Navigating treatment choices in high-risk early-stage melanoma

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Predicting high-risk recurrence in patients with early-stage melanoma

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What is the risk of recurrence in patients with early-stage melanoma?

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Recurrence is high in stage IIB/C melanoma

AJCC 8th edition staging system[1] may not reflect recurrence risk at each stage in all practice settings[2]

Recent studies on recurrence and RFS provide new insights

Prospective, single-centre, US study (1993–2013)[3]

338 patients with stage IIB or IIC melanoma
Median follow-up: 52 months

Recurrence	IIB	IIC
Overall	32%	46%
Of which:		
Local/in-transit	47%	29%
Regional nodal	23%	19%
Systemic	30%	52%
5-yr cumulative incidence*	18.9%	23.3%

US community oncology clinic study (2008–2017)[4]

567 patients with stage IIB and IIC resected melanoma
Median follow-up: 38.8 months

Recurrence	IIB	IIC
Overall	37.3%	43.2%
Locoregional	20.3%	19.8%
Distant metastasis	27.5%	35.4%

Danish observational study (2008–2021)[2]

1,432 patients with stage IIB or IIC melanoma; 1,509 with IIIA or IIIB
Median follow-up: 5.9 years

Recurrence	IIB	IIC	IIIA	IIIB
Overall	30.6%	35.2%	24.8%	33.1%
Locoregional	18.3%	20.5%	13.3%	20.8%
Distant metastasis	24.9%	29.1%	19.1%	24.9%
10-yr cumulative incidence	33.2%	36.8%	29.7%	35.9%

Patients with **stage IIB and IIC** melanoma had a **poorer prognosis** than stage **IIIA and IIIB**

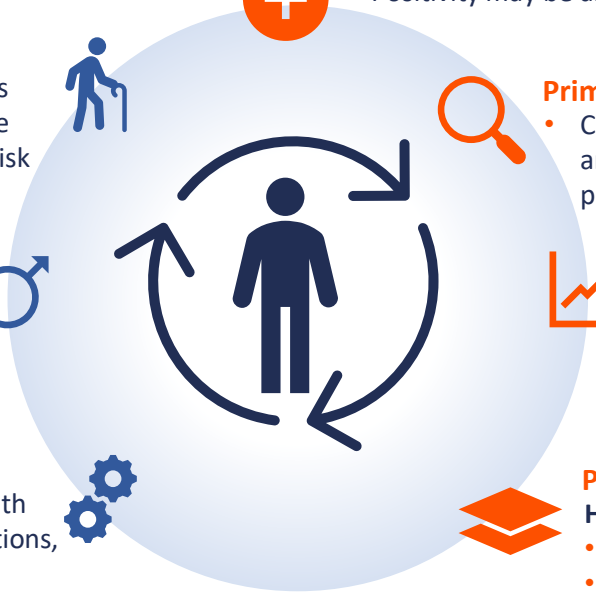
*Patient-detected (rates for physician- and imaging-detected cumulative incidence differed).
AJCC, American Joint Committee on Cancer; RFS, recurrence-free survival; yr, year.

1. Gershenwald JE, et al. *CA Cancer J Clin*. 2017;67:472–92; 2. Helvind NM, et al. *JAMA Dermatol*. 2023;159:1213–22; 3. Lee AY, et al. *Ann Surg Oncol*. 2017;24:939–46; 4. Samlowski W, et al. *Future Oncol*. 2022;18:3755–67.

What are the patient and tumour factors associated with increased risk of recurrence in early-stage melanoma?

Factors impacting recurrence risk in stage IIB/C

Patient and tumour aspects



SLNB status[3,4]

- Strong predictor of survival
- Positivity may be associated with recurrence

Older age[1]

- Those >75 years vs 65–75 years of age may have higher risk

Primary tumour location[3,5]

- Certain locations, e.g. head and neck, have been linked to poorer outcomes

Sex[2]

- Men are more likely to experience recurrence than women

Mitotic rate[3,5–7]

- Removed from AJCC 8th edition staging criteria[5,6]
- However, recent studies report its relevance[2,4,6]

Comorbidities[1]

- E.g. CHF, diabetes with associated complications, chronic lung disease

Primary tumour thickness[5,6]

High-risk stage IIB/C:

- Breslow depth >4.0 mm **or**
- Breslow depth >2.1 mm **+** ulceration

AJCC, American Joint Committee on Cancer; CHF, congestive heart failure; SLNB, sentinel lymph node biopsy.

1. Jang S, et al. *Dermatol Ther (Heidelb)*. 2020;10:985–99; 2. Feigelson HS, et al. *Cancer Med*. 2019;8:4508–16; 3. von Schuckmann LA, et al. *JAMA Dermatol*. 2019;155:688–93; 4. NCCN Clinical Practice Guidelines. Melanoma: Cutaneous. Version 3.2024. Available at: www.nccn.org (accessed 26 November 2024); 5. Dedeilia A, et al. *Ann Surg Oncol*. 2024;31:2713–26; 6. Gershenwald JE, et al. *CA Cancer J Clin*. 2017;67:472–92; 7. Iqbal A, et al. *Am Acad Dermatol*. 2023;89:154–5.

How can a patient's risk profile inform treatment decisions in early-stage melanoma?

