19as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2024
MADRID 20 - 21 NOVIEMBRE 2024

# MELANOMA EN ESTADIOS PRECOCES

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Hospital General Universitario Gregorio Marañón
Universidad Complutense de Madrid
21-11-2024

CONFLICTOS DE INTERÉS

Advisory role: Amgen, Astra Zeneca, BiolineRx, BMS, Celegene, GSK, Highlight Therapeutics, Immunocore, Merck Serono, MSD, Novartis, Pierre Fabre, Regeneron, Roche, Sanofi, Sun Pharma

Travel accommodation and congress: Amgen, BMS, GSK, Highlight Therapeutics, MSD, Novartis, Pierre Fabre, Roche, Sun Pharma

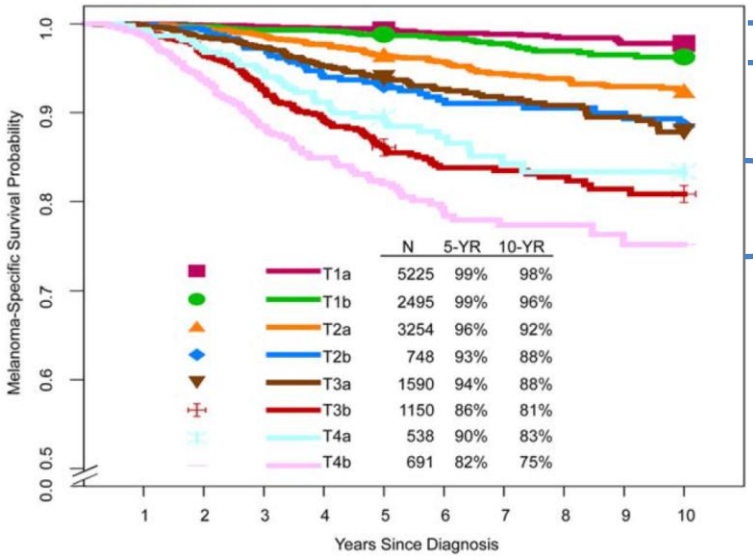
Clinical trial participation as PI: Ab Science, Aduro, Agenus, Alkermes, Amgen, Astra Zeneca, Biontech, BMS, Erasca, Genentech, GSK, Highlight Therapeutics, Idera, Immunocore, Incyte, Iovance, Kartos, Merck Serono, MSD, Novartis, Pfizer, Regeneron, Roche, Sairopa.

If you find something I have missed, please e-mail me: ivanpantic@hotmail.com

# DEFINAMOS “PRECOZ”

- Limitado a piel y/o ganglios que puede ser extirpado
- Estadios IA a IIID
- Candidatos a seguimiento (I-IIA), adyuvancia o neoadyuvancia (III)

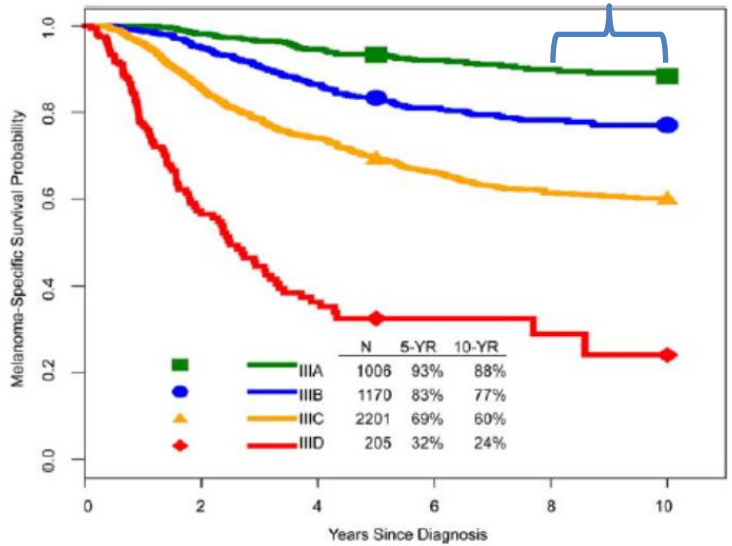
# EL AMPLIO ESPECTRO DE “LOCALIZADO”




