Management of Early-stage Melanoma

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Disclosures

- **Research support**: BMS, Merck, Regeneron, Replimune, Philogen, Vaccinex
- **Advisory Board**: Regeneron, Replimune

Objectives

- Describe surgical management of early-stage melanoma
- Discuss how to incorporate gene expression profiling into the management of melanoma patients
- Describe how systemic therapies should be incorporated in the management of early-stage melanoma

Surgical Management of Early-stage Melanoma: *Excision*

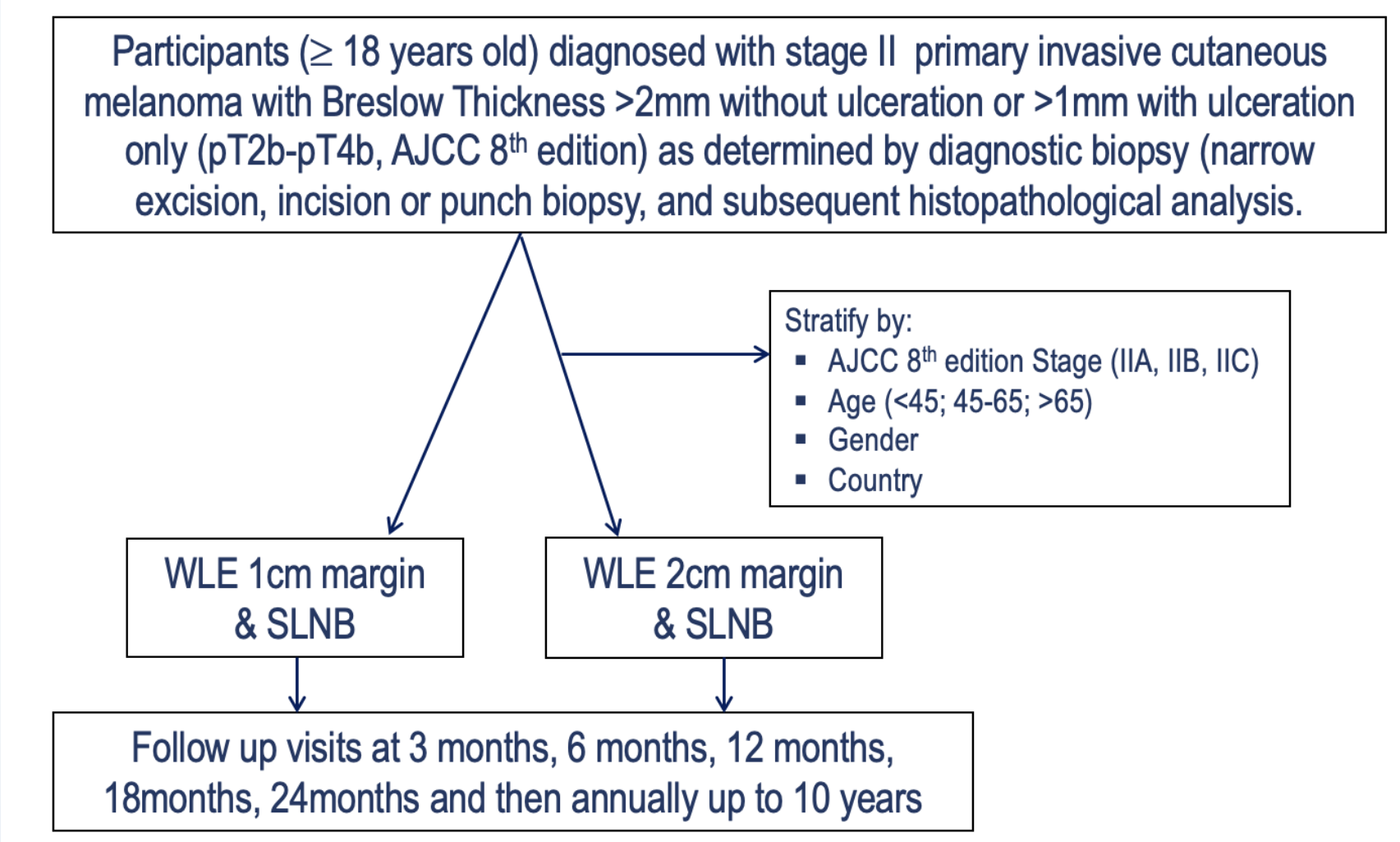
Study	Year	N	Follow-up (years)	Thickness (mm)	Margin (cm)	LR	OS
WHO	1991	612	8	≤2	1 vs 3	NS	NS
Sweden	2000	989	11	>0.8-2.0	2 vs 5	NS	NS
Intergroup	2001	468	10	1-4	2 vs 4	NS	NS
France	2003	326	16	≤2	2 vs 5	NS	NS
Sweden	2011	936	6.7	>2	2 vs 4	NS	NS