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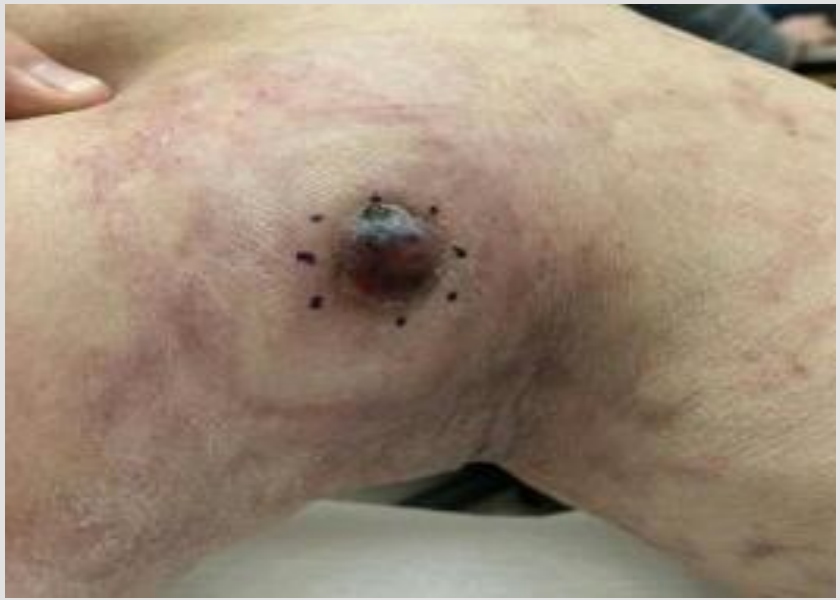
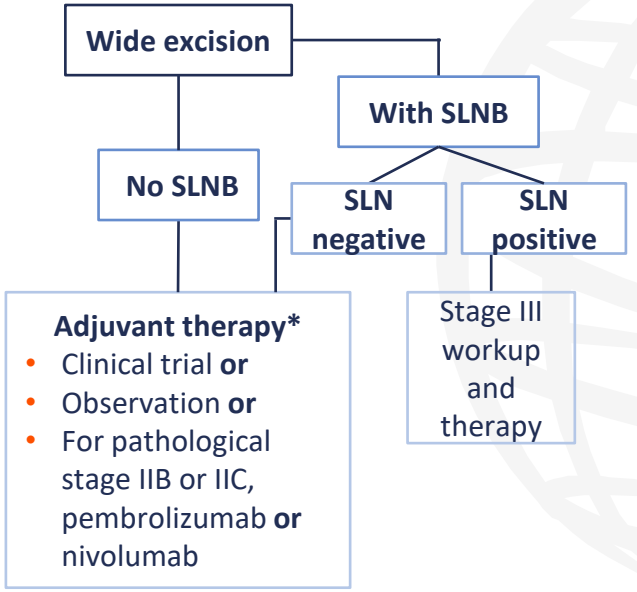
Considering risk factors when selecting therapy

Patient with T4b, 8 mm nodular melanoma[1]



NCCN guidance for stage IIB/C melanoma[2]



*Category 2B recommendations are not shown; please refer to the full NCCN guidelines for further information.
NCCN, National Comprehensive Cancer Network; SLN, sentinel lymph node; SLNB, SLN biopsy.
1. Case study provided courtesy of Dr Hieken; 2. NCCN Clinical Practice Guidelines. Melanoma: Cutaneous. Version 3.2024. Available at: www.nccn.org (accessed 26 November 2024).

What promising strategies are under investigation to optimize assessment of recurrence risk in early-stage melanoma?

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Emerging biomarkers for melanoma recurrence

Gene expression profiling[1]

CP-GEP test[2]

- **GEP** score **+ clinicopathologic factors** combined
- The **test** was a **significant predictor** of RFS, DMFS and MSS in low-risk population

CP-GEP model[3]

- Combined **GEP + clinicopathologic factors** to identify patients with <5% risk of nodal metastasis
- **Negative predictive value** was **>95%** across tumour thickness groups
- Model may identify **low-risk** patients **not requiring SLNB**

CP-GEP study[4]

- Patients stratified as low risk or high risk by algorithm including **GEP + clinicopathologic factors**
- CP-GEP **test** may identify patients at **high risk of recurrence** who are considered **low risk by AJCC 8th edition criteria**
- **Prospective trial ongoing**[5]

Circulating tumour DNA[1]

- Association between **ctDNA detection** and **recurrence** preoperatively or during observation in stage II/III disease has been reported[6]
- High pre- and postoperative ctDNA ***BRAFV600E*** and **S100B** was associated with **high risk of recurrence** and **unfavourable** prognosis in early melanoma[7]

Genetic mutations[8]

- ***KIT*** and ***CDH1*** **mutations** have been associated with **shorter DMFS**[8]
- ***KIT*** mutation has been associated with **shorter RFS** in stage II melanoma[8]

The role of available tests in treatment selection is yet be established[9]

AJCC, American Joint Committee on Cancer; CP-GEP, clinicopathologic factors with GEP; ctDNA, circulating tumour DNA; DMFS, distant metastasis-free survival; GEP, gene expression profiling; MSS, melanoma-specific survival; RFS, recurrence-free survival; SLNB, sentinel lymph node biopsy.

