
# Oncology Updates: Melanoma

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A Comprehensive Cancer Center Designated by the National Cancer Institute

UC San Diego
Moores Cancer Center

# Disclosures

Dr Joel Baumgartner

- None

Dr Gregory A Daniels

- None

# Learning Objectives

Neoadjuvant surgical considerations regarding extent and timing of tumor resection

Understanding which immune therapy to choose for neoadjuvant treatment

What are the options for therapy beyond PD1 based treatments in advanced melanoma

Evaluation of patients for tumor infiltrating lymphocyte therapy, surgical considerations for tumor infiltrating lymphocyte tumor harvest

# 40 y/o with an Axillary Mass

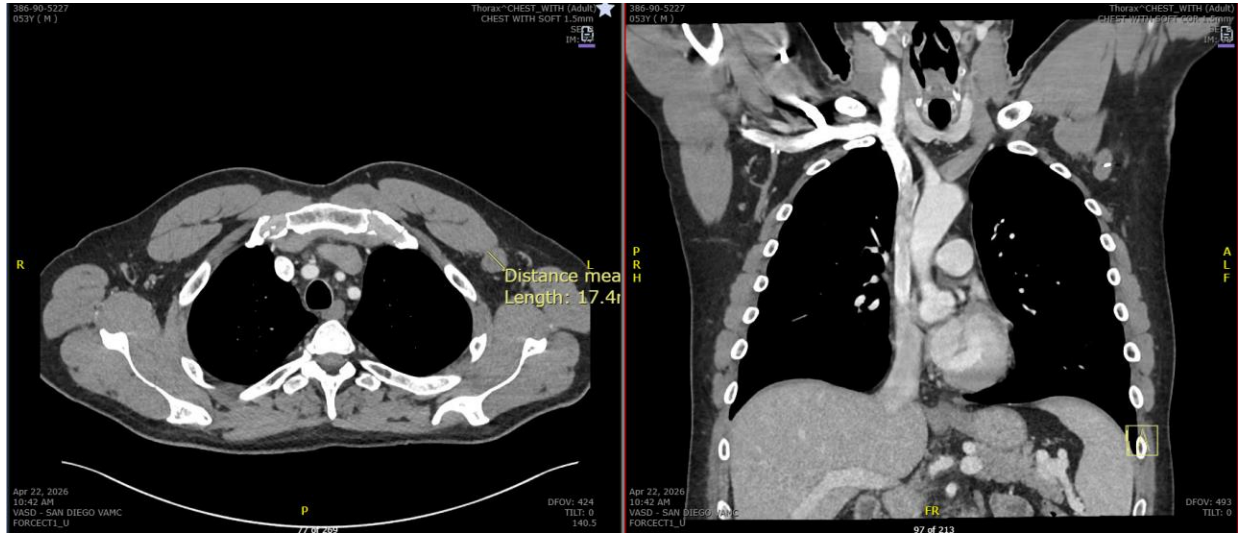
- 7/25: Palpable mass in LEFT axilla, intermittently painful, progressively enlarged to the size of a walnut
- 12/9/25: LEFT axillary US with 3.1cm lymph node
- 12/11/25: Biopsy =melanoma
- 1/21/26: MRI brain with NED
- 1/28/26: PET CT with LEFT axillary intense metabolic activity, no other sites of disease

**Best next step for this patient?**

A. NGS directed therapy
B. Neoadjuvant PD1
C. Neoadjuvant PD1/CTLA4
D. Surgery followed by adjuvant therapy

# Two Cycles of Ipilimumab/Nivolumab

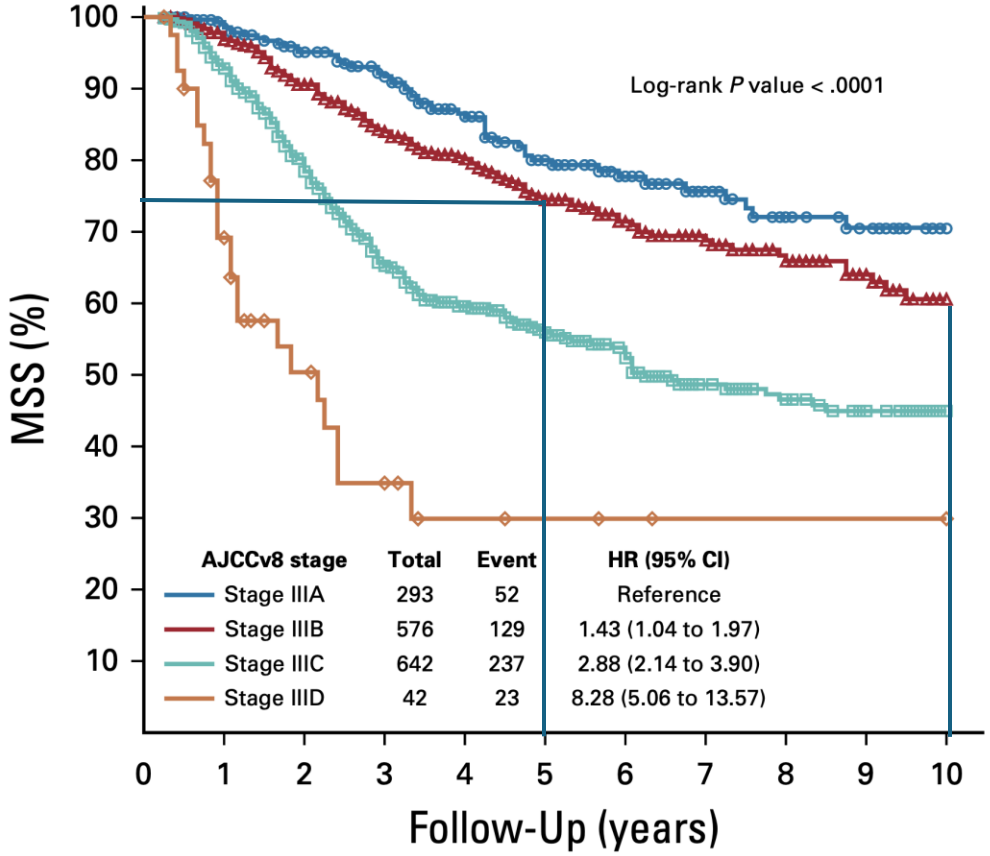
- 3/10/26: C1D1 ipi 1/ nivo 3
- 3/30/26: LN reduced in size, reported some rash, involving <10% BSA, managed with topical steroid and proceeded with C2D1 ipi 1/ nivo 3
- 4/15/26: General surgery, recommended CT chest to confirm no other nodes involved; if not, will proceed with surgical excision of L axillary index node after completion of 2 cycles of IO



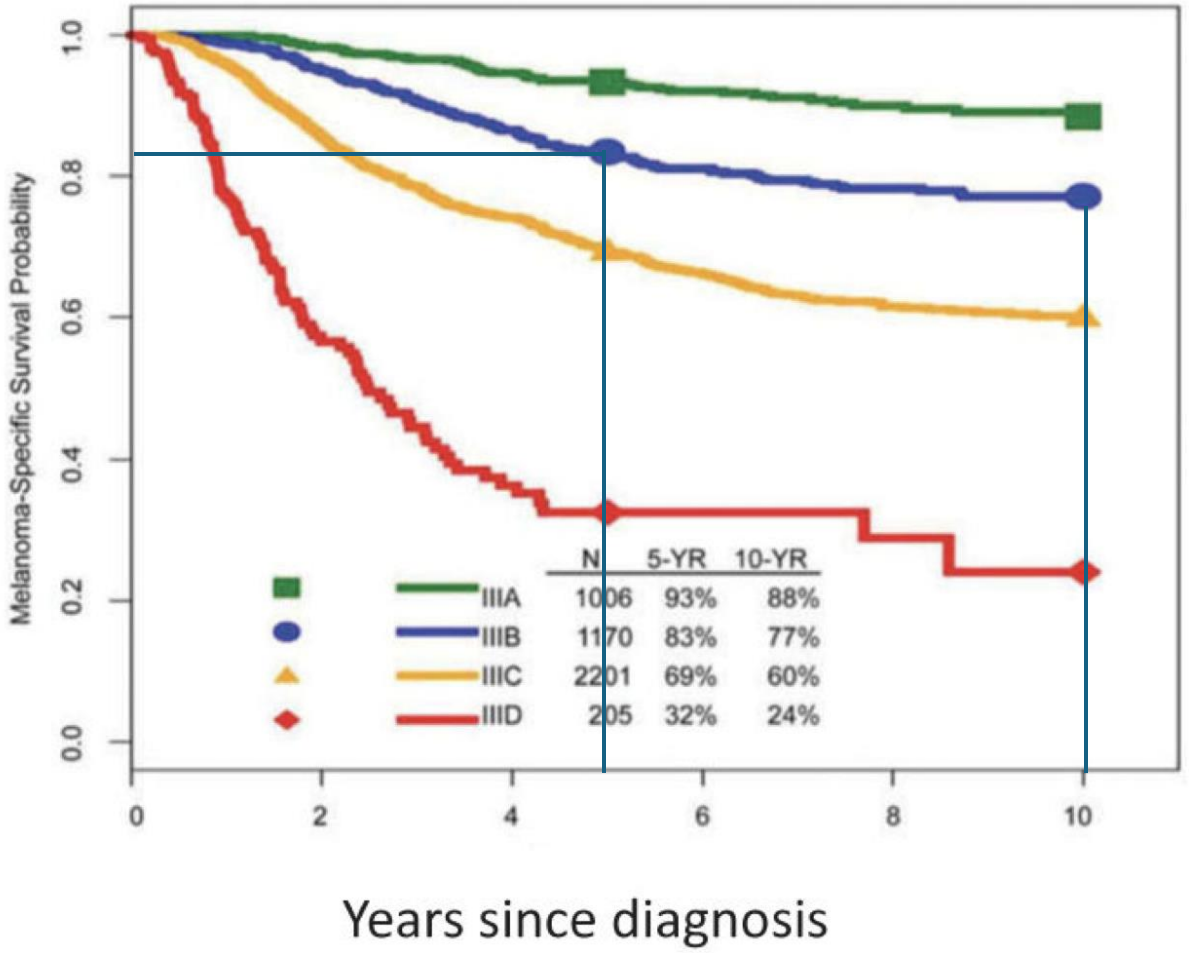

Microscopic Diagnosis:
A. Left axillary lymph node, excision
DX: LYMPH NODE WITH NECROTIC TUMOR CONSISTENT WITH NECROTIC MELANOMA
FINDINGS CONSISTENT WITH TREATMENT EFFECT ON MELANOMA
EXUBERANT HISTIOCYTIC AND GRANULOMATOUS INFLAMMATORY RESPONSE
TO NECROTIC MELANOMA
MANY HISTIOCYTES INCLUDE MELANIN PIGMENT (PIGMENTED MACROPHAGES)
FOCAL ZONES OF FIBROSIS
NO VIABLE MELANOMA IDENTIFIED (PATHOLOGIC COMPLETE RESPONSE - pCR)
SEE COMMENT

COMMENT: The history of previous biopsy at Sharp Hospital showing metastatic melanoma as well as the previous treament with Ipilimumab and Nivolumab is noted. Given that no viable melanoma remains in the lymph node, any additional molecular studies needed would required the original biopsy material.

# Melanoma Specific Survival Stage III (risk)




Garba J Clin Oncol 38:2543-2551




Keung Expert Rev Anticancer Ther . 2018

MSS =the time between the date of primary diagnosis of stage III cutaneous melanoma and the date of death from melanoma

# Questions

What are the considerations regarding the extent of lymph node dissection?

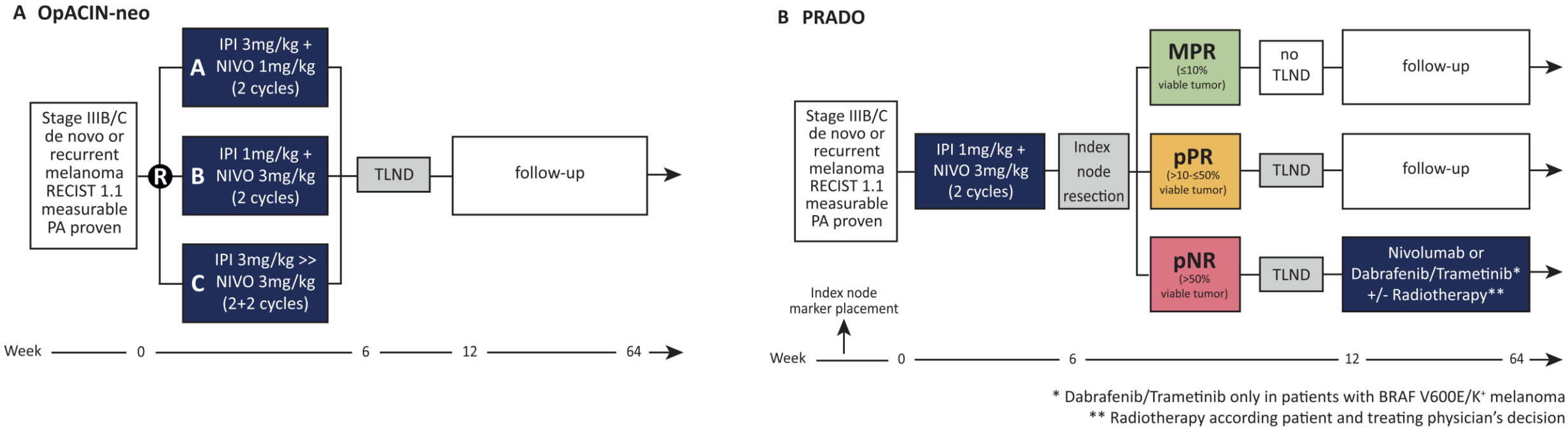
How long after neoadjuvant therapy should one wait to do surgery?

