



SOLCA
NÚCLEO DE QUITO



Terapias actuales en el manejo del cáncer de mama triple negativo

Dra. María Jose Muñoz Viteri
ONCOLOGA CLINICA

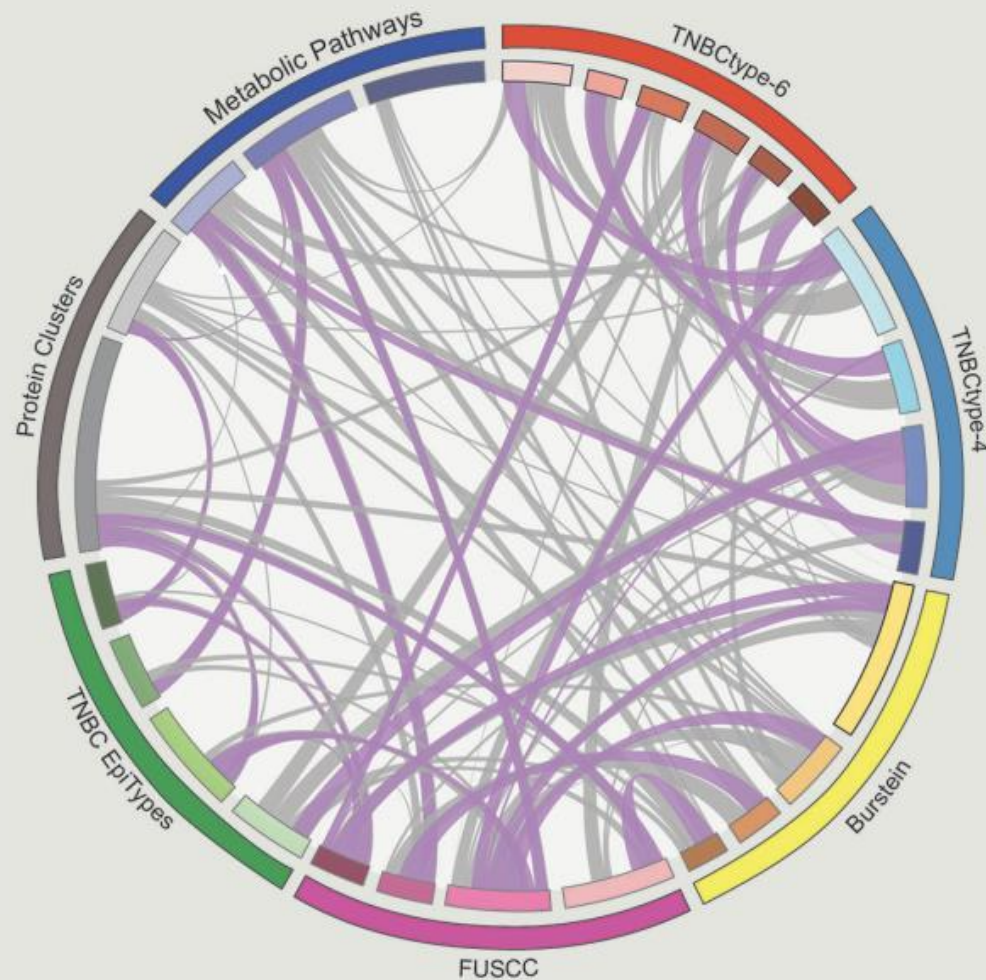
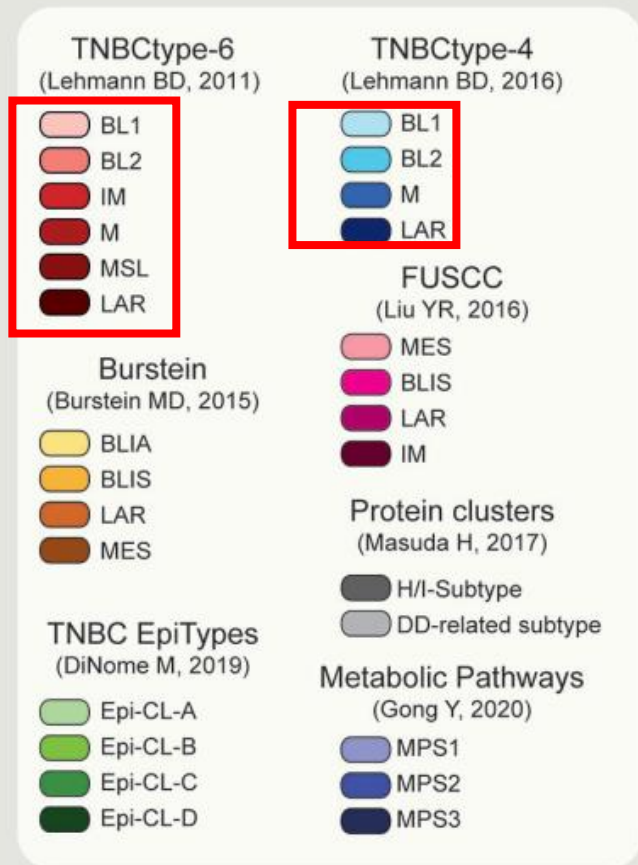
20 de julio del 2024

El cáncer de mama triple negativo constituye el 15% de los tumores mamarios



SEER* Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2024 Apr 17. [cited 2024 May 23]. Available from: <https://seer.cancer.gov/statistics-network/explorer/>. Data source(s): SEER Incidence Data, November 2023 Submission (1975-2021).

A





SOLCA
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desde 1954
DÉCADAS
de atención especializada en cáncer

Enfermedad inicial

NEOADYUVANCIA

ESMO

- Tumor > 2 cm
- Triple negativo, HER 2 +

NCCN

- HER 2 +, triple negativo $\geq$ ct2 o $\geq$ cN1
- Considerar en cT1, cN0 Triple negativo

St. Gallen

- Pacientes con alto riesgo Triple negativo o HER 2 +

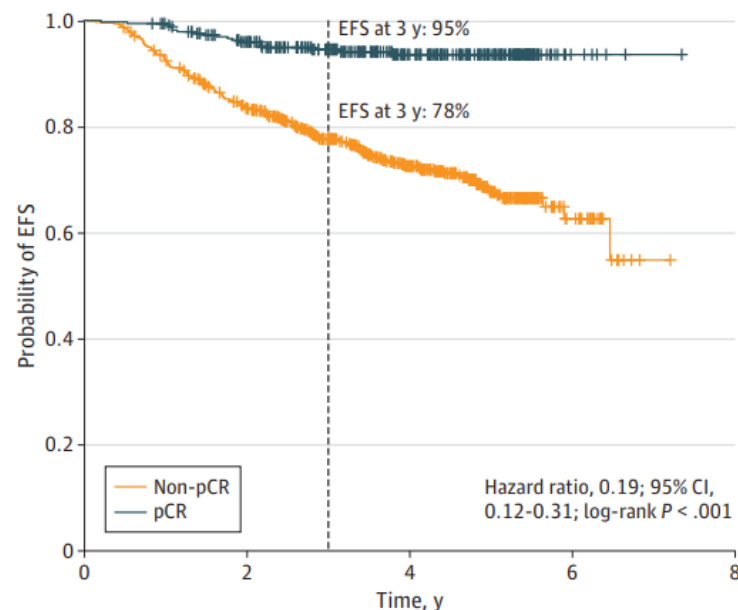
ASCO

- Neoadyuvancia tratamiento preferido inicial en pacientes con EC 2 o 3 HER 2 +, triple negativo

Association of Event-Free and Distant Recurrence–Free Survival With Individual-Level Pathologic Complete Response in Neoadjuvant Treatment of Stages 2 and 3 Breast CancerThree-Year Follow-up Analysis for the I-SPY2 Adaptively Randomized Clinical Trial

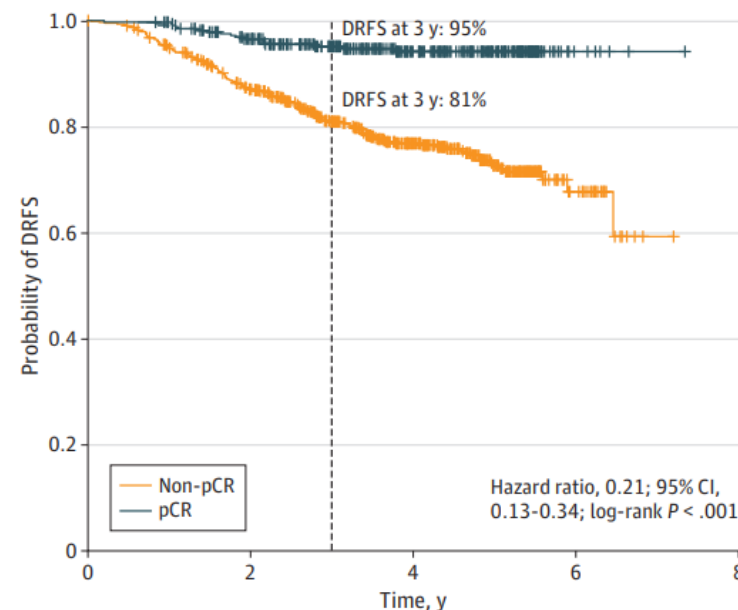
Figure 2. Kaplan-Meier Survival Curves

A EFS in patients with and without pCR



No. at risk	620	565	484	369	241	132	24	1	0
Non-pCR									
pCR	330	324	290	230	161	98	6	1	0

B DRFS in patients with and without pCR

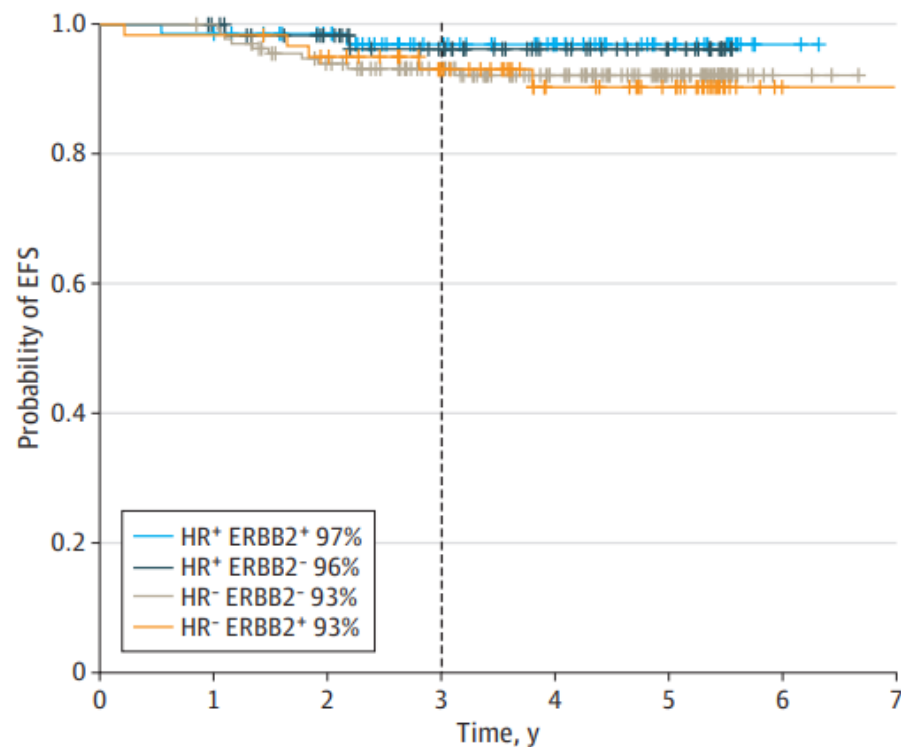


No. at risk	620	578	502	383	254	139	26	1	0
Non-pCR									
pCR	330	325	292	231	161	98	6	1	0