1. Sun J, et al. *Cancers (Basel)*. 2024;16:583; 2. Jarell A, et al. *J Am Acad Dermatol*. 2022;87:1312–20; 3. Bellomo D, et al. *JCO Precis Oncol*. 2020;4:319–34;
4. Amaral T, et al. *Eur J Cancer*. 2023;182:155–62; 5. ClinicalTrials.gov. NCT04759781. Available at https://clinicaltrials.gov/study/NCT04759781 (accessed 26 November 2024);
6. Brunsgaard EK, et al. *Melanoma Res*. 2023;33:184–91; 7. Polivka J, et al. *Cancer Med*. 2024;13:e70313; 8. Dedeilia A, et al. *Ann Surg Oncol*. 2024;31:2713–26;
9. NCCN Clinical Practice Guidelines. Melanoma: Cutaneous. Version 3.2024. Available at: www.nccn.org (accessed 26 November 2024).

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Advances in adjuvant immuno-oncology therapies for stage IIB/C melanoma

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National Research Institute of Oncology

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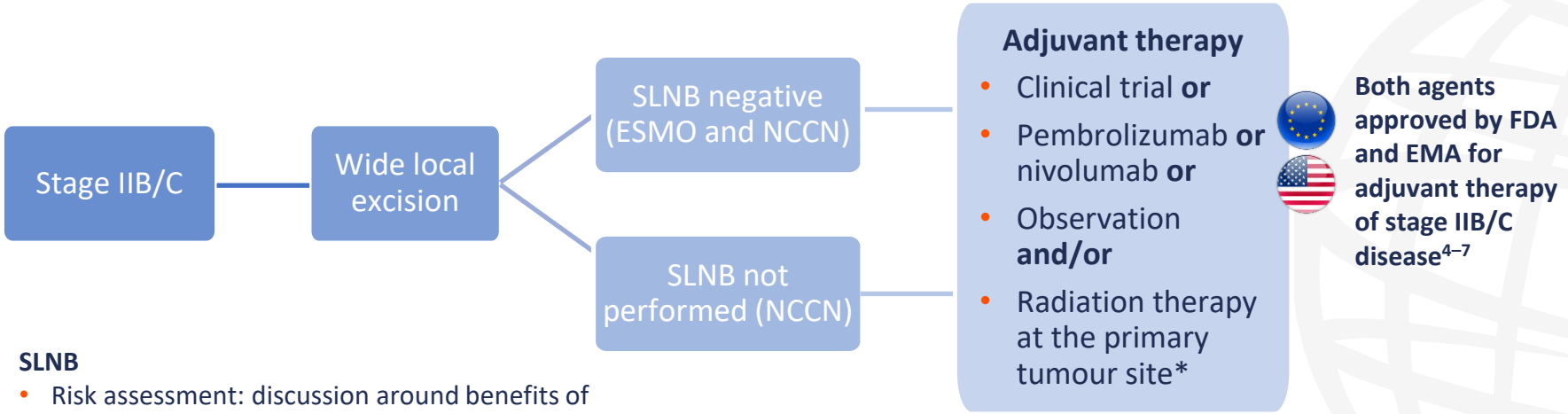
What is the standard-of-care treatment for patients with stage IIB/C melanoma?

Guideline recommendations for stage IIB/C melanoma[1,2]



SLNB

- Risk assessment: discussion around benefits of adjuvant therapy with each patient[1]
- Regional control improvement[1]
- May be replaced by a biomarker in due course[1,3]

*Consider in patients with desmoplastic histology and/or neurotropism.
EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network; SLNB, SLN biopsy.

1. NCCN Clinical Practice Guidelines. Melanoma: Cutaneous. Version 3.2024. Available at: www.nccn.org (accessed 26 November 2024);
2. Amaral T, et al. *Ann Oncol*. 2024. doi: 10.1016/j.annonc.2024.11.006 [Epub ahead of print]; 3. van Akkooi ACJ, et al. *Eur J Cancer*. 2023;182:163–9; 4. FDA. Pembrolizumab PI. Available at: https://bit.ly/4e7d67R (accessed 26 November 2024); 5. FDA. Nivolumab PI. Available at: https://bit.ly/4eZIHt7 (accessed 26 November 2024); 6. EMA. Pembrolizumab SmPC. Available at: https://bit.ly/4hhcBuu (accessed 26 November 2024); 7. EMA. Nivolumab SmPC. Available at: https://bit.ly/3YhBldi (accessed 26 November 2024).

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What are the latest data supporting the use of approved adjuvant immunotherapies for stage IIB/C disease?

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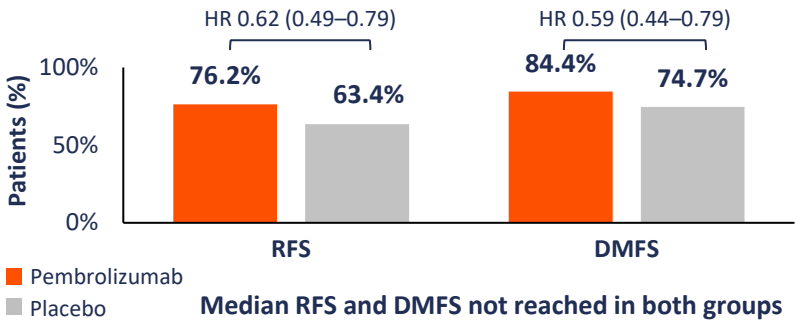
Phase III KEYNOTE-716 trial

