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Navigating treatment choices in high-risk early-stage melanoma

Practice aid for early-stage melanoma

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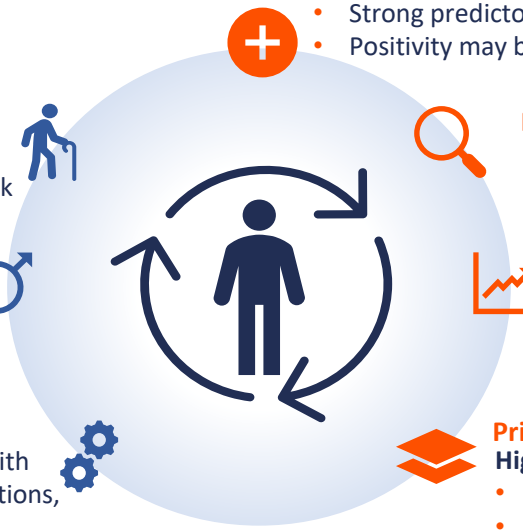
Risk of recurrence in stage IIB/C melanoma

- The AJCC 8th edition staging system for melanoma[1] may not reflect recurrence risk at each stage in all practice settings[2]
- Three real-world studies identified overall recurrence rates of **30.6–37.3%** in **stage IIB** and **35.2–46%** in **stage IIC** melanoma[2–4]
- A Danish study found that patients with **stage IIB and IIC** melanoma had **a poorer prognosis** than those with **stage IIIA and IIIB** disease[2]

Patient and tumour factors impacting recurrence risk



SLNB status[7,8]
- Strong predictor of survival
- Positivity may be associated with recurrence

Older age[5]
- Those >75 years vs 65–75 years of age may have higher risk

Primary tumour location[7,9]
- Certain locations, e.g. head and neck, have been linked to poorer outcomes

Sex[6]
- Men are more likely to experience recurrence than women

Mitotic rate[1,7,9,10]
- Removed from AJCC 8th edition staging criteria[5,6]
- However, recent studies report its relevance[2,4,6]

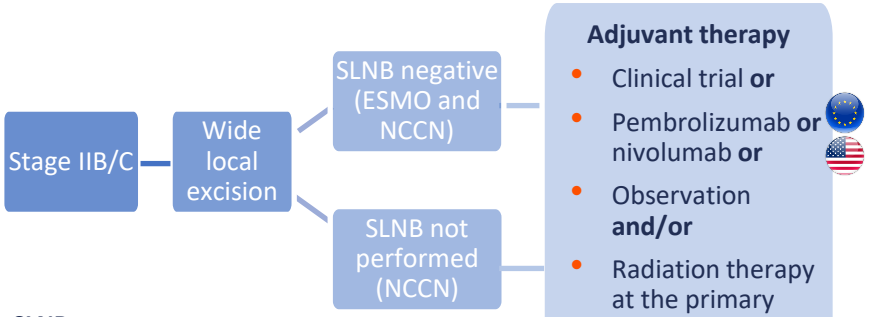
Comorbidities[5]
- E.g. CHF, diabetes with associated complications, chronic lung disease

Primary tumour thickness[1,9]

High-risk stage IIB/C:
- Breslow depth >4.0 mm **or**
- Breslow depth >2.1 mm **+** ulceration

Treatment selection stage IIB/C melanoma

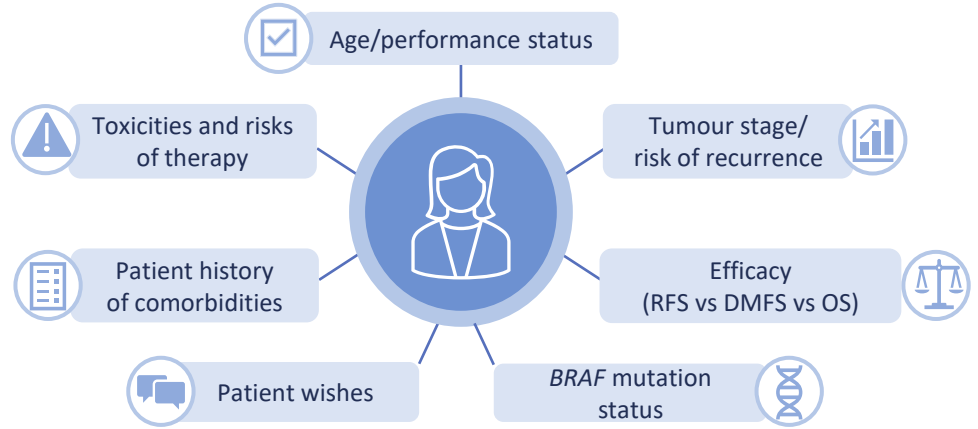
NCCN and ESMO guidelines[8,11]



Both agents approved by FDA and EMA for adjuvant therapy of stage IIB/C disease[12–15]

SLNB
- Risk assessment: discussion around benefits of adjuvant therapy with each patient[8]
- Regional control improvement[8]

Factors impacting adjuvant therapy choice[8,16–18]



*Consider in patients with desmoplastic histology and/or neurotropism.

