Neoadjuvant therapy for melanoma

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Intent

INFORM

EMPOWER

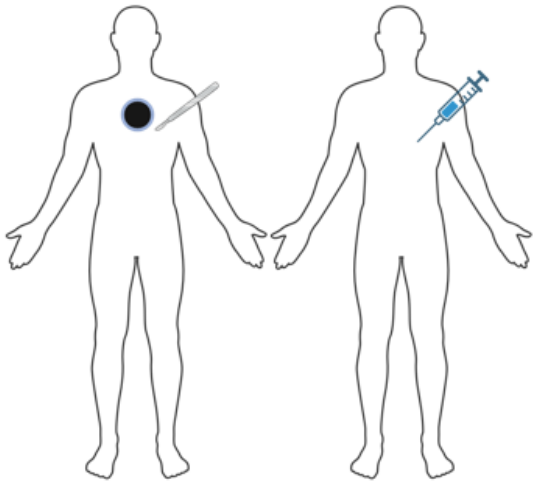
INSPIRE

Melanoma care is multidisciplinary

Melanoma drug therapy

Adjuvant - 'mop-up'

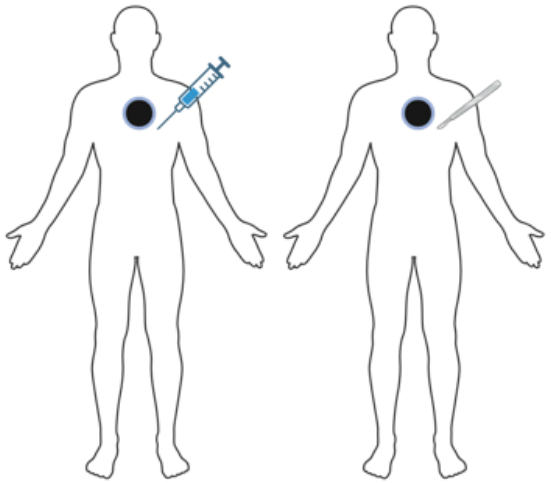
Stage III



Dabrafenib + Trametinib
Nivolumab
Pembrolizumab

Neoadjuvant - before melanoma surgically removed

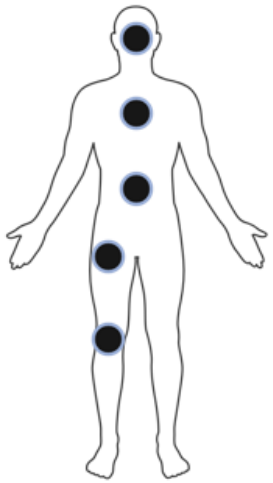
Stage III



Pembrolizumab
Ipilimumab + Nivolumab

Advanced/metastatic - not surgically resectable

Stage III / IV



Nivolumab or Pembrolizumab
Ipilimumab + Nivolumab
Nivolumab + Relatlimab
Dabrafenib + Trametinib
Encorafanib + Binimetinib
Vemurafenib + Cobimetinib

