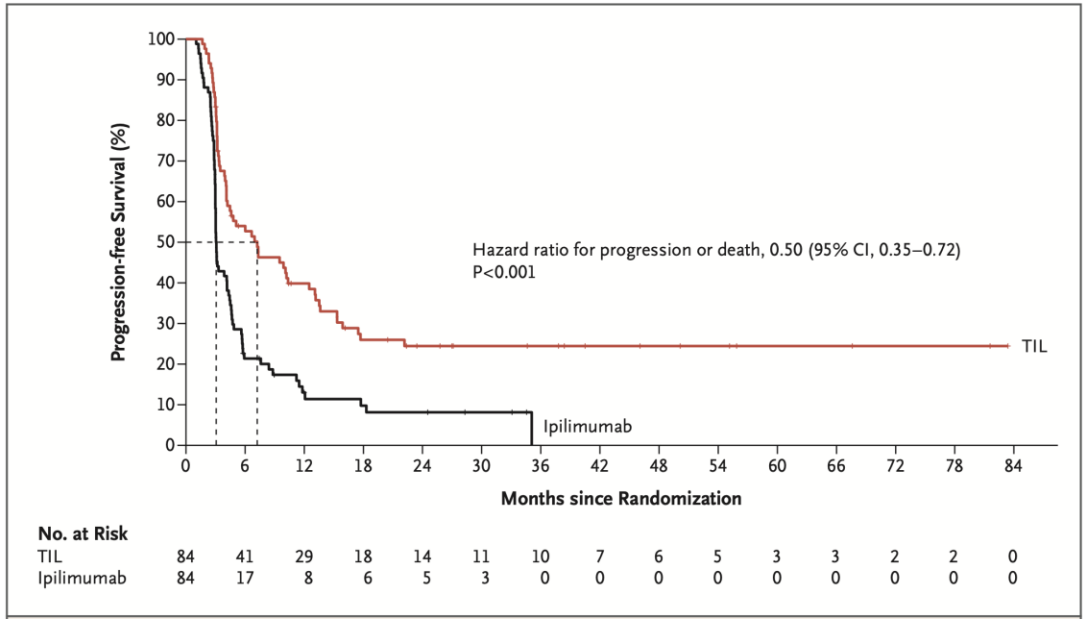


Figure 1. Progression-free Survival.

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

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.

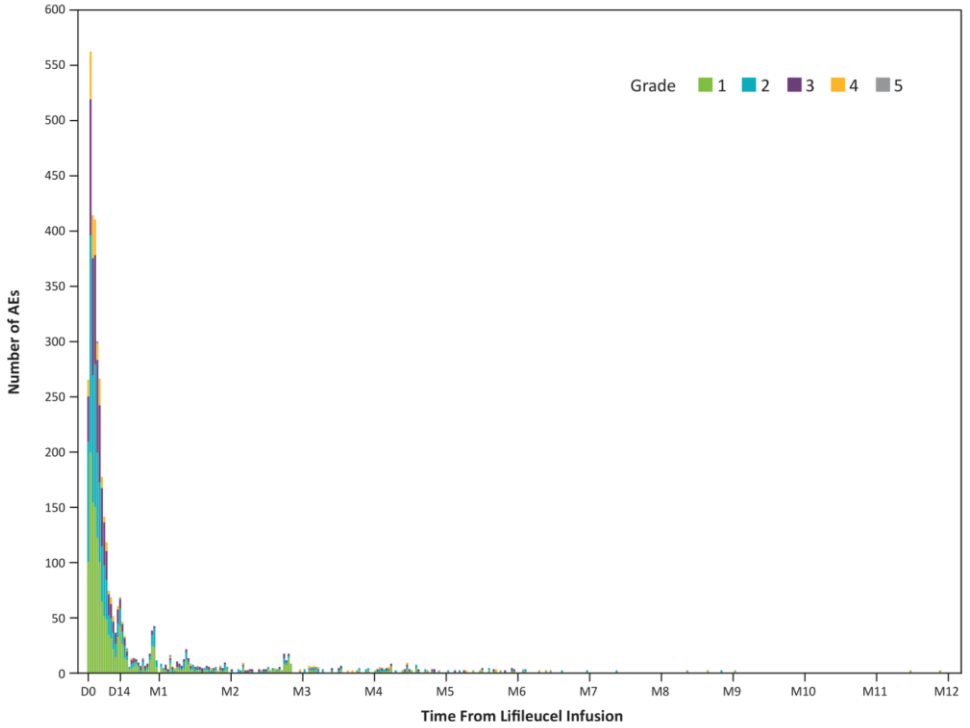


Figure 3 Incidence of AEs over time (Safety Analysis Set).* All occurrences of AEs were counted if a patient experienced a new onset of the same AE at different time points. If multiple records were reported on the electronic case report form because of toxicity grade decrease of the same AE that had 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%).

JITC 2022 Chesney


Joel Baumgartner, MD
Surgeon
CHELSEA FC
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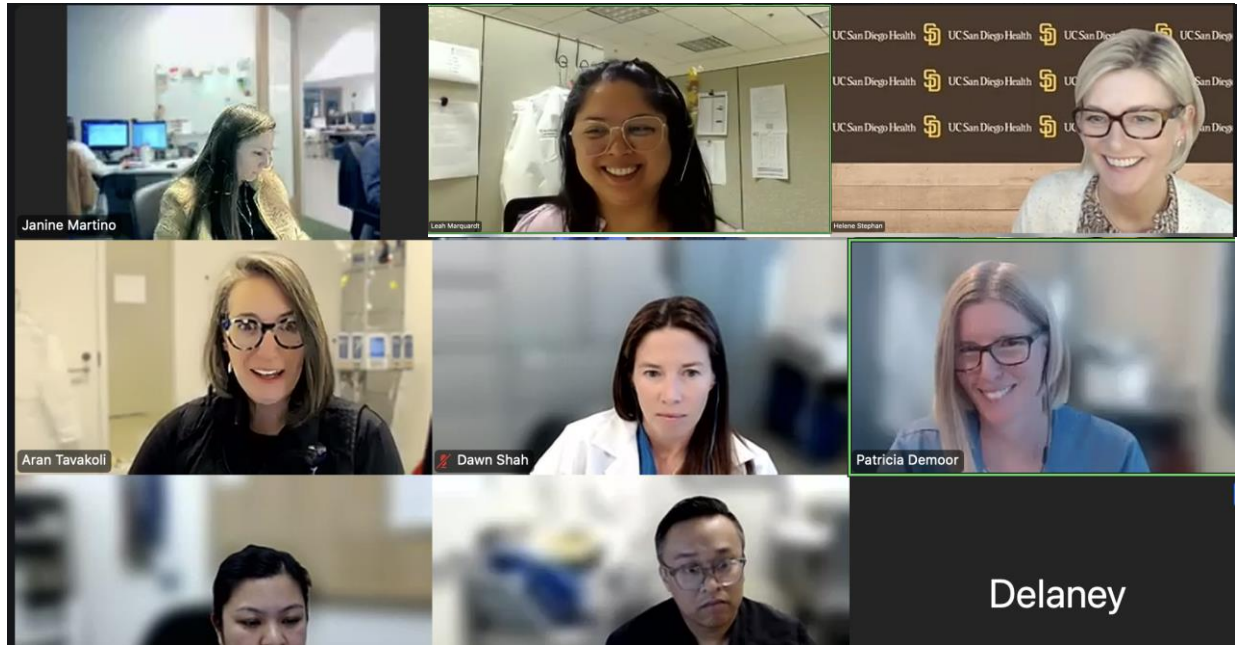
ConMed
stryker

TILs takes a team and processes



UCSD is an Authorized Treatment Center (ATC)

TIL coordinator
Stem cell lab
Finance
Cell Regenerative team
Administration

Surgery
Medical oncology
Social Work
Pharmacy
Nursing

Who is the correct patient for TILs?

