Inmunoterapia en melanoma 2024: Adyuvancia y neoadyuvancia

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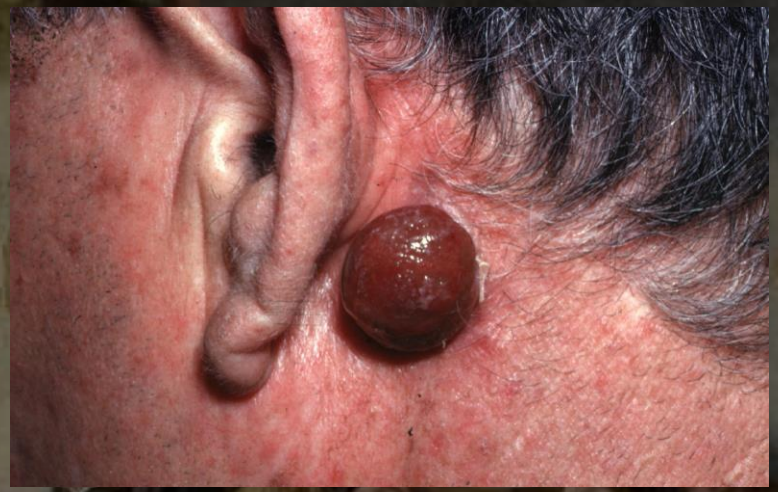
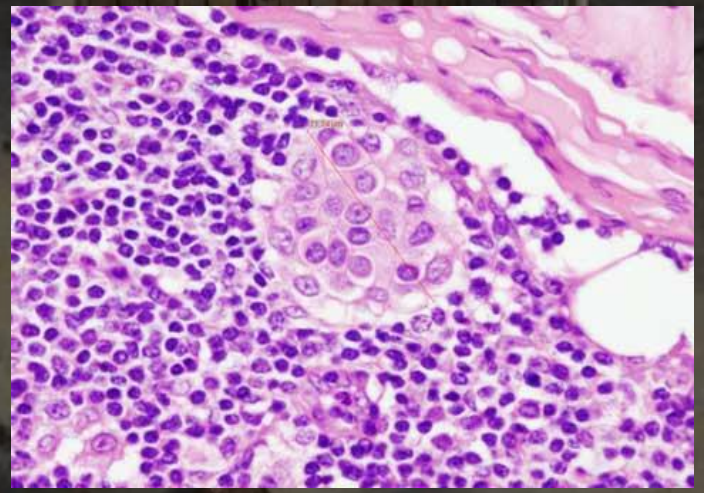
Unidad de Melanoma
Hospital Universitario Virgen Macarena
Sevilla

The New Pupil. Thomas Brooks 1854



Estadio IIB-IIC



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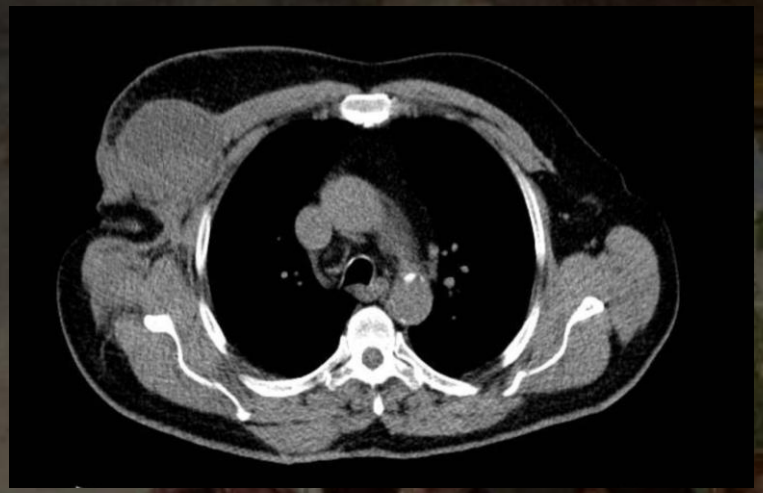

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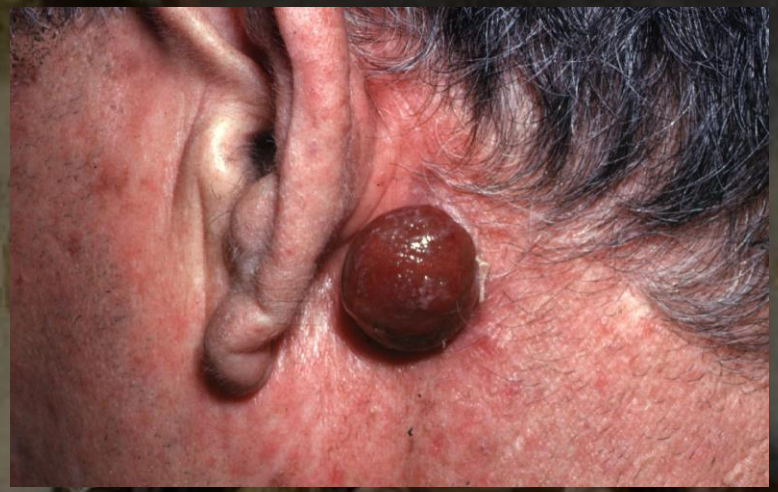

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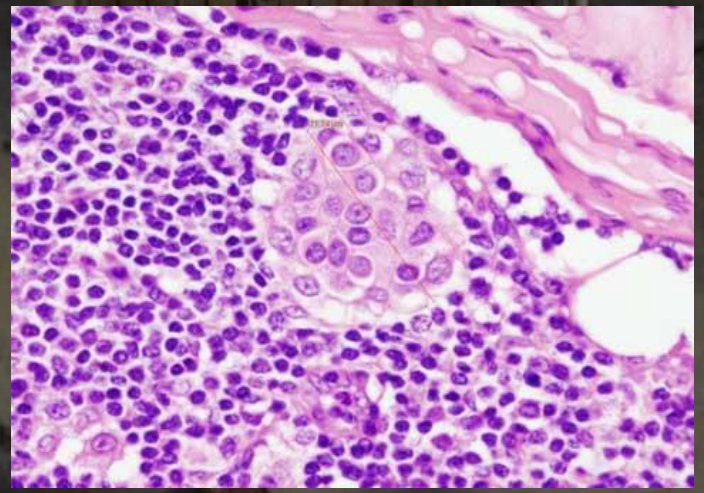

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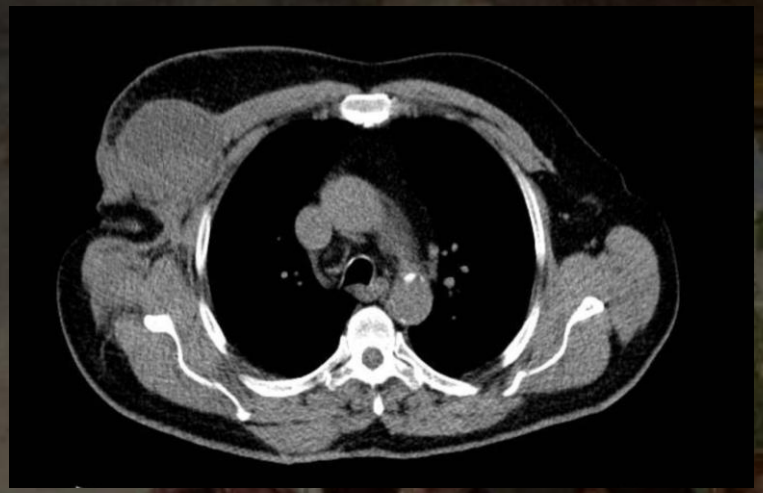
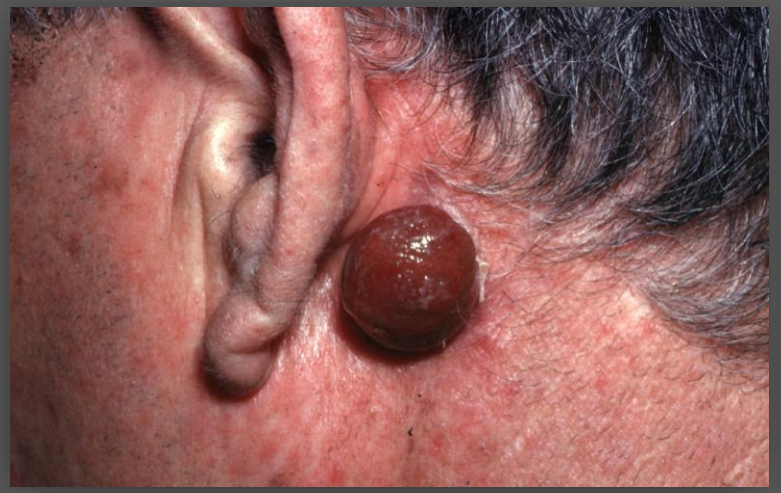


Estadio IIIBb-C

Inmunoterapia adyuvante

Inmunoterapia neoadyuvante

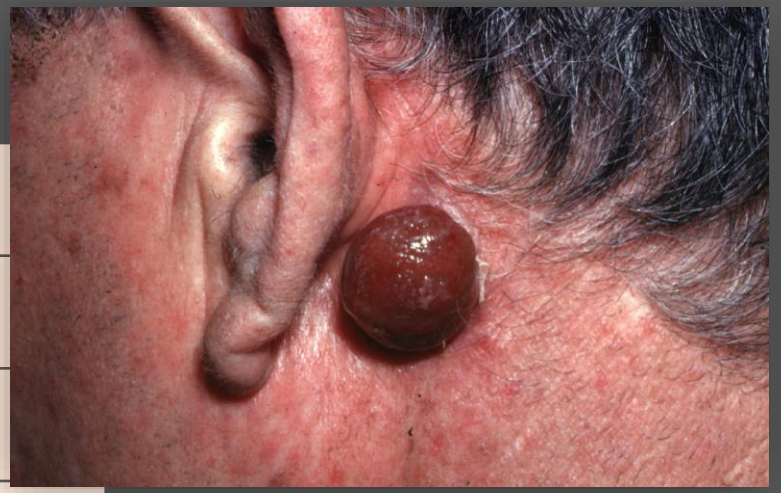


Adyuvancia en el paciente con tumor primario de alto riesgo no metastásico

Melanoma **≥T3b**
estadio **IIB-IIC**

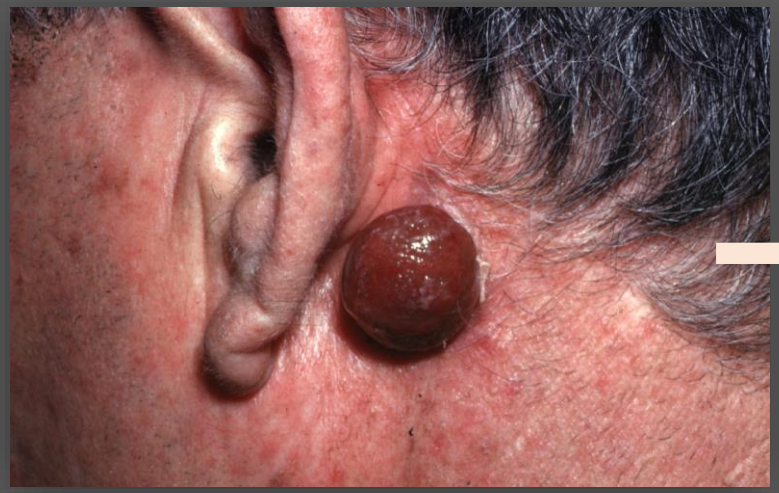
	5 años	10 años
IA	99%	98%
IB	97%	94%
IIA	95%	88%
IIIA	93%	88%
IIB	87%	82%
IIIB	83%	77%
IIC	82%	75%
IIIC	69%	60%
IIID	32%	24%

AJCC 2017

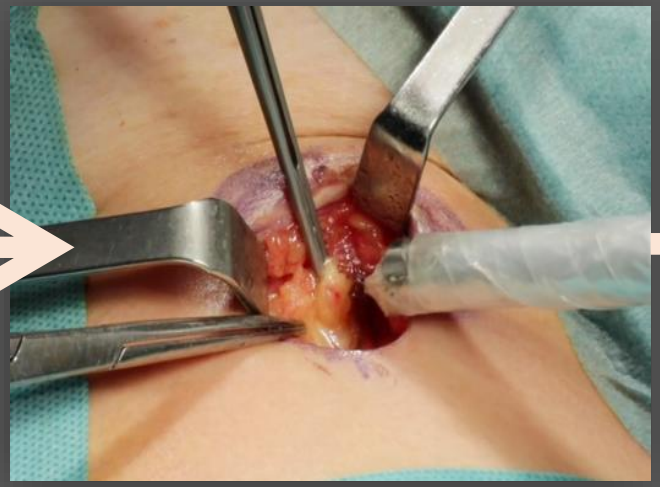


Estadio IIB-IIC

Supervivencia Específica por Melanoma



Estadio IIB-IIC
T3b-T4bN0M0



Biopsia Selectiva del Ganglio Centinela

IIIC-IIID

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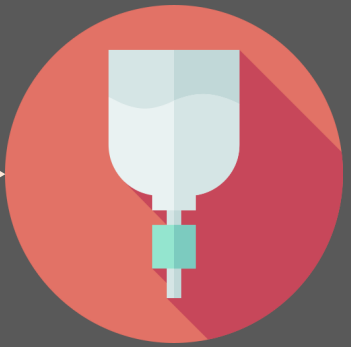

Inmunoterapia adyuvante

Seguimiento ecográfico

	5 años	10 años
IA	99%	98%
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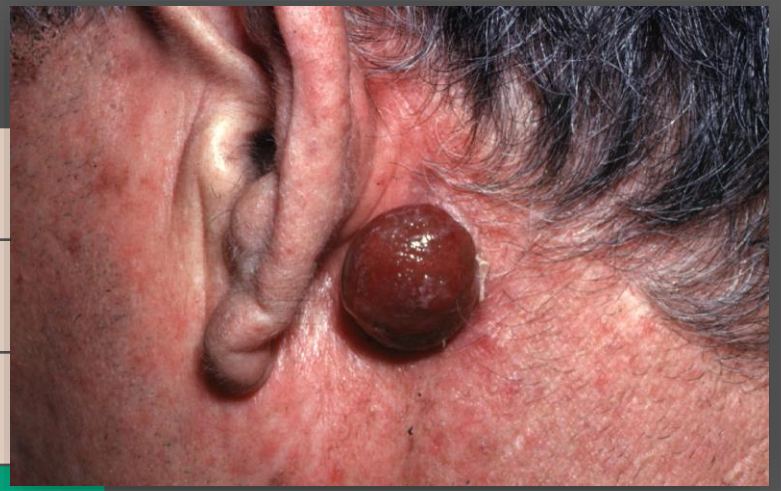
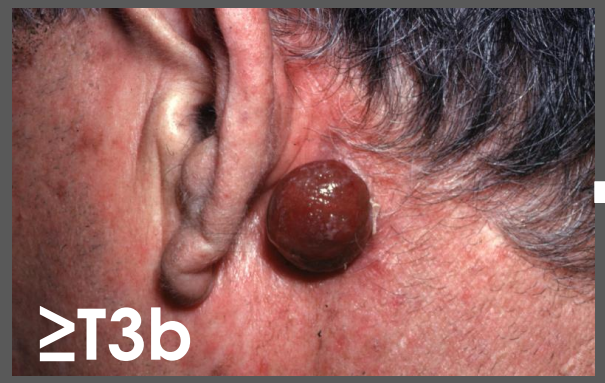