Surgical Management of Early-stage Melanoma: *Excision*

Tumor Thickness	Recommended Clinical Margins
In situ[a]	0.5–1.0 cm
≤1.0 mm	1.0 cm (category 1)
>1.0–2 mm	1–2 cm (category 1)
>2.0–4 mm	2.0 cm (category 1)
>4 mm	2.0 cm (category 1)

Surgical Management of Early-stage Melanoma: *Excision*

Melanoma Margins Trial (Mel-MarT II, SWOG 2015)



Surgical Management of Early-stage Melanoma: *Excision*

Melanoma Margins Trial (Mel-MarT II, SWOG 2015)

Primary Endpoint: **3-year Disease-Free Survival**

Statistics

- **Non-inferiority** log-rank test with an overall sample size of **2,998 patients** (1,499 in each arm) will achieve 90% power at a 0.05 significance level to detect a non-inferiority HR of 1.25

Completed enrollment with interim analysis by the end of 2026 and results expected for ASCO 2027

Surgical Management of Early-stage Melanoma: *SLNB*

NCCN guidelines:

- ***Do*** SLNB for ***>10%*** risk of metastatic disease
- ***Consider*** SLNB for ***5-10%*** risk
- ***Do Not*** perform SLNB for ***<5%*** risk

Surgical Management of Early-stage Melanoma: *SLNB*

What factors are associated with SLN positivity?

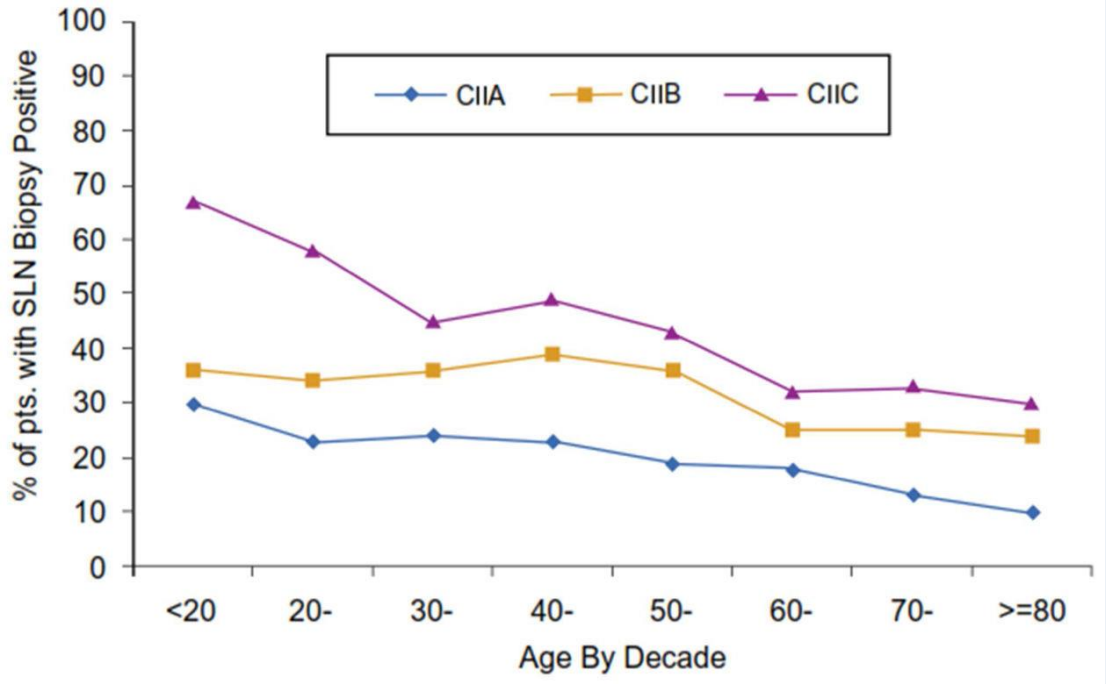
Breslow Thickness

- Residual clinical disease or positive deep margin on shave biopsy

Tumor biology

- Ulceration
- Lymphovascular invasion
- Elevated Mitosis (≥2)

