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

Quimioinmunoterapia neoadyuvante en el cáncer de mama triple negativo: datos de supervivencia

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Hospital General Universitario Gregorio Marañon

Employment:

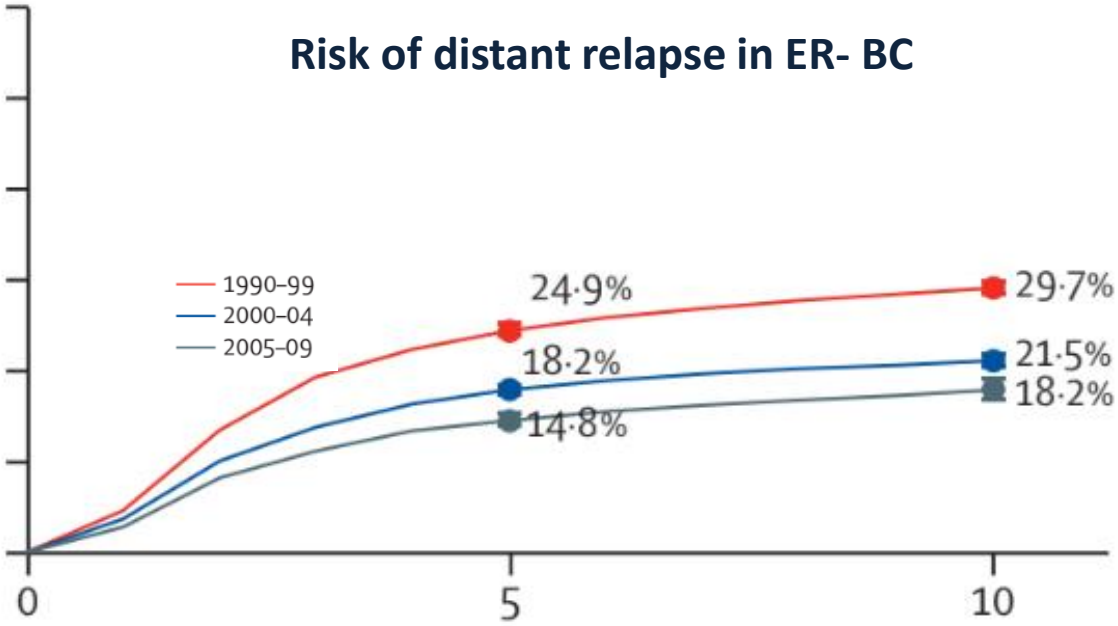
- Hospital General Universitario Gregorio Marañon.
- Spanish Society of Medical Oncology

Consultant or Advisory Role: Lilly, AstraZeneca, Daiichi Sankyo

Speaking: Lilly, AstraZeneca, Daiichi Sankyo, Pfizer, Novartis, Roche, Gilead, Pierre Fabre

Reductions in recurrence in women with early breast cancer entering clinical trials between 1990 and 2009: a pooled analysis of 155 746 women in 151 trials

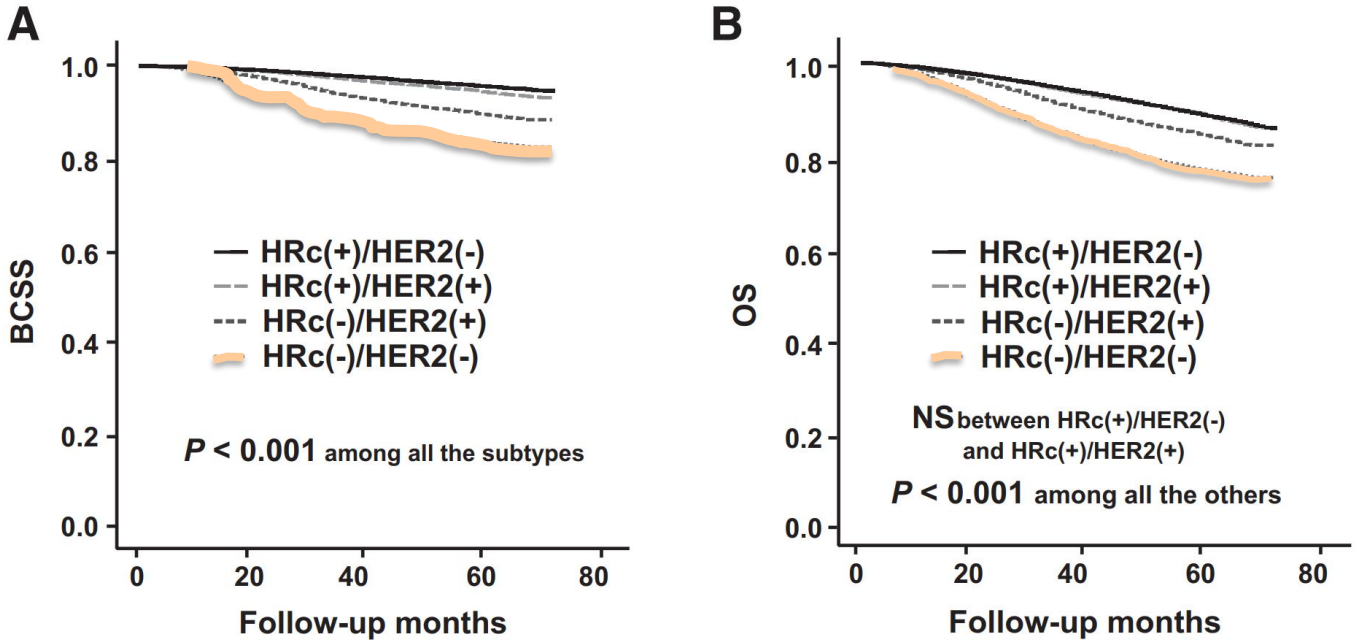
*Early Breast Cancer Trialists' Collaborative Group**



37,7%

EBCTCG. Lancet 2024

El reto del CMTN



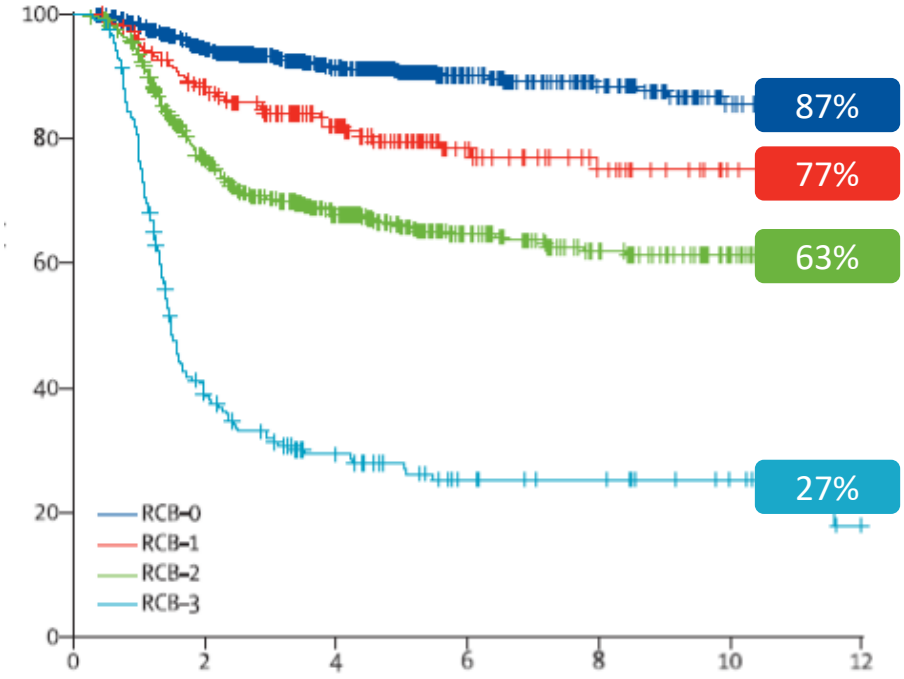
Hwang et al. Clin Cancer Res 2019

Quimioterapia neoadyuvante como estándar de tratamiento en CMTN

- Paradoja CMTN: mayor agresividad pero mayor quimiosensibilidad

- Quimioterapia neoadyuvante como estándar de tratamiento:
  - Tratamiento de la enfermedad micrometastásica
  - Monitorización de la respuesta
  - Desescalada cirugía: mama / axila
  - Ventana para la realización de estudio genético germinal.

Valor pronóstico de la respuesta a QTNA en la era pre-ICI



10y DRFS

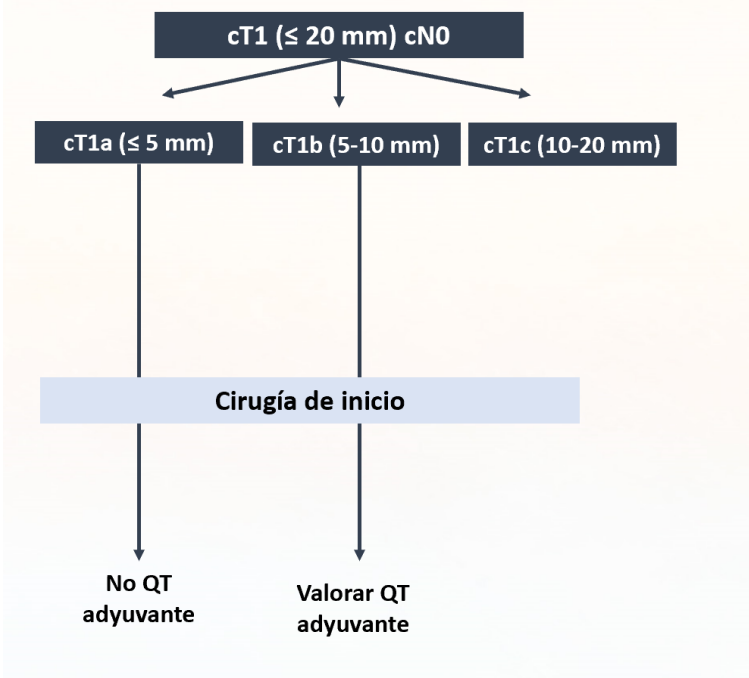
Mayoría de las recaídas a distancia

SG 18-24 meses desde la recidiva

La neo/adyuvancia como momento único para curar a estas pacientes

Yau et al. Lancet Oncol 2021

ALGORTIMO TERAPÉUTICO CMTN: cT1a-b cN0

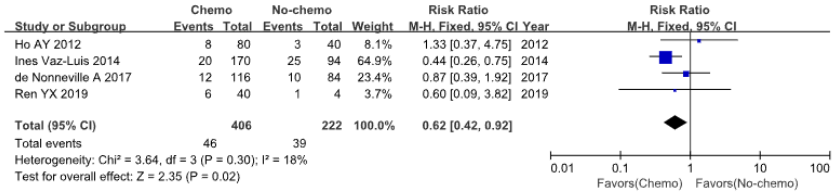


Ayala de la Peña F et al. Clin Transl Oncol 2023. Han et al. ASCO Educat Book 2023. Curigliano G et al.