Paradoja estadio I:
Mayoría e IV provienen de un estadio I previo

IIB-C
hasta 25% fallecidos

Paradoja estadio IIIA:
Mejor pronóstico que estadio IIB-C

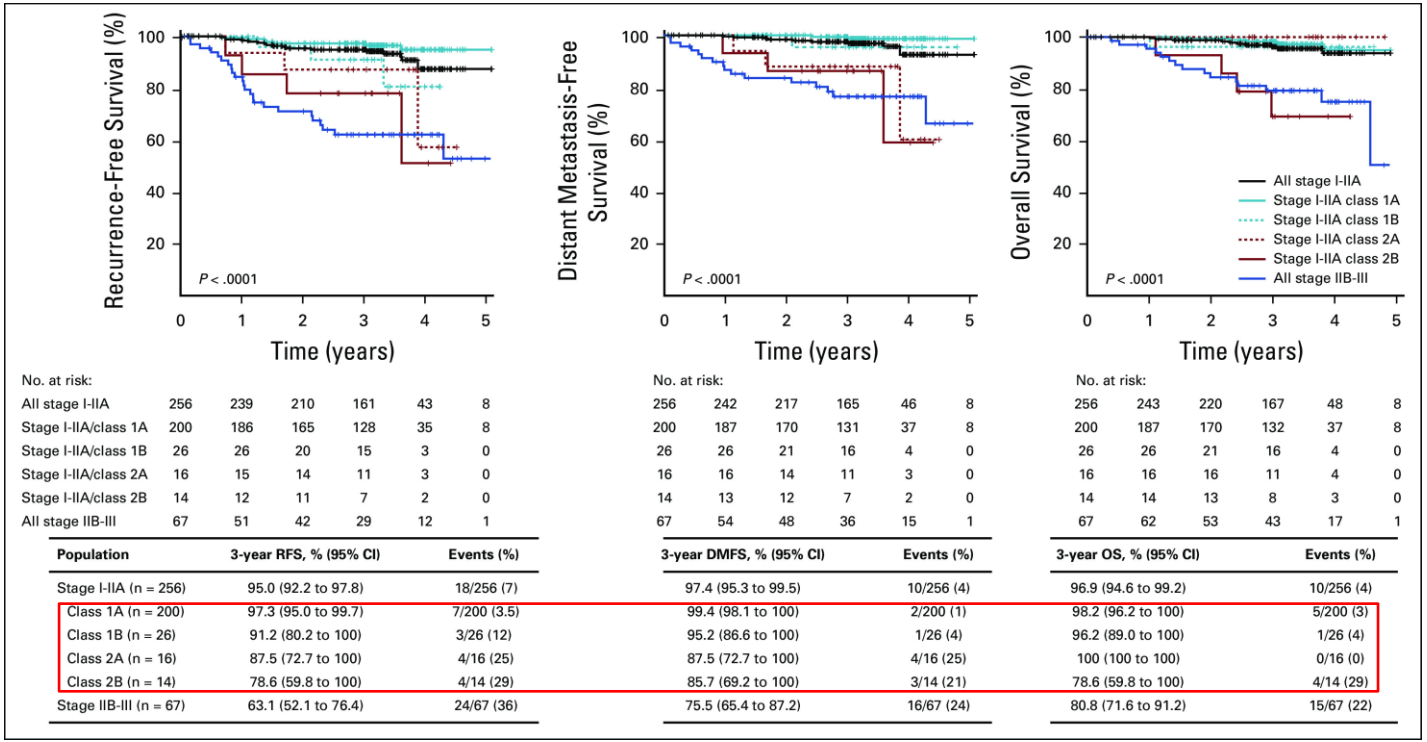



Gershenwald 2017 CA: Can J Clin

# ESTADIO I-IIA

- No hay estrategia adyuvante definida, por defecto todos candidatos a **observación**
- Alta curabilidad pero recaídas muchos años después
- ¿Quiénes? ¿Qué hacer?

# GEP 31 genes




No. at risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| All stage I-IIA | 256 | 239 | 210 | 161 | 43 | 8 |
| Stage I-IIA/class 1A | 200 | 186 | 165 | 128 | 35 | 8 |
| Stage I-IIA/class 1B | 26 | 26 | 20 | 15 | 3 | 0 |
| Stage I-IIA/class 2A | 16 | 15 | 14 | 11 | 3 | 0 |
| Stage I-IIA/class 2B | 14 | 12 | 11 | 7 | 2 | 0 |
| All stage IIB-III | 67 | 51 | 42 | 29 | 12 | 1 |

No. at risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| All stage I-IIA | 256 | 242 | 217 | 165 | 46 | 8 |
| Stage I-IIA/class 1A | 200 | 187 | 170 | 131 | 37 | 8 |
| Stage I-IIA/class 1B | 26 | 26 | 21 | 16 | 4 | 0 |
| Stage I-IIA/class 2A | 16 | 16 | 14 | 11 | 3 | 0 |
| Stage I-IIA/class 2B | 14 | 13 | 12 | 7 | 2 | 0 |
| All stage IIB-III | 67 | 54 | 48 | 36 | 15 | 1 |

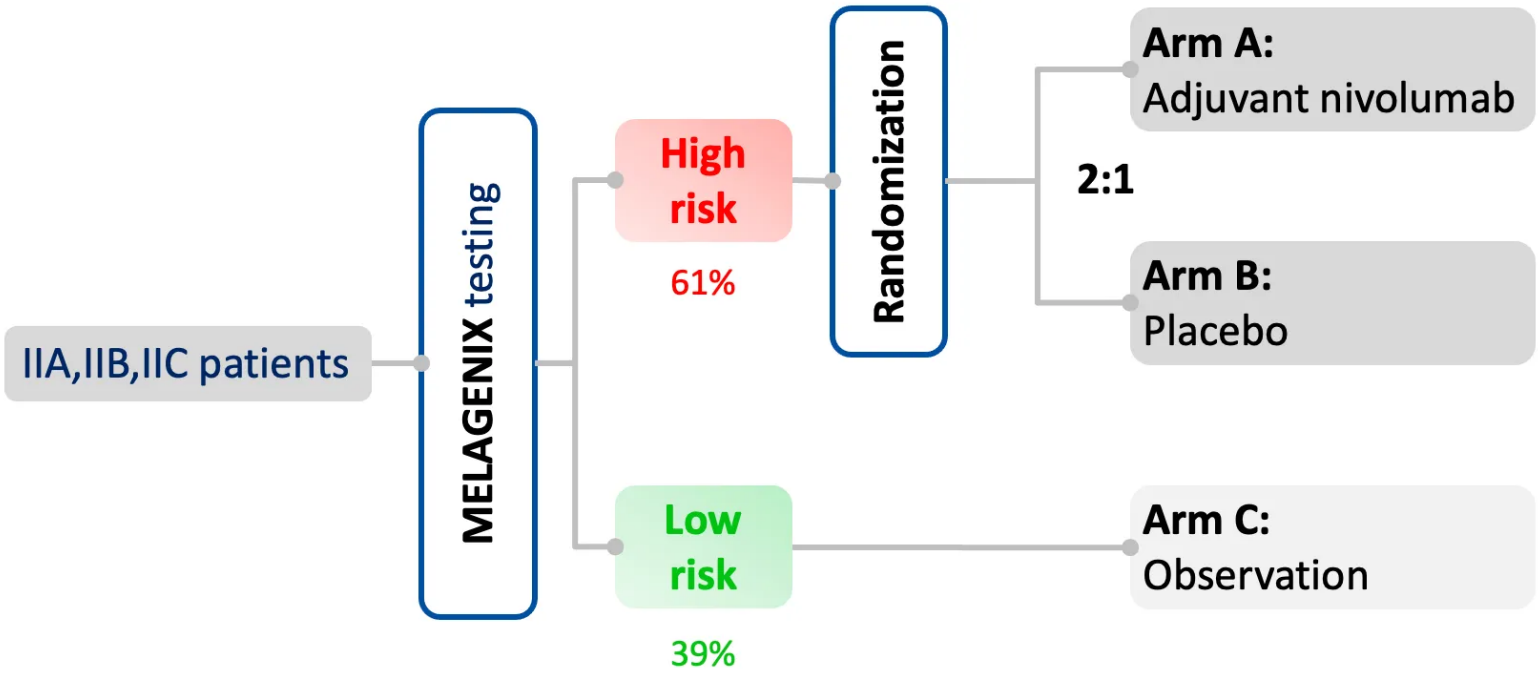
No. at risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| All stage I-IIA | 256 | 243 | 220 | 167 | 48 | 8 |
| Stage I-IIA/class 1A | 200 | 187 | 170 | 132 | 37 | 8 |
| Stage I-IIA/class 1B | 26 | 26 | 21 | 16 | 4 | 0 |
| Stage I-IIA/class 2A | 16 | 16 | 16 | 11 | 4 | 0 |
| Stage I-IIA/class 2B | 14 | 14 | 13 | 8 | 3 | 0 |
| All stage IIB-III | 67 | 62 | 53 | 43 | 17 | 1 |