Age



Balch CM et al *Ann Surg Oncol*. 2014;21:1075–81

Surgical Management of Early-stage Melanoma: *SLNB*

How do we calculate likelihood of SLN positivity for a patient?

- AJCC staging/clinicopathologic features
- SLN nomograms
- Gene expression profiling (GEP) assays

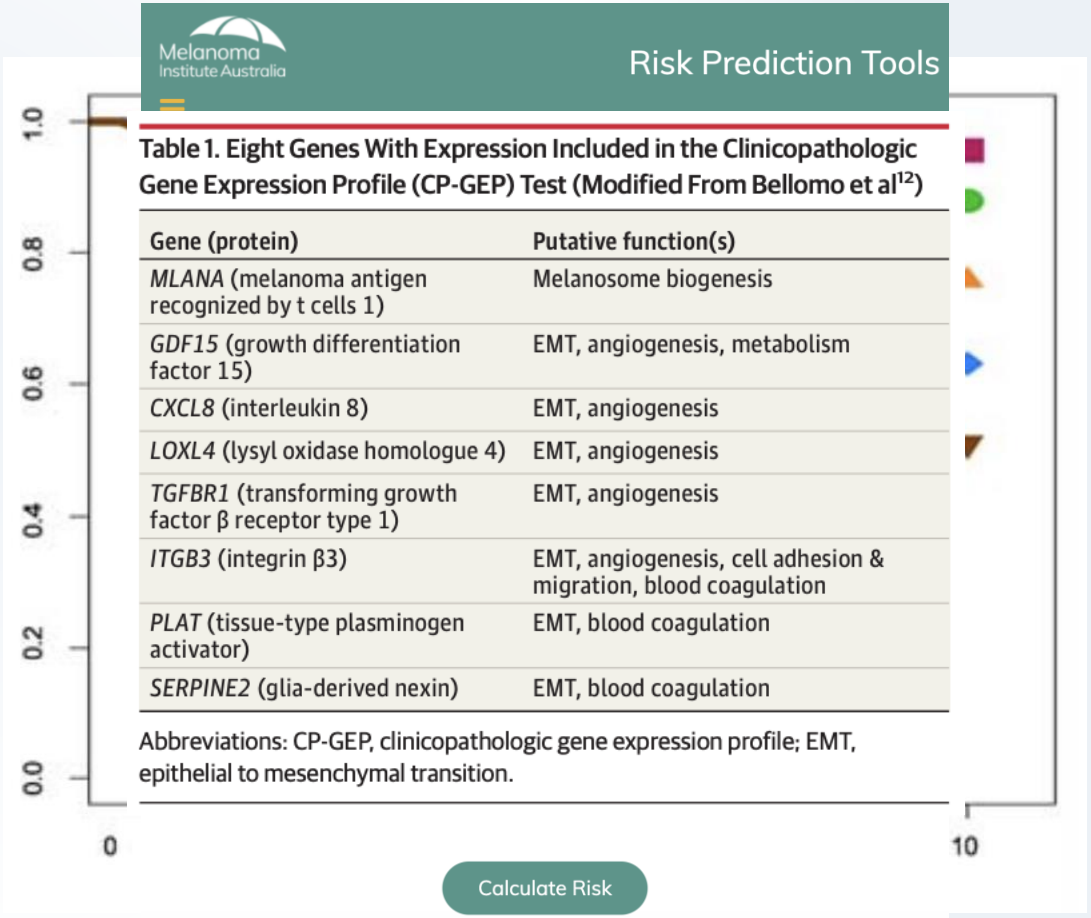


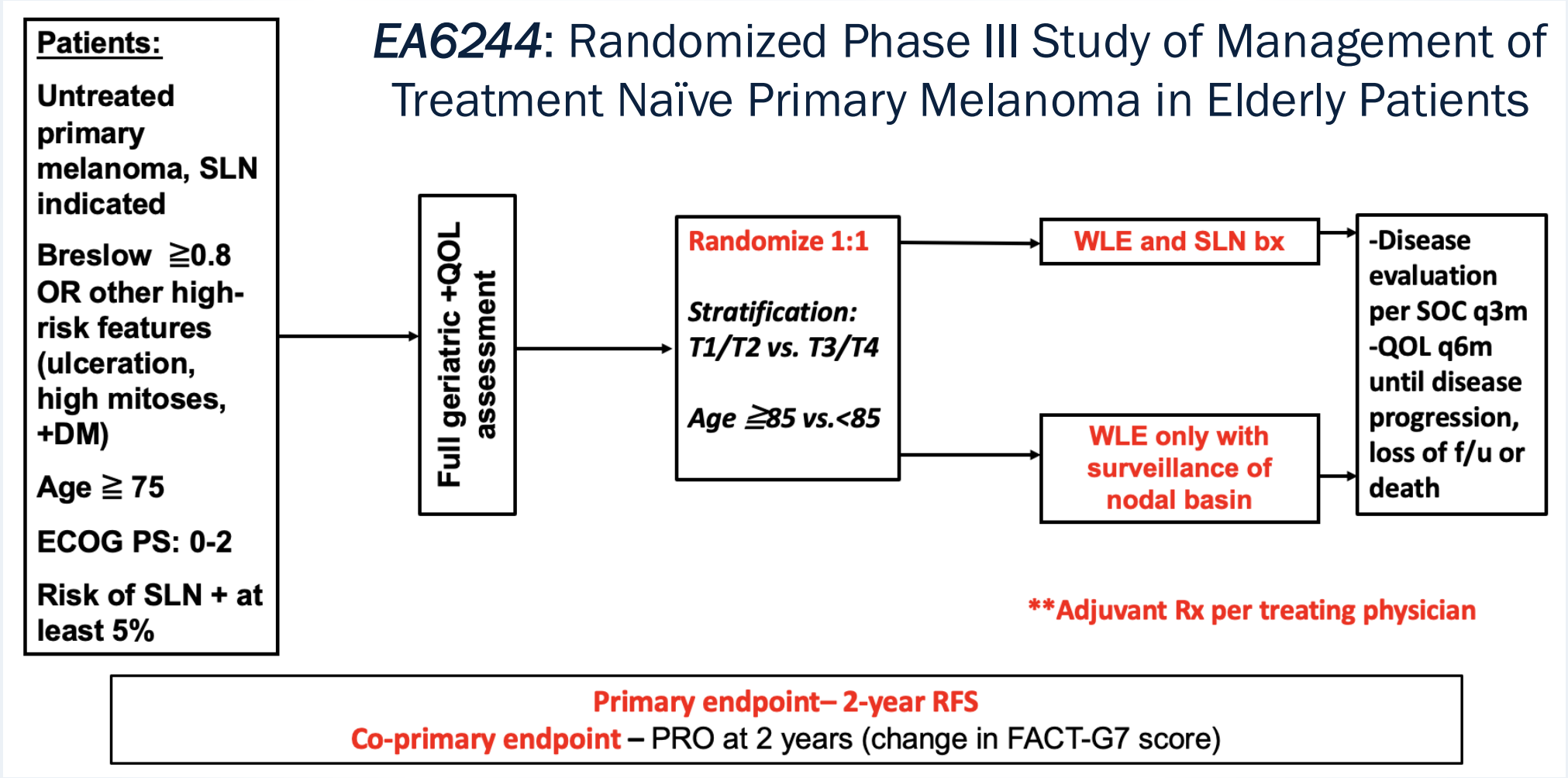
Table 1. Eight Genes With Expression Included in the Clinicopathologic Gene Expression Profile (CP-GEP) Test (Modified From Bellomo et al[12])

Gene (protein)	Putative function(s)
MLANA (melanoma antigen recognized by t cells 1)	Melanosome biogenesis
GDF15 (growth differentiation factor 15)	EMT, angiogenesis, metabolism
CXCL8 (interleukin 8)	EMT, angiogenesis
LOXL4 (lysyl oxidase homologue 4)	EMT, angiogenesis
TGFBR1 (transforming growth factor β receptor type 1)	EMT, angiogenesis
ITGB3 (integrin β3)	EMT, angiogenesis, cell adhesion & migration, blood coagulation
PLAT (tissue-type plasminogen activator)	EMT, blood coagulation
SERPINE2 (glia-derived nexin)	EMT, blood coagulation

Abbreviations: CP-GEP, clinicopathologic gene expression profile; EMT, epithelial to mesenchymal transition.