ALGORTIMO TERAPÉUTICO CMTN: cT1a-b cN0

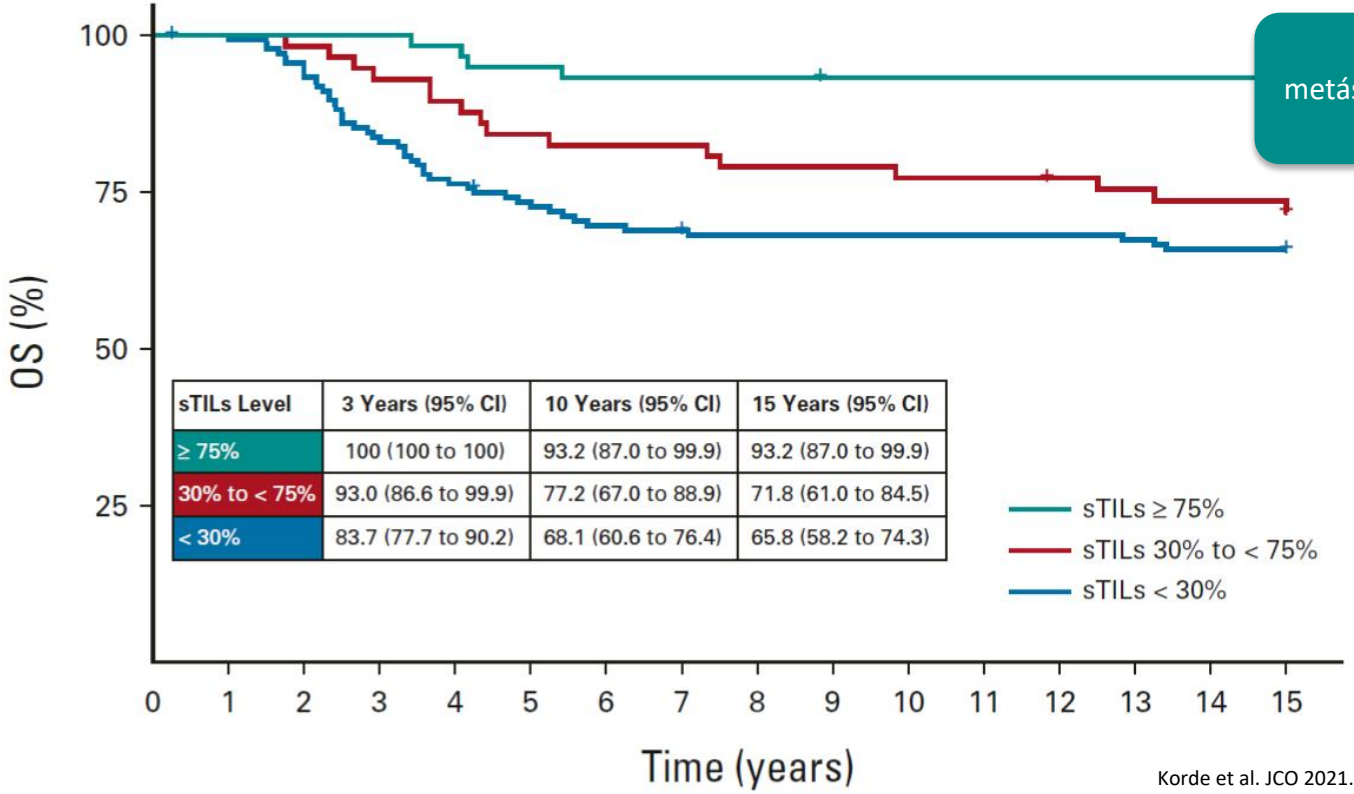
- No indicación de quimioterapia neoadyuvante
- No evidencia de beneficio con QT adyuvante en pT1a pN0.
- Posible beneficio con la QT adyuvante en pT1b pN0

Adjuvant Chemotherapy for Small, Lymph Node–Negative, Triple-Negative Breast Cancer: A Single-Center Study and a Meta-Analysis of the Published Literature



Korde et al. JCO 2021. De Jong V. JCO 2022. An et al. Cancer 2020.

Valor pronóstico de las TILs en CMTN cT1 cN0 sin quimioterapia



sTILs Level	3 Years (95% CI)	10 Years (95% CI)	15 Years (95% CI)
≥ 75%	100 (100 to 100)	93.2 (87.0 to 99.9)	93.2 (87.0 to 99.9)
30% to < 75%	93.0 (86.6 to 99.9)	77.2 (67.0 to 88.9)	71.8 (61.0 to 84.5)
< 30%	83.7 (77.7 to 90.2)	68.1 (60.6 to 76.4)	65.8 (58.2 to 74.3)

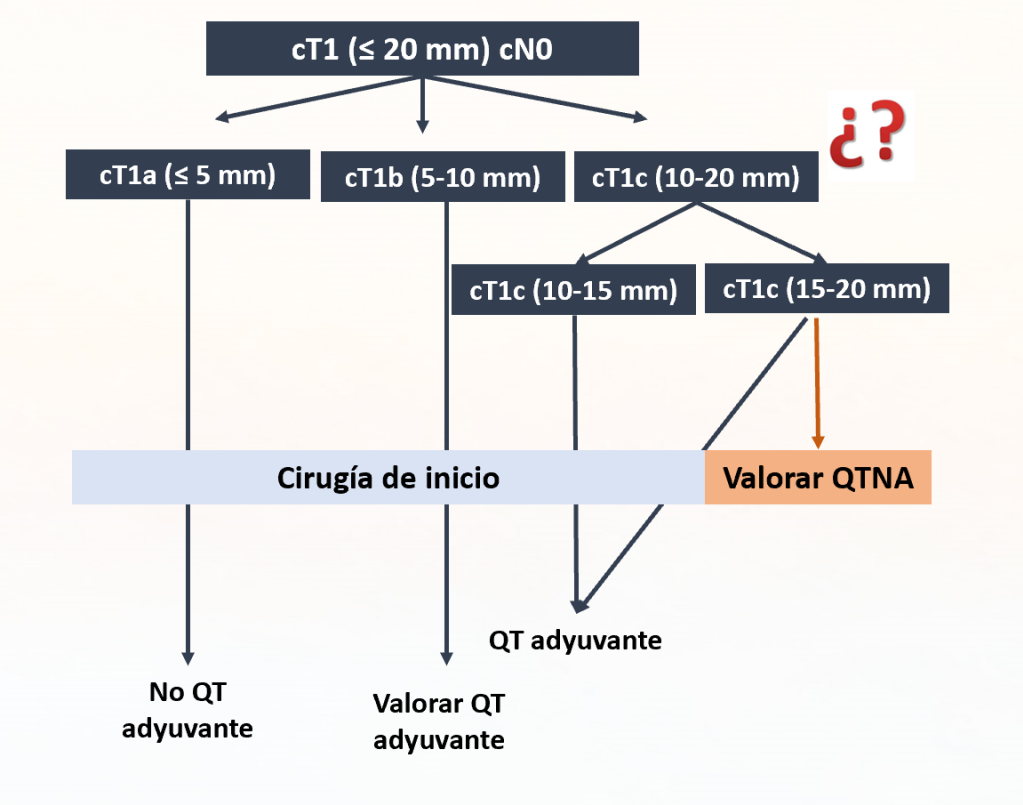
2,1% riesgo de metástasis o muerte a 10 años

¿?

¿Podríamos desescalar de forma segura la QT/QTNA en estas pacientes?

Korde et al. JCO 2021. De Jong V. JCO 2022. An et al. Cancer 2020.

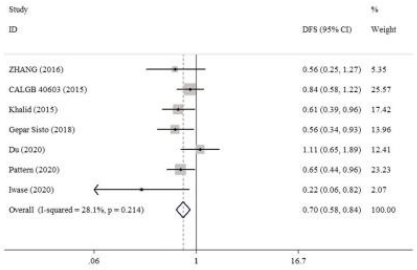
QTNA como estándar en CMTN ≥ 15-20 mm y/o cN+



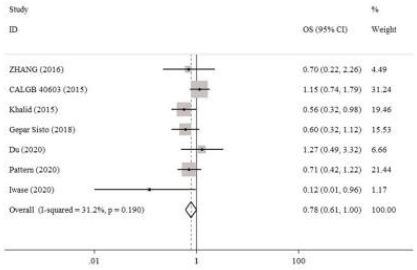
Han et al. ASCO Educat Book 2023

La neoadyuvancia en la era pre-ICI o en cT1c cN0

Uso de platinos



SLE
HR=0,70

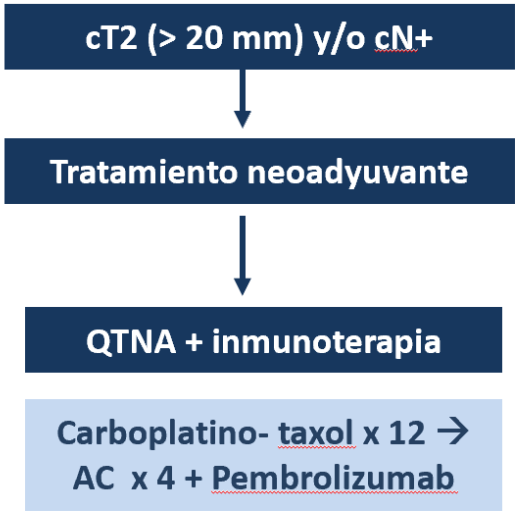


SG
HR=0,78

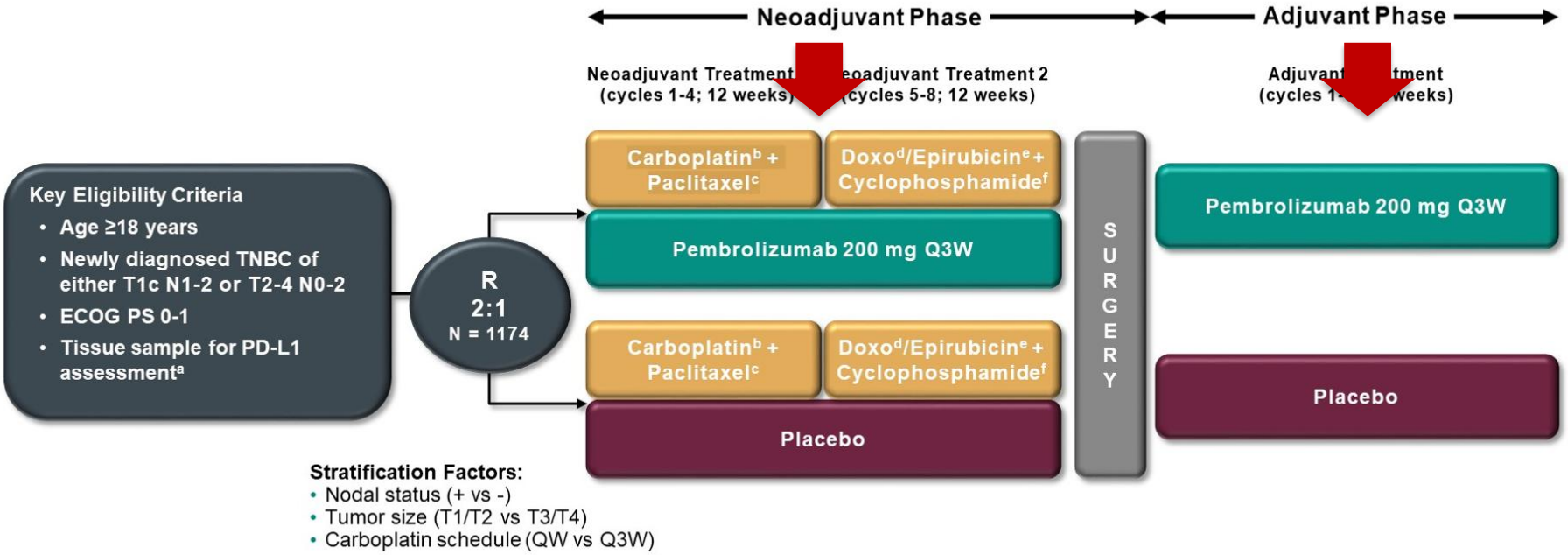
Esquemas sin antraciclinas

Poggio et al. Ann Oncol 2018. Bian et al. NPJ Breast Cancer 2021

La neoadyuvancia en CMTN ≥ cT2 y/o cN+



KEYNOTE-522 Study Design (NCT03036488)