Adyuvancia

Supervivencia Específica por Melanoma

AJCC 2017

KEYNOTE 716

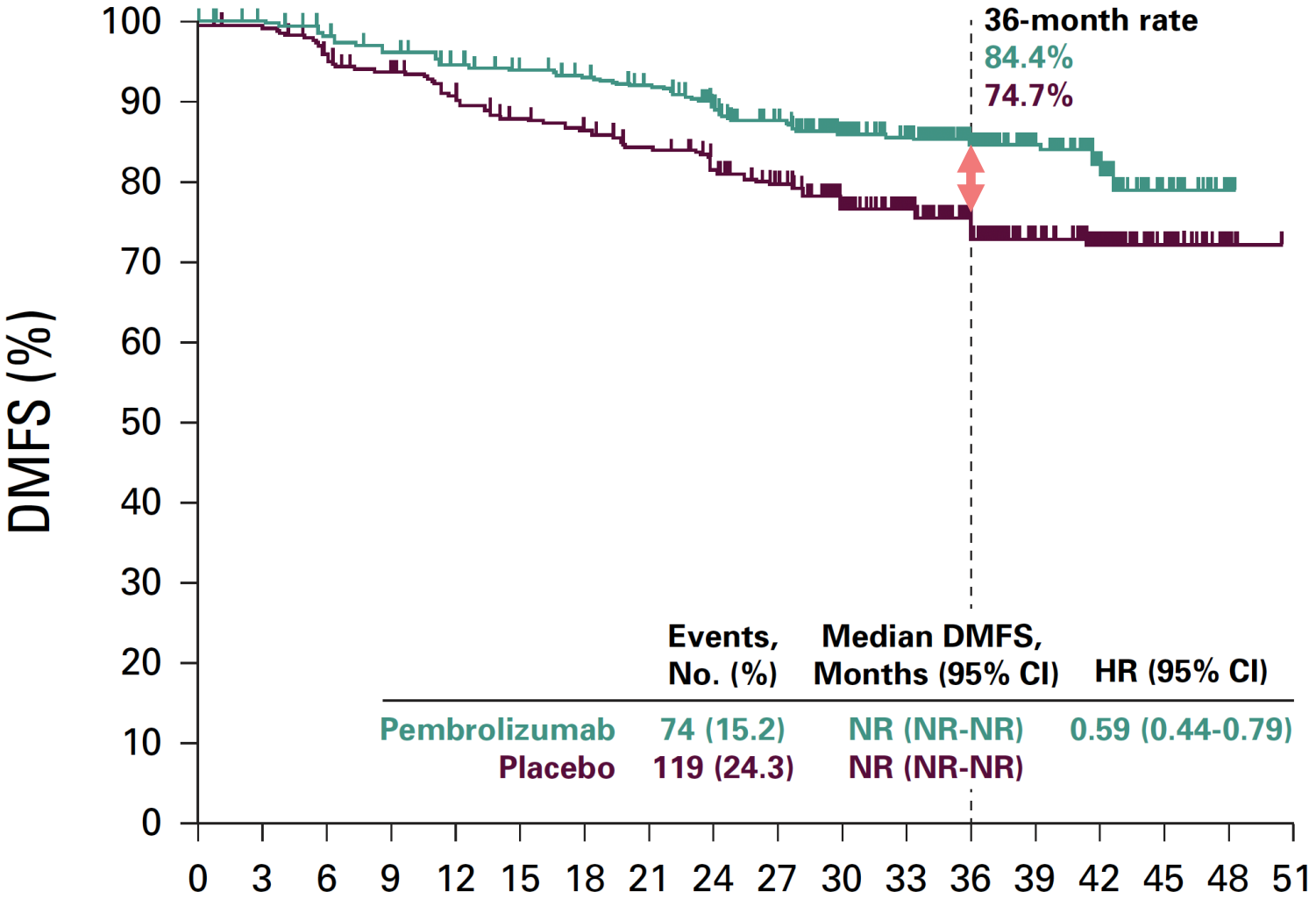


pembrolizumab
200mg/3sem x 17 ciclos

placebo

Supervivencia libre de metástasis a distancia

Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma: final analysis of distant metastasis-free survival in the pase III **KEYNOTE-716**. JJ Luke et al. J Clin Oncol 2024



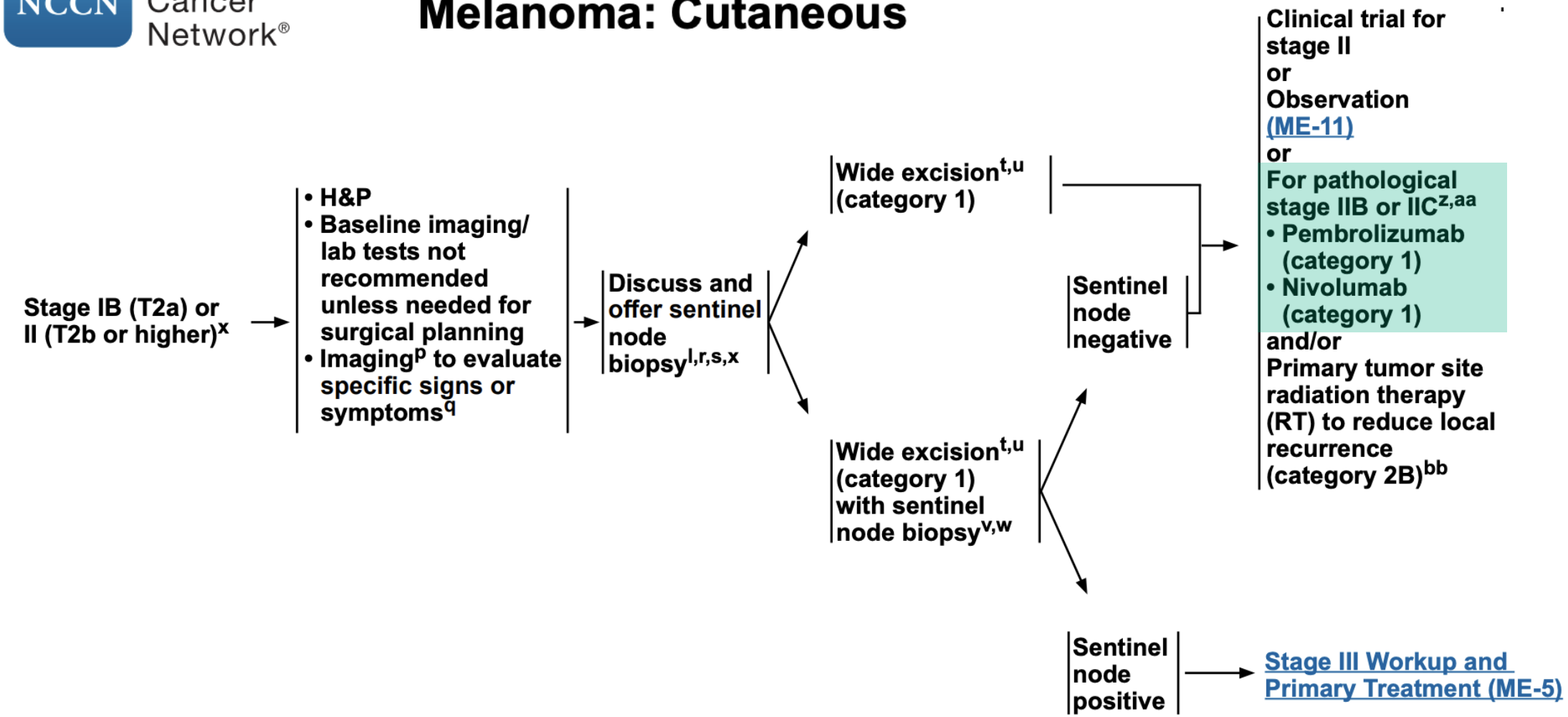
Adyuvancia con **pembrolizumab** en paciente con melanoma **estadio IIB-IIC:**

RAR=9,7%

Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma: final análisis of distant metastasis-free survival in the pase III **KEYNOTE-716**. JJ Luke et al. J Clin Oncol 2024

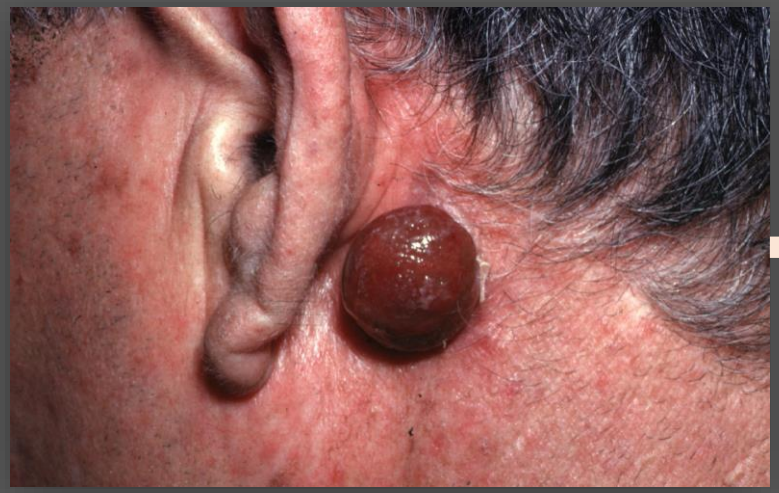
National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Melanoma: Cutaneous

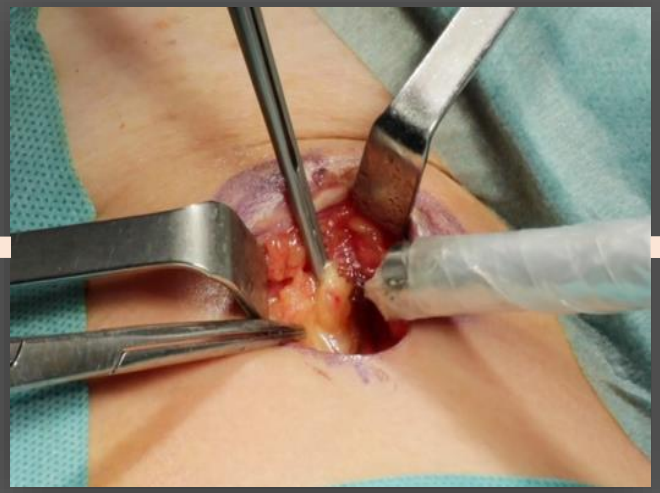


Pembrolizumab y **nivolumab** en monoterapia está indicado para el **tratamiento adyuvante** en adultos y adolescentes a partir de 12 años de edad con **melanoma en estadio IIB, IIC** o III y que hayan sido sometidos a resección completa

Ficha técnica pembrolizumab y nivolumab 2023



Estadio IIB-IIC



Biopsia Selectiva del Ganglio Centinela

IIIC-IIID

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Inmunoterapia adyuvante

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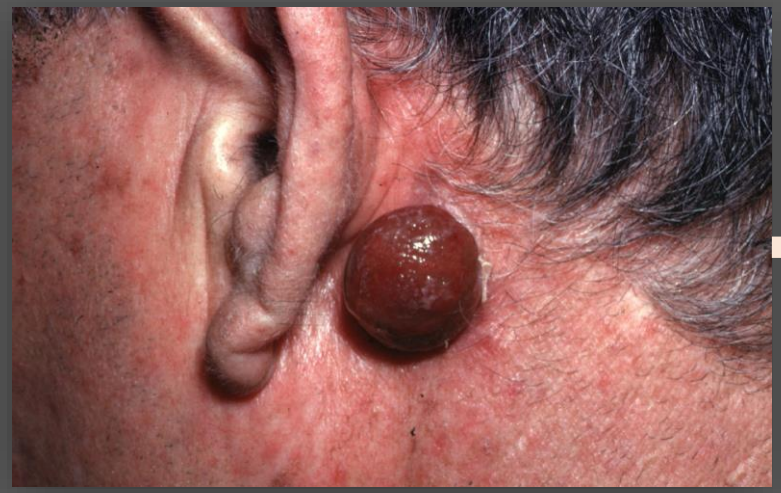
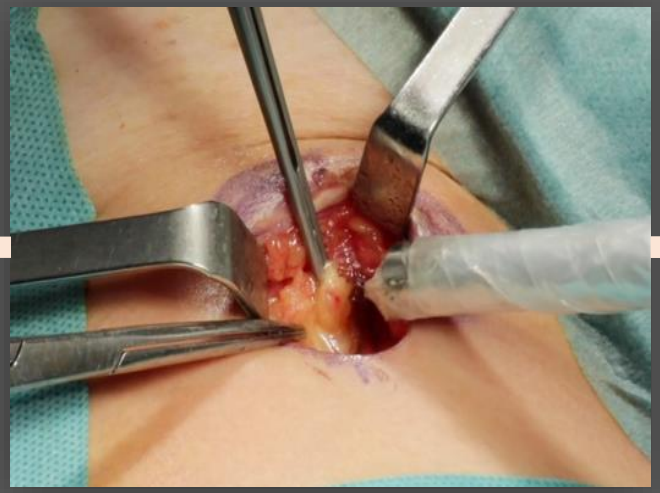
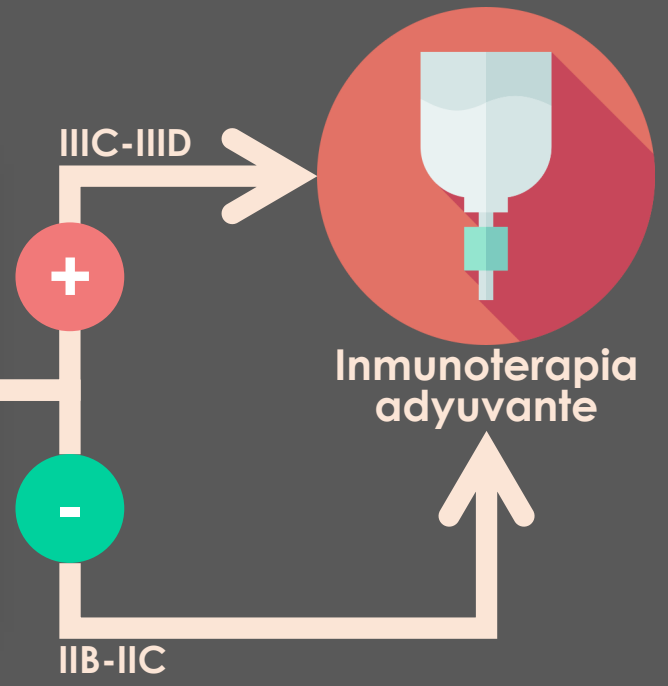
Seguimiento ecográfico