Do you commonly mark the index lymph node?

What is the optimal neoadjuvant therapy?

What are some considerations in choosing which therapy?

# Early Neoadjuvant Trials




C

| | OpACIN-neo | PRADO |
|---|---|---|
| MPR | TLND ✓ Adj ST ✗ Adj RT ✗ | TLND ✗ Adj ST ✗ Adj RT ✗ |
| pNR | TLND ✓ Adj ST ✗ Adj RT ✓ | TLND ✓ Adj ST ✓ Adj RT ✓ |

MPR=
Major Pathologic Response

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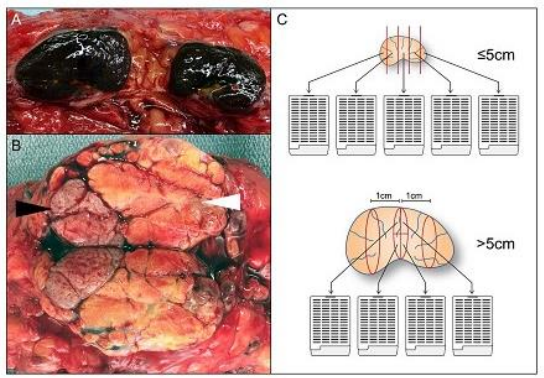
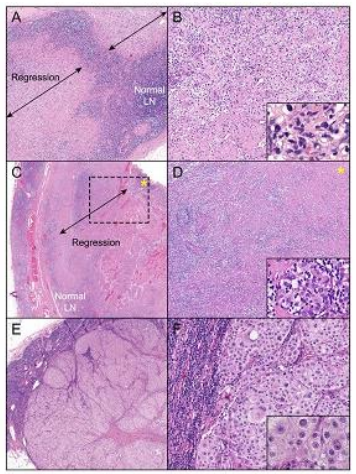
# International Neoadjuvant Melanoma Consortium

## Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma

M. T. Tetzlaff[1,2*], J. L. Messina[3], J. E. Stein[4], X. Xu[5], R. N. Amaria[6], C. U. Blank[7], B. A. van de Wiel[7], P. M. Ferguson[8], R. V. Rawson[8], M. I. Ross[9], A. J. Spillane[10], J. E. Gershenwald[9,11], R. P. M. Saw[8], A. C. J. van Akkooi[7], W. J. van Houdt[7], T. C. Mitchell[12], A. M. Menzies[10], G. V. Long[13], J. A. Wargo[9,14], M. A. Davies[2,6,15], V. G. Prieto[1,16], J. M. Taube[4†] & R. A. Scolyer[8†]




Ann Oncol. 2018;29(8):1861-8.

**White Paper**

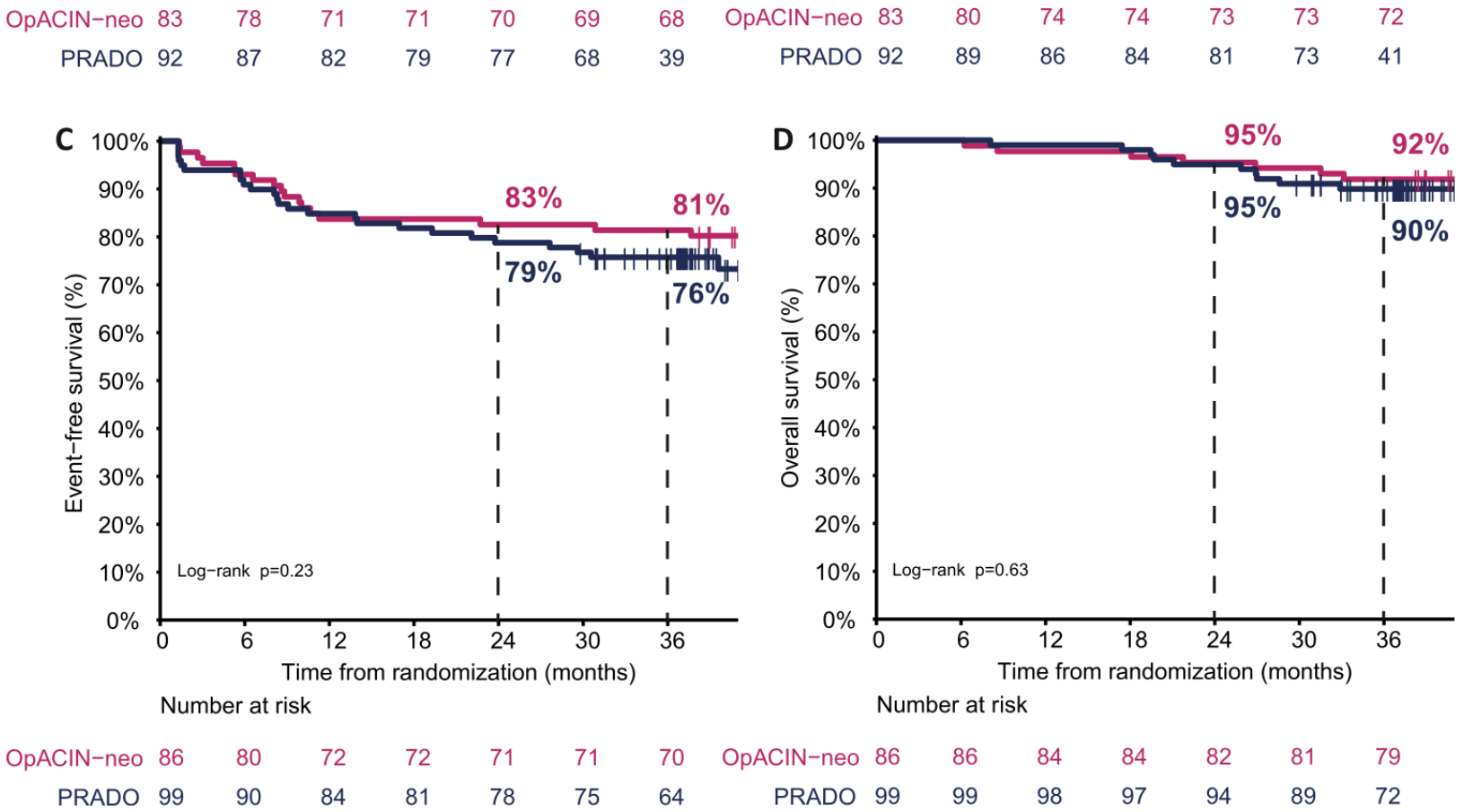
**Shaping the Future of Neoadjuvant Systemic Therapy in Melanoma: Recommendations of the International Neoadjuvant Melanoma Consortium (INMC)**

Agreed principles for neoadjuvant trials:

- Population
- Duration of therapy
- Biospecimens
- Endpoints

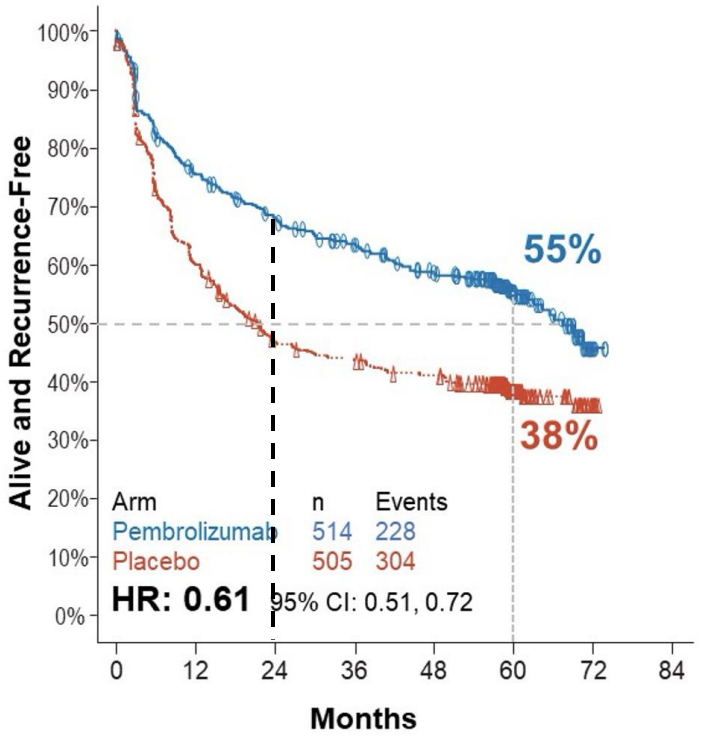
***Amaria, Menzies, Burton et al Lancet Oncology, 2019 in press***

# Neoadjuvant Therapy Associated with Improved Outcomes










**KEYNOTE-054[2]**
Pembrolizumab vs placebo

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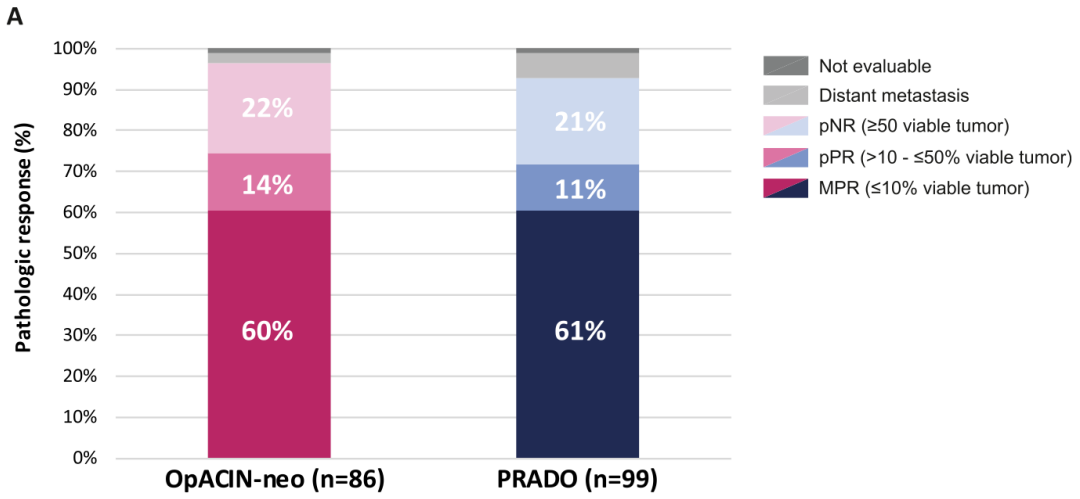
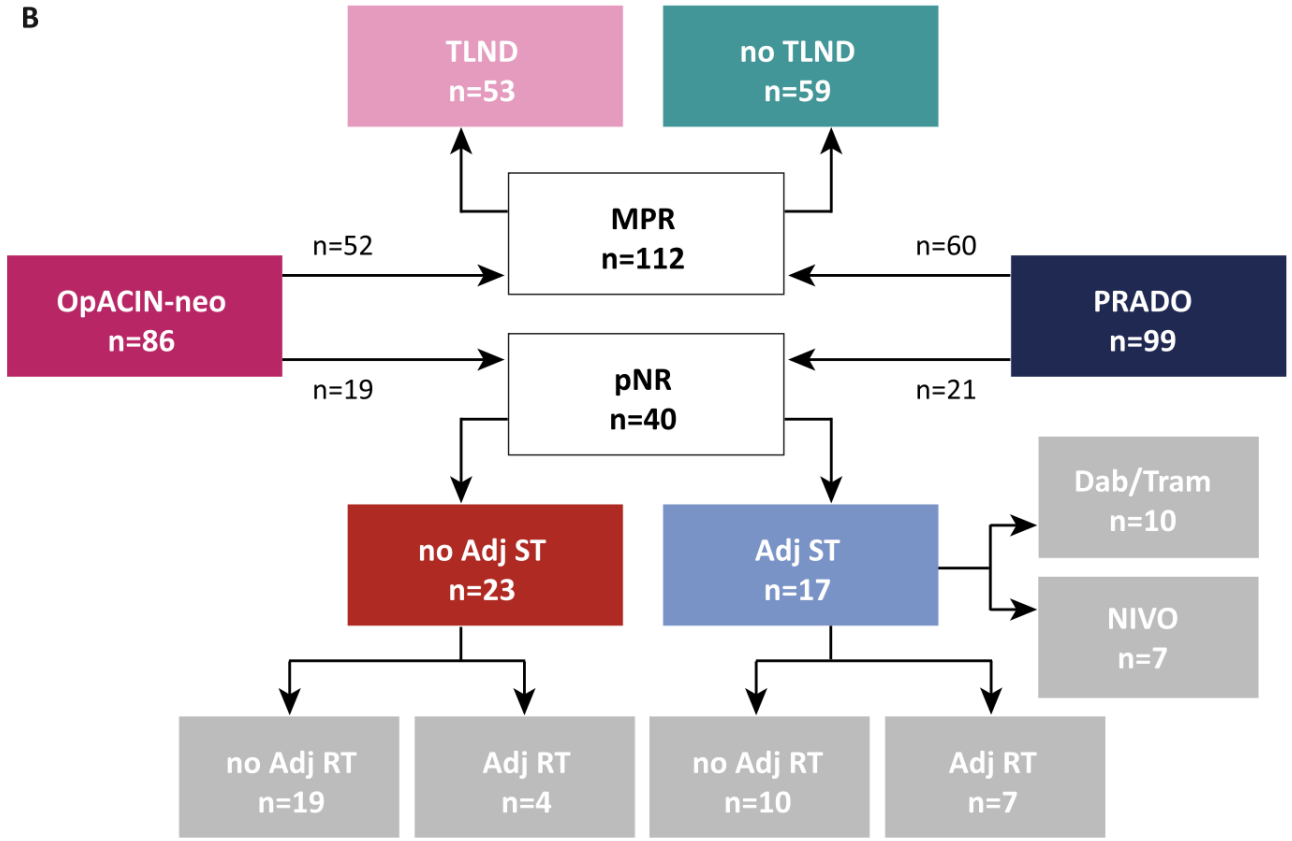
Eggermont NEJM 2022