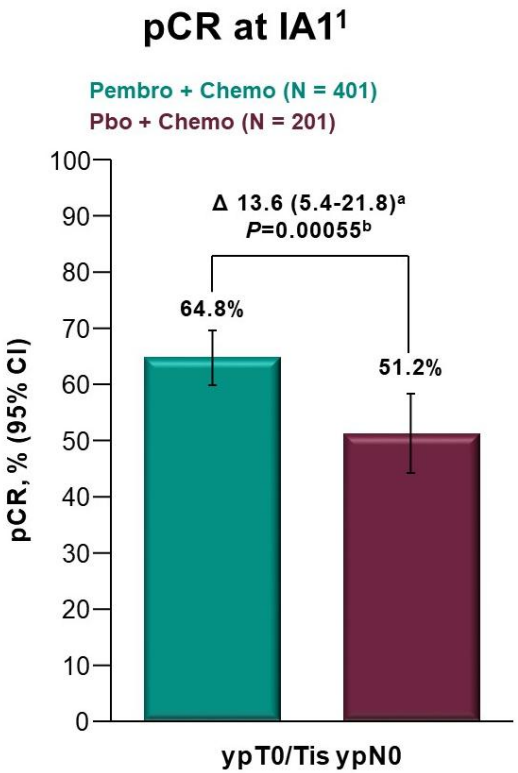


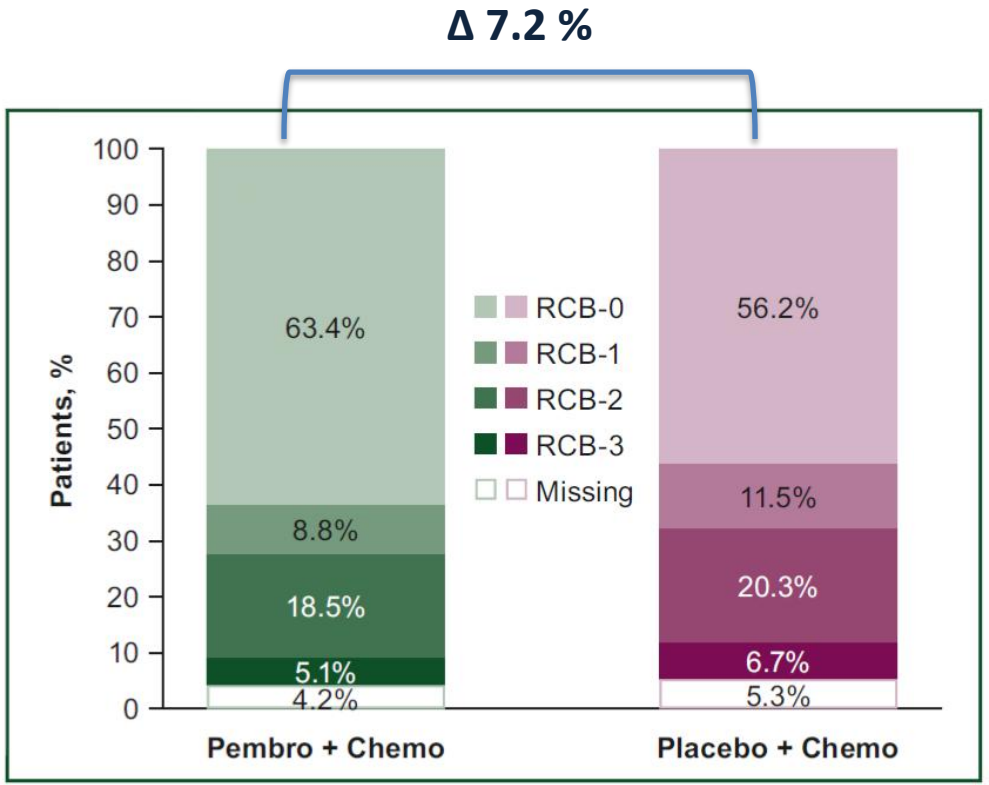
Objetivo primario: pCR y EFS en ITT

Objetivo secundario clave: OS

Pusztai L et al. ASCO 2022. Pusztai L et al. Ann Oncol 2024

Pembrolizumab incrementa las pCR

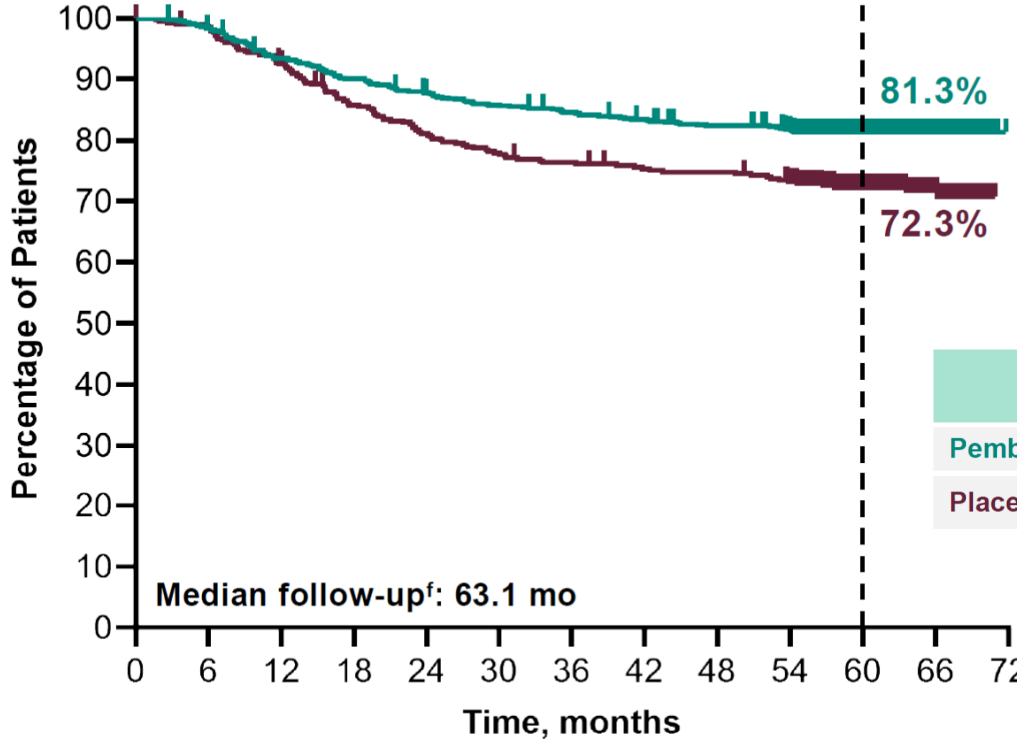




Pusztai L et al. ASCO 2022. Pusztai L et al. Ann Oncol 2024

Pembrolizumab incrementa la SLE

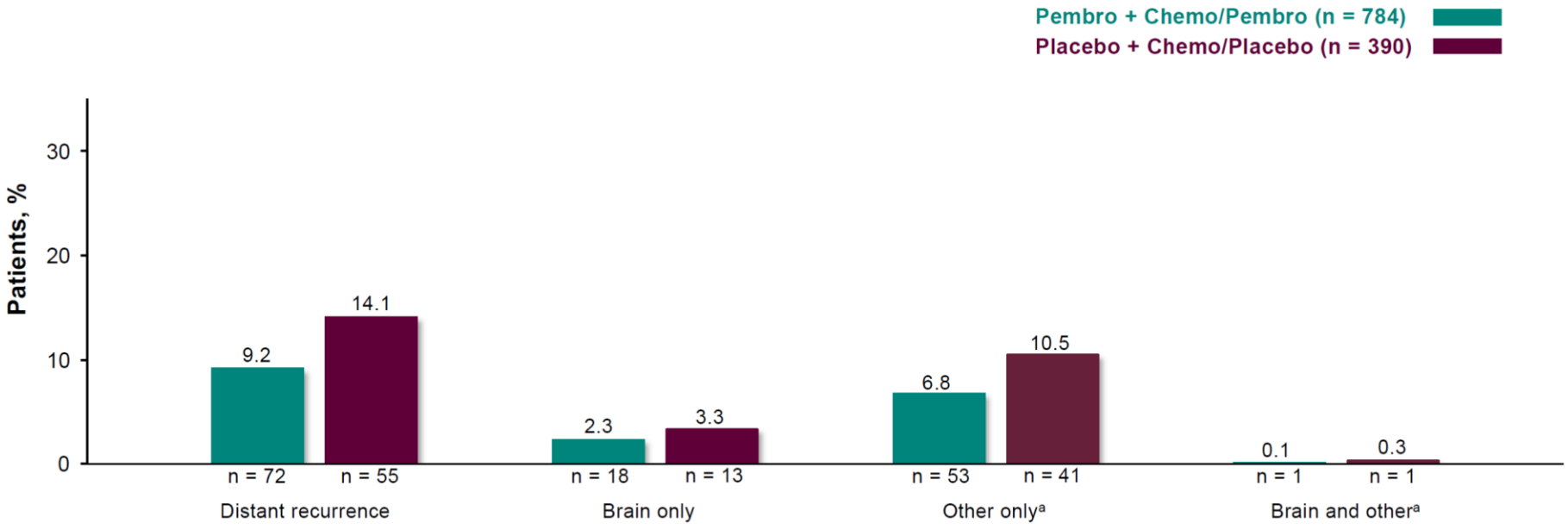
EFS at IA6



IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	

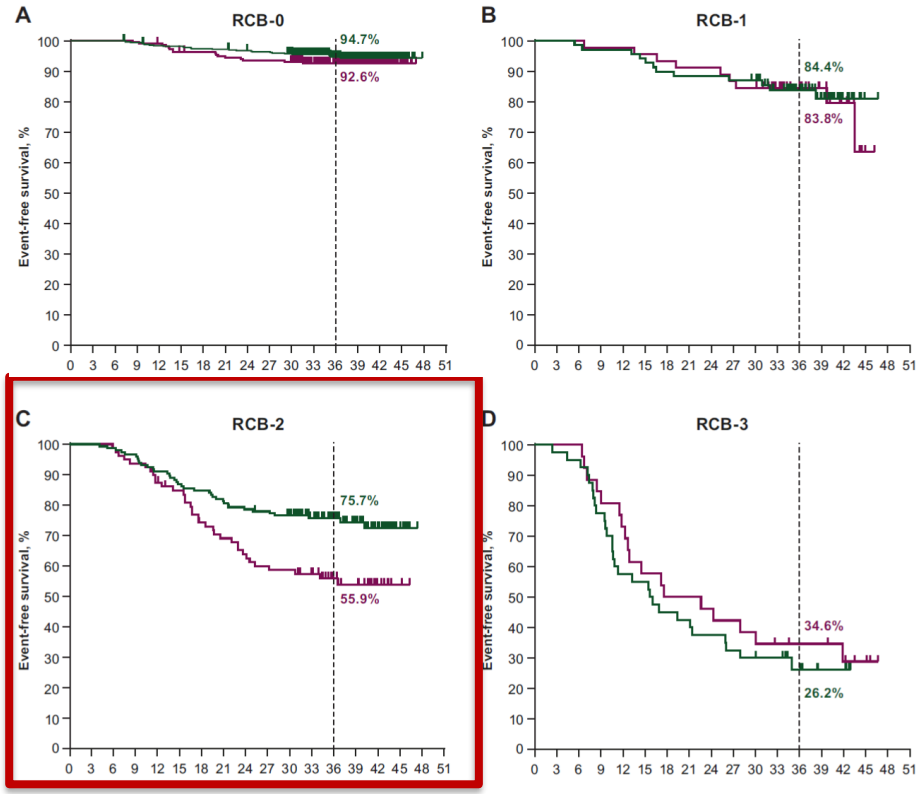
Schmid P et al. SABCS 2023

Distant Recurrence as First EFS Event



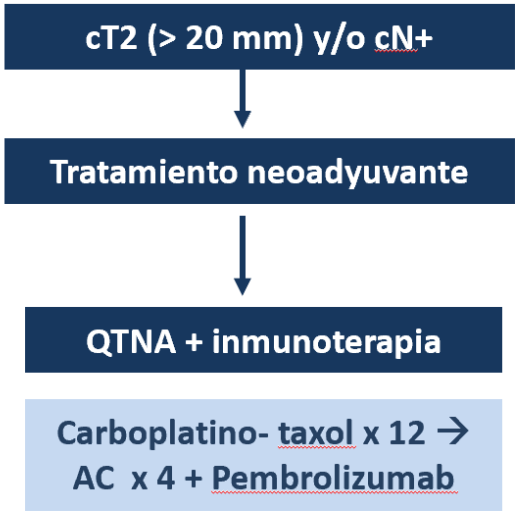
Schmid P et al. SABCS 2023

Impacto en EFS según enfermedad residual



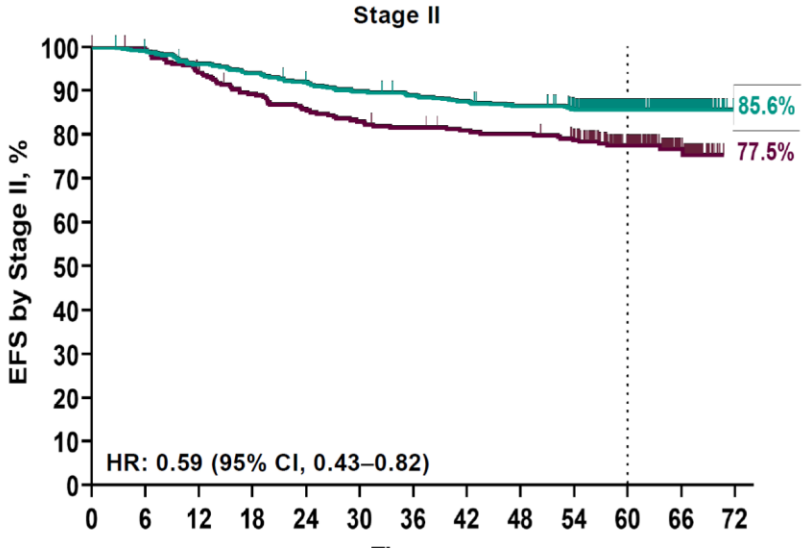