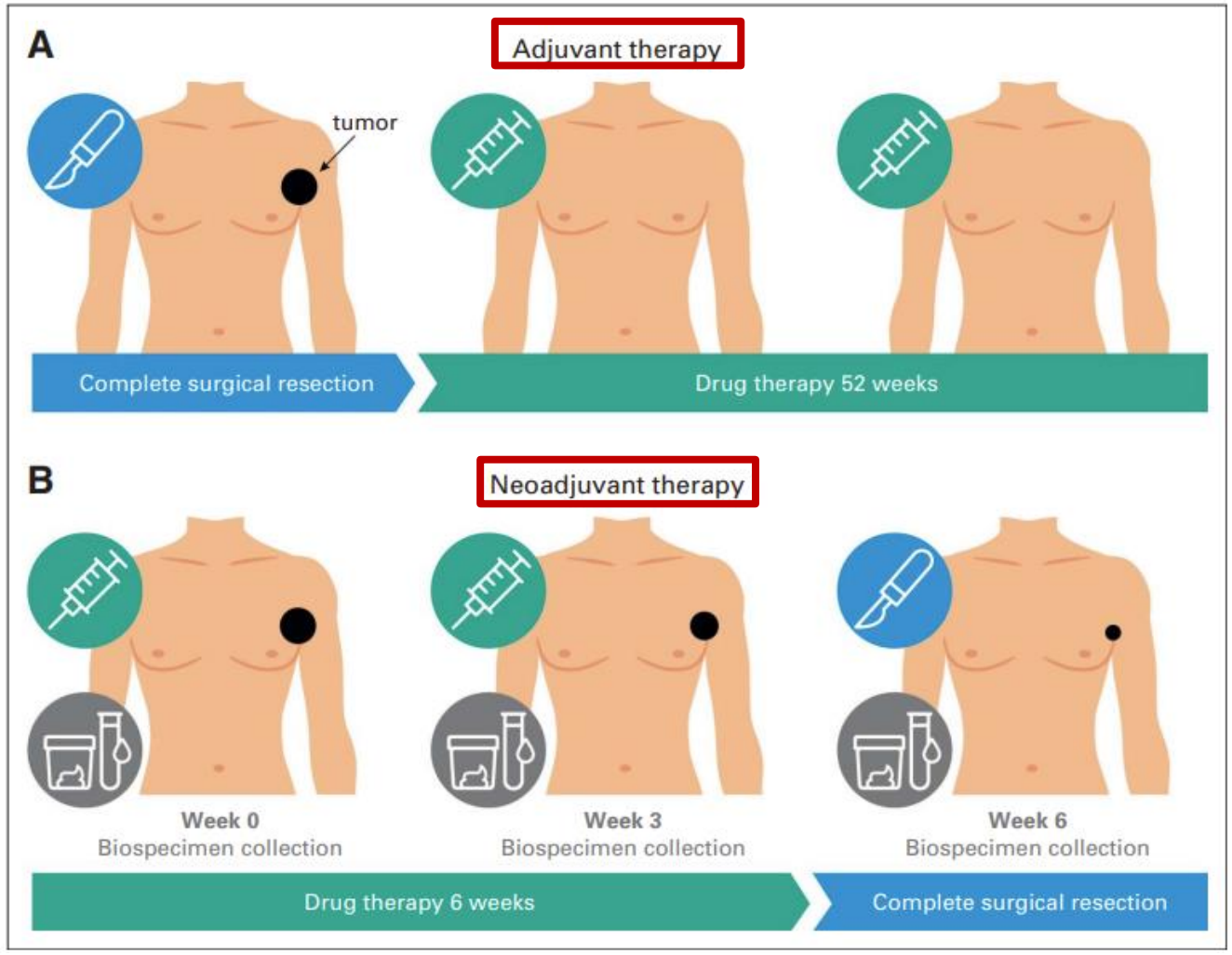
Melanoma staging

STAGE	DESCRIPTION	FREQUENCY	SURGERY	DRUG THERAPY
I and II-A	Thin melanomas	++++	✓	×
II B-C	Thick melanomas	+++	✓	✓ (not funded)
III A	Thin melanomas + lymph gland	+	✓	Not funded
III B-D	Thin/thick melanomas + lymph gland	++	✓	✓
Unresectable stage III or IV	Advanced or metastatic melanoma	+	×	✓✓

Stage III melanoma – focus on neoadjuvant approach

- macroscopic/clinical stage III melanoma

Neoadjuvant approach is standard of care for resectable macroscopic stage III melanoma