- Minimum of 15x15x15mm lesion(s) for resection AND another site of residual disease
- Progressive disease after PD1 based therapy and BRAFi therapy if class 1 mutated (or intolerant)
- ECOG=0 to1
- Normal/near normal kidney, liver, heart and lung function
- NO active brain metastasis (stability AFTER treatment must be demonstrated)
- Rapidly progressive disease are NOT good TIL candidates

TIL Referrals

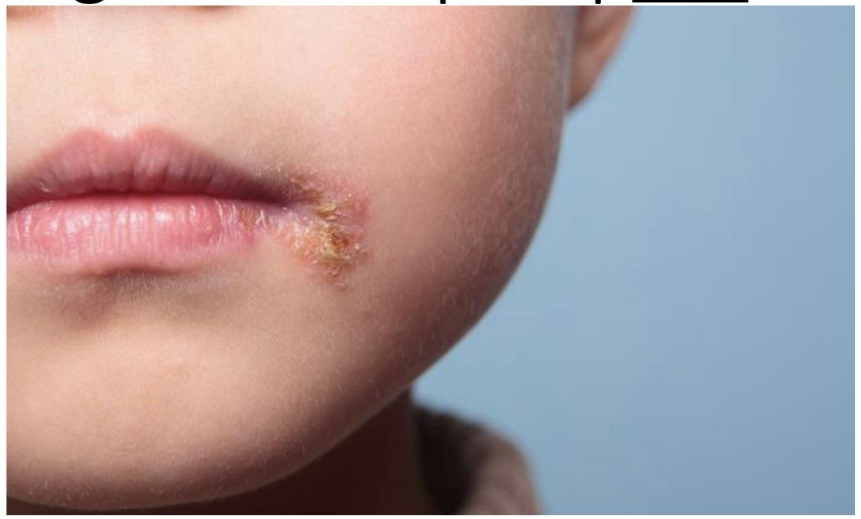
- Consider referral after PD1 progression
  - Can be seen while on second-line
  - Do not need to progress on BRAFi for a referral
- Work-up to consider prior to referral/first visit
  - PET/CT and MRI brain within 30 days
  - Echocardiogram and pulmonary function tests within 90 days

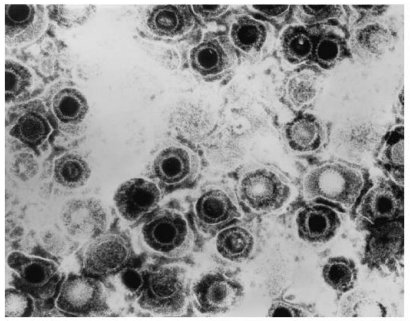
- TIL coordinators: Leah Marquardt, Edison Go-Soco
- 858-822-6100

Intralesional injections

- TLR agonists
- SRS
- Oncolytic virus
- STING agonist
- Cytokine
- etc

Talimogene laherparepvec



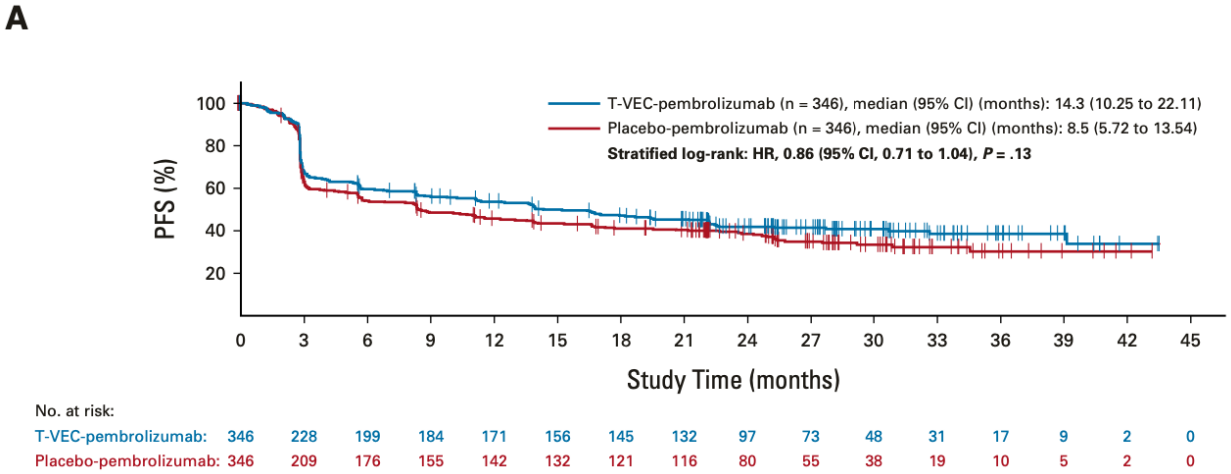


HSV-1 (JS1 strain)

- Deleted for ICP34.5=more selective tumor replication
- Deleted for ICP47=more antigen presentation better growth
- Insertion of GM-CSF=?enhance immune response

Combination of IT therapy and checkpoints

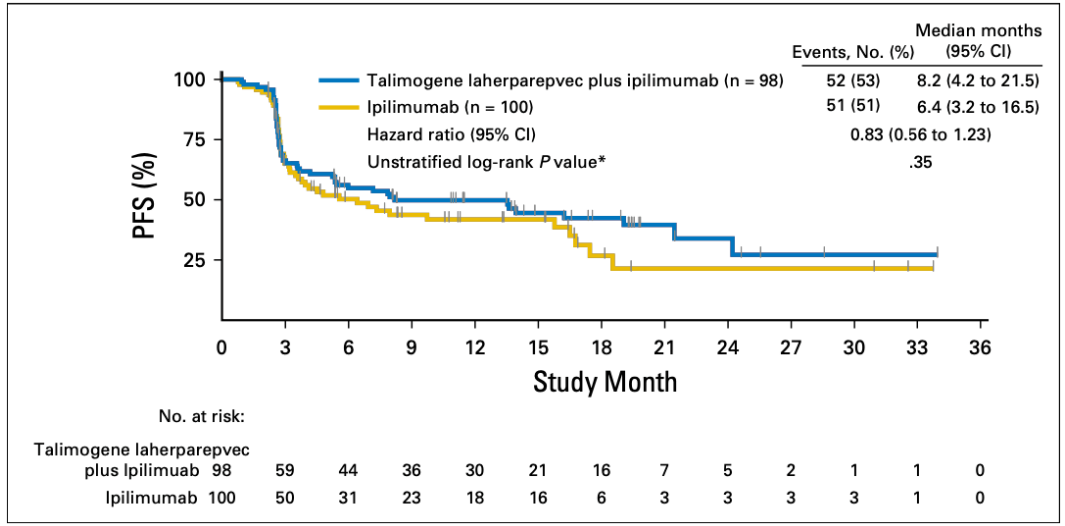
- Talimogene Laherparepvec in Combination With Pembrolizumab Versus Pembrolizumab



Immune therapy naive

Chesney JCO 2022

- Talimogene Laherparepvec in Combination With Ipilimumab Versus Ipilimumab



Zero to one prior line of therapy

Chesney JCO 2018

IGNYTE Study design (Anti-PD-1 failed melanoma cohort)

Anti–PD-1–failed cutaneous melanoma cohort (140 pts; 16 pts treated in prior cohorts: Total 156)

Screening — *28 days* → **First dose** RP1 1×10^6 pfu/mL — *2 weeks* → **RP1+nivolumab**[a] 1×10^7 pfu/mL, 240 mg — *2 weeks* → **Nivolumab** 240 mg — *2 weeks* → **Nivolumab** 480 mg (Q4W)

100-day safety follow-up

Cycle 1 | Cycles 2–8 | Cycle 9 | Cycles 10–30[b]

3-year follow-up from last patient enrolled

***Tumor response assessment**: Radiographic imaging (CT) at baseline and every 8 weeks from first dose and every 12 weeks after confirmation of response*

Primary objectives
- To assess the safety and efficacy (by independent central review [mRECIST]) of RP1 in combination with nivolumab

Secondary objective
- **ORR by investigator review (mRECIST)**
- To assess the efficacy of RP1 in combination with nivolumab as determined by DOR, CR rate, DCR, PFS, by central & investigator review, 1-year and 2-year OS

Key eligibility
Advanced melanoma having ***confirmed progression while on prior anti-PD-1 therapy***[c]; at least 1 measurable and injectable lesion (≥1 cm LD), including deep/visceral; adequate organ function; no prior treatment with oncolytic therapy; ECOG performance status 0–1

Criteria for prior anti–PD-1–failure
≥8 weeks of prior anti–PD-1, confirmed progression while on anti–PD-1; anti–PD-1 must be the last therapy before the clinical trial. Patients on prior adjuvant therapy must have progressed while on prior adjuvant treatment (progression can be confirmed by biopsy)

Primary analysis to be conducted when all patients have ≥ 12 months follow up

[a]Dosing with nivolumab begins at dose 2 of RP1 (C2D15). [b]Option to reinitiate RP1 for 8 cycles if criteria are met.
c. Non-neurological solid tumors CR, complete response; CT, computed tomography; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; LD, longest diameter; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; pfu, plaque-forming unit; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