Pusztai L et al. Ann Oncol 2024

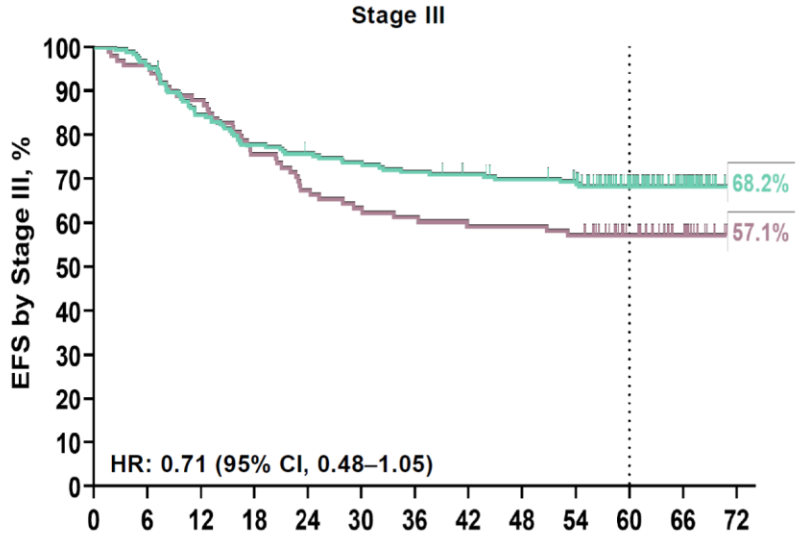
La neoadyuvancia en CMTN ≥ cT2 y/o cN+



¿Podemos identificar pacientes que no se benefician de pembrolizumab?

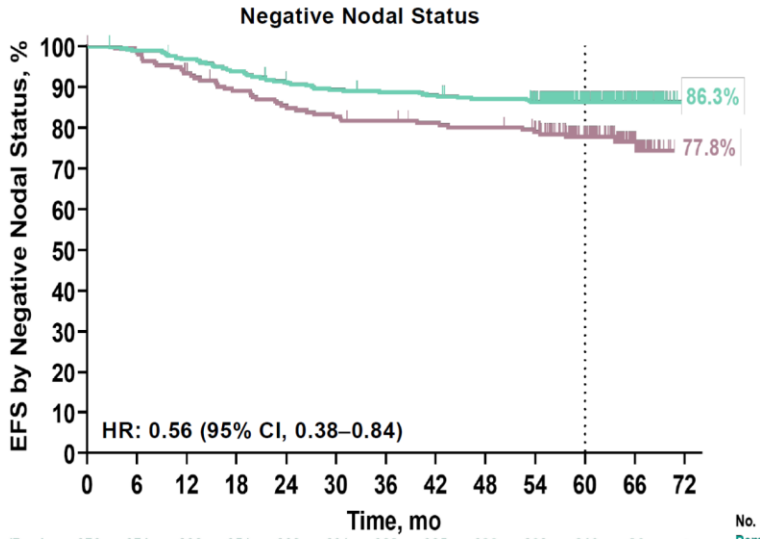
EFS at IA6 by Disease Stage

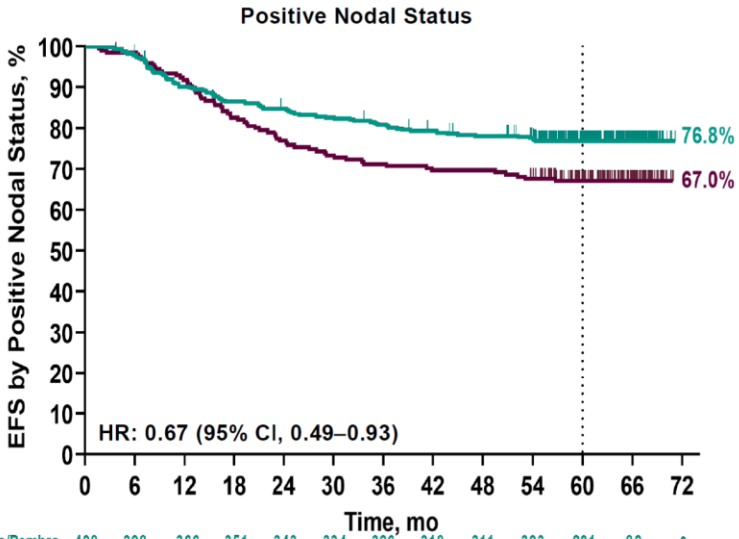




Schmid P et al. SABCS 2023

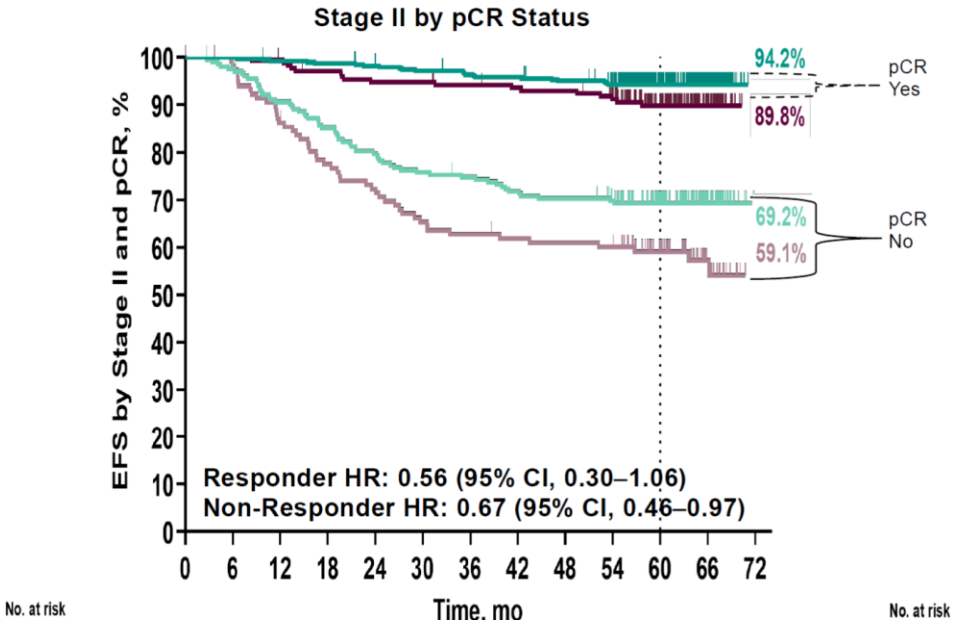
EFS at IA6 by Nodal Status

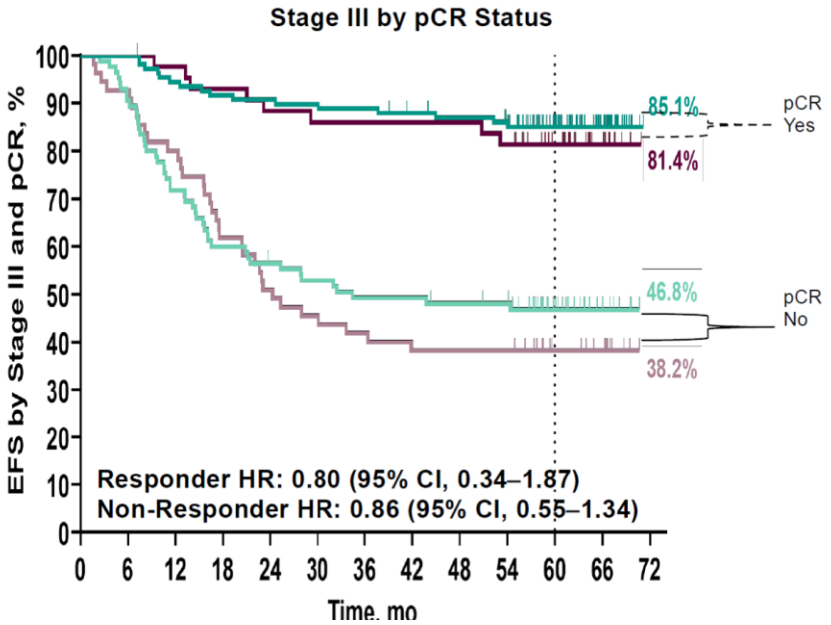




Schmid P et al. SABCS 2023

EFS at IA6 by Disease Stage in Patients With and Without pCR

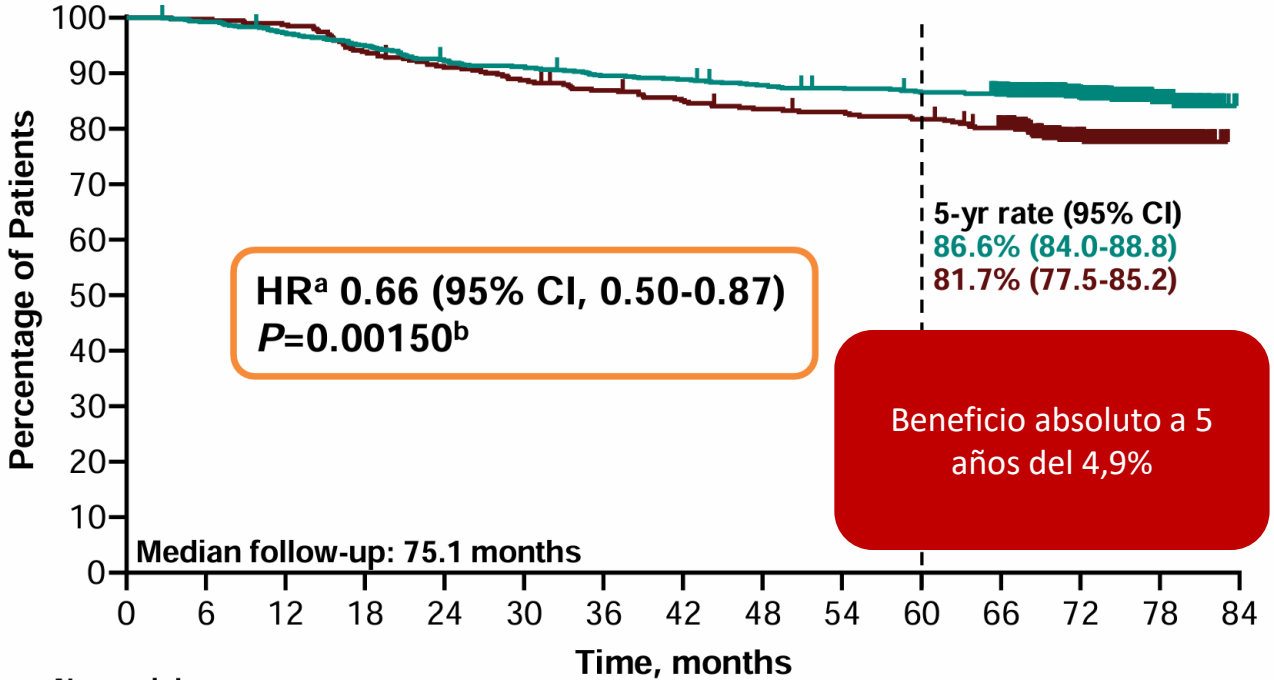




Schmid P et al. SABCS 2023

Pembrolizumab incrementa la SG

Key Secondary Endpoint: Overall Survival



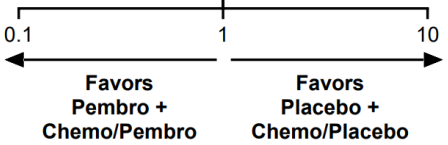
	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