Gershenwald et al. *CA Cancer J Clin* 2017
Lo et al. *J Clin Oncol* 2020
Hieken et al. *JAMA Surgery* 2025

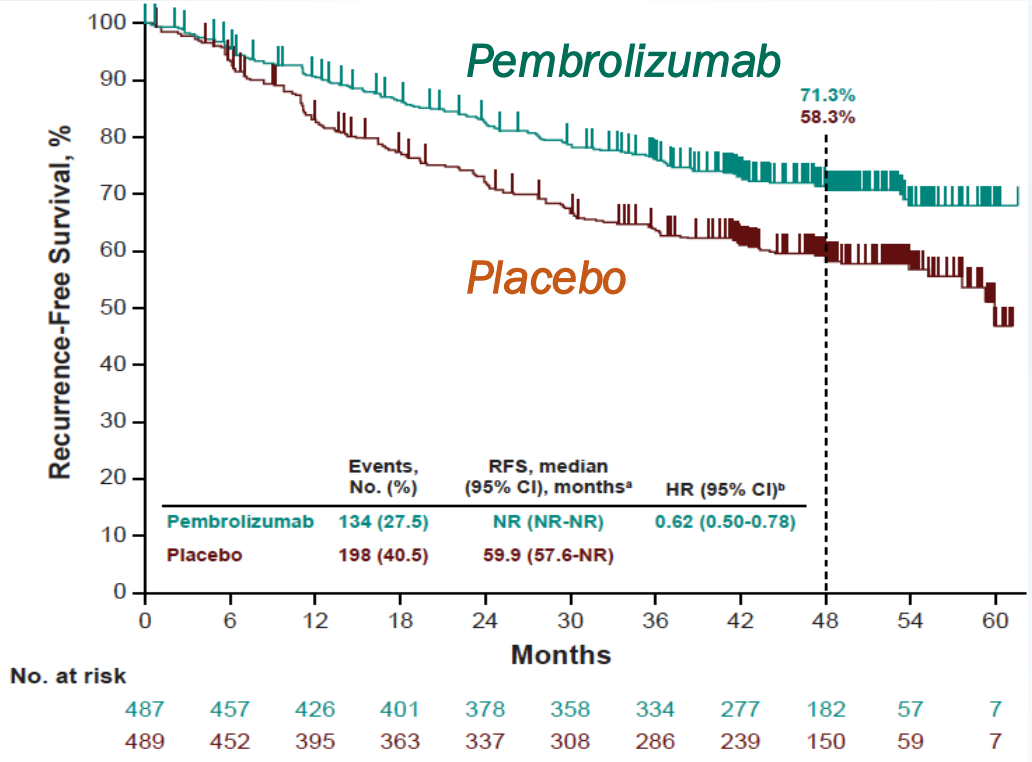
Surgical Management of Early-stage Melanoma: *SLNB*