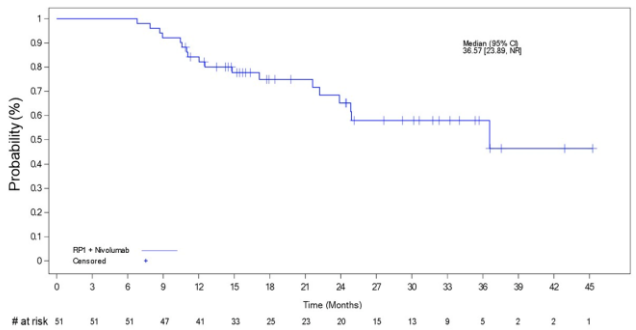
2024 ASCO ANNUAL MEETING #ASCO24

PRESENTED BY: **Dr. Michael K. Wong**, MD, PhD, FRCPC

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

VUSOLIMOGENE ODERPAREVEC (RP1)
rHSV-1hGM-CSF/GALV-GP R-

Duration of Response



>6 months	>12 months	>18 months	>24 months
100%	84.2%	74.9%	65.2%

The median follow up for responders is 27.9 months (range 10.5-55.5)

Conclusions

RP1 combined with nivolumab in melanoma patients who had **confirmed progression** on prior anti-PD-1 continues to show:
- Deep and durable, systemic responses
- A favorable safety profile, with generally 'on target' and transient grade 1–2 side effects indicative of systemic immune activation

- **Approximately 1 in 3 patients experienced a response**
  - 27% ORR in patients had prior anti–PD-1/anti–CTLA-4
  - 34% ORR in patients who had primary resistance to their immediate prior anti-PD-1 therapy
  - Clinically meaningful activity was seen across all enrolled subgroups
  - Approximately 55% of patients experienced clinical benefit (CR + PR + SD)

- **Responses were highly durable**
  - All patients followed for at least 12 months
  - All responses lasted at least 6 months, with median DOR >36 months

Based on these results, a confirmatory randomized phase 3 study is in the start-up phase (IGNYTE-3; NCT06264180); Poster #TPS9604
Centrally reviewed primary & secondary endpoint data from the study will be presented separately once available

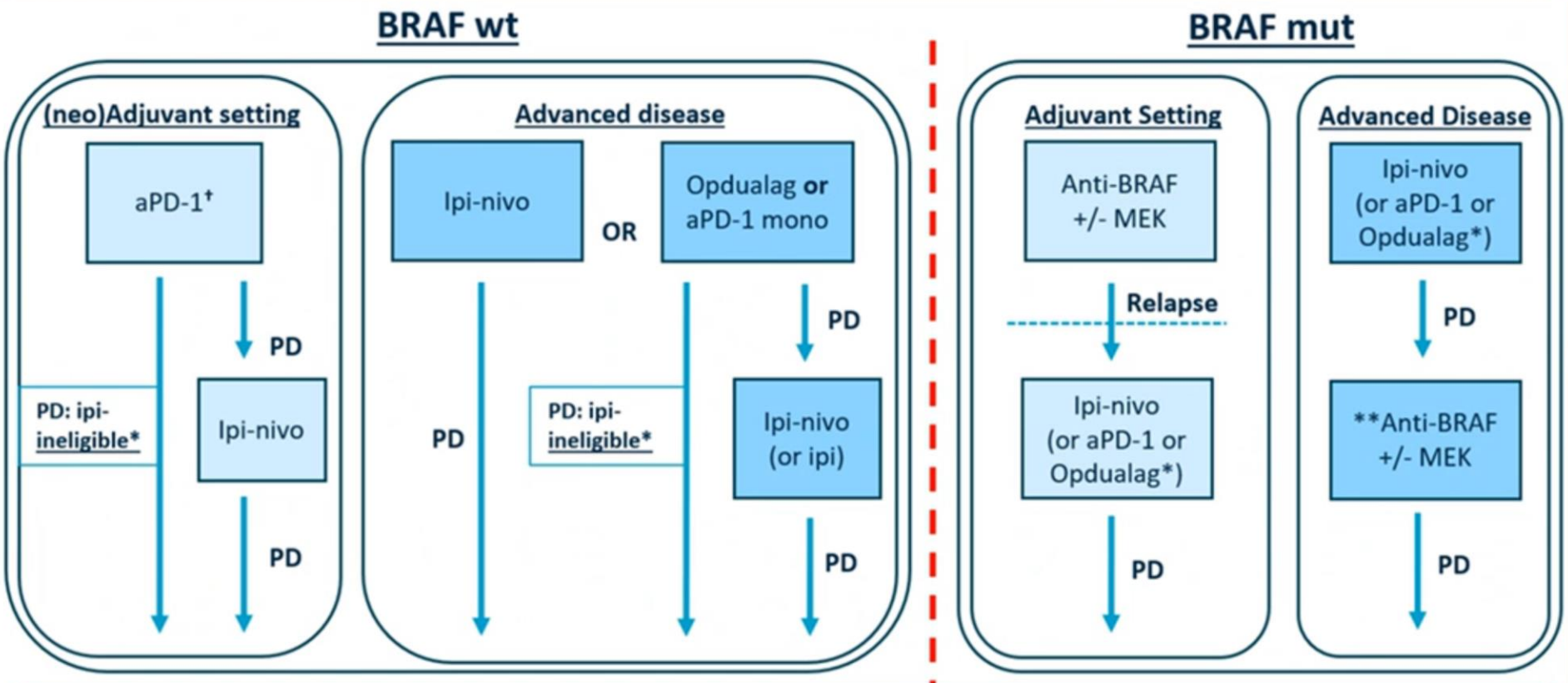
Wong ASCO 2024

IGNYTE-3 (RP1-104) Eligibility Guide

Replimune

Please contact the Replimune Medical Monitor with any questions about eligibility: RP1-104_EnrollmentForm@replimune.com

Confirmed unresectable or metastatic Stage IIIb through IV/M1a through M1d cutaneous melanoma



Key Inclusion ✓

- Two scans ≥ 4 weeks apart to confirm PD (can include baseline scan)
- ≥ 1 measurable lesion and ≥ 1 injectable lesion
- ECOG 0 to 1 / Lansky PS ≥ 80

Key Exclusion ⊘

- Primary mucosal or uveal melanoma
- > 2 lines of systemic therapy for advanced disease
- Active CNS metastases
- Serum LDH > 2x ULN

IGNYTE-3

*Ipilimumab ineligibility must be based on a clinical rationale. Patient refusal or Investigator treatment preference are not sufficient.

† If a patient received neo-adjuvant Ipi-Nivo, re-treatment is not required if progression/relapse is within 6 months from the last dose.

**One line of BRAF-directed therapy (with or without a MEK inhibitor) can be the most recent systemic treatment administered before randomization.

Right around the corner—ASCO 2025

ABSTRACTS & PRESENTATIONS
2025 ASCO Annual Meeting - Poster Session

Presenter:
Milton Jose De Barros E Silva, MD

ctDNA versus 18F-FDG PET-CT in predicting long-term disease control in patients with advanced melanoma undergoing immune checkpoint blockade therapy.

Abstract: 9559 | Poster Bd #: 42

ABSTRACTS & PRESENTATIONS
2025 ASCO Annual Meeting - Poster Session

Presenter:
Mark Schuiveling, MD

AI-detected tumor-infiltrating lymphocytes and response to PD-1 based treatment in advanced melanoma.

Abstract: 9541 | Poster Bd #: 24

ABSTRACTS & PRESENTATIONS
2025 ASCO Annual Meeting - Poster Session

Presenter:
Caroline Robert, MD, PhD

Use of artificial intelligence to identify high risk profiles in early stage melanoma patients from pathology slides.

Abstract: 9579 | Poster Bd #: 62

ABSTRACTS & PRESENTATIONS
2025 ASCO Annual Meeting - Poster Session

Presenter:
Gino Kim In, MD, MPH

Response analysis for injected and non-injected lesions and of the safety and efficacy of superficial and deep/visceral RP1 injection in the registrational cohort of anti–PD-1–failed melanoma patients of the IGNYTE...

Abstract: 9537 | Poster Bd #: 20

ABSTRACTS & PRESENTATIONS
2025 ASCO Annual Meeting - Rapid Oral Abstract Session

Presenter:
Jason Alan Chesney, MD, PhD

OBX-115 engineered tumor-infiltrating lymphocyte (TIL) cell therapy with regulatable membrane-bound IL15 (mbIL15) in patients (pts) with immune checkpoint inhibitor (ICI)–resistant advanced melanoma: Phase 1 results of...

Abstract: 9517

ABSTRACTS & PRESENTATIONS
2025 ASCO Annual Meeting - Poster Session

Presenter:
Hussein A. Tawbi, MD, PhD

RELATIVITY-020: Intracranial (IC) activity of nivolumab + relatlimab (NIVO + RELA) in patients (pts) with PD-(L)1 refractory melanoma with melanoma brain metastases (MBM).