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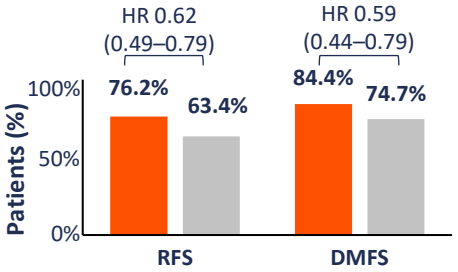
Key data supporting adjuvant therapies approved for use in stage IIB/C melanoma

Phase III KEYNOTE-716 trial

976 patients with resected stage IIB/C melanoma: adjuvant pembrolizumab or placebo (double-blind), pembrolizumab rechallenge/crossover if recurrence occurred (unblinded)[19]

Pembrolizumab | Placebo

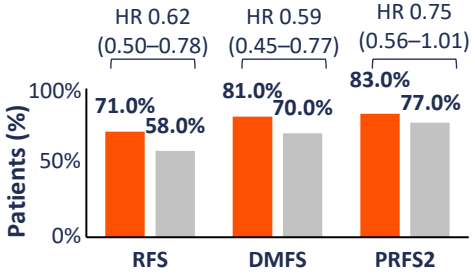
Final analysis at 36 months[20]



Median RFS and DMFS not reached

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

Outcomes at 48 months[21]



No new safety signals observed during rechallenge/ crossover

Using 48-month data:[21]
- **RFS NNT** was **5.3**
- **DMFS NNT** was **7.8**

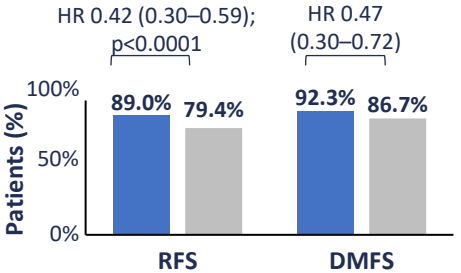
Using 36-month RFS data:[22]
- **NNH** was **4.9**

Phase III CheckMate 76K trial

790 patients with resected stage IIB/C melanoma were randomized 2:1 to receive nivolumab or placebo[23]

Nivolumab | Placebo

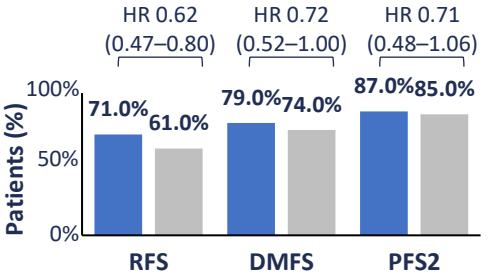
Interim analysis at 12 months[23]



Median RFS and DMFS not reached

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		

Outcomes at 36 months[24]



No new safety signals observed following primary analysis

At 24 months:[24]
- **NNT** to avoid 1 recurrence was **8** (95% CI 6–18)
- **Number** needed for **1 additional grade 3/4 TRAE** was **8** (95% CI 6–12)

Increasing role of neoadjuvant therapy in melanoma and factors impacting sequencing

Evolving role of neoadjuvant therapy

Patients
Resectable, clinical stage III–IV melanoma[25,26]
Select patients with macroscopic disease[26,27]

Unmet need
Suboptimal long-term outcomes with SoC surgery + adjuvant therapy[28]

Emerging data
Research shows benefits of neoadjuvant therapy e.g. on RFS, EFS, DMFS[29–31]

Guideline updates
Addition of neoadjuvant ICI for resectable stage III–IV melanoma to ESMO, ASCO and NCCN guidelines[8,11,32]

Stage II

Phase II NeoReNi II[33]	Neoadjuvant nivolumab + relatlimab **+/-** adjuvant cycles depending on pathologic response
Phase II UPCC 09618 study[34]	Neoadjuvant pembrolizumab + adjuvant pembrolizumab

Pathologic response to neoadjuvant therapy[8]

Pathologic complete response (pCR)
No residual viable tumour

Near-pCR
<10% viable tumour cells

Major pathologic response (MPR)

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

NCCN considerations post-neoadjuvant therapy[8]

- **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)

95% confidence intervals presented in brackets following HR. *Owing to TRAEs.

Abbreviations and references

Abbreviations

AJCC, American Joint Committee on Cancer; ASCO, American Society of Clinical Oncology; CHF, congestive heart failure; CI, confidence interval; DMFS, distant metastasis-free survival; EFS, event-free survival; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; IRR, infusion-related reaction; MPR, major pathologic response; NCCN, National Comprehensive Cancer Network; NNH, number needed to harm; NNT, number needed to treat; OS, overall survival; pCR, pathologic complete response; PFS2, progression-free survival 2 (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); pNR, pathologic non-response; pPR, pathologic partial response; PRFS2, progression-/recurrence-free survival 2; RFS, recurrence-free survival; SLNB, sentinel lymph node biopsy; SoC, standard of care; TRAE, treatment-related adverse event.

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