Melanoma Surgery in the Era of Effective Systemic Treatments

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University Hospitals
Seidman Cancer Center
Cleveland | Ohio

Case Western Reserve University
Case Comprehensive Cancer Center

Disclosures

- Advisory Board: **M3D, inc.**

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Objectives:

- Past data leading to Surgical De-escalations for Melanoma
- Standard systemic melanoma treatments and how they have impacted surgical care
- Ongoing efforts to Personalize Melanoma Surgery

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Melanoma Epidemiology

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Epidemiology:

	Common Types of Cancer	Estimated New Cases 2024	Estimated Deaths 2024
1.	Breast Cancer (Female)	310,720	42,250
2.	Prostate Cancer	299,010	35,250
3.	Lung and Bronchus Cancer	234,580	125,070
4.	Colorectal Cancer	152,810	53,010
5.	**Melanoma of the Skin**	**100,640**	**8,290**
6.	Bladder Cancer	83,190	16,840
7.	Kidney and Renal Pelvis Cancer	81,610	14,390
8.	Non-Hodgkin Lymphoma	80,620	20,140
9.	Uterine Cancer	67,880	13,250
10.	Pancreatic Cancer	66,440	51,750

Melanoma of the skin represents 5.0% of all new cancer cases in the U.S.

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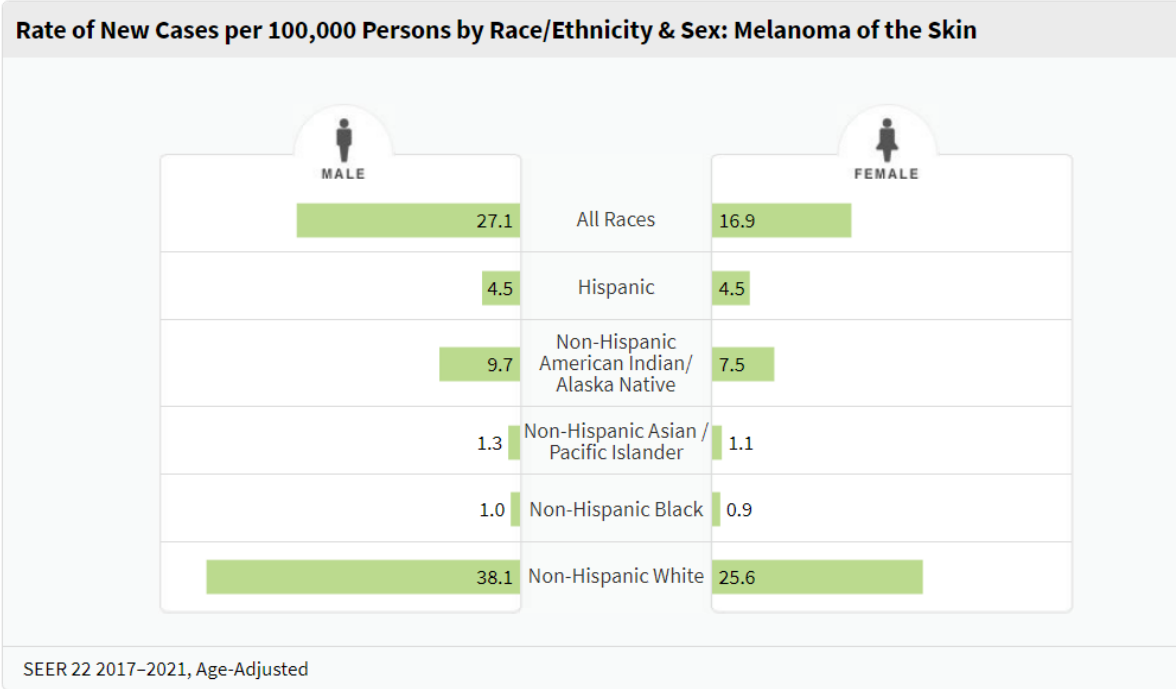
SEER.cancer.gov. 2024 Cancer Stat Facts: Melanoma of the Skin

Epidemiology:

- **Sex:**
  - **M > W**



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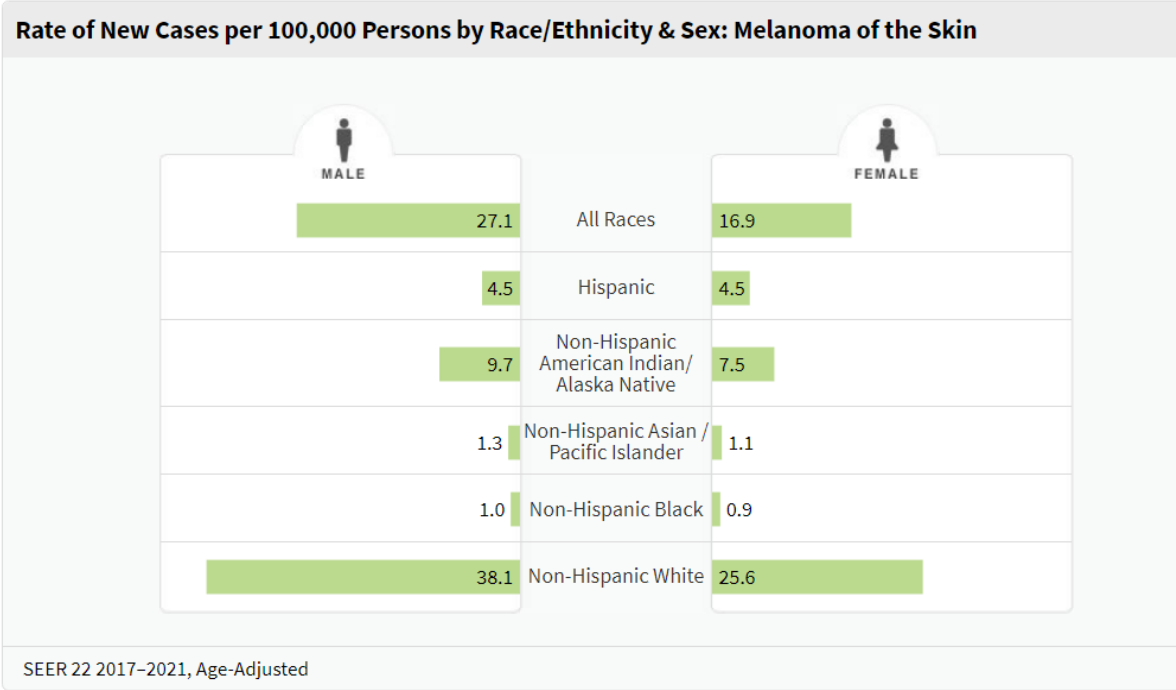
1) SEER.cancer.gov. 2020 Cancer Stat Facts: Melanoma of the Skin
2) American Cancer Society
3) Tripathi R, et al. J Am Acad Derm 2020

Epidemiology:

- Sex:
  - M > W
- **Average Age:**
  - **66 years old**
  - **(2nd most common in young adults)**



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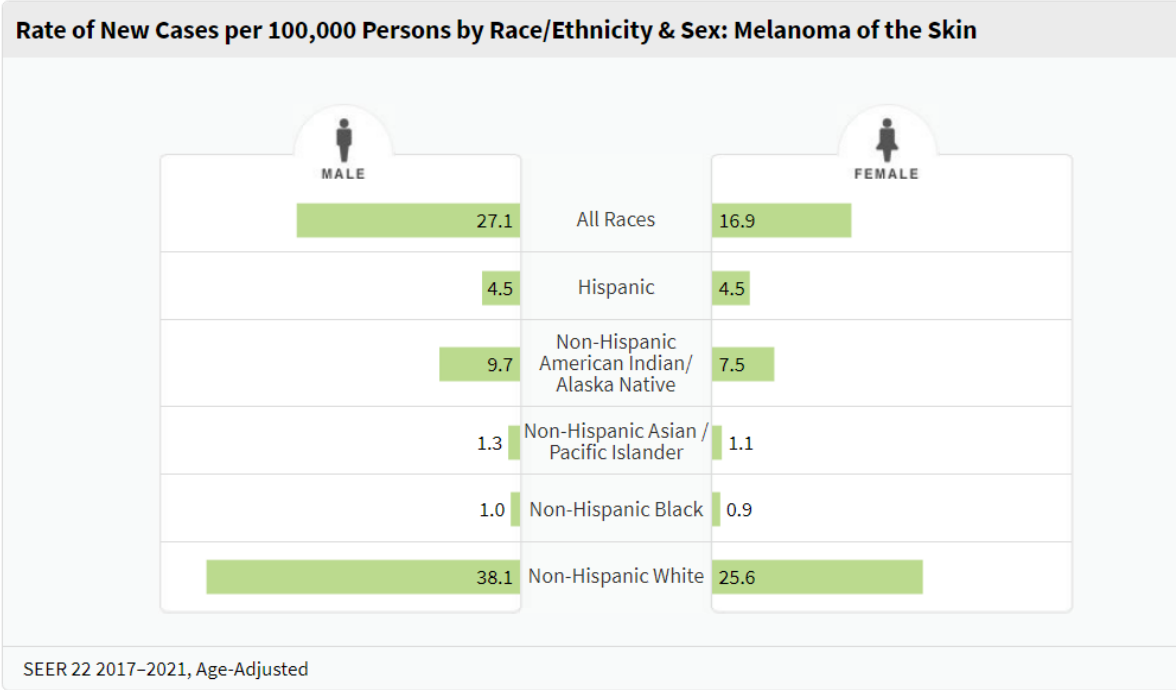
1) SEER.cancer.gov. 2020 Cancer Stat Facts: Melanoma of the Skin
2) American Cancer Society
3) Tripathi R, et al. J Am Acad Derm 2020

Epidemiology:

- Sex:
  - M > W
- Average Age:
  - 66 years old
  - (2nd most common in young adults)
- **Race/Ethnicity:**
  - **Non-Hispanic White**



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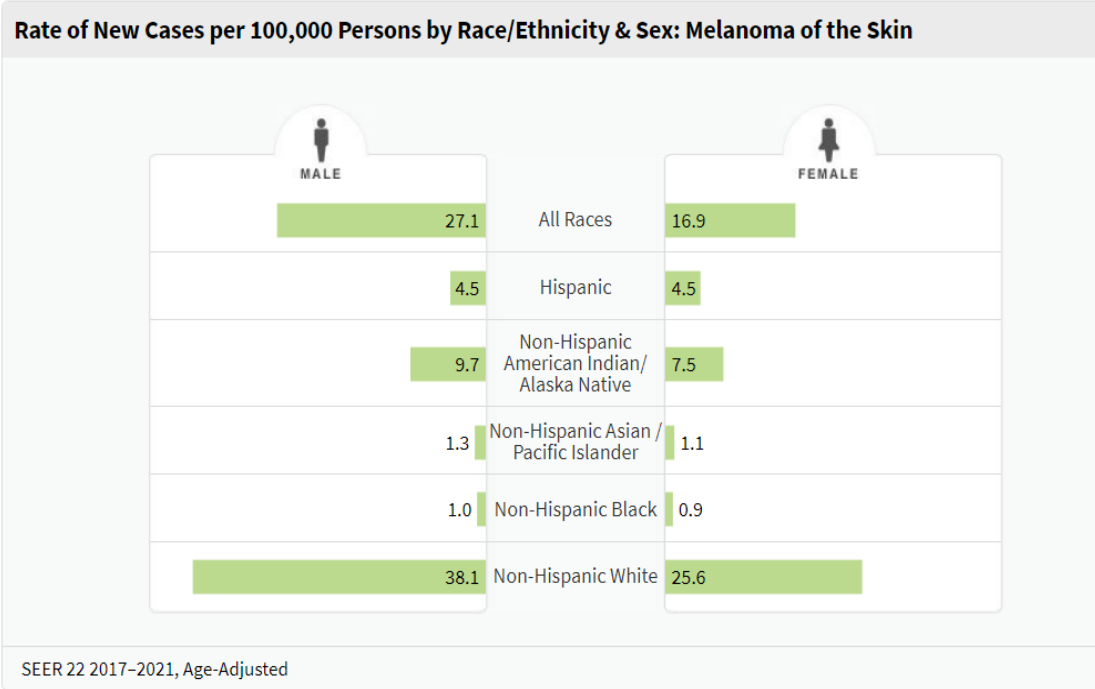
1) SEER.cancer.gov. 2020 Cancer Stat Facts: Melanoma of the Skin
2) American Cancer Society
3) Tripathi R, et al. J Am Acad Derm 2020

Epidemiology:

- Sex:
  - Men > Women
    (<50 years old: Women > Men)
- Average Age:
  - 66 years old
  - (2nd most common in young adults)
- Race/Ethnicity:
  - Non-Hispanic White
- **Lifetime Risk:**
  White – 2.6%
  Hispanic – 0.6%
  Black – 0.1%

5-year Overall Survival:
94%
69%



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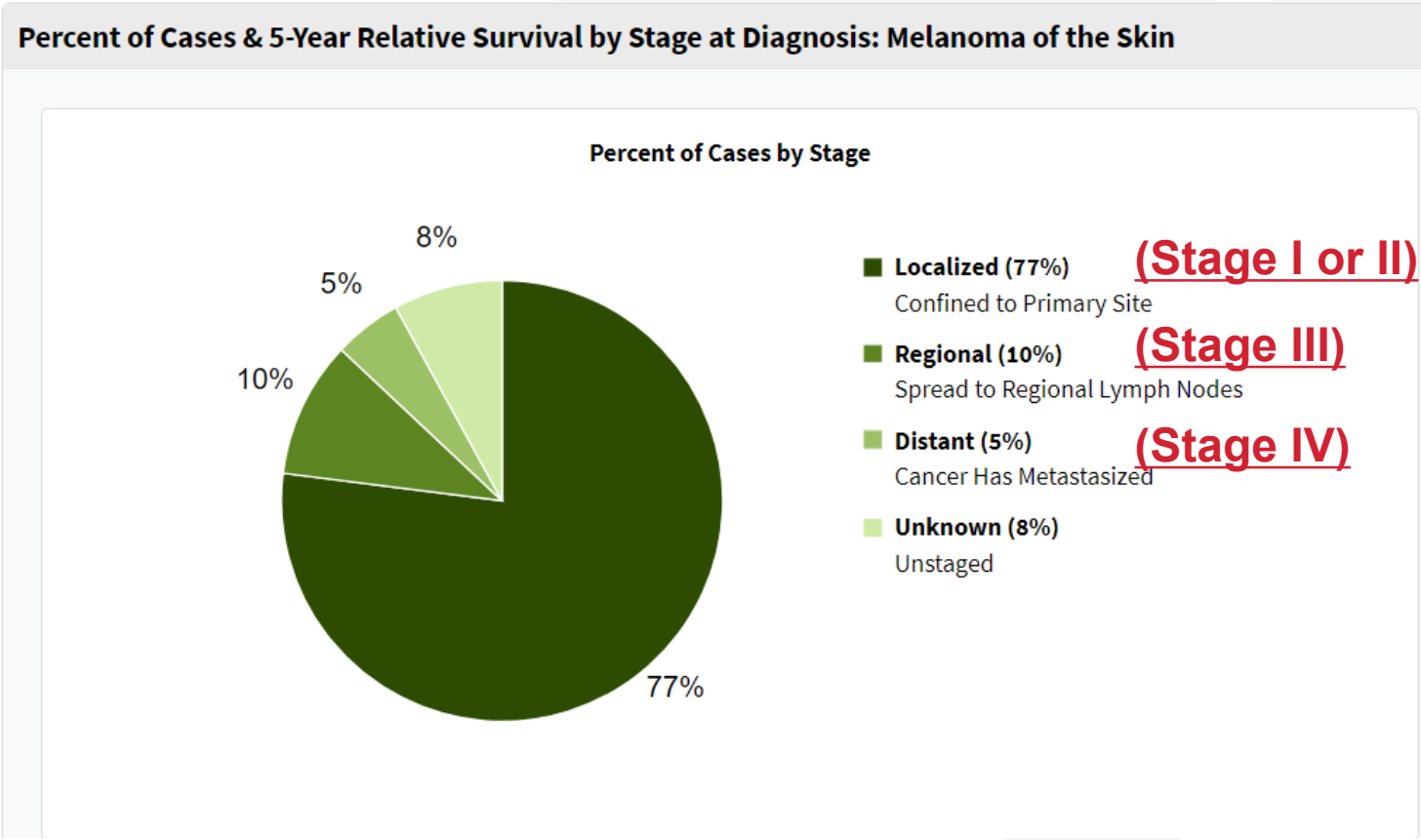
2) American Cancer Society
3) Tripathi R, et al. J Am Acad Derm 2020

Melanoma by Stage:



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SEER.cancer.gov. 2024 Cancer Stat Facts: Melanoma of the Skin

Prognosis and Systemic Therapy

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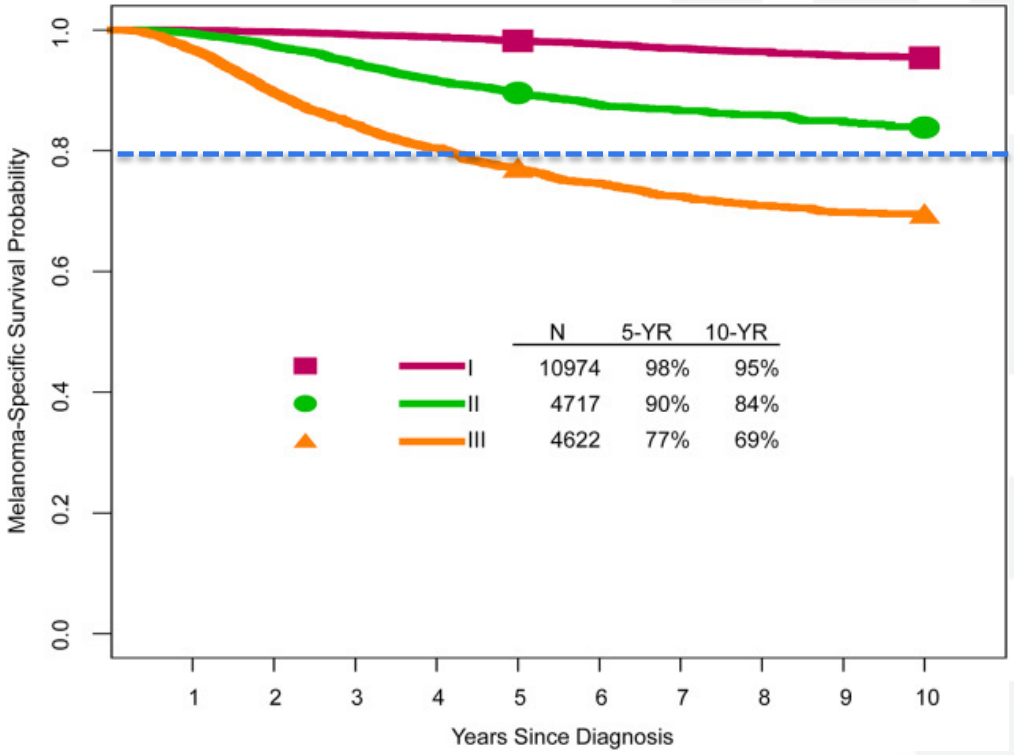
Survival for Stage I - III



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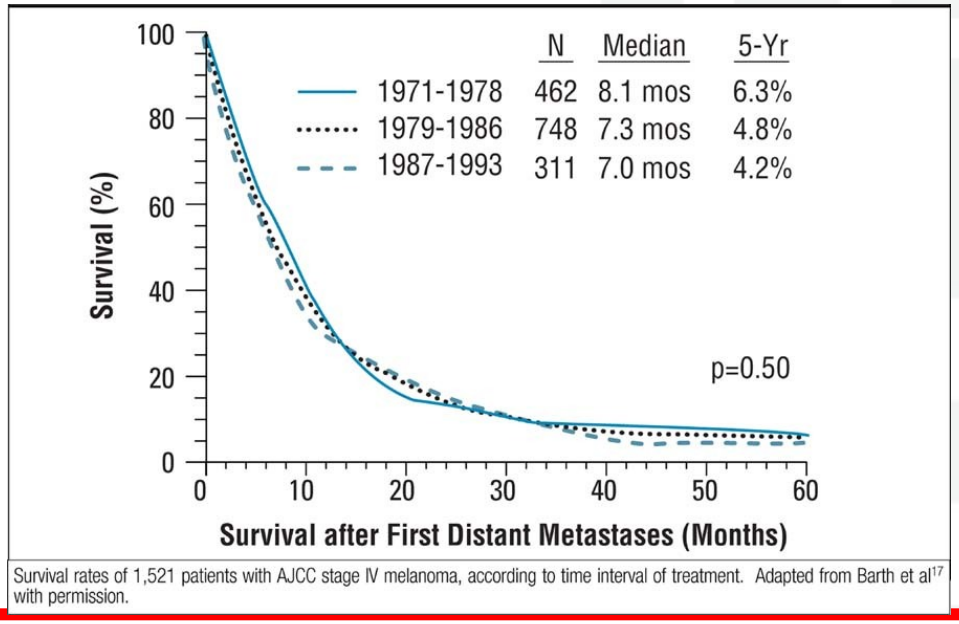
Gershenwald JE, et al. CA Cancer J Clin. 2017 Nov;67(6):472-492.

Survival for Stage IV (Metastatic) Melanoma, 1971-1993



Survival rates of 1,521 patients with AJCC stage IV melanoma, according to time interval of treatment. Adapted from Barth et al[17] with permission.

No significant improvement in overall survival for metastatic melanoma in three decades

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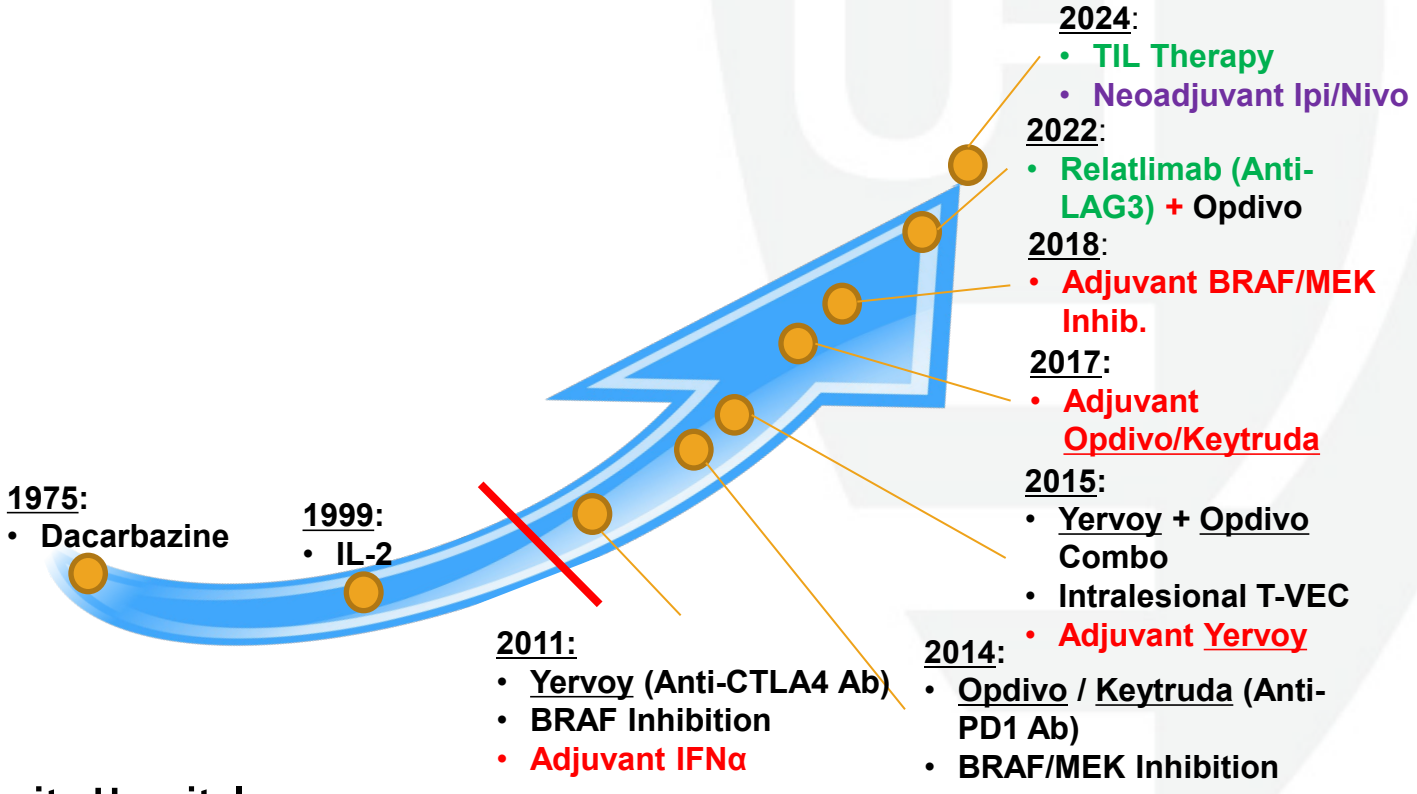
Barth, et al. *J Am Coll Surg* 1995;181:193-201

Melanoma: Therapeutic Timeline



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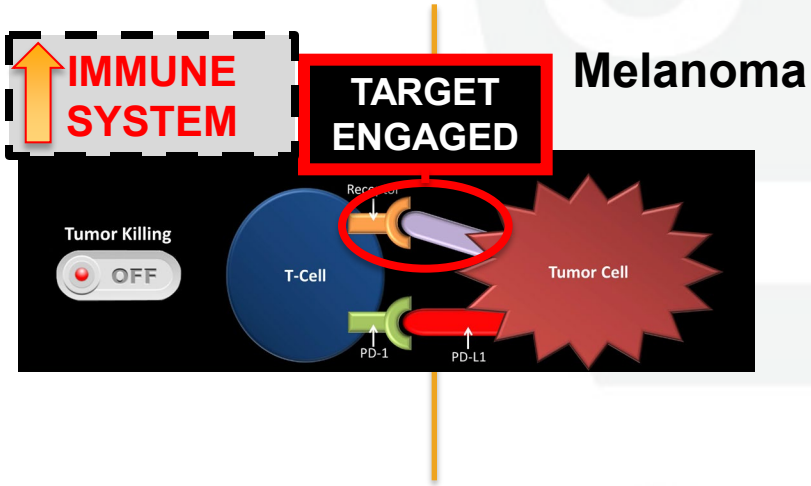
Checkpoint Inhibitor Immunotherapy



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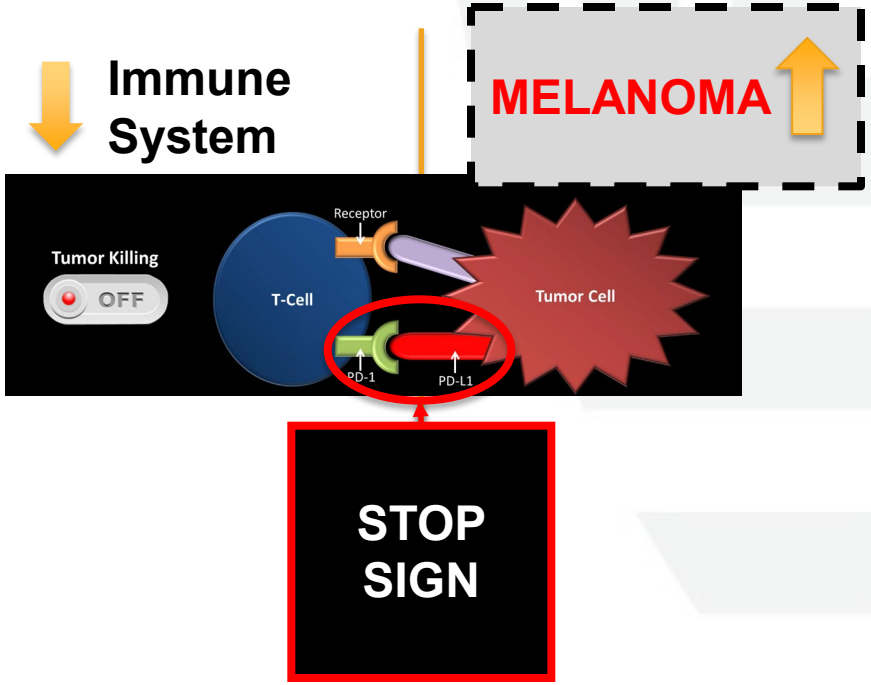

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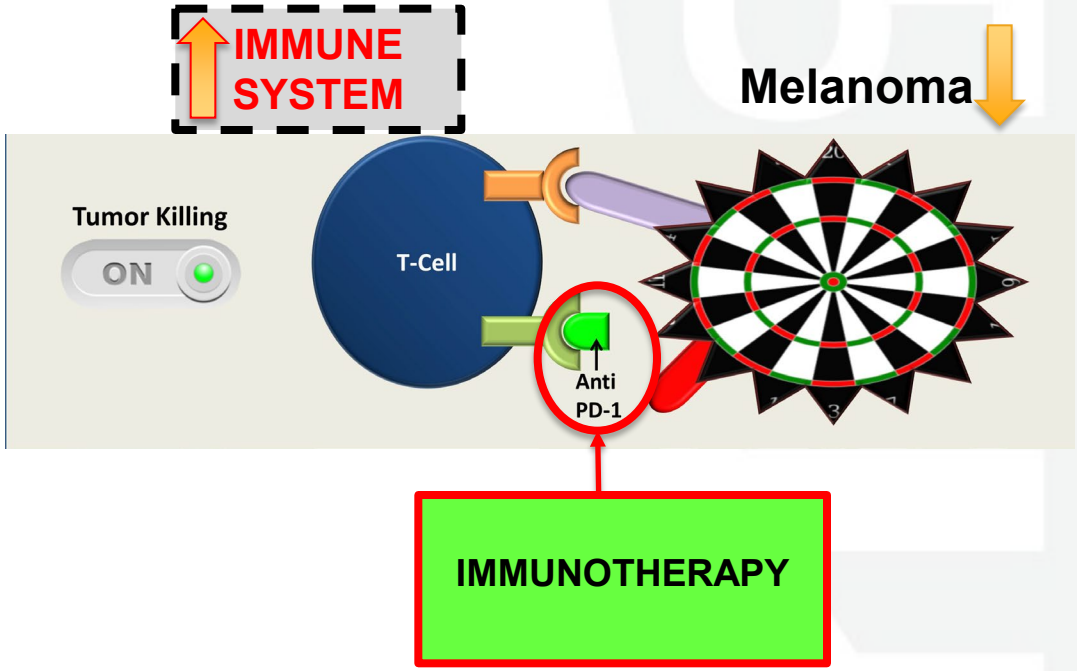

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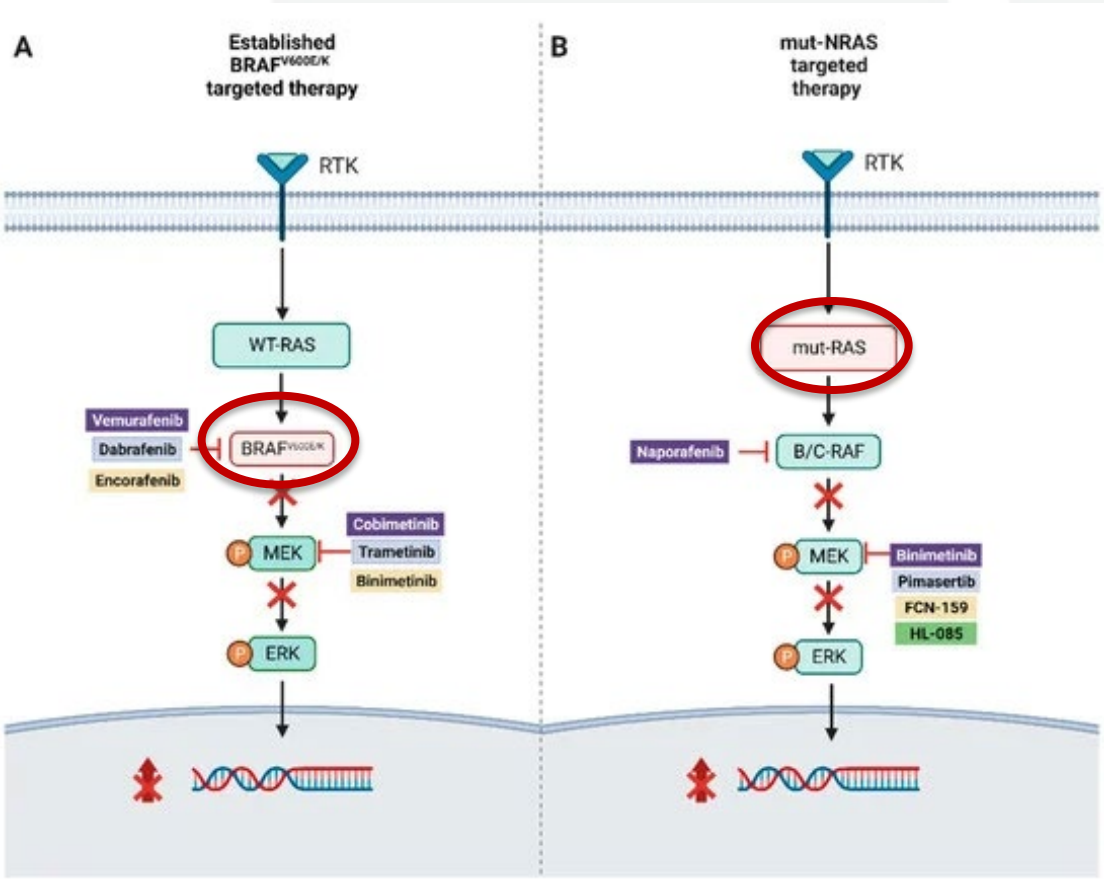
Targeted Therapies

BRAF and MEK Inhibitors



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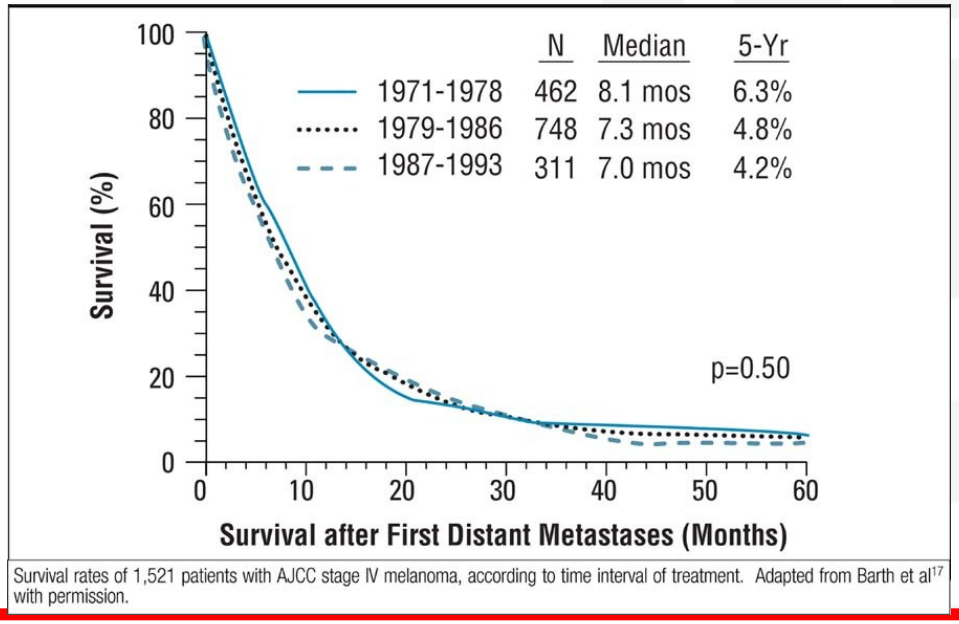
Fernandez MF, Choi J, Sosman J. Cancers (Basel). 2023 Jun 17;15(12)

Survival for Stage IV (Metastatic) Melanoma, 1971-1993



Survival rates of 1,521 patients with AJCC stage IV melanoma, according to time interval of treatment. Adapted from Barth et al[17] with permission.

No significant improvement in overall survival for metastatic melanoma in three decades

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Barth, et al. *J Am Coll Surg* 1995;181:193-201

Systemic Therapies for Metastatic Disease

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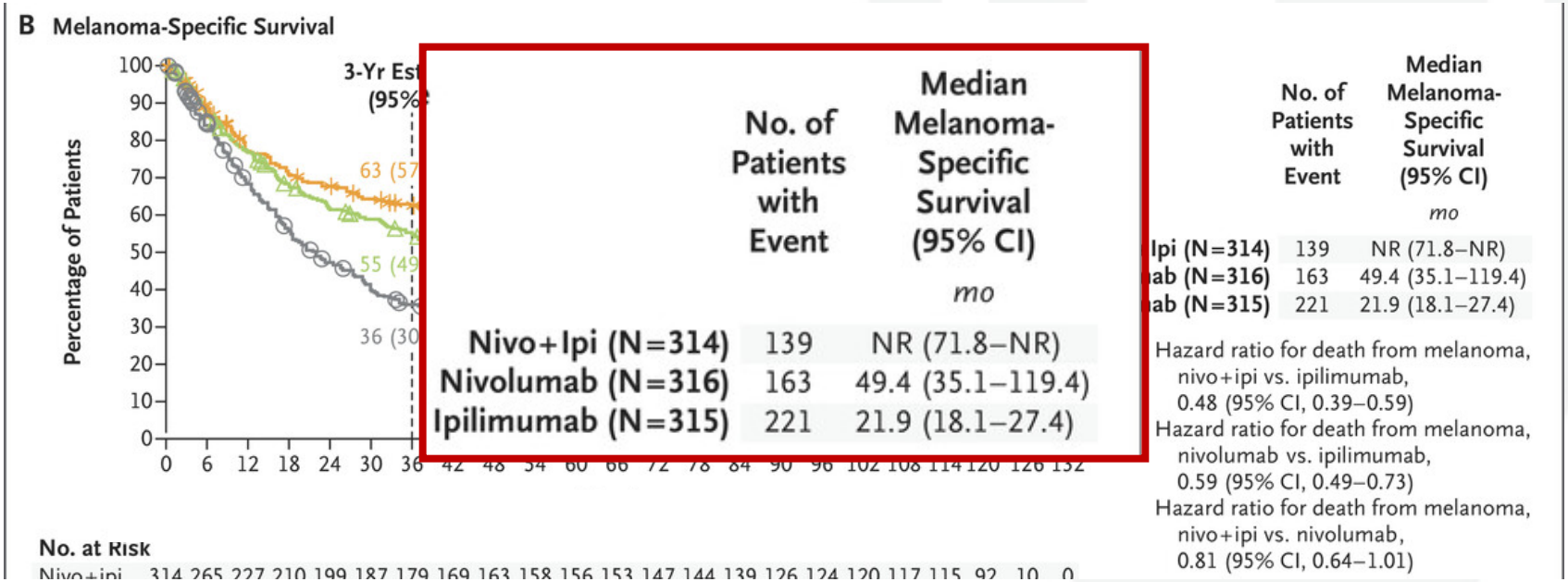
CHECKMATE 067 Trial



	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)

	No. of Patients with Event	Median Melanoma-Specific Survival (95% CI) mo
Ipi (N=314)	139	NR (71.8–NR)
ab (N=316)	163	49.4 (35.1–119.4)
ab (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)

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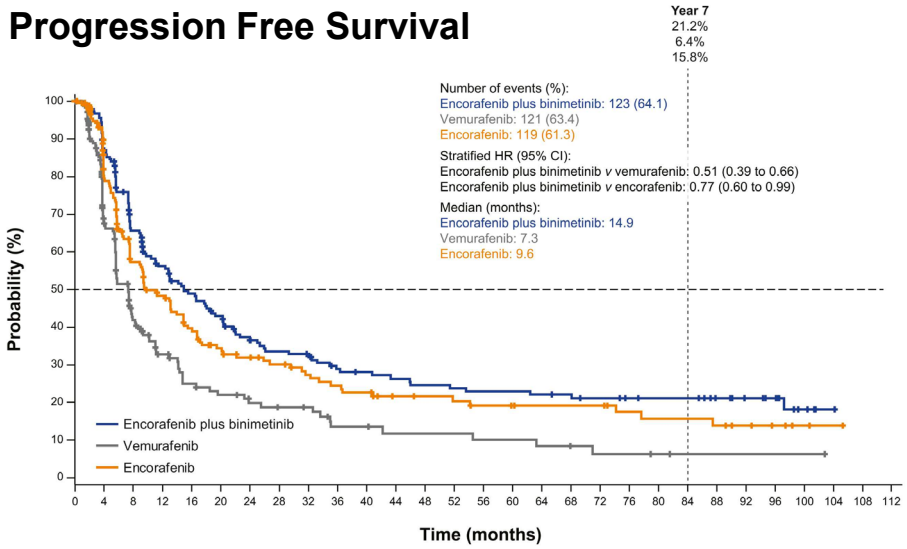
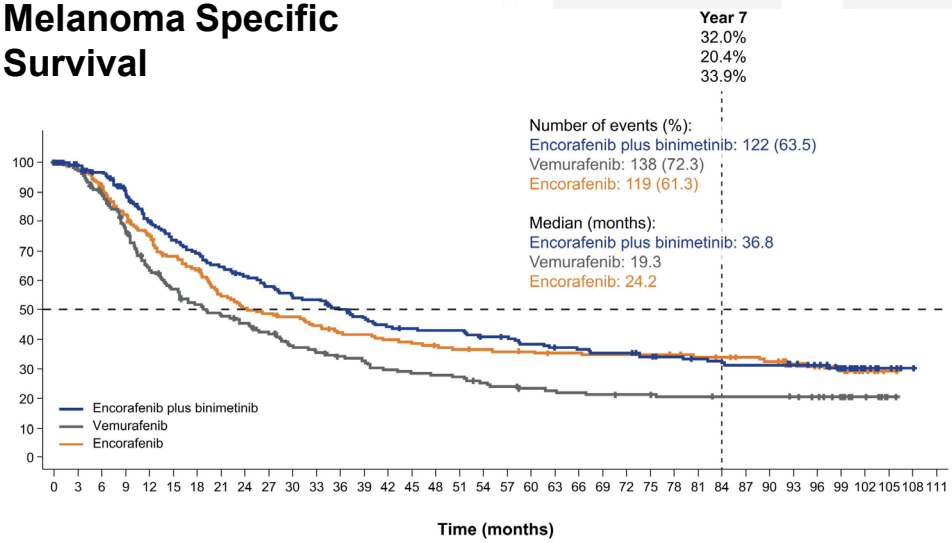
Wolchok JD, et al. N Engl J Med. 2024 Sep 15.

COLUMBUS Trial (Encorafenib/Binimetinib)

Progression Free Survival



Melanoma Specific Survival



Schadendorf D, et al. Eur J Cancer. 2024 Jun;204:114073.

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Adjuvant Therapies

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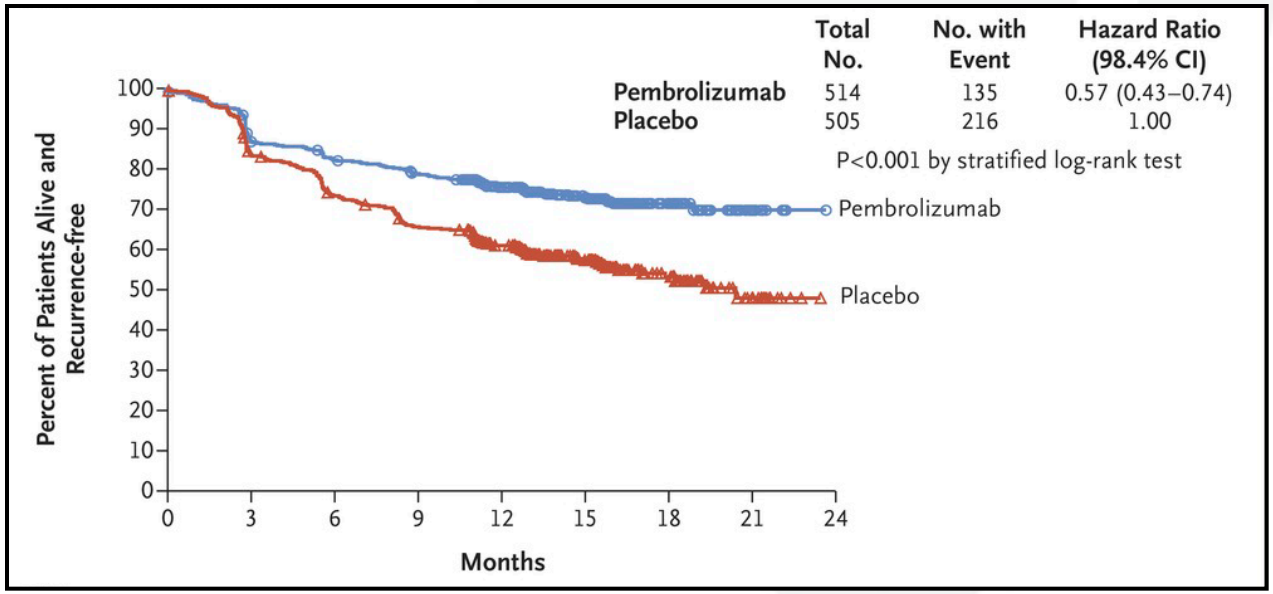
KEYNOTE-054 Trial

- **<u>Adjuvant</u> Pembrolizumab versus Placebo**
- Stage IIIA (>1mm), IIIB, IIIC (CLND mandated)
- Ulcerated melanoma and macroscopic lymph node benefited.
- Grade 3/4 adverse Events
  - IrAE- ~7%
  - Overall- 14%



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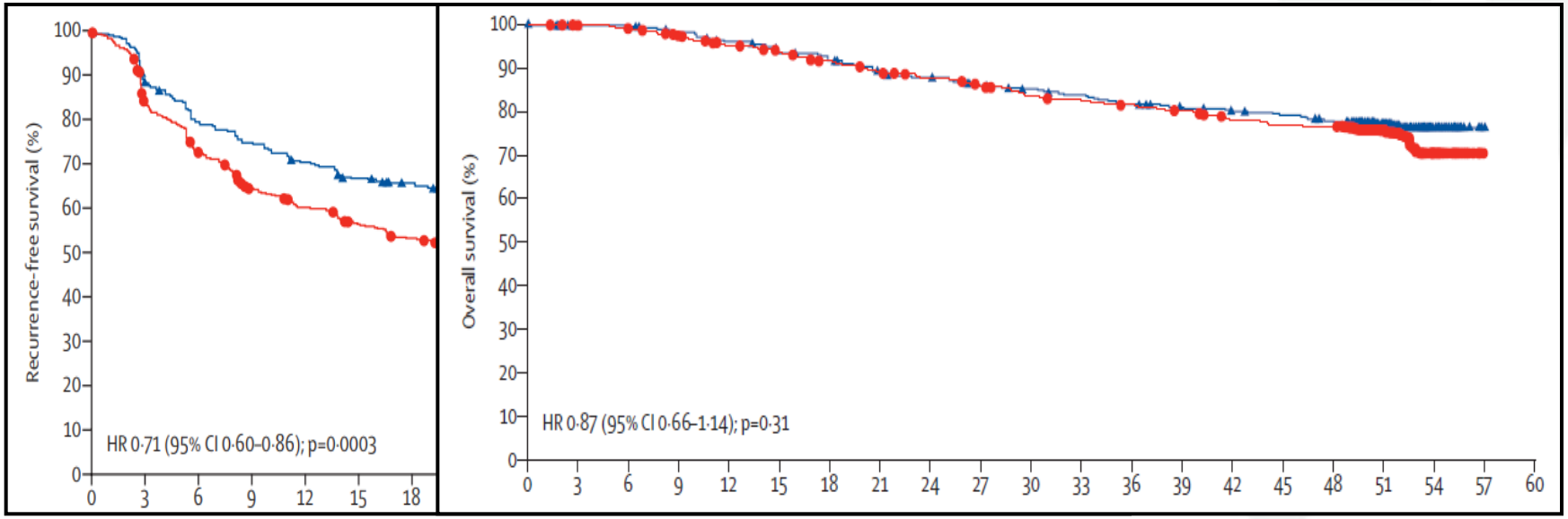
Eggermont et al. *NEJM 2018*

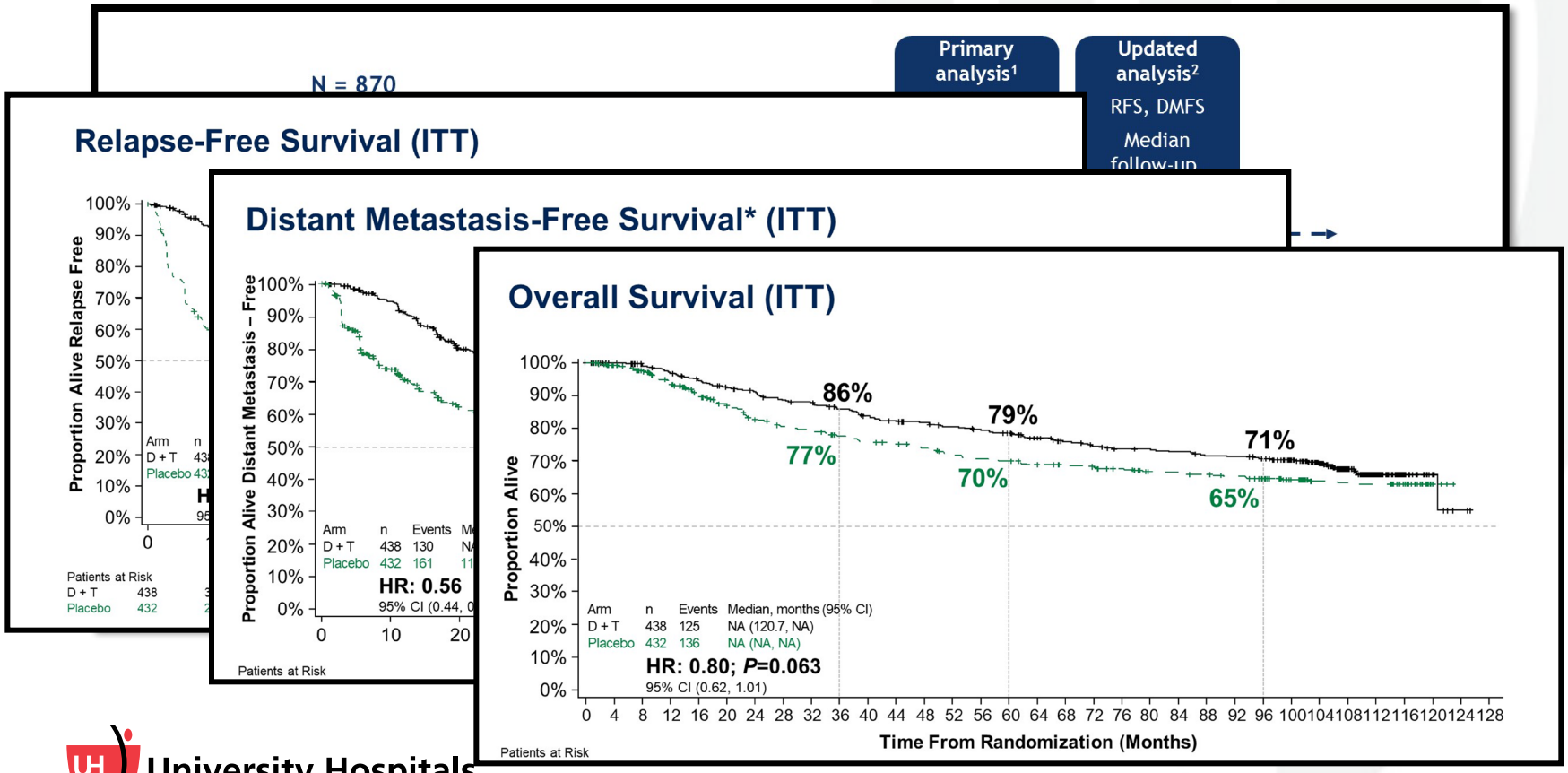
CHECKMATE 238 Trial

- Adjuvant Nivolumab 3mg/kg versus Ipilimumab 10mg/kg
- Stage IIIB, IIIC, IV completely resected (CLND mandated)
- Grade 3/4 adverse Events
  - Overall- 14%



Weber NEJM 2017

COMBI-AD Trial



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What Role Does Surgery Play in Melanoma Management?

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Oncologic Surgery:

Wide Excision of the Primary Melanoma

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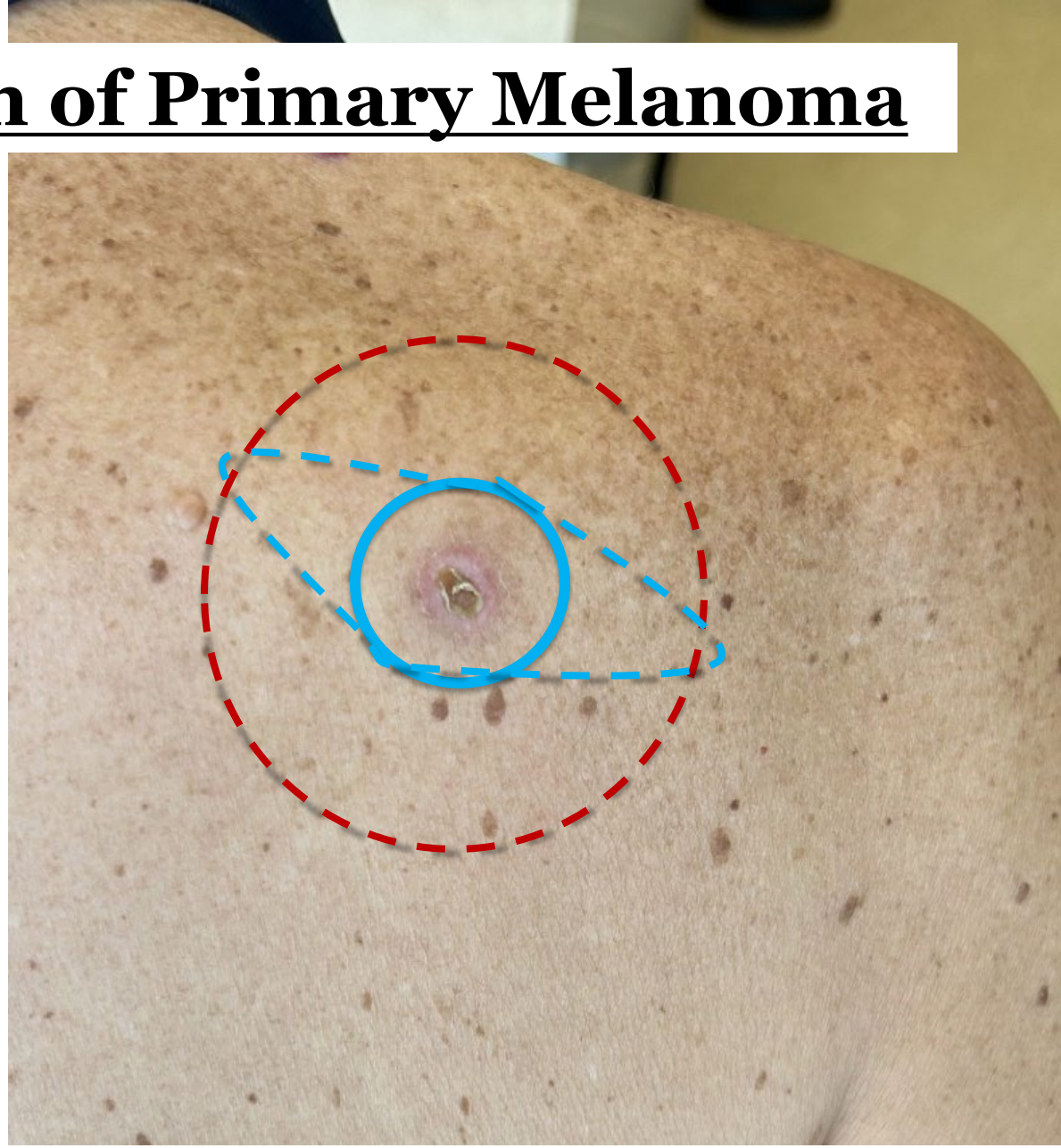
Wide Excision of Primary Melanoma

Thin Melanomas *(≤2mm)*

– 3cm margins

3cm = 1cm Margin

- Veronesi, et al. N Engl J Med. 1988 May 5;318(18):1159-62.



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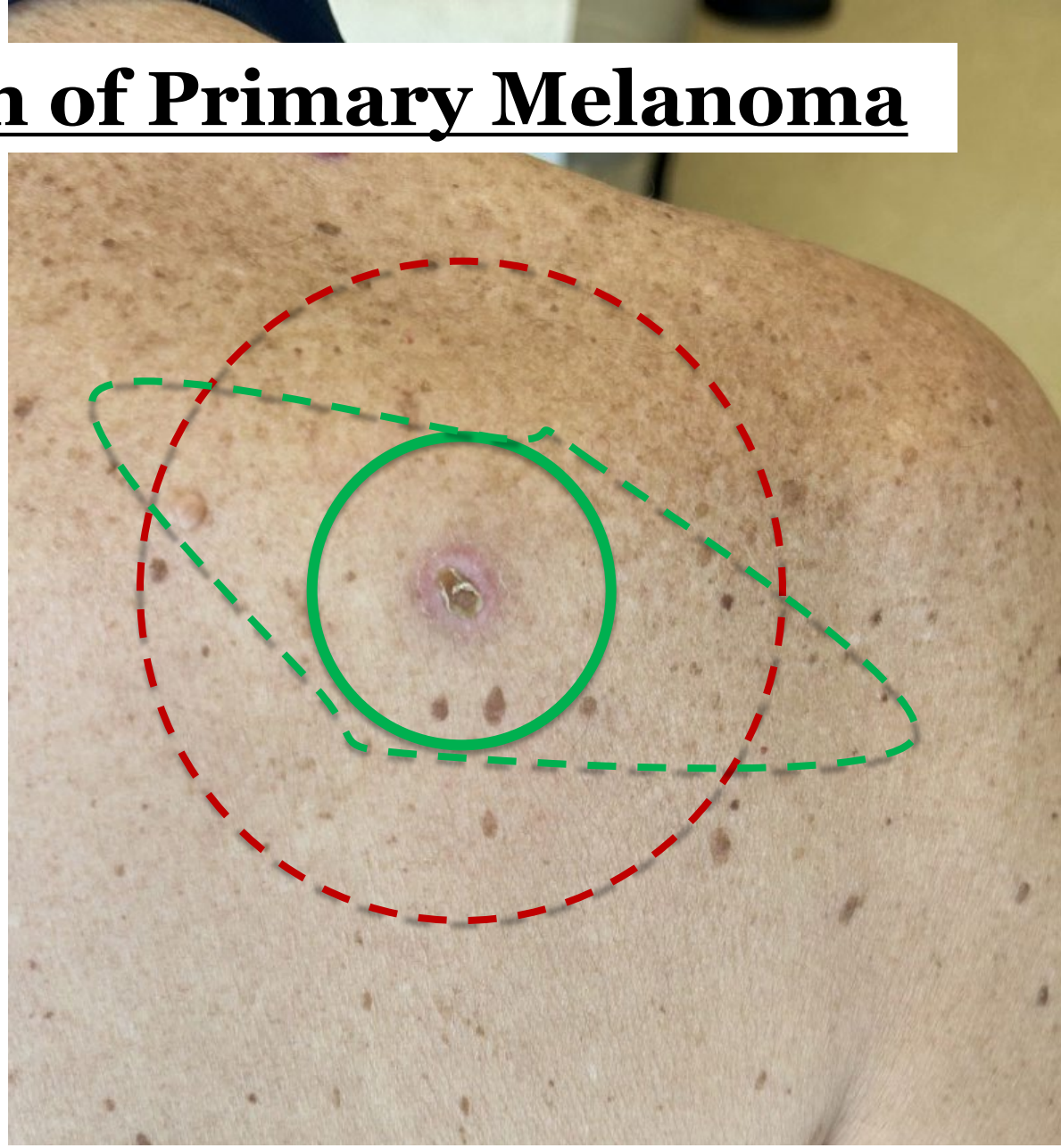
Wide Excision of Primary Melanoma

Thick Melanomas **(≥1mm)**

– 4-5cm margins

4cm = 2cm Margin

- Balch, et al. Ann Surg. 1993 Sep;218(3):262-7



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NCCN Guidelines:

- **1.0mm or less -> 1cm margin**
- **1.1 – 2.0mm -> 1-2cm margins**
- **>2.0mm -> 2cm margins**

De-escalation

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Ongoing!

Melanoma Margins Trial - MelMarT-II

International, Multi-Institutional
12/2019 – Ongoing

Is a 1cm margin adequate for most patients?

Secondary Outcomes: Local Recurrence, Distant DFS, Quality of Life

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De-escalation?

Surgical Nodal Staging:

Nodal Basins

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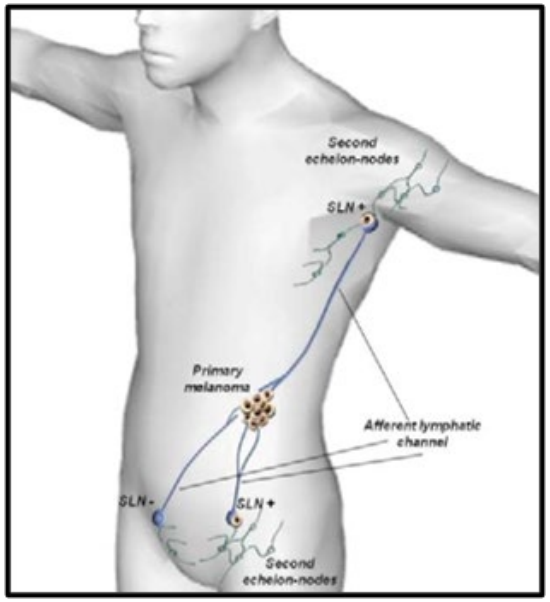
Nodal Management



Elective Lymph Node Dissection

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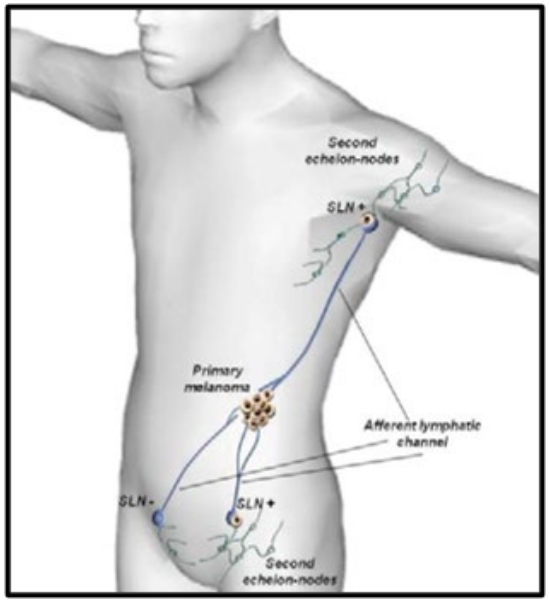
Nodal Management



Therapeutic Lymph Node Dissection
(for clinically recurrent disease)

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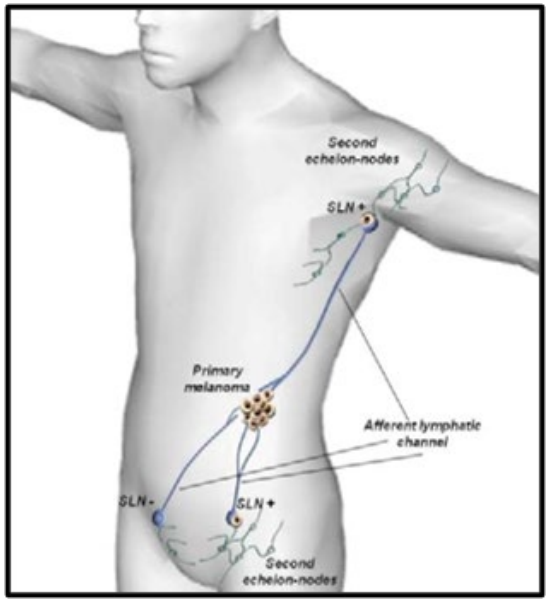
Nodal Management



1990 –**Sentinel Lymph Node Biopsy** introduced at the Society of Surgical Oncology (SSO)

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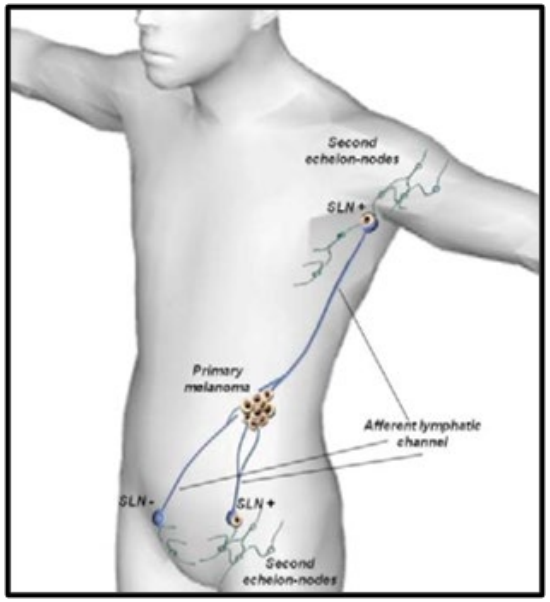
Nodal Management – Occult Nodal Disease



MSLT-I trial

1661 patients
1347 intermediate
344 thick
10-year mean follow-up

Does SLNB with reflex CLND improve Melanoma Specific Survival (MSS)?

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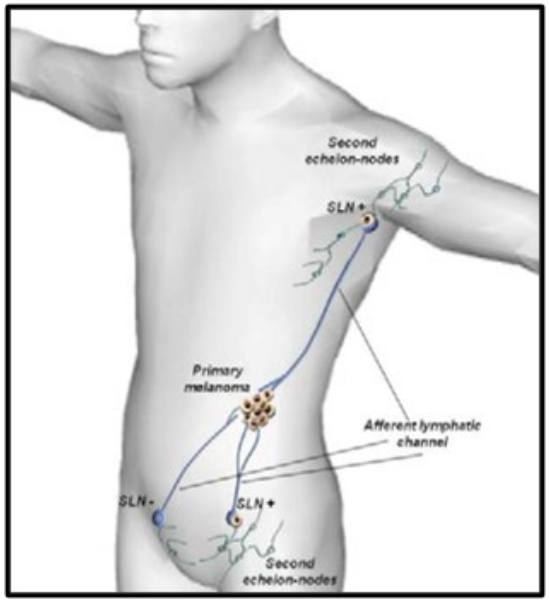
Nodal Management – Occult Nodal Disease



MSLT-I trial

- ***Improved Disease Free Survival***
  (specifically nodal recurrence)
- ***No Difference in MSS for all patients***
- ***Prognosis: SLN neg > SLN pos***
- ***Incidence of nodal mets***
  - SLNB: Intermed – 16%; Thick – 32%
  - OBS $_{10\ yrs}$: Intermed – 19%; Thick – 41%

Morton D, et al. N Engl J Med 2006; 355:1307-1317

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Importance of sentinel lymph node

Table 1. Multivariate Hazard Ratios for Disease Recurrence and Death among Patients with Intermediate-Thickness Melanoma Who Underwent Sentinel-Node Biopsy, According to Prognostic Indicator.

Prognostic Indicator	Disease Recurrence		Death from Melanoma	
Sex (male vs. female)	0.94 (0.70–1.26)	0.66	1.22 (0.82–1.79)	0.32
Age (per 1-yr increase)	1.01 (1.00–1.02)	0.07	1.01 (0.99–1.02)	0.33
Clark level (IV or V vs. III)	1.27 (0.94–1.71)	0.12	1.07 (0.74–1.54)	0.73

* This group served as the reference group.

SLN status is the most important prognostic factor

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Current Standard Surgical Practice:

High-Risk Primary Melanoma

Wide excision
- Nodal Observation
  or
- Elective Lymph Node Dissection

Wide excision
- Sentinel Lymph Node Biopsy

De-escalation

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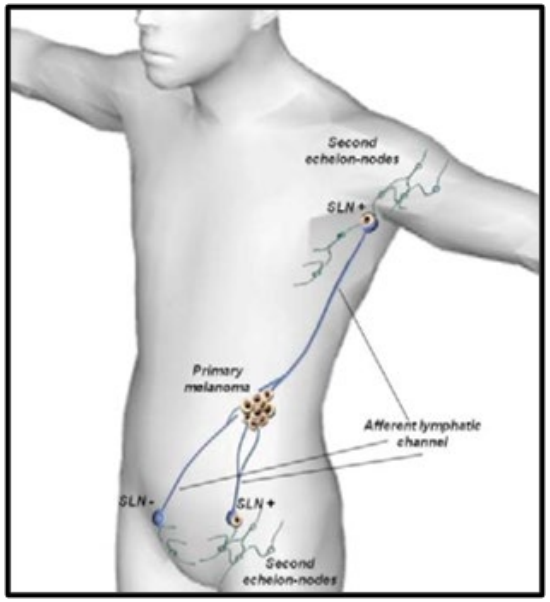
Nodal Management – Occult Nodal Disease



MSLT-II trial

Cutaneous Melanoma

Intermediate or thick melanoma (≥1.2mm Breslow depth)

Positive SLN

***QUESTION*:**

Does Immediate CLND improve Melanoma Specific Survival vs. Active Surveillance?

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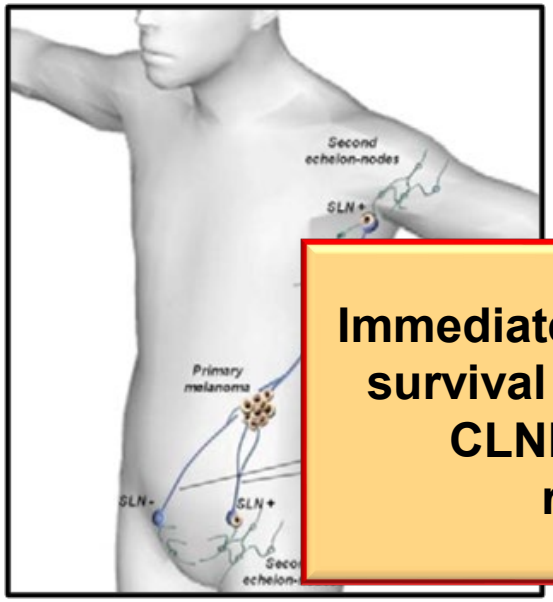
Nodal Management – Occult Nodal Disease



MSLT-II trial

43 month median follow up

- **3-year MSS: 86% vs 86%**
- **%**
- **nce 8% vs 23%**
- **6%**
- **und in ~20%**
- **No Subgroups were benefited by immediate CLND**

Immediate CLND provides no survival benefit vs delayed CLND at the time of recurrence.

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Prior Standard Surgical Practice:

Positive Sentinel Nodes (Microscopic)

Immediate CLND

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Current Surgical Practice:

Positive Sentinel Nodes (Microscopic)

~~Immediate CLND~~ → **Active Surveillance**

+ Delayed Lymph Node Dissection, if needed

De-escalation

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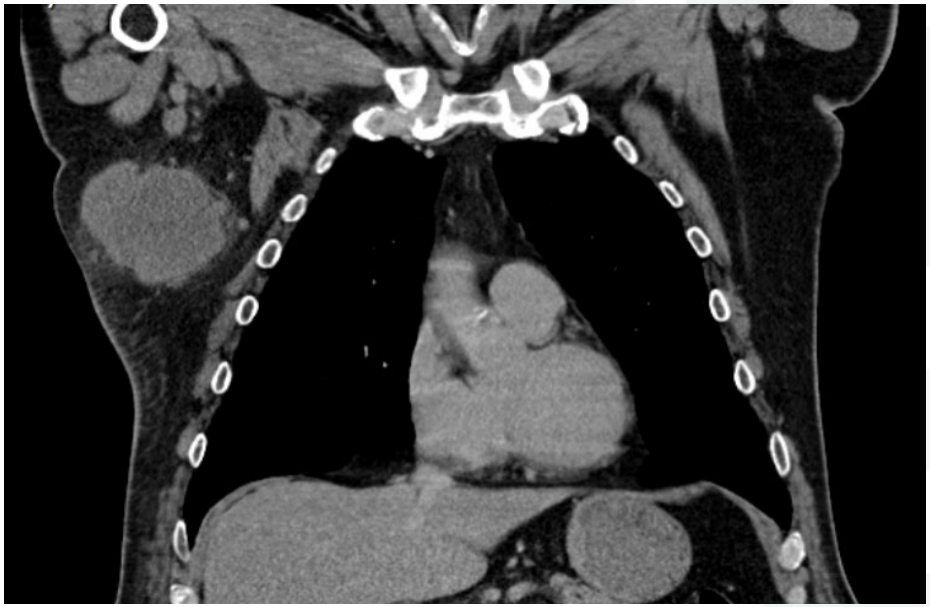
Nodal Management – Clinically Positive Disease



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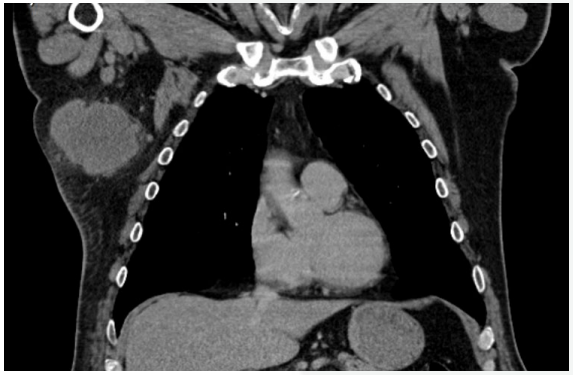
Current Surgical Practice:

Positive Clinical Nodes (Macroscopic)

Therapeutic Lymph Node Dissection (TLND)
+
Adjuvant therapy



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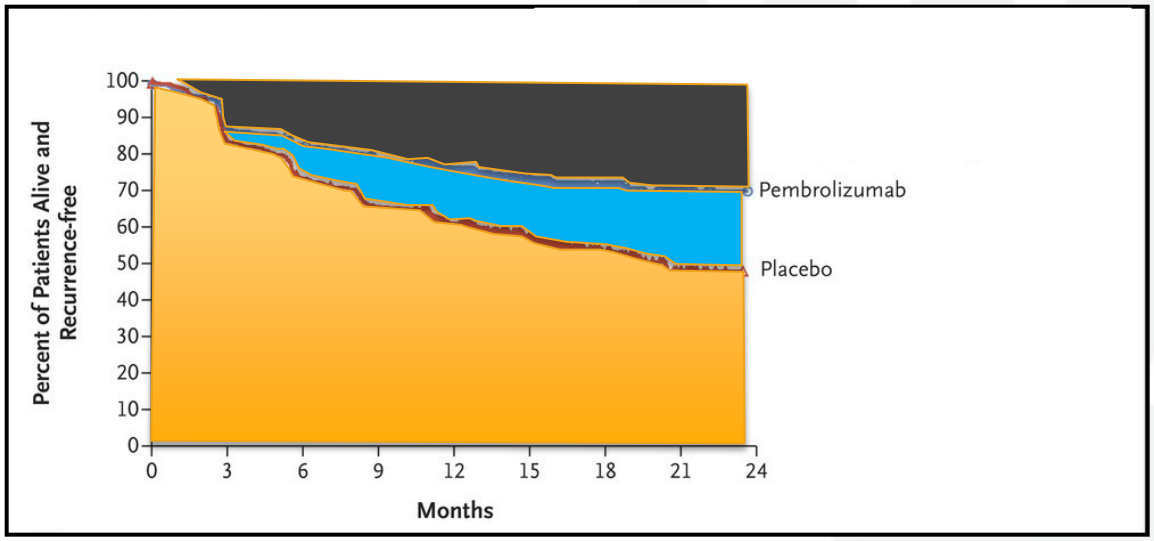
Is Adjuvant Immunotherapy for Everyone?

KEYNOTE 054 – Adjuvant Pembrolizumab



Can we do better?

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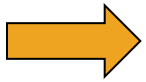
Current Surgical Practice:

Positive Clinical Nodes (Macroscopic)

Therapeutic Lymph Node Dissection (TLND)
+
Adjuvant therapy



Neoadjuvant Immunotherapy
+
TLND

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Why Neoadjuvant Therapy?

SWOG 1801 (2023)
Phase II

NADINA Trial (2024)
Phase III

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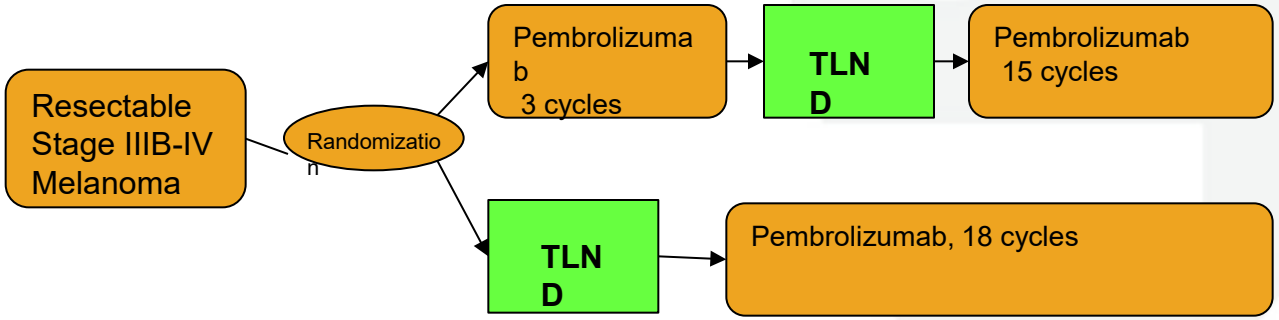
SWOG 1801 – Trial Design

Phase II



Patel SP, et al. N Engl J Med. 2023

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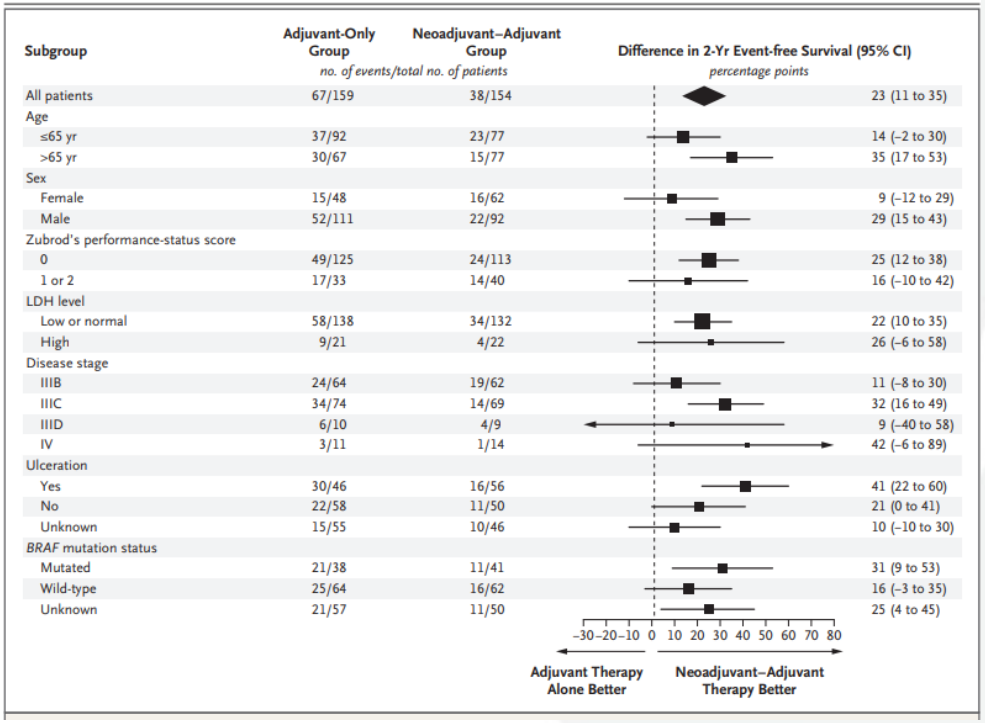
SWOG 1801

2-year Event-Free Survival (EFS) rate:

72% vs 49%



Subgroup	Adjuvant-Only Group	Neoadjuvant–Adjuvant Group
	no. of events/total no. of patients	
All patients	67/159	38/154
Age		
≤65 yr	37/92	23/77
>65 yr	30/67	15/77
Sex		
Female	15/48	16/62
Male	52/111	22/92
Zubrod's performance-status score		
0	49/125	24/113
1 or 2	17/33	14/40
LDH level		
Low or normal	58/138	34/132
High	9/21	4/22
Disease stage		
IIIB	24/64	19/62
IIIC	34/74	14/69
IIID	6/10	4/9
IV	3/11	1/14
Ulceration		
Yes	30/46	16/56
No	22/58	11/50
Unknown	15/55	10/46
BRAF mutation status		
Mutated	21/38	11/41
Wild-type	25/64	16/62
Unknown	21/57	11/50

Patel SP, et al. N Engl J Med. 2023

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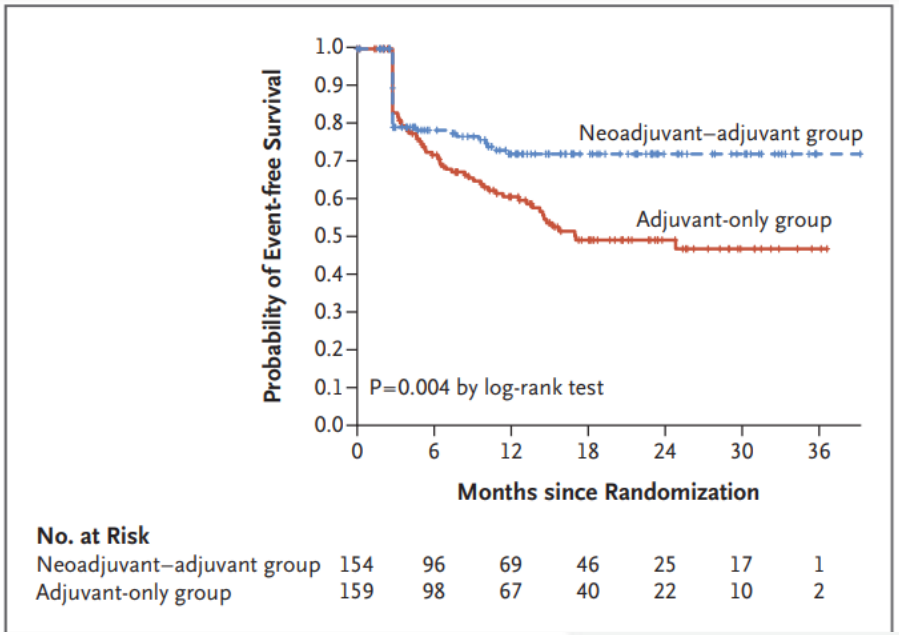
SWOG 1801

Primary Outcome:
Event-Free Survival

- **Hazard Ratio 0.58**



Patel SP, et al. N Engl J Med. 2023

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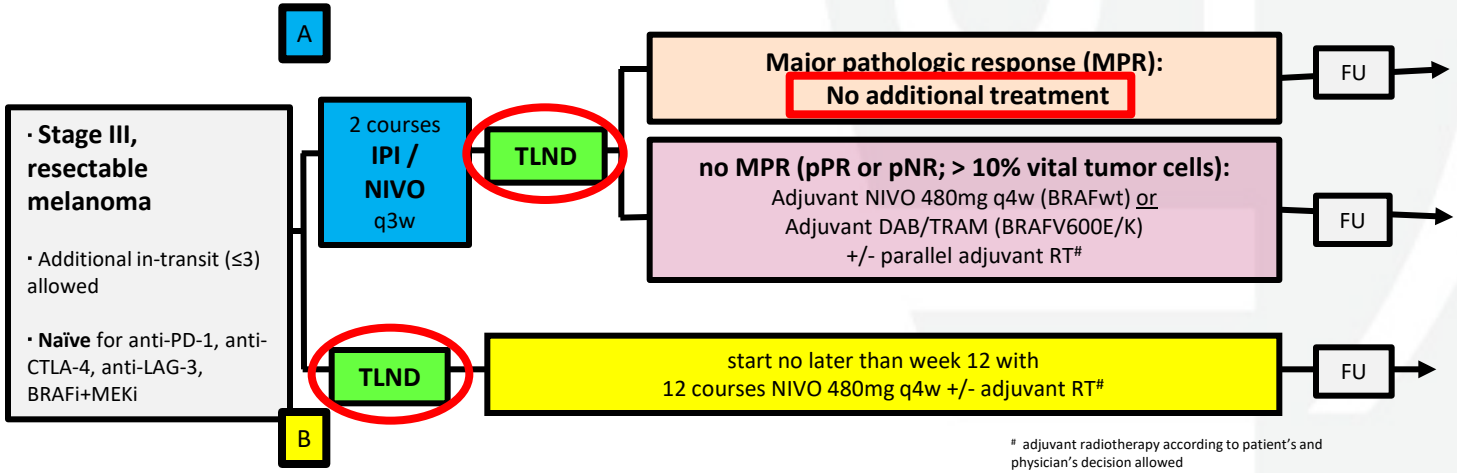
NADINA - Trial Design



adjuvant radiotherapy according to patient's and physician's decision allowed

Adapted from Christian U. Blank

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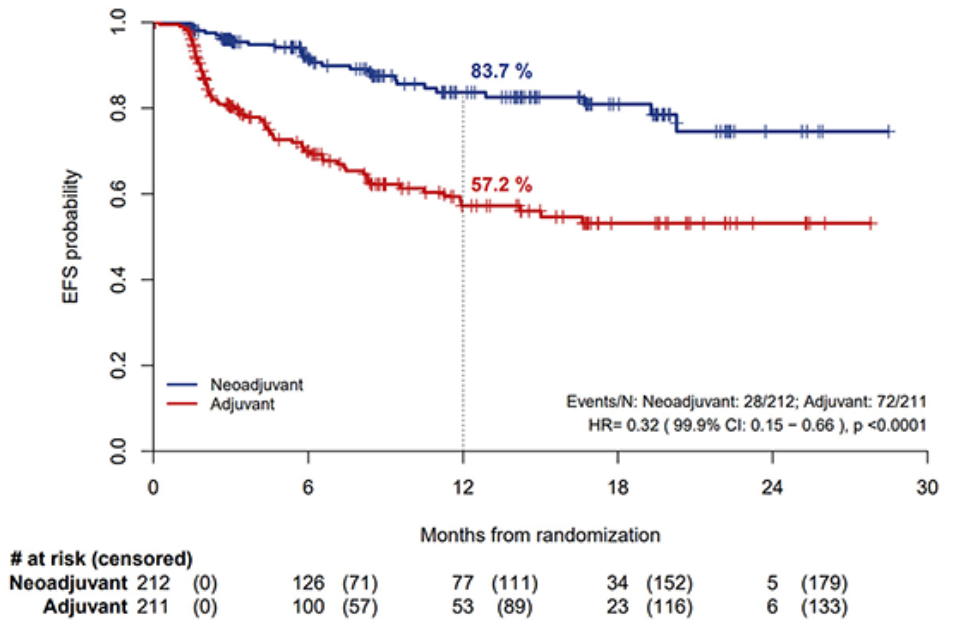
NADINA Trial

Primary Outcome:
Event-Free Survival

- **Hazard Ratio: 0.32**



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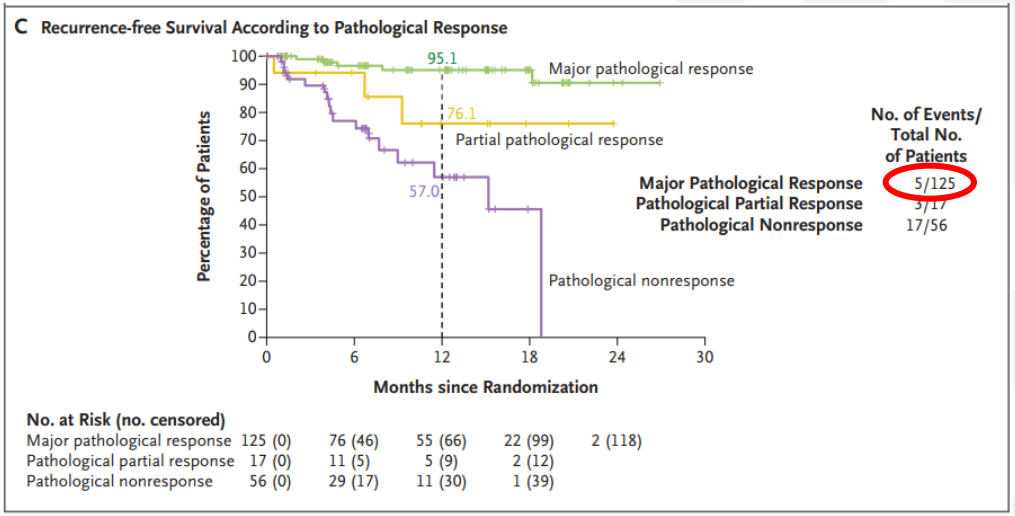
Blank CU, et al. N Engl J Med. 2024 Jun 2.

NADINA Trial



60 %

Blank CU, et al. N Engl J Med. 2024 Jun 2.

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Current Surgical Practice:

Positive Clinical Nodes (Macroscopic)

TLND
+
Adjuvant therapy

<

Neoadjuvant Therapy + TLND

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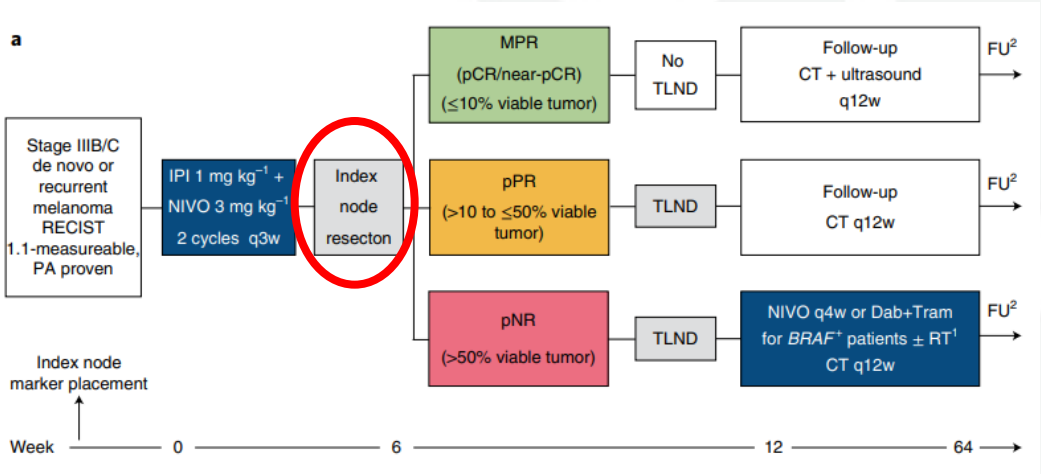
If Personalization of Surgery is the goal,

Can we identify the MPR and avoid TLND?

PRADO Trial



Reijers, I.L.M., et al. Nat Med 28, 1178–1188 (2022).

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Future Directions in Melanoma Surgery:

Is ***Index Node Resection*** adequate to select patients for no further surgery?

Perhaps ***MSLT-III***?

De-escalation?

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How does Neoadjuvant Therapy affect Surgery for melanoma?

- **No Surgery d/t distant disease progression** - 5-10%
  - *No/rare loss of regional disease control*
- **Difficulty of surgical dissection**
  - *Manageable*
- **Adverse effects**
  - *Similar rates to adjuvant*

Hieken TJ, et al. Am Soc Clin Oncol Educ Book. 2023 Jan;43:e390614.

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The Goal of Melanoma Surgery:

1. CURE
2. STAGING
3. REGIONAL DISEASE CONTROL
4. SURGICAL CONSOLIDATION
5. PALLIATION

How has Melanoma Surgery evolved?

Personalization of Surgical Care

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Seidman Cancer Center

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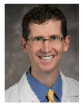

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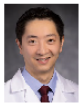

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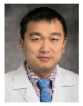

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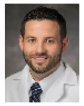

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