Abstract: 9525 | Poster Bd #: 8

Non-Melanoma Skin Cancer

Disclosures

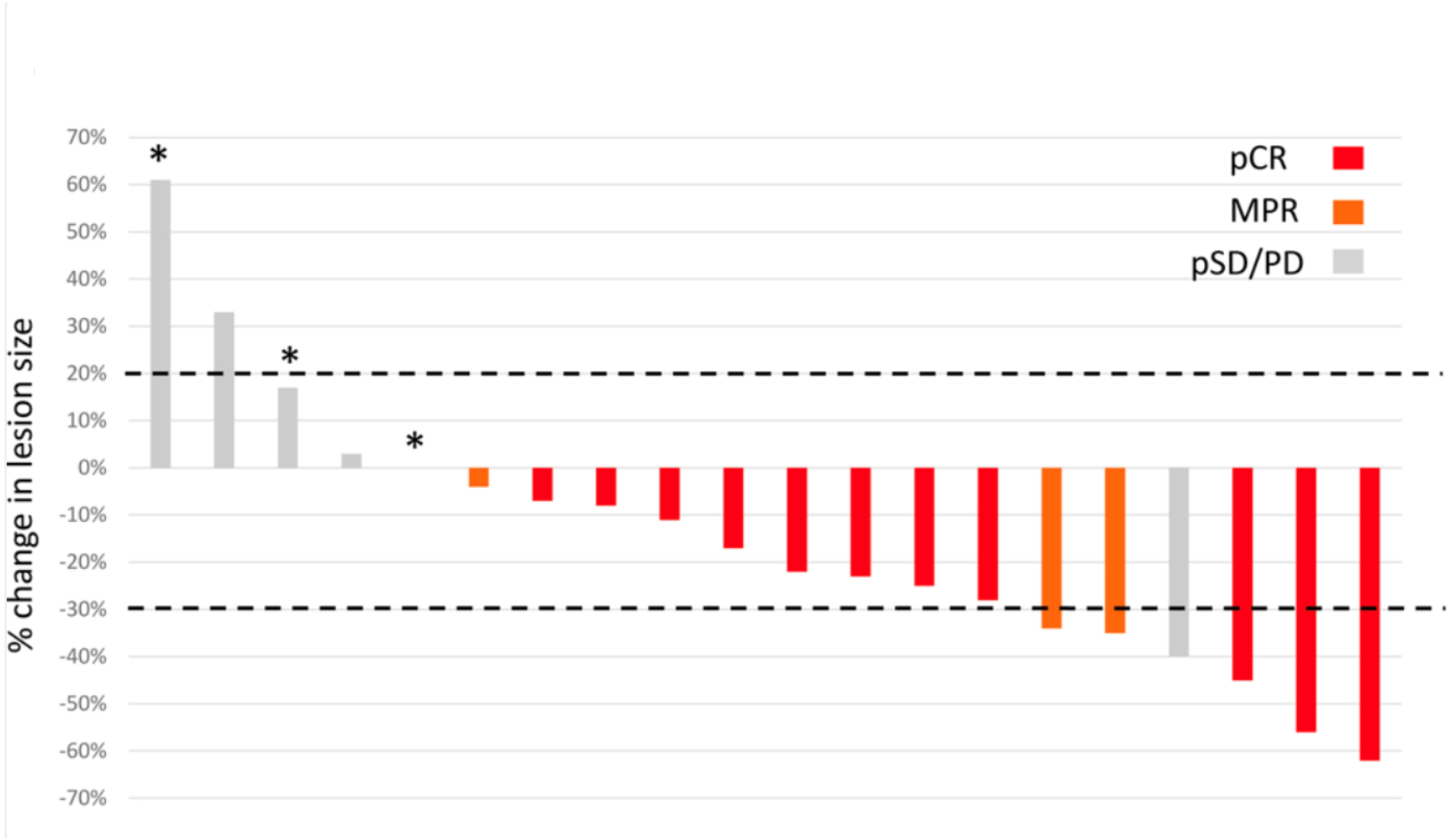
- Consulting: Regeneron
- Research funding: BMS

- Local investigator on clinical trials
- Associate Professor of Medicine UC San Diego
- Staff physician VAMC San Diego

Pilot Neoadjuvant PD1 in CSCC

Table 1. Patient characteristics.

Patient characteristics		*N* = 20
Age, average (SD)		68.4 (10.9)
Gender, *n* (%)	Female	2 (10)
	Male	18 (90)
Location, *n* (%)		
	Cheek	2 (10)
	External auditory canal	1 (5)
	Forehead	3 (15)
	Neck	1 (5)
	Neck nodes	7 (35)
	Nose	1 (5)
	Parotid	2 (10)
	Scalp	3 (15)
Recurrent disease, *n* (%)		
	No	13 (65)
	Yes	7 (35)
T classification, *n* (%)		
	1	2 (10)
	2	1 (5)
	3	6 (30)
	4	2 (10)
	x	9 (45)
N classification, *n* (%)		
	0	5 (25)
	1	4 (20)
	2b	9 (45)
	2c	1 (5)
	3b	1 (5)
Clinical stage, *n* (%)[a]		
	III	8 (40)
	IV	12 (60)



Ferrarotto et al. Clin Cancer Res. 2021

Phase II Neoadjuvant PD1 in CSCC

- Patients with resectable Stage II, III, or IV (M0) CSCC
  - Up to 4 doses of cemiplimab
  - Primary endpoint was pCR
  - 51% pCR, 13% MPR

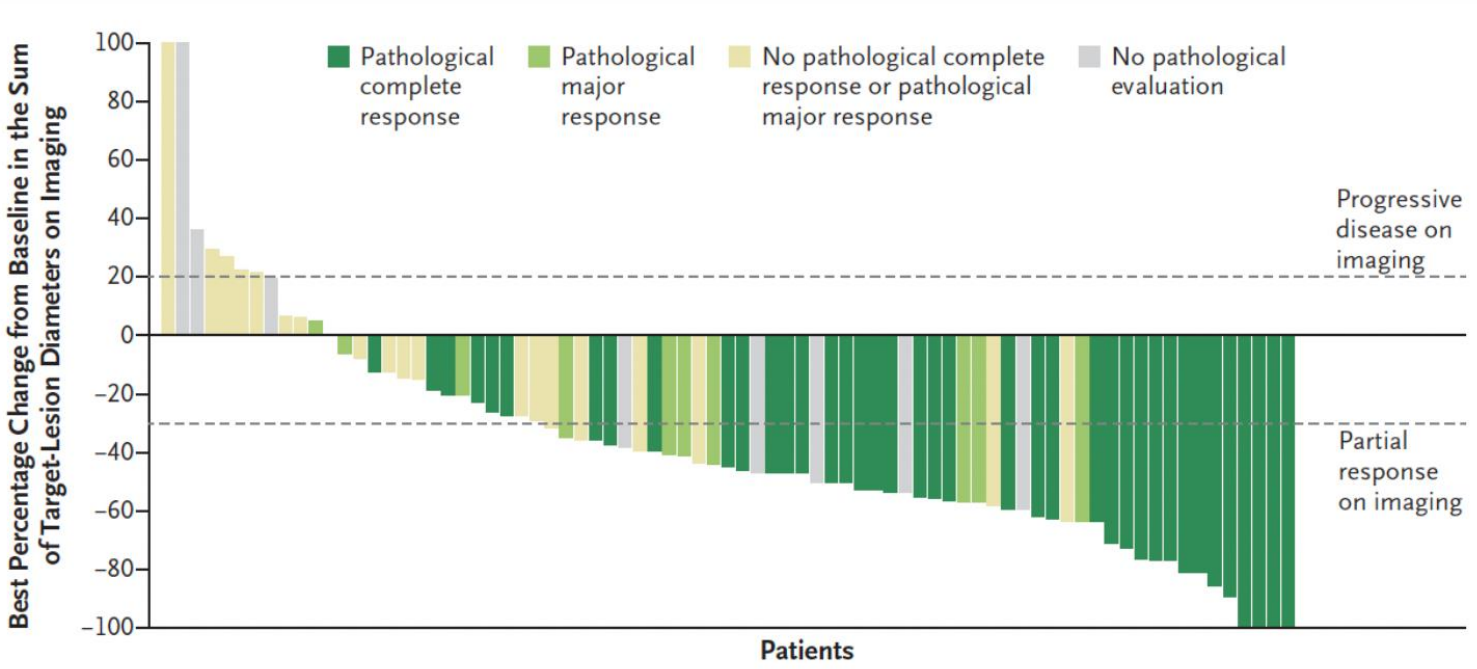


Table 1. Characteristics of the 79 Patients at Baseline.*

Characteristic	Value
Median age (range) — yr	73 (24–93)
Male sex — no. (%)	67 (85)
Race — no. (%)†	
White	69 (87)
Other	2 (3)
Not reported	8 (10)
Not Hispanic or Latinx — no. (%)†	74 (94)
Primary tumor site — no. (%)	
Head and neck	72 (91)
Trunk, arms, and legs	7 (9)
Stage group — no. (%)‡	
II	5 (6)
III	38 (48)
IV (M0)	36 (46)
Tumor stage at screening — no. (%)‡	
TX	23 (29)
Tis	1 (1)
T1	4 (5)
T2	10 (13)
T3	39 (49)
T4a	2 (3)
Node stage at screening — no. (%)‡	
NX	1 (1)
N0	31 (39)
N1	13 (16)
N2§	11 (14)
N2b	9 (11)
N2c	1 (1)
N3¶	1 (1)
N3a	1 (1)
N3b	11 (14)
ECOG performance-status score — no. (%)‖	
0	60 (76)
1	19 (24)