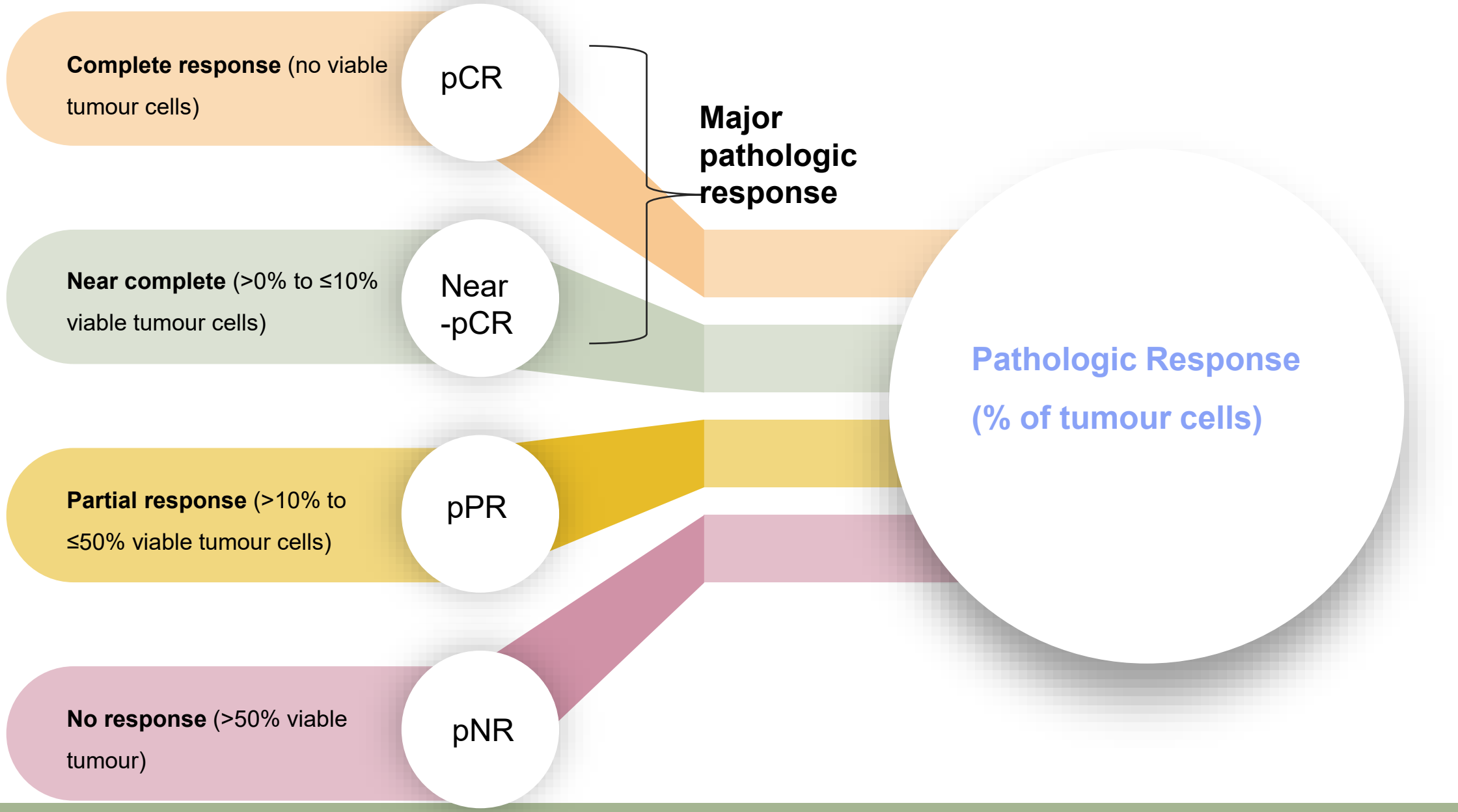


Long et al. JCO. 2023

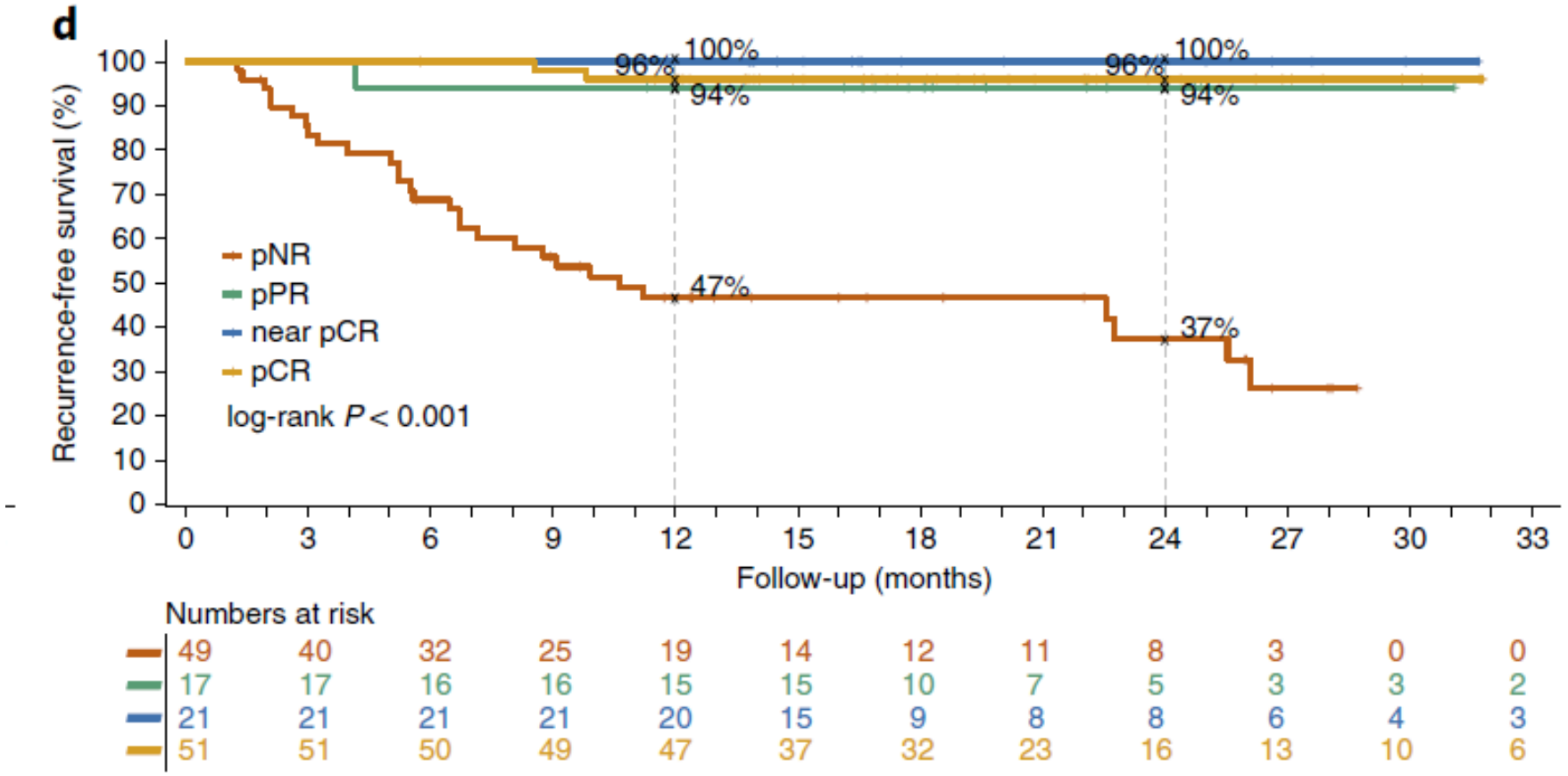
Checkpoint inhibitors in the neoadjuvant setting