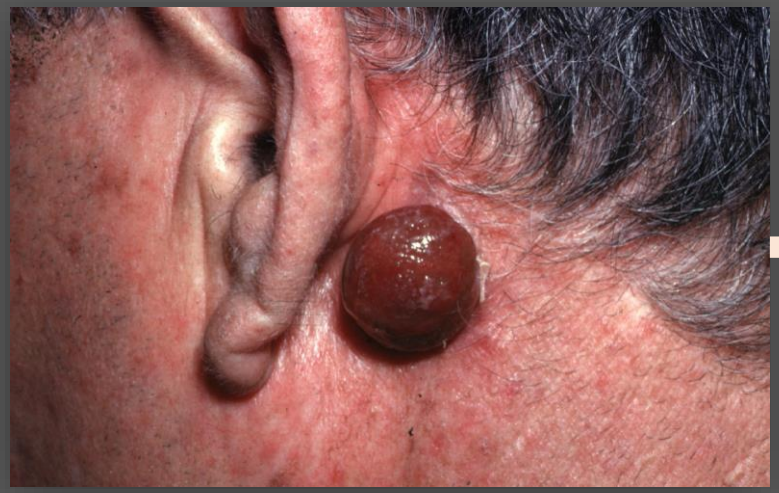


Estadio IIB-IIC

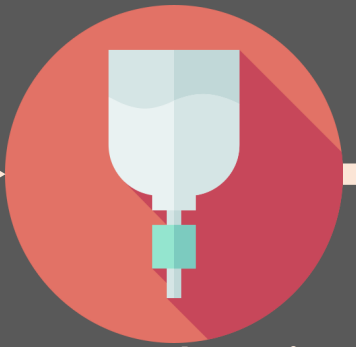


Biopsia Selectiva del Ganglio Centinela





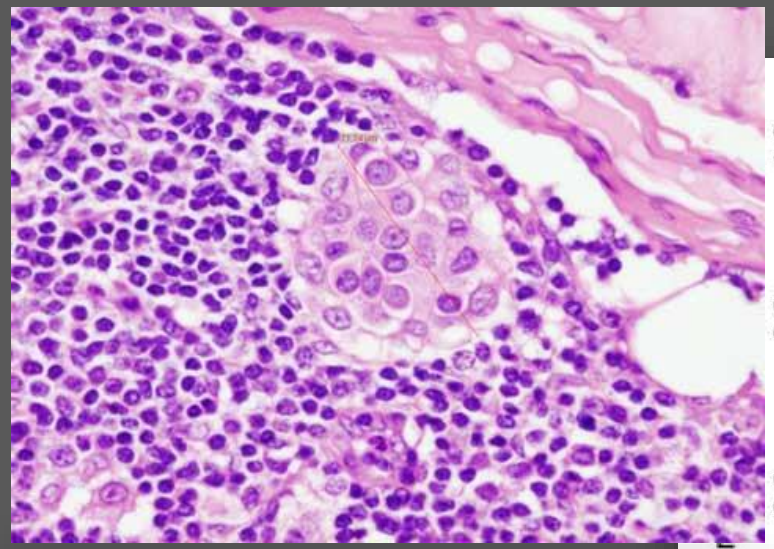
Estadio IIB-IIC

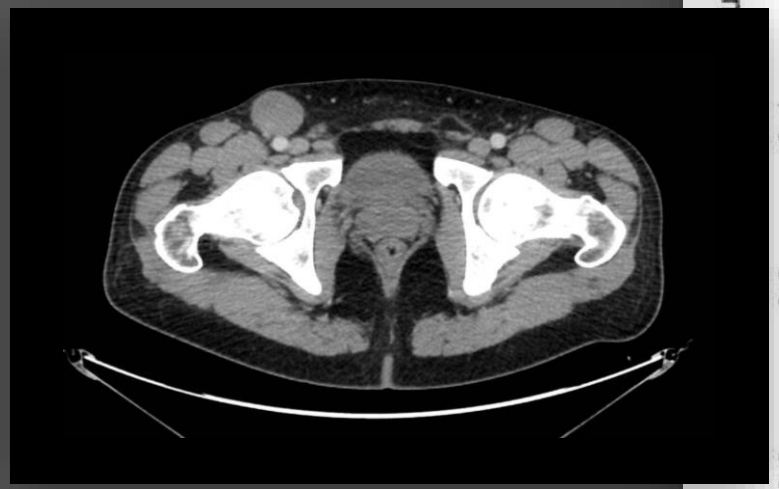


Inmunoterapia adyuvante

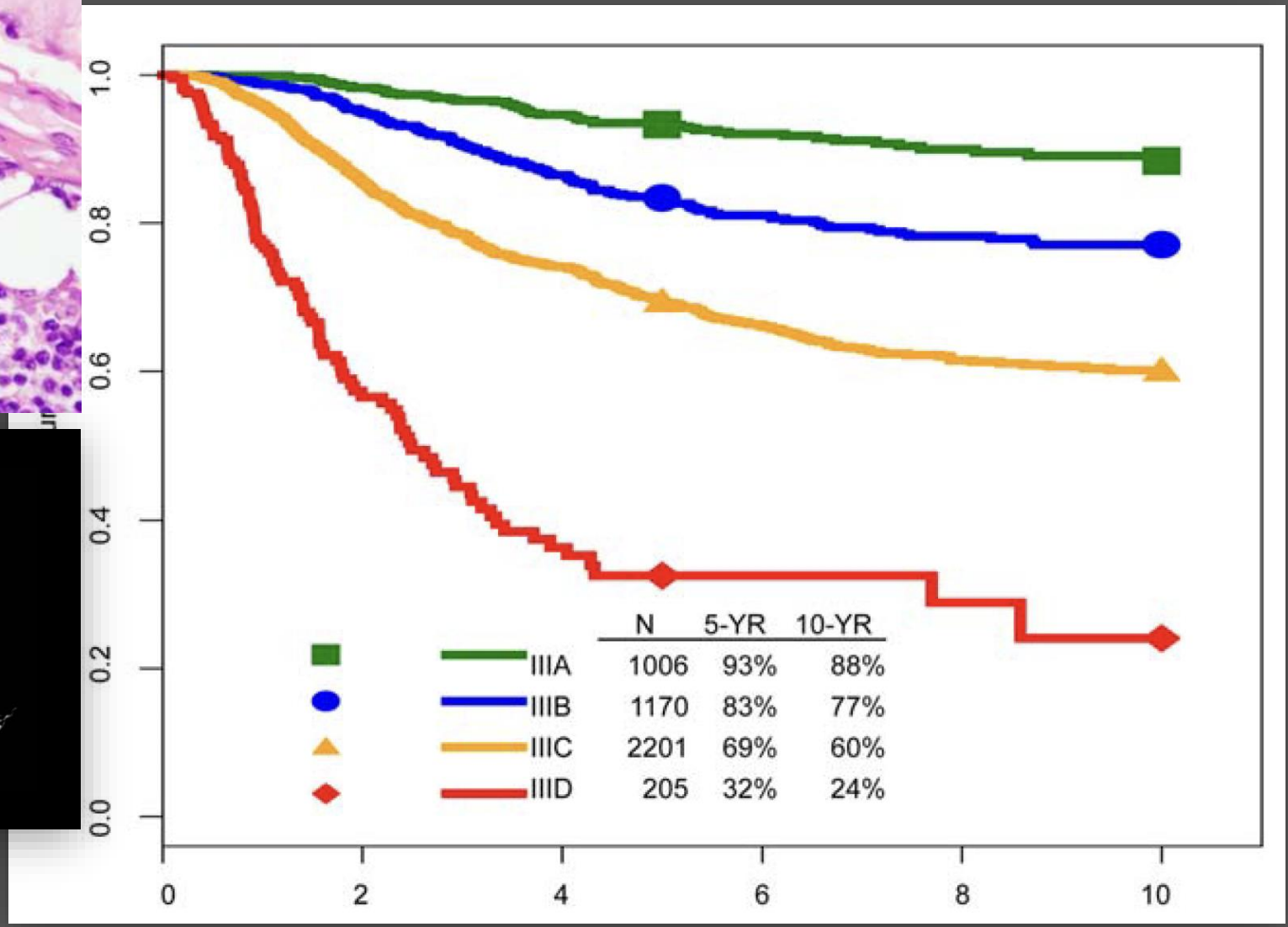
Seguimiento ecográfico

Adyuvancia en el paciente con metástasis ganglionares resecadas estadio IIIA-IIIC





Estadio III



AJCC 2017

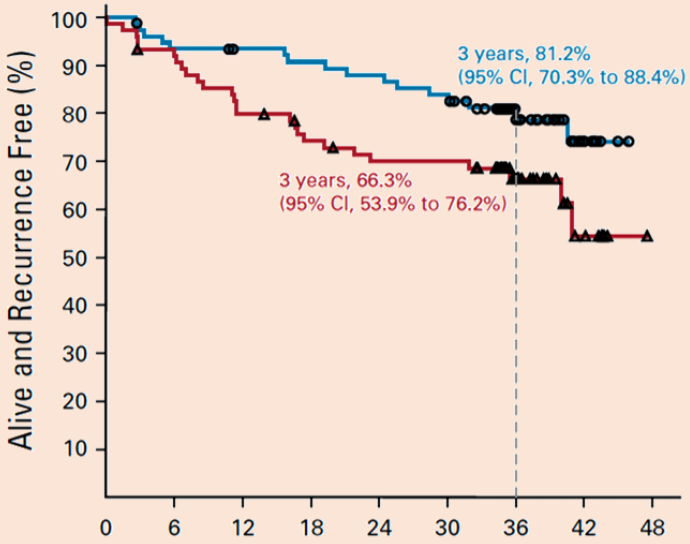
Indicaciones actuales de tratamiento adyuvante Estadio III

Adjuvant therapy in stage III/IV	Evidence-based recommendation
Level of recommendation A	Adjuvant therapy (anti–PD-1 or targeted therapy) shall be offered to all patients in stages IIIA – IIID and fully resected stage IV.
	Adjuvant anti–PD-1 therapy can be offered to patients in stages IIIA – IIID and fully resected stage IV irrespective of the mutational status. Adjuvant BRAF/MEK inhibitor therapy can be offered to patients with BRAFV600 E/K mutation in stages IIIA – IIID.
	For stage IIIA with nodal metastasis of less than 1 mm in diameter, the risk/benefit ratio should be carefully discussed with the patient.
Level of evidence: 1b	De novo literature research [69–71] Consensus rate: 100%

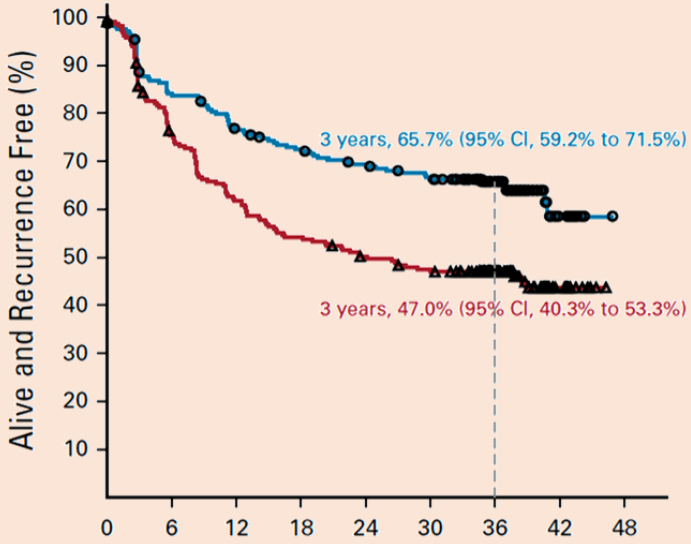
EADO Melanoma Guidelines
Eur J Cancer 2024 (in press)