# OpACIN and PRADO Trials

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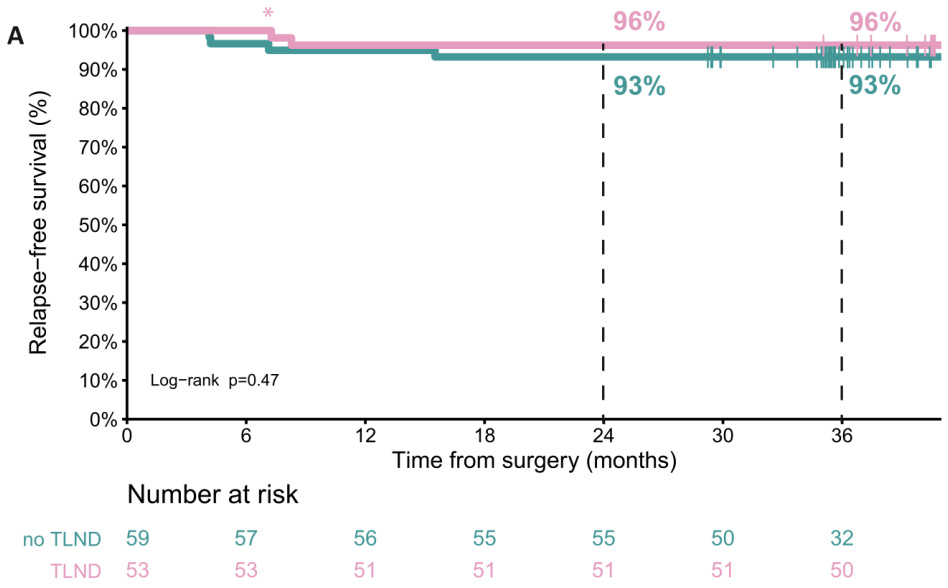
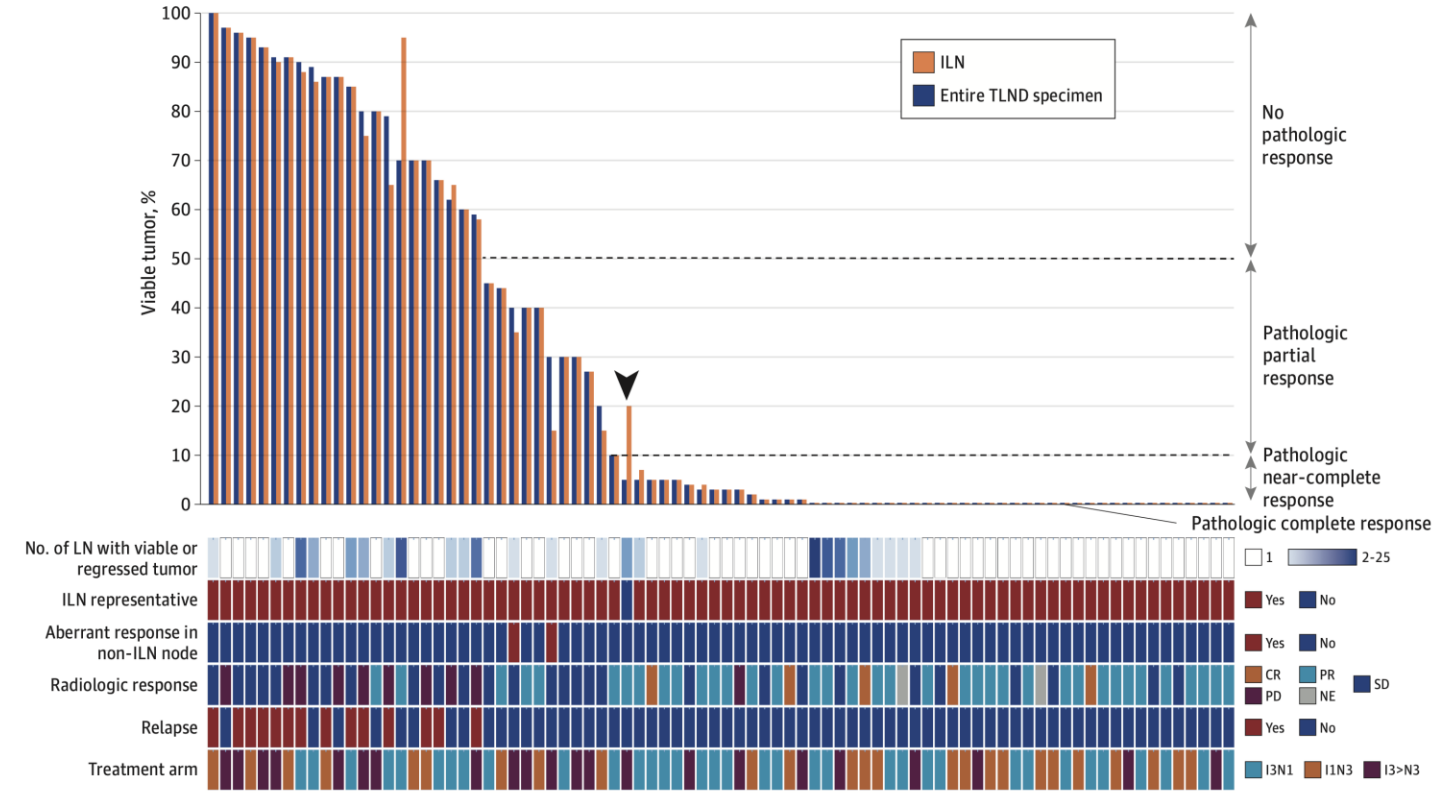
# Index Lymph Node Appears to Predict Overall Nodal Response




Outcomes for patients with MPR

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# Neoadjuvant Trials

## NADINA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma

C.U. Blank, M.W. Lucas, R.A. Scolyer, B.A. van de Wiel, A.M. Menzies, M. Lopez-Yurda, L.L. Hoeijmakers, R.P.M. Saw, J.M. Lijnsvelt, N.G. Maher, S.M. Pulleman, M. Gonzalez, A. Torres Acosta, W.J. van Houdt, S.N. Lo, A.M.J. Kuijpers, A. Spillane, W.M.C. Klop, T.E. Pennington, C.L. Zuur, K.F. Shannon, B.A. Seinstra, R.V. Rawson, J.B.A.G. Haanen, S. Ch'ng, K.A.T. Naipal, J. Stretch, J.V. van Thienen, M.A. Rtshiladze, S. Wilgenhof, R. Kapoor, A. Meerveld-Eggink, L.G. Grijpink-Ongering, A.C.J. van Akkooi, I.L.M. Reijers, D.E. Gyorki, D.J. Grünhagen, F.M. Speetjens, S.B. Vliek, J. Placzke, L. Spain, R.C. Stassen, M. Amini-Adle, C. Lebbé, M.B. Faries, C. Robert, P.A. Ascierto, R. van Rijn, F.W.P.J. van den Berkmortel, D. Piersma, A. van der Westhuizen, G. Vreugdenhil, M.J.B. Aarts, M.A.M. Stevense-den Boer, V. Atkinson, M. Khattak, M.C. Andrews, A.J.M. van den Eertwegh, M.J. Boers-Sonderen, G.A.P. Hospers, M.S. Carlino, J.-W.B. de Groot, E. Kapiteijn, K.P.M. Suijkerbuijk, P. Rutkowski, S. Sandhu, A.A.M. van der Veldt, and G.V. Long

NEJM 2 June 2024

## SWOG 1801

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

S.P. Patel, M. Othus, Y. Chen, G.P. Wright, Jr., K.J. Yost, J.R. Hyngstrom, S. Hu-Lieskovan, C.D. Lao, L.A. Fecher, T.-G. Truong, J.L. Eisenstein, S. Chandra, J.A. Sosman, K.L. Kendra, R.C. Wu, C.E. Devoe, G.B. Deutsch, A. Hegde, M. Khalil, A. Mangla, A.M. Reese, M.I. Ross, A.S. Poklepovic, G.Q. Phan, A.A. Onitilo, D.G. Yasar, B.C. Powers, G.C. Doolittle, G.K. In, N. Kokot, G.T. Gibney, M.B. Atkins, M. Shaheen, J.A. Warneke, A. Ikeguchi, J.E. Najera, B. Chmielowski, J.G. Crompton, J.D. Floyd, E. Hsueh, K.A. Margolin, W.A. Chow, K.F. Grossmann, E. Dietrich, V.G. Prieto, M.C. Lowe, E.I. Buchbinder, J.M. Kirkwood, L. Korde, J. Moon, E. Sharon, V.K. Sondak, and A. Ribas

NEJM 2 March 2023

# Neoadjuvant Trials

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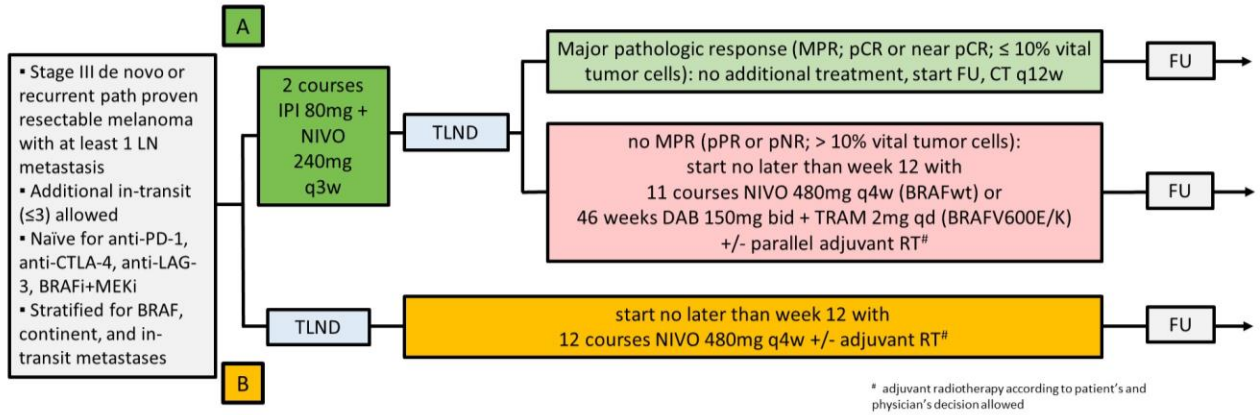
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma




A.A.M. van der Veldt, and G.V. Long

NEJM 2 June 2024

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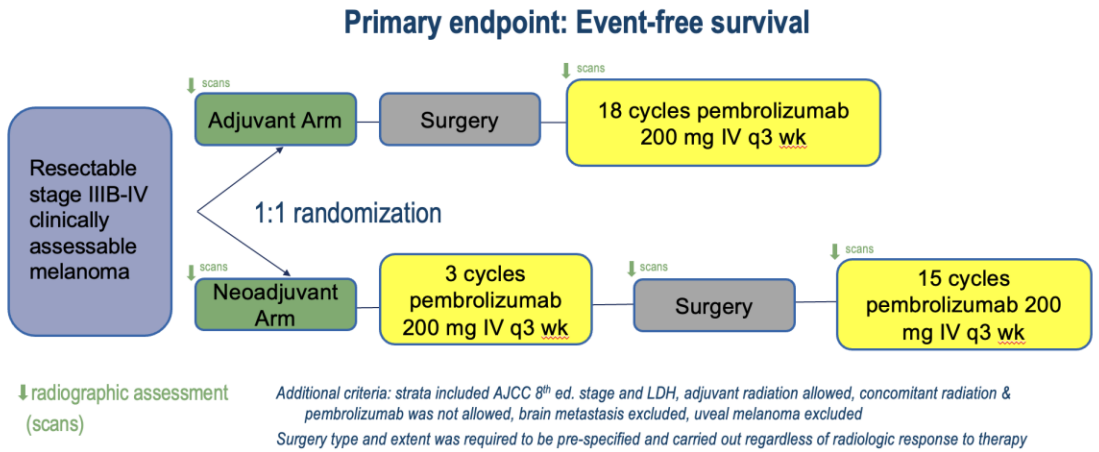
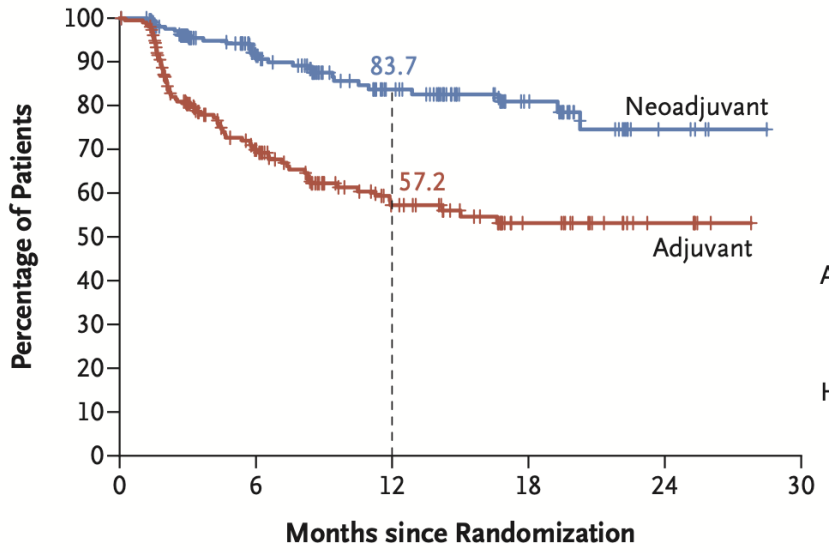