✗ TARGETED THERAPY

✓ CHECKPOINT INHIBITORS


Complete response (no viable tumour cells)
pCR
Near complete (>0% to ≤10% viable tumour cells)
Near -pCR
Partial response (>10% to ≤50% viable tumour cells)
pPR
No response (>50% viable tumour)
pNR
Major pathologic response
Pathologic Response
(% of tumour cells)

Pathologic response correlates with survival



Menzies et al. Nature Medicine. 2021

SWOG S1801. NEJM, 2023

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

NADINA. NEJM, 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma

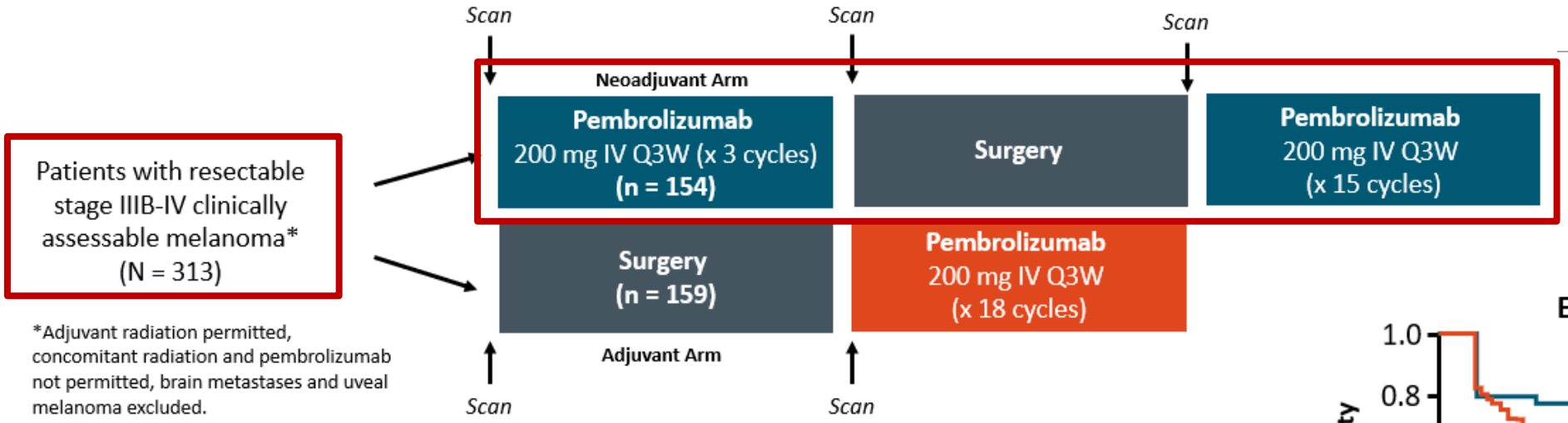
C.U. Blank, M.W. Lucas, R.A. Scolyer, B.A. van de Wiel, A.M. Menzies, M. Lopez-Yurda, L.L. Hoeijmakers, R.P.M. Saw, J.M. Lijnsvelt, N.G. Maher, S.M. Pulleman, M. Gonzalez, A. Torres Acosta, W.J. van Houdt, S.N. Lo, A.M.J. Kuijpers, A. Spillane, W.M.C. Klop, T.E. Pennington, C.L. Zuur, K.F. Shannon, B.A. 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