Adyuvancia estadio III

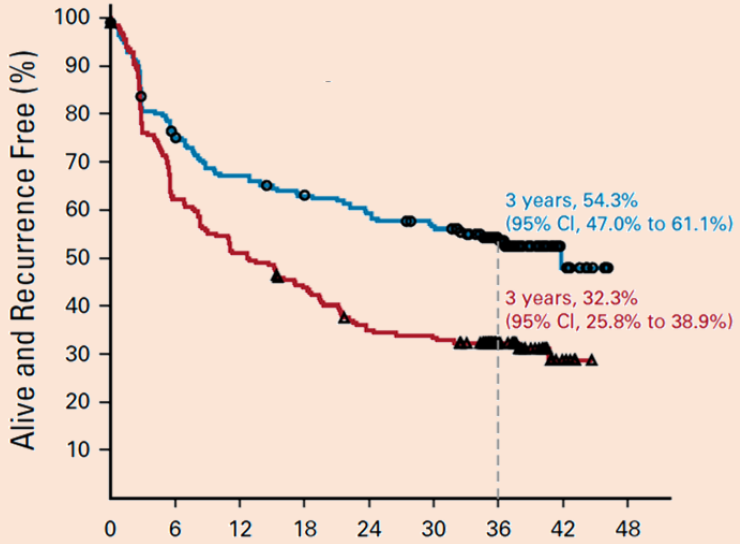
Pembrolizumab vs placebo



Estadio IIIA



Estadio IIIB

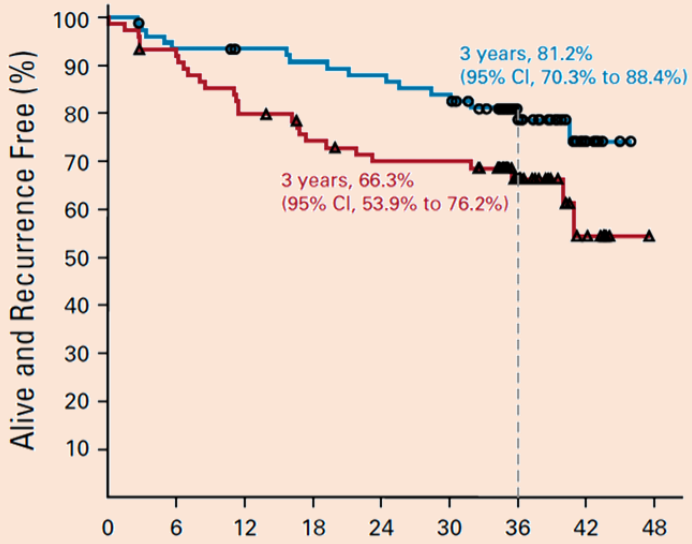


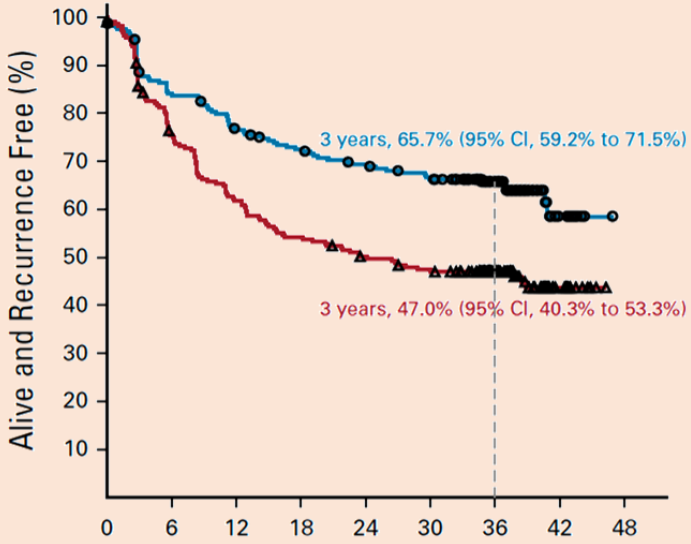
Estadio IIIC

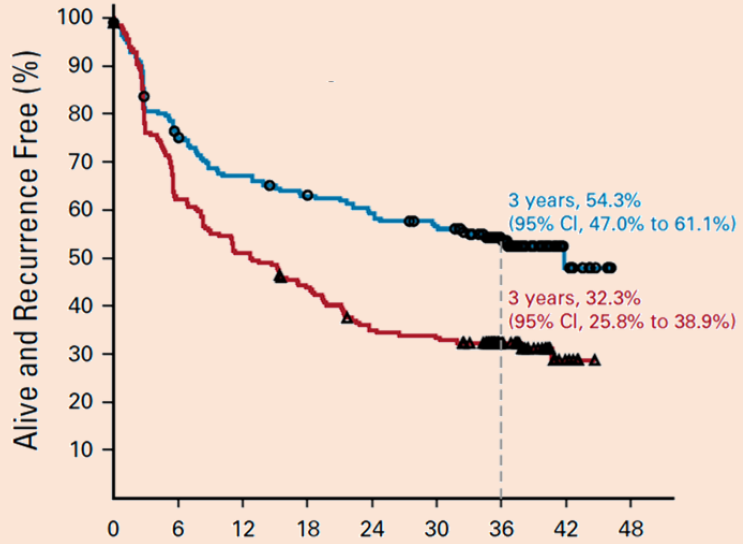
Eggermont et al. Longer Follow-Up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results. From the EORTC 1325-MG/KEYNOTE-054 Trial. J Clin Oncol 2020

Adyuvancia estadio III

Pembrolizumab vs placebo







Estadio IIIA
RAR=14,9%
NNT=6,7

Estadio IIIB
RAR=18,7%
NNT=5,3

Estadio IIIC
RAR=22,0%
NNT=4,5

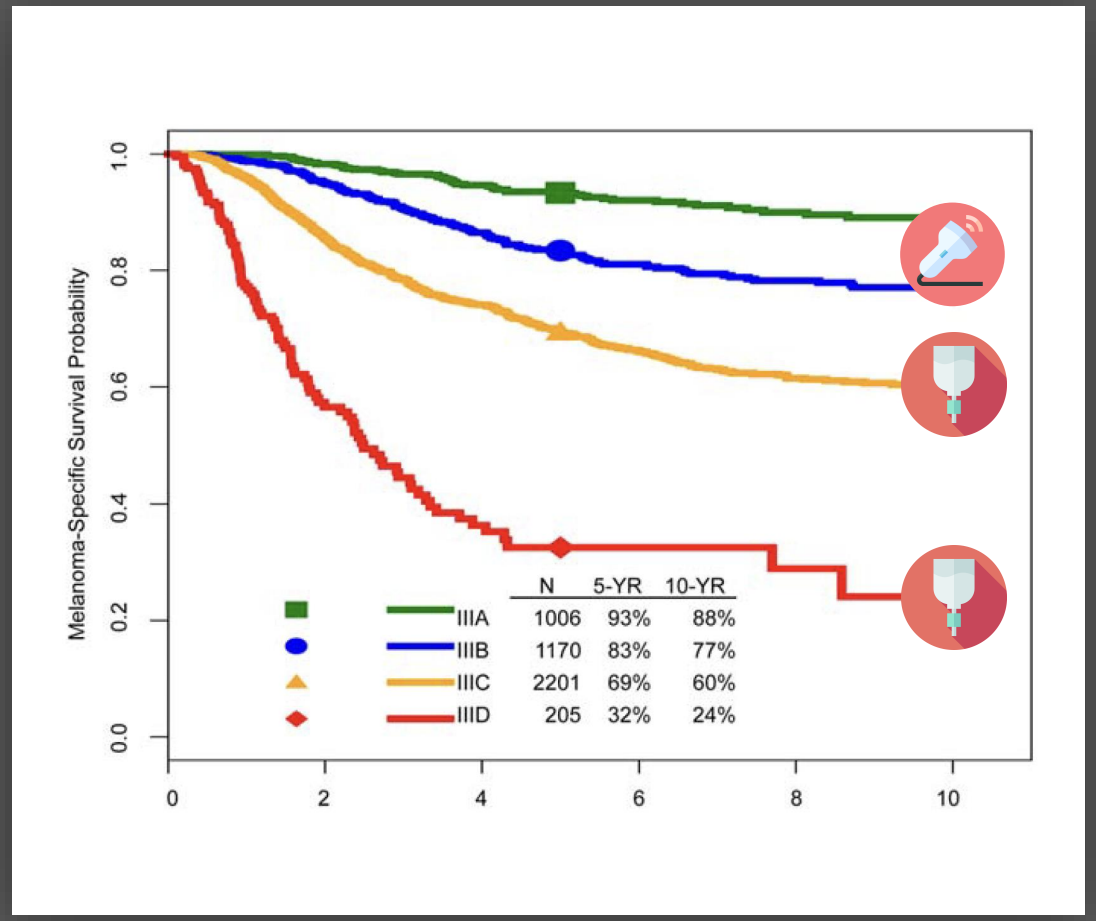
Eggermont et al. Longer Follow-Up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results. From the EORTC 1325-MG/KEYNOTE-054 Trial. J Clin Oncol 2020

Informe de Posicionamiento Terapéutico

Pembrolizumab, nivolumab

La Dirección General de Cartera Común de Servicios del SNS y Farmacia ha emitido resolución de **financiación para** la indicación de **nivolumab y pembrolizumab** en monoterapia para el tratamiento **adyuvante** en adultos con melanoma con **estadios IIIC y IIID** o enfermedad metastásica que hayan sido sometidos a resección completa.

www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/2022/IPT_15-2022-Keytruda.pdf



Dermatología MQyV
Unidad de Melanoma

Pacientes:

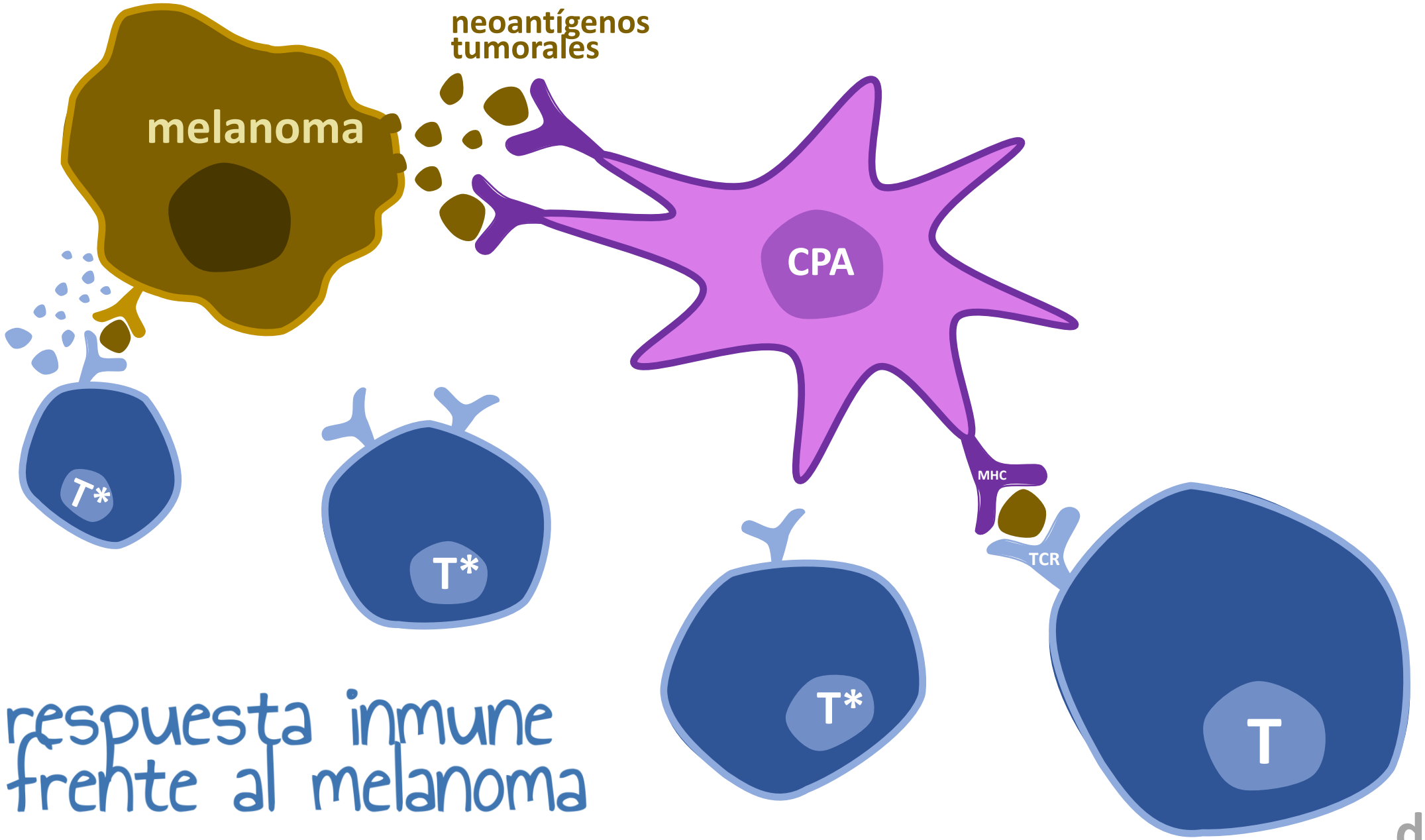
- Melanoma estadio **IIIC-IIID**
- Libres de enfermedad
- ECOG-PS 0-1
- Sin enfermedad autoinmune
- 52 semanas de seguimiento

Pembrolizumab iv
200mg cada 3 semanas o
400 mg cada 6 semanas

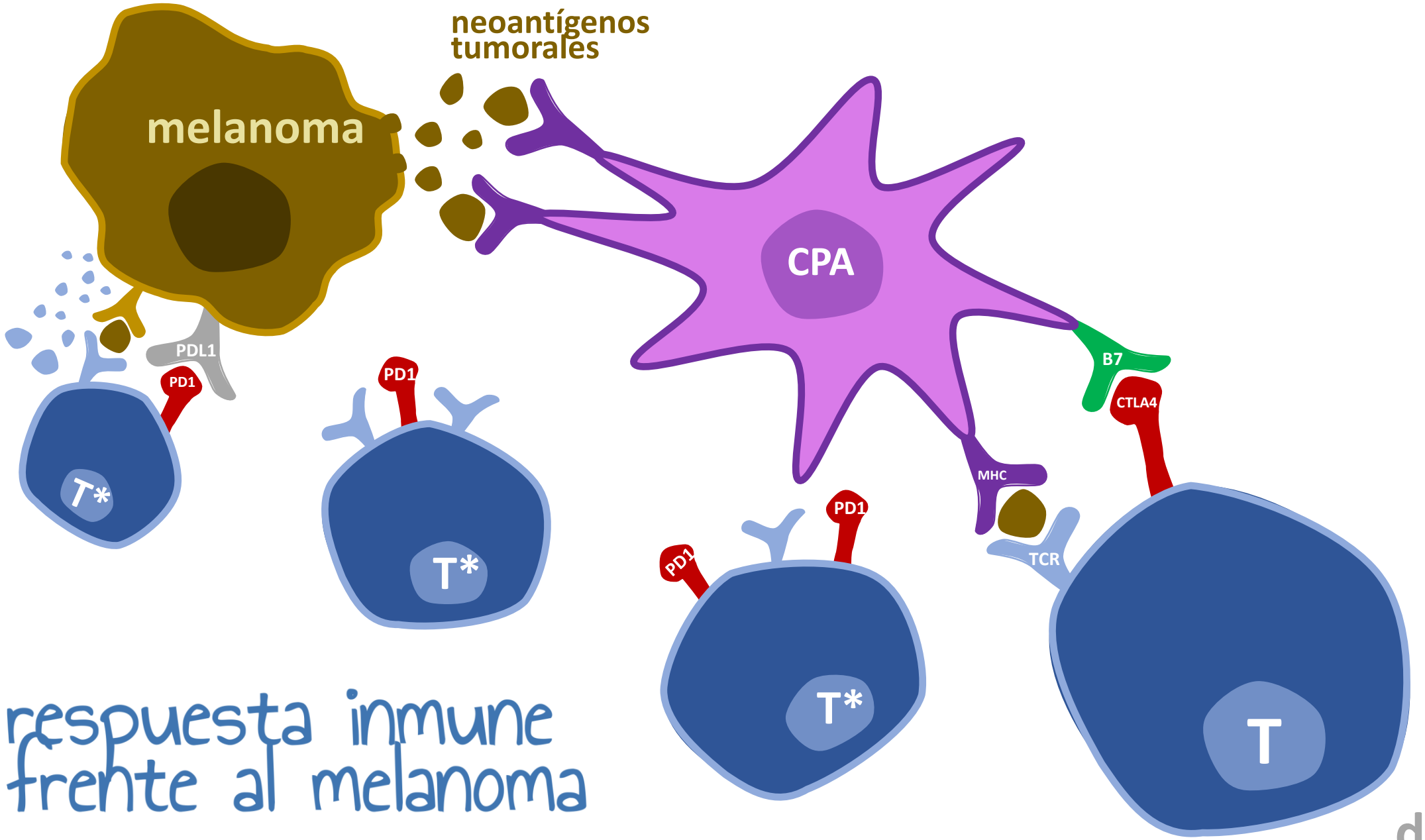
Nivolumab iv
240 mg cada 2 semanas o
480 mg cada 4 semanas

¿Cómo podemos mejorar los resultados de la inmunoterapia adyuvante?