Schmid P et al. ESMO 2024

Pembrolizumab incrementa la SG

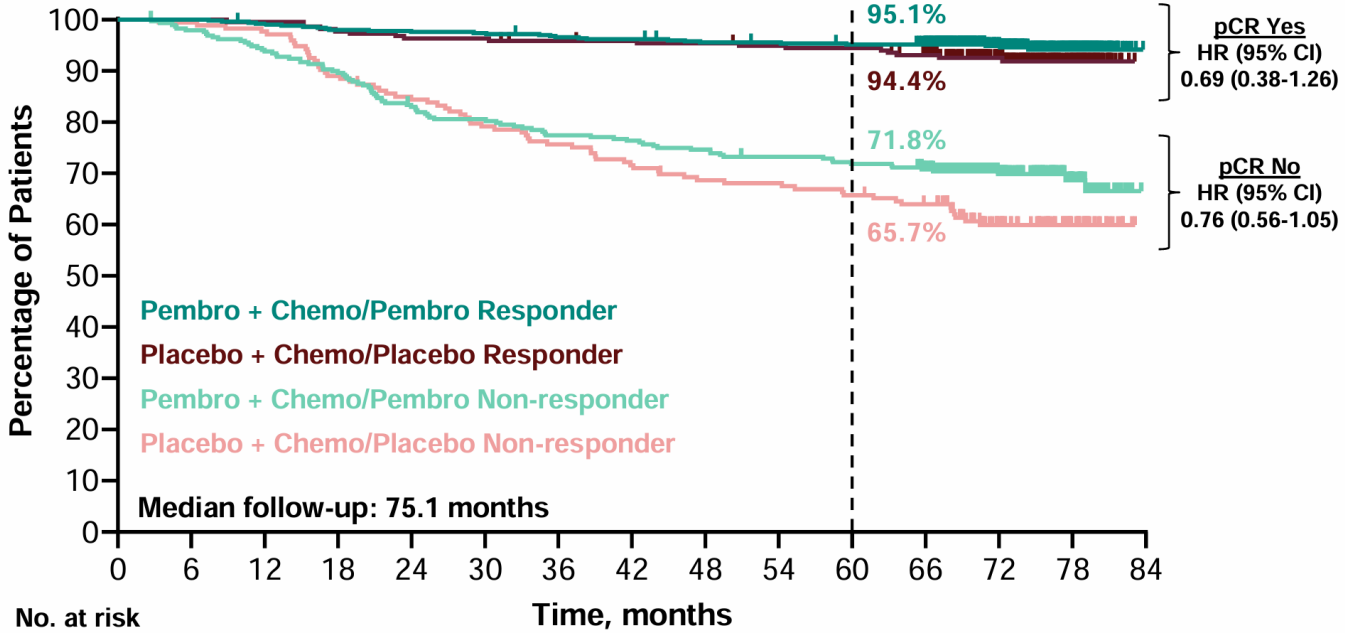
Overall Survival in Patient Subgroups

Subgroup	No. Events/No. Patients (%) Pembro + Chemo/Pembro	Placebo + Chemo/Placebo	Hazard Ratio (95% CI)
Overall	115/784 (14.7)	85/390 (21.8)	0.66 (0.50 to 0.87)
Nodal status			
Positive	78/408 (19.1)	56/196 (28.6)	0.65 (0.46 to 0.91)
Negative	37/376 (9.8)	29/194 (14.9)	0.65 (0.40 to 1.05)
Tumor size			
T1/T2	54/580 (9.3)	51/290 (17.6)	0.51 (0.35 to 0.75)
T3/T4	61/204 (29.9)	34/100 (34.0)	0.88 (0.58 to 1.34)
Carboplatin schedule			
Every 3 weeks	46/334 (13.8)	36/167 (21.6)	0.63 (0.41 to 0.97)
Weekly	68/444 (15.3)	49/220 (22.3)	0.67 (0.46 to 0.96)
PD-L1 status			
CPS ≥1	92/656 (14.0)	62/317 (19.6)	0.70 (0.51 to 0.97)
CPS <1	23/128 (18.0)	23/69 (33.3)	0.51 (0.28 to 0.91)
Age category			
<65 years	93/700 (13.3)	72/342 (21.1)	0.62 (0.45 to 0.84)
≥65 years[a]	22/84 (26.2)	13/48 (27.1)	0.96 (0.48 to 1.91)



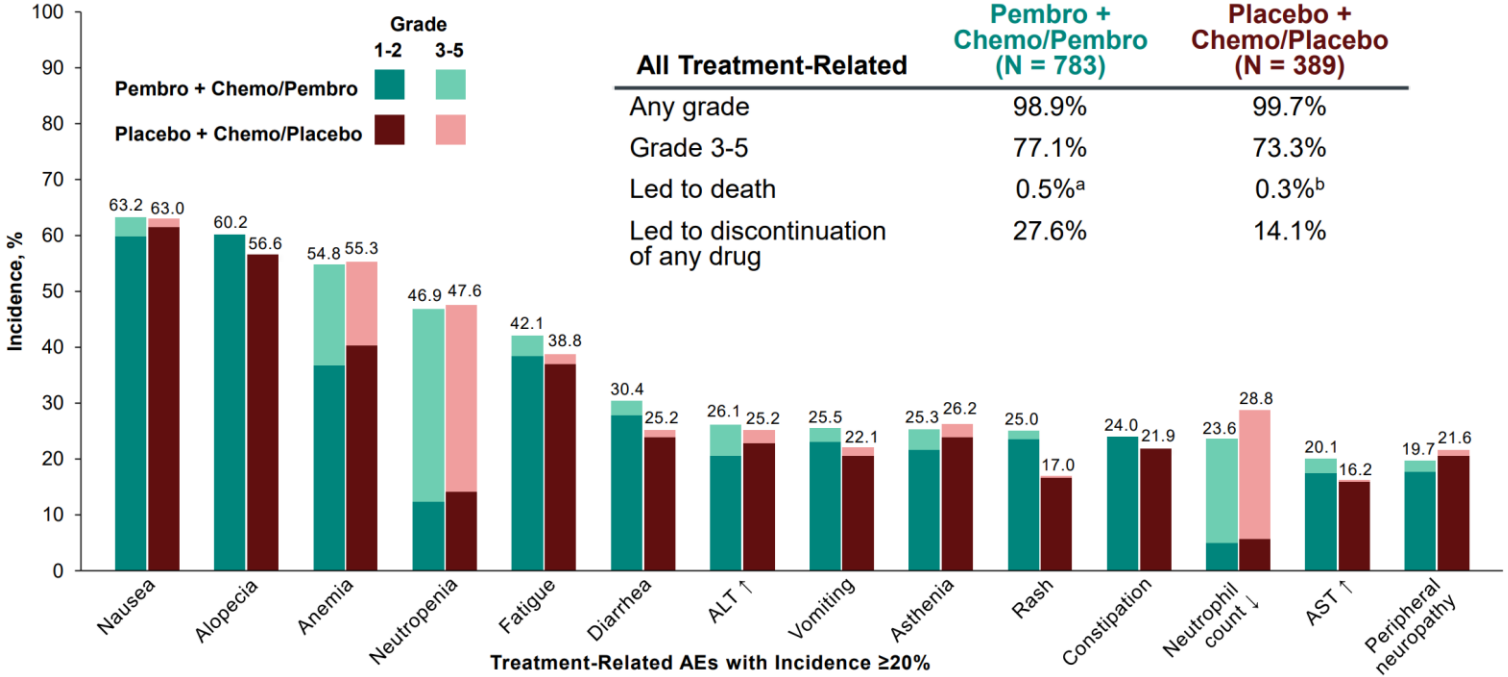
Schmid P et al. ESMO 2024

Overall Survival by Pathologic Complete Response (yp T0/Tis ypN0)



Schmid P et al. ESMO 2024

Treatment-Related Adverse Events



All Treatment-Related	Pembro + Chemo/Pembro (N = 783)	Placebo + Chemo/Placebo (N = 389)
Any grade	98.9%	99.7%
Grade 3-5	77.1%	73.3%
Led to death	0.5%[a]	0.3%[b]
Led to discontinuation of any drug	27.6%	14.1%

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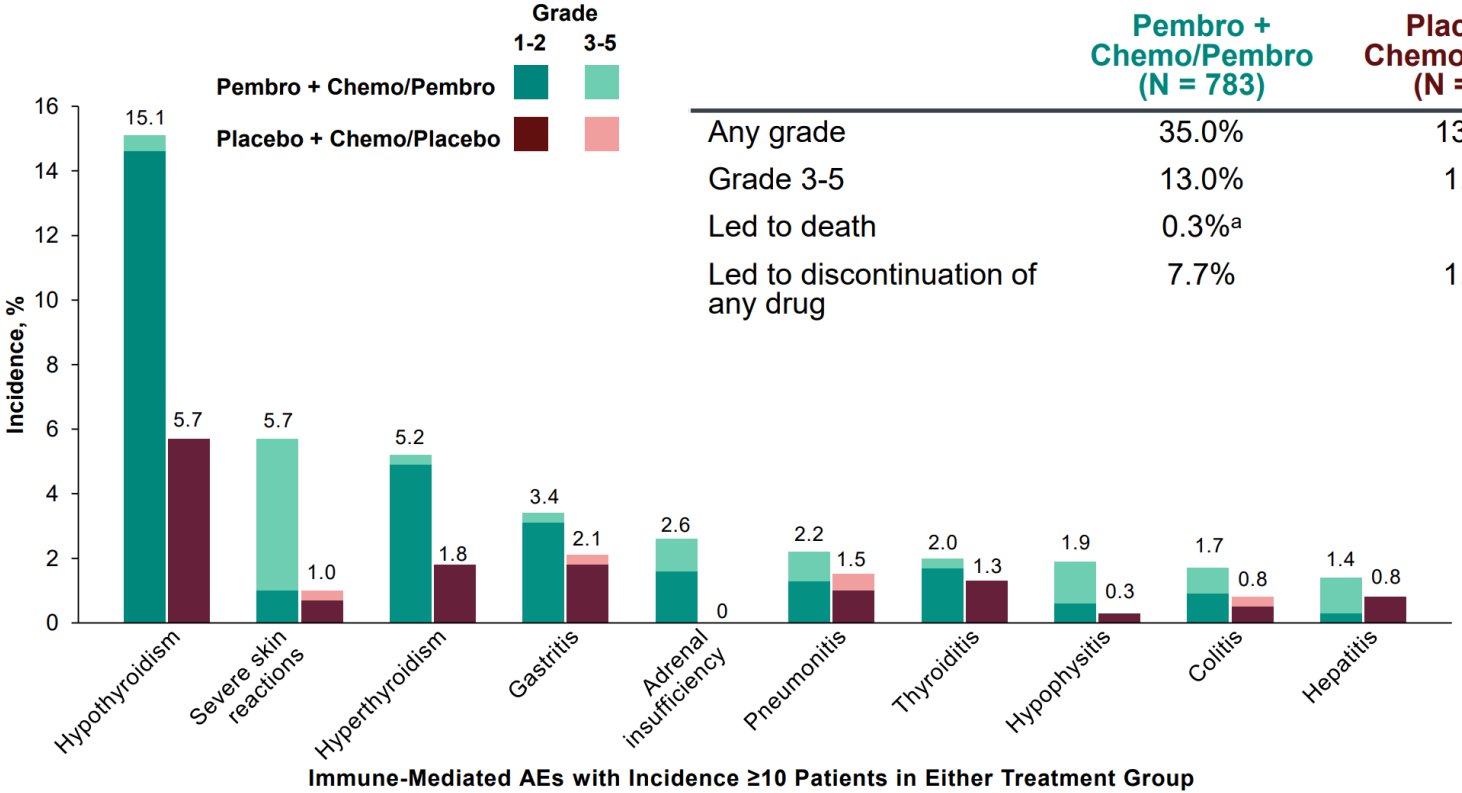
Immune-Mediated Adverse Events



Immune-Mediated AEs with Incidence ≥10 Patients in Either Treatment Group

	Pembro + Chemo/Pembro (N = 783)	Placebo + Chemo/Placebo (N = 389)
Any grade	35.0%	13.1%
Grade 3-5	13.0%	1.5%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	7.7%	1.0%

Schmid P et al: ESMO 2024

Real-world safety and effectiveness of neoadjuvant chemotherapy combination with pembrolizumab in triple-negative breast cancer

Table 3. All-grade adverse events: highest grade per patient (CTCAE v5.0)