NEJM 2 March 2023

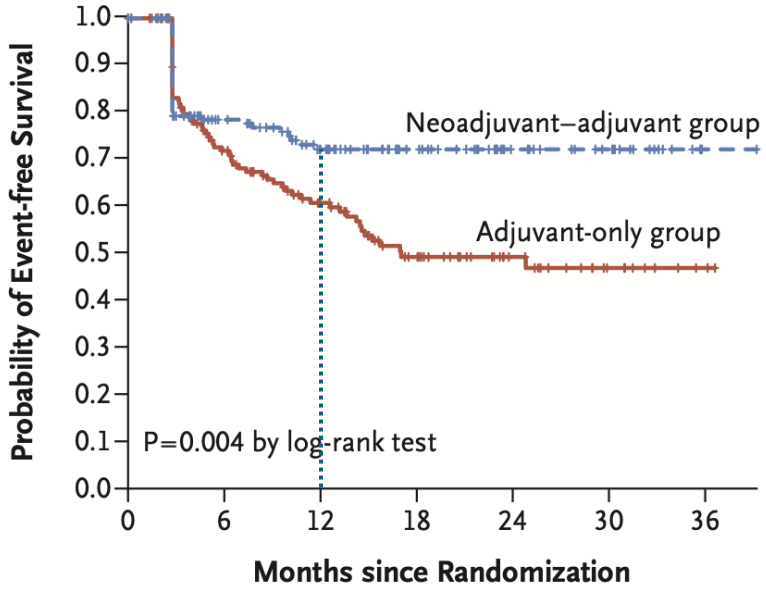
# Event-Free survival

## NADINA neo Ipi1/nivo3 +/- adj nivo v adj nivo




| No. at Risk (no. censored) | | | | | |
|---|---|---|---|---|---|
| Neoadjuvant | 212 (0) | 126 (71) | 77 (111) | 34 (152) | 5 (179) |
| Adjuvant | 211 (0) | 100 (57) | 53 (89) | 23 (116) | 6 (133) |

## SWOG Pembro neo and adj v adj Pembro




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Neoadjuvant–adjuvant group | 154 | 96 | 69 | 46 | 25 | 17 | 1 |
| Adjuvant-only group | 159 | 98 | 67 | 40 | 22 | 10 | 2 |

Included about 10% stage IV disease

# Confirmation Pathologic Response Predicts Outcome*

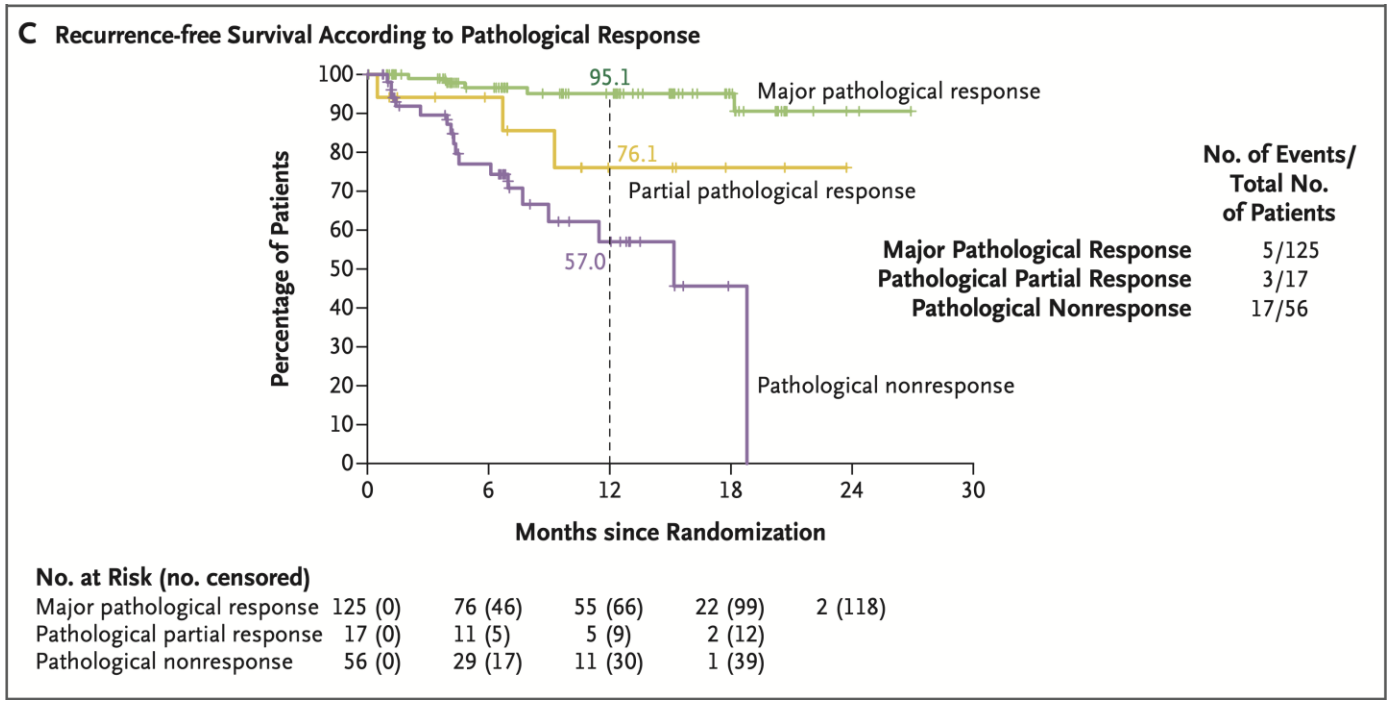



Table 3. Adverse Events.*

| Event | Neoadjuvant Group (N=212) | Adjuvant Group (N=208) |
|---|---|---|
| Any adverse event — no. (%) | 204 (96.2) | 194 (93.3) |
| Any grade ≥3 adverse event — no. (%) | 100 (47.2) | 71 (34.1) |
| Serious adverse event — no. (%) | 77 (36.3) | 49 (23.6) |
| Treatment-related adverse event — no. (%) | 196 (92.5) | 178 (85.6) |
| Treatment-related grade ≥3 adverse event — no. (%) | 82 (38.7) | 50 (24.0) |
| Surgery-related adverse event — no./total no. (%) | 120/198 (60.6) | 151/208 (72.6) |
| Surgery-related grade ≥3 adverse event — no./total no. (%) | 28/198 (14.1) | 30/208 (14.4) |
| Adverse event related to systemic treatment — no./total no. (%) | 181/212 (85.4) | 123/170 (72.4) |
| Grade ≥3 adverse event related to systemic treatment — no./total no. (%) | 63/212 (29.7) | 25/170 (14.7) |
| Discontinuation of treatment due to adverse event — no. (%) | 19 (9.0) | 30 (14.4) |
| Death due to treatment-related adverse event — no. (%) | 0 | 1 (0.5) |

Grade >3 was higher in the neoadjuvant group

Confirmed that patients with MPR (majority of patients) do not need additional adjuvant therapy

Pathologic not responders need something else

OS comparison pending
Did not compare to neoadjuvant PD1 (SWOG 1801)
Did not report grade 2 (ie-thyroid dysfunction, adrenal)

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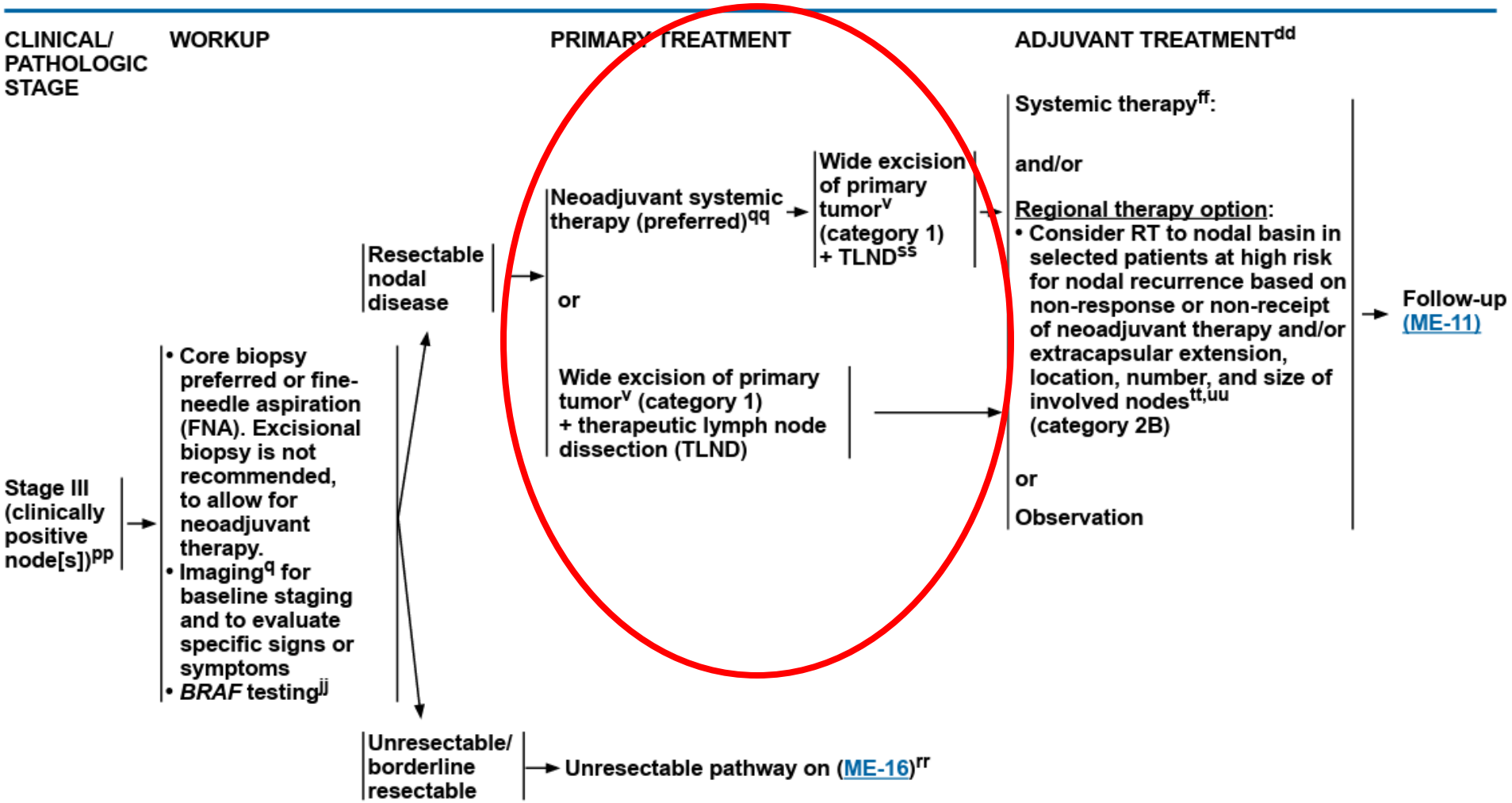
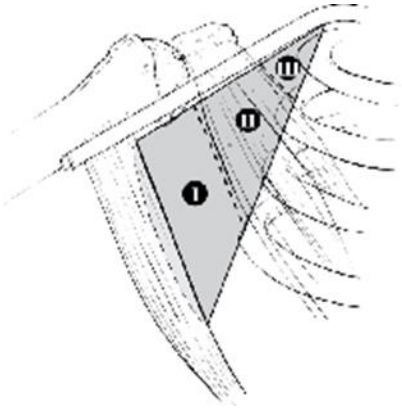
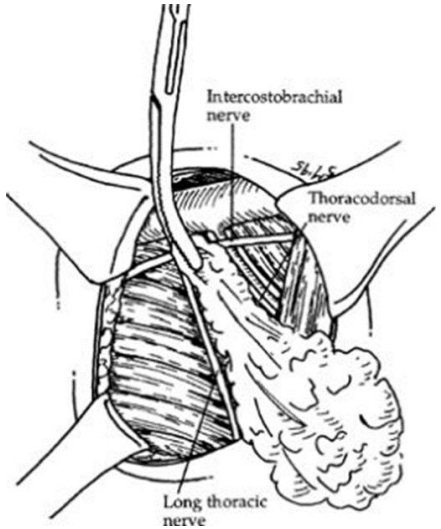
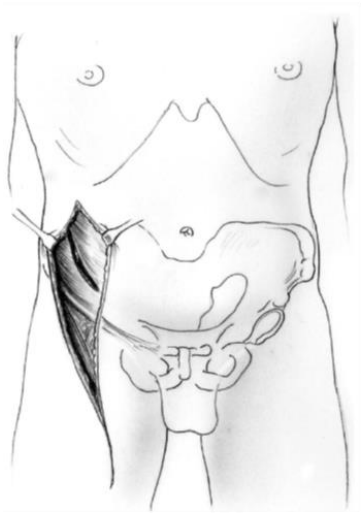
* For PD1/CTLA4 based therapy

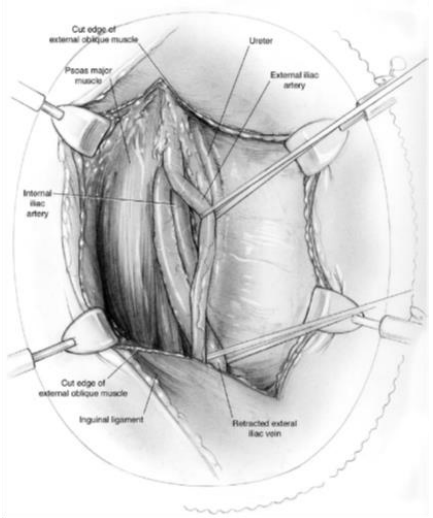


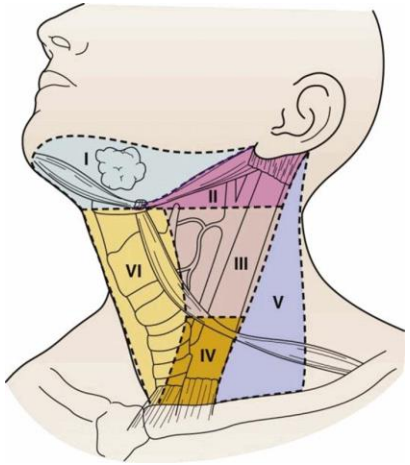
# Lymph Node Dissection

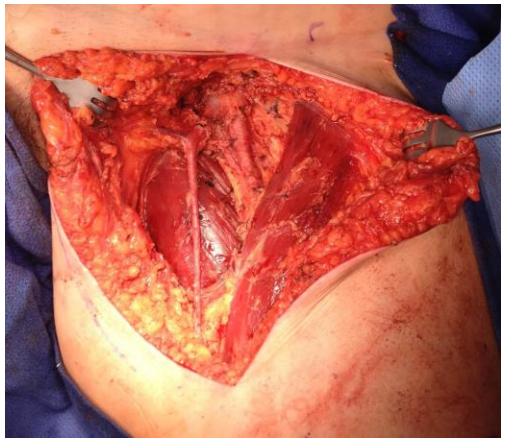




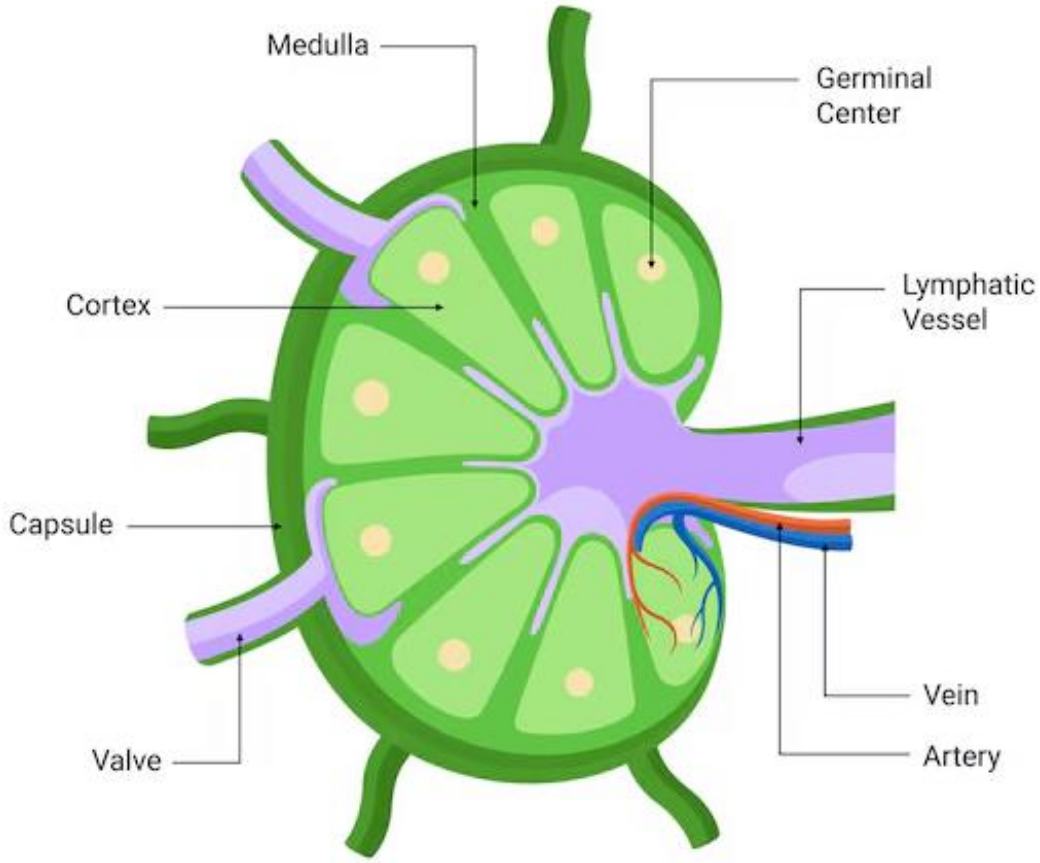



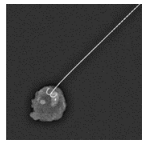
| Complication | ALND | ILND |
|---|---|---|
| Wound infection | 15% | 20-45% |
| Wound dehiscence | 3% | 20% |
| Lymphocele | 15% | 20-35% |
| Lymphedema | 5-10% | 20-25% |

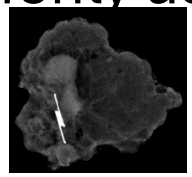
# Surgical Considerations with Neoadjuvant Treatment for Stage III Melanoma

- Index LN often is/becomes non-palpable with NA treatment, need to localize LN intraoperatively
  - This is often done after initial LN biopsy
  - Best evaluated by surgeon preoperatively to determine if necessary
  - Techniques largely developed for breast cancer localization



# Surgical Considerations with Neoadjuvant Treatment for Stage III Melanoma

- Index LN localization techniques
  - Wire: not practical 
  - Radar: Savi Scout: most commonly used 

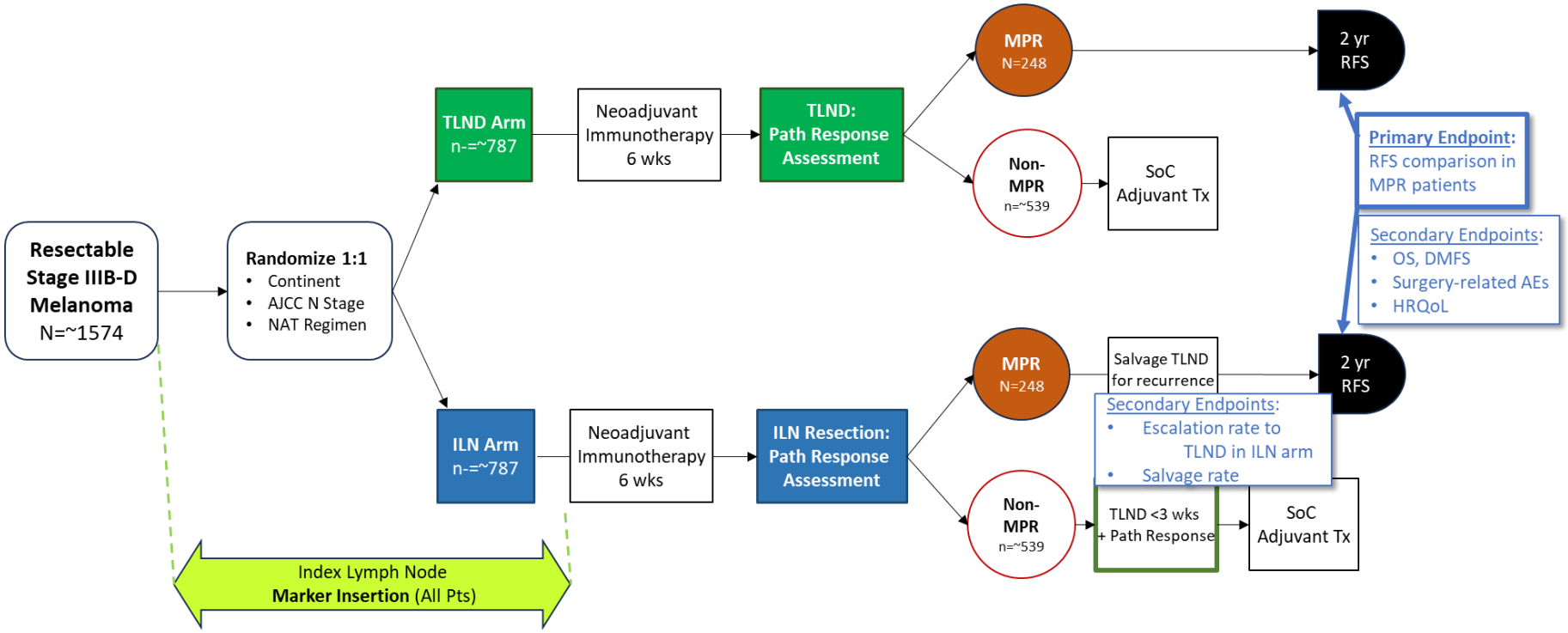

  - Magnetic: Memaloc 

  - Ultrasound: UltraCor Twirl, HydroMARK; degrades, most difficult to identify 

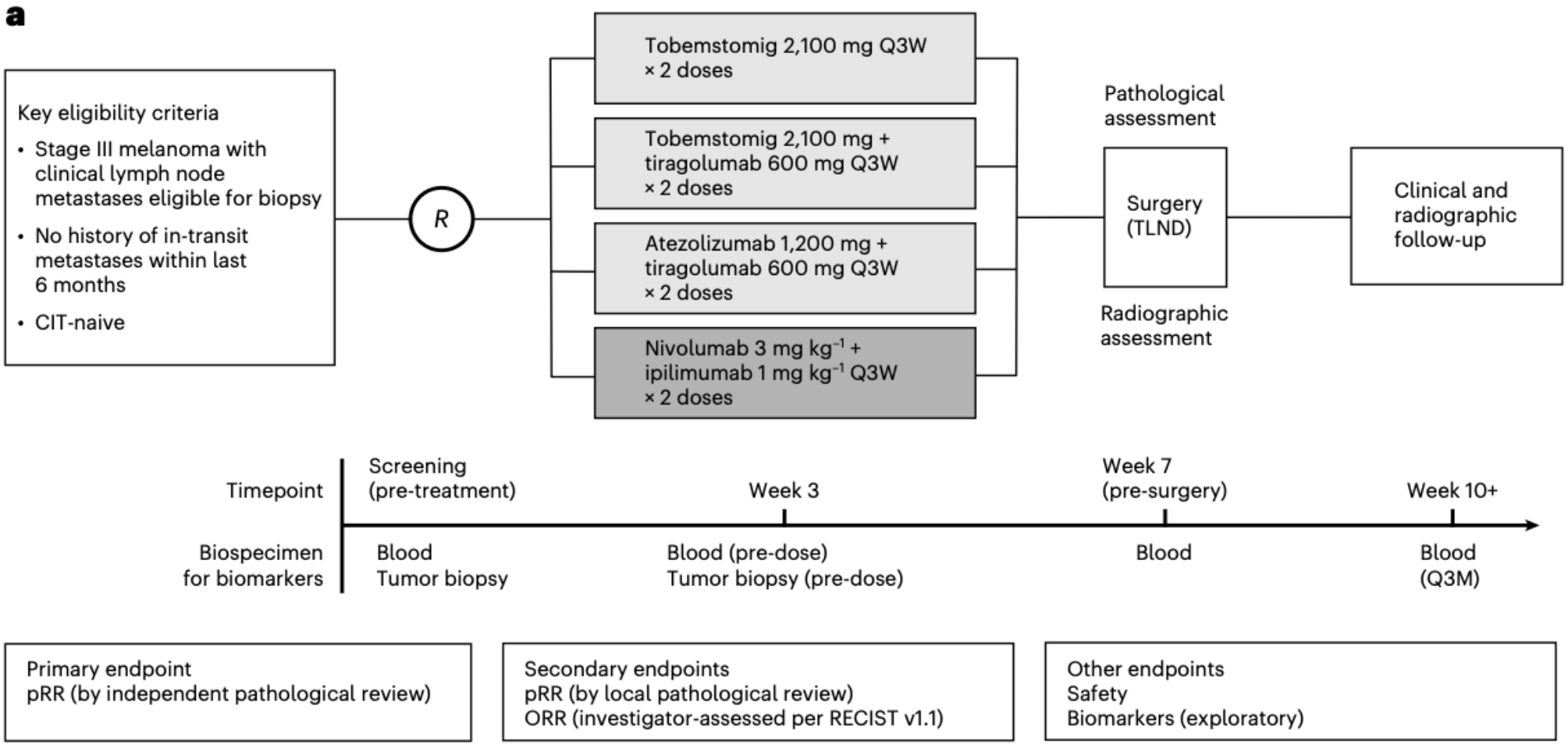

  - Radioactive: IsoSeed. decays, uses available equip., must remove 


# Surgical Considerations with Neoadjuvant Treatment for Stage III Melanoma

- Is Index LN excision enough?
- MSLT-3

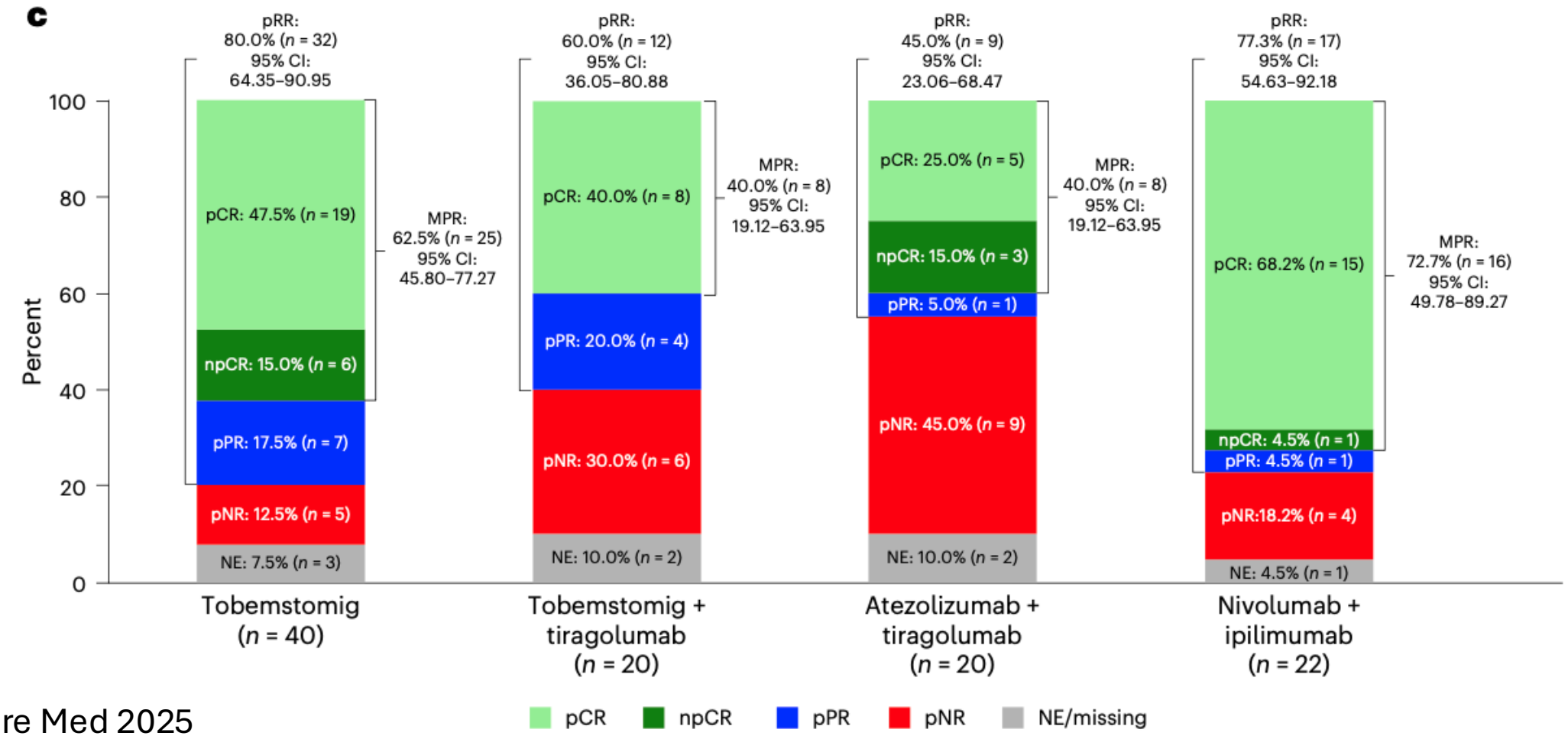


# Morpheus trial



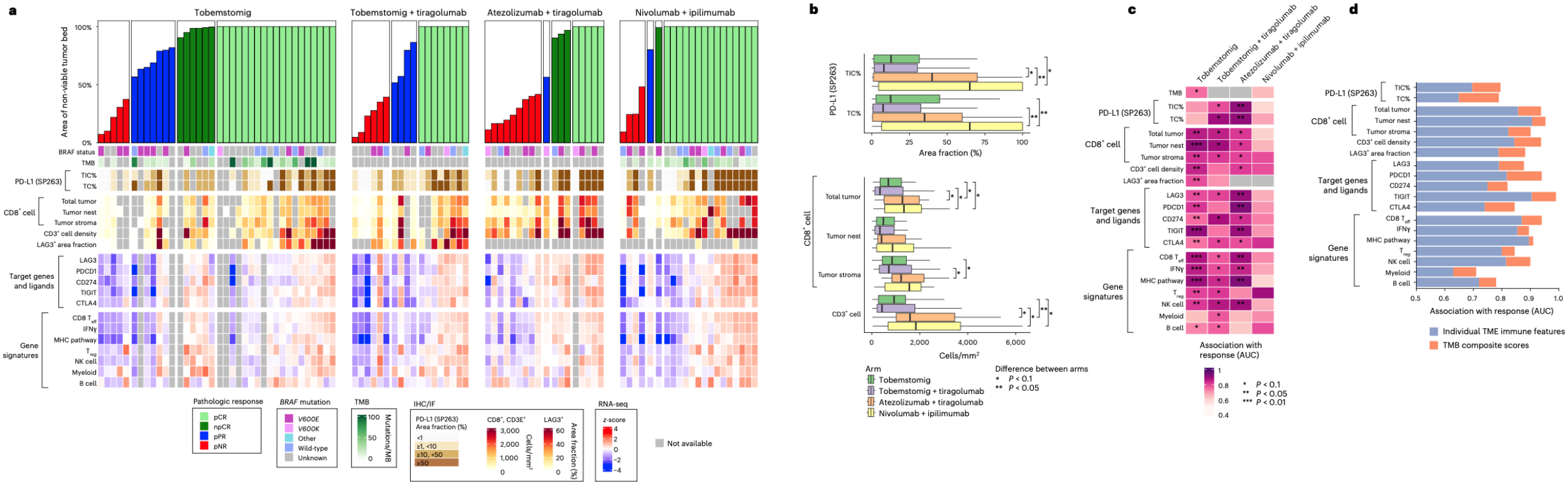

Long Nature Med 2025

# Efficient Testing of Novel Agents




Long Nature Med 2025

# Translational Platform




Long Nature Med 2025

# Neoadjuvant Therapy Advantages

- Opportunity to decrease surgical interventions.
  - Total LN dissection v Index node
  - Still waiting for prospective randomized trial
- Opportunity to decrease systemic therapy.
  - Patients with MPR do well without additional adjuvant therapy
  - This is for patients who have had Ipilimumab/Nivolumab
- Improved outcomes for pathologic complete responders.
- Platform to test novel therapies—window of opportunity trials.

# Questions

- What are the considerations regarding the extent of lymph node dissection?
- How long after neoadjuvant therapy should one wait to do surgery?
- Do you commonly mark the index lymph node?
- What is the optimal neoadjuvant therapy?
- What are some considerations in choosing which therapy?

# Learning Objectives

~~Neoadjuvant surgical considerations regarding extent and timing of tumor resection~~

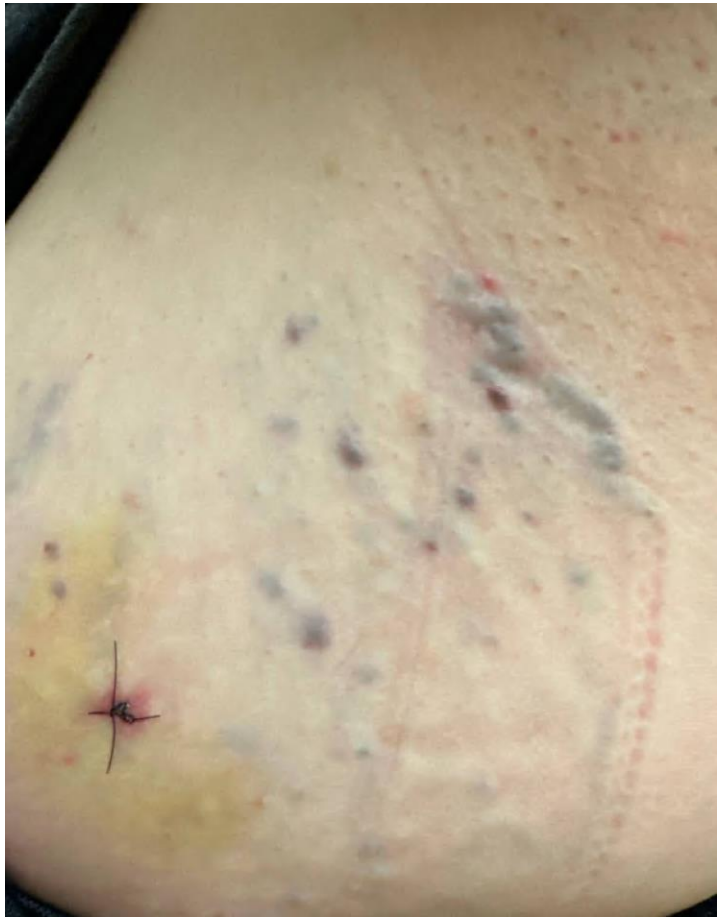
~~Understanding which immune therapy to choose for neoadjuvant treatment~~

What are the options for therapy beyond PD1 based treatments in advanced melanoma

Evaluation of patients for tumor infiltrating lymphocyte therapy, surgical considerations for tumor infiltrating lymphocyte tumor harvest

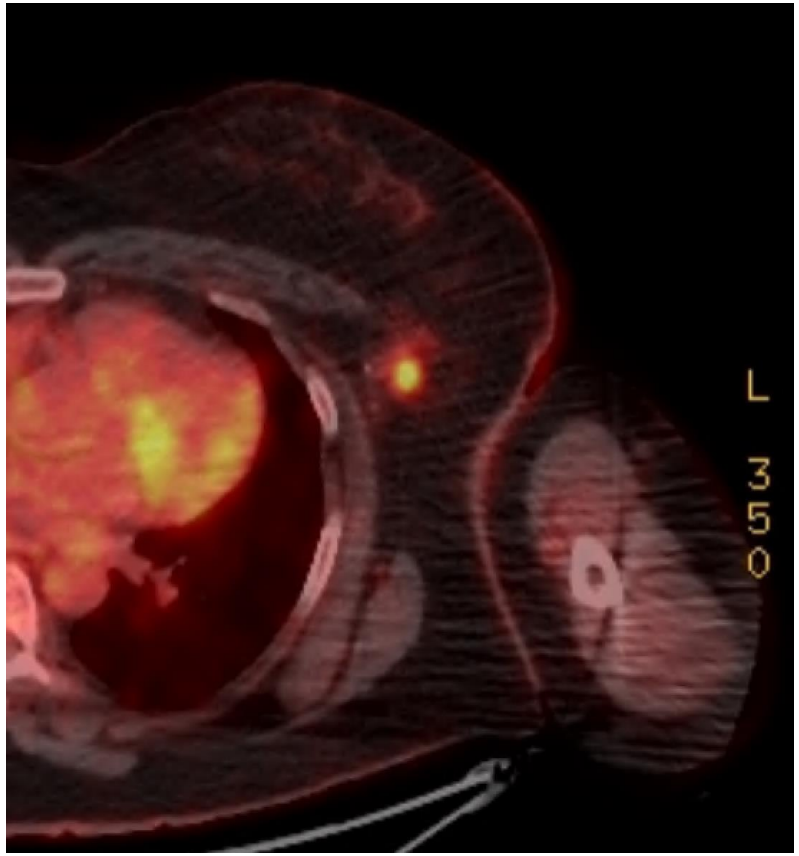
# 50 y/o with Metastatic Melanoma

- 2023-WLE and SLN for T3aN1a cutaneous melanoma of the back
- Treated with adjuvant Pembrolizumab for 4 months. Stopped early due to move
- Six months later with biopsy=in transit recurrence



# Skin and LN Involvement

- BRAF V600E, TMB 4mut/MB



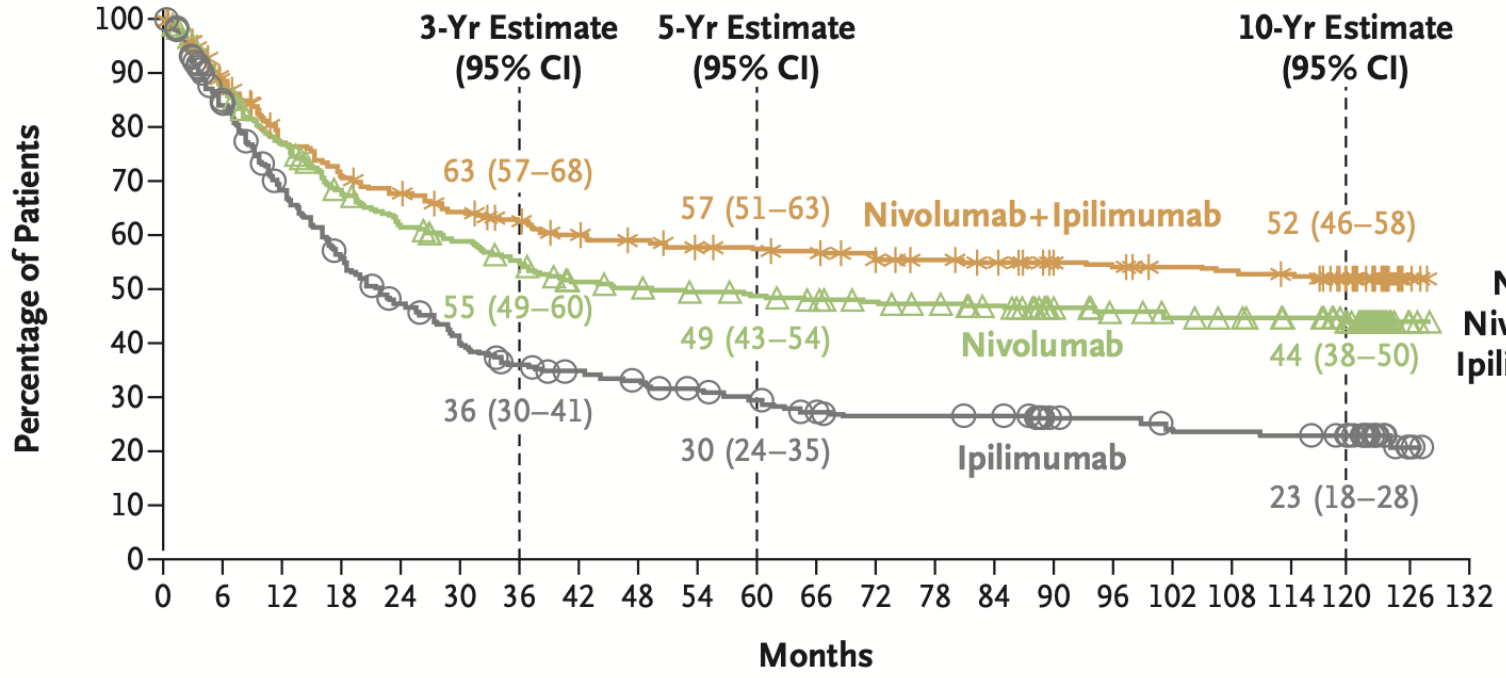

Therapy options

A. Dabrafenib/Trametinib*
B. Ipilimumab/Nivolumab
C. Opdualag
D. Pembrolizumab or Nivolumab
E. Tumor Infiltrating Lymphocytes

* Or other FDA approved BRAF/MEK combination

# Checkmate 067

**Melanoma-Specific Survival**




| No. at Risk | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivo+ipi | 314 | 265 | 227 | 210 | 199 | 187 | 179 | 169 | 163 | 158 | 156 | 153 | 147 | 144 | 139 | 126 | 124 | 120 | 117 | 115 | 92 | 10 | 0 |
| Nivolumab | 316 | 265 | 231 | 201 | 181 | 171 | 158 | 145 | 141 | 137 | 134 | 130 | 126 | 123 | 118 | 107 | 102 | 98 | 96 | 92 | 77 | 4 | 0 |
| Ipilimumab | 315 | 253 | 203 | 163 | 135 | 113 | 100 | 94 | 87 | 81 | 75 | 68 | 64 | 64 | 63 | 50 | 49 | 44 | 43 | 42 | 35 | 3 | 0 |

| | No. of Patients with Event | Median Melanoma-Specific Survival (95% CI) |
|---|---|---|
| | | *mo* |
| **Nivo+Ipi (N=314)** | 139 | NR (71.8–NR) |
| **Nivolumab (N=316)** | 163 | 49.4 (35.1–119.4) |
| **Ipilimumab (N=315)** | 221 | 21.9 (18.1–27.4) |

Hazard ratio for death from melanoma, nivo+ipi vs. ipilimumab, 0.48 (95% CI, 0.39–0.59)

Hazard ratio for death from melanoma, nivolumab vs. ipilimumab, 0.59 (95% CI, 0.49–0.73)

Hazard ratio for death from melanoma, nivo+ipi vs. nivolumab, 0.81 (95% CI, 0.64–1.01)

Wolchok NEJM 2024

# Progressed AND Toxicity with PD1/CTLA4

- Ipi3/Nivo1 x 3 cycles
  - Limited by hepatitis
  - Required prednisone/mycophenolate
  - Ultimately developed adrenal insufficiency
- Transitioned to BRAFi
  - Response
  - Stopped after 2 months
- TVEC (Talimogene Laherparepvec)
- Progressed in the brain and skin

Options for PD1 refractory disease

A. Clinical trial
B. TILs
C. Opdualag
D. Resume BRAF inhibitor
E. Radiation

# Adoptive Transfer of Autologous T cells with IL2

## 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 ($8.0 \times 10^9$ to $2.3 \times 10^{11}$ 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.

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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.

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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.

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## SPECIAL REPORT

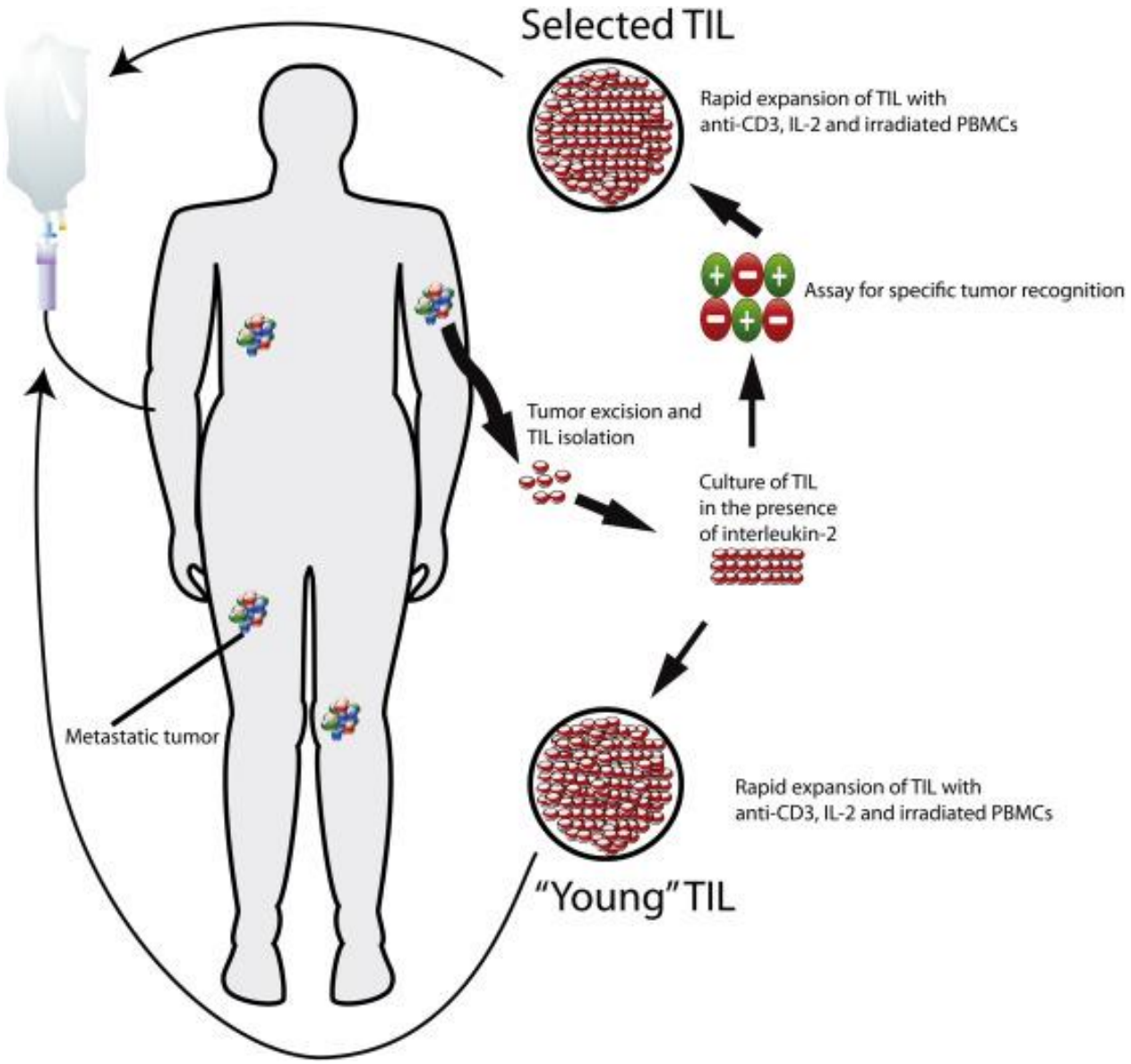
### USE OF TUMOR-INFILTRATING LYMPHOCYTES AND INTERLEUKIN-2 IN THE IMMUNOTHERAPY OF PATIENTS WITH METASTATIC MELANOMA

#### 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-infilitrating lymphocytes are expanded and infused back into the patient
- IL-2 to tolerance

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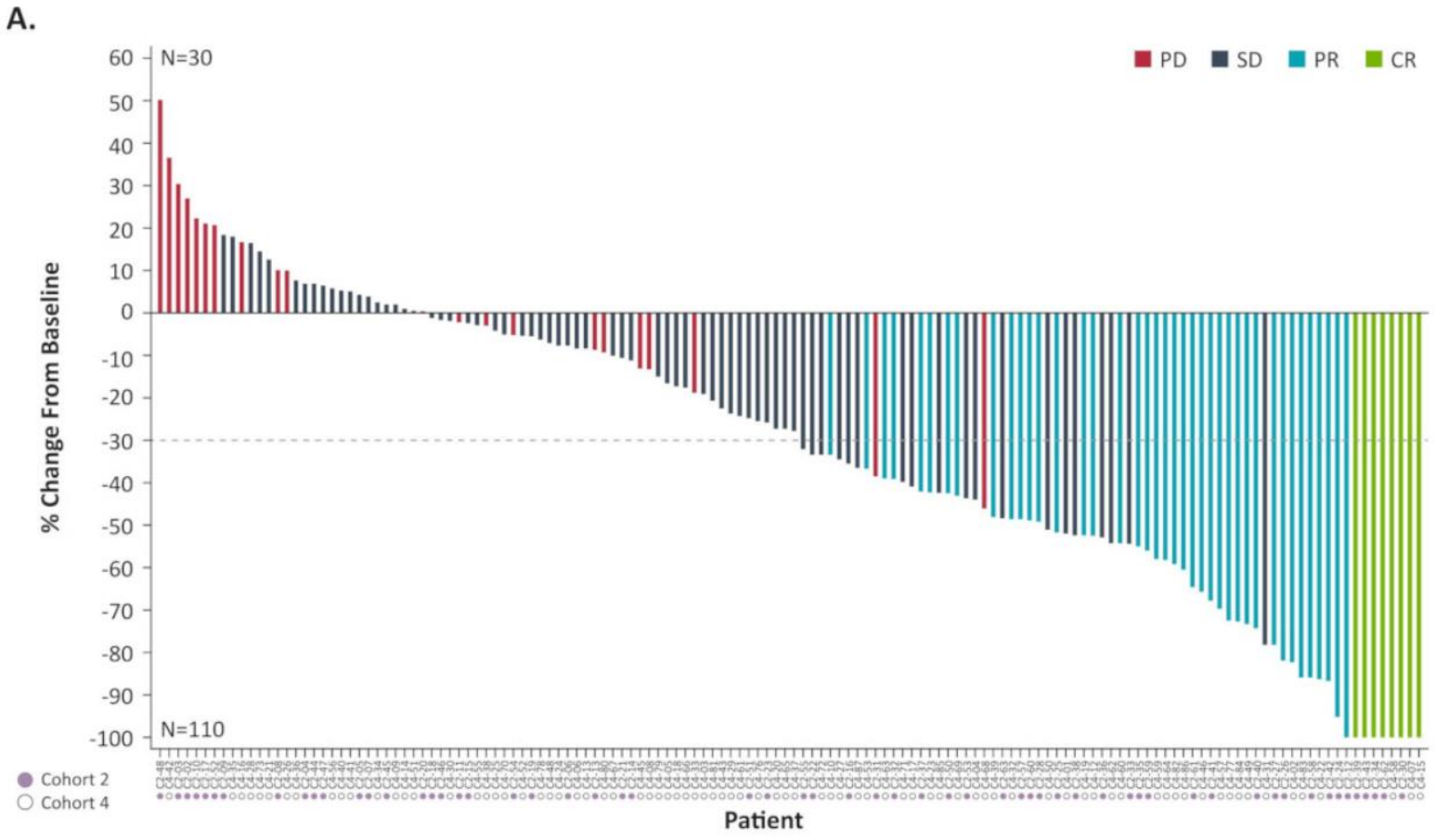
# TIL Best Response




JITC 2022 Chesney

# TIL Outcome Duration in PD1 Refractory Patients

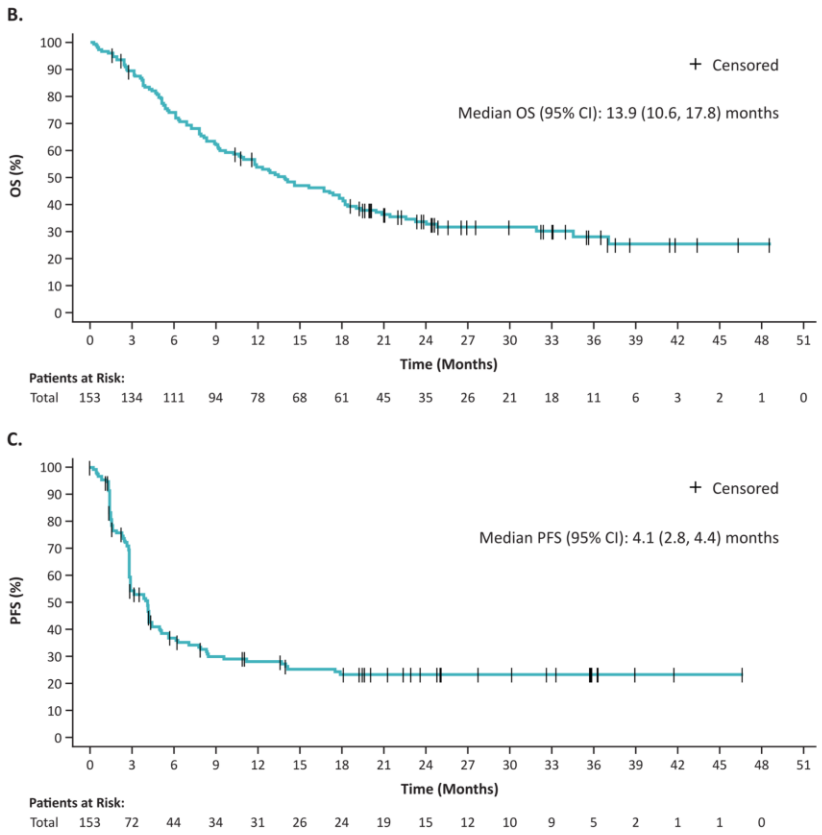



**Figure 2** DOR in confirmed responders (PRor better) by IRC assessment per Response Evaluation Criteria in Solid Tumors V.1.1 (A), OS (B), and PFS (C) for pooled Cohorts 2 and 4. DOR, duration of response; IRC, independent review committee, NR, not reached; OS, overall survival; PFS, progression-free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

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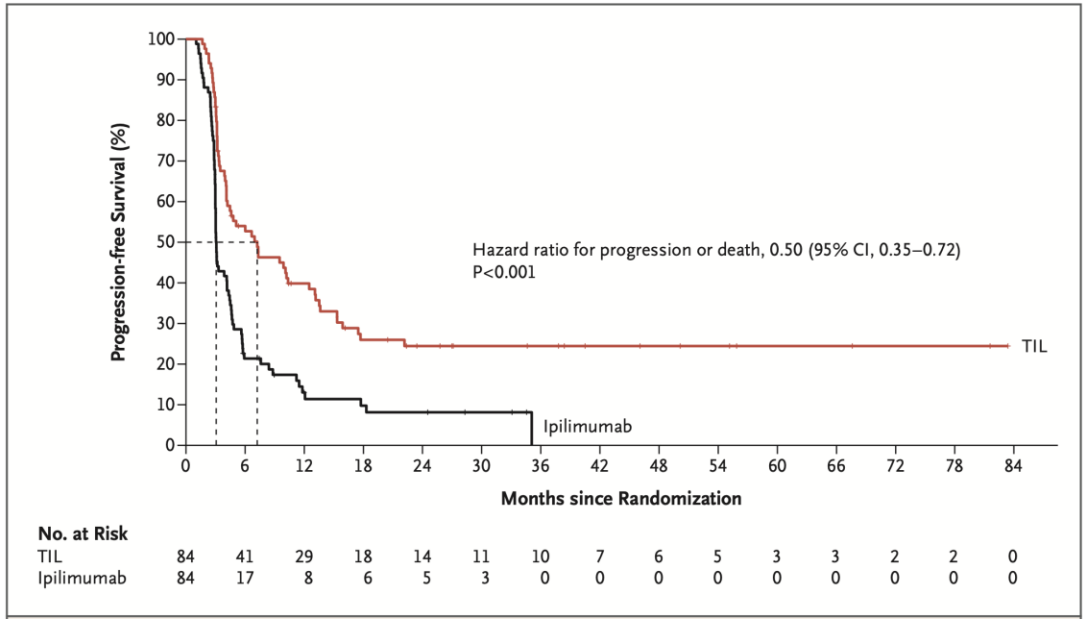


**Figure 1. Progression-free Survival.**

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

# TIL Toxicity

**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.

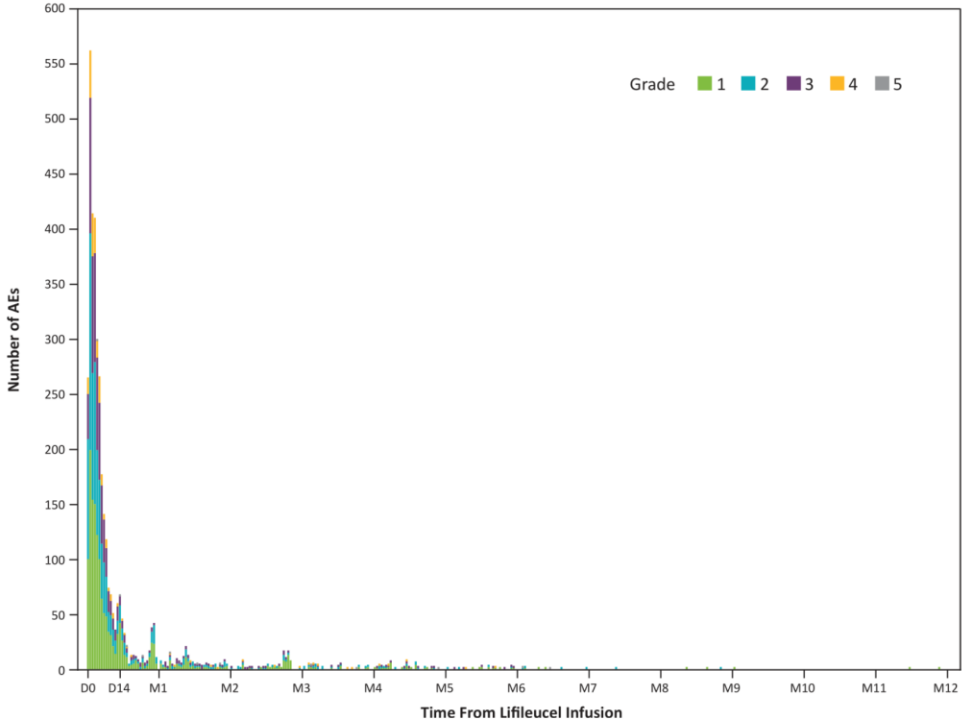


**Figure 3** Incidence of AEs over time (Safety Analysis Set).* All occurrences of AEs were counted if a patient experienced a new onset of the same AE at different time points. If multiple records were reported on the electronic case report form because of toxicity grade decrease of the same AE that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

- Minimum of 15x15x15mm lesion(s) for resection AND another site of residual disease
- Progressive diseases 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

# Therapy Components

- Cyclophosphamide
  - 60mg/kg, days -7 and -6
  - Mesna 60mg/kg IV over 24 hours
- Fludarabine
  - 25mg/m2, days -7 to -3
- Lifileucil
  - Day 0 (at least 24 hours post chemotherapy)
  - 1cc/min, titrate up to 10cc/min
- IL2
  - 600,000IU/kg
  - Bolus over 15 minutes
  - Up to 6 doses per stopping criteria
  - Start 3 to 24 hours after cell infusion
- G-CSF
  - Day 1
  - Until ANC >1000

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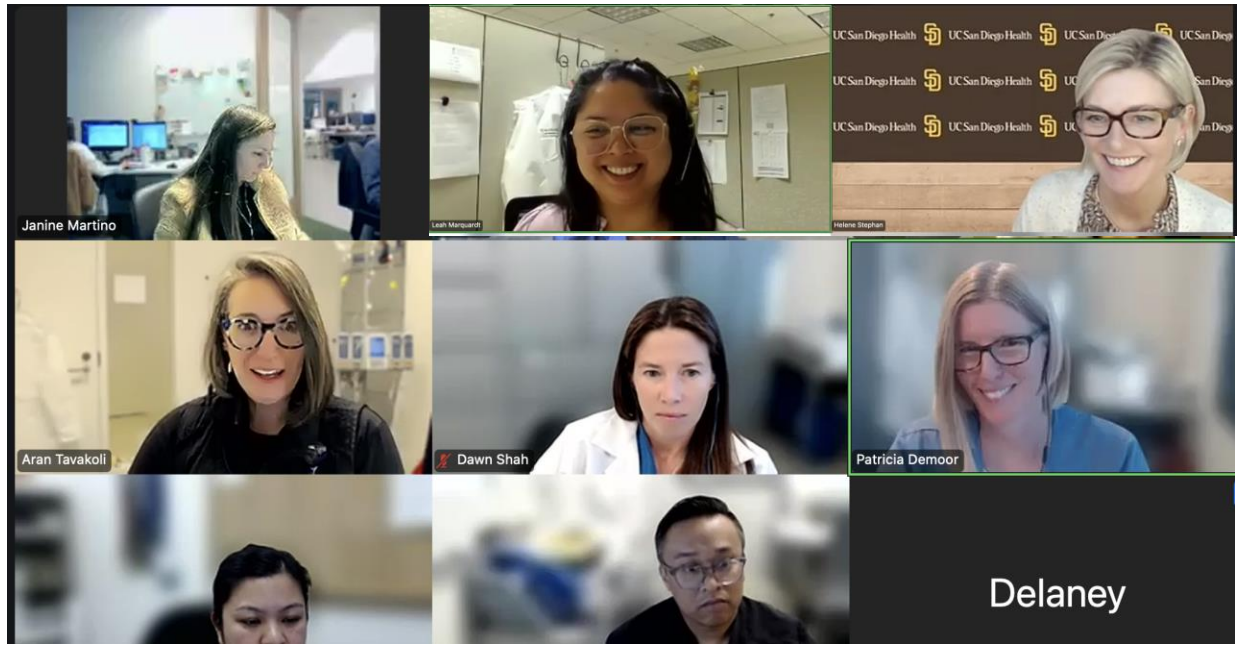
# TILs Takes a Team and Processes


UCSD as Authorized Treatment Center




TIL coordinator
Stem cell lab
Finance
Cell Regenerative team
Administration

Surgery
Medical oncology
Social Work
Pharmacy
Nursing


Joel Baumgartner, MD
Surgeon
CHELSEA FC
146


ConMed
stryker

# Post-surgery Pre-TIL

- CRM review
  - Team review
  - Admission plan
  - Conditioning inpatient v outpatient
- Restaging
  - CT CAP (measurable disease)
  - MR brain (if not done in the last 3 months or history of brain lesions)
- Bridging therapy
  - Targeted therapy
  - Other

# Post Hospital Care

Discharged when:

- ANC is >500 cells/mm or trending to >500 cells/mm3 in next 24 hours
- Afebrile for 24 hours after stopping intravenous antibiotics and fluconazole (~7–10 days post TIL infusion).
- Platelet counts should be >20 000/mm3 independent of transfusion.

UC San Diego Health Cell and Regenerative Medicine Antimicrobial Prophylaxis Guide

**Table 1. Prophylaxis Medications and Durations for CRM Patients**

| Type | Prophylaxis & Dose | Start | Duration |
|---|---|---|---|
| Bacterial | Levaquin 500mg daily[a] | ▪ TILs: Day 0<br>▪ All others: when ANC<1000 cells/mm$^3$ | TILs: Until ANC>500 cells/mm$^3$<br>All others: Until ANC >1000 cells/mm$^3$ |
| Pneumocystis Pneumonia | Bactrim DS daily 3x/week[b] | Day +21 | Until ALC >1000 cells/mm$^3$ or CD4>200 |
| Fungal | Fluconazole 400 mg PO (or IV) daily[c] | Day +1 | TILs: Until ANC>500 cells/mm$^3$<br>Others: ANC>1000 cells/mm$^3$ |
| HSV and VZV | Acyclovir 400 mg bid[d] | ▪ TILs Day +7 (if HSV serology pos, Day +1)<br>▪ All others Day -1[e] | Continue to Day +90 |
| CMV | ▪ No prophylaxis.<br>▪ If fludarabine based conditioning, recommend weekly CMV monitoring Day +7 through Day +100<br>▪ Start treatment for detectable (≥35 IU/mL) CMV levels x2 tests<br>▪ Recommend ID consult for treatment recommendations | | |

Abbreviations: ANC = Absolute Neutrophil Count; HSV = Herpes Simplex Virus; VZV = Varicella Zoster Virus; CMV = Cytomegalovirus

***Always defer to specific protocol recommendations first**, however, if not specified may follow recommendations above

a) If allergic to fluoroquinolones, the alternative should be cefpodoxime 200mg PO BID
b) If sulfa-allergy, check a G6PD and choose alternative. Note: alternatives to Bactrim do not cover for toxoplasmosis.
    1. If G6PD negative: Dapsone 100mg PO daily
    2. If G6PD positive: Atovaquone 1500mg PO daily
    3. Pentamidine 4mg/kg IV q28 days
c) Alternative: Micafungin 100mg IV daily
d) Acyclovir requires renal dose adjustment. See BMT manual for IV recommendations.
e) Okay to start on admission, no need for outpatient prescription

# Questions

If TIL are not for everyone, what other options would you consider?

What are the surgical considerations for TIL therapy?

If a patient had toxicity with immune checkpoints, can they have TILs?

What other cell products are in development?

# Learning Objectives

~~Neoadjuvant surgical considerations regarding extent and timing of tumor resection~~

~~Understanding which immune therapy to choose for neoadjuvant treatment~~

What are the options for therapy beyond PD1 based treatments in advanced melanoma

Evaluation of patients for tumor infiltrating lymphocyte therapy, surgical considerations for tumor infiltrating lymphocyte tumor harvest

# Thank you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- gdaniels@health.ucsd.edu