| Population | 3-year RFS, % (95% CI) | Events (%) | 3-year DMFS, % (95% CI) | Events (%) | 3-year OS, % (95% CI) | Events (%) |
|---|---|---|---|---|---|---|
| Stage I-IIA (n = 256) | 95.0 (92.2 to 97.8) | 18/256 (7) | 97.4 (95.3 to 99.5) | 10/256 (4) | 96.9 (94.6 to 99.2) | 10/256 (4) |
| Class 1A (n = 200) | 97.3 (95.0 to 99.7) | 7/200 (3.5) | 99.4 (98.1 to 100) | 2/200 (1) | 98.2 (96.2 to 100) | 5/200 (3) |
| Class 1B (n = 26) | 91.2 (80.2 to 100) | 3/26 (12) | 95.2 (86.6 to 100) | 1/26 (4) | 96.2 (89.0 to 100) | 1/26 (4) |
| Class 2A (n = 16) | 87.5 (72.7 to 100) | 4/16 (25) | 87.5 (72.7 to 100) | 4/16 (25) | 100 (100 to 100) | 0/16 (0) |
| Class 2B (n = 14) | 78.6 (59.8 to 100) | 4/14 (29) | 85.7 (69.2 to 100) | 3/14 (21) | 78.6 (59.8 to 100) | 4/14 (29) |
| Stage IIB-III (n = 67) | 63.1 (52.1 to 76.4) | 24/67 (36) | 75.5 (65.4 to 87.2) | 16/67 (24) | 80.8 (71.6 to 91.2) | 15/67 (22) |

Hsueh 2021 JCO Precis Oncol

# NIVOMELA CA209-7DL (ESTADIO IIA-C)

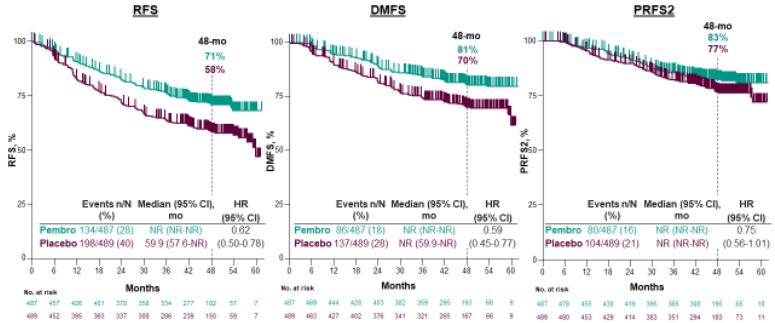



NCT04309409

# ESTADIO IIB-IIC

Luke KN716 ESMO 2024

## RFS, DMFS, and PRFS2 in Part 1



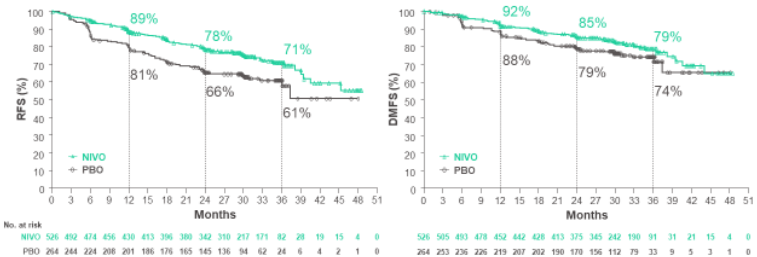

PRFS2 was defined as time from randomization to first disease progression beyond the initial unresectable disease recurrence, second recurrence, or death. Data cutoff date: Feb 16, 2024.