Adverse event	Grade 1-2 *n* (%)	Grade 3-5 *n* (%)
Fatigue	67 (67)	1 (1)
Nausea	56 (56)	7 (7)
Neutropenia	8 (8)	52 (52)
Anemia	30 (30)	22 (22)
Thyroid dysfunction	29 (29)	0
Thrombocytopenia	9 (9)	21 (21)
Peripheral neuropathy	43 (43)	6 (6)
Rash	24 (24)	6 (6)
Liver function tests elevation	13 (13)	11 (11)
Diarrhea	17 (17)	2 (2)
Isolated troponin increase	17 (17)	0
Hypophysitis	8 (8)	0
Adrenal insufficiency	6 (6)	0
Arthritis	3 (3)	1 (1)
Pneumonitis	2 (2)	0
Hepatitis	2 (2)	8 (8)
Myositis	5 (5)	0
Myocarditis	3 (3)	1 (1)
Sarcoidosis	2 (3)	0
Acute kidney injury	2 (2)	1 (1)
Diabetic ketoacidosis	0	2 (2)

Rached L et al. ESMO Open 2024

Real-world safety and effectiveness of neoadjuvant chemotherapy combination with pembrolizumab in triple-negative breast cancer

Table 2. Dose modifications and treatment exposure in the neoadjuvant setting

Total number ($n = 100$)	*n* (%)
Dose reduction of any drug	50 (50)
All drugs interruption	36 (36)
Dose omissions (≥ 3)	21 (21)
Patients who received >75% of planned dose for paclitaxel–carboplatin	85 (85)
Patients who received >75% of planned dose for epirubicin–cyclophosphamide ($n = 82$)	78 (95)
Patients who received >75% of planned dose for neoadjuvant pembrolizumab	69 (69)
Early interruption of all treatments for toxicity	35 (35)

Rached L et al. ESMO Open 2024

La neoadyuvancia en CMTN ≥ cT2 y/o cN+

cT2 (> 20 mm) y/o cN+

↓

Tratamiento neoadyuvante

↓

QTNA + inmunoterapia

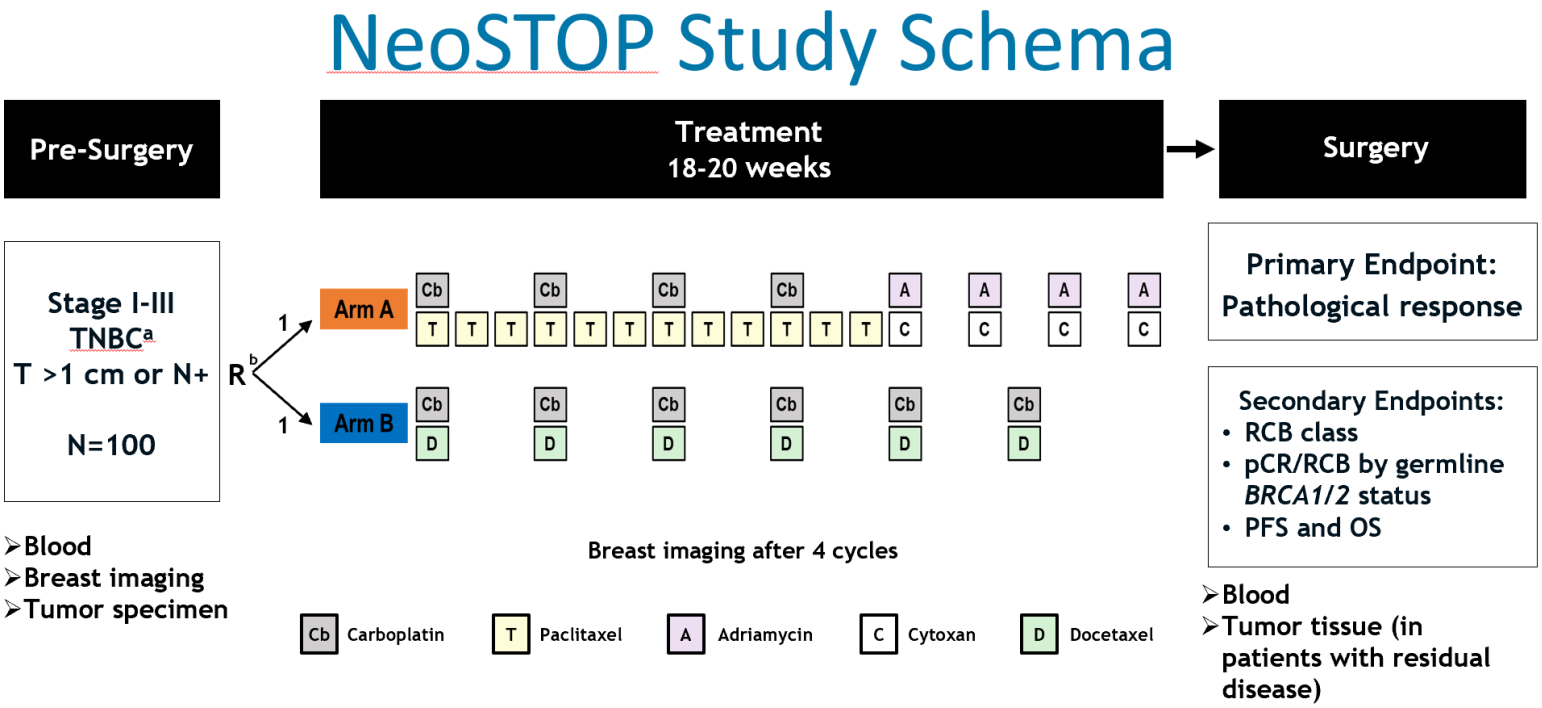
Carboplatino- taxol x 12 → AC x 4 + Pembrolizumab

¿?

¿Podemos identificar pacientes que no se benefician de pembrolizumab?

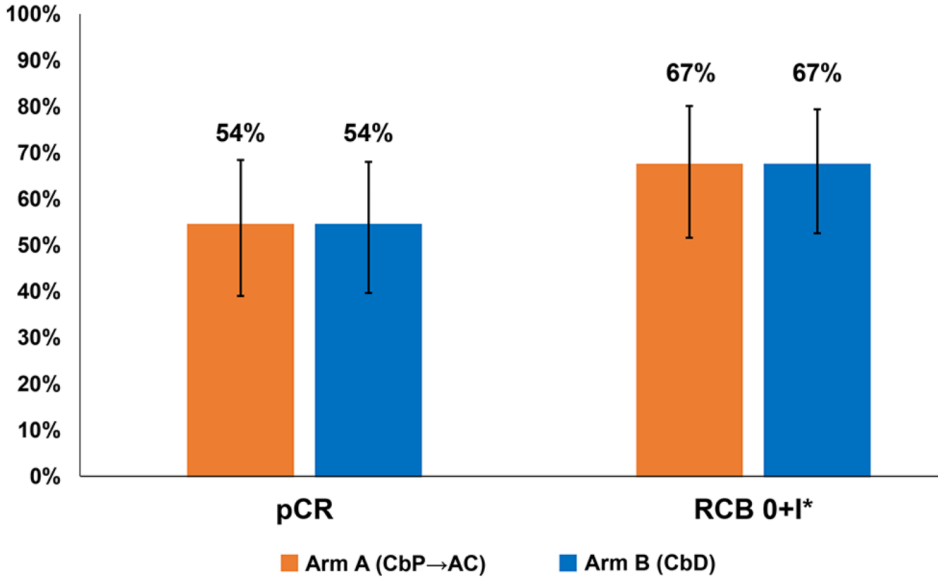
¿Esquemas de QTNA sin antraciclinas?

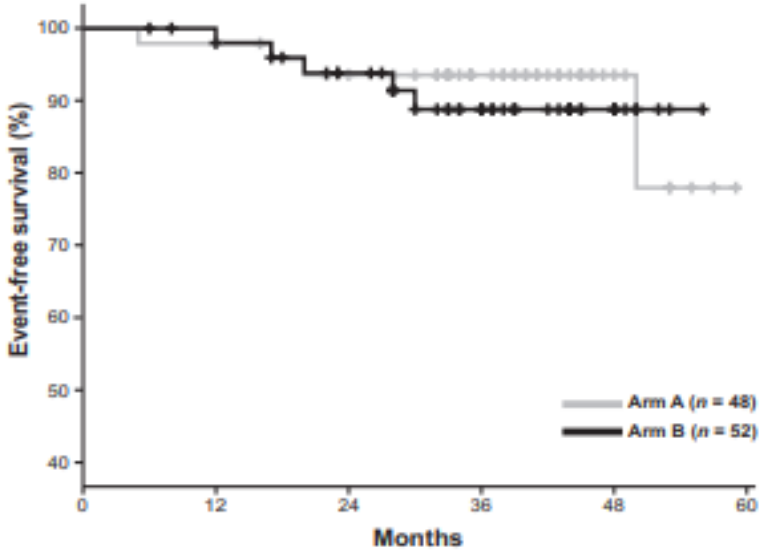
Esquemas sin antraciclinas: Carbo-Taxol → AC vs TCb



Sharma P et al. ASCO 2019. Sharma P et al. Clin Cancer Res 2021

Esquemas sin antraciclinas: eficacia equiparable, menor toxicidad





Sin diferencias en pCR ni SLE

Sharma P et al. ASCO 2019. Sharma P et al. Clin Cancer Res 2021

Esquemas sin antraciclinas: eficacia equiparable, menor toxicidad

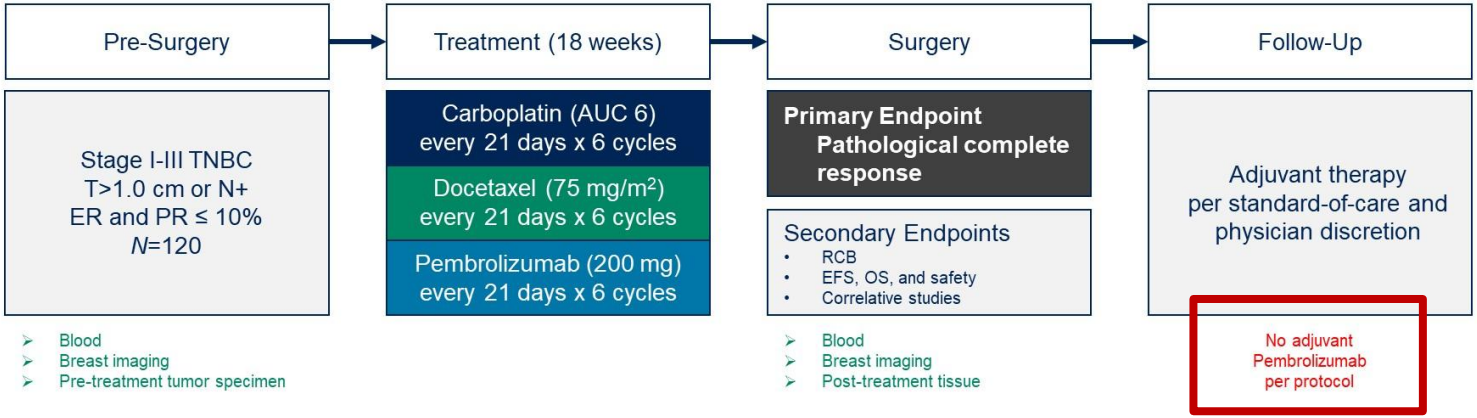
Grade 3 and 4 Treatment Related Toxicities

Adverse Events	Arm A – N (%)	Arm B – N (%)	*p*
Anemia	22 (46%)	2 (4%)	0.0001
Arthralgia	0	0	1
Constipation	1 (2%)	0	0.48
Diarrhea	1 (2%)	4 (8%)	0.36
Fatigue	1 (2%)	0	0.48
Febrile neutropenia	9 (19%)	0	0.0001
Hypokalemia	2 (4%)	1 (2%)	0.61
Hyponatremia	2 (4%)	1 (2%)	1
Nail changes	0	0	1
Nausea	1 (2%)	0	0.48
Neutrophil count decrease	29 (60%)	4 (8%)	0.0001
Pain	1 (2%)	1 (2%)	1
Peripheral sensory neuropathy	2 (4%)	0	0.23
Platelet count decrease	8 (17%)	2 (4%)	0.05
Rash	0	2 (4%)	0.50
Sepsis	2 (4%)	0	0.23
Urinary Tract Infection	1 (2%)	0	0.48
Vomiting	0	0	1