Gross et al. NEJM. 2022

Neoadjuvant PD1 in CSCC

Pathological response	% of patients N = 79	95% CI
Complete response	51	39–62
Major response (≤ 10% viable tumor)	13	6–22
No pCR or MPR (≥ 10% viable tumor)	25	—
No pathological evaluation	11	—

Radiological response	% of patients N = 79	95% CI
Complete response	6	—
Partial response	62	—
Progressive disease	10	—
Non-evaluable	1	—

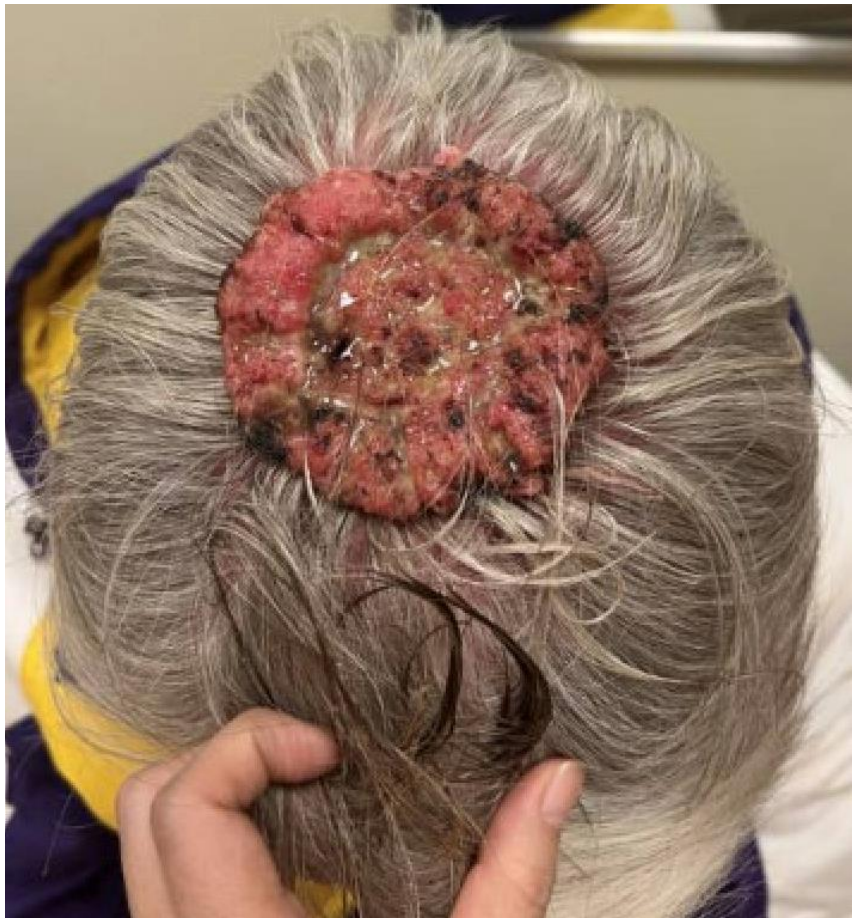
Neoadjuvant PD1 in CSCC

Event-free survival					
	All patients who received neoadjuvant cemiplimab (N = 79)	Patients with pCR (n = 40)	Patients with MPR (n = 10)	Patients with pathological partial response (n = 7)	Patients with no response or not evaluable (n = 22)
Median (95% CI) event-free survival, mos	NR (NE–NE)	NR (NE–NE)	NR (8.3–NE)	NR (NE–NE)	25 (8–NE)
12-month event-free survival, % (95% CI)	89% (79–94)	95% (81–99)	89% (43–98)	100% (NE–NE)	72% (44-88)
Events, n (%)	11 (14%)	3 (8%)	1 (10%)	0	7 (32%)
Progressive disease that precludes surgery	2 (3%)	0	0	0	2 (9%)
Disease recurrence	3 (4%)	0	1 (10%)	0	2 (9%)
Death	6 (8%)	3 (8%)	0	0	3 (14%)
Censored patients, n (%)	68 (86%)	37 (93%)	9 (90%)	7 (100%)	15 (68%)

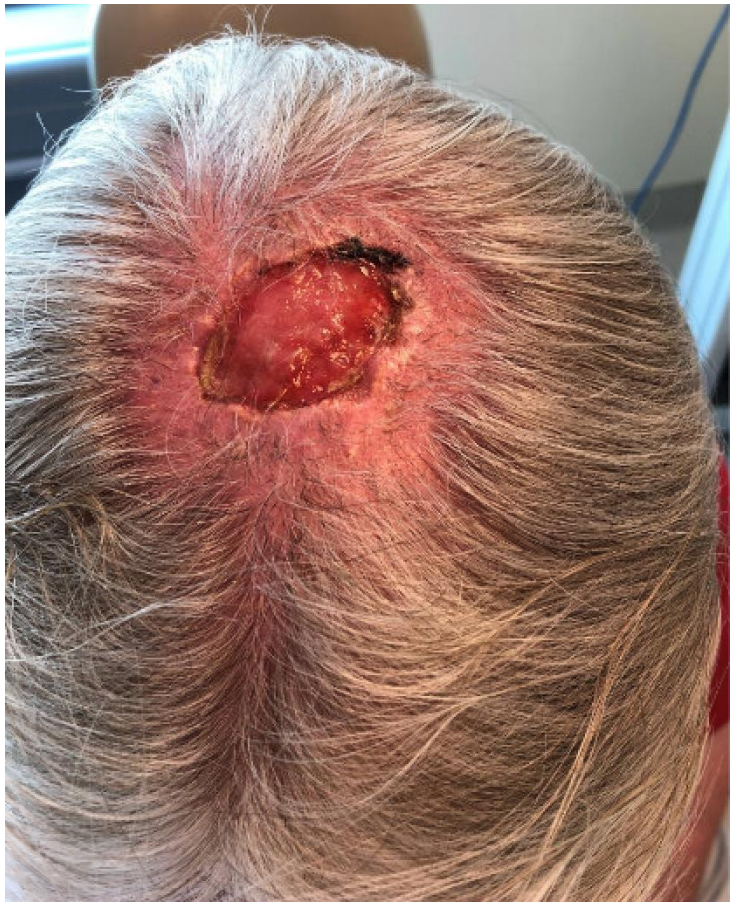
*Cemiplimab is not FDA-approved for neoadjuvant cSCC.

Neoadjuvant PD1 in CSCC

- 58 yo male with a Stage III (AJCC T3) CSCC of the scalp



4 cycles of cemiplimab



Post surgery

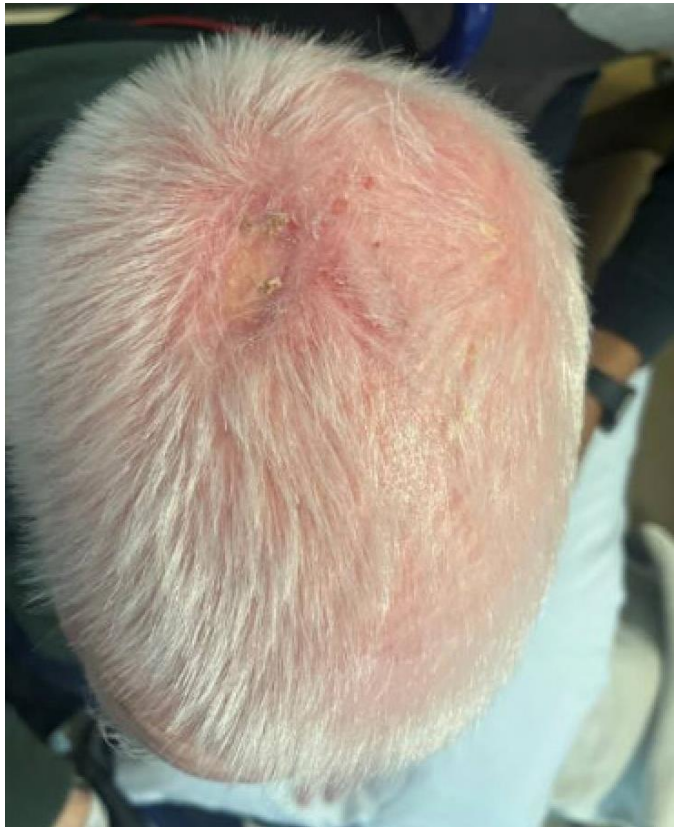
FINAL PATHOLOGIC DIAGNOSIS:
A: Excision tumor scalp:
-Skin with chronic inflammation, giant cell formation and scar consistent with prior procedure.
-No residual squamous cell carcinoma identified.