CheckMate 76K

## RFS and DMFS

| RFS[a] | NIVO | PBO |
|---|---|---|
| Events, n/N | 133/526 | 95/264 |
| Median, months (95% CI) | NR (40.7-NR) | NR (36.1-NR) |
| Stratified HR (95% CI) | 0.62 (0.47-0.80) | |

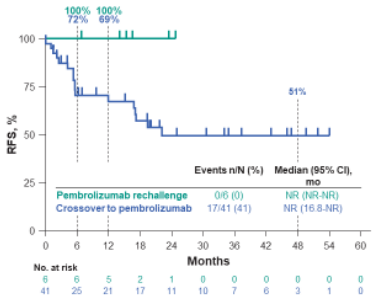
| DMFS[b] | NIVO | PBO |
|---|---|---|
| Events, n/N | 96/526 | 61/264 |
| Median, months (95% CI) | NR | NR |
| Stratified HR (95% CI) | 0.72 (0.52-1.00) | |




[a]RFS was defined as the time between randomization and first recurrence (recurrence events included local, regional, or distant recurrence, new primary melanomas [including *in situ*], and death [due to any cause]). [b]DMFS was defined as time between randomization and first distant recurrence or death (due to any cause).

## Efficacy Outcomes in Part 2

### Resectable disease




### Unresectable disease

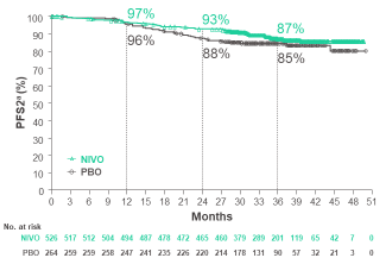
| | Pembrolizumab rechallenge n = 3 | Crossover to pembrolizumab n = 30 |
|---|---|---|
| **ORR, % (95% CI)** | 0 (0-71) | 43 (26-63) |
| **Best overall response, n (%)** | | |
| CR | 0 | 8 (27) |
| PR | 0 | 5 (17) |
| SD | 1 (33) | 9 (30) |
| PD | 1 (33) | 7 (23) |
| No assessment[a] | 1 (33) | 1 (3) |
| **PFS, median (95% CI), months** | NR (2.5-NR) | 22.0 (4.5-NR) |

RFS is defined as the time from treatment initiation in part 2 to any recurrence as assessed by the investigator, or death due to any cause. PFS is defined as the time from treatment initiation in part 2 to first documented disease progression as assessed by the investigator, or death due to any cause. [a]Includes patients without a post-baseline assessment. Data cutoff date: Feb 16, 2024.

CheckMate 76K

## PFS2

| | NIVO | PBO |
|---|---|---|
| Events, n/N | 60/526 | 41/264 |
| Median PFS2, months (95% CI) | NR | NR |
| Stratified HR (95% CI) | 0.71 (0.48-1.06) | |




### Subsequent systemic therapy

| | NIVO (n = 526), n (%) | PBO (n = 264), n (%) |
|---|---|---|
| Patients with a recurrence | 97 (18%) | 81 (32%) |
| Systemic therapy[b] | 61 (12%) | 71 (27%) |
| Anti-PD-(L)1 therapy | 18 (3%) | 49 (19%) |
| Anti-CTLA-4 therapy | 3 (1%) | 3 (1%) |
| NIVO + IPI | 31 (6%) | 21 (8%) |
| Anti-PD-(L)1 + LAG-3 | 2 (< 1%) | 3 (1%) |
| BRAF + MEK inhibitor | 12 (2%) | 9 (3%) |

[a]PFS2 was 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). [b]Patients may have received > 1 type of subsequent therapy. Subsequent therapy data for the whole study, both blinded and open-label phases, are reported.