Management of Early-stage Melanoma: *Adjuvant Therapy*

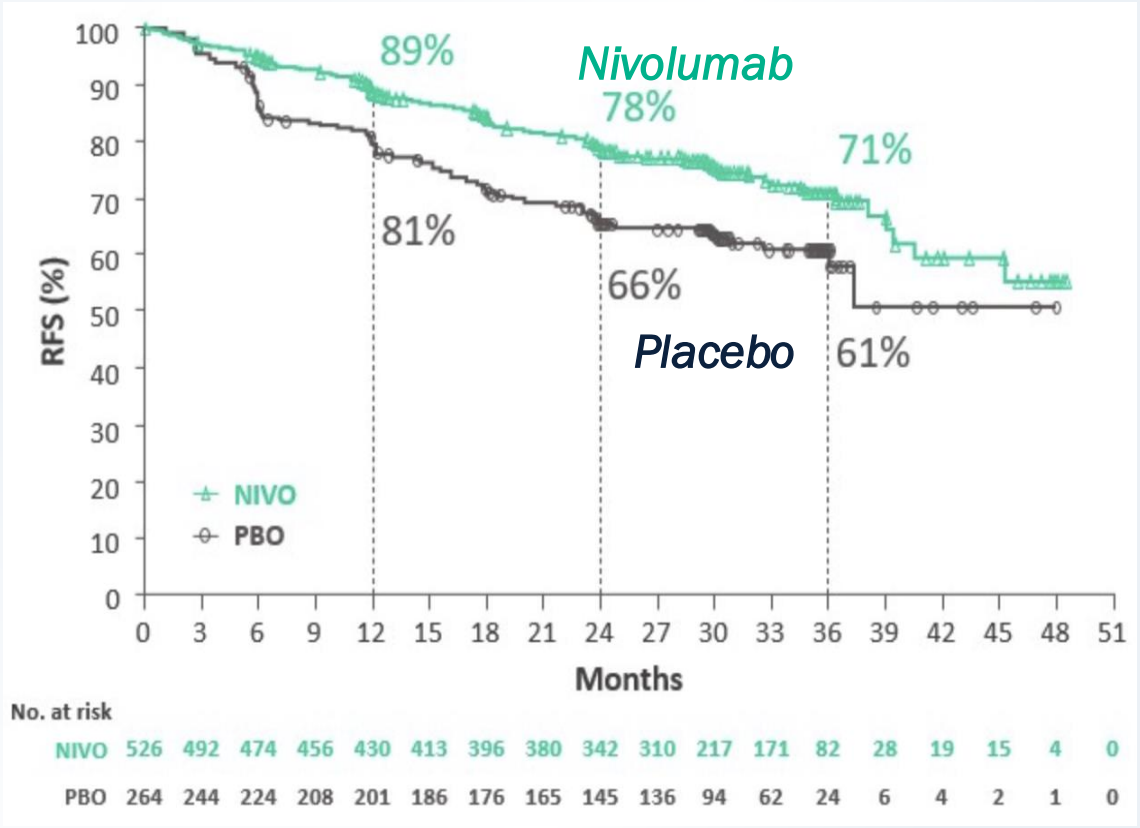
KEYNOTE-716

13% RFS advantage at 48 months



CheckMate-76k

10% RFS advantage at 36 months

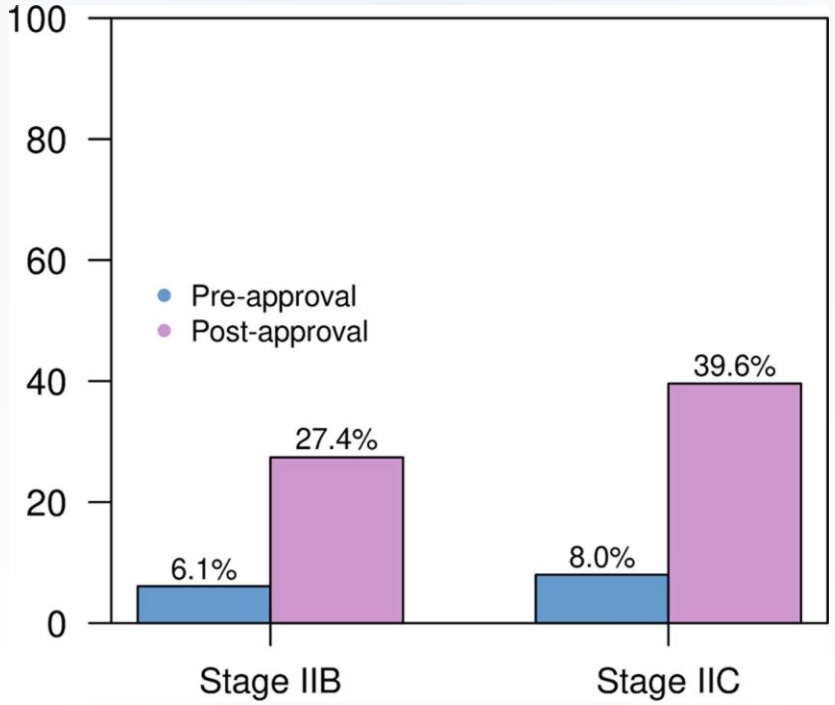


Luke et al. *Eur J Canc* 2024
Long GV et al. presented at ESMO 2024

Management of Early-stage Melanoma: *Adjuvant Therapy*

Reasons to **continue to perform SLNB** for high-risk stage II melanoma:

1. Not **all** patients will receive adjuvant therapy



Jakub J et al. *JITC* 2025

Management of Early-stage Melanoma: *Adjuvant Therapy*

Reasons to **continue to perform SLNB** for high-risk stage II melanoma:

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2. Prognostication: ***upstaging*** is valuable information

pT2bN0

	N	5-YR	10-YR
IA	5225	99%	98%
IB	5749	97%	94%
IIA	2338	94%	88%
IIB	1688	87%	82%
IIC	691	82%	75%

pT2bN1a

	N	5-YR	10-YR
IIIA	1006	93%	88%
IIIB	1170	83%	77%
IIIC	2201	69%	60%
IIID	205	32%	24%

Gershenwald J et al. *CA* 2017

Management of Early-stage Melanoma: *Adjuvant Therapy*

Reasons to **continue to perform SLNB** for high-risk stage II melanoma:

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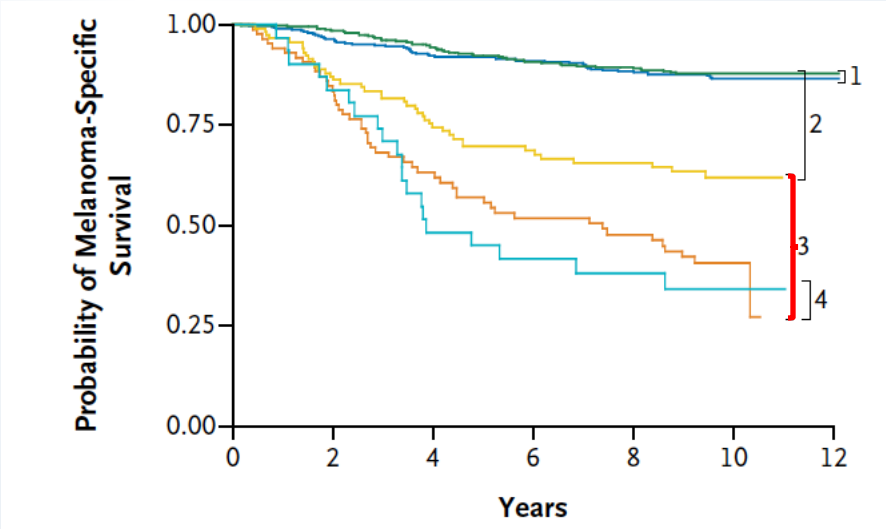
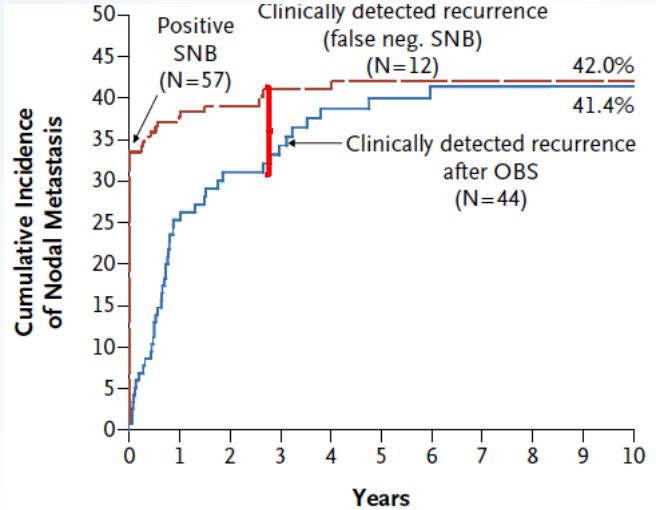
3. MSS benefit for intermediate (≤3.5mm) **RFS** benefit for thick (>3.5mm) melanoma