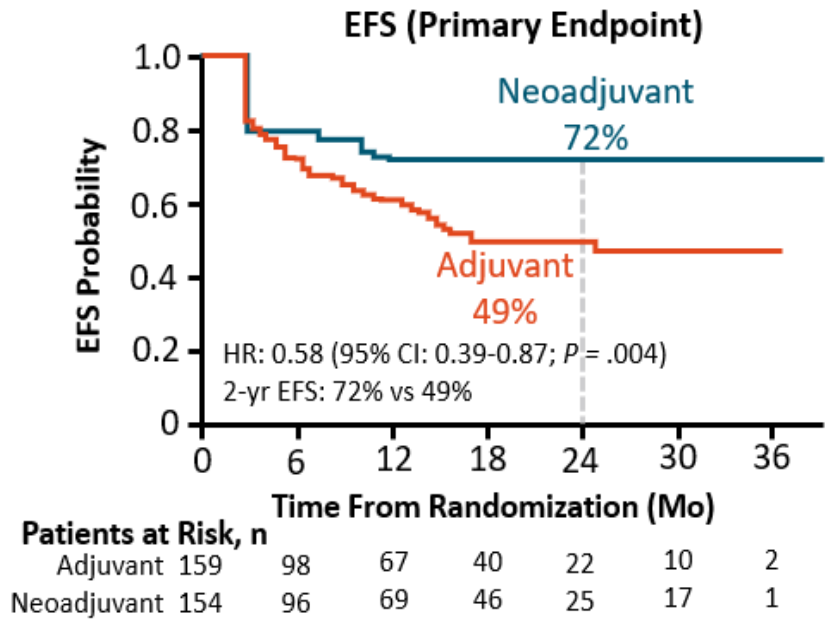
2022 SWOG S1801	Neoadjuvant PD-1	Surgery	Adjuvant PD-1	**HR 0.58** vs adjuvant PD-1 (EFS)[6]
2024 NADINA	Neoadjuvant PD-1 plus CTLA-4	Surgery	Response-directed adjuvant PD-1 or BRAF/MEK	**HR 0.32** vs adjuvant PD-1 (EFS)[7]

SWOG S1801 vs. NADINA

	SWOG	NADINA
Type of study	Phase II	Phase III
Eligibility	• Macroscopic resectable stage III • Resectable stage IV (M1a, M1b,M1c) • Cutaneous, unknown, acral or mucosal included • ITMs included (needed nodal disease) • Measurable disease as per RECIST • Patients with metastases in multiple regional nodal basins were eligible	• Macroscopic resectable stage III • Cutaneous, acral or unknown • ≥1 pathologically proven lymph-node metastasis ± ≤3 ITMs. RECIST measurements not needed
Neoadjuvant immunotherapy	Three cycles of pembrolizumab every 3 weeks	Two cycles of ipilimumab (80 mg) plus nivolumab (240 mg) every 3 weeks
Timing of surgery	Within 5 weeks of last dose of pembrolizumab	Week 6 (week 0; first dose of immunotherapy)
Adjuvant treatment	Pembrolizumab (irrespective of pathologic response)	Pathologic response directed adjuvant treatment (no therapy, nivolumab or targeted therapy)

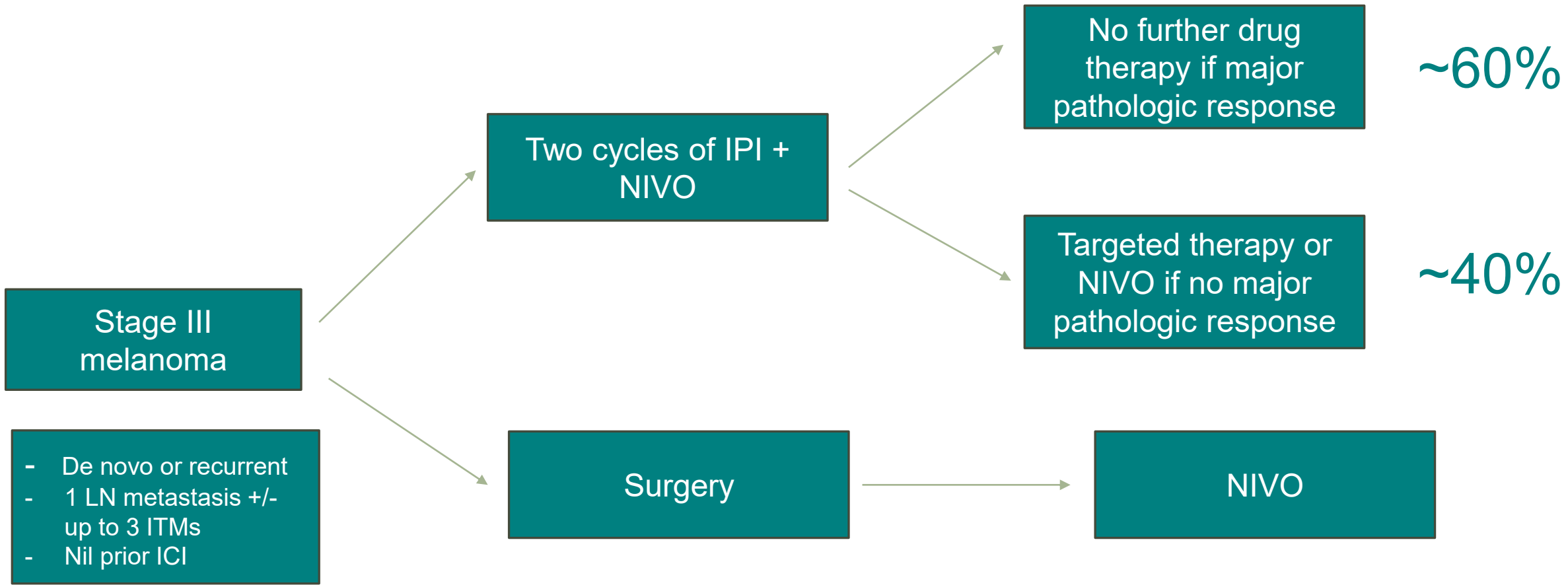
Phase 2 SWOG S1801: Neoadjuvant vs Adjuvant Pembrolizumab