The New Pupil. Thomas Brooks 1854

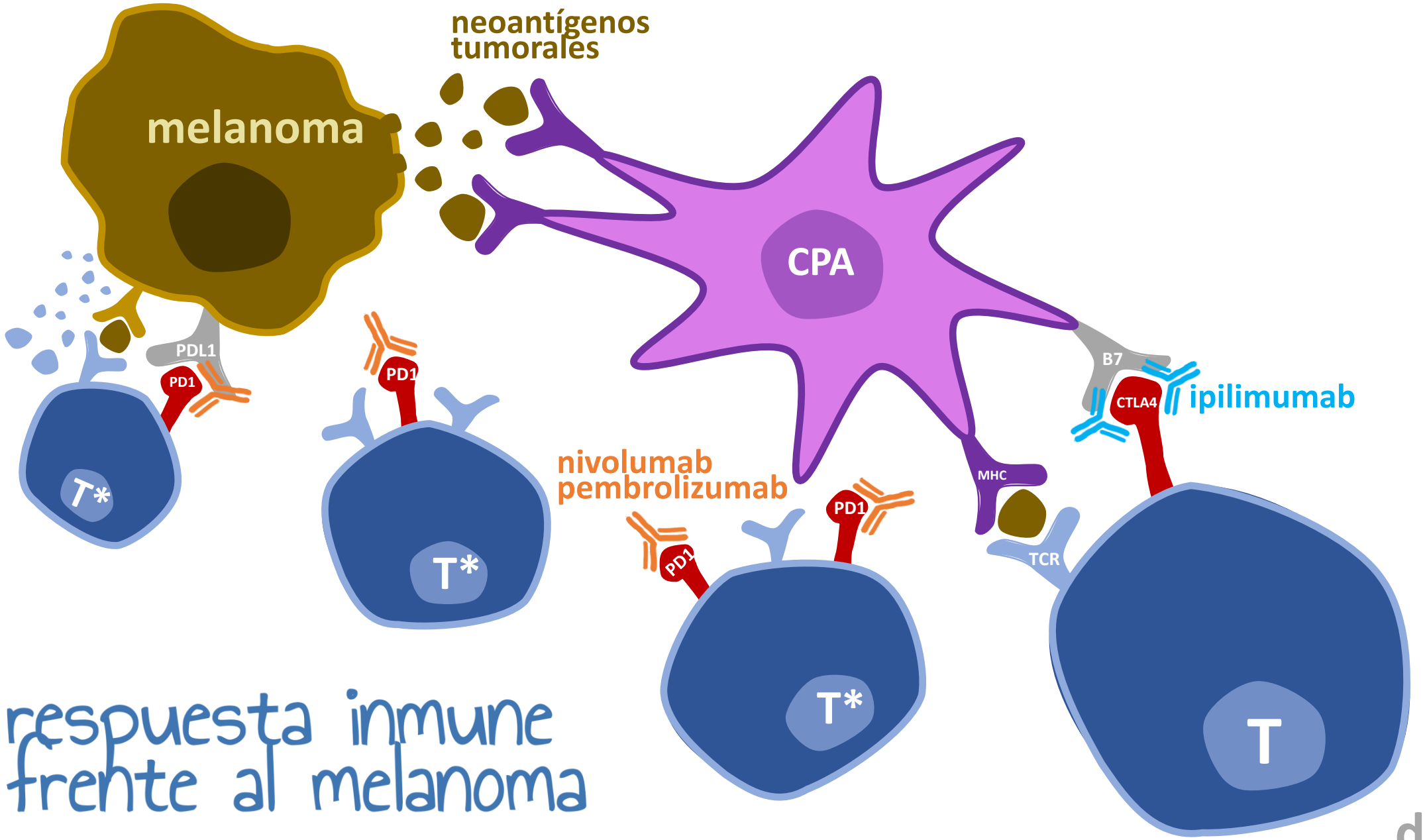


respuesta inmune frente al melanoma



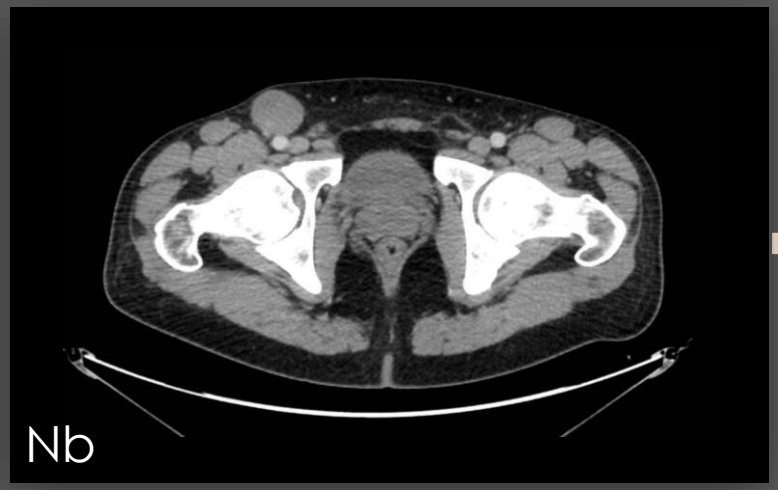
respuesta inmune frente al melanoma

dmr24

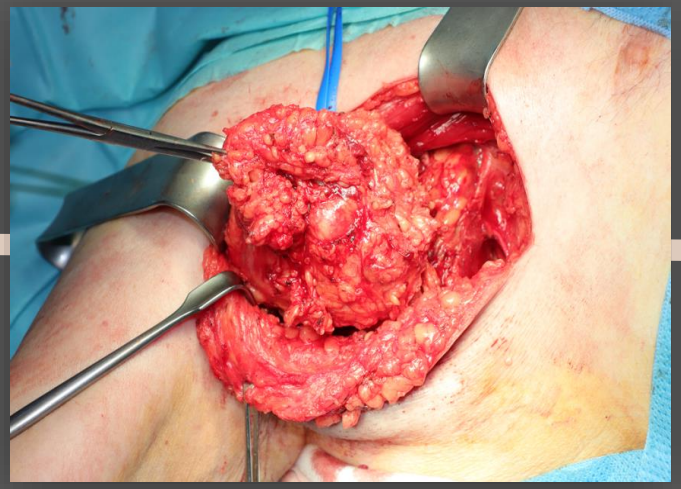


respuesta inmune frente al melanoma

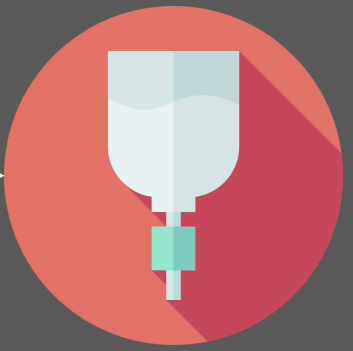
dmr24



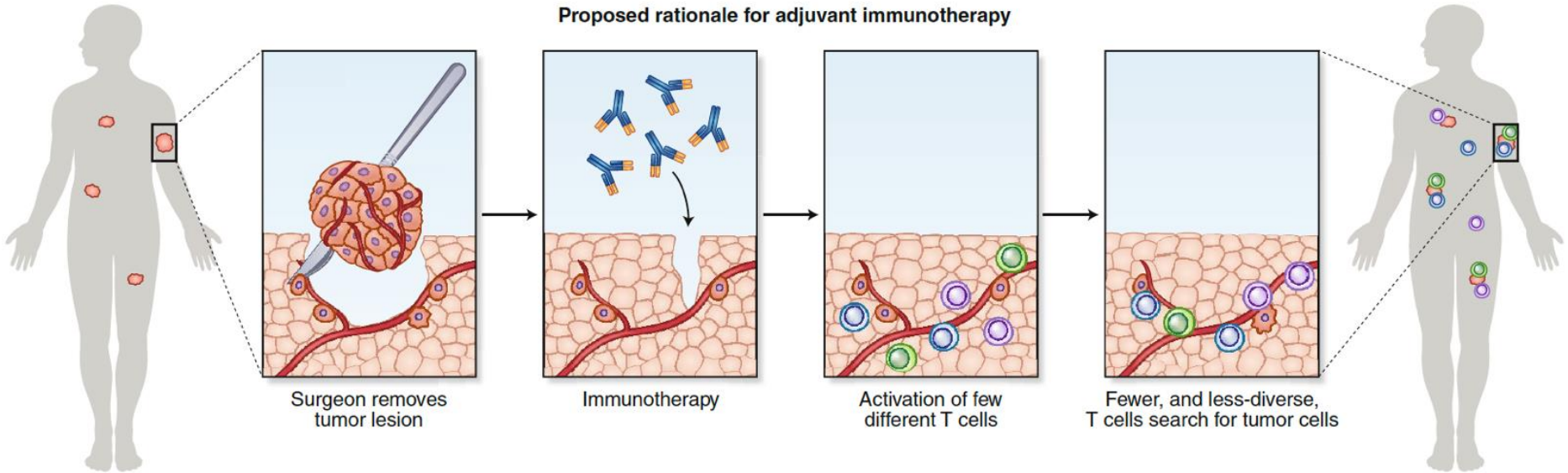
Estadio IIIB-IIIC



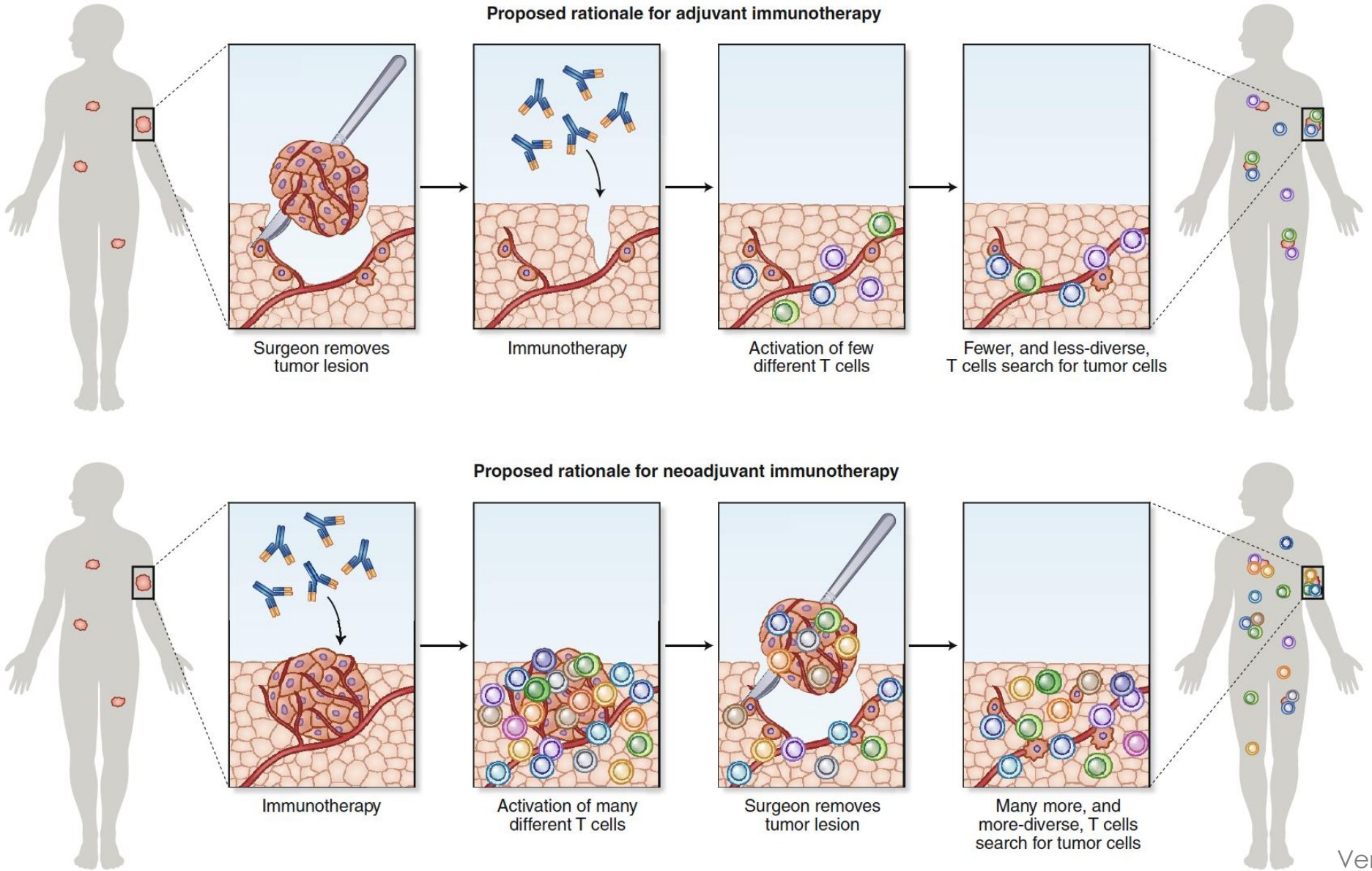
Disección Ganglionar Completa



Inmunoterapia adyuvante



Versluis et al.
Nature Medicine 2020



Versluis et al.
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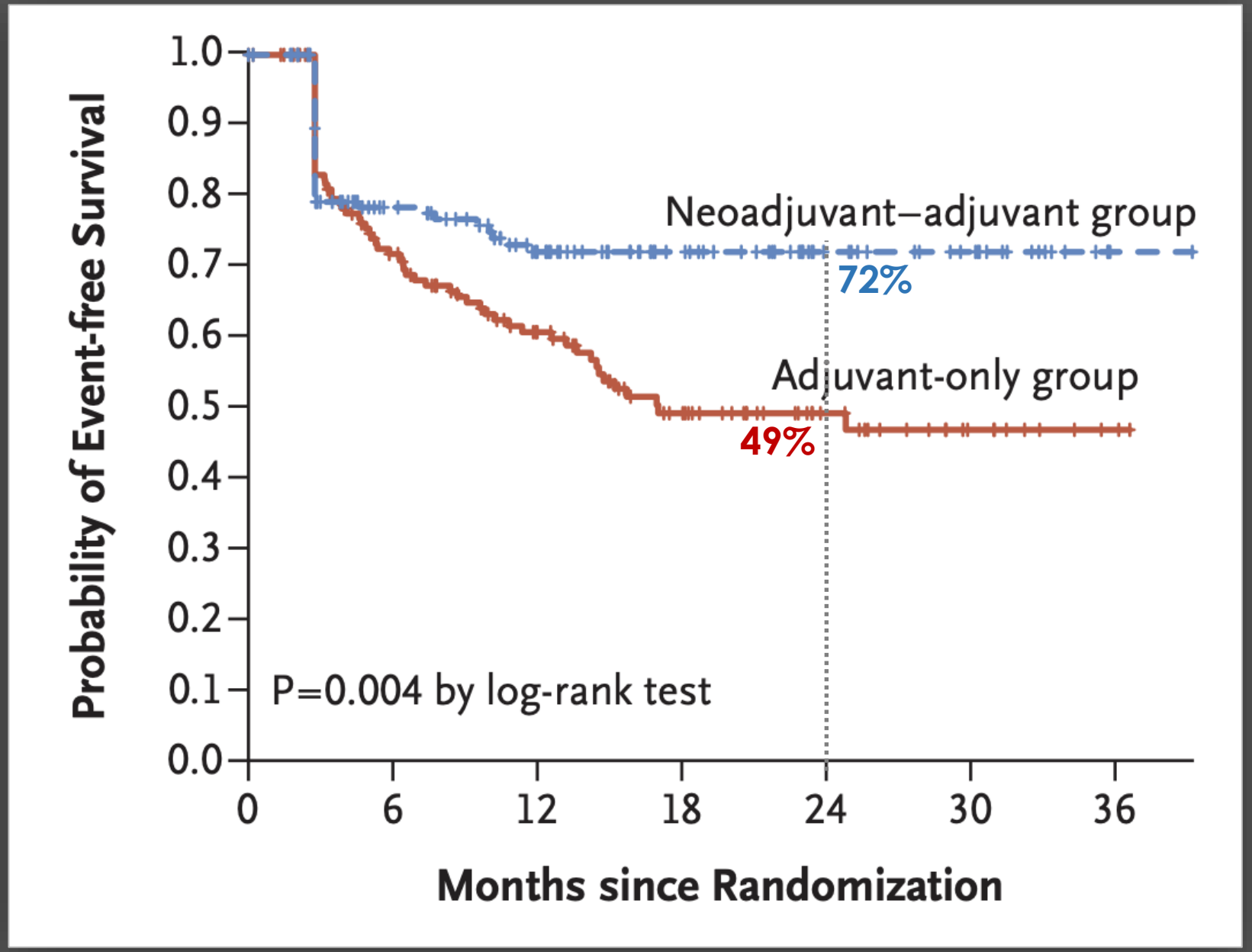
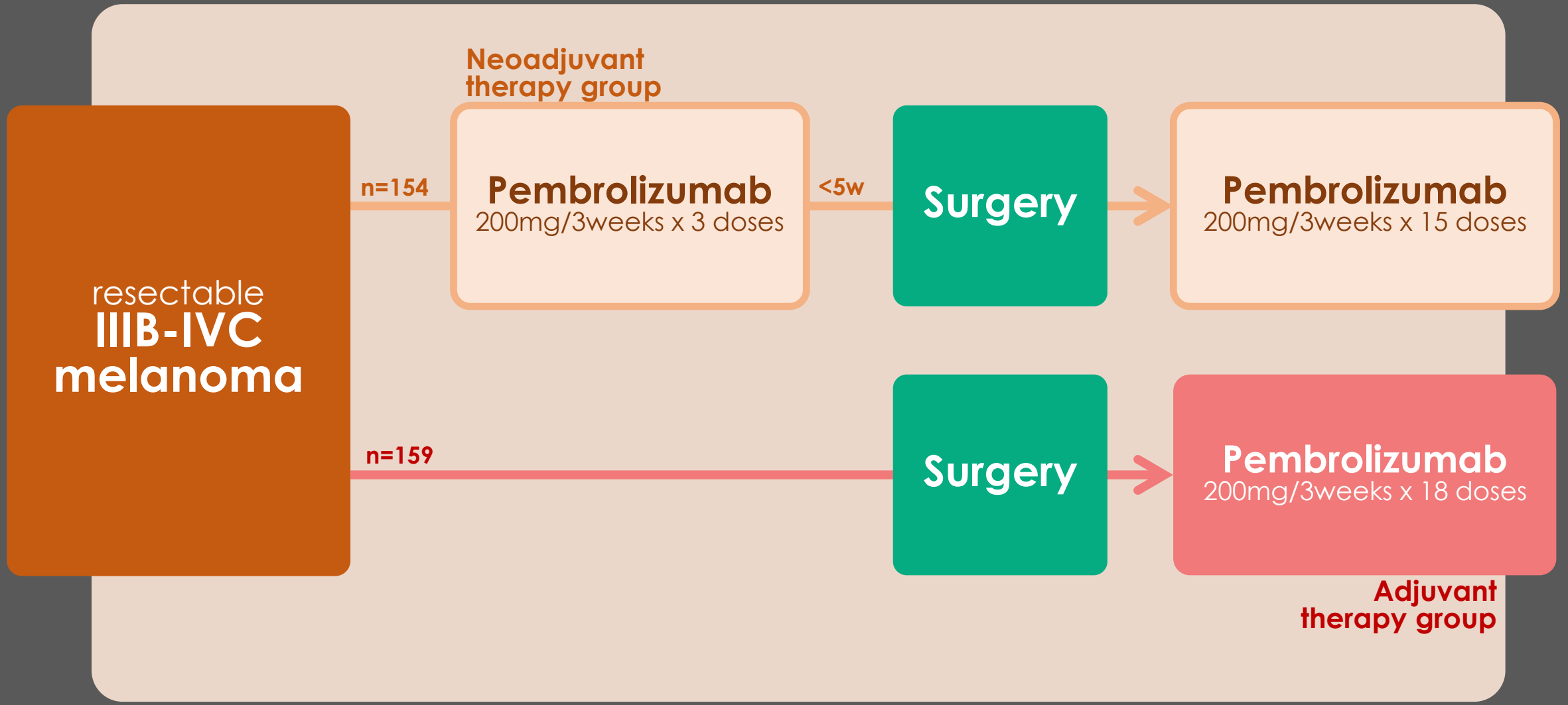


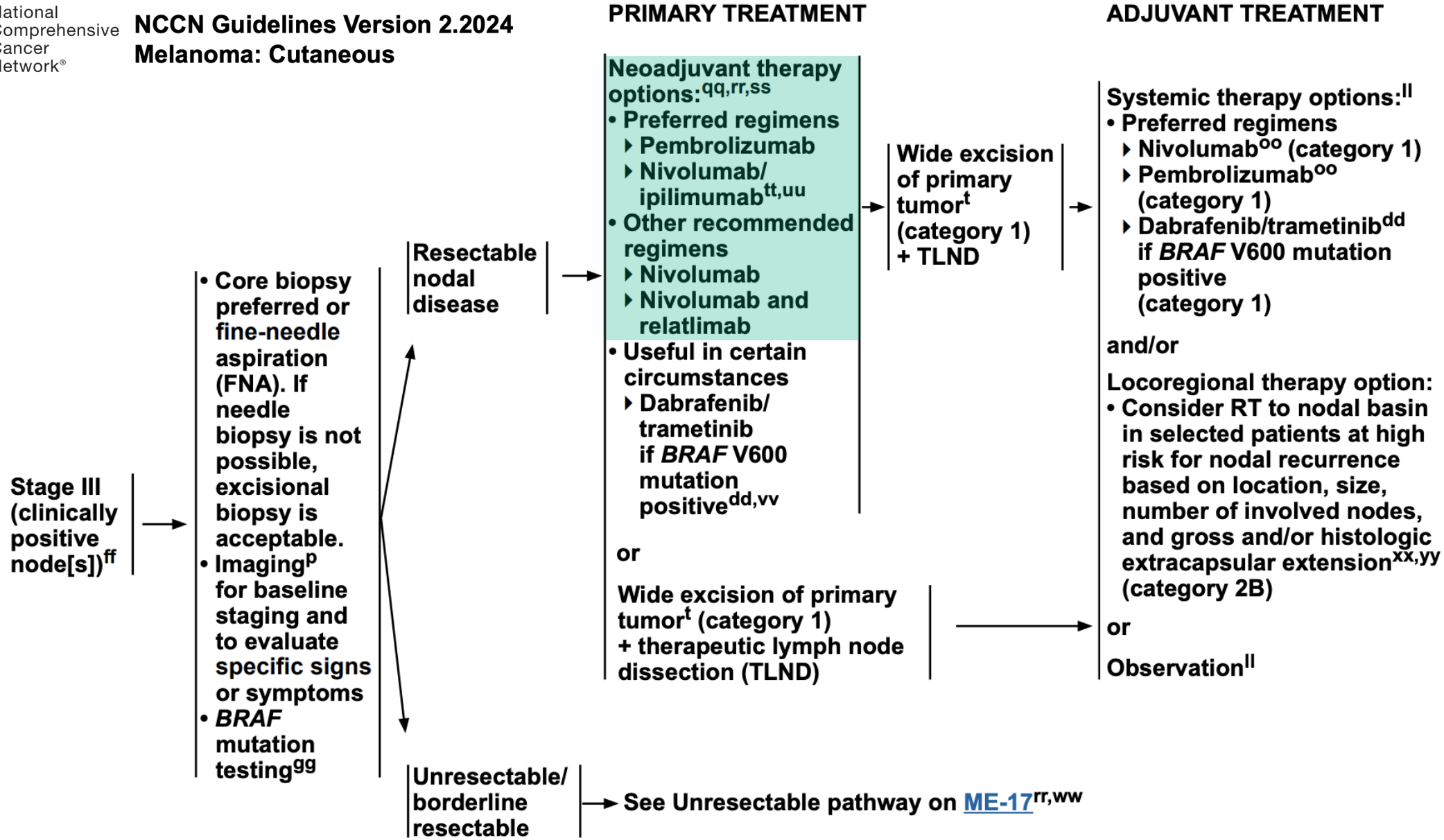
Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma
Patel. NEJM 2023



Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma.
Patel. NEJM March 2023

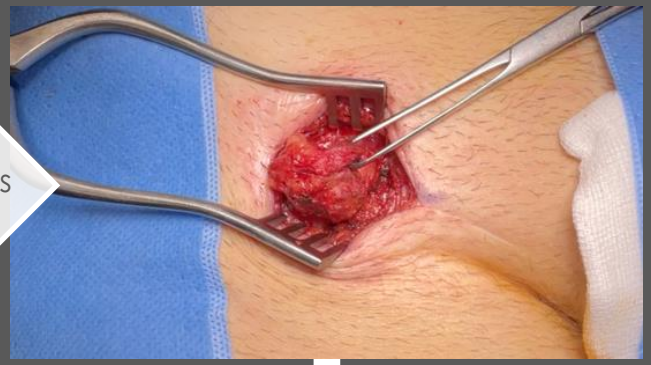
National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Melanoma: Cutaneous



ipilimumab
+
nivolumab

6 weeks



Index node resection

pMR
≤10% viable tumor
61%