Kaplan-Meier survival curves for event-free survival (EFS) (A), and distant recurrence–free survival (DRFS) (B), in populations achieving pathologic complete response (pCR) at surgery (gray) and those with residual disease at time of surgery (orange). Kaplan-Meier survival curves for EFS among patients

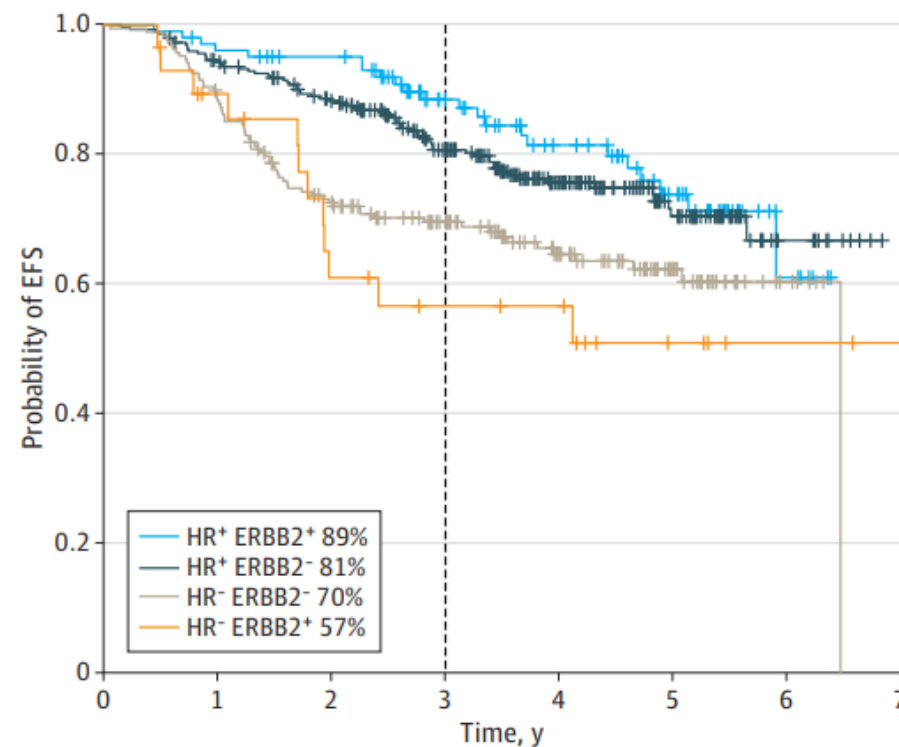
achieving pCR (C) and those who did not (D), stratified by hormone receptor (HR) and ERBB2 subtype (HR⁺ ERBB2⁺: light blue; HR⁺ ERBB2[−]: dark blue; HR[−] ERBB2[−]: gray; HR[−] ERBB2⁺: orange).

C EFS in patients with pCR stratified by subtype



Kaplan-Meier survival curves for event-free survival (EFS) (A), and distant recurrence-free survival (DRFS) (B), in populations achieving pathologic complete response (pCR) at surgery (gray) and those with residual disease at time of surgery (orange). Kaplan-Meier survival curves for EFS among patients

D EFS in patients without pCR stratified by subtype



achieving pCR (C) and those who did not (D), stratified by hormone receptor (HR) and ERBB2 subtype (HR+ ERBB2+: light blue; HR+ ERBB2-: dark blue; HR- ERBB2-: gray; HR- ERBB2+: orange).

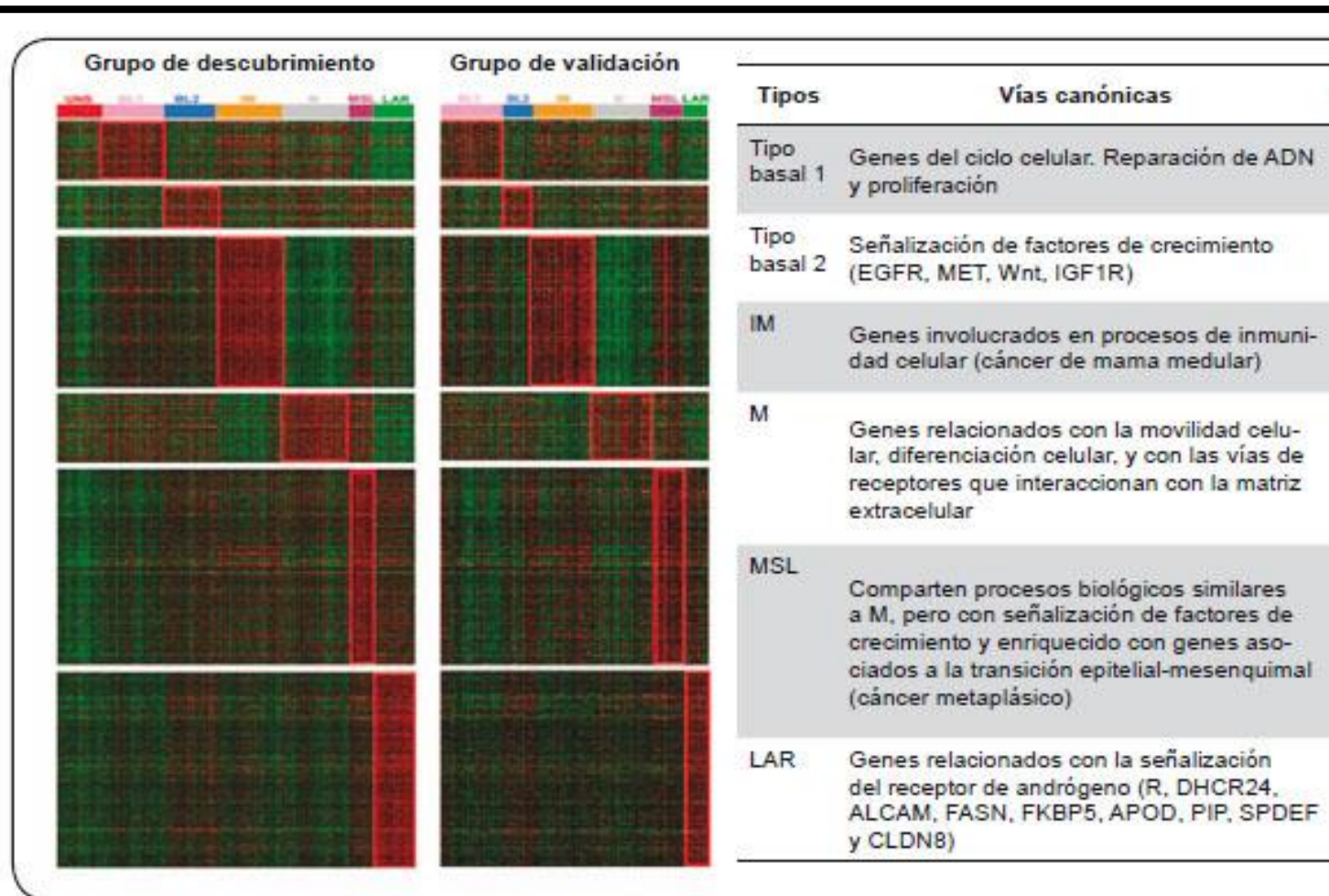
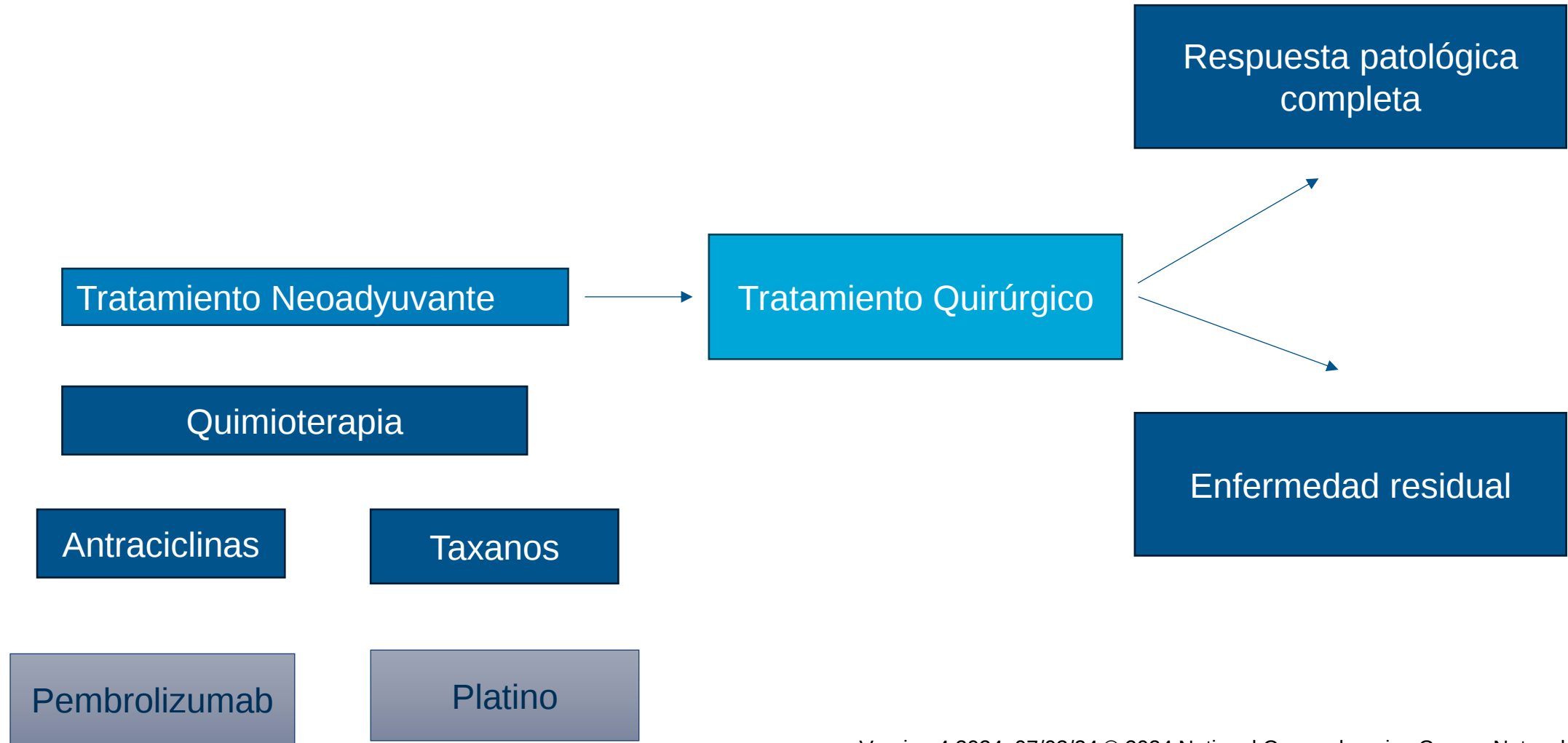


Figura 1. Características moleculares y de respuesta a la quimioterapia neoadyuvante de los cánceres de mama triple negativo
 % RPo: porcentaje de respuesta patológica completa.
 Modificado de Lehmann et al. ⁽¹⁰⁾, con permiso de la American Society for Clinical Investigation.