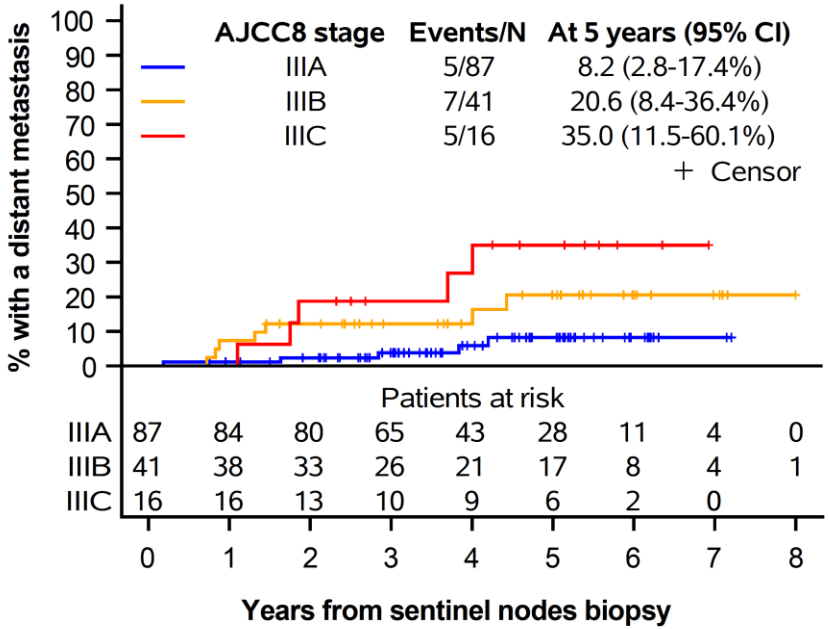
KN716
Pembro vs placebo

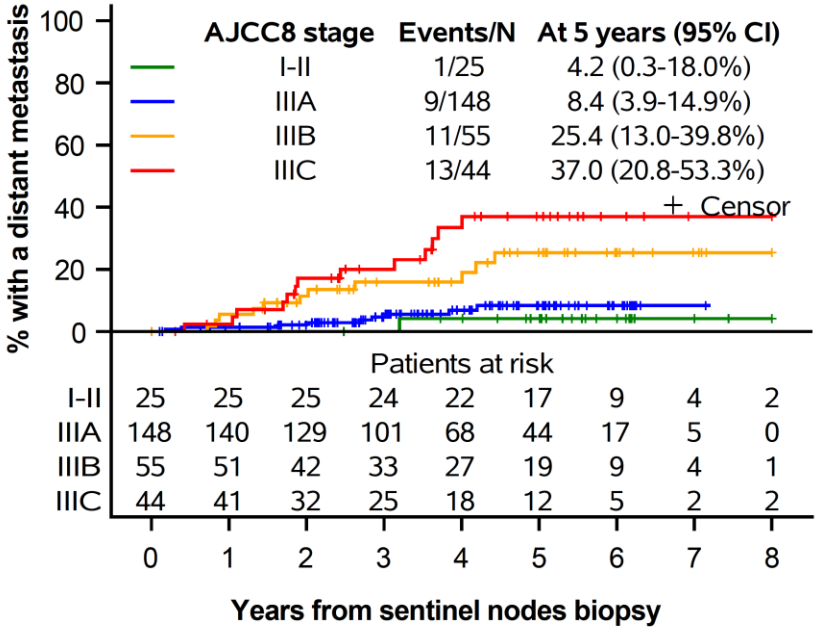
CM76K
Nivo vs placebo

Composite predictive model in progress

Luke ESMO 2024; Long ESMO 2024

# ESTADIO IIIA CON MÍNIMA CARGA TUMORAL GANGLIONAR (<0,4 MM SUBCAPSULAR, <0,1 MM NO-SUBCAPSULAR)

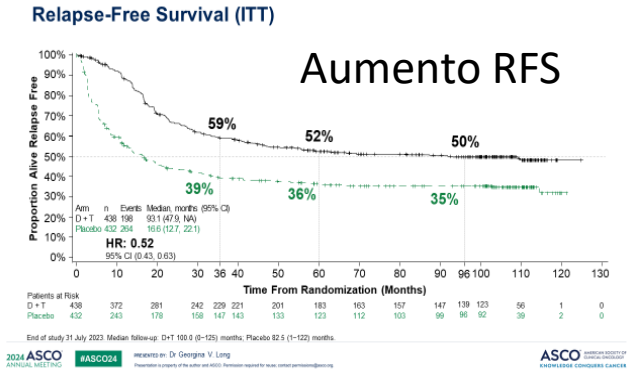


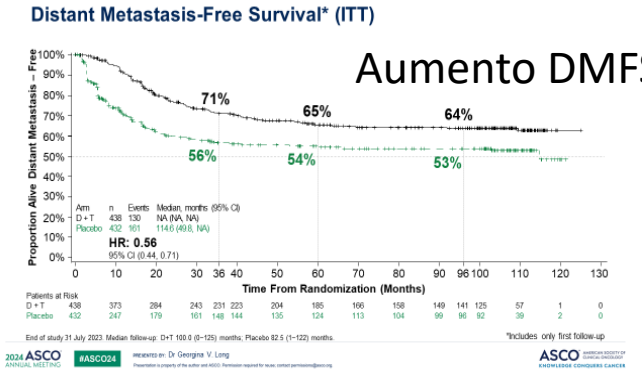

RECORDAD: ENSAYOS IIIA OBLIGATORIO >1MM

Van Akkooi ESMO 2024

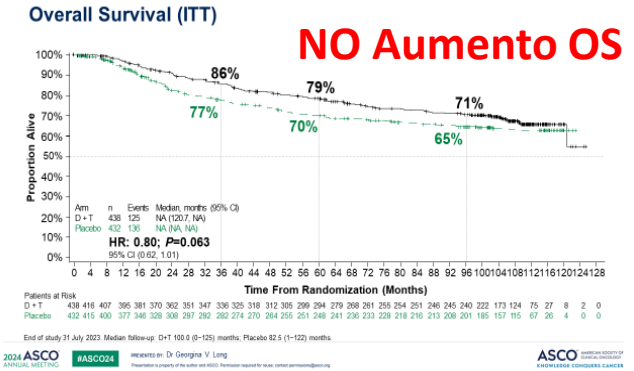
# ESTADIO III TERAPIA DIRIGIDA ADYUVANTE: ESTUDIO COMBI-AD



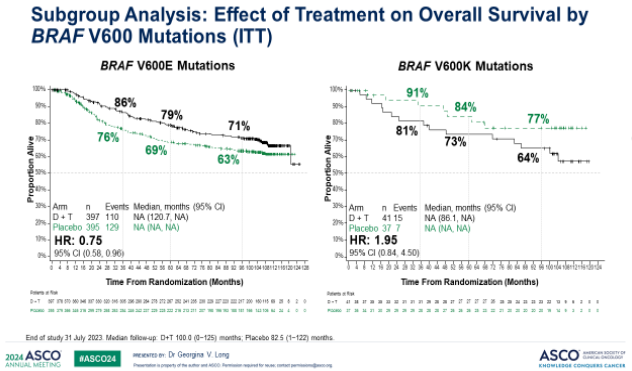

Aumento RFS




Aumento DMFS




NO Aumento OS

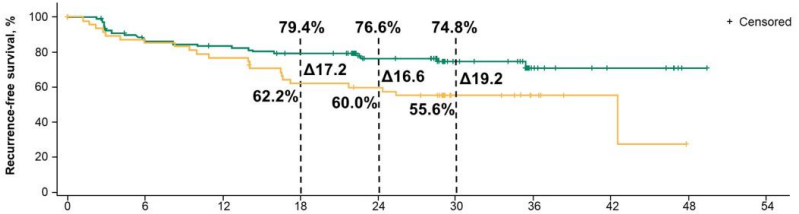



¿BRAFV600K PEOR?

