II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025

PAPEL DE LA INMUNOTERAPIA EN CÁNCER DE MAMA

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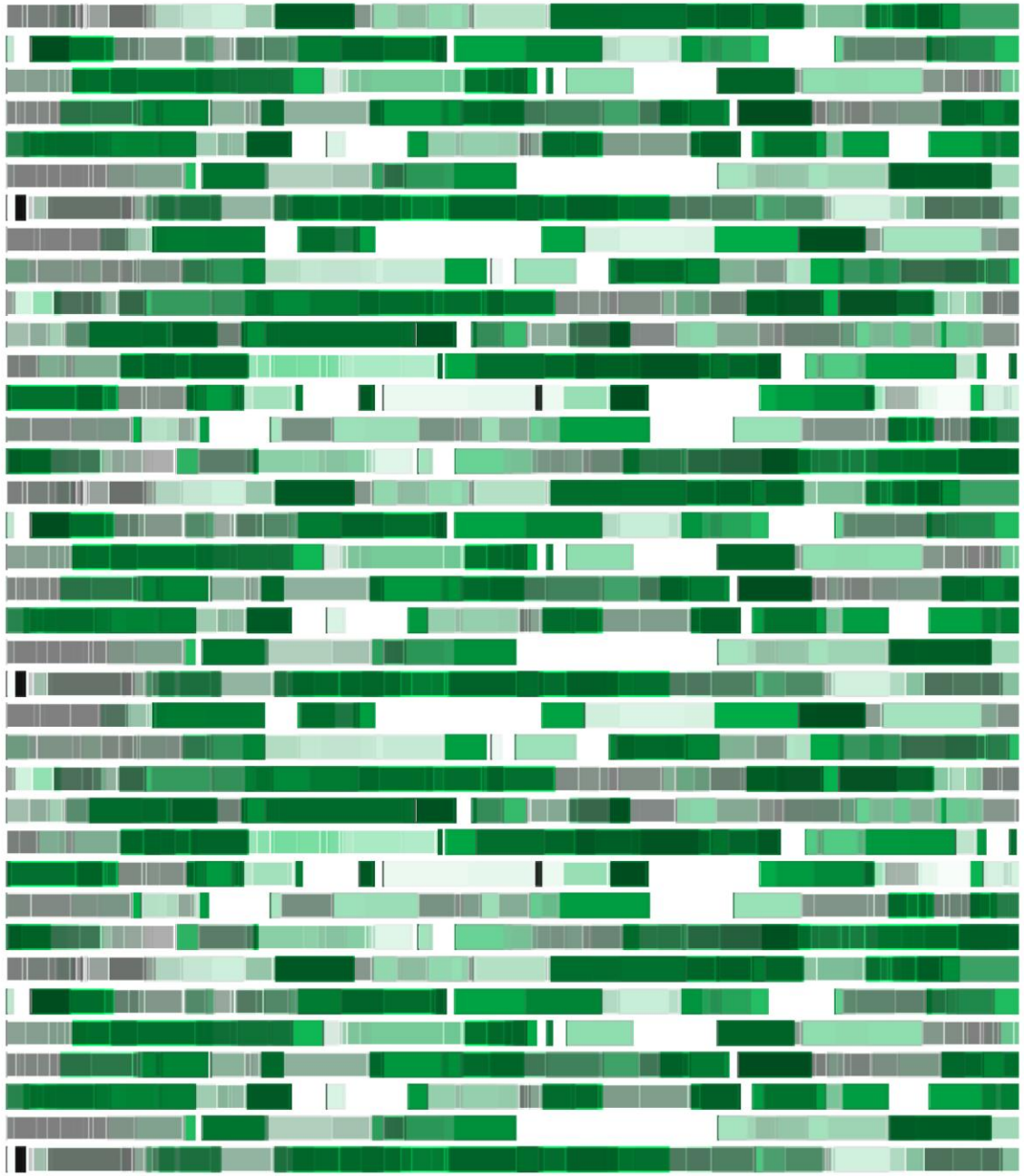
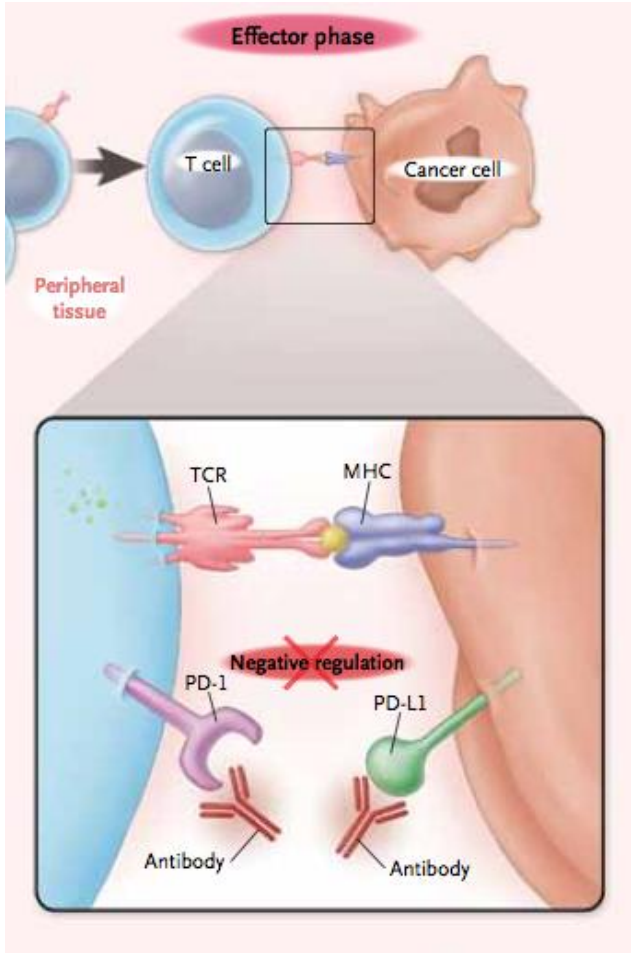
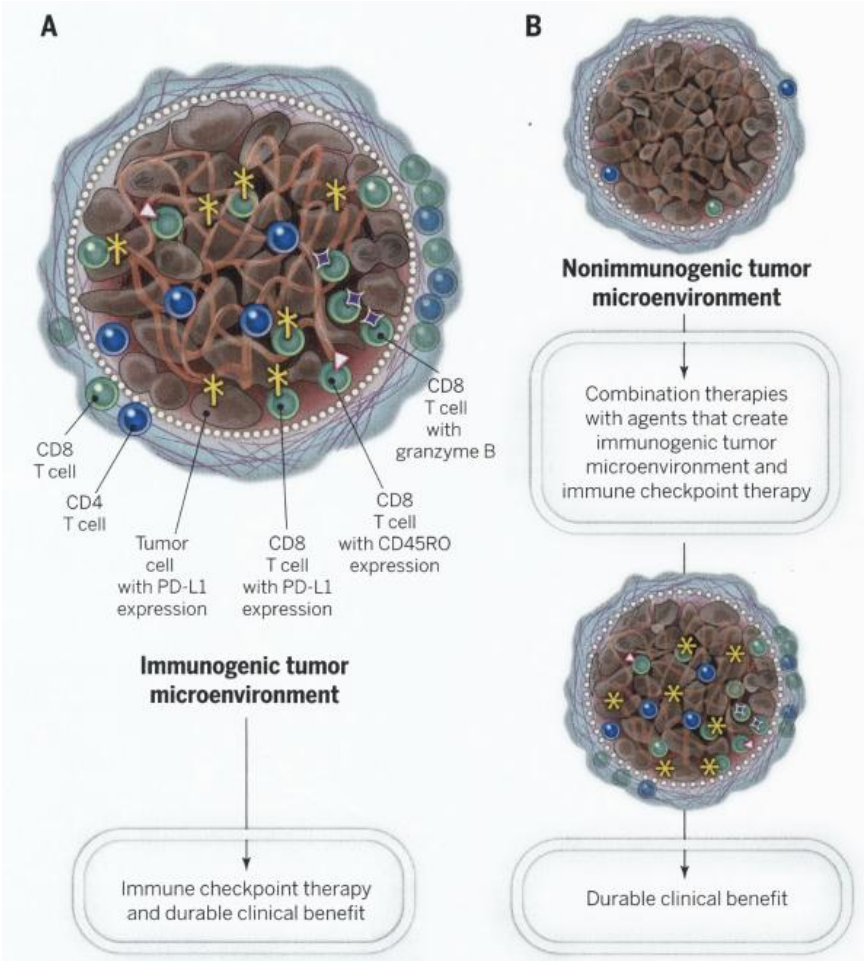
Hospital Universitario Virgen Macarena. Sevilla.

Servicio de Oncología Médica



LA ERA DE LA INMUNOTERAPIA EN ONCOLOGÍA





Sharma P, Allison JP. Science. 2015;348(6230):56-61
Ribas A. N Engl J Med. 2012;366(26):2517-9

APROBACIONES ACTUALES DE INMUNOTERAPIA EN CÁNCER DE MAMA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, T. Foukakis, P.A. Fasching, F. Cardoso, M. Untch, L. Jia, V. Karantza, J. Zhao, G. Aktan, R. Dent, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer

J. Cortes, H.S. Rugo, D.W. Cescon, S.-A. Im, M.M. Yusof, C. Gallardo, O. Lipatov, C.H. Barrios, J. Perez-Garcia, H. Iwata, N. Masuda, M. Torregroza Otero, E. Gokmen, S. Loi, Z. Guo, X. Zhou, V. Karantza, W. Pan, and P. Schmid, for the KEYNOTE-355 Investigators*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The NEW ENGLAND JOURNAL of MEDICINE

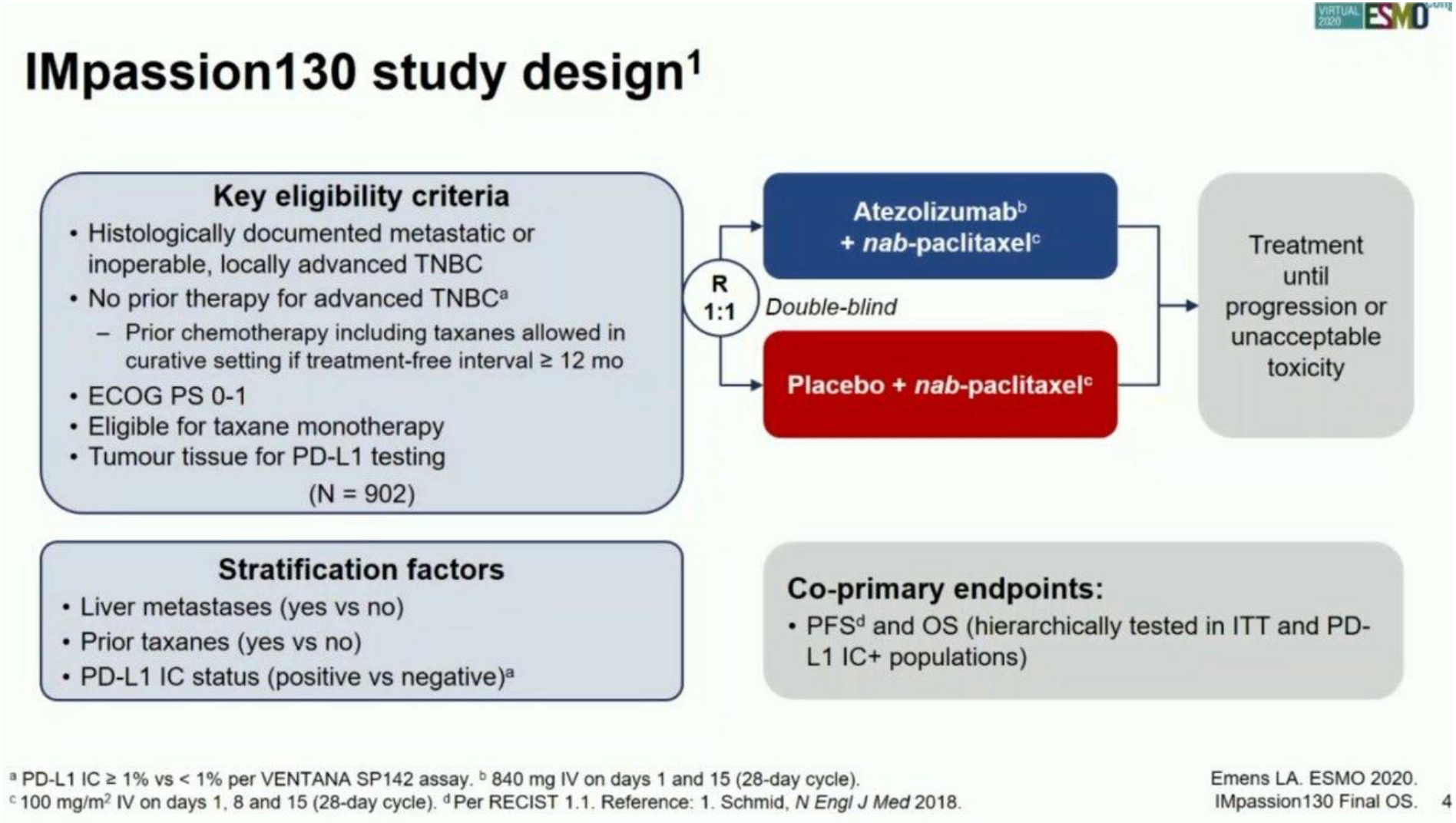
ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Trial Investigators*