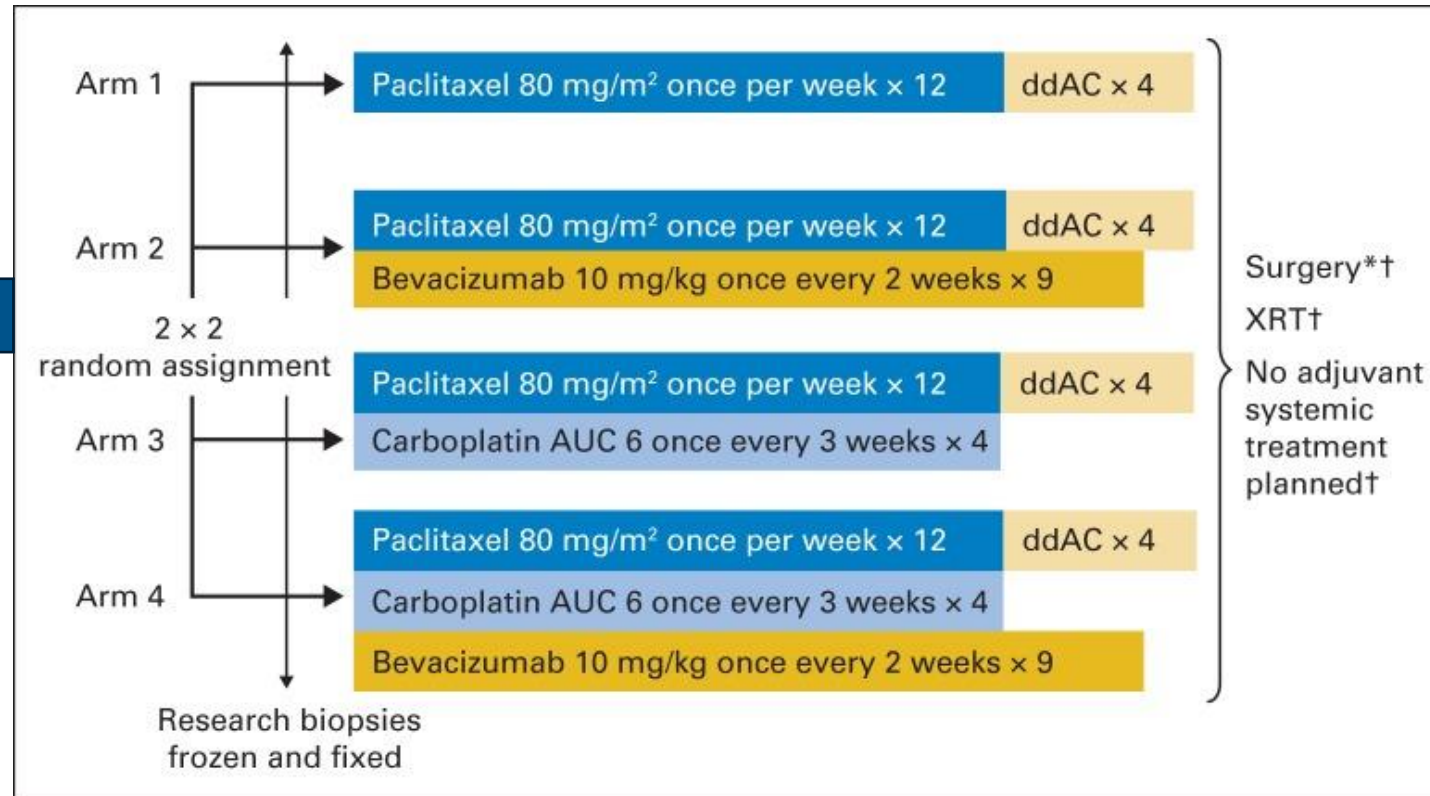


Version 4.2024, 07/03/24 © 2024 National Comprehensive Cancer Network® (NCCN®)

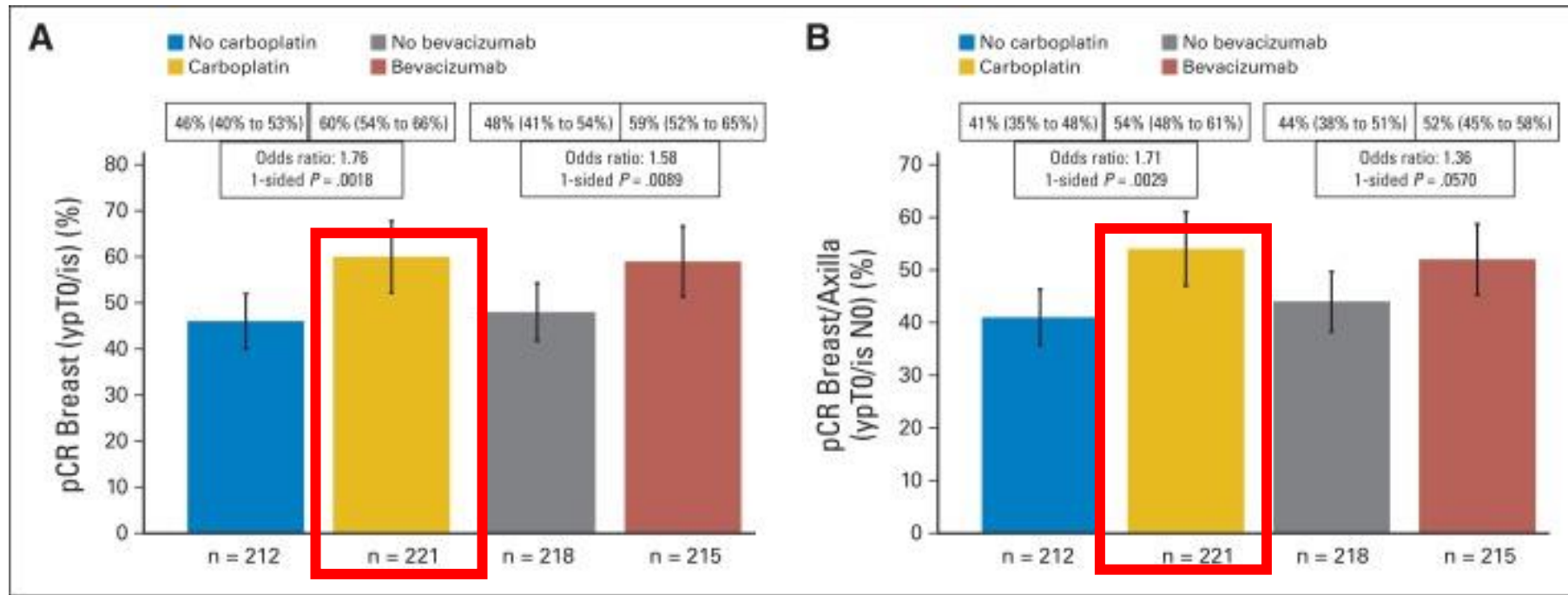
Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance)

PLATINOS

454



CALGB 40603 (Alliance). J Clin Oncol. 2015 Jan 1;33(1):13-21. doi: 10.1200/JCO.2014.57.0572. Epub 2014 Aug 4. PMID: 25092775; PMCID: PMC4268249.



No mejoró la SSE a cinco años.

CALGB 40603 (Alliance). J Clin Oncol. 2015 Jan 1;33(1):13-21. doi: 10.1200/JCO.2014.57.0572. Epub 2014 Aug 4. PMID: 25092775; PMCID: PMC4268249.

Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial (2014)

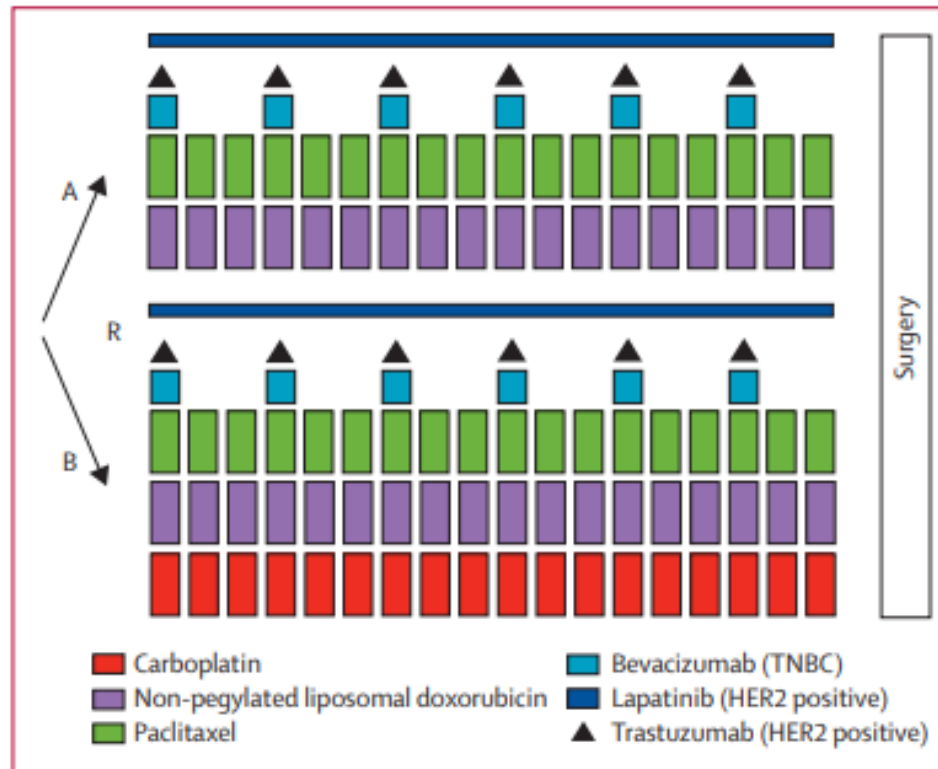
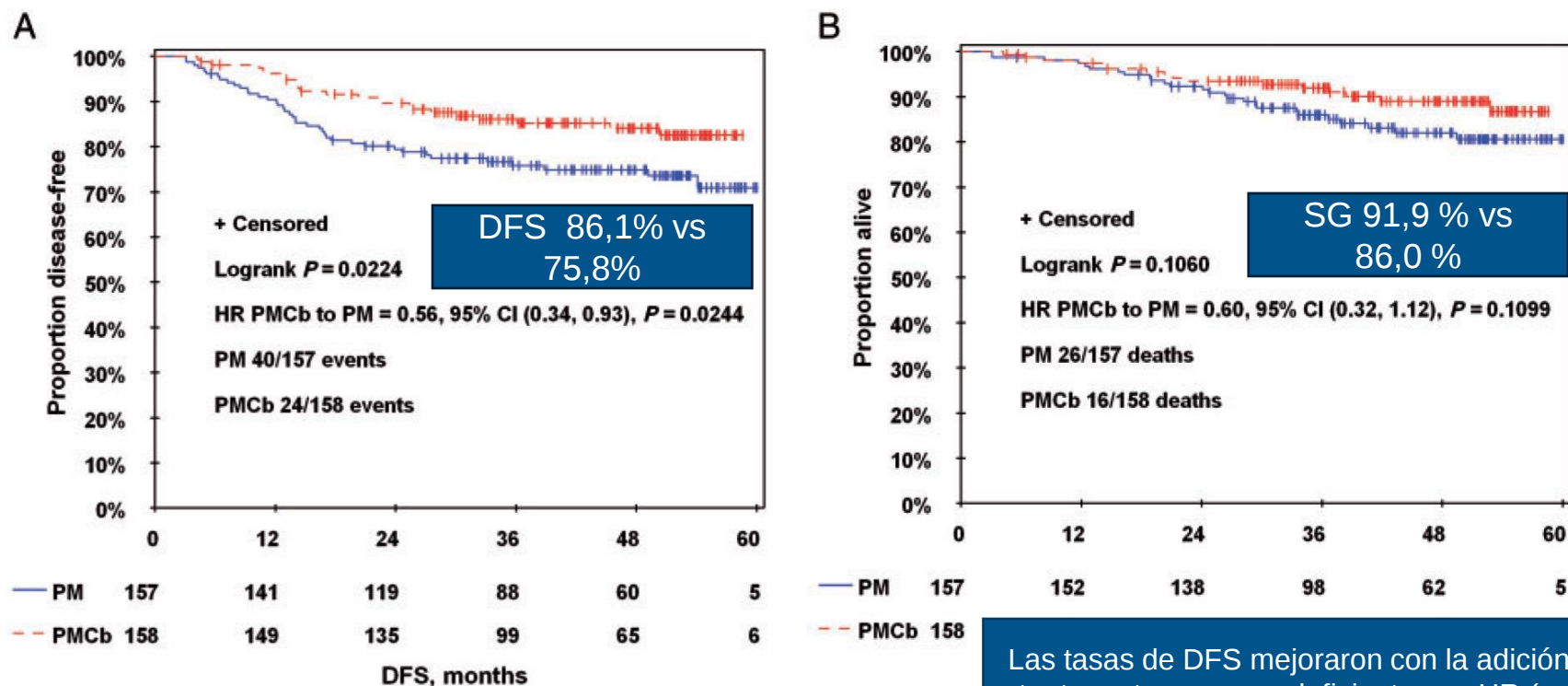


Figure 1: Trial design

Regimens were without (A) and with (B) carboplatin. TNBC=triple-negative breast cancer.

La adición de carboplatino neoadyuvante a un régimen de un taxano, una antraciclina y terapia dirigida aumenta significativamente la proporción de pacientes que logran una respuesta patológica completa.

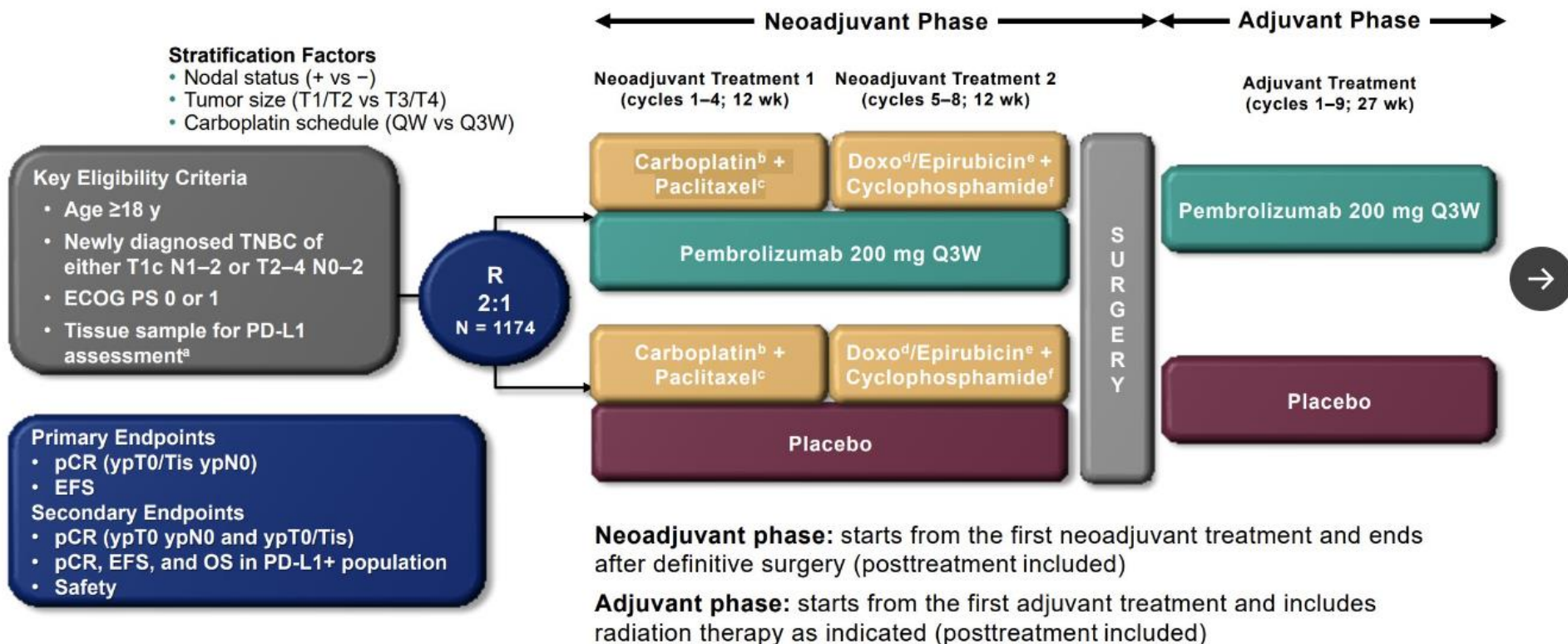
Análisis de supervivencia de carboplatino añadido a quimioterapia neoadyuvante basada en antraciclinas/taxanos y la puntuación deficiencia de recombinación homóloga como predictor de la respuesta: resultados finales de GeparSixto (2018)



Las tasas de DFS mejoraron con la adición de carboplatino, tanto en tumores no deficientes en HR (cociente de riesgo 0,44, 0,17-1,17, $P = 0,086$) como en tumores deficientes en HR (cociente de riesgo 0,49, 0,23-1,04, $P = 0,059$).

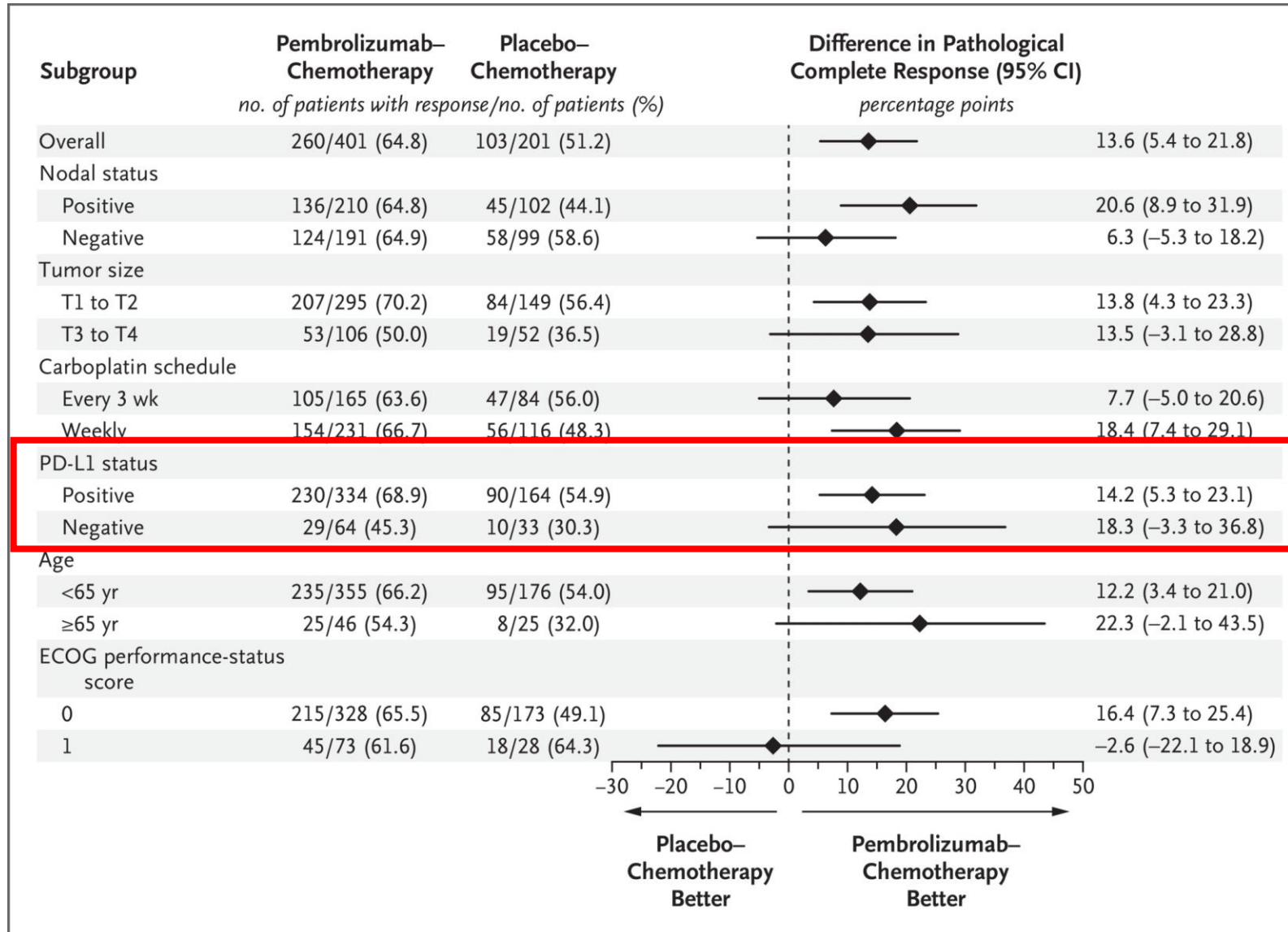
KEYNOTE-522 Study Design (NCT03036488)

INMUNOTERAPIA



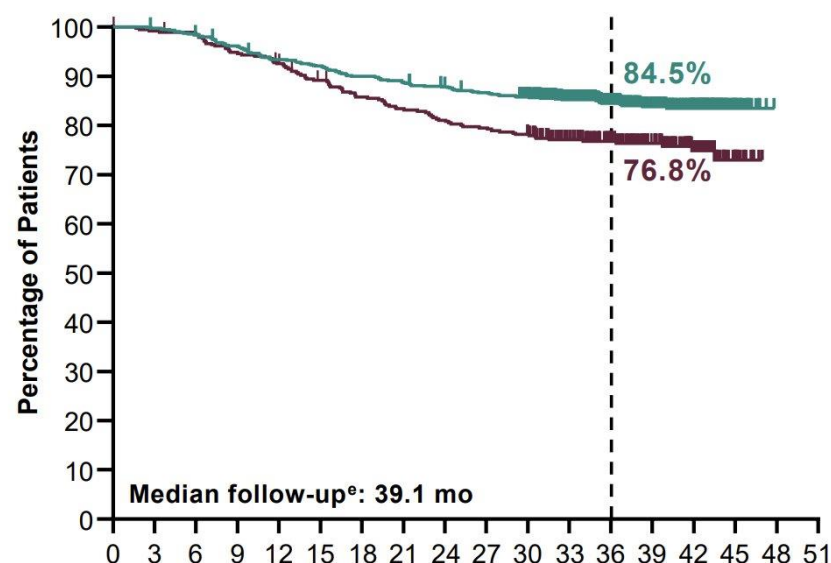
^aMust consist of at least 2 separate tumor cores from the primary tumor. ^bCarboplatin dose was AUC 5 Q3W or AUC 1.5 QW. ^cPaclitaxel dose was 80 mg/m² QW. ^dDoxorubicin dose was 60 mg/m² Q3W. ^eEpirubicin dose was 90 mg/m² Q3W. ^fCyclophosphamide dose was 600 mg/m² Q3W.

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EFS at IA4 and IA6

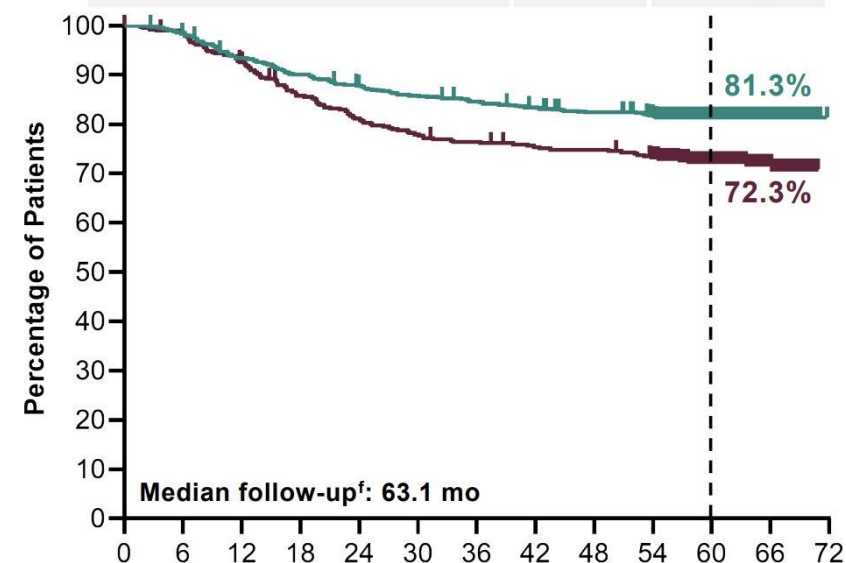
IA4 ^a	Events	HR (95% CI)	P value
Pembro + Chemo/Pembro	15.7%	0.63 ^c (0.48–0.82)	0.00031 ^d
Placebo + Chemo/Placebo	23.8%		



No. at risk

784 781 769 751 728 718 702 692 681 671 652 551 433 303 165 28 0 0
390 386 382 368 358 342 328 319 310 304 297 250 195 140 83 17 0 0

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

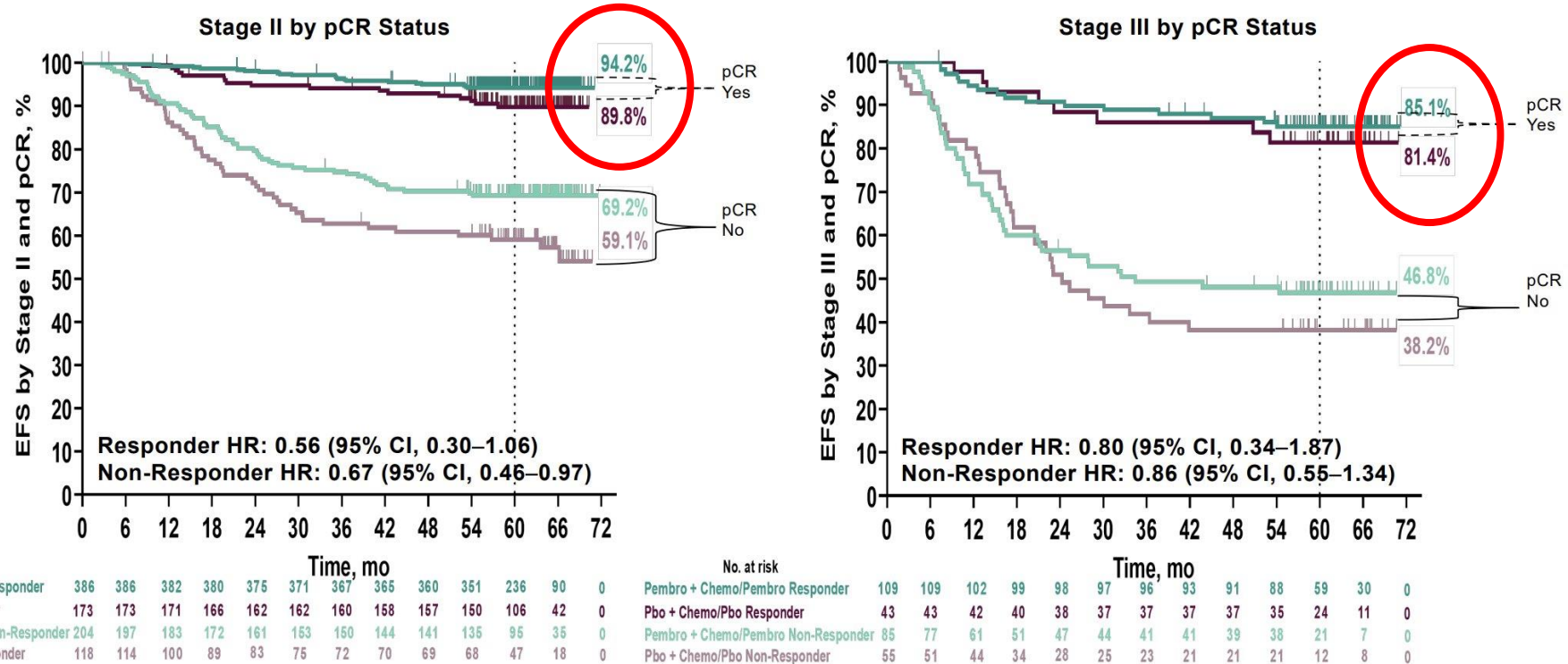


No. at risk

784 769 728 702 681 665 654 643 631 612 411 162 0
390 382 358 329 311 299 292 286 284 274 189 79 0

^aThe 4th prespecified interim analysis of EFS was calendar-driven planned to occur ~48 months after the first participant was randomized. ^bThe 6th prespecified interim analysis of EFS was calendar-driven planned to occur ~72 months after the first participant was randomized. ^cHazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. ^dPrespecified P-value boundary of 0.00517 was crossed. ^eDefined as the time from randomization to the data cutoff date of March 23, 2021. ^fDefined as the time from randomization to the data cutoff date of March 23, 2023. This presentation is the intellectual property of the author/presenter. Contact them at p.schmid@qmul.ac.uk for permission to reprint and/or distribute.

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



Data cutoff date of March 23, 2023.

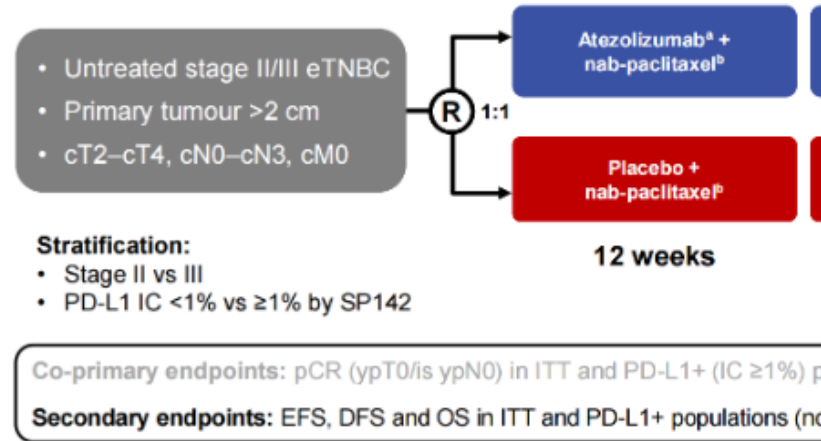
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N Engl J Med 2020;382:810-821 DOI: 10.1056/NEJMoa1910549

Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy

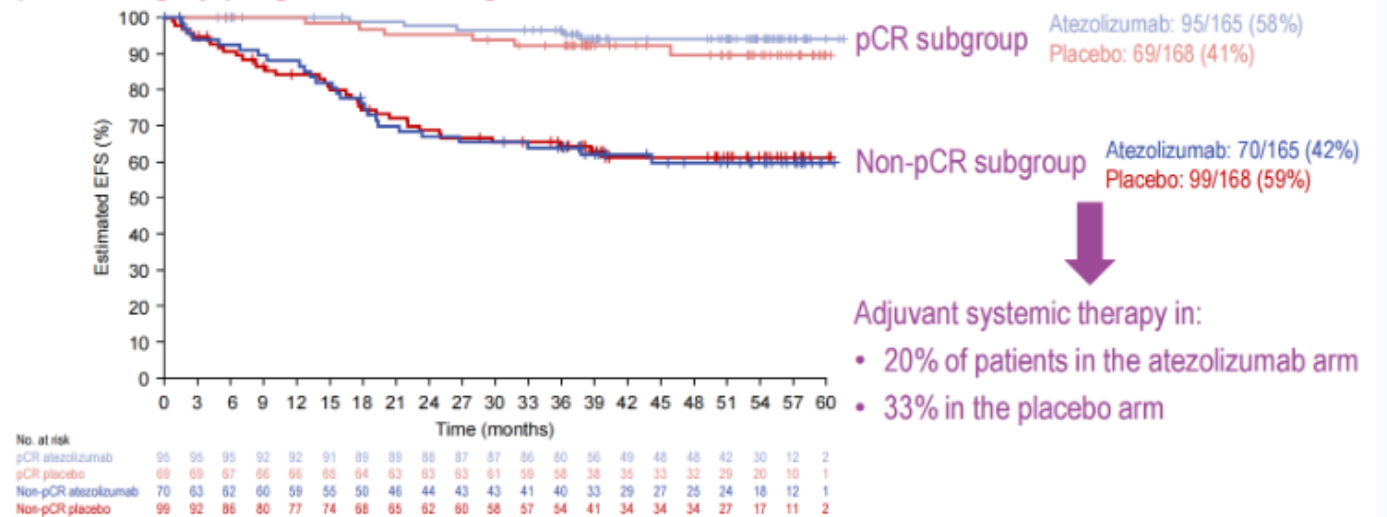
IMpassion031 TRIAL DESIGN

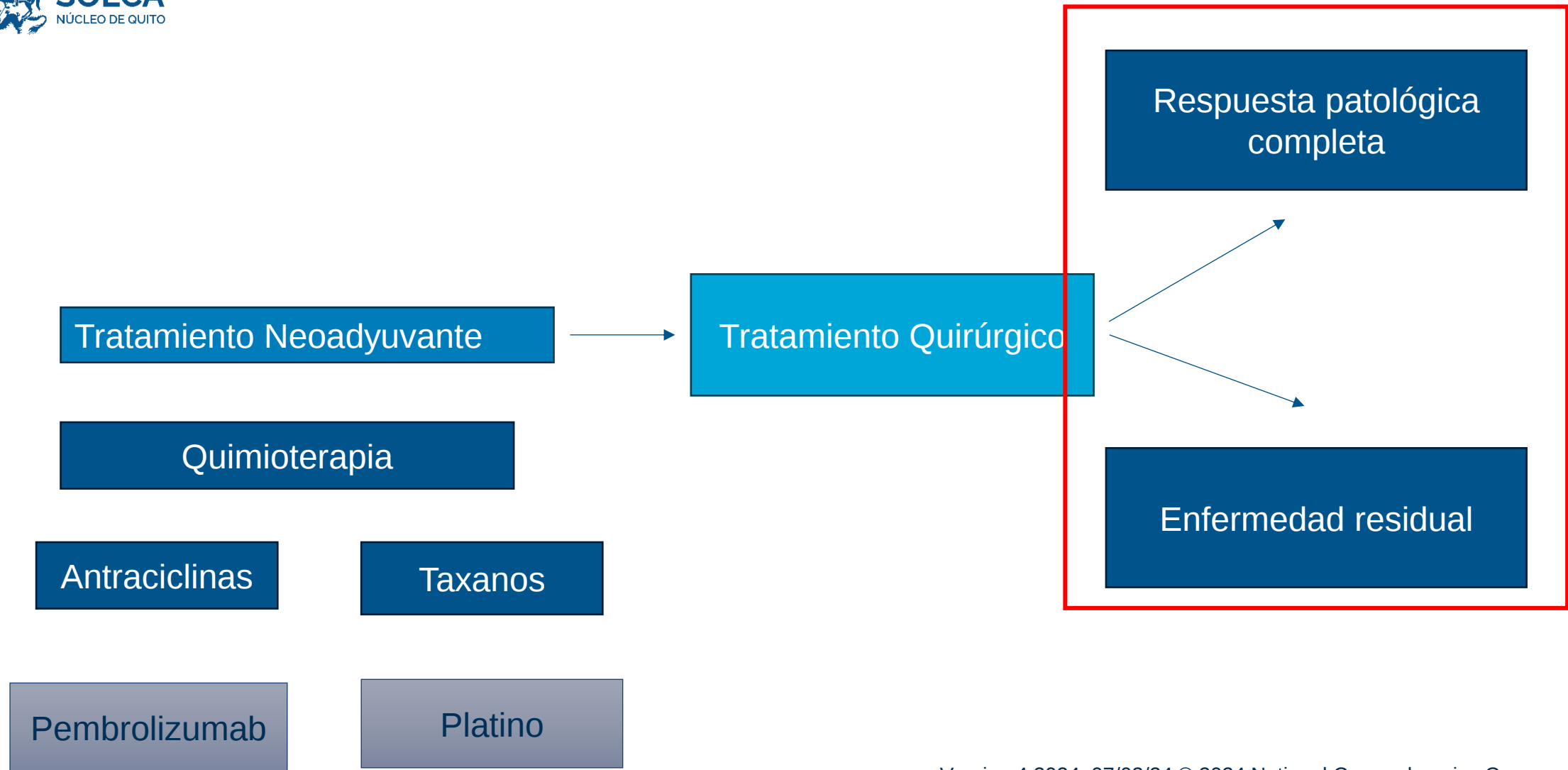
Randomised international phase 3 trial

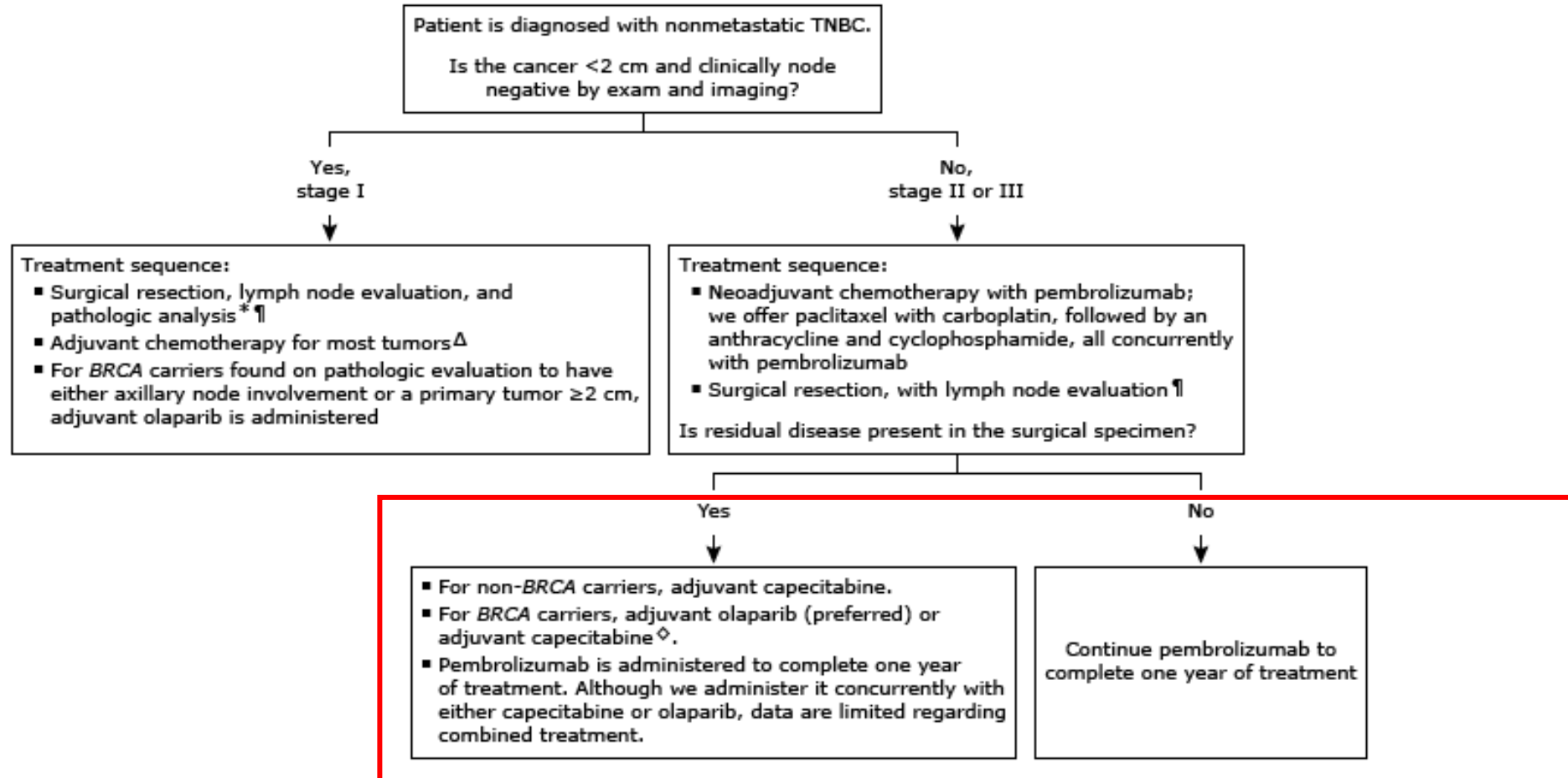


EXPLORATORY ANALYSIS: EFS BY pCR STATUS

pCR is highly prognostic for long-term outcome









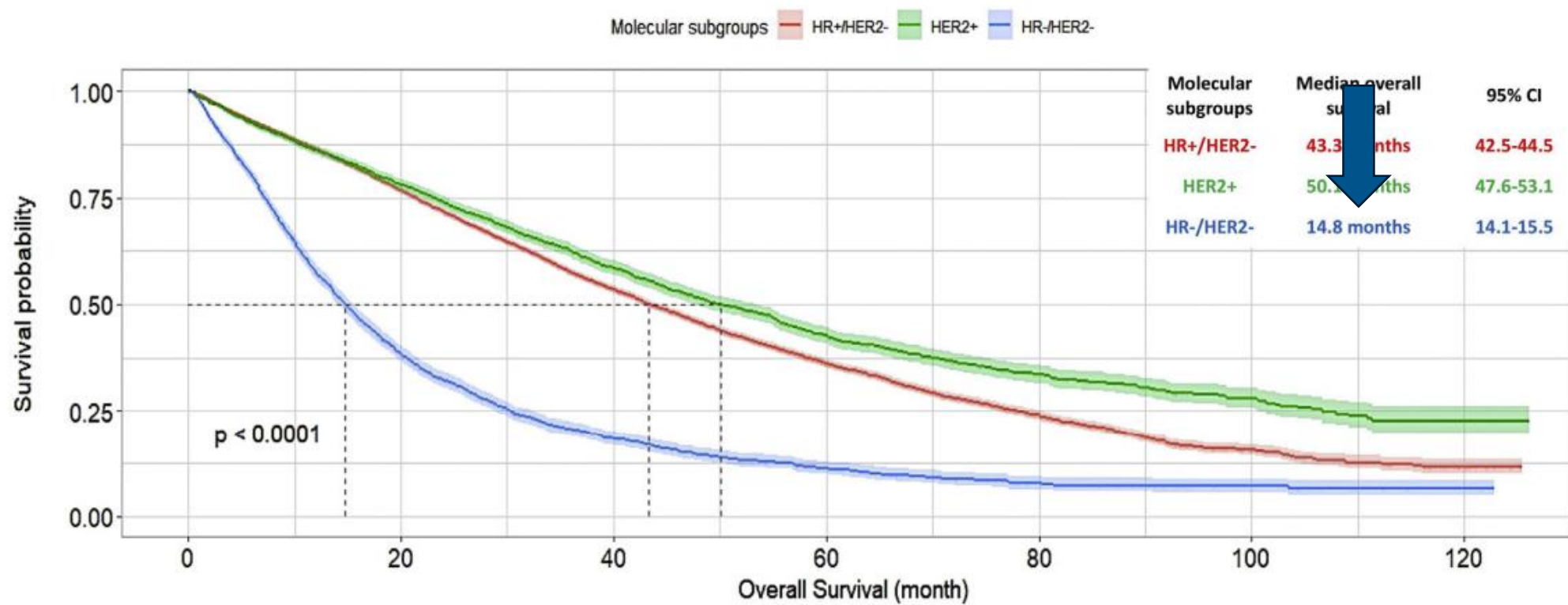
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desde 1954
DÉCADAS
de atención especializada en cáncer

Enfermedad metastásica

Overall survival in the three subcohorts with number at risk and 95% CI



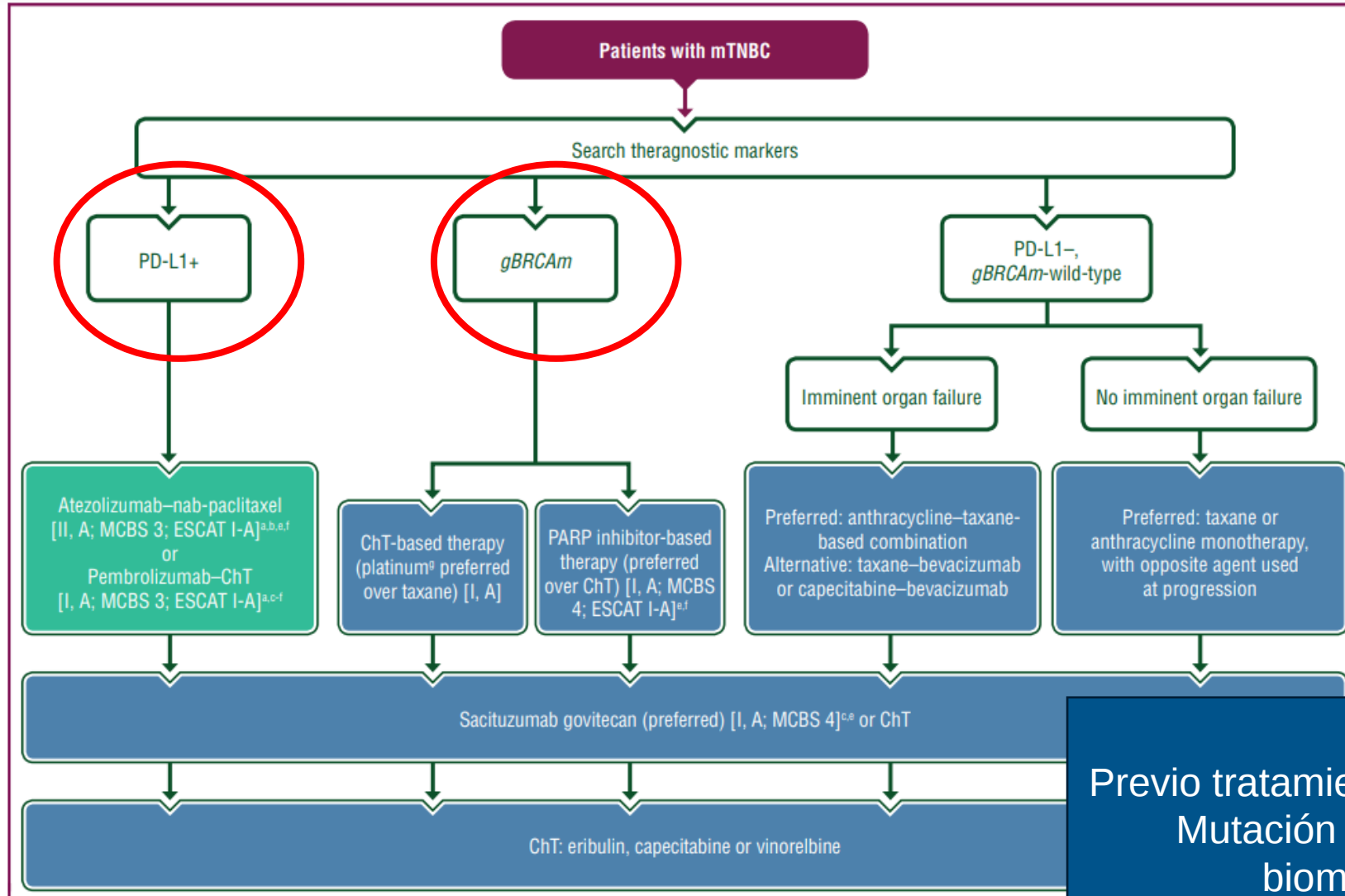
Eur J Cancer. 2020 Apr;129:60-70. doi: 10.1016/j.ejca.2020.01.016. Epub 2020 Mar 2. PMID: 32135312.

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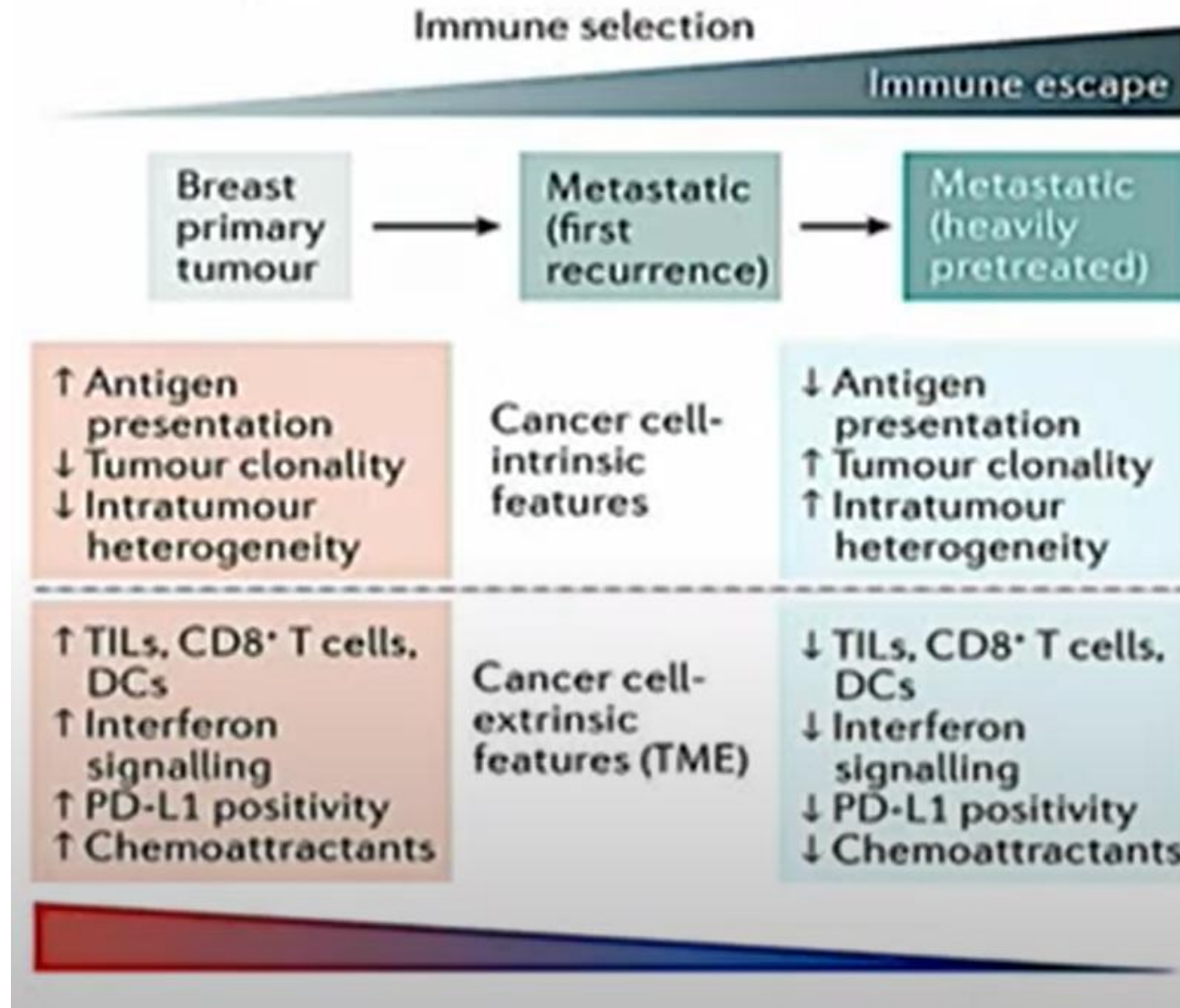
Invasive Breast Cancer

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE^a

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	Subtype/Biomarker	Regimen
First Line 	PD-L1 CPS $\geq 10^9$ regardless of germline <i>BRCA</i> mutation status ^b	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin) ^h (Category 1, preferred)
	PD-L1 CPS $< 10^9$ and no germline <i>BRCA1/2</i> mutation ^b	Systemic chemotherapy BINV-Q (5)
	PD-L1 CPS $< 10^9$ and germline <i>BRCA1/2</i> mutation ^b	• PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line 	Germline <i>BRCA1/2</i> mutation ^b	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan ⁱ (Category 1, preferred) Systemic chemotherapy BINV-Q (5)
	No germline <i>BRCA1/2</i> mutation ^b and HER2 IHC 1+ or 2+/ISH negative ^d	Fam-trastuzumab deruxtecan-nxki ^e (Category 1, preferred)
Third Line and beyond 	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents BINV-Q (6)
	Any	Systemic chemotherapy BINV-Q (5)



Previo tratamiento conocer PD-L1,
Mutación BRCA ½, otros
biomarcadores



pCR = PDL1 + O

40% BENEFICIO
INMUNOTERAPIA

Bianchini, G., De Angelis, C., Licata, L. *et al.* Treatment landscape of triple-negative breast cancer — expanded options, evolving needs. *Nat Rev Clin Oncol* 19, 91–113 (2022).

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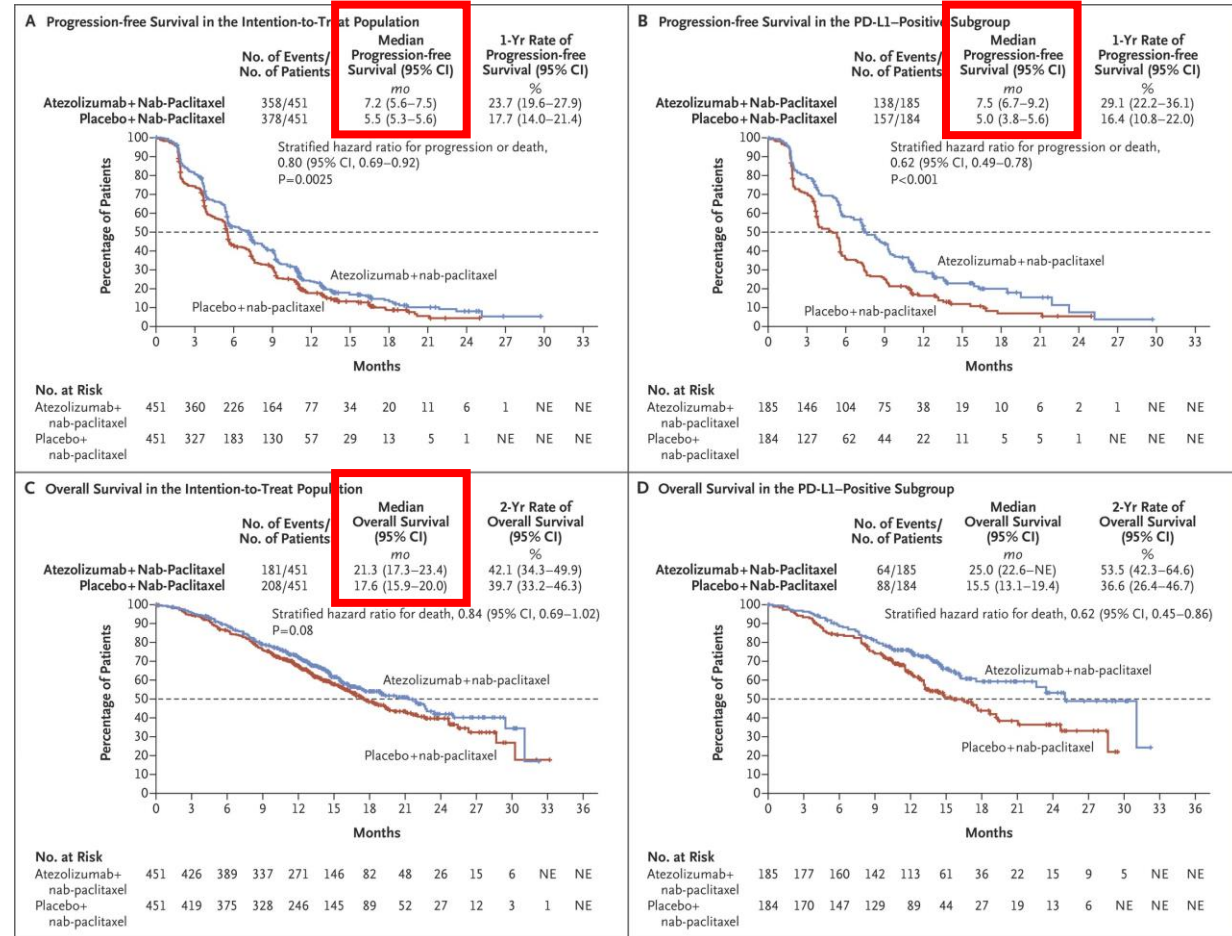
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Second Line	Germline <i>BRCA1/2</i> mutation ^b	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan ⁱ (Category 1, preferred) Systemic chemotherapy BINV-Q (5)
	No germline <i>BRCA1/2</i> mutation ^b and HER2 IHC 1+ or 2+/ISH negative ^d	Fam-trastuzumab deruxtecan-nxki ^e (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents BINV-Q (6)
	Any	Systemic chemotherapy BINV-Q (5)

IMpassion 130 Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

Combinación con quimioterapia funciona



KEYNOTE-355 Study Design (NCT02819518)

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

847

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)

Patient characteristics

Age	Median 53 years
PD-L1 + CPS ≥1	75.1%
PD-L1 + CPS ≥10	36.7 – 38.9%
Chemo on study	45% Taxane 55% Gem/carbo

Primary Endpoint: PFS and OS in PD-L1+ tumors and ITT population

Secondary EP: ORR, DOR, DCR, safety

847 pts randomized 2:1 with median f/u ~26m

3W)

y 28 days
days
and 8 every 21 days

^cNormal saline

^dTreatment may be continued until confirmation of progressive disease

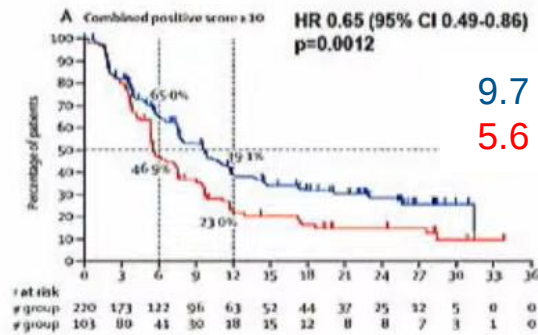
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group;

PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

CPS=combined positive score

KN355: Pembrolizumab + CT

PD-L1 CPS ≥ 10



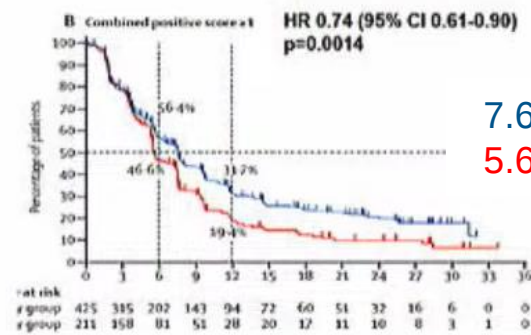
PFS superiority CPS ≥ 10
boundary $\alpha=0.00411$

Pembrolizumab + chemo (n = 220)

Placebo + chemo (n = 103)

38% of patients

PD-L1 CPS ≥ 1



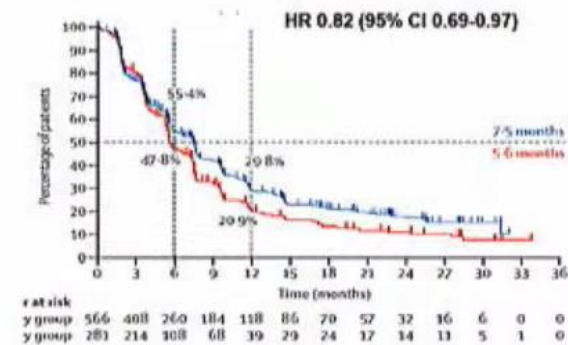
PFS superiority CPS ≥ 1
boundary $\alpha=0.00111$ not met

Pembrolizumab + chemo (n = 425)

Placebo + chemo (n = 211)

75% of patients

ITT population



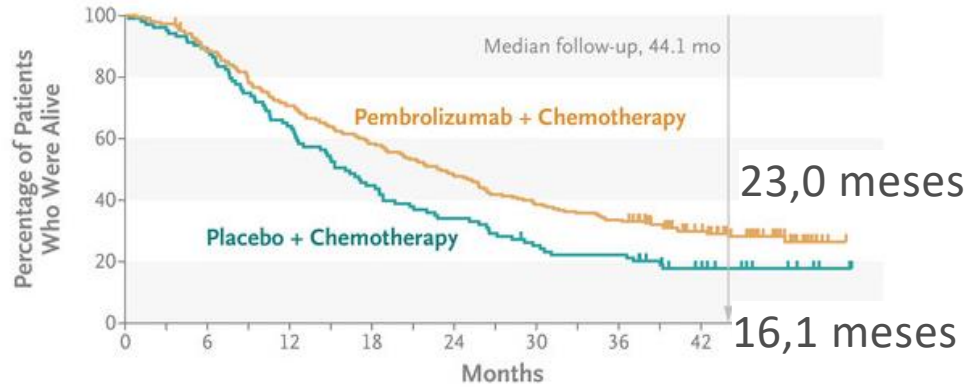
Significance not tested according to
hierarchical statistical design

Pembrolizumab + chemo (n = 566)

Placebo + chemo (n = 281)

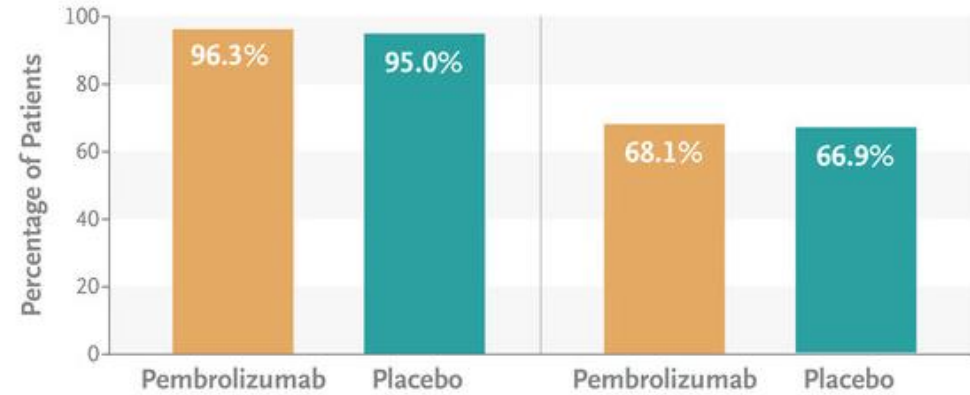
Overall Survival in the CPS-10 Subgroup

HR for death, 0.73 (95% CI, 0.55–0.95); P=0.0185



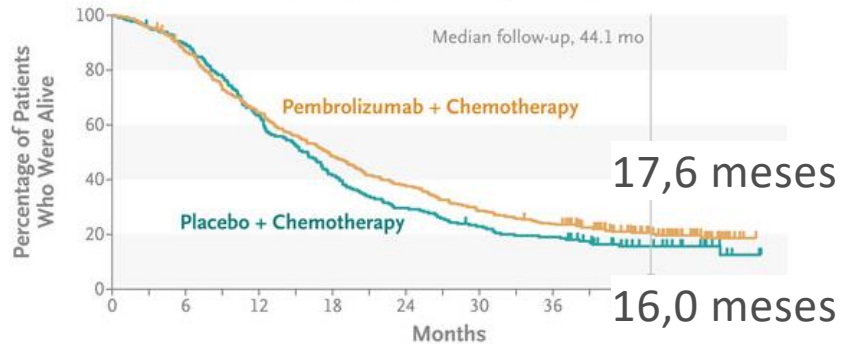
Any Treatment-Related Adverse Event

Grade ≥3 Treatment-Related Adverse Event



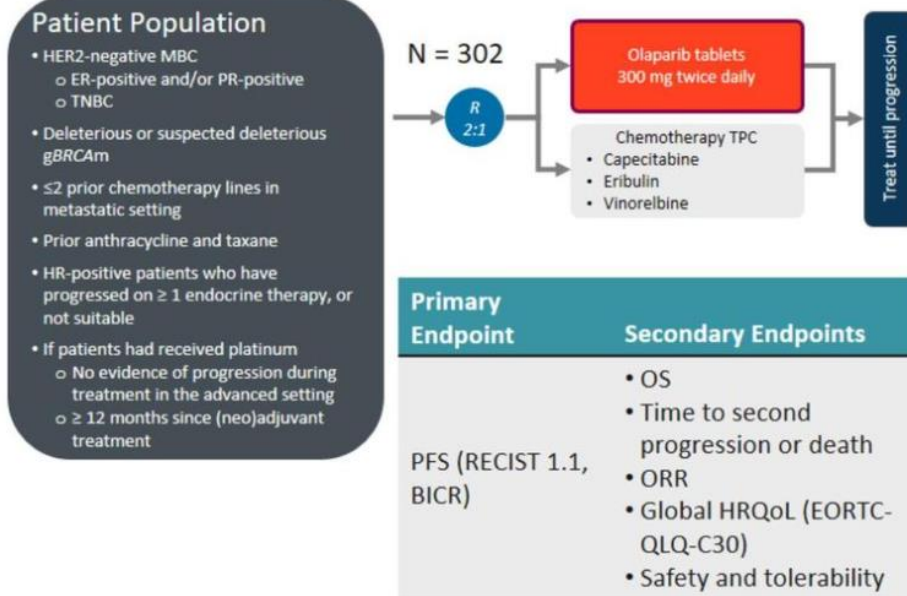
Overall Survival in the CPS-1 Subgroup

HR for death, 0.86 (95% CI, 0.72–1.04); P=0.1125

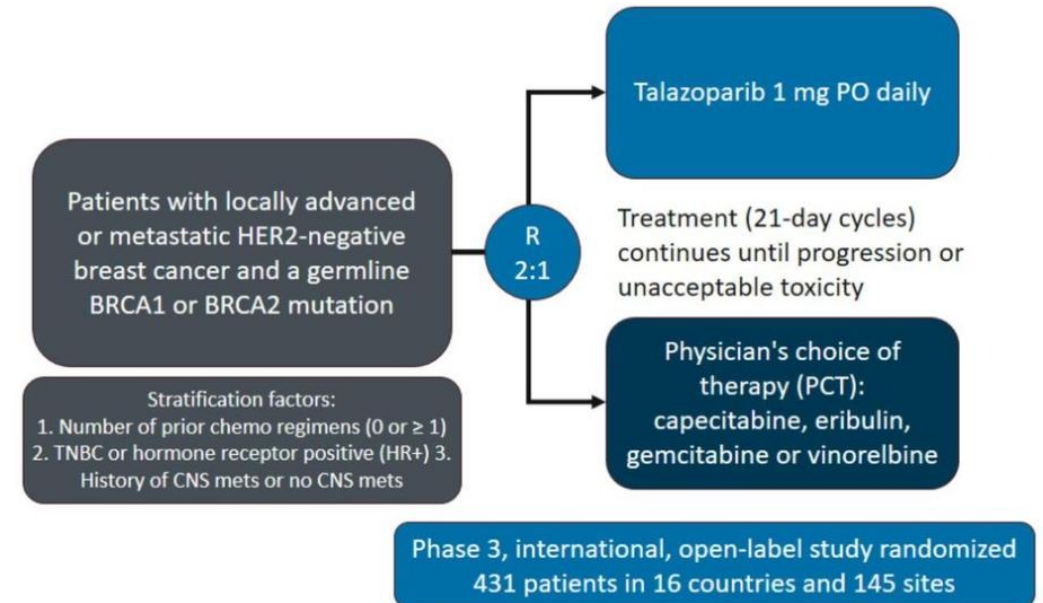


Tumores expresan PD-L1 con un CPS de 10 o más, la adición de pembrolizumab a la quimioterapia resultó en una supervivencia