Long ASCO 2024

# ESTADIO III INMUNOTERAPIA ADYUVANTE: VACUNAS PERSONALIZADAS mRNA (asumimos aquí pembro o nivo son estándar por KN054 y CM238)

## Sustained improvement of RFS primary efficacy endpoint




| Patients at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| mRNA-4157 (V940) + pembrolizumab | 107 | 87 | 83 | 77 | 52 | 29 | 12 | 6 | 1 | 0 |
| Pembrolizumab | 50 | 41 | 37 | 29 | 27 | 10 | 5 | 2 | 0 | 0 |

| | Median (95% CI), months | Events, % (n/N) | Hazard ratio (95% CI)[a] |
|---|---|---|---|
| mRNA-4157 (V940) + pembrolizumab | NE | 23.4 (25/107) | 0.510 (0.288–0.906) *P* = 0.019[b] |
| pembrolizumab | 42.51 (16.59–NE) | 44.0 (22/50) | |

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) + pembrolizumab versus pembrolizumab were estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIB or IIC or IID vs stage IV) used for randomization. The *P* value is based on a 2-sided log-rank test stratified by disease stage (stages IIB or IIC or IID vs stage IV) used for randomization. [b]Formal hypothesis testing of RFS was performed using November 2022 data cut. *P* value reported above used the November 2023 data cut; it's nominal and not for formal hypothesis testing. NE, not estimable.

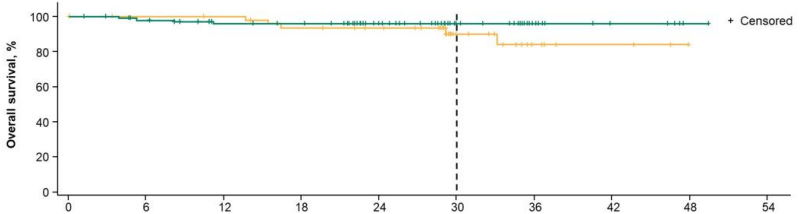








## Overall survival shows encouraging trend with mRNA-4157 (V940) + pembrolizumab




| Patients at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| mRNA-4157 (V940) + pembrolizumab | 107 | 100 | 92 | 90 | 65 | 35 | 14 | 6 | 1 | 0 |
| Pembrolizumab | 50 | 48 | 47 | 43 | 40 | 18 | 7 | 3 | 0 | 0 |

| | Median (95% CI), Months | Events, % (n/N) | Hazard ratio (95% CI)[a] |
|---|---|---|---|
| mRNA-4157 (V940) + pembrolizumab | NE | 3.7 (4/107) | 0.425 (0.114–1.584) |
| Pembrolizumab | NE | 10.0 (5/50) | |

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab were estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIB or IIC or IID vs stage IV) used for randomization.



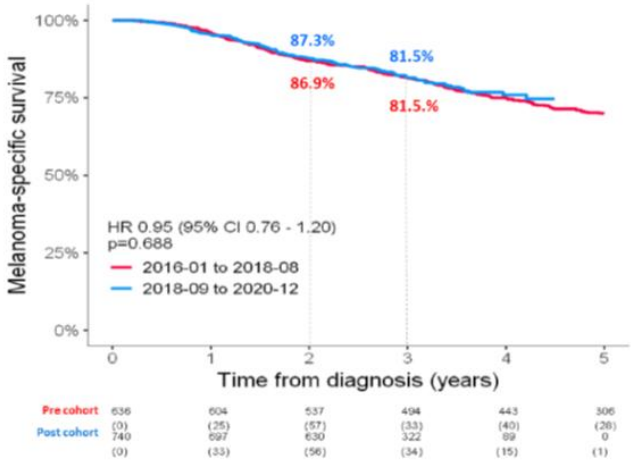


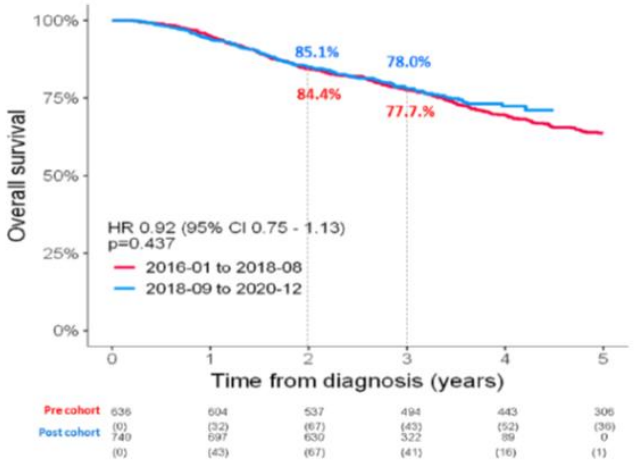


Weber ASCO 2024

# DATOS DE VIDA REAL

## Melanoma specific survival (MSS) and Overall Survival (OS)
### -Median follow-up 69 + 39 months




BARCELONA 2024 ESMO congress

Hildur Helgadottir

Abstract FPN 1079MO

Helgadottir ESMO 2024

# NEOADYUVANCIA

# The NADINA effect

nature medicine

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nature > nature medicine > research highlights > article

RESEARCH HIGHLIGHT | 17 June 2024

## Neoadjuvant immunotherapy a new standard of care for melanoma

**The phase 3 NADINA trial showed impressive responses to neoadjuvant nivolumab plus ipilimumab relative to adjuvant nivolumab (the current best practice), revealing a new standard of care for patients with stage III melanoma.**

"Take away: adjuvant therapy being replaced by upfront immunotherapy…"

The ASCO Post

Upon hearing the results, Plenary Session co-moderator, outgoing ASCO President, and melanoma expert **Lynn Schuchter, MD, FASCO**, Director of the Tara Miller Melanoma Center and the Madlyn and Leonard Abramson Professor of Clinical Oncology at Penn Medicine, Philadelphia, commented, "I'll be back in the clinic Thursday, and for the first time I am going to consider [ipilimumab/nivolumab]. I have not been using combination

Oncology News Central | Cancer Types | Treatment | Business | Conferences | Expert Insights

"As oncologists, we are trained to do more, and do something. It takes some educational paradigm shift to train [the] oncology community that more treatment is not always in patients' best interest," he said.