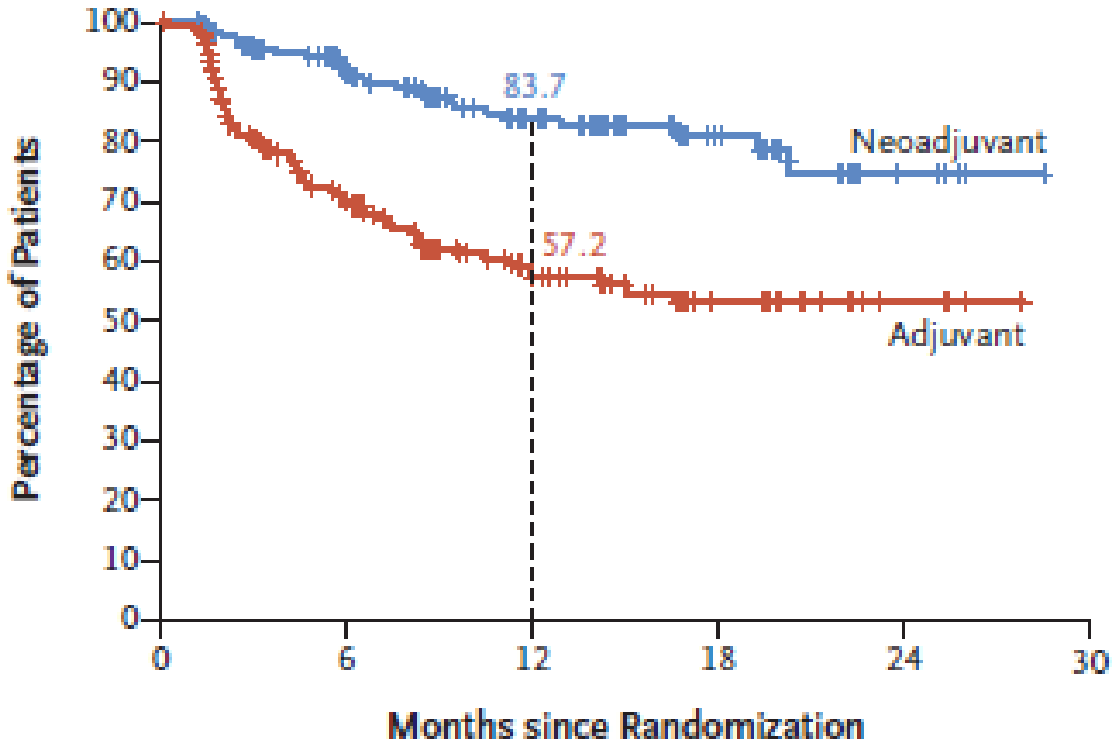


- Better outcomes with the neoadjuvant approach

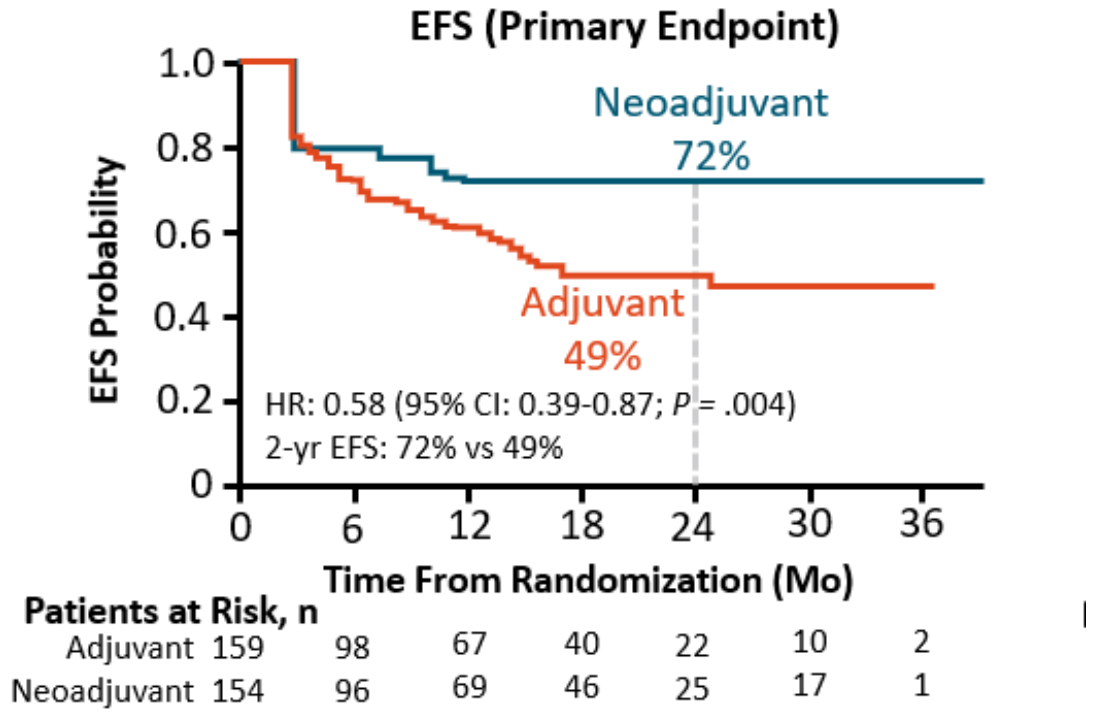
Phase 3 NADINA – neoadjuvant ipilimumab and nivolumab vs. adjuvant nivolumab



NEOADJUVANT APPROACH TRUMPS



NADINA- 12-month event-free survival 84% vs 57%



SWOG S1801- 12-month event-free survival 73% vs 60%

Why neoadjuvant?

Advantages

- Personalised response
  - Tailored prognosis
  - Tailored follow-up
  - Alternative adjuvant treatment (second crack)
- Reduce tumour burden
- Baseline biomarker identification
- Economic, QoL improvements

Disadvantages

- Progression before surgery
- More toxic (combination)
- Surgical delays (toxicity)

Neoadjuvant pembrolizumab and neoadjuvant ipilimumab + nivolumab are now PBS listed.

Pooled analysis (n=818)

Reasons for omission of surgery (n=36)

	Non-trial (N=185)	Trial (N=633)	BRAF/MEK (N=88)	ICI (N=610)	ICI plus TT (N=120)	Total (N=818)
No surgery, n (%)	19 (10)	17 (2.7)	0	34 (5.6)	2 (1.7)	36 (4.4)
Progression*	10 (5)	10 (2)	–	19 (3)	1 (1)	20 (2.4)
Local	9	7	–	15	1	16
Distant	6	8	–	13	1	14
Response	6 (3)	0	–	6 (1)	0	6 (1)
Toxicity	0	4	–	4	0	4
Other	1	6	–	6	1	7

*a subset of patients have both local and distant metastases