- Given pCR, no adjuvant therapy was recommended
- Doing well with no recurrence

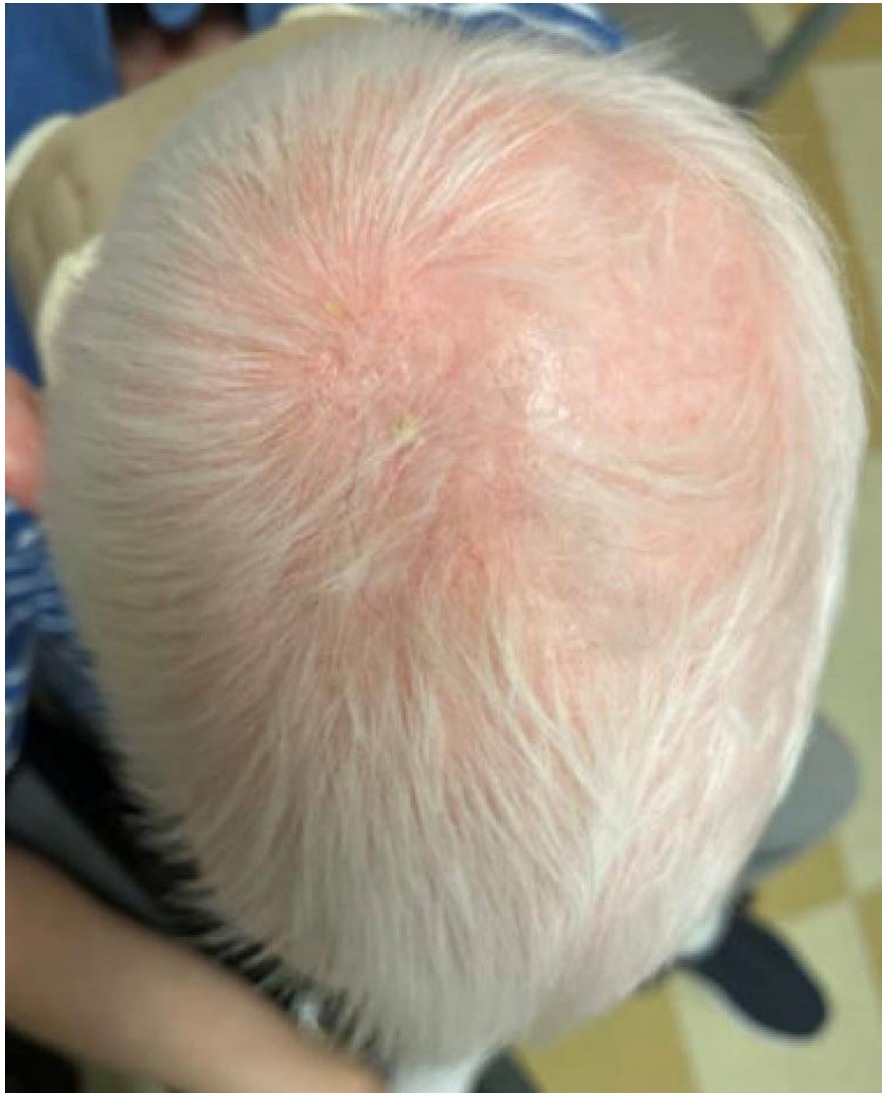
Definitive Primary Approach with PD1

- 83 yo male with a large fleshy CSCC of the scalp, ECOG 3-4
- Did not tolerate awake Mohs, cannot remain still for radiation

5 cycles of cemiplimab



Definitive Primary Approach with PD1

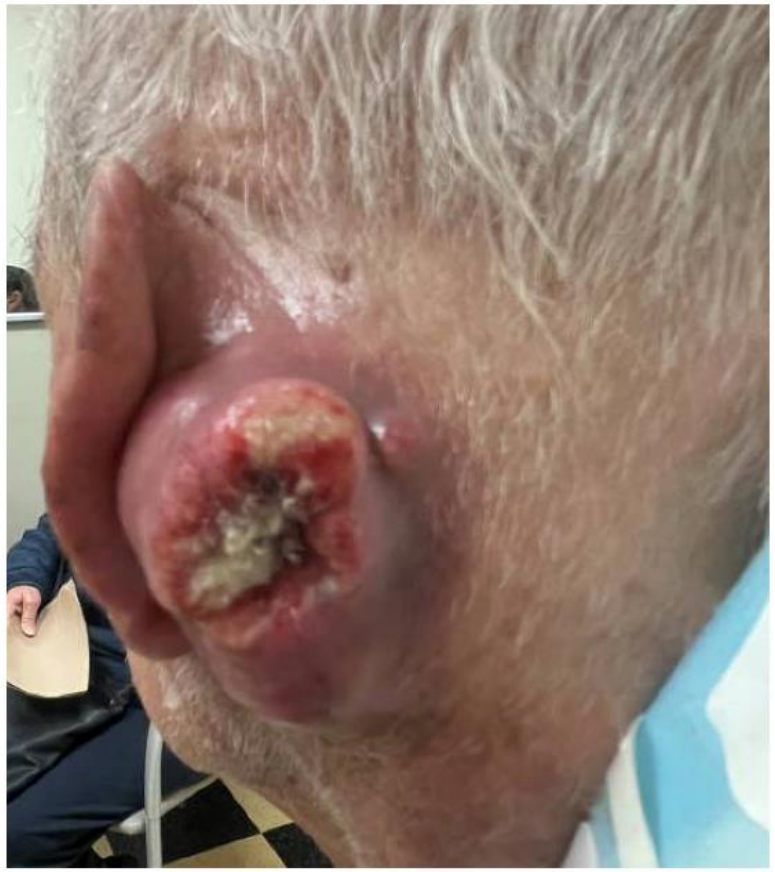


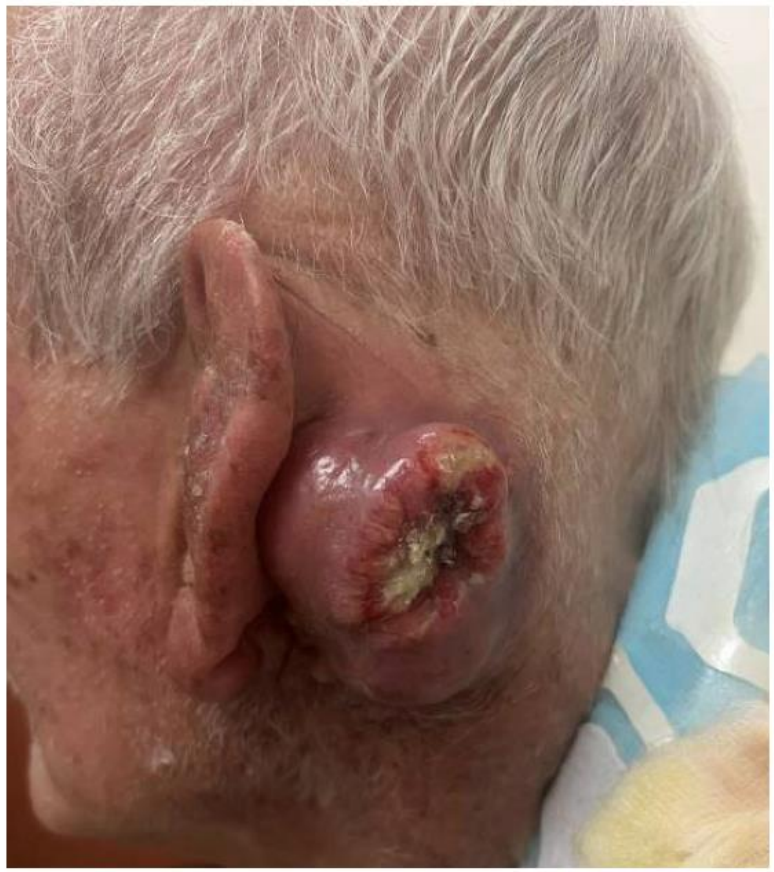
Treated for additional 6 months beyond CR