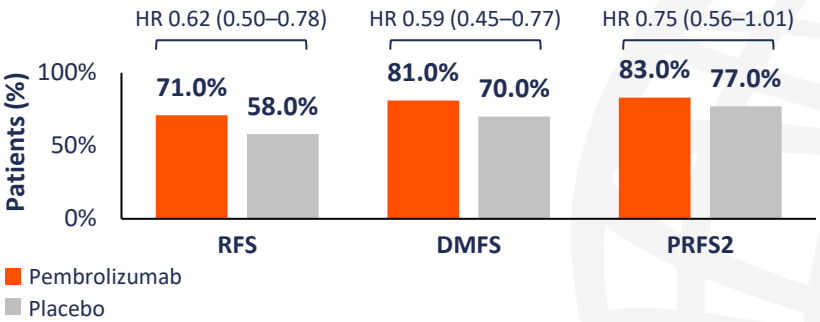
976 patients with resected stage IIB or IIC melanoma received: adjuvant pembrolizumab or placebo in part 1 (double-blind period), pembrolizumab as rechallenge or crossover in part 2 if recurrence occurred (unblinded period)[1]

Final analysis at 36 months[2]



Median RFS and DMFS not reached in both groups

Outcomes at 48 months[4]



TRAEs	Pembrolizumab	Placebo
Overall	82.6%	63.6%
Discontinued*	15.9%	2.5%
Grade 3/4	17.2%	5.1%
irAEs and IRRs	37.9%	9.5%
Death	0	0

Using 36-month RFS data:[3]

- **NNT** to avoid one recurrence in patients with high-risk resected stage IIB/C melanoma was **7.8**
- **NNH** was **4.9**

No new safety signals observed during rechallenge/crossover

Using 48-month data:[4]

- **RFS NNT** was **5.3**
- **DMFS NNT** was **7.8**

95% confidence intervals presented in brackets following HR. *Owing to TRAEs.
DMFS, distant metastasis-free survival; HR, hazard ratio; irAE, immune-related adverse event; IRR, infusion-related reaction; NNH, number needed to harm; NNT, number needed to treat; PRFS2, progression-/recurrence-free survival 2; RFS, recurrence-free survival; TRAE, treatment-related adverse event.

1. Luke JJ, et al. *Lancet*. 2022;399:1718–29; 2. Luke JJ, et al. *J Clin Oncol*. 2024;42:1619–24; 3. van Akkooi ACJ, et al. *EJC Skin Cancer*. 2024;2:100021.
4. Luke JJ, et al. Presented at the European Society for Medical Oncology Congress; 13–17 September 2024; Barcelona, Spain. Abstract 1078MO.

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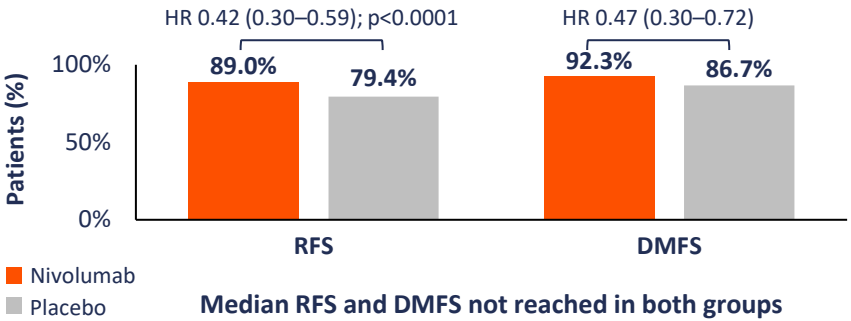
Phase III CheckMate 76K trial

790 patients with resected stage IIB/C melanoma were randomized 2:1 to receive nivolumab or placebo[1]

Pre-specified interim analysis at 12 months[1]



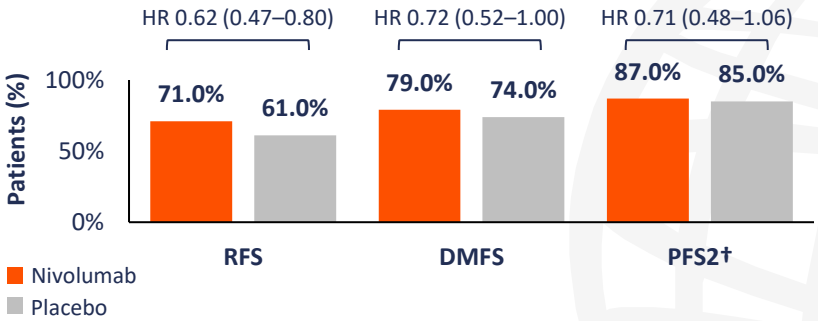
Median RFS and DMFS not reached in both groups

TRAEs	Nivolumab	Placebo
Overall	**82.6%**	**53.8%**
Discontinued*	**14.7%**	**2.7%**
Grade 3/4	**10.3%**	**2.3%**
IRRs	**5.2%**	**0.8%**
Death	**0.2%**	**0**
Endocrine and non-endocrine irAEs occurred		

At 24 months:[2]

- **NNT** with nivolumab to avoid one recurrence was **8** (95% CI 6–18)
- **Number** needed for one additional grade 3 or 4 TRAE was **8** (95% CI 6–12)

Outcomes at 36 months[2]



No new safety signals observed following primary analysis

95% CIs presented in brackets following HR. *Owing to TRAEs; †Defined as time between randomization and second recurrence/progression after initiation of a subsequent systemic anticancer therapy, initiation of a second systemic anticancer therapy, or death (due to any cause).

CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; irAE, immune-related adverse event; IRR, infusion-related reaction; NNT, number needed to treat; PFS, progression-free survival; RFS, recurrence-free survival; TRAE, treatment-related adverse event.

1. Kirkwood JM, et al. *Nat Med*. 2023;29:2835–43; 2. Long GV, et al. Presented at the European Society for Medical Oncology Congress; 13–17 September 2024; Barcelona, Spain. Abstract 1077MO.