AE G3-4 73% vs 21%

Sharma P et al. ASCO 2019. Sharma P et al. Clin Cancer Res 2021

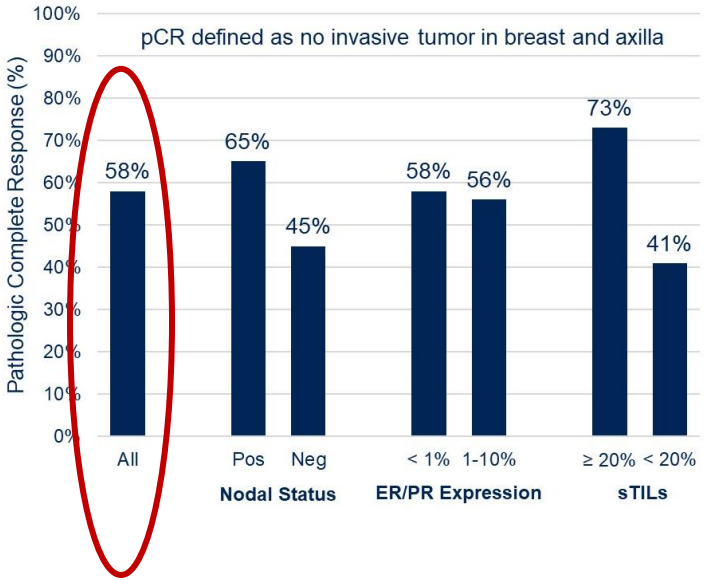
NeoPACT: Neoadjuvant Phase II Study of Pembrolizumab and Carboplatin Plus Docetaxel in Triple-Negative Breast Cancer (NCT03639948)

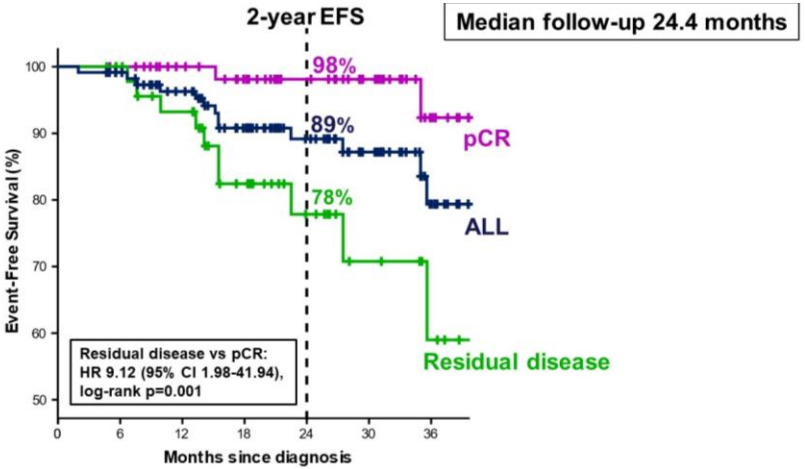


Sharma, Stecklein et al ASCO 2022 (Abstract #513)

PRESENTED BY: Shane Stecklein, MD, PhD

NeoPACT



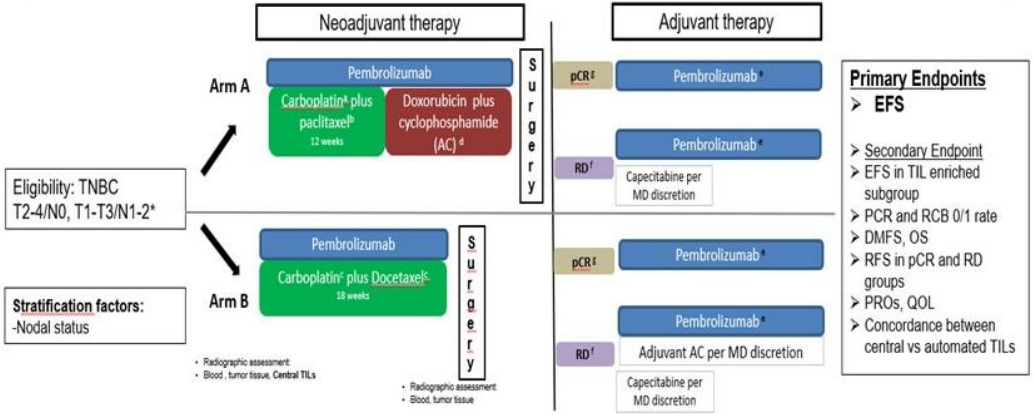


Stecklein S et al. ASCO 2023

Shorter anthracycline-free Chemoimmunotherapy Adapted to pathological Response in Early TNBC (SCARLET)

Randomized non-inferiority trial

Hypothesis: In patients with early stage TNBC, carboplatin-taxane chemoimmunotherapy is non-inferior to taxane-platinum-anthracycline-based chemoimmunotherapy



*T4/N+ , any N3 and inflammatory breast cancer excluded
[a]Carboplatin QW or Q 3W, [b] Paclitaxel QW.
[c] Carboplatin Q3W, Docetaxel Q 3W, [d] AC every 2 or 3 weeks
[e] Total duration of neo plus adjuvant pembrolizumab = 51 weeks
[f] Olaparib per MD discretion in gBRCA allowed
[g] No Further Adjuvant chemotherapy.

PI: P. Sharma and Z. Mitri

SWOG CANCER RESEARCH NETWORK

La neoadyuvancia en CMTN ≥ cT2 y/o cN+

cT2 (> 20 mm) y/o cN+

↓

Tratamiento neoadyuvante

↓

QTNA + inmunoterapia

Carboplatino- taxol x 12 → AC x 4 + Pembrolizumab

¿Podemos identificar pacientes que no se benefician de pembrolizumab?

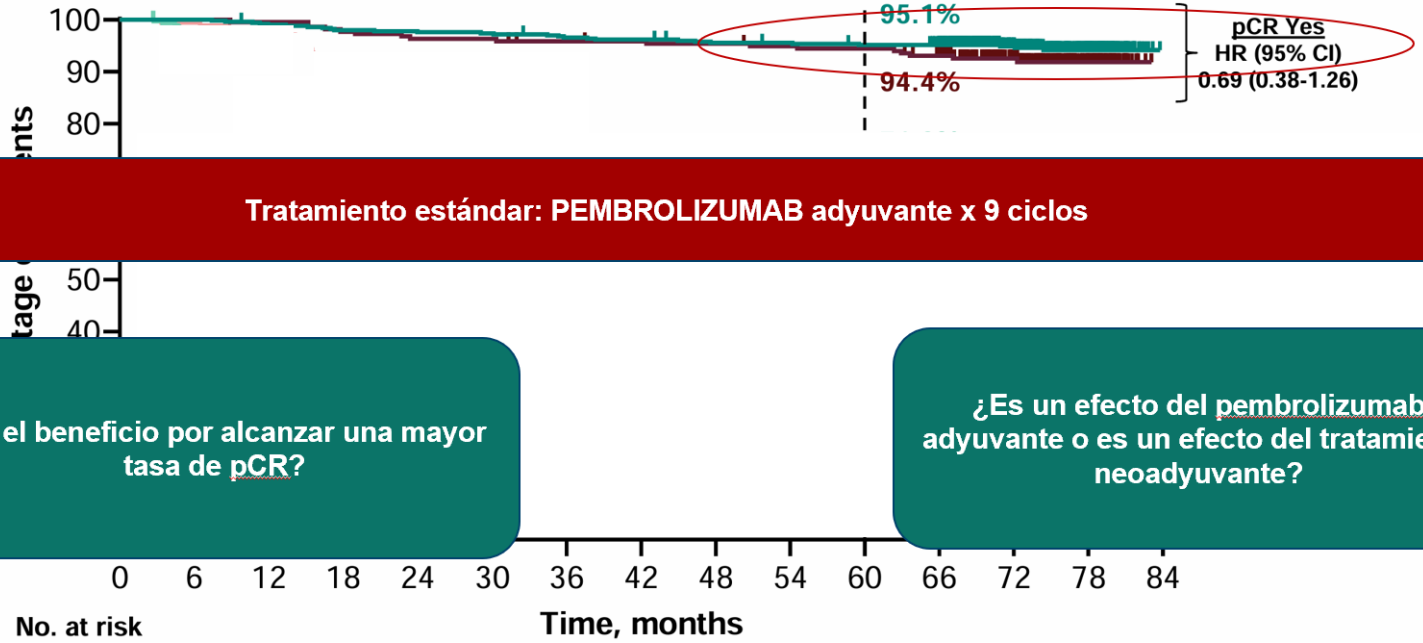
¿?

¿Esquemas de QTNA sin antraciclinas?

¿Valor de pembrolizumab adyuvante si pCR?

HOTEL MELIÁ CASTILLA

Overall Survival by Pathologic Complete Response (yp T0/Tis ypN0)



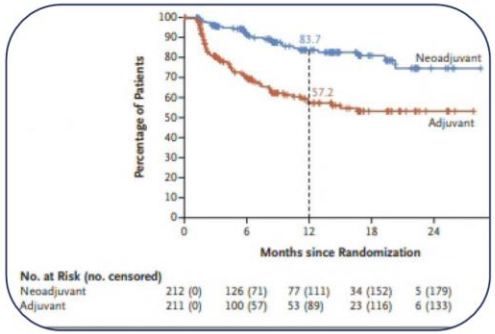
Tratamiento estándar: PEMBROLIZUMAB adyuvante x 9 ciclos

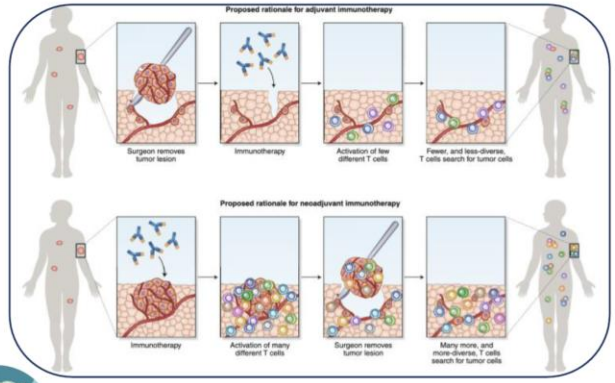
¿Es el beneficio por alcanzar una mayor tasa de pCR?

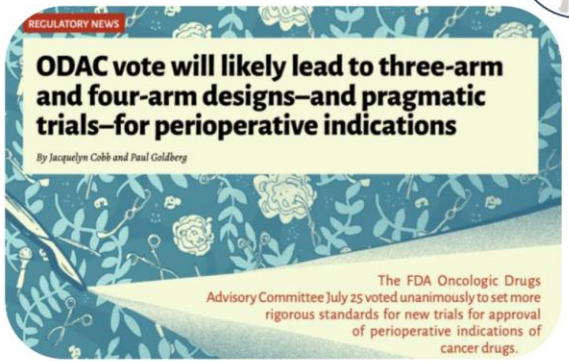
¿Es un efecto del pembrolizumab adyuvante o es un efecto del tratamiento neoadyuvante?