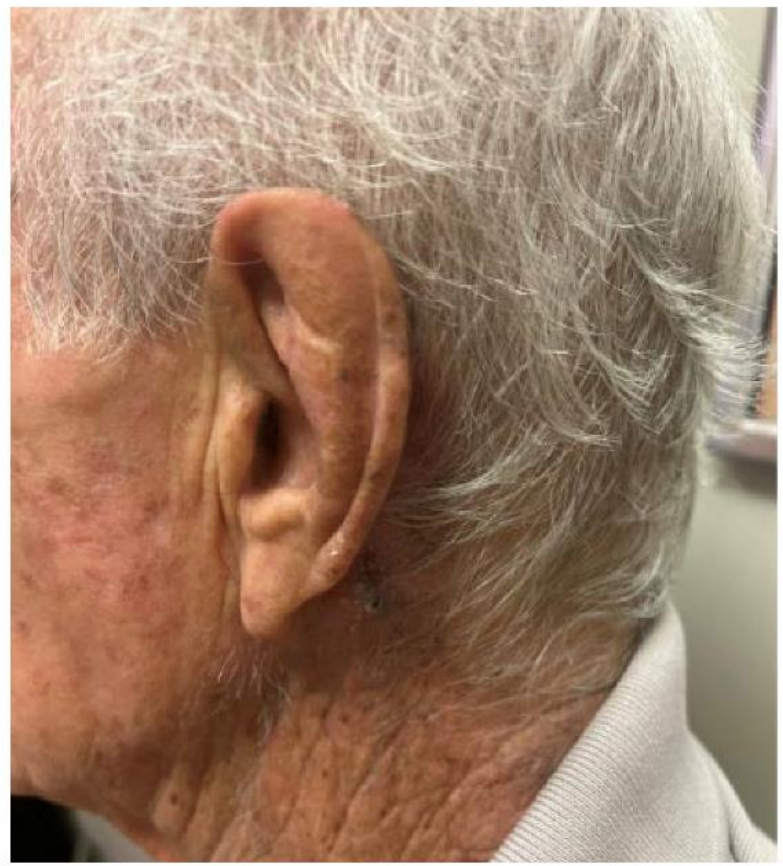
Not based on any robust data

Rechallenge concerns

Definitive Primary Approach with PD1







78 yo male with Parkinson’s disease, ECOG 3, CR after 4 cycles of cemiplimab
Received an additional 5 cycles (3.8 months) before stopping for psychiatric issues

Primary Immunotherapy Monotherapy (PRIMO) in Locally Advanced CSCC

Background

- Cutaneous squamous cell carcinoma (cSCC) is the second most common form of skin cancer in the United States.
- Deaths from cSCC now exceed those for melanoma due to the subgroup of patients who present with locally advanced (LA), recurrent, or metastatic disease that is not amenable to curative surgery or radiation.
- Advancements in immunotherapy have offered improved oncologic outcomes in the salvage and, more recently, in the neoadjuvant setting.
- Given that neoadjuvant immunotherapy produces impressive responses prior to surgery, the need for additional therapy is unclear.
- Our institution has evolved toward the use of PRIMO in patients with LA cSCC, reserving surgery or radiation for progression only.
- This is our initial report on the efficacy of PRIMO in a cohort of patients with both resectable and unresectable non-metastatic LA cSCC.

Methods

- A total of 36 patients with a median follow-up of 13.5 months and with primary or recurrent LA cSCC (AJCC 8th T3-4 or node positive or in-transit metastases) treated with PRIMO between 2017-2023 were included in an IRB-approved database.
- Patients with distant metastases were excluded.
- Patients were treated with IV cemiplimab (350 mg q 3 weeks) or pembrolizumab (200 mg q 3 weeks)
- Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were scored according to iRECIST criteria.
- Kaplan-Meier analysis was used to estimate overall survival (OS) and progression-free survival (PFS)

Conclusions

PRIMO for locally advanced cSCC produces high rates of **durable responses.**

This is an attractive alternative to the emerging neoadjuvant paradigm that deserves prospective validation with longer term follow up.

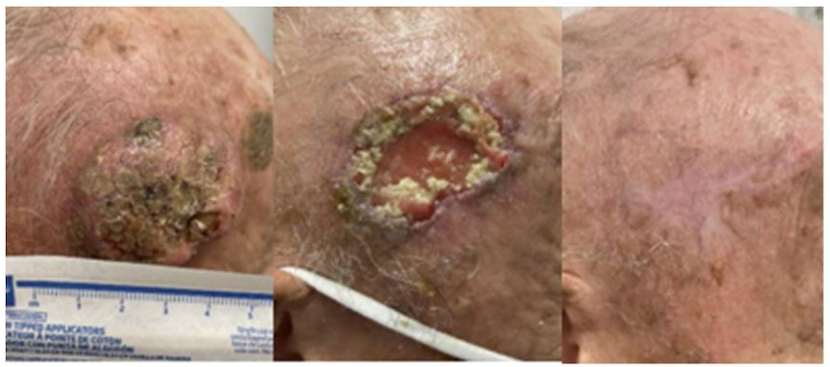


Figure 1: An 89-year-old man with a 4.0 cm SCC of right temple, AJCC 8th T3N0M0, stage III. Surgery and radiation were deferred due to age and frailty. Lesion before cemiplimab (left), after 4 cycles (middle), and after completion of 22 cycles (right). Patient achieved a complete response by the 12th cycle and remains in remission two years from diagnosis.

Results

Table 1. Patient Characteristics

Male:Female	9 (25%): 27 (75%)
Age (mean (SD))	80.3 (8.9)
Follow up, months (median [IQR])	13. 5 [8.0, 20.5]
Head/Neck	32 (89%)
Non-HN	4 (11%)

Table 2. Tumor Characteristics

Location	Head/Neck	32 (89%)
	Non-HN	4 (11%)
Primary vs. Recurrent	Primary	10 (28%)
	Recurrent	26 (72%)
T-stage	T0	6 (17%)
	T2	3 (8%)
	T3	10 (28%)
	T4	13 (36%)
	Tx - ITM	4 (11%)
N-stage	N0	24 (67%)
	N1	5 (14%)
	N2a	1 (3%)
	N2b	3 (8%)
	N2c	1 (3%)
	N3	2 (6%)
M-stage	M0	0 (0%)

Table 3. Treatment Characteristics

Type of immunotherapy	Pembrolizumab	5 (14%)
	Cemiplimab	31 (86%)
# of infusions (median [IQR])	13 [7.0, 18.8]	
Therapy modified due to toxicity?	No	24 (67%)
	Yes	12 (33%)

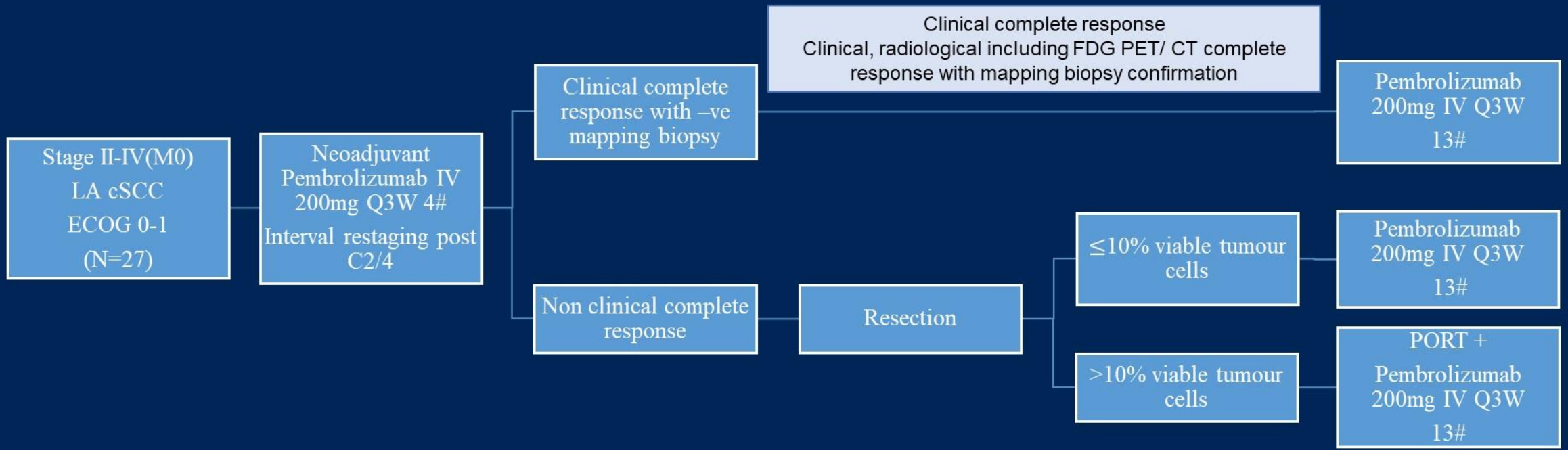
Table 4. Best Response and Ultimate Progression Rates