pPR
>10% to ≤50% viable tumor
10%

pNR
>50% viable tumor
21%

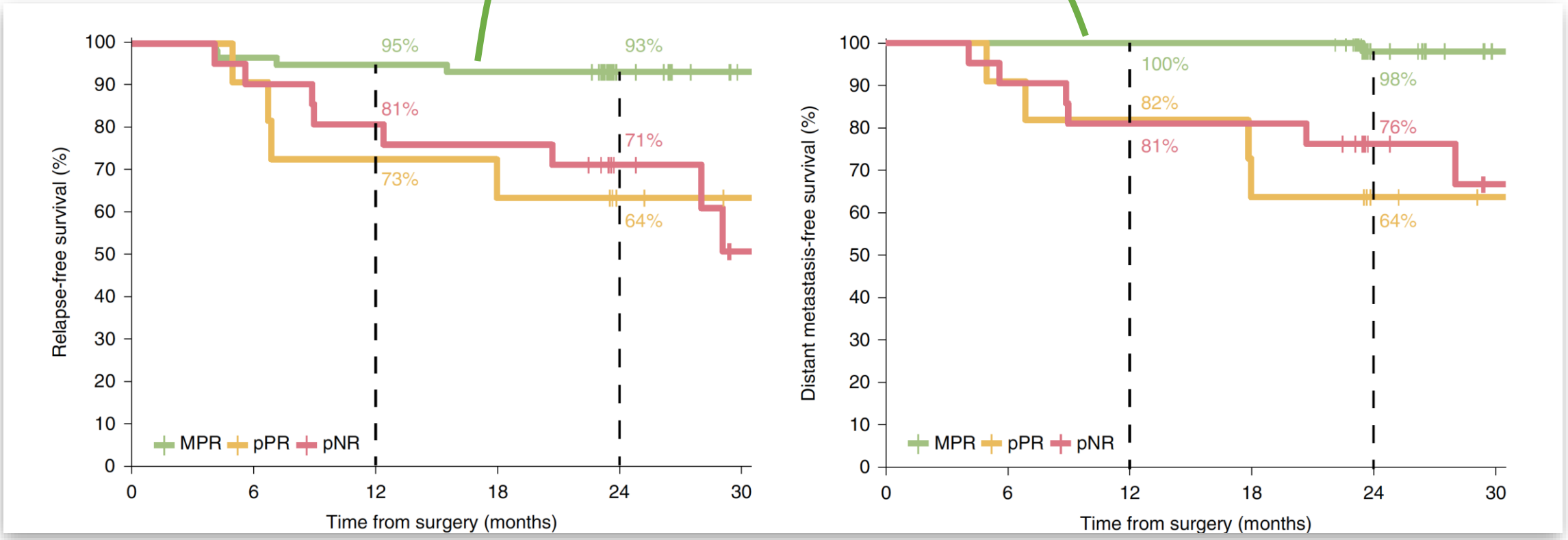
complete lymph node dissection

adjuvant immunotherapy

US-based follow-up

Reijers et al. Personalized response- directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: the PRADO trial. Nature Medicine 2022

In patients achieving MPR, CLND might be safely replaced by ILND



Reijers et al. Personalized response- directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: the PRADO trial. Nature Medicine 2022

La **inmunoterapia neoadyuvante** debe incorporarse como **estándar de tratamiento** del paciente con **melamoma metastásico**

From the:
EADO, EORTC, INMC, MWS
Garbe et al. Nature Med may 2023

https://doi.org/10.1038/s41591-023-02336-1

Neoadjuvant immunotherapy for melanoma is now ready for clinical practice

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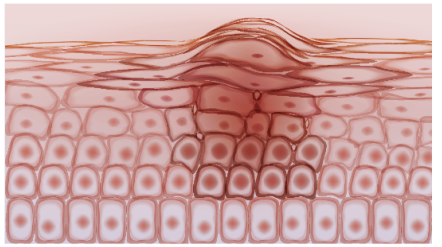
Individuals with cutaneous melanoma who are treated with neoadjuvant immunotherapy show a substantial improvement; this should be incorporated into standard care.