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What factors inform the selection of adjuvant therapy for stage IIB/C melanoma in clinical practice?

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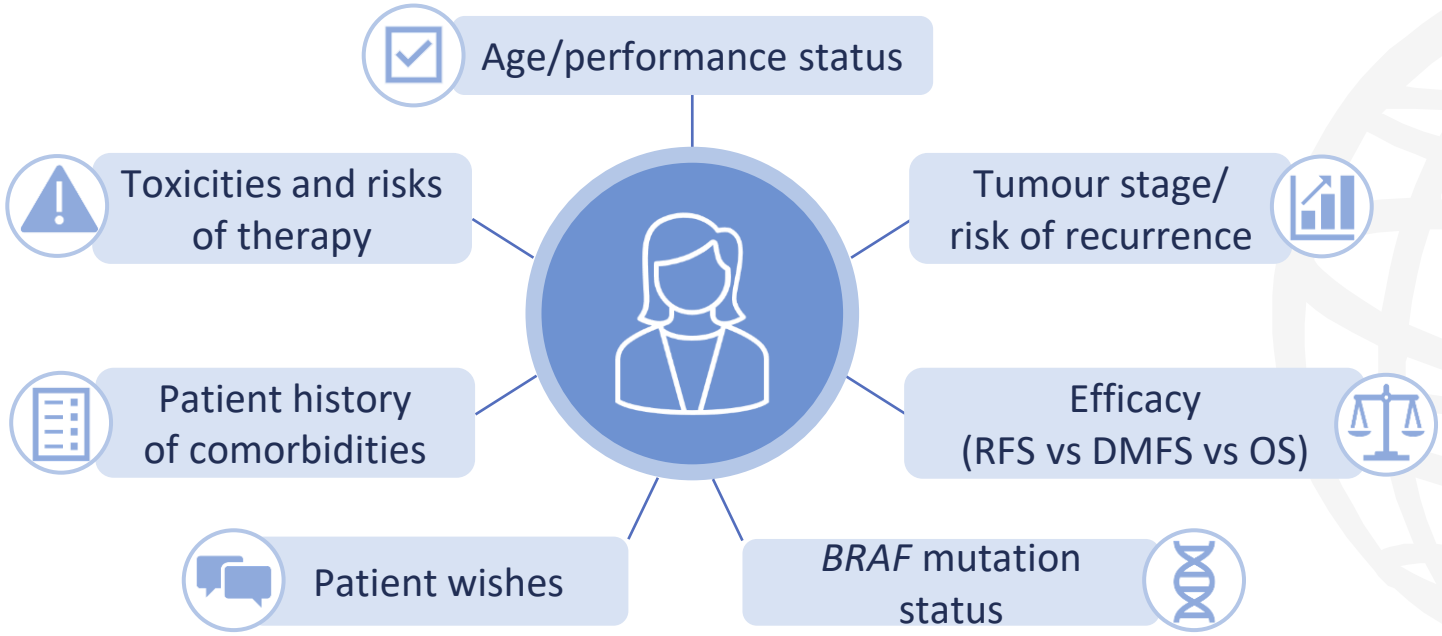
Factors impacting adjuvant therapy choice[1–4]



OS, overall survival; DMFS, distant metastasis-free survival; RFS, recurrence-free survival.

1. Rutkowski P, Mandala MP. *Eur J Surg Oncol*. 2024;50:107969; 2. Kobeissi I, Tarhini AA. *Ther Adv Med Oncol*. 2022;14:17588359221134087;
3. NCCN Clinical Practice Guidelines. Melanoma: Cutaneous. Version 3.2024. Available at: www.nccn.org (accessed 26 November 2024); 4. Karakousis G. *Lancet Oncol*. 2020;21:319–20.

What novel adjuvant therapies are being explored for stage IIB/C melanoma?

Phase III adjuvant trials including stage IIB/C melanoma

	Study design	Endpoints	Data for later stages
INTerpath-001 (V940-001)[1] NCT05933577	1,089 pts randomized 2:1 to **V940 (mRNA-4157)** + pembrolizumab **vs** placebo + pembrolizumab	• **Primary: RFS** • Key secondary: DMFS, OS, safety, QoL	**IIIB–IV:**[2,3] 3-year RFS and DMFS benefit and improved OS trend **vs** pembrolizumab + placebo
COLUMBUS-AD[4] NCT05270044	~815 pts with *BRAF*V600 mutation randomized 1:1 to **encorafenib + binimetinib vs** placebo	• **Primary: RFS** • Key secondary: DMFS, OS, safety, QoL	**IIIB–IV:**[5] 7-year PFS and OS benefit vs vemurafenib
Fianlimab + Cemiplimab[6] NCT05608291	1,530 pts randomized 1:1:1 to compare **fianlimab + cemiplimab vs** pembrolizumab	• **Primary: RFS** • Key secondary: OS, MSS, safety	**IIIB–IV:**[7] 2-year outcomes showed high clinical activity and increasing CRs over time
KEYVIBE-010[8] NCT05665595	1,560 pts randomized 1:1 to **pembrolizumab + vibostolimab vs** pembrolizumab	• **Primary: RFS** • Key secondary: DMFS, OS, safety, QoL	Study discontinued and negative[9]

CR, complete response; DMFS, distant metastasis-free survival; MSS, melanoma-specific survival; OS, overall survival; PFS, progression-free survival; pts, patients; QoL, quality of life; RFS, recurrence-free survival.

1. Weber JS, et al. *J Clin Oncol*. 2024;42:TPS9616; 2. Weber JS, et al. *Lancet*. 2024;403:632–44; 3. Weber JS, et al. Presented at the American Society of Clinical Oncology; 31 May–4 June 2024; Chicago, IL, USA. Abstract LBA9512 ; 4. van Akkooi ACJ, et al. *J Clin Oncol*. 2023;41(Suppl. 16):TPS9601; 5. Schadendorf D, et al. *Eur J Cancer*.2024;204:114073; 6. Panella TJ, et al. *J Clin Oncol*. 2023;41(Suppl. 16):TPS9598; 7. McKean M, et al. *Ann Oncol*. 2024;35(Suppl. 2):S712–48; 8. Long GV, et al. *J Clin Oncol*. 2023;41(Suppl. 16):TPS9611; 9. American Journal of Managed Care. Press release. Available at: www.ajmc.com/view/late-stage-trial-discontinued-due-to-adverse-events (accessed 26 November 2024).

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How do you foresee the use of adjuvant therapy in stage IIB/C melanoma evolving considering new data and studies?

Role of neoadjuvant therapies and biomarkers in the management of melanoma

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What is the rationale for neoadjuvant therapy in stage III/IV resectable melanoma?

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Evolving role of neoadjuvant therapy

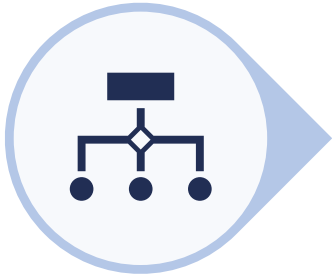
Patients

Resectable, clinical stage III–IV melanoma[1,2]

Select patients with macroscopic disease[2,3]

Unmet need

Suboptimal long-term outcomes with SoC surgery + adjuvant therapy[4]



Emerging data

Research shows benefits of neoadjuvant therapy e.g. on RFS, EFS, DMFS[5–7]

Guideline updates

Addition of neoadjuvant ICI for resectable stage III–IV melanoma to ESMO, ASCO and NCCN guidelines[8–10]

ASCO, American Society of Clinical Oncology; DMFS, distant metastasis-free survival; EFS, event-free survival; ESMO, European Society for Medical Oncology; ICI, immune checkpoint inhibitor; NCCN, National Comprehensive Cancer Network; RFS, recurrence-free survival; SoC, standard of care.

1. Kakish H, et al. *Crit Rev Oncol Hematol*. 2024;193:104193; 2. Therien AD, et al. *Surg Oncol*. 2024;56:102127; 3. van Akkooi ACJ, et al. *Eur J Cancer*. 2023;182:38–42; 4. Hieken TJ, et al. *Am Soc Clin Oncol Educ Book*. 2023;43:e390614; 5. Bushara O, et al. *Cancers*. 2023;15:3344; 6. Lucas MW, et al. Presented at the European Society for Medical Oncology Congress; 13–17 September 2024; Barcelona, Spain. Abstract LBA42; 7. Patel SP, et al. *N Engl J Med*. 2023;388:813–23; 8. Amaral T, et al. *Ann Oncol*. 2024. doi: 10.1016/j.annonc.2024.11.006 (Epub ahead of print); 9. Seth R, et al. *J Clin Oncol*. 2023;41:4794–820; 10. NCCN Clinical Practice Guidelines. Melanoma: Cutaneous. Version 3.2024. Available at: www.nccn.org (accessed 26 November 2024).

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What are the latest trial data supporting the use of neoadjuvant strategies in high-risk melanoma?

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Key studies in stage ≥III melanoma

- **OpACIN-neo:** provided insights into the benefits of neoadjuvant therapy for resectable melanoma using IPI + NIVO[1,2]
- **PRADO**: assessed personalized neoadjuvant IPI + NIVO regimen guided by pathologic response[1,2]

Phase III NADINA[3]

Neoadjuvant IPI + NIVO + TLND **vs** TLND + adjuvant nivolumab (N=423)

Neoadjuvant | Adjuvant

18-mo EFS

Adjusted HR 0.32
p<0.0001

18-mo DMFS

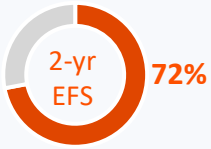
Adjusted HR 0.37
p<0.0001

18-mo RFS

Phase II SWOG 1801[4]

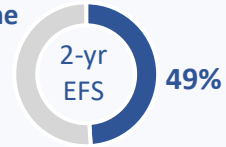
Neoadjuvant PEM + surgery + adjuvant PEM **vs** surgery + adjuvant PEM (N=313)

Neoadjuvant + adjuvant



Recurrence in 9/154 pts

Adjuvant alone

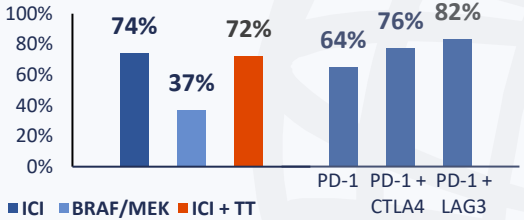


Recurrence in 41/159 pts

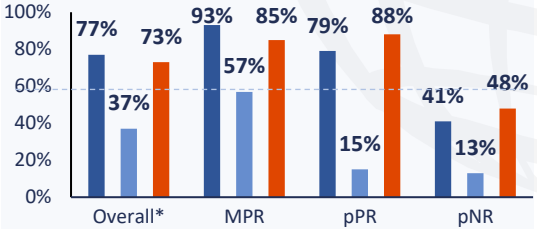
INMC pooled analysis[5]

Neoadjuvant ICI **vs** BRAF/MEK inhibitor **vs** ICI + TT (+ surgery in all three groups; N=818)

3-year EFS



3-year RFS



*Excludes 36 patients who did not receive surgery. BRAF, v-Raf murine sarcoma viral oncogene homolog B; CTLA4, cytotoxic T-lymphocyte associated protein 4; DMFS distant metastasis-free survival; EFS, event-free survival; HR, hazard ratio; ICI, immune checkpoint inhibitor; INMC, International Neoadjuvant Melanoma Consortium; IPI, ipilimumab; LAG3, lymphocyte activation gene 3; MEK, mitogen-activated extracellular signal-regulated kinase; MPR, major pathologic response; NIVO, nivolumab; PD-1, programmed cell death protein 1; PEM, pembrolizumab; pNR, pathologic non-response; pPR, pathologic partial response; pts, patients; RFS, recurrence-free survival; TLND, tumour lymph node dissection; TT, targeted therapy.

1. Reijers ILM, et al. *J Clin Oncol*. 2023;41(Suppl. 16): Abstract 101; 2. Therien AD, et al. *Surg Oncol*. 2024;56:102127; 3. Lucas MW, et al. Presented at the European Society for Medical Oncology Congress; 13–17 September 2024; Barcelona, Spain. Abstract LBA42; 4. Patel SP, et al. *N Engl J Med*. 2023;388:813–23; 5. Long GV, et al. Presented at the European Society for Medical Oncology Congress; 13–17 September 2024; Barcelona, Spain. Abstract LBA41.

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Other studies

Stage II–IV cSCC

Phase II/III INTerpath-007 adaptive study[1]
Neoadjuvant **and** adjuvant pembrolizumab + V940

Stage ≥III melanoma

Phase I/II KEYMAKER-U02 substudy 02C[2]	Phase II NeoACTIVATE[3]	Phase III PIVOTAL[4,5]	Phase II REDUCTOR[6,7]
Neoadjuvant pembrolizumab + vibostolimab **or** favezelimab* **or** MK-4830 **or** gebasaxturev + adjuvant pembrolizumab	Neoadjuvant vemurafenib + cobimetinib + atezolizumab (*BRAF*-mutated) **or** cobimetinib + atezolizumab (*BRAF* wild-type)	Neoadjuvant L19IL2/L19TNF (daromun); prior treatment allowed, and adjuvant therapy at investigator's choice	Neoadjuvant dabrafenib + trametinib in previously unresectable *BRAF*-mutated tumours

Stage II melanoma

Phase II NeoReNi II[8]	Neoadjuvant nivolumab + relatlimab +/- adjuvant cycles depending on pathologic response
Phase II UPCC 09618 study[9]	Neoadjuvant pembrolizumab + adjuvant pembrolizumab

*Favezelimab was co-formulated with pembrolizumab. cSCC, cutaneous squamous cell carcinoma.

1. Ladwa R, et al. Presented at the European Society for Medical Oncology Congress; 13–17 September 2024; Barcelona, Spain. Abstract 940TiP; 2. Menzies AM, et al. Presented at the European Society for Medical Oncology Congress; 13–17 September 2024; Barcelona, Spain. Abstract 10820; 3. Hieken TJ, et al. *Nat Commun*. 2024;15:1430; 4. Hauschild A, et al. *J Clin Oncol*. 2024;42(Suppl. 17): Abstract LBA9501; 5. ClinicalTrials.gov. NCT02938299. Available at: https://clinicaltrials.gov/study/NCT02938299 (accessed 5 November 2024); 6. Burgers F, et al. Presented at the European Society for Medical Oncology Congress; 13–17 September 2024; Barcelona, Spain. Abstract 1118P; 7. Blankenstein SA, et al. *Ann Surg*. 2021;274:383–9; 8. Gonzalez M, et al. *J Clin Oncol*. 2023; 41(Suppl. 16):Abstract TPS9610; 9. ClinicalTrials.gov. NCT03757689. Available at: https://clinicaltrials.gov/study/NCT03757689 (accessed 5 November 2024).

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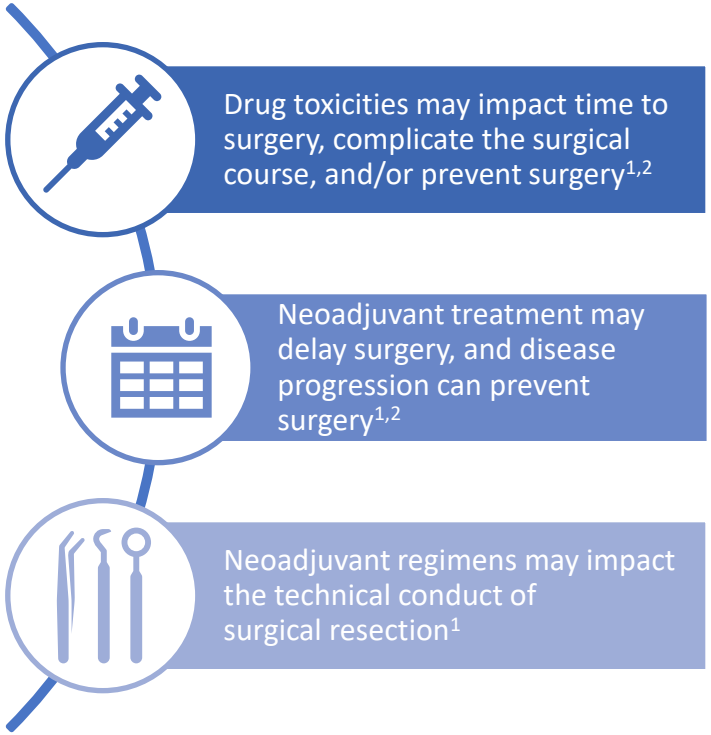
What are the clinical concerns associated with using a neoadjuvant strategy?

Limitations of a neoadjuvant approach



Drug toxicities may impact time to surgery, complicate the surgical course, and/or prevent surgery[1,2]

Neoadjuvant treatment may delay surgery, and disease progression can prevent surgery[1,2]

Neoadjuvant regimens may impact the technical conduct of surgical resection[1]

Expert clinical insights

- **SWOG 1081 trial approach used in practice**
- **In *BRAF* wild-type non-responders, options are limited**
- **In minority who don't respond to ipilimumab/nivolumab, clinical trial, surgery or radiation therapy if possible**

1. Hieken TJ, et al. *Am Soc Clin Oncol Educ Book*. 2023;43:e390614; 2. Erstad DJ, et al. *Clin Adv Hematol Oncol*. 2022;20:47–55.

How can response to neoadjuvant therapy be used to inform subsequent treatment decisions in practice?

Factors impacting treatment sequencing

Pathologic response to neoadjuvant therapy[1]

Pathologic complete response (pCR)
No residual viable tumour

Near-pCR
<10% viable tumour cells

Pathologic partial response (pPR)
<50% of tumour bed occupied by viable tumour cells

Pathologic non-response (pNR)
>50% tumour bed occupied by viable tumour cells

Major pathologic response (MPR)

- **2021 INMC pooled analysis:** pathologic response to neoadjuvant immunotherapy corresponded with improved RFS and OS in stage III melanoma[2]
- It is a potential surrogate endpoint[3,4]

Available data on therapies[1]

NCCN considerations post-neoadjuvant therapy

- **Neoadjuvant pembrolizumab:** withholding adjuvant therapy following MPR not routinely advised
- **Neoadjuvant ipilimumab + nivolumab:** adjuvant nivolumab or observation in patients with MPR, continued systemic therapy if no MPR
- **Neoadjuvant nivolumab + relatlimab:** consider adjuvant PD-1 inhibitor (optimal approach not well defined and adjustment based on pathologic response not studied)

INMC, International Neoadjuvant Melanoma Consortium; MPR, major pathologic response; NCCN, National Comprehensive Cancer Network; OS, overall survival; pCR, pathologic complete response; PD-1, programmed cell death protein 1; pNR, pathologic non-response; pPR, pathologic partial response; RFS, recurrence-free survival.

1. NCCN Clinical Practice Guidelines. Melanoma: Cutaneous. Version 3.2024. Available at: www.nccn.org (accessed 26 November 2024);
2. Menzies AM, et al. *Nat Med*. 2021;27:301–9; 3. van Akkooi ACJ, et al. *Ann Surg Oncol*. 2022;29:3694–708; 4. Pavlick AC, et al. *J Immunother Cancer*. 2023;11:e006947.

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What other biomarkers show promise in facilitating patient selection for neoadjuvant therapy?

Data for biomarkers are limited but promising: Dynamic evaluation is possible

IFN-γ[1,2*]

OpACIN-neo, PRADO & DONIMI trials

Analysis of **primary tumour** from patients with stage III melanoma

High baseline IFN-γ associated with significantly prolonged 3-year DMFS, EFS, RFS and OS with neoadjuvant ipilimumab + nivolumab

Other potential biomarkers observed in clinical trials

OpACIN-neo and NCT02519322 (ipilimumab + nivolumab)

- IFN-γ and TMB may serve as biomarkers for response[2,3]
- Higher CD8+ T-cell transcripts in patients with pathologic response[4,5]

CombiNeo and NeoCombi (dabrafenib + trametinib)

- Lower phosphorylation of ERK in patients who achieved pCR in CombiNeo[6]
- Similar association not observed in NeoCombi[7]

More research is needed to establish validated biomarkers to guide neoadjuvant therapy and further research on non-invasive biomarkers is warranted[4]

*Patients received neoadjuvant anti-PD-1 +/- anti-CTLA4 +/- domatinostat.

CD8, cluster of differentiation 8; CTLA4, cytotoxic T-lymphocyte associated protein 4; DMFS, distant metastasis-free survival; EFS, event-free survival; ERK, extracellular signal-regulated kinase; IFN-γ, interferon gamma; OS, overall survival; pCR, pathologic complete response; PD-1, programmed cell death protein 1; RFS, recurrence-free survival; TMB, tumour mutational burden.

1. Hoeijmakers L, et al. Presented at the European Society for Medical Oncology Congress; 13–17 September 2024; Barcelona, Spain. Abstract 1090P;
2. Rozeman EA, et al. *Ann Oncol*. 2019;30(Suppl. 5):Abstract LBA75; 3. Rutkowski P, Mandala MP. *Eur J Surg Oncol*. 2024;50:107969; 4. Błoński PJ, et al. *Biomedicines*. 2024;12:669;
5. Amaria RN, et al. *Nat Med*. 2018;24:1649–54; 6. Amaria RN, et al. *Lancet Oncol*. 2018;19:181–93; 7. Long GV, et al. *Lancet Oncol*. 2019;20:961–71.

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