Dr. Gyawali is a founding member of Common Sense Oncology, an organization launched in 2023 that is dedicated to promoting effective treatments and challenging interventions that might cause more harm than good. "NADINA is an important trial, and the type of patient-centric trial that we celebrate at Common Sense Oncology," he said.

"Currently, we believe we are treating too many patients for too long [a] time at too high a dose at too-frequent intervals. These de-escalation trials are therefore meaningful and patient-centric," Dr. Gyawali added.

ESMO 2024 Fri, 13.09.2024

**14:00 - 15:30** **Type: Special symposium** **Oviedo Auditorium - Hall 3**

**Title: Why neoadjuvant immunotherapy is the future for melanoma**

BARCELONA 2024 ESMO congress

Iván Márquez Rodas

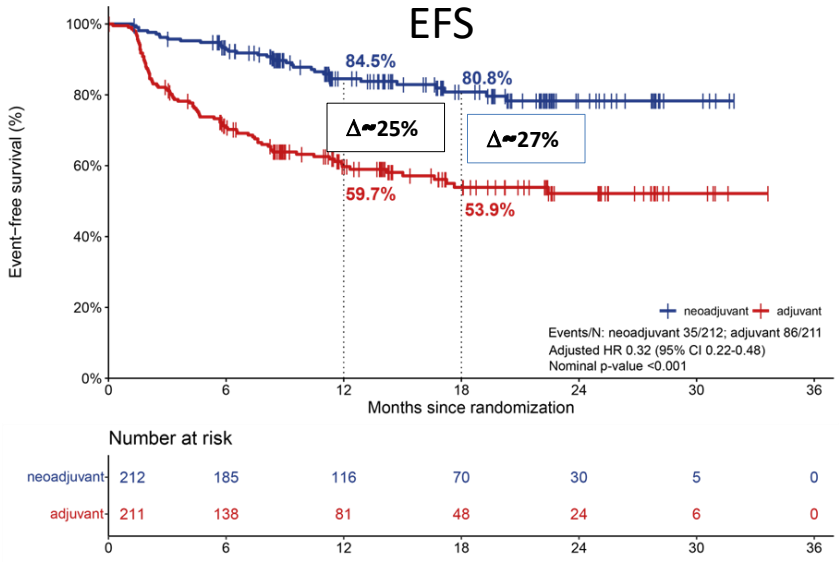
https://www.nature.com/articles/d41591-024-00045-x

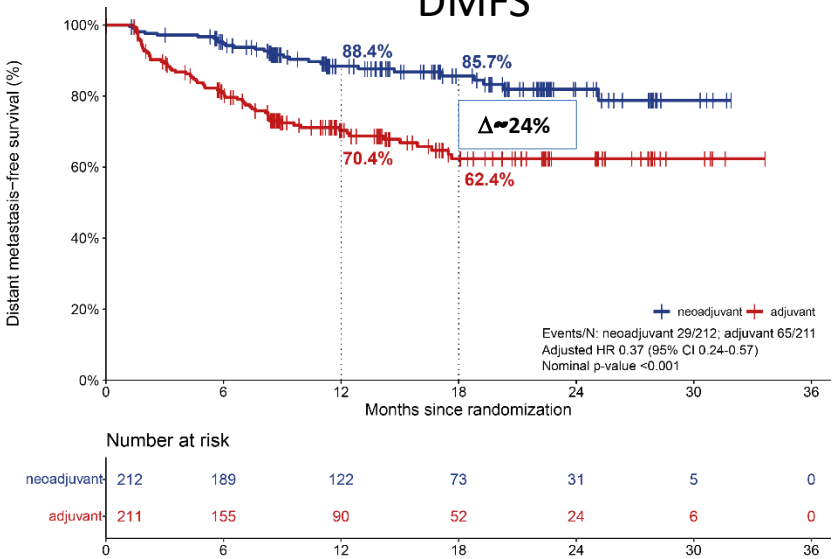
https://ascopost.com/issues/june-10-2024/nadina-trial-shows-robust-benefit-for-neoadjuvant-nivolumab-plus-ipilimumab-in-stage-iii-melanoma/

https://www.oncologynewscentral.com/article/new-standard-in-melanoma-may-save-1-billion-while-improving-lives

ASCO 2024 oral session discussion

# LBA42 shows us, with longer follow (aprox 15 months), a new endpoint: Distant metastasis free survival (DMFS)

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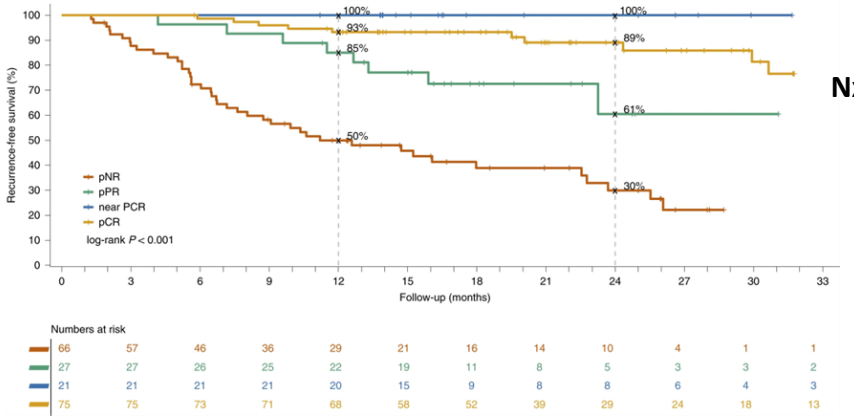
# LBA41: the International Neoadjuvant Melanoma Consortium (INMC)