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Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – MELANOMA

The Effect of Neoadjuvant Systemic Therapy on Surgical Outcomes After Lymph Node Dissections for Stage III Melanoma; An Australian Cohort

Lisanne P. Zijlker, MD[1,2,3], Henry Chen, BSc[4], Andrew J. Spillane, MD, PhD[3,4,5,6], Maria Gonzalez, MSc[3], Thomas E. Pennington, MD[3,4,7], Alexander M. Menzies, MD, PhD[3,4,5,6], Serigne N. Lo, MD, PhD[3,4], Peter Ferguson, MD, PhD[3,4,7,8], Robert Rawson, MD, PhD[3,4,7,8], Andrew J. Colebatch, MD[3,4,7,8], Jonathan R. Stretch, MD, PhD[3,4,7], John F. Thompson, MD, PhD[3,4,6,7], Sydney Ch'ng, MD, PhD[3,4,7], Omgo Nieweg, MD, PhD[3,4,7], Kerwin F. Shannon, MD[3,4,7], Georgina V. Long, MD, PhD[3,4,5,6], Richard A. Scolyer, MD, PhD[3,4,7,8,9], Robyn P. M. Saw, MD, PhD[3,4,7], and Alexander C. J. van Akkooi, MD, PhD[3,4,7]

Aim: explored how neoadjuvant targeted therapy and immunotherapy influenced surgical outcomes after lymph node dissection in terms of complications, morbidity, and textbook outcomes

Patients: The study included 89 NAST-treated patients and 79 upfront surgery-treated patients.

Results:

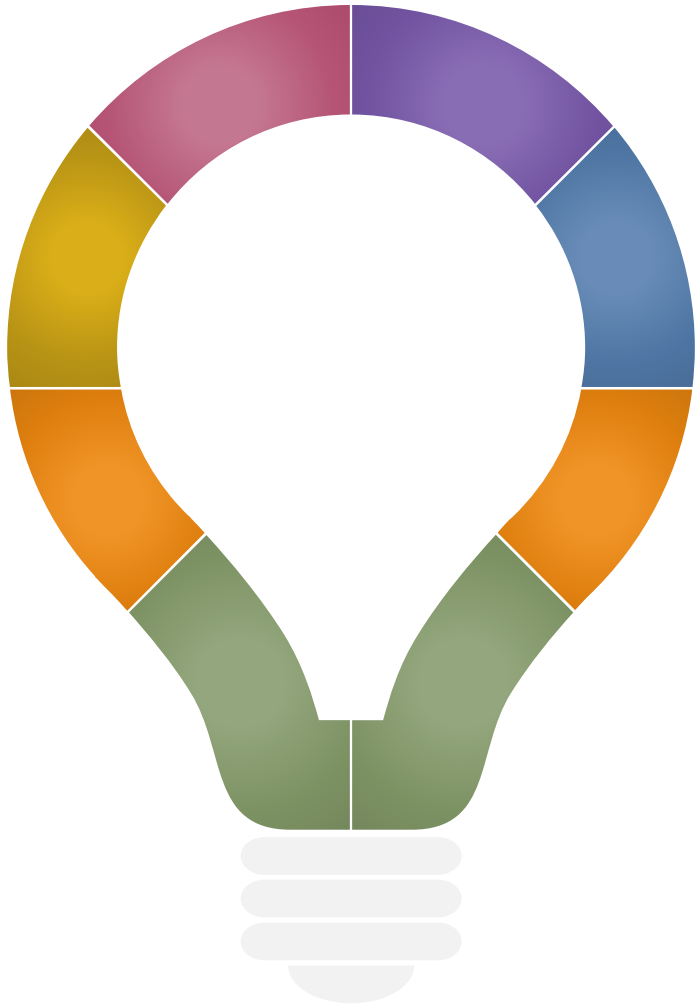
- The rate of postoperative complications did not differ between the NAST- and upfront surgery-treated patients (55% vs. 51%; p=0.643)
- Steroid treatment for drug toxicity did not influence the complication rate (odds ratio [OR], 1.1; 95% confidence interval [CI], 0.4–3; p=0.826).
- No significant differences in postoperative morbidity were observed in terms of seroma (23% vs. 11%; p=0.570) or lymphedema (36% vs. 51%; p=0.550).
- The rate of achieving a textbook outcome was comparable for the two groups (61% vs. 57%; p=0.641)

Future directions

Biomarker driven treatment selection

Prediction tools

Management of non-responders. Monitor for recurrence. Patterns of recurrence and success of salvage therapy

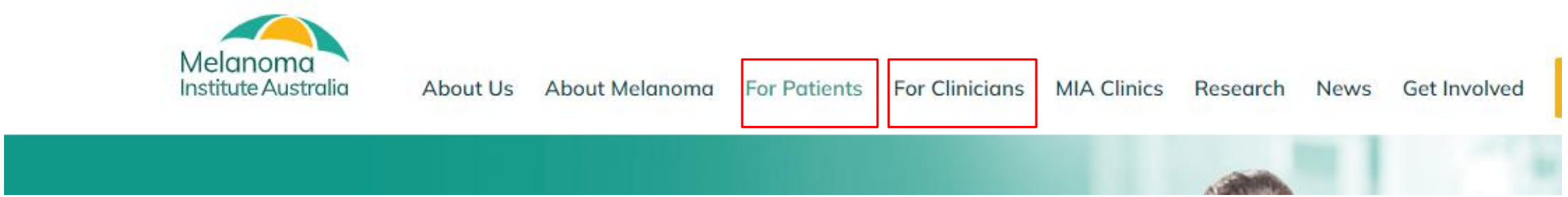


Minimising toxicity of drug therapy

Role of gut microbiome and diet

Minimising surgical morbidity – resection of index node vs therapeutic lymph node dissection

MIA's website provides valuable patient resources



https://melanoma.org.au/for-patients/

Information on melanoma

- Diagnosis
- Treatment
- Patient information
- Patient support
- Clinical Research

Conclusion

- Neoadjuvant therapy is the standard-of-care for clinical stage III melanoma.
- Highest major pathologic selection, recurrence-free survival and event-free survival rates achieved with combination checkpoint inhibitor.
- Neoadjuvant BRAF/MEK therapy is not as effective as checkpoint inhibitor.

Thank You

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