CREDIT: BENJAMIN TOTH / DIGITALVISION VECTORS / GETTY

Neoadjuvant therapy — the use of chemotherapy and/or radiotherapy before a primary course of treatment — was originally developed to improve the operability of tumors, for example in breast cancer, lung cancer and sarcomas. With the advent of systemic immune-checkpoint inhibitors, however, the role of neoadjuvant therapy has undergone a seismic shift. The ability of checkpoint inhibitors to elicit an immune response to cancer cells has implications for long-term tumor control and survival that are optimized when these drugs are administered prior to resection, and go far beyond improved operability[1–3].

In a landmark paper, tumor-resident T cell clones were shown to increase in diversity and amplitude in peripheral blood to a much greater extent following neoadjuvant treatment with ipilimumab plus nivolumab, as compared with the same drug regimen given as adjuvant therapy (post-surgery)[4]. Similarly, in the randomized SWOG S1801 trial, patients with resectable stage III or IV melanoma received either the approved standard Keynote-054 adjuvant regimen of 18 doses of pembrolizumab after lymph-node dissection[5], or the first 3 doses before surgery and the remaining 15 doses after surgery; the latter resulted in a 42% reduction in the risk of relapse[6].

This is a remarkable outcome. Compared with placebo, the currently approved adjuvant pembrolizumab regimen also elicits a 42% reduction in the risk of relapse compared with no therapy[7]. Therefore, taken together, the combined neoadjuvant plus adjuvant SWOG S1801 regimen offers an approximate 65% reduction in the relative risk of relapse compared with surgery alone (the combined hazard ratio (HR) from both trials was 0.35).

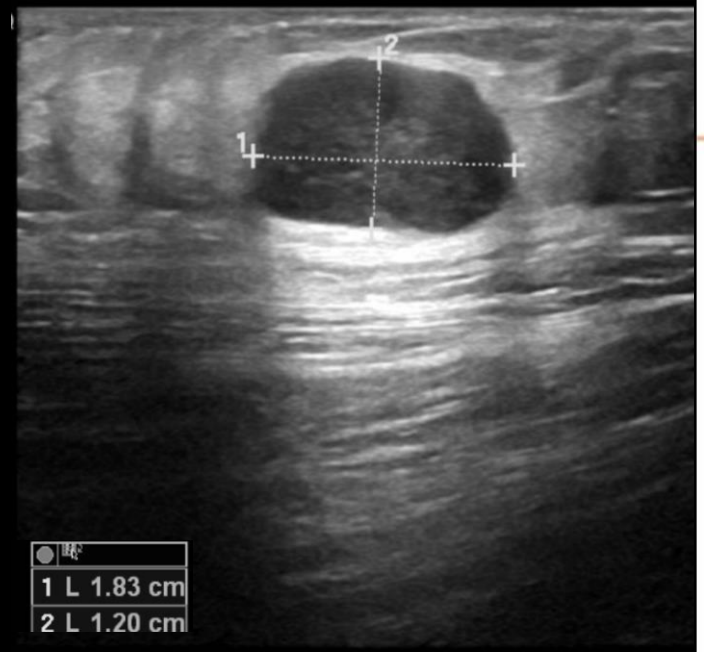
Results from several early studies of neoadjuvant therapy for resectable metastatic melanoma have also shown greater event-free and recurrence-free landmark survival rates compared with adjuvant therapy[8–10]. The past decade has seen numerous drug developments and approvals in advanced and resectable melanoma, emerging largely from trials sponsored by the pharmaceutical industry. The neoadjuvant case is different. To date, the results have mostly been generated by investigator-initiated academic trials, and it is unlikely that pharmaceutical companies will conduct the large studies that are traditionally required to obtain regulatory approval for neoadjuvant therapy. The result is a lack of appropriate drug-approval pathways to a highly effective treatment approach, which leads to an important question: can neoadjuvant therapy be used in practice without the approval of healthcare regulators?

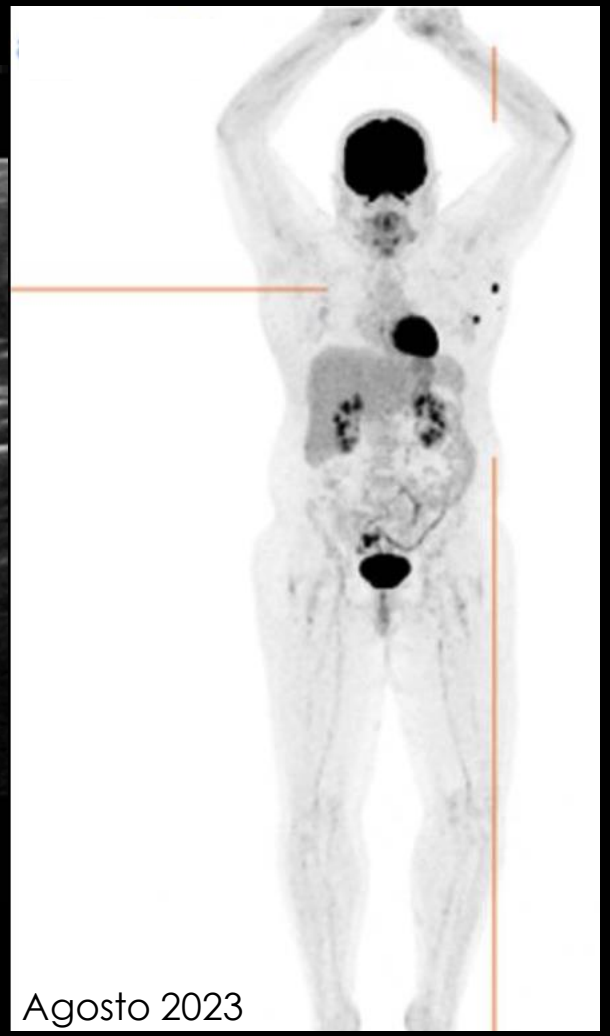
Survival benefits

Results from two prospective phase 2 randomized trials of neoadjuvant therapy in melanoma have been reported so far, focusing on individuals with macroscopic lymph-node metastases or in-transit metastases[6,11,12]. The aim of these trials was to determine whether neoadjuvant therapy improves disease-free survival and/or overall survival; however, only one compared neoadjuvant therapy with adjuvant therapy — the aforementioned SWOG S1801 trial (ClinicalTrials.gov identifier NCT03698019)[6]. In addition, a phase 3 trial of two cycles of neoadjuvant nivolumab (3 mg kg^{-1}) combined with ipilimumab (1 mg kg^{-1}) versus standard adjuvant nivolumab in biopsy-proven resectable clinical stage III melanoma is underway (the NADINA trial; NCT04949113).

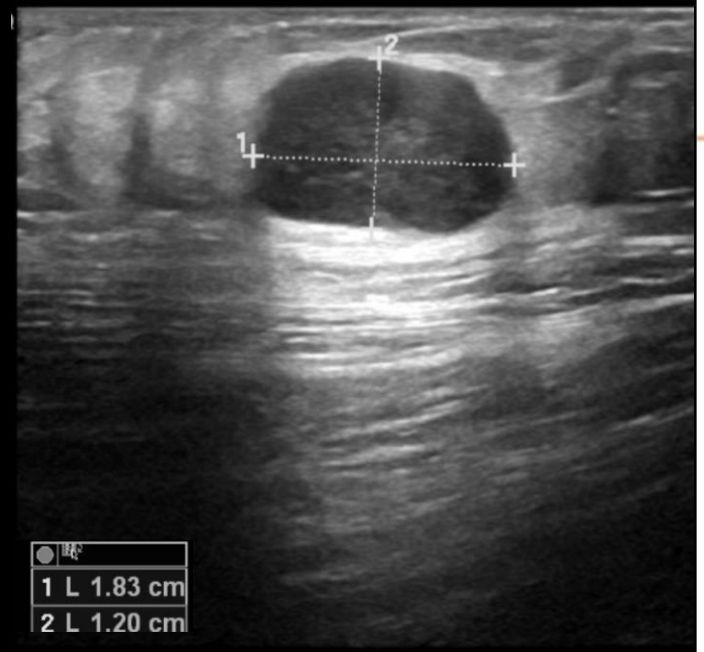
In the SWOG S1801 trial, 18 cycles of 200 mg pembrolizumab (a flat dose) were administered every three weeks to 313 patients with resectable stage IIIB–IV melanoma. In one group, three cycles of pembrolizumab were administered as neoadjuvant therapy, followed by an additional 15 cycles post-operatively. In the other group, surgical therapy was carried out upfront, followed by all 18 cycles of pembrolizumab post-operatively. With a median follow-up of 14 months, there was a remarkable difference in event-free survival; the two-year estimated event-free survival was 72% in the neoadjuvant group and 49% in the adjuvant group (HR = 0.58, $P = 0.004$). With only 36 deaths reported, the overall survival benefit is not yet clear (HR = 0.63, $P = 0.18$)[6].

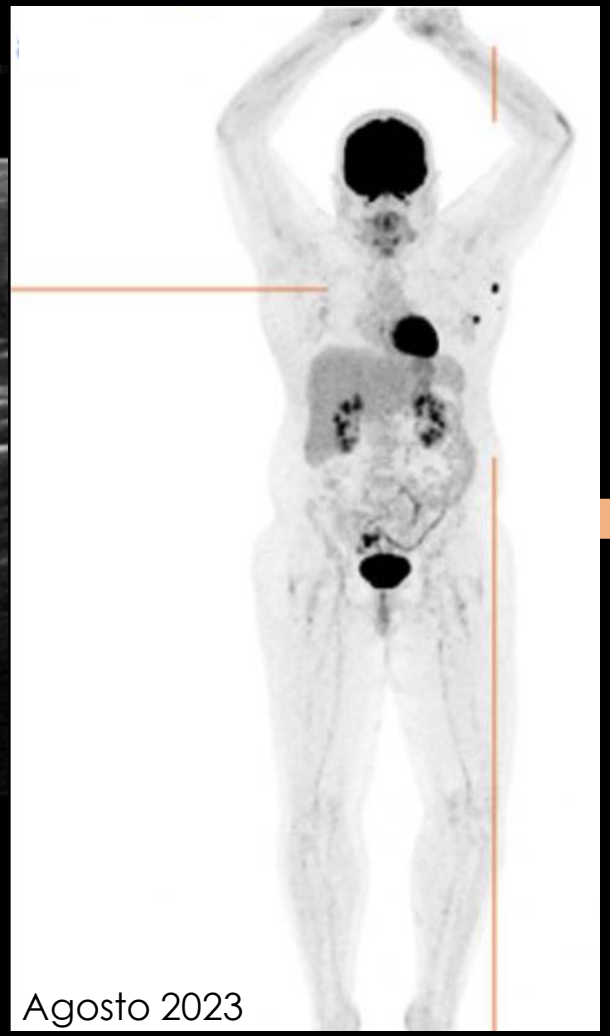
Mujer, 49 años
Melanoma IIIB
T2aN2bM0



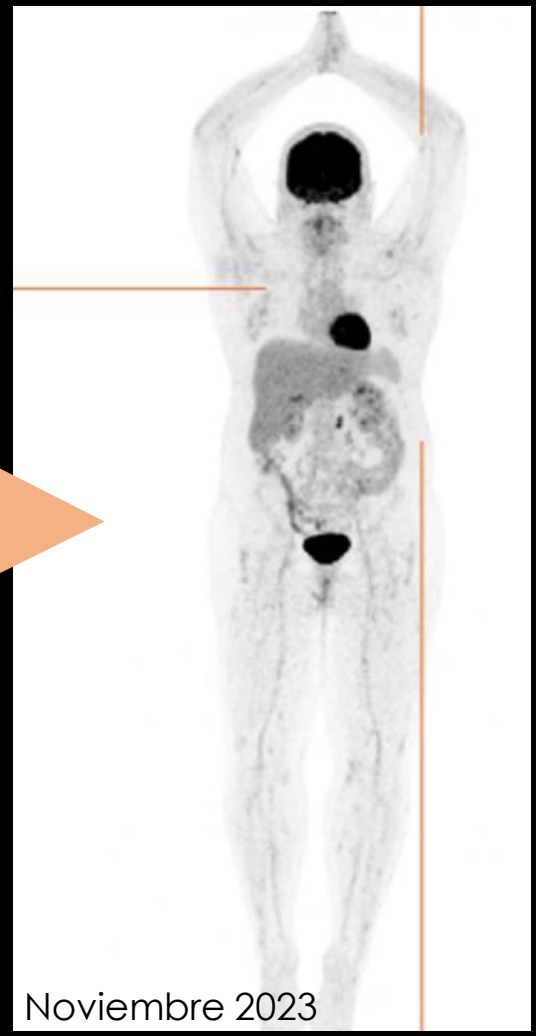


Mujer, 49 años
Melanoma IIIB
T2aN2bM0




Agosto 2023

Pembrolizumab
200mg/3 semanas x 3 dosis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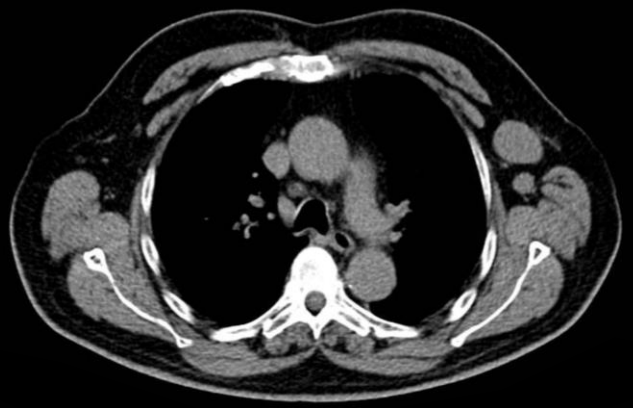
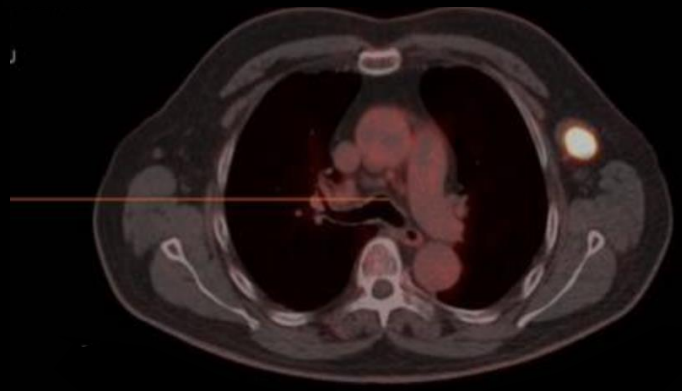
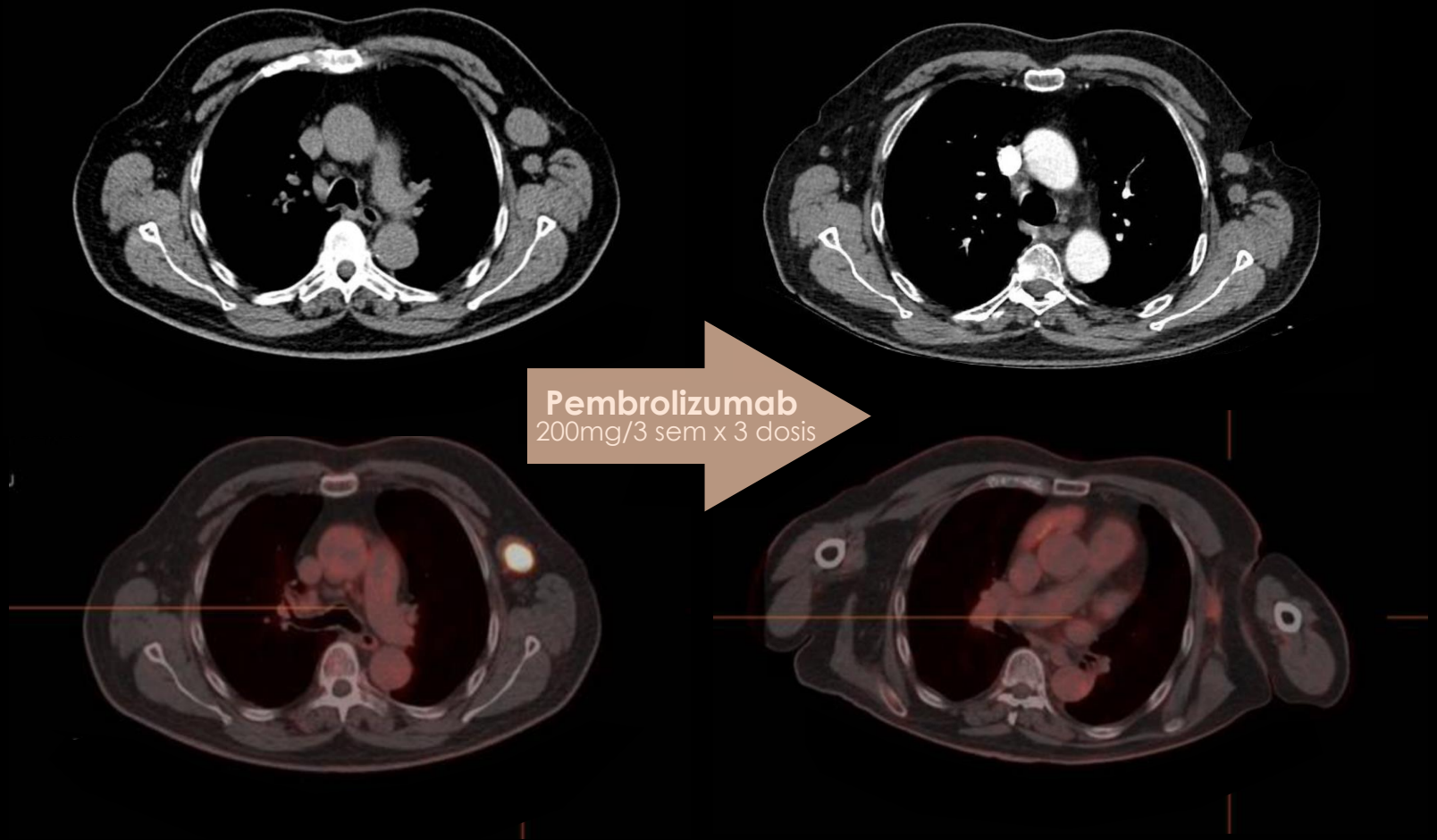
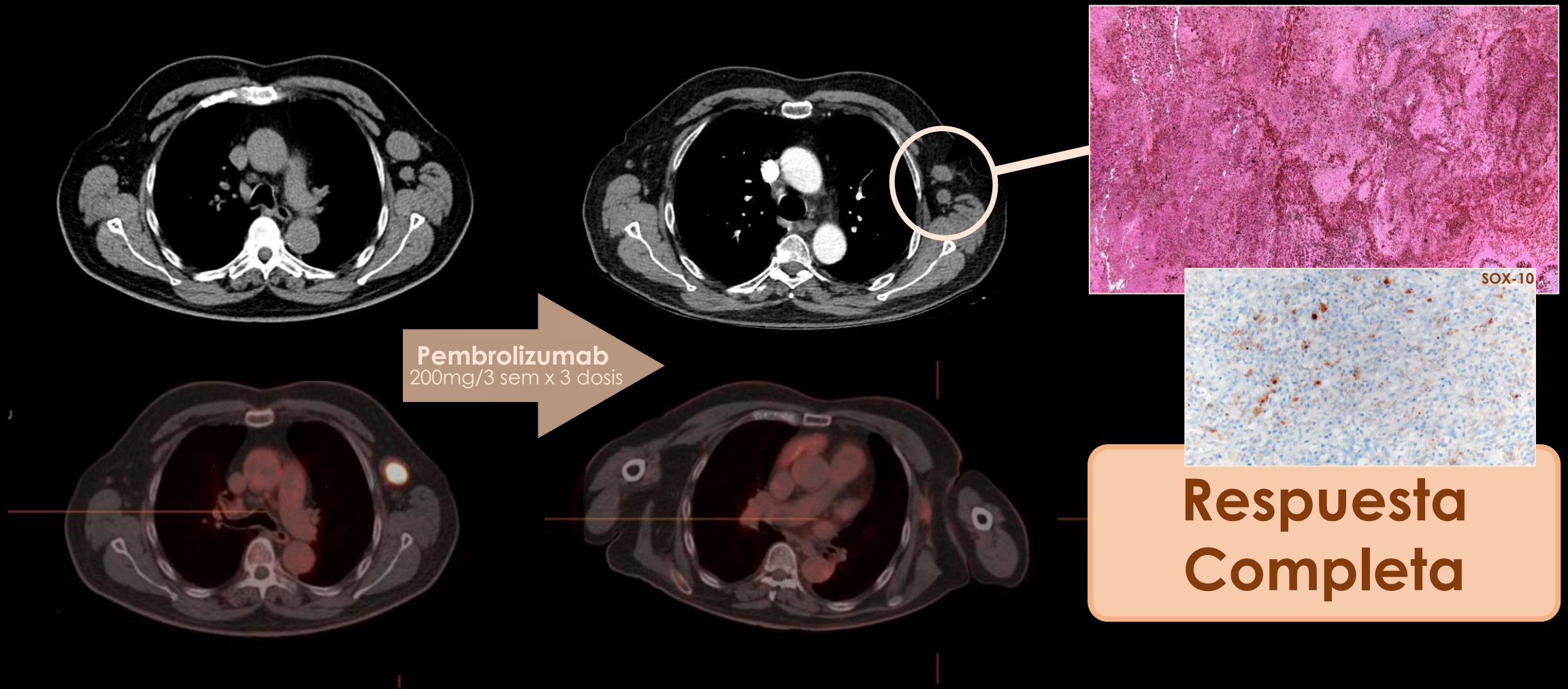




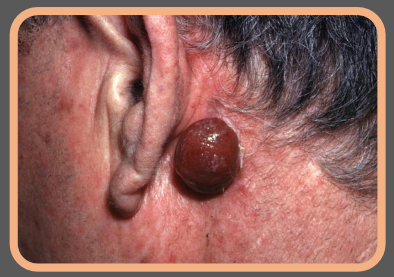
Hombre, 78 años
IIIC T4aN2bM0



Hombre, 78 años
IIIC T4aN2bM0



Hombre, 78 años
IIIC T4aN2bM0

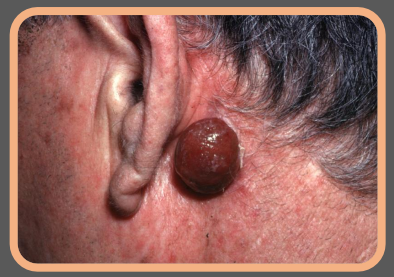


IIB-IIC
T3b-T4bN0M0

Pembrolizumab
200mg/3 sem x **18 dosis**

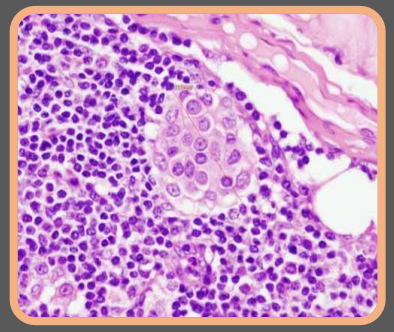
Dermatología MQyV
Unidad de Melanoma

Inmunoterapia perioperatoria
melanoma 2024



IIB-IIC
T3b-T4bN0M0

Pembrolizumab
200mg/3 sem x **18 dosis**



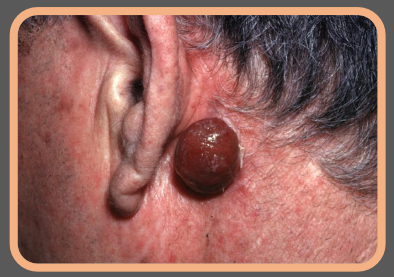
IIIA
Na carga ≤1mm

IIIA
Na carga >1mm

Pembrolizumab
200mg/3 sem x **18 dosis**

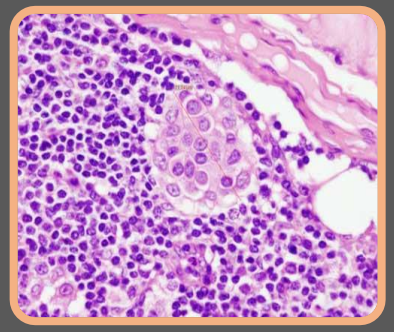
Inmunoterapia perioperatoria melanoma 2024

Dermatología MQyV
Unidad de Melanoma



IIB-IIC
T3b-T4bN0M0

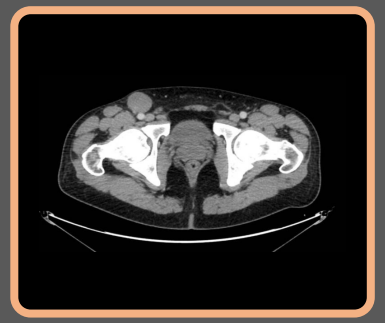
Pembrolizumab
200mg/3 sem x **18 dosis**



IIIA
Na carga ≤1mm

IIIA
Na carga >1mm

Pembrolizumab
200mg/3 sem x **18 dosis**



IIIB
T0-T3a N1b

IIIC-D
T3b-T4b N1b2b3b

Pembrolizumab
200mg/3 sem x **3 dosis**

RxC

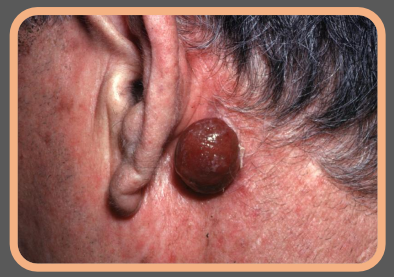
Pembrolizumab
200mg/3 sem x **15 dosis**

No RxC

DGC vs DGRadical

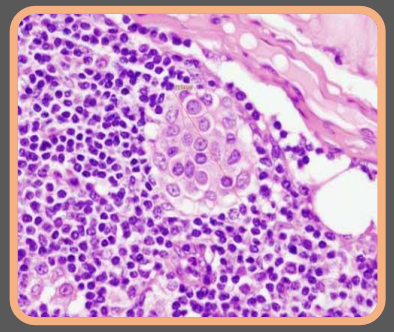
Inmunoterapia perioperatoria melanoma 2024

HUM
Dermatología MQyV
Unidad de Melanoma



IIB-IIC
T3b-T4bN0M0

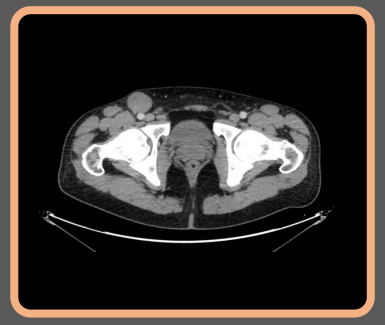
Pembrolizumab
200mg/3 sem x 17 dosis



IIIA
Na carga ≤1mm

IIIA
Na carga >1mm

Pembrolizumab
200mg/3 sem x 17 dosis



IIIB
T0-T3a N1b

IIIC-D
T3b-T4b N1b2b3b

DGC vs DGRadical

Pembrolizumab
200mg/3 sem x 3 dosis

RxC

Pembrolizumab
200mg/3 sem x 14 dosis

No RxC

DGC vs DGRadical

Inmunoterapia perioperatoria melanoma 2024

“Los ganglios linfáticos son las escuelas donde aprenden los linfocitos T”

A. Eggermont
EADO París 2024