Faries J et al. *NEJM* 2017

Intermediate: *MSS benefit of 20.6% at 10 years*



Thick: *RFS benefit of 7.2% at 3 years*

Management of Early-stage Melanoma: *Adjuvant Therapy*

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2. Prognostication: **upstaging** is valuable information
3. **MSS** benefit for intermediate (≤3.5mm) **RFS** benefit for thick (>3.5mm) melanoma
4. Nodal basin recurrences are **demoralizing** and can be **difficult to manage**

Management of Early-stage Melanoma: *Adjuvant Therapy*

Reasons to **continue to perform SLNB** for high-risk stage II melanoma:

1. Not **all** patients will receive adjuvant therapy
2. Prognostication: **upstaging** is valuable information
3. **MSS** benefit for intermediate (≤3.5mm) **RFS** benefit for thick (>3.5mm) melanoma
4. Nodal basin recurrences are **demoralizing** and can be **difficult to manage**
5. SLNB is an extremely **low risk procedure**
   - Especially compared to the 15-20% risk of grade 3 or higher toxicity with pembro or nivo

Management of Early-stage Melanoma: *Neoadjuvant Therapy*

Primary endpoints:

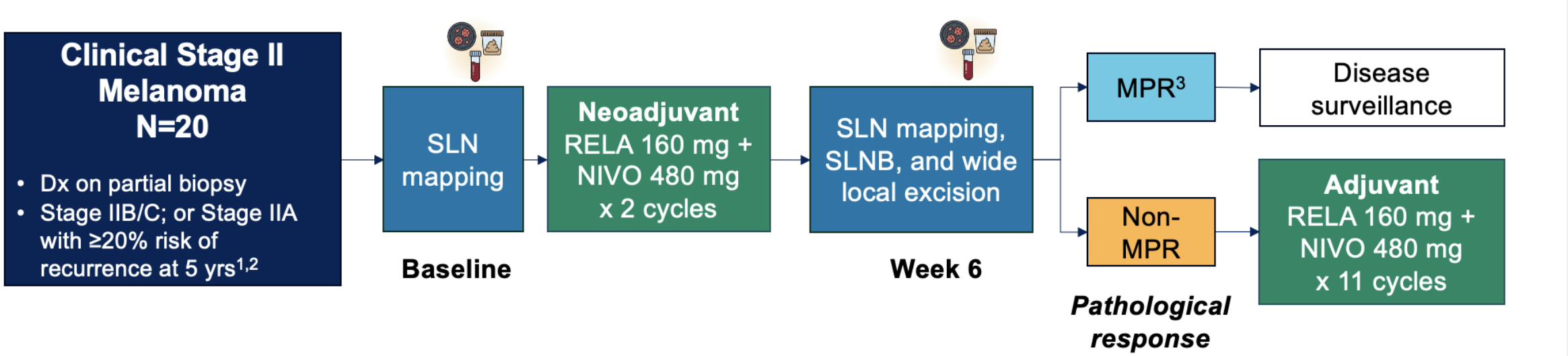
- SLN positivity rate
- Safety and tolerability of PD-1 blockade in the peri- and post-operative setting

Hypothesis: Neoadjuvant anti-PD1 therapy would decrease SLN positivity rate by 50% compared to historical control

	Trial Cohort % (No./total)	IIB/IIC	Historical Cohort %	% decrease	p-value*
SLN positivity rate	27 (17/63)	33/30	32.1	16	0.384

Karakousis G et al. presented at ASCO 2025.

Management of Early-stage Melanoma: *Neoadjuvant Therapy*



Co-Primary Endpoints:
1. Pathological response rate
2. Feasibility and acceptability

Secondary Endpoints:
1. SLNB positivity rate
2. Melanoma EFS, RFS, and OS
3. Adverse event profile

Long G et al. presented at ASCO 2026.

Management of Early-stage Melanoma: *Summary*

- All patients should undergo definitive excision with appropriate margins
  - Stay tuned for MelMarT-II results!
- AJCC staging and risk nomograms should guide decisions about SLNB
  - Patients with a risk of at least 5% should be offered SLNB
- All patients with stage IIB and IIC should be considered for adjuvant pembrolizumab or nivolumab
  - All clinical stage II patients should be offered SLNB regardless of plan for adjuvant
- Neoadjuvant immunotherapy for stage II melanoma should be performed on a clinical trial

Q&A