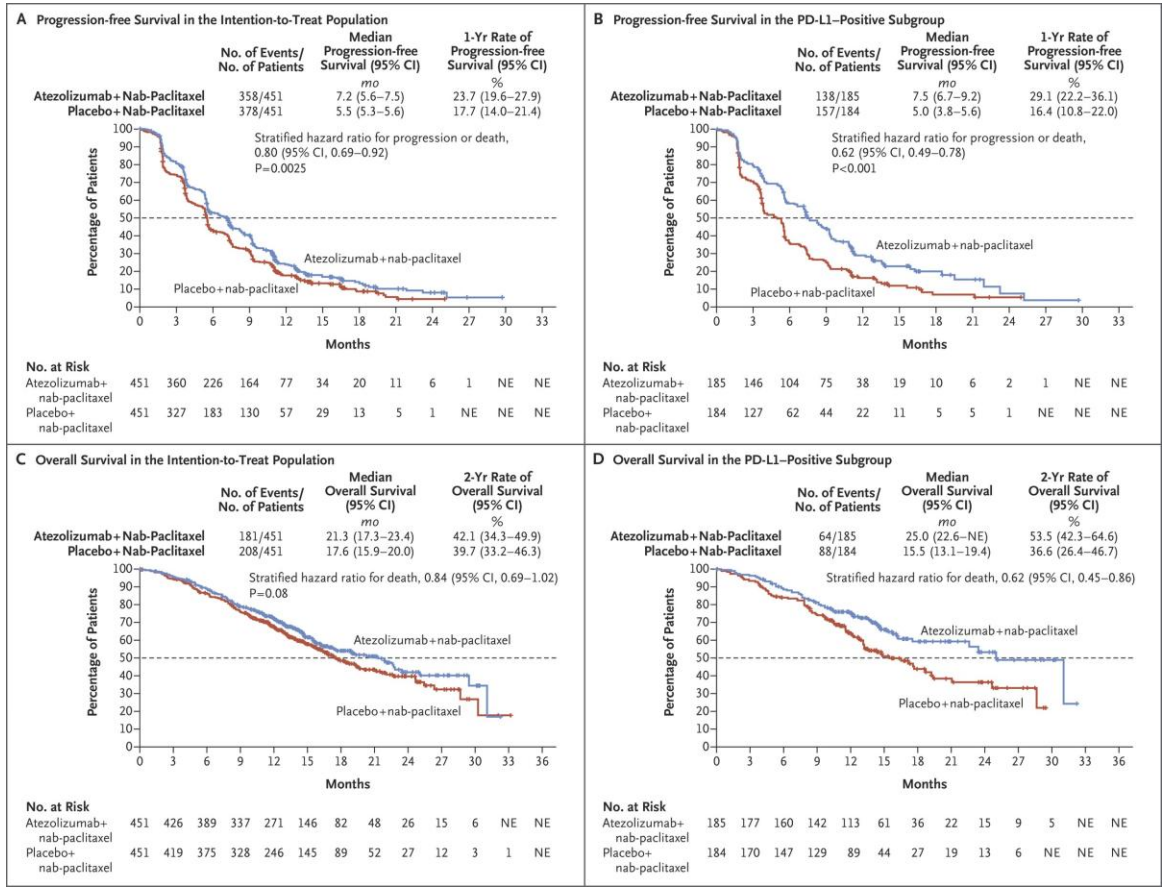
ENFERMEDAD METASTÁSICA

IMPASSION 130



RESULTADOS IMPASSION 130

La adición de Atezolizumab a Nab-Paclitaxel en primera línea para pacientes con CMMTN incrementa la SLP y la SG especialmente en pacientes con tumores PDL1+



OS PDL-1:
25.0 vs 15.5

Schmid P et al. N Engl J Med 2018;379:2108-2121

KEYNOTE 355

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease

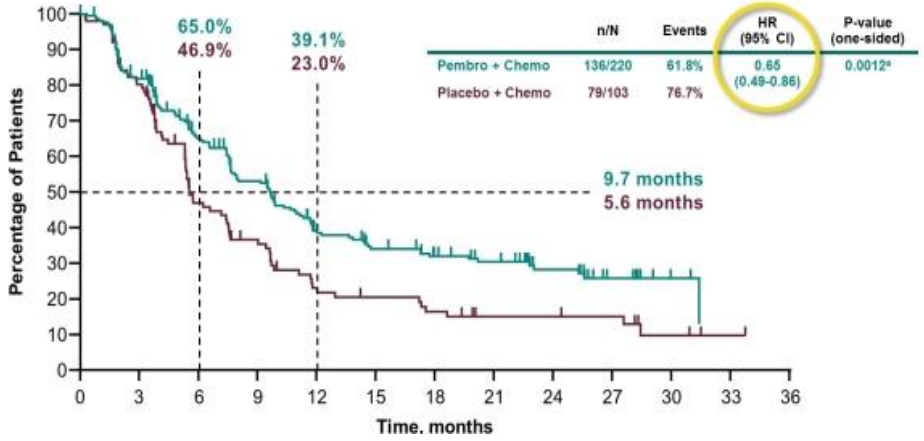
R 2:1

- Pembrolizumab[a] + Chemotherapy[b]
- Placebo[c] + Chemotherapy[b]

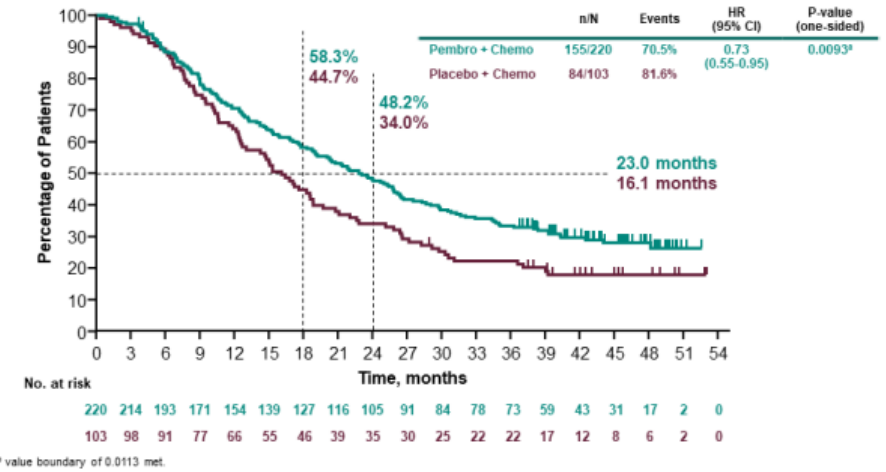
→ Progressive disease[d]/cessation of study therapy

Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

Progression-Free Survival: PD-L1 CPS ≥10



Overall Survival: PD-L1 CPS ≥10

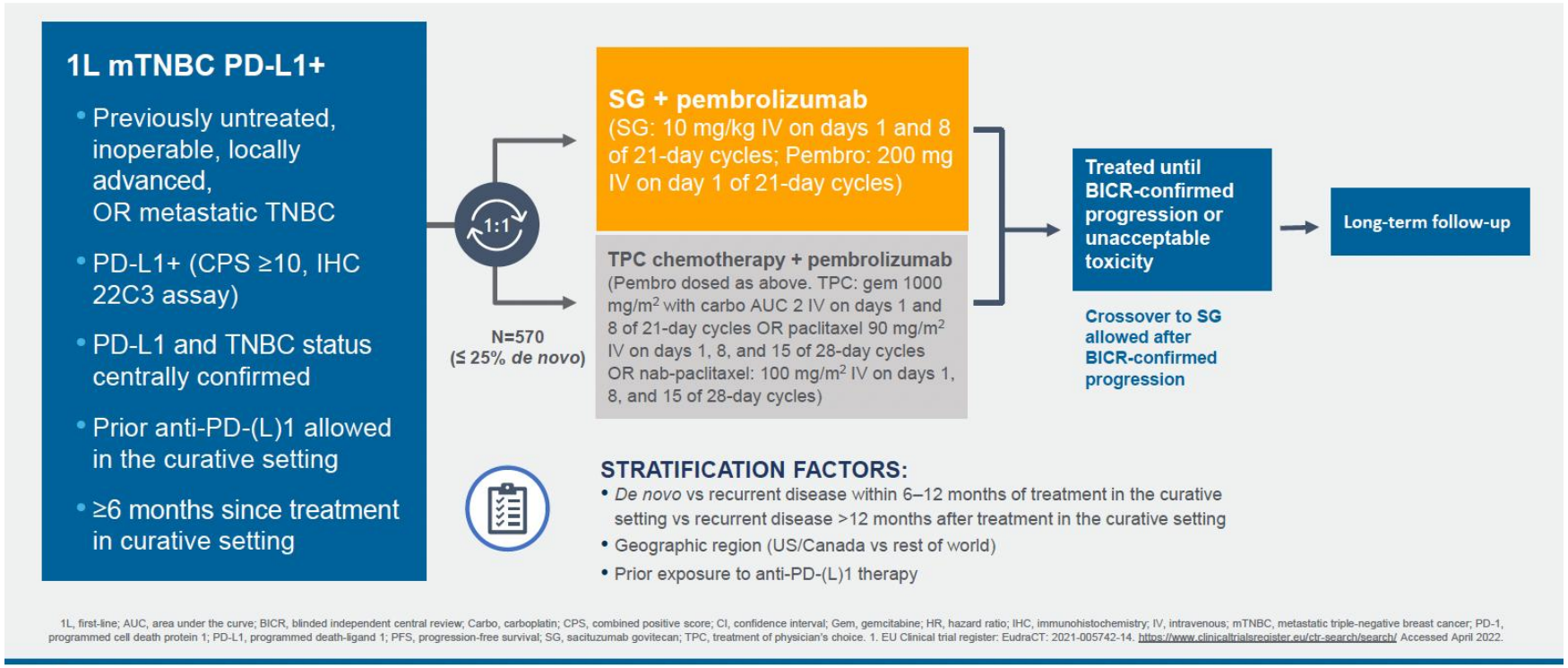


[a]Prespecified *P* value boundary of 0.0113 met.

Cortes J, et al. Lancet. 2020;396(10265):1817-1828.
Cortes J, et al. N Engl J Med. 2022 Jul 21;387(3):217-226.

FUTURO

ASCENT 04: Sacituzumab govitecan + pembrolizumab vs TPC + pembrolizumab in 1L PD-L1+ mTNBC, NCT05382286



1L, first-line; AUC, area under the curve; BICR, blinded independent central review; Carbo, carboplatin; CPS, combined positive score; CI, confidence interval; Gem, gemcitabine; HR, hazard ratio; IHC, immunohistochemistry; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice. 1. EU Clinical trial register: EudraCT: 2021-005742-14. https://www.clinicaltrialsregister.eu/ctr-search/search/ Accessed April 2022.

¿PUEDEN COMBINARSE ADC + INMUNOTERAPIA?

BEGONIA Study Design

- Metastatic TNBC
- No prior treatment for stage IV disease
- ECOG PS 0 -1
- RECIST evaluable
- Patients may have relapsed from earlier stage disease but must be ≥ 12 months since prior taxane treatment
- Arm 6: Locally confirmed HER2 IHC 1-2+ (ISH-)

PART 1

1: Durva + Paclitaxel (n = 20) ✓
2: Durva + Pac + Capivasertib (AKT) (n = 30) ✓
5: Durva + Pac + Oleclumab (CD73) (n = 30) ✓
6: Durva + DS-8201a (T-DXd) (n = 30)
7: Durva + Novel ADC (n=30)

ARMS 2-6:
Safety run-in: 6 DLT evaluable patients for 28 days (Arms 2-5) or 21 days (Arms 6 and 7) with ≤ 1 DLT

ORR ≥ 57% (17/30)

PART 1:
Primary Endpoint: Safety and tolerability
Secondary Endpoint: ORR, PFS, DoR, OS, PK/ADA

PART 2 Expansion (TBD)

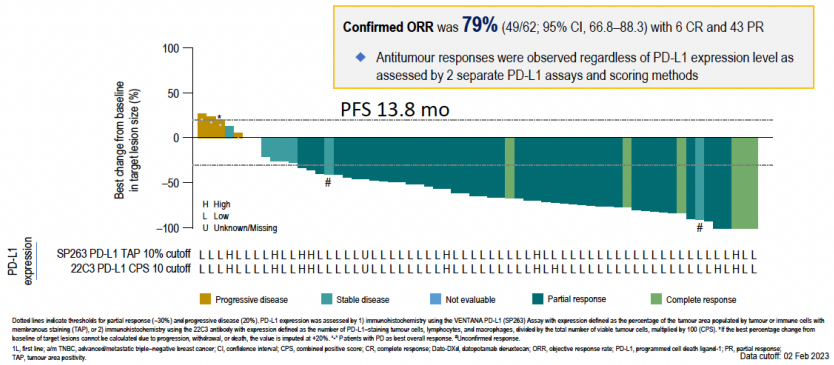
Durva Combination (n = 27)
Durva Combination (n = 27)

PART 2:
Primary Endpoint: ORR
Secondary Endpoint: Safety and tolerability, PFS, DoR, OS, PFS6m

NOTE:
- Arms 3 (Durva + selumetinib + pac) and Arms 4 (Durva + danvatirsen + pac) were removed before patient enrollment
- Part 1 of this study is considered Stage 1 of the Simon 2-Stage design, and Part 2 of this study is considered Stage 2
- Amendment for a new arm (Arm 7) to include a novel combination of durvalumab + a novel ADC (will include HER2-0 patients)

✓ = Enrollment complete; only Arm 6 is open at this time

BEGONIA: Dato-DXd + durvalumab in 1L m TNBC



Schmid P et al. ESMO 2023

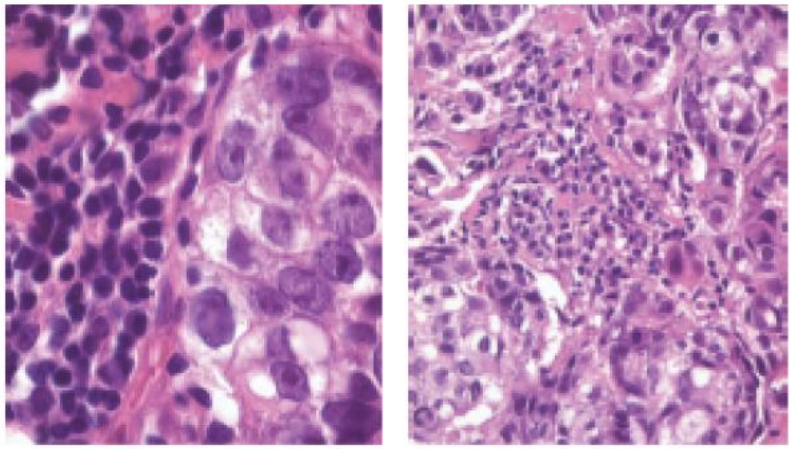
ENFERMEDAD PRECOZ TN

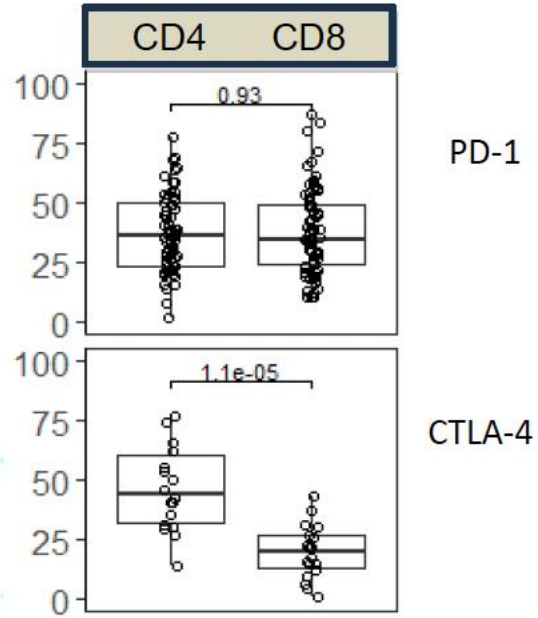
CÁNCER DE MAMA PRECOZ. ¿PORQUÉ USAR INMUNOTERPIA?

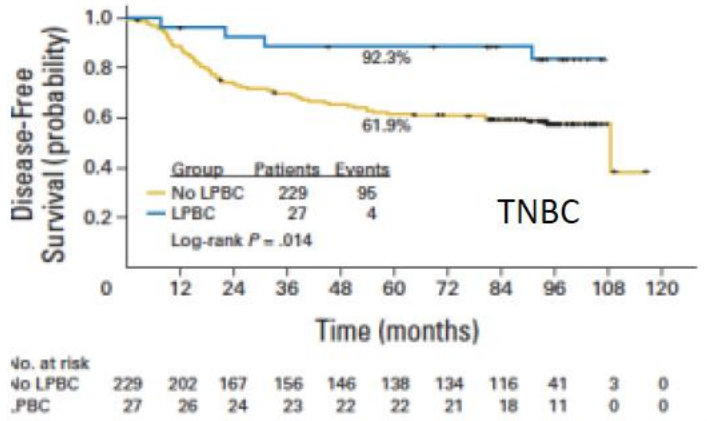
- El cáncer de mama triple negativo en enfermedad localizada normalmente tiene altos niveles de infiltrado inmune (>99%)

- El infiltrado inmunológico comprende células T con alta expresión de PDL-1/CTLA-4 (y baja expresión de otras moléculas de control inmunitario inhibitorias) en todos los subtipos de cáncer de mama.

- La cantidad de infiltrado inmunológico tiene **valor pronóstico:** a mayor cantidad, mejor pronóstico en TNBC tanto enfermedad precoz como avanzada, y en HER2+, pero no en HR+







Savas Nat Med 2019; Loi JCO 2013

Checkpoint Inhibitors in Early TNBC

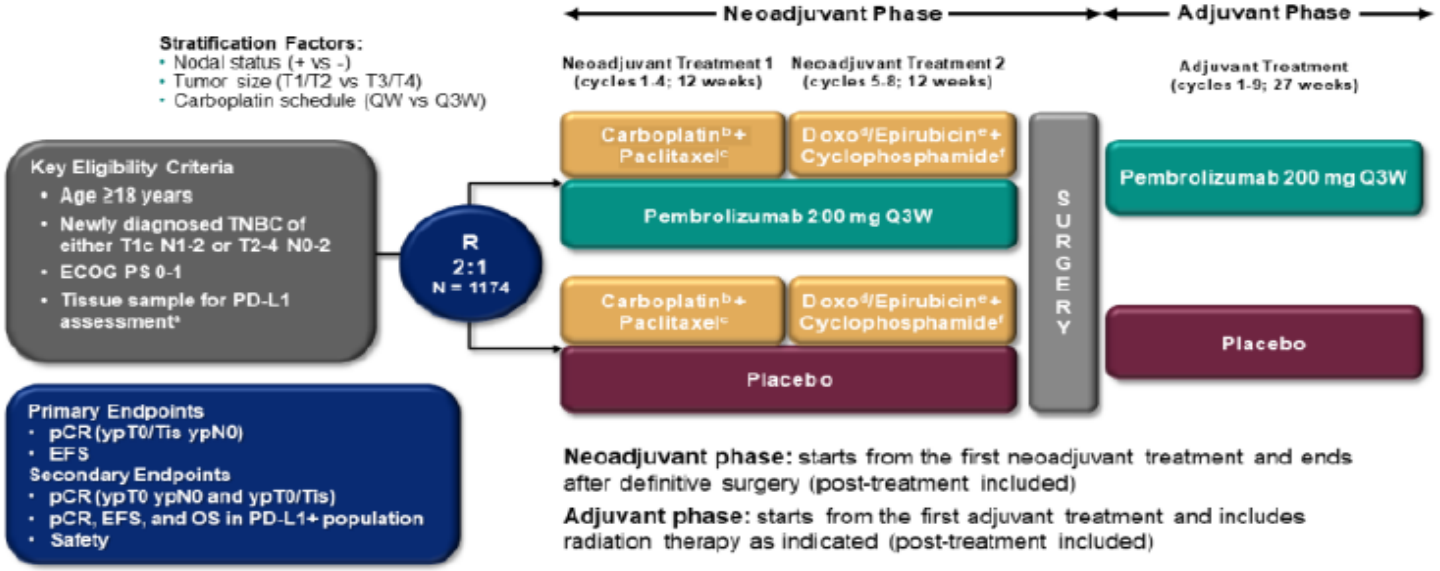
Variable	I-SPY	KEYNOTE-522	IMPASSION 031	NeoTRIP	GeparNUEVO
Total patients	69/180	1174 (602)	333	280	174
Type of CPi	PD1 Pembro x 4	PD1 Pembro x 1 year	PD-L1 Atezo x 1 year	PD-L1 Atezo x 8	PD-L1 Durva x 8
Stage	Stage II/III	Stage II/III	Stage II/III	+ N3 disease	35% stage I
Anthracycline pre-op	yes	yes	yes	No*	yes
Included carboplatin	no	yes	No (nab-pac)	Yes (nab-pac) 2 wks on, 1 wk off x 8	no
Improved pCR	Yes	Yes 51.2 v 64.8% P=0.00055	Yes 41.1 v 57.6% P=0.0044	No	Numeric improvement (44 v 53%, p=0.18)
Improved EFS	NR: pCR>nonpCR	Yes	NR	NR	Yes EFS, DDFS and OS

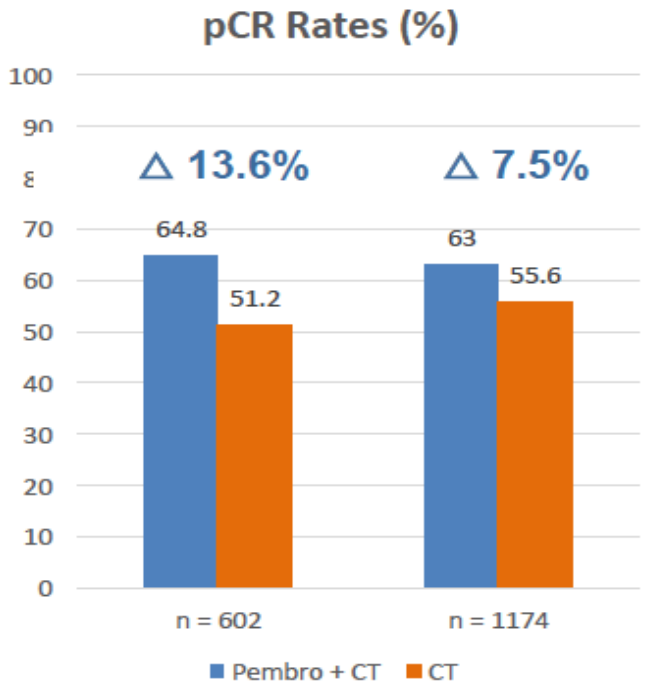
Nanda et al, JAMA Onc 2020; Schmid et al, NEJM 2020 & ESMO Plenary 2021; Mittendorf et al, Lancet 2020; Gianni et al, SABCS 2019; Loibl et al, Ann Oncol 2019 & ASCO 2021

*Callari et al, PD10-09:, SABCS 2021: role of anthracyclines in the modulation of the immune microenvironment

KEYNOTE 522

Pembrolizumab added to neoadjuvant chemotherapy in early TNBC
KEYNOTE-522

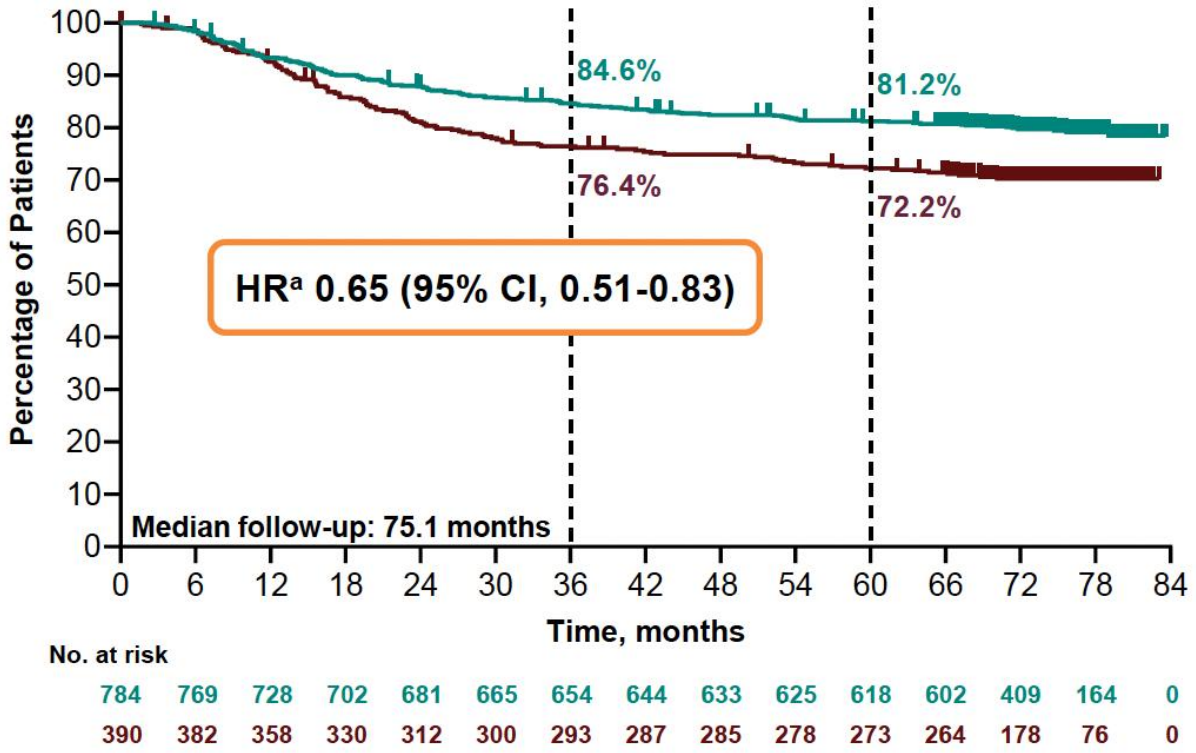




Schmid P,et al. N Engl J Med. 2020;382(9):810-821.
Schmid P, et al. N Engl J Med. 2022;386(6):556-567

Benefit seen regardless of PD-L1 status

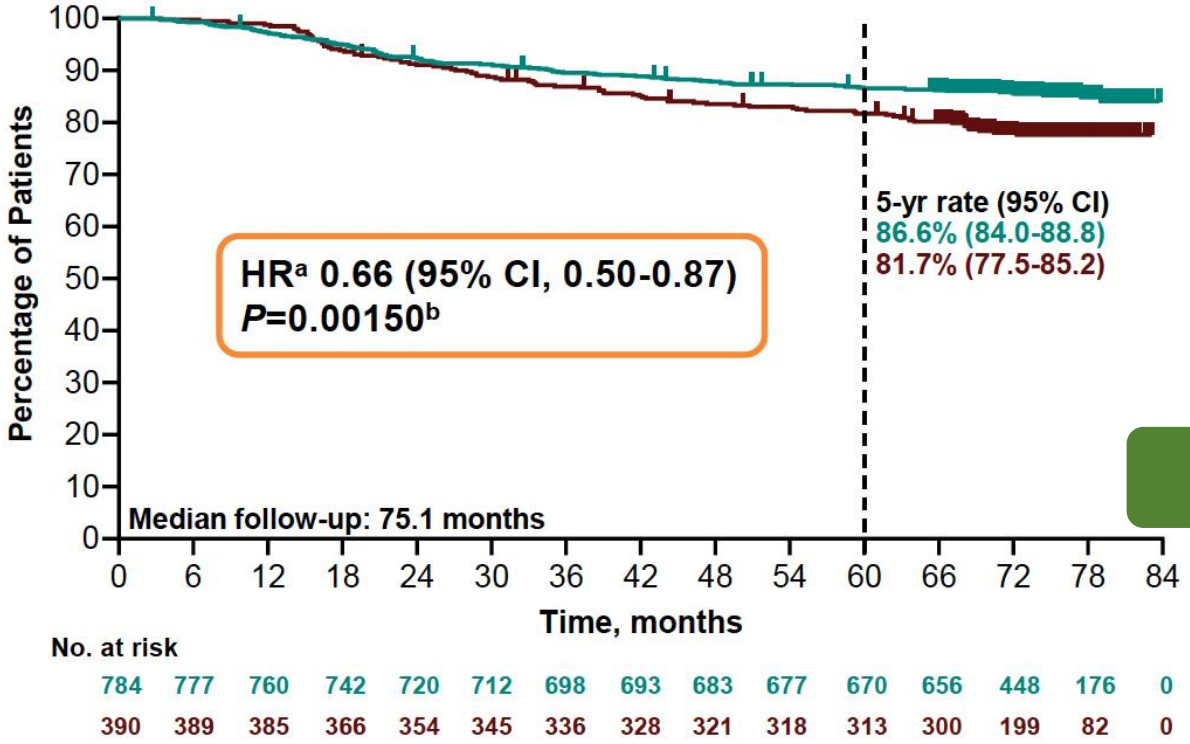
SLP



	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%

P. Schmid ESMO 2024

SG

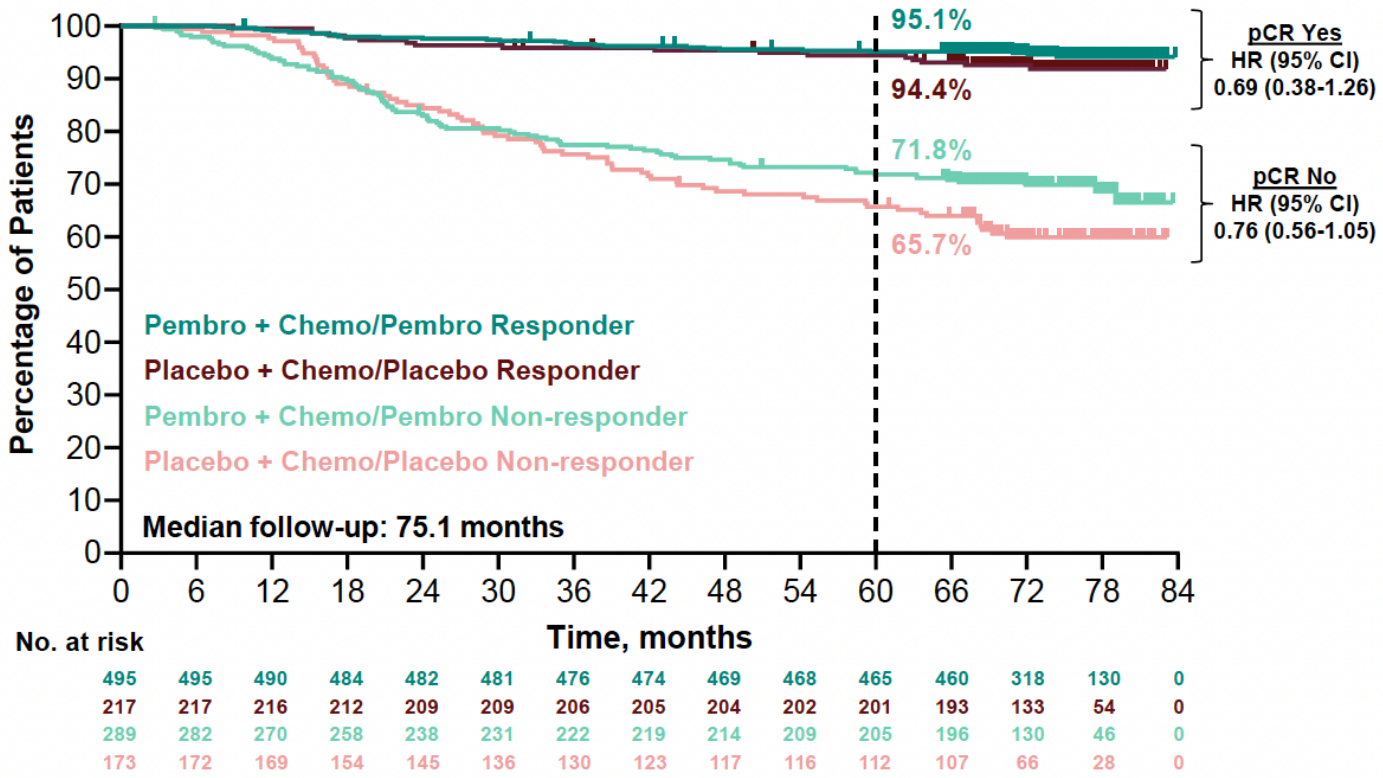


	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

4.9% curadas con pembrolizimab
¿Cómo identificar a esas pacientes?

P. Schmid ESMO 2024

SG SEGÚN LA RESPUESTA



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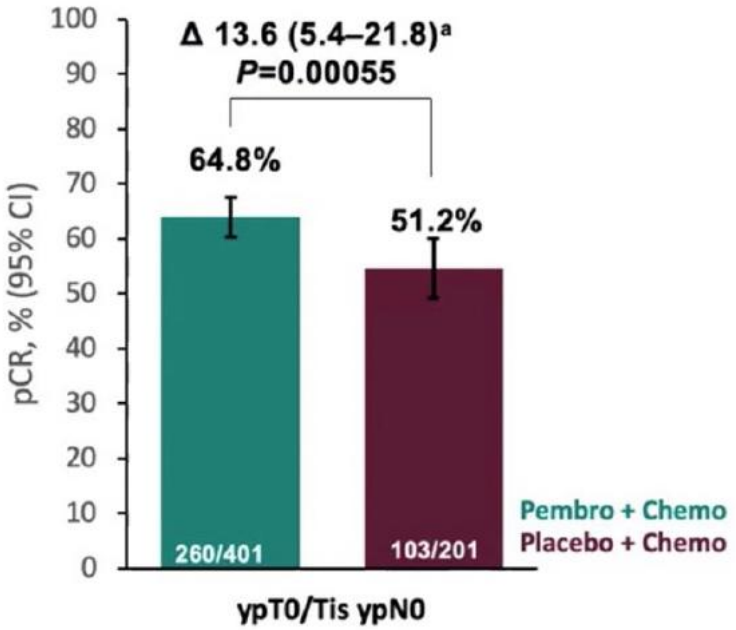
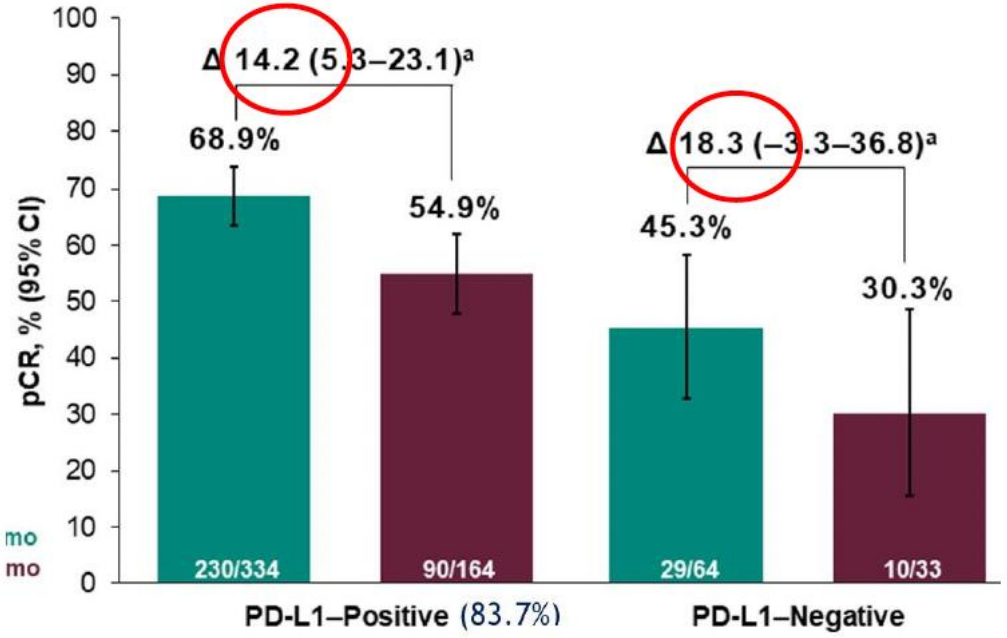
PCR: PDL1 NO PREDICE EL BENEFICIO A TRATAMIENTO

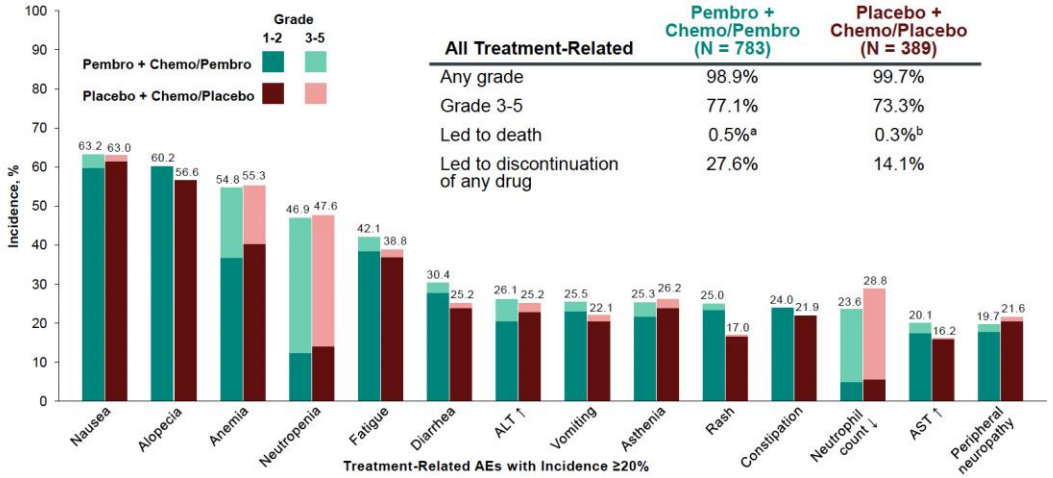
pCR in ITT Population (ypT0/Tis ypN0)



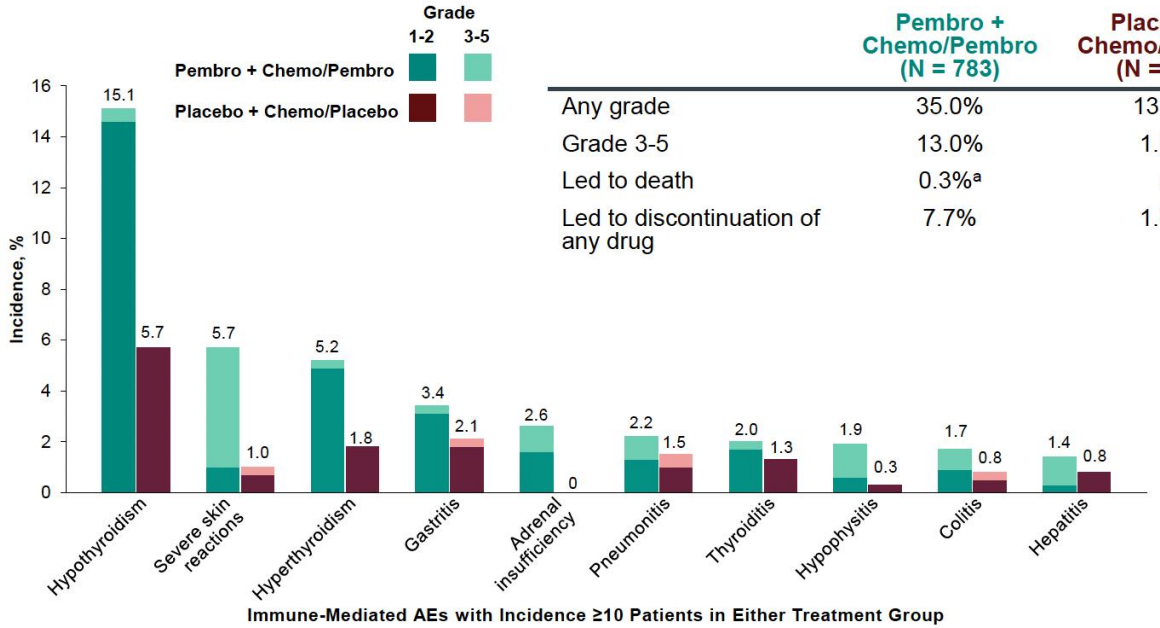
pCR by PD-L1 Status



TOXICIDAD



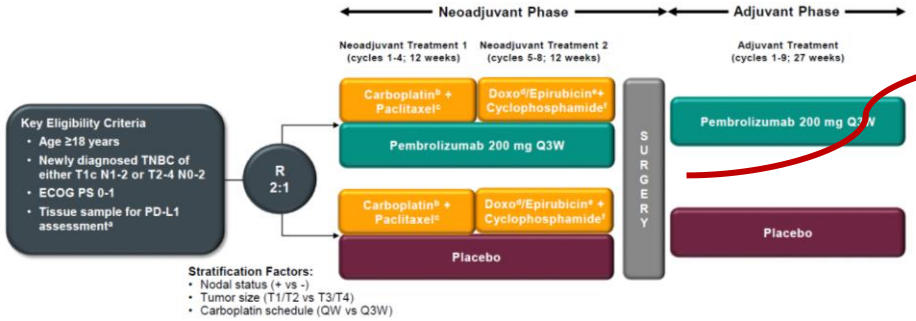
All Treatment-Related	Pembro + Chemo/Pembro (N = 783)	Placebo + Chemo/Placebo (N = 389)
Any grade	98.9%	99.7%
Grade 3-5	77.1%	73.3%
Led to death	0.5%[a]	0.3%[b]
Led to discontinuation of any drug	27.6%	14.1%

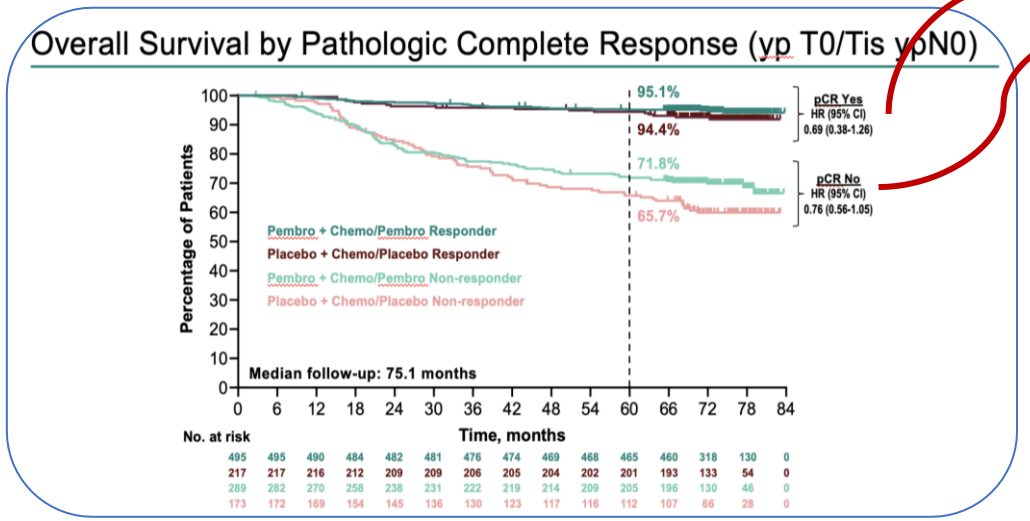


	Pembro + Chemo/Pembro (N = 783)	Placebo + Chemo/Placebo (N = 389)
Any grade	35.0%	13.1%
Grade 3-5	13.0%	1.5%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	7.7%	1.0%

P. Schmid ESMO 2024

¿QUIÉN NECESITA PEMBROLIZUMAB ADYUVANTE?



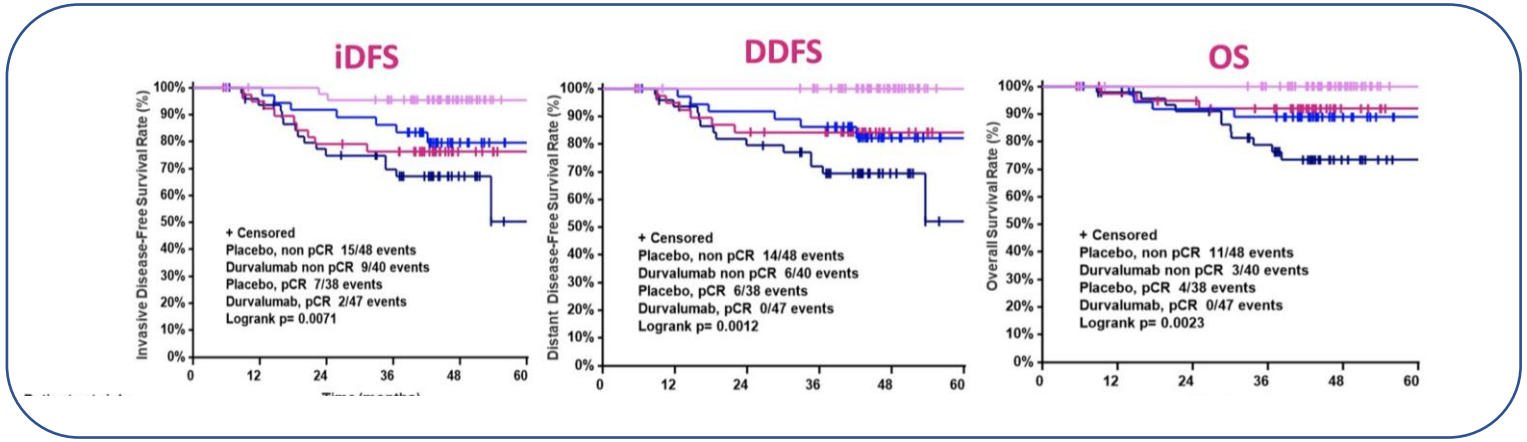


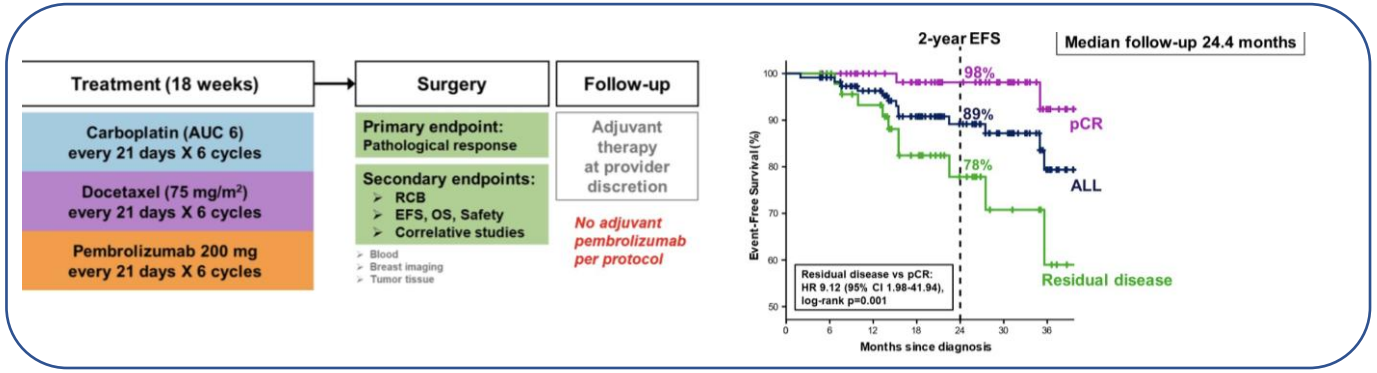
<u>Diseño KN522</u>
Una segunda randomización podría haber dado información sobre la duración del tratamiento

<u>Patientes con pCR</u>
El beneficio de pembro es mínimo, si lo hay

<u>Patientes con no-pCR</u>
La separación de las curvas podría deverse solamente por el tratamiento neoadyuvante

VALOR DE LA ADICIÓN DE INMUNOTERAPIA ADYUVANTE





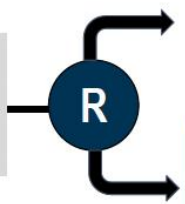
GEPARNUEVO & NEOPACT

Excellent outcomes without adjuvant aPD1

Loibl et al. Ann Oncol 2022, Sharma et al. JAMA Oncology 2024

OptimICE-pCR

Key Eligibility:
pCR after preop chemo x min 6 cycles with pembrolizumab

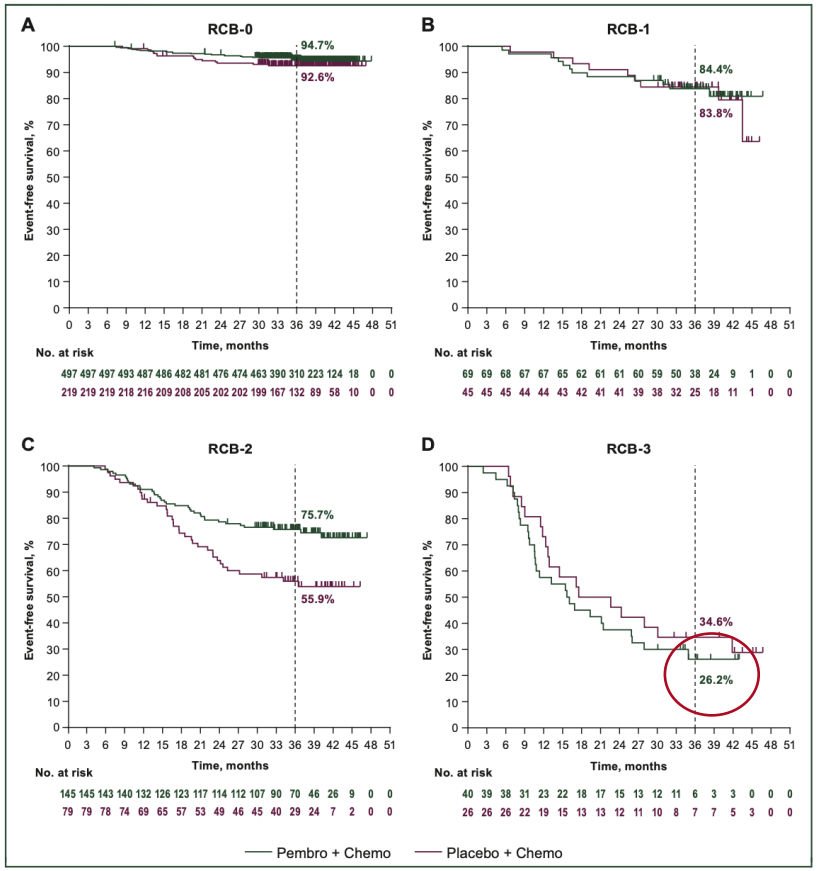


Pembrolizumab x 27 wks

Observation

Stratification Factors:

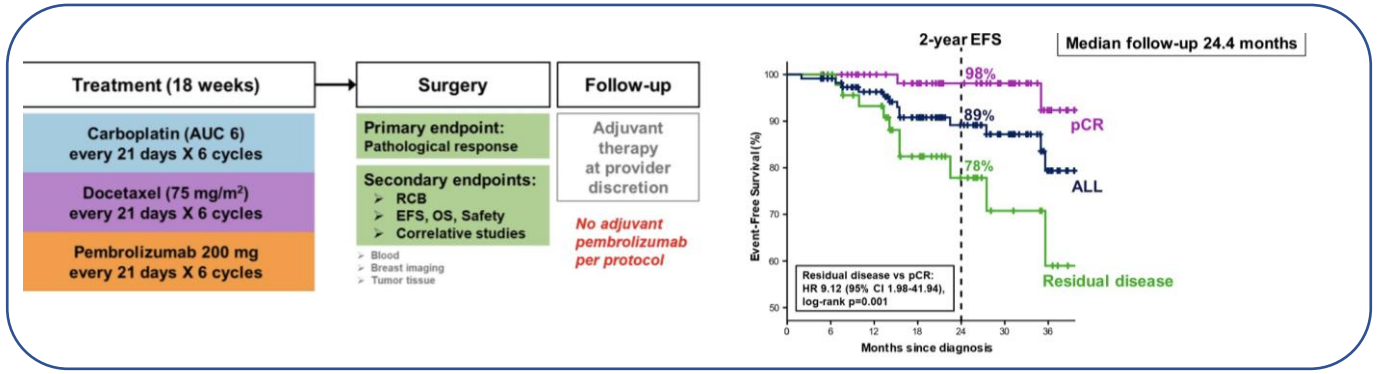
- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

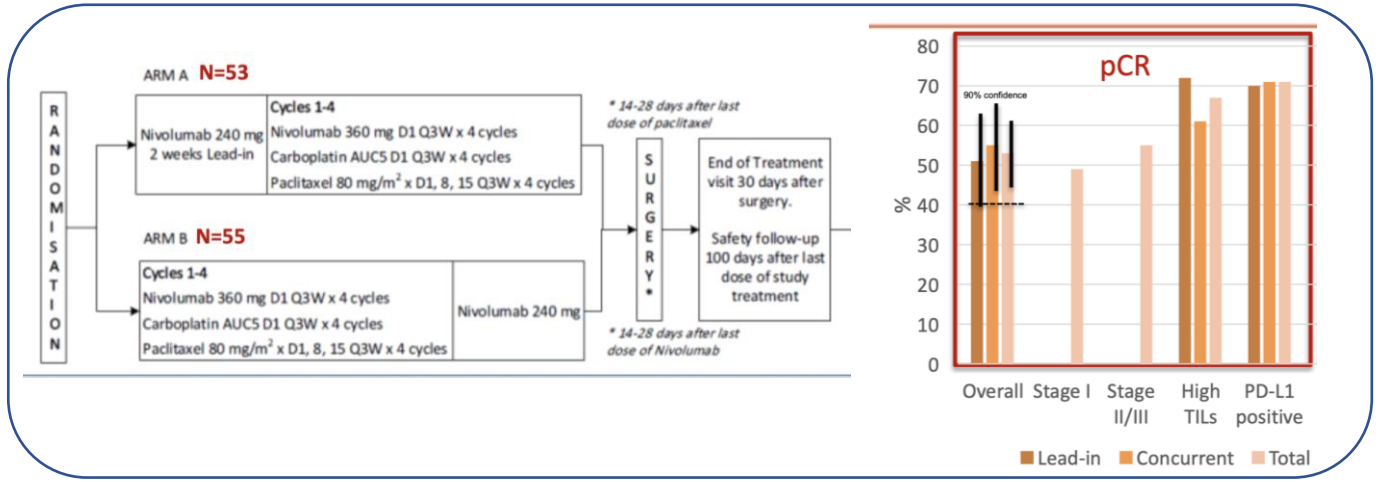


- Debe añadirse pembrolizumab adyuvante a Capecitabina u olaparib? Ambos son tratamiento estandar
- Nuevas estrategias para pacientes con RCB 2 and 3 -> ADCs, nueva generación de inmunoterapia?

Pusztai et al. Ann Oncol 2024

DESESCALADA DE TRATAMIENTO. ANTIPD1 SIN ANTRACICLINAS





S2212: Shorter Anthracycline-free Chemoimmunotherapy Adapted to pathological Response in Early TNBC (SCARLET), n=2,400

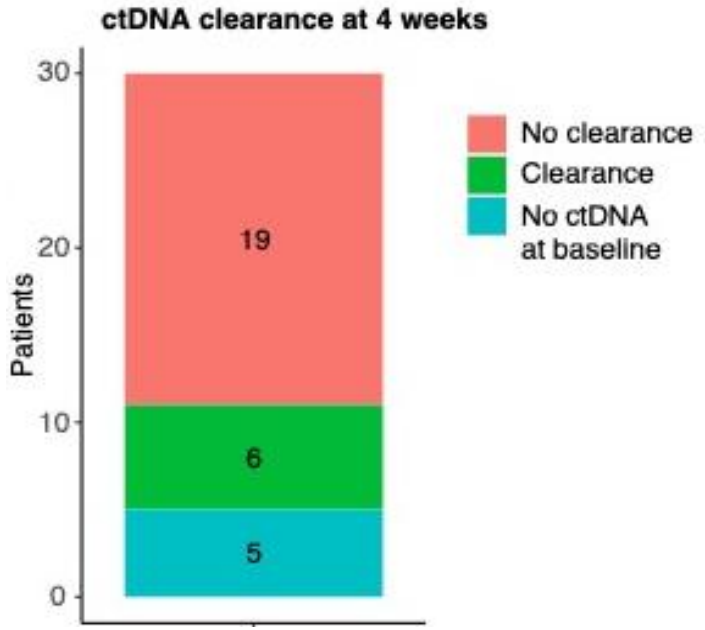
PI: P. Sharma

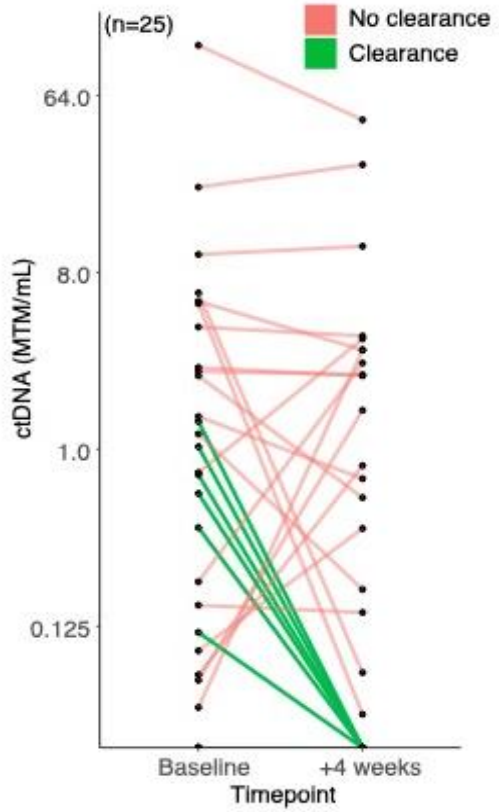
Sharma et al. JAMA Onc 2024
Zdenkowski et al. SABCS 2023

POTENCIAL DEL CTDNA PARA GUIAR EN LA DESESCALADA

- tumor-informed circulating-tumor-DNA analyses, Signatera
- 25/30 (83%) patients with detectable ctDNA at baseline

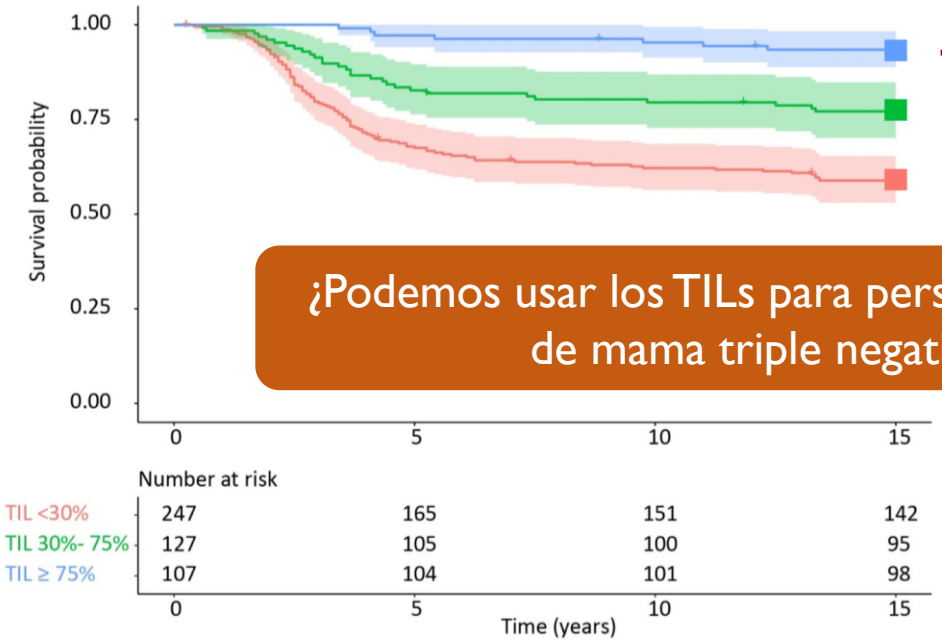
Exploratory data from BELLINI phase II trial





Nederlof et al. Nat Med 2024

NO TRATAMIENTO SISTÉMICO PARA NO, ALTO TILS CMTN

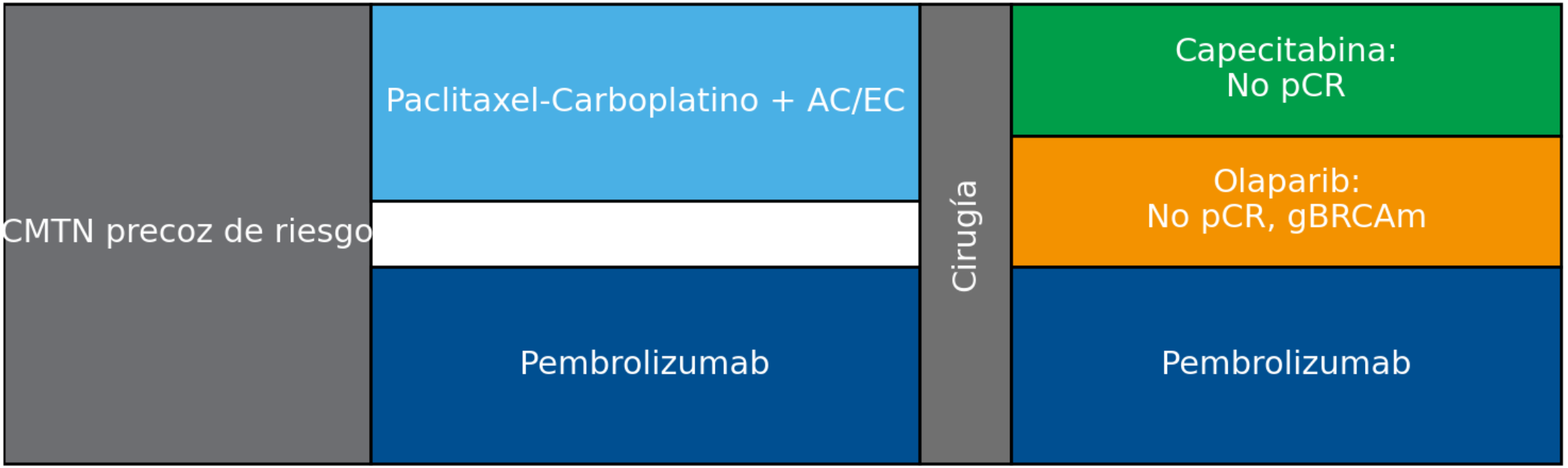


Solo 2% de enfermedad metastásica a distancia a 15 años sin quimioterapia

¿Podemos usar los TILs para personalizar el tratamiento para cáncer de mama triple negativo de buen pronóstico?

De Jong et al. JCO 2022. See also: Park et al. Ann Oncol 2019, Leon-Ferre et al. JAMA 2024

TRATAMIENTO EN CÁNCER DE MAMA TRIPLE NEGATIVO LOCAL



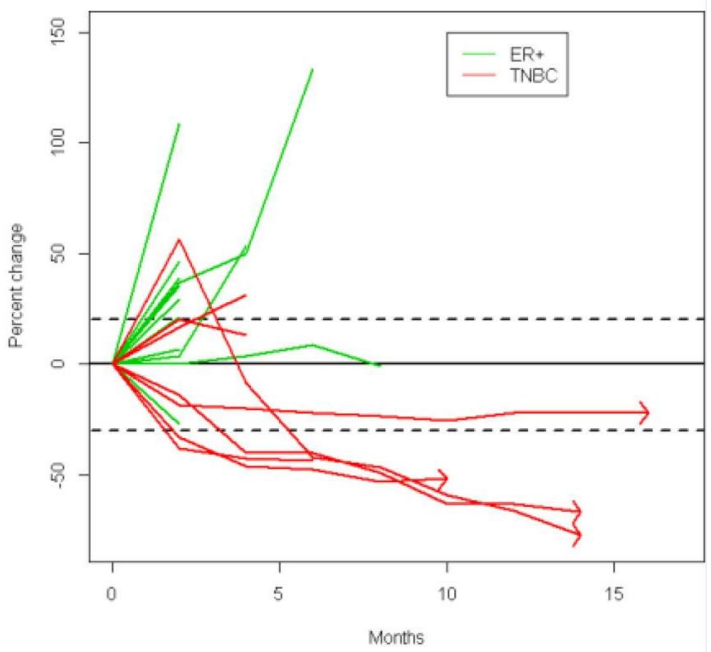
CÁNCER DE MAMA LUMINAL

INMUNOTERAPIA EN RE+ METASTÁSICO TIENE TASAS DE RESPUESTAS BAJAS

KN-028: single agent pembrolizumab in later line metastatic ER+ disease PD-L1 CPS ≥1 (n=25) → *ORR 12%*

Durvalumab+tremelimumab: later line metastatic HER2- MBC (11 evaluable ER+ and 7 TNBC) → *ORR 0% ER+* (43% TNBC)

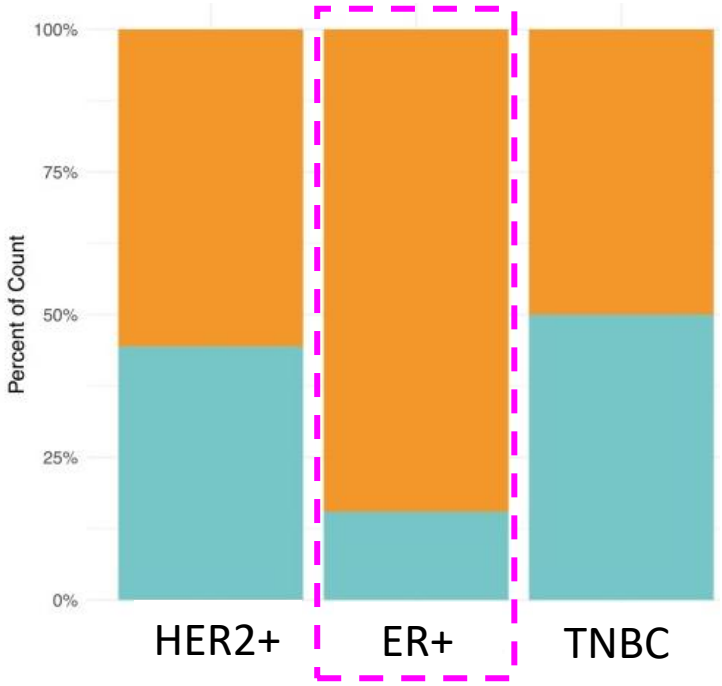
Eribulin +/- pembrolizumab: randomized study (n=88) in heavily pretreated metastatic ER+ breast cancer → *no difference in PFS/OS in ITT or PDL1+ cohort*



Frenel et al. JCO 2017
Santa-Maria et al. Oncotarget 2018
Tolaney et al. JAMA Oncol 2020

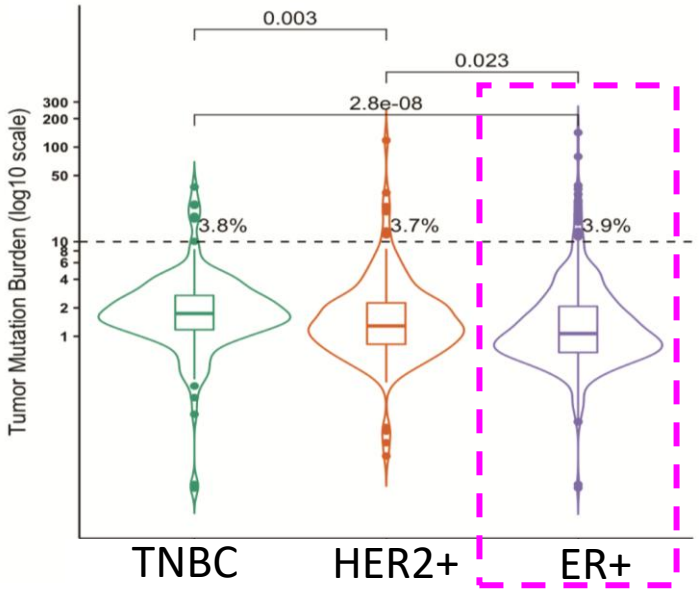
PDL1 Y TMB ESTATUS EN LOS DIFERENTES SUBTIPOS DE CÁNCER DE MAMA

PDL1 levels lower in ER+ BC



Danziger et al Oncologist 2023

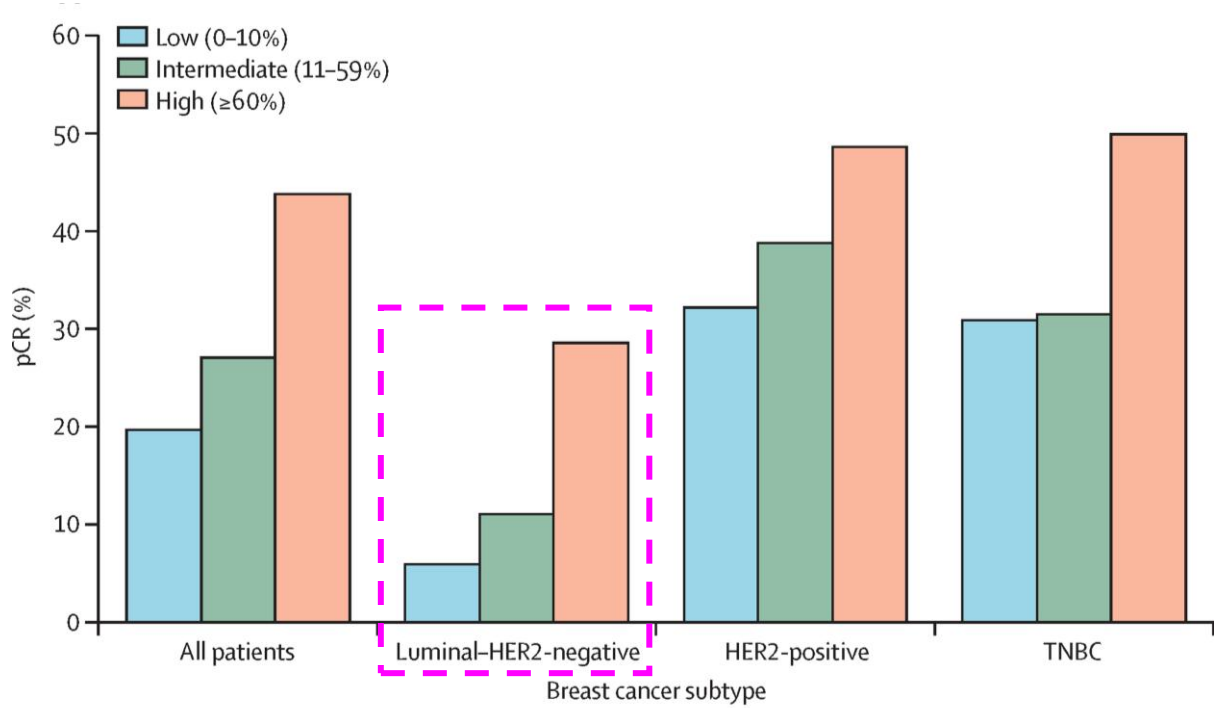
Average TMB lower in ER+ BC, but proportion of hypermutated (ie TMB ≥10) similar across subtypes



Barroso-Sousa et al Ann Oncol 2020

TILS EN CÁNCER DE MAMA LUMINAL ENFERMEDAD LOCALIZADA

Los TILs son más bajos en los cánceres de mama luminales, pero una mayor cantidad de TILs se asocia con mayores tasas de respuesta patológica completa (pCR) a la quimioterapia neoadyuvante.



Denkerk et al Lancet 2018

2 ESTUDIOS PRESENTADOS EN ESMO 2023

KEYNOTE-756: Phase 3 Study of Neoadjuvant Pembrolizumab or Placebo + Chemotherapy Followed by Adjuvant Pembrolizumab or Placebo + Endocrine Therapy for Early-Stage High-Risk ER+/HER2– Breast Cancer

Fatima Cardoso[1], Heather McArthur[2], Peter Schmid[3], Javier Cortes[4], Nadia Harbeck[5], Melinda L Telli[6], David W. Cescon[7], Joyce O' Shaughnessy[8], Peter A. Fasching[9], Zhimin Shao[10], Delphine Loirat[11], Yeon Hee Park[12], Manuel Gonzalez Fernandez[13], Zhenzhen Liu[14], Hiroyuki Yasojima[15], Yu Ding[16], Liyi Jia[16], Vassiliki Karantza[16], Konstantinos Tryfonidis[16], Aditya Bardia[17]

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MADRID 2023 ESMO congress

A randomized, double-blind trial of nivolumab vs placebo with neoadjuvant chemotherapy followed by adjuvant endocrine therapy in patients with high-risk, ER+ HER2– primary breast cancer

Sherene Loi,[1] Giuseppe Curigliano,[2,3] Roberto Salgado,[1,4] Roberto Iván Romero Díaz,[5] Suzette Delaloge,[6] Carlos Ignacio Rojas García,[7] Marleen Kok,[8] Cristina Saura,[9] Nadia Harbeck,[10] Elizabeth A. Mittendorf,[11] Denise A. Yardley,[12] Lajos Pusztai,[13] Alberto Suárez Zaizar,[14] Andrei Ungureanu,[15] Felipe Ades,[16] Rajalakshmi Chandra,[16] Raheel Nathani,[16] Misena Pacius,[16] Jenny Qun Wu,[16] Heather McArthur[17]

[1]Peter McCallum Cancer Center, Melbourne, Australia; [2]European Institute of Oncology, IRCCS, Milan, Italy; [3]University of Milan, Milan, Italy; [4]GZA-ZNA Hospitals, Antwerp, Belgium; [5]Consultorio de Oncólogo Médico, Oaxaca, Mexico; [6]Institut Gustave Roussy, Villejuif, France; [7]Bradford Hill Investigación Clinica, Región Metropolitana, Santiago, Chile; [8]Netherlands Cancer Institute, Amsterdam, The Netherlands; [9]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [10]Ludwig Maximilians University Hospital, Munich, Germany; [11]Dana Farber Cancer Institute, Boston, MA, USA; [12]Sarah Cannon Research Institute and Tennessee Oncology PLLC, Nashville, TN, USA; [13]Smilow Cancer Hospital at Yale, New Haven, CT, USA; [14]CENEIT Oncológicos, Mexico City, Mexico; [15]Radiotherapy Center CLUJ S.R.L., Florești, Romania; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]University of Texas Southwestern Medical Center, Dallas, TX, USA

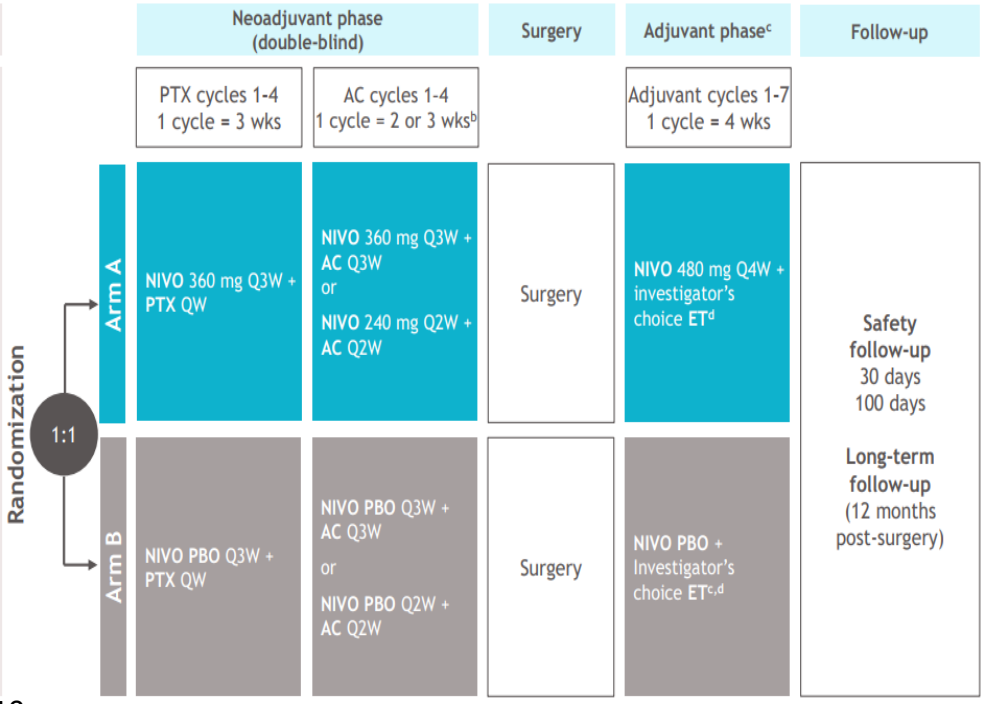
Presentation number LBA20

CHECKMATE 7FL: AC/T +/- NIVOLUMAB EN RE+

Screening

Key inclusion criteria
- Newly diagnosed ER+ HER2– breast cancer
- Confirmed ER+ breast cancer
- T1c (tumor size 2 cm only)-T2, cN1-cN2 or T3-T4, cN0-cN2
- Grade 3 with ER ≥ 1% or grade 2 with ER 1-10%[a]
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0-1

Stratification factors
- PD-L1 IC (≥ 1% or < 1%) by SP142
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC frequency (Q3W or Q2W)

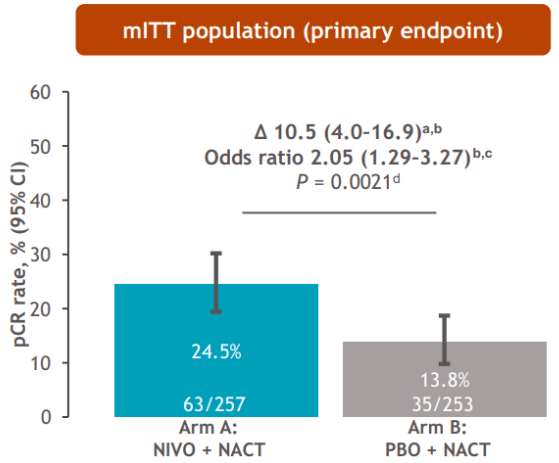


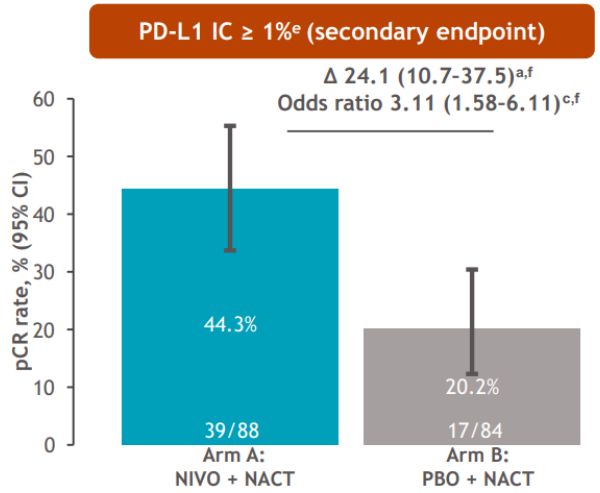
IIT n=510

Primary endpoint: pCR

Secondary endpoints: pCR and RCB by PDL1 status, safety

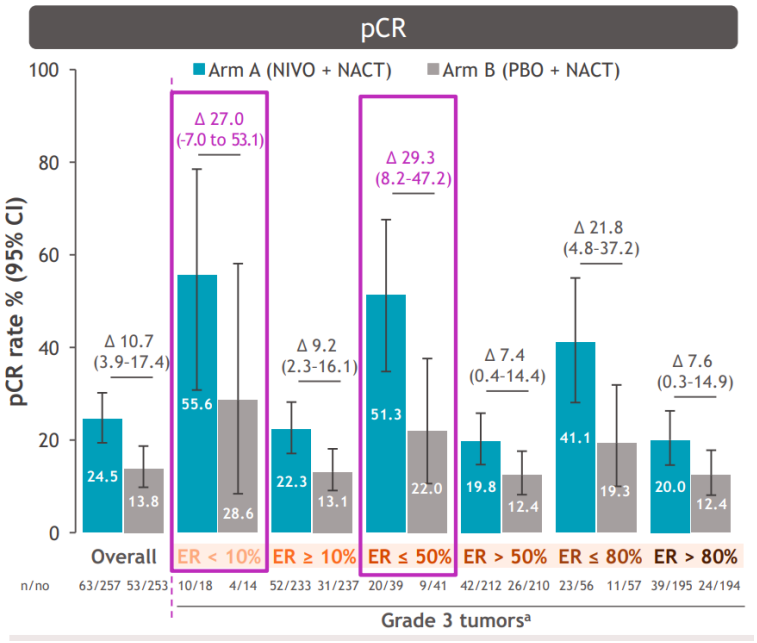
Exploratory endpoints: other pCR, ORR, EFS, OS, DFS, DMFS, PDL1 analysis, PKs, PROs

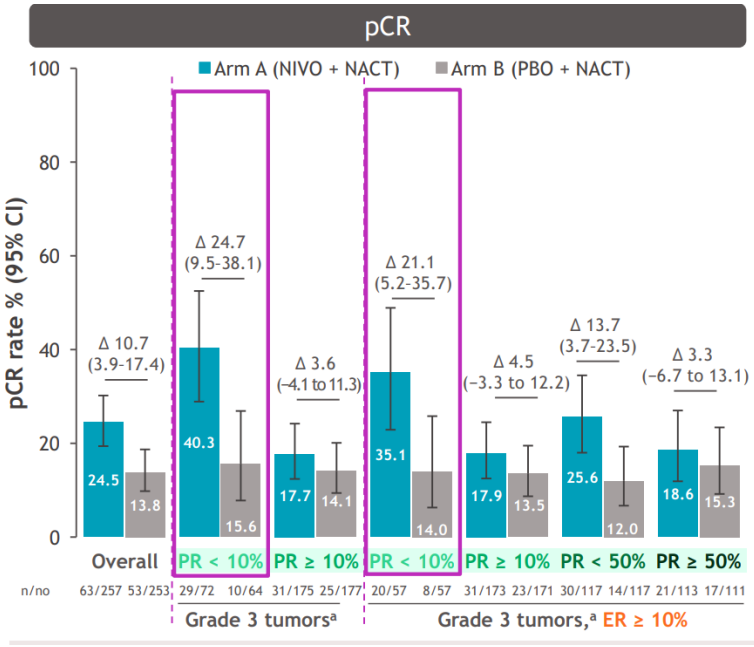


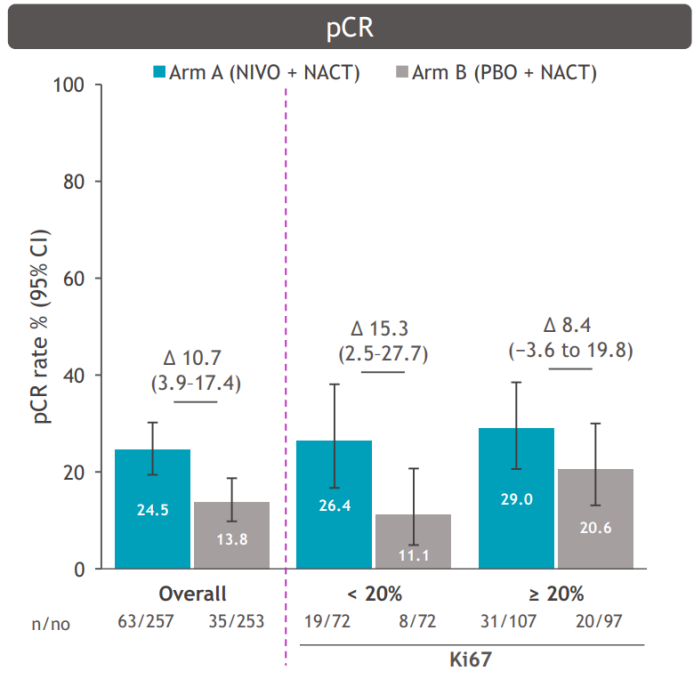


Loi et al ESMO 2023

BIOMARCADORES RE, RP, KI67





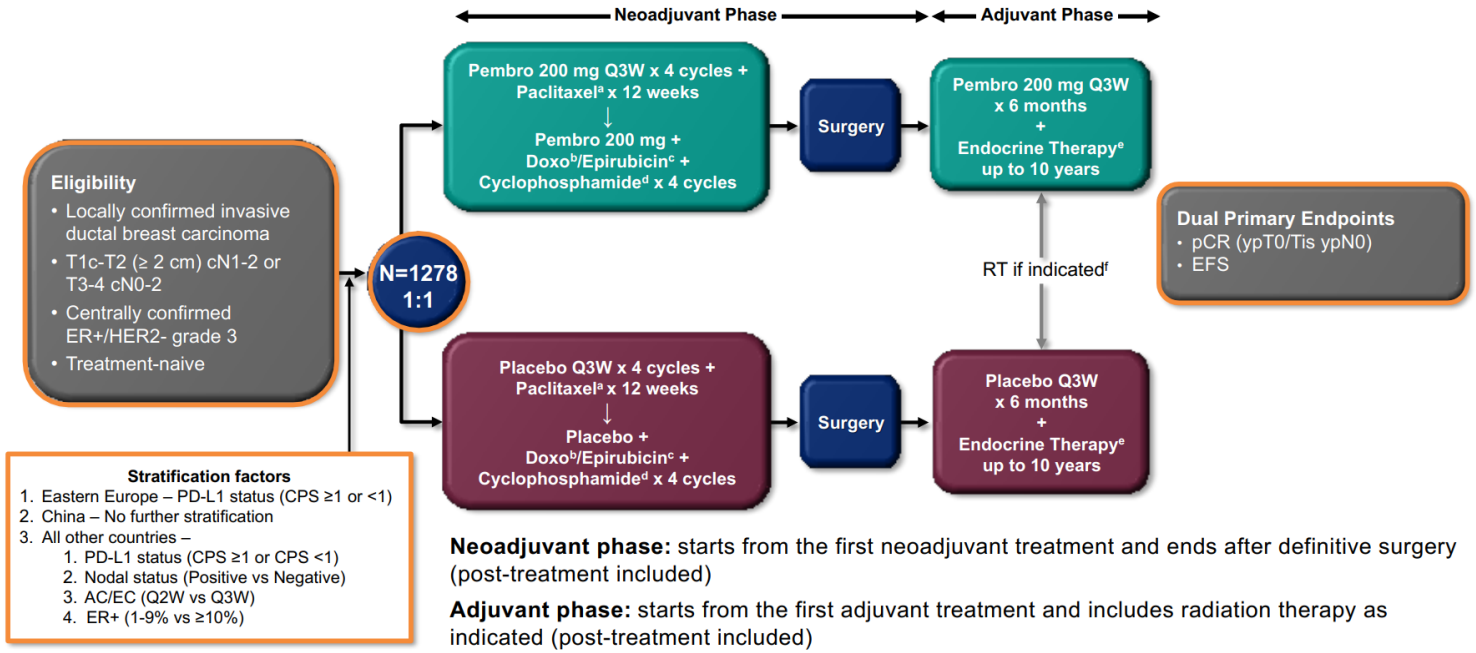


Beneficio con Nivolumab mayor con baja expression de receptores hormonales

Ki67 no asociado con beneficio a Nivolumab

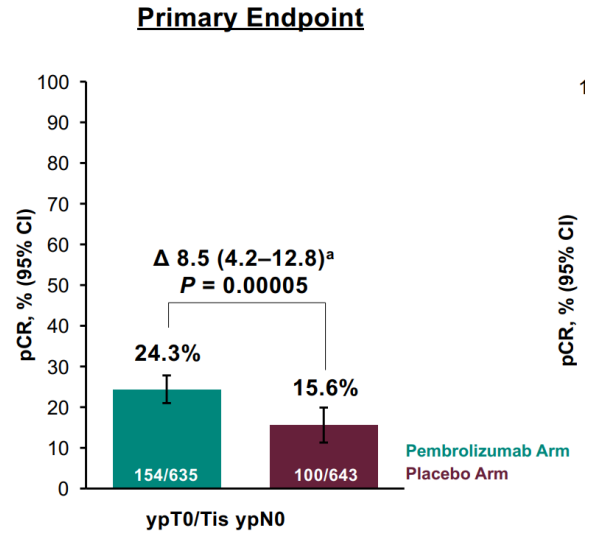
Loi et al SABCS 2023

KEYNOTE-756: AC/T +/- PEMBROLIZUMAB EN RE+ PRECOZ



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)



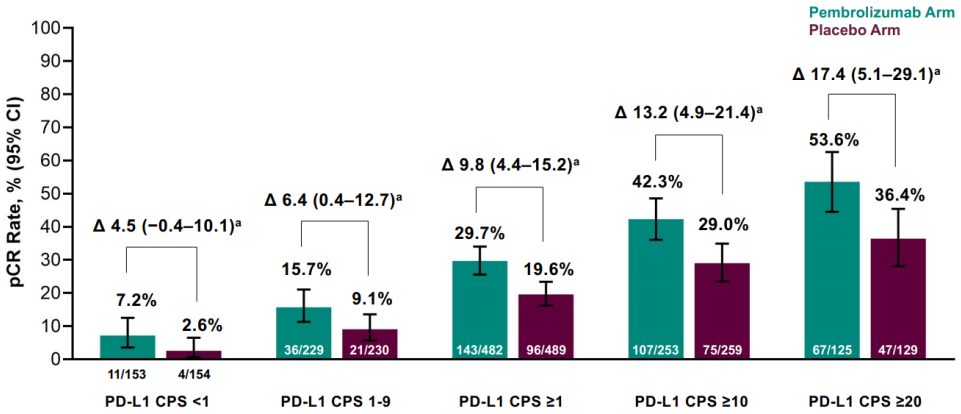
Primary endpoint: pCR + EFS

Secondary endpoints: other pCR , OS, PDL1 status, safety

Exploratory endpoints: RCB

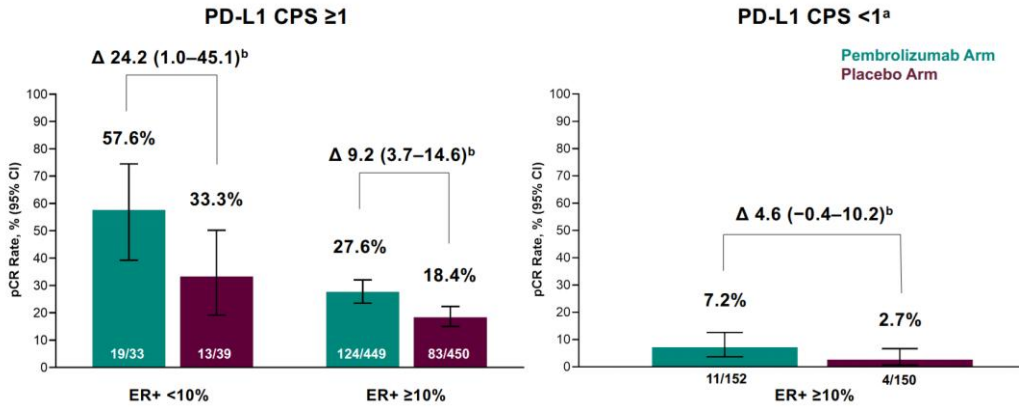
Cardoso et al ESMO 2023

ANÁLISIS DE BIOMARCADORES: PDL1 Y ESTADO RE



Higher PDL1 status associated with higher pCR rates (to both arms), BUT also associated with greater pembrolizumab benefit

Benefit highest in ER-low, PDL1CSP ≥1



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FUTURO

ASCENT-05 / OptimICE-RD: Phase III, Randomized, Open-label, Study of Adjuvant SG + Pembrolizumab vs TPC in TNBC Patients with Residual Disease After Neoadjuvant Therapy and Surgery

Residual invasive TNBC in Breast or Positive Node(s) After Neoadjuvant Therapy and Surgery

- History of cT1,cN1-2 or cT2-4, cN0-2 disease
- Received at least 6-cycles of neoadjuvant anthracycline- and/or taxane-based chemotherapy with or without an aPD-(L)1 agent
- TNBC diagnosis: ER and PR <10%, HER2 negative per ASCO/CAP
- gBRCA mutants excluded

R 1:1

N=1514

Sacituzumab Govitecan + Pembrolizumab x 8 cycles
SG: 10 mg/kg IV on d 1 and 8 of 21-d cycles
Pembro: 200 mg IV on d 1 of 21-d cycles

Treatment of Physician's Choice x 8 cycles
Pembro: 200 mg IV on d 1 of 21-d cycles
or
Pembro + capecitabine: pembro 200 mg IV on d 1 plus capecitabine 1000 mg/m^2 PO BID on d 1-14 of 21-d cycles

Long-term Follow Up

Stratification Factors:
- Prior aPD-(L)1 therapy (yes vs no)
- Prior anthracycline-based therapy (yes vs no)
- Pathologic nodal status at the time of surgery (ypN0 vs ypN+)
- Geographic region (US vs East Asia vs RoW)

Endpoints

Primary
- iDFS (iBCFS per STEEP v2.0)

Secondary
- OS
- dDFS
- Incidence of TEAEs and clinical laboratory abnormalities
- TTW of QoL based on FACT-B TOI scores

Exploratory Biomarkers
- Trop-2, PD-L1
- TIL, ctDNA

QoLs
- PRO-CTCAE
- FACT-B
- EQ-5D-5L

TROPION-Breast03 Study Design

Phase 3 Dato-DXd +/- Durvalumab in Adjuvant Residual Disease TNBC

KEY ELIGIBILITY CRITERIA
- Histologically confirmed invasive TNBC (ER<1%, PR<1%, HER2-negative)
- Completed at least 6 cycles of neoadjuvant therapy containing an anthracycline and/or a taxane with or without carboplatin, with or without pembrolizumab.
- Residual invasive disease after neoadjuvant therapy
- No evidence of locoregional or distant relapse
- Radiotherapy delivered before the start of study treatment
- No adjuvant systemic therapy
- ECOG PS 0 or 1
- Adequate bone marrow reserve and organ function
- No known germline BRCA1 or BRCA2 mutation

STRATIFICATION FACTORS:
- Prior neoadjuvant pembrolizumab (Yes vs No); cap No at 40%
- Residual disease (< 1 cm vs ≥ 1 cm); cap < 1 cm (in the absence of lymph node involvement) at 20%
- Prior neoadjuvant platinum chemotherapy (Yes vs No)

2:1:2

Dato-DXd 6 mg/kg IV Q3W x 8 Cycles + Durva 1120 mg IV Q3W x 9 Cycles

Dato-DXd 6 mg/kg IV Q3W x 8 Cycles

Investigator's Choice of Therapy (ICT)*

*capecitabine, pembrolizumab, or capecitabine + pembrolizumab

Primary Endpoint
Dato+Durva vs ICT: iDFS

Secondary Endpoints
Dato+Durva vs ICT: DDFS, OS
Dato vs ICT: iDFS, DDFS, OS
Dato+Durva vs Dato: iDFS, DDFS
PROs, PK, immunogenicity, safety

TB04 Study Design: Ph3 Dato-DXd + Durva in Neoadjuvant/Adjuvant TNBC

TROPION-Breast04

Neoadjuvant | Surgery | Adjuvant

Key Eligibility Criteria
- Histologically confirmed Stage II or III unilateral or bilateral primary invasive breast cancer.
- TNBC (ER and PR < 1%) or hormone receptor-low breast cancer (ER and/or PR 1% to < 10%, neither hormone receptor may be ≥ 10%), and HER2-negative. e, f
- No evidence of distant disease.
- No prior surgery, radiation, or systemic anticancer therapy.
- ECOG PS 0 or 1.
- Adequate hematologic and organ function.

Stratification factors:
- Lymph node status (positive versus negative)
- Tumour stage (cT1 to cT2 versus cT3 to cT4
- Hormone receptor status (hormone receptor-negative [ER and PR < 1%] versus hormone receptor-low (ER and/or PR 1% to < 10%, neither hormone receptor may be ≥ 10%])
- Geographic region (US/Canada/Europe/Australia versus Rest of World).

1:1

Experimental Arm
Dato-DXd + durvalumab Q3W x 8 (24 weeks)
→ Durvalumab x 9 cycles +/- chemotherapy a, b, c

Control Arm
Pembrolizumab + carboplatin + paclitaxel Q3W x 4 (12 weeks)
→ Pembrolizumab + doxorubicin or epirubicin + cyclophosphamide Q3W x 4 (12 weeks)
→ Pembrolizumab x 9 cycles +/- chemotherapy a, c, d

Dual primary endpoints:
pCR and EFS

Secondary endpoints:
OS, DDFS, safety and tolerability, PROs, PK, immunogenicity

Exploratory endpoints include but are not limited to:
TROP2, PD-L1 e

a. Endocrine therapy is permitted for participants with hormone receptor-low tumours. No adjuvant CDK4/6 inhibitor (eg, abemaciclib, ribociclib).
b. Adjuvant chemotherapy may be given in combination with durvalumab for participants with residual disease. Chemotherapy options at discretion of investigator, either: doxorubicin/epirubicin + cyclophosphamide, followed by paclitaxel + carboplatin; doxorubicin/epirubicin + cyclophosphamide followed by paclitaxel, carboplatin + paclitaxel, capecitabine.
c. Olaparib may be administered to participants who are *gBRCA*-positive with residual disease.
d. Adjuvant capecitabine may be given in combination with pembrolizumab for participants with residual disease, at the discretion of investigator.
e. Hormone receptor, HER2: local testing. *BRCA*: no mandatory testing, use local testing results. PD-L1 and TROP2: retrospective central small batch testing.
f. *BRCA* mutation is allowed.

CONCLUSIONES

1.- Inmunoterapia en CMMTN Metastásico: Estándar. Aumento en SLP y SG en PDL1+

2.- Enfermedad Precoz: **Pembrolizumab + quimioterapia** muestra beneficio en **SLP** y **SG** en CMMTN

3.- Toxicidad y Selección de Pacientes

4.- Desescalada de Tratamiento: El uso de **ctDNA** para guiar la desescalada y el uso de inmunoterapia sin antraciclinas está mostrando prometedores resultados en pacientes de buen pronóstico. TILS

5.- Resultados prometedores en cáncer de mama luminal

6.- Futuro: Nuevas combinaciones de **inmunoterapia** con **ADC** podrían revolucionar el tratamiento del cáncer de mama.

GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025