Pusztai L et al. Ann Oncol 2024. Schmid P et al. ESMO 2024

2. Neoadjuvant vs adjuvant part: contribution of components







2 academic non-inferiority trials for pts with pCR. Adjuvant pembro vs no adjuvant treatment

1) OptimICE-pCR, 270/1956 recruited
PI: Sara Tolaney (DFCI, USA)

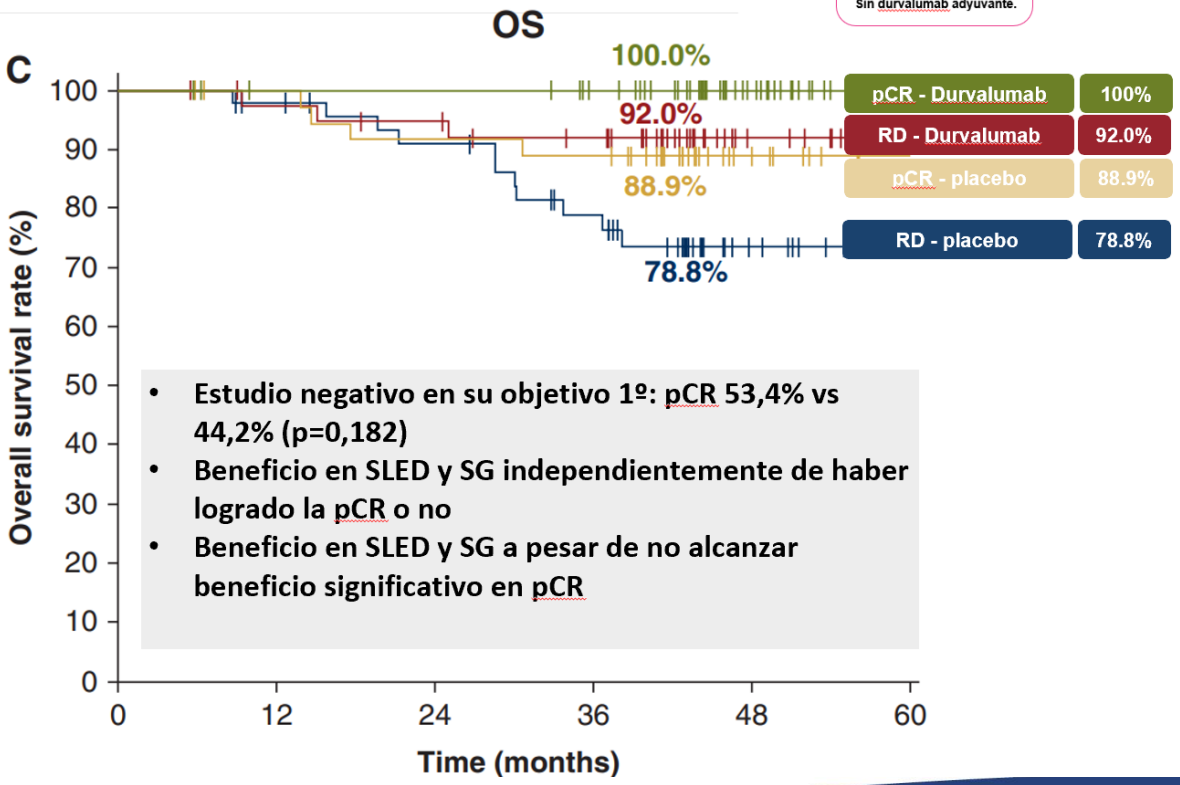
2) OPT-PEMBRO, n=2454, start Q4 '24
PI: Joana Ribeiro (IGR, France)

Versluis et al. Nat Med 2020, Blank et al. NEJM 2024, www.cancerletter.com

¿Efecto en SG del ICI adyuvante post-neoadyuvante?

Gepar Nuevo

Sin durvalumab adyuvante.



- Estudio negativo en su objetivo 1º: pCR 53,4% vs 44,2% (p=0,182)
- Beneficio en SLED y SG independientemente de haber logrado la pCR o no
- Beneficio en SLED y SG a pesar de no alcanzar beneficio significativo en pCR

Loibl S et al. Ann Oncol 2019. ASCO 2021

34% irAEs ocurrieron durante la fase adyuvante

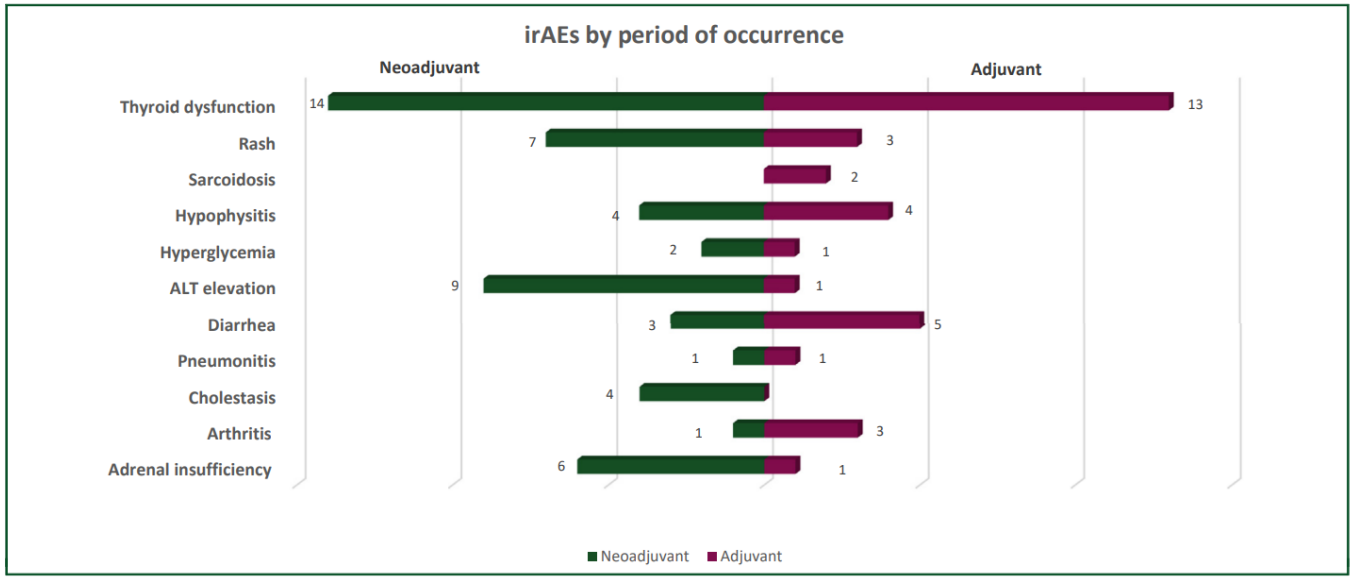
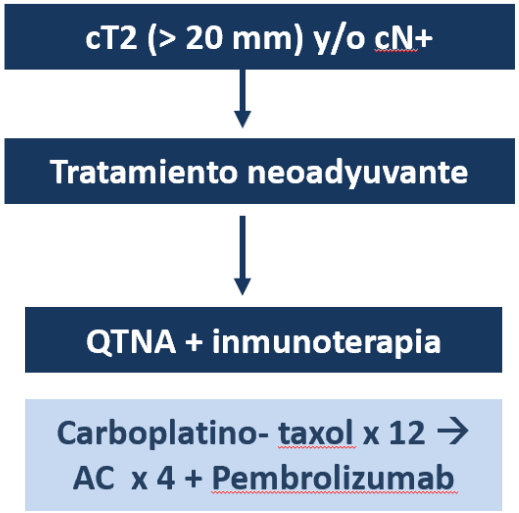


Figure 2. irAEs by period of occurrence. Comparison of irAEs occurring in two periods: the neoadjuvant period (left) and the adjuvant period (right). Numbers and bar sizes represent the count of these adverse events in each respective period.
ALT, alanine aminotransferase; irAEs, immune-related adverse events.

Rached L et al. ESMO Open 2024

La neoadyuvancia en CMTN ≥ cT2 y/o cN+



¿Podemos identificar pacientes que no se benefician de pembrolizumab?

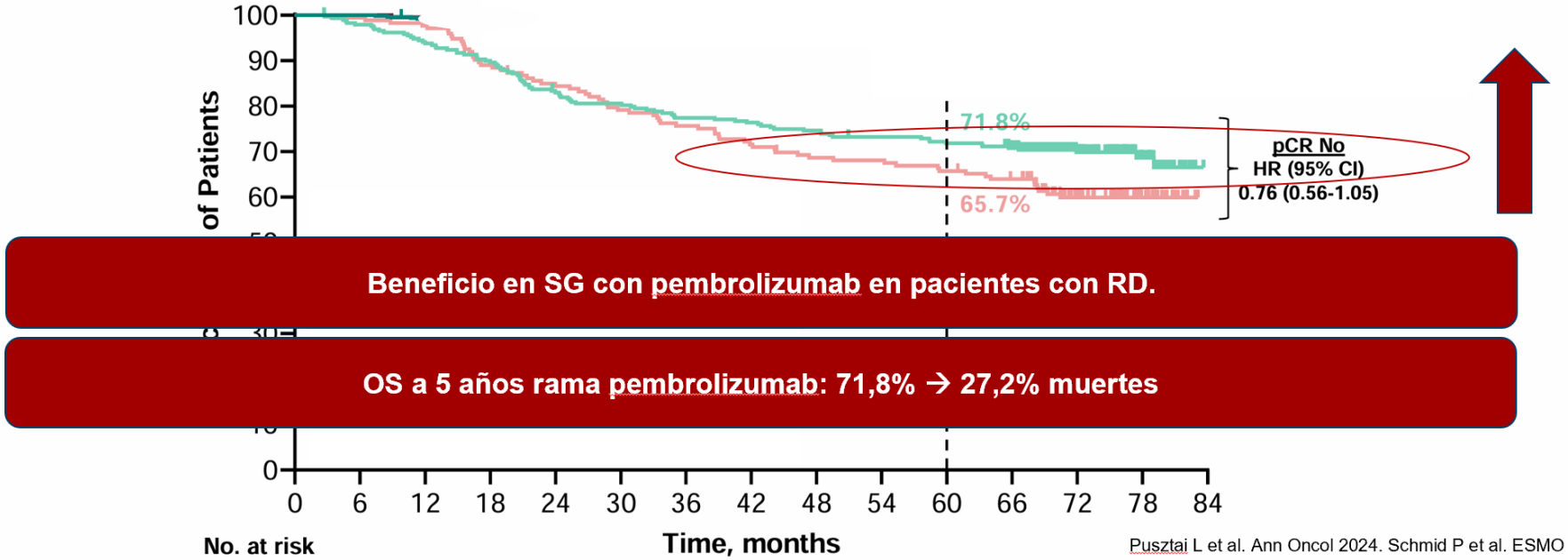
¿Esquemas de QTNA sin antraciclinas?

¿Cómo podemos mejorar el pronóstico de las pacientes con RD?

¿Valor de pembrolizumab adyuvante si pCR?

Enfermedad residual

Overall Survival by Pathologic Complete Response (yp T0/Tis ypN0)



Beneficio en SG con pembrolizumab en pacientes con RD.

OS a 5 años rama pembrolizumab: 71,8% → 27,2% muertes

Pusztai L et al. Ann Oncol 2024. Schmid P et al. ESMO 2024

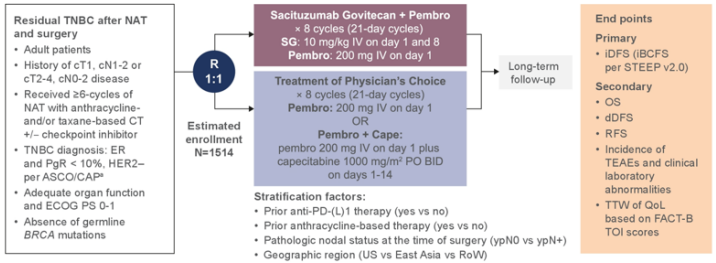
Estrategias de combinación: CAPECITABINA + PEMBROLIZUMAB

ADCs

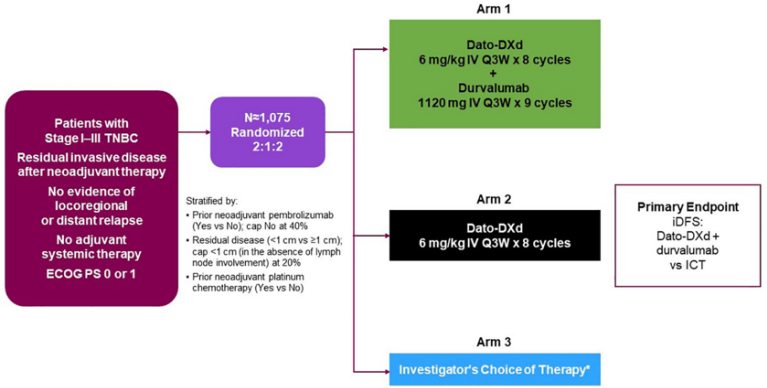
iPARP

ASCENT-05/OptiImICE-RD

Figure 2. An open-label, global, multicenter, randomized phase 3 study of adjuvant SG combined with pembro versus TPC in patients with TNBC and RD after neoadjuvant therapy and surgery (NCT05633654)



TROPION-Breast03



Tolaney S et al. SABCS 2023. Tolaney S et al. ASCO 2023. Bardia A et al. SAGE 2024

CONCLUSIONES

- QT + pembrolizumab aumenta la pCR, SLE y SG de las pacientes con CMTN

- Nuevo estándar de tratamiento en CMTN ≥ cT2 y/o N+

- Varias preguntas aún sin responder:
  - ¿Podemos simplificar el esqueleto de QT?
  - Esquemas sin antraciclinas podrían ser una opción alternativa al esquema KEYNOTE

  - ¿Es necesario el pembrolizumab adyuvante?
  - Pendientes del OPTIMICE-pCR

  - Necesidad de mejorar el pronóstico de las pacientes con enfermedad residual extensa tras QTNA-ICI