Best Initial Response		Eventual Progression on/after immunotherapy?	
		No	Yes
Complete response	15 (42%)	15 (100%)	0 (0%)
Partial response	14 (39%)	11 (79%)	3 (21%)
Stable disease	3 (8%)	0 (0%)	3 (100%)
Progressive disease	4 (11%)	0 (0%)	4 (100%)
Total	36 (100%)	26 (72%)	10 (28%)
Duration of response in months (median [IQR])		15.5 [8.8, 23.2]	3.0 [2.0, 6.8]

Table 5. Survival Rates

	Overall Survival (95% CI)
1 year	76% (63-92)
2 year	64% (48-87)
	Progression-Free Survival (95% CI)
1 year	72% (58-88)
2 year	51% (35-73)

De-Squamate Study Design



Primary Endpoint

Histopathological response as determined by a combination of pCR: (no viable tumour cells) + mPR: (≤10% viable tumour cells) + Clinical CR following up to 4 cycles of neoadjuvant therapy

Clinical Practice Considerations

- Neoadjuvant PD1 in CSCC
  - Select T3 or higher
  - Recurrent disease
  - Node positive
- In-transit metastases should be considered for definitive PD1
- All unknown primary SCCs should be sequenced at the time of biopsy

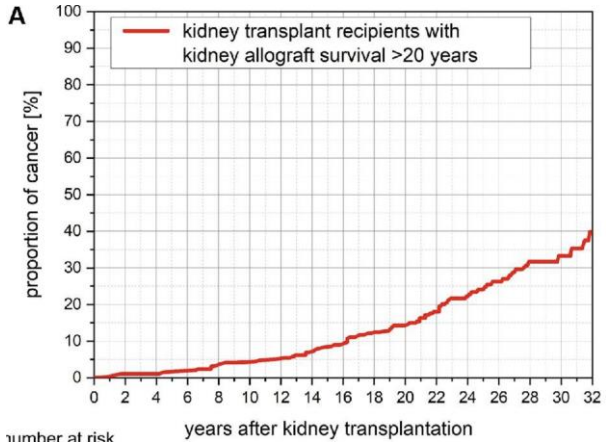
Neoadjuvant PD1 in High-risk Resectable BCC

- Phase 2 study of **Ne**oadjuvant **O**pdualag vs **N**ivolumab (**NEON**)
- Randomized 2:1
- High-risk BCC defined as 2.0 cm or greater in H&N region or BCC that is 4.0 cm or greater for trunk/extremities
- Technically resectable but at increased risk for cosmetic disfigurement, functional deficits, poor oncologic control, or anticipated to require extensive skin grafting or free flap reconstruction
- Open to enrollment

Solid Organ Transplant and Skin Cancers

- >46,000 transplants in 2023
  - 8.7% increase over 2022
  - >100,000 on the waiting list
- Incidence of skin cancers
  - Related to intensity and duration of immune suppression
  - Rates vary by agent
  - NMSC rates vary

Skin Tumors	Standard Incidence Ratio
Squamous Cell	65-250
Merkel Cell	24
Basal Cell	10
Melanoma	5



Risk increases exponentially for CSCC over time from transplant

Conundrum

- Risk of graft loss ranges 40-80%
- No alternative for graft replacement except for kidney
- What is needed to maintain the graft?
- Can you separate tumor response from graft preservation?

Immunotherapy + Low-dose Immunosuppression

		CD8+ Immunohistochemistry (0-3= none, mild, moderate & severe; *no specimen available)			NIVO		IPI+NIVO	
Pt ID	Diagnosis	Pre-NIVO	On-NIVO	On-IPI/NIVO	Tumor response	Allograft loss	Tumor response	Allograft loss
1	MCC	1	1	*	PD	N	PD	N
2	CSCC	1	2	3	PD	N	CR	N
3	MCC	1	0	0	PD	N	PD	Y
4	CSCC	1	*	*	PD	N	PD	N
5	CSCC	1	*	N/A	PD	N	N/A	N/A
6	CSCC	3	2	*	PD	N	CR	Y
7	MEL	1	1	*	PD	Y	PD	N
8	CSCC	1	*	N/A	PD	N	N/A	N/A

Learning points:

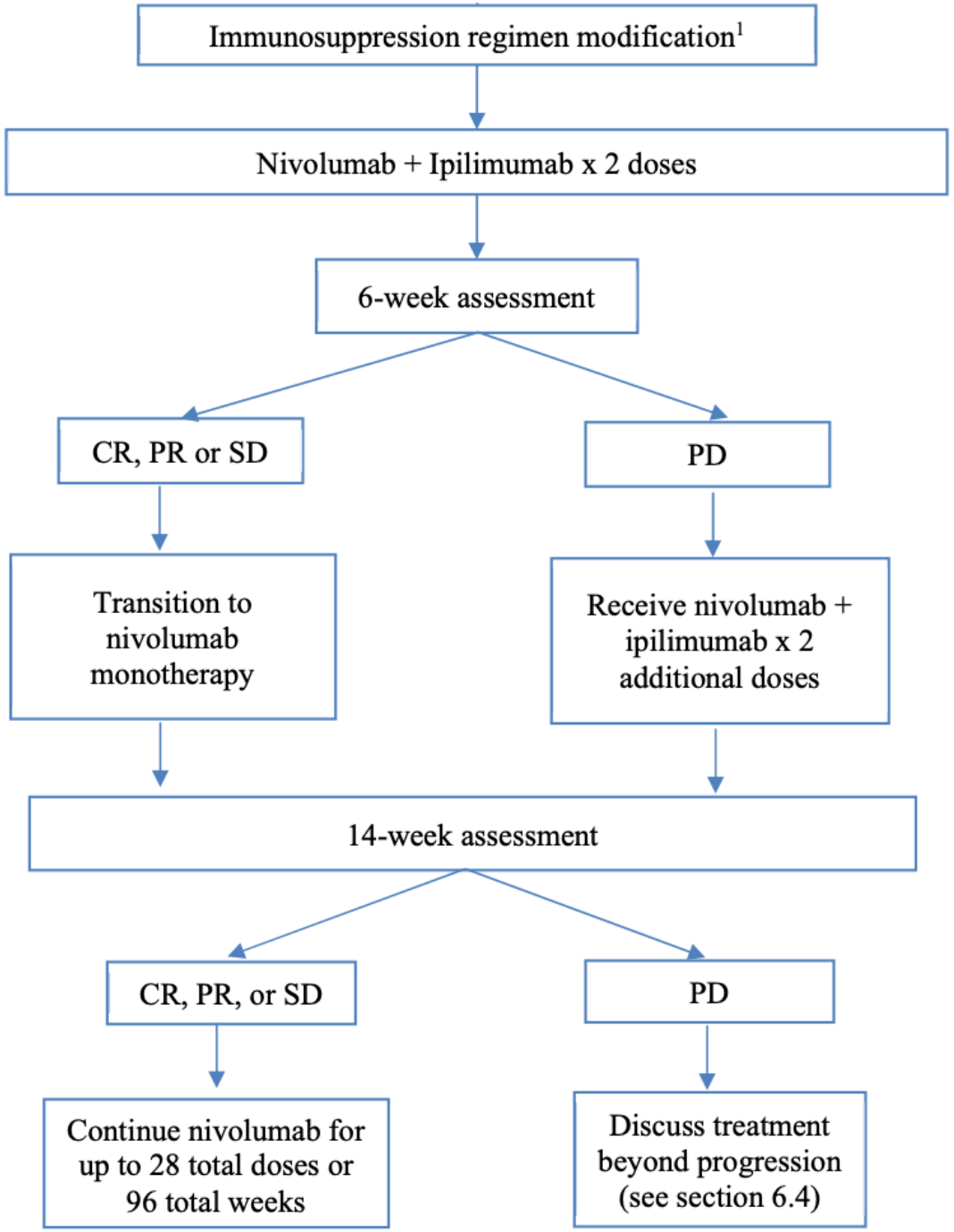
- Can follow dd-cfDNA to predict kidney rejection
- Nivolumab alone is not enough
- Addition of ipilimumab can help
- Tacrolimus and prednisone was insufficient to prevent graft rejection

Nivolumab + tacrolimus + prednisone +/- ipilimumab for kidney SOTR with advanced skin cancers

Schenk et al. JCO. 2024

ETCTN 10614

A Phase 2 Study of Nivolumab and Ipilimumab in Combination with Sirolimus and Prednisone in Kidney Transplant Recipients with Selected Unresectable or Metastatic Cutaneous Cancers



Thank you

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