192 pts

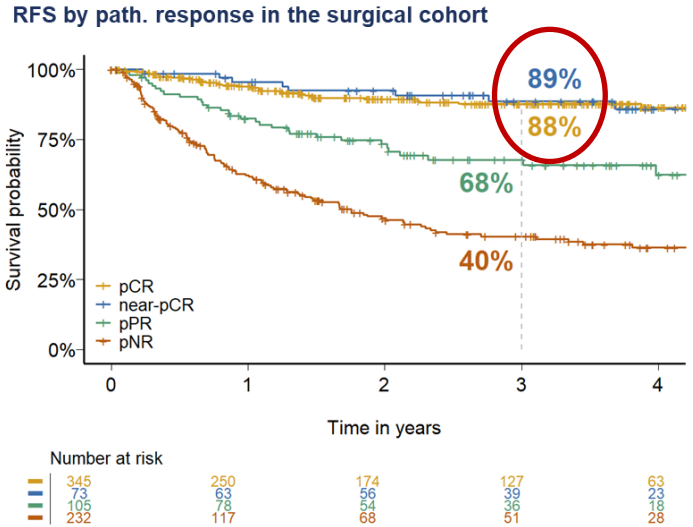
**~21 months FUP**




**Nx4 patients in 3y!**

818 pts (including 185 non-trial)

**~39 months FUP**



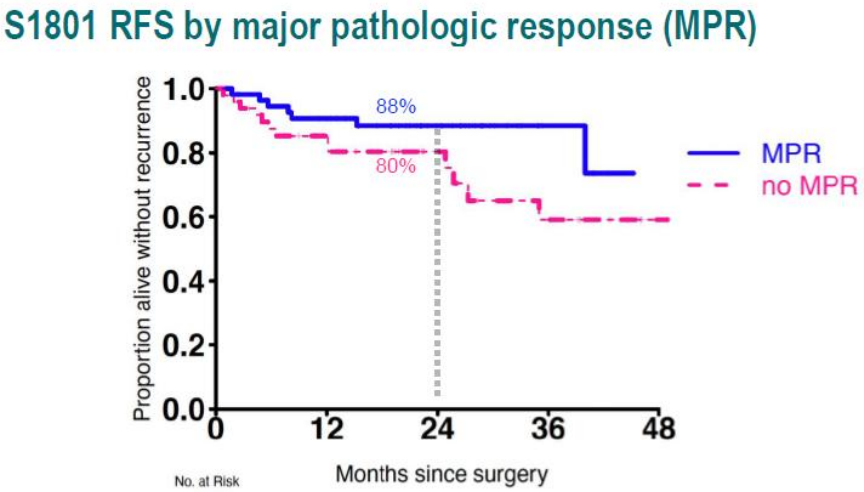



Iván Márquez Rodas



Menzies 2021 Nat Med; Long ESMO 2024

# ¿TIENE QUE SER LA NEOADYUVANCIA CON IPI-NIVO?




| | NADINA NEOADJUVANT IPI+NIVO | NADINA ADJUVANT NIVO | SWOG1801 NEAODJUVANT PEMBRO (+ADJUVANT PEMBRO) |
|---|---|---|---|
| Any G3-4 AEs | ~47% | ~34% | - |
| Any IO G3-4 AEs | ~30% | ~15% | 7% (12% during adjuvant phase) |
| Deaths (N) | 0 | 1 | 0 |

53% MPR in S1801=88% 2yRFS

Patel ESMO 2023; Márquez-Rodas ESMO 2024

# Neoadjuvant is for CLINICALLY detected stage III melanoma

*"Clinical detectable:*

- *lymph nodes are defined as either one:*
- *o a palpable node, confirmed as melanoma by pathology;*
- *o a non-palpable but enlarged lymph node according to RECISTv1.1 (**at least 15 mm** in short axis), confirmed as melanoma by pathology;*
- *o a PET scan positive lymph node of any size confirmed as melanoma by pathology"*

| | | |
|---|---|---|
| Short-axis diameter of largest lymph node — no. (%)¶ | | |
| <15 mm | 67 (31.6) | 74 (35.1) |
| 15–30 mm | 115 (54.2) | 102 (48.3) |
| 31–50 mm | 24 (11.3) | 29 (13.7) |
| >50 mm | 4 (1.9) | 4 (1.9) |
| No lymph node reported on CT scan | 2 (0.9) | 2 (0.9) |
| Median sum of diameters of lymph nodes (range) — mm² | 25 (15–74) | 25 (15–82) |

You really must look for them!


**Caution with subgroups**: "*The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects*".





Blank 2024 NEJM

# Not every stage III is CLINICALLY detected: three data examples

| | KN054 (AJCC7) | Danish national cohort (AJCC8) | Spanish GEM1801 cohort (AJCC8) |
|---|---|---|---|
| % of clinical detected among stage III | **64** | 40 | 36 |
| % of **non-clinically** detected among stage III | 36 | **60** | **64** |



Iván Márquez Rodas



Eggermont NEJM evidence 2022; Helvind Jama derm 2023; GEM1801, unpublished

# CONCLUSIONES

- “Todavía” ninguna estrategia adyuvante o neoadyuvante en la **era moderna** (sí INF $\alpha$ en los inicios, sí ipilimumab 10mg/kg) ha demostrado aumento formal de supervivencia global
- Sí que está claro:
  - Estadios I-IIA: no hay datos. ¿Quién tiene riesgo de recaer?
  - Estadios IIB-IIID resecados:
    - Anti PD-1 adyuvante estándar por aumento RFS y DMFS.
    - Igual, terapia dirigida BRAF + IIIA-IIID (no evidencia en II)
    - Alto riesgo de sobretratamiento en estadios IIIA
  - Neaodyuvancia basada en anti PD-1 **mejor** que adyuvancia en III **clínicamente detectable** en los mismos términos
- Biomarcadores y algo tan sofisticado como hablar con el/la paciente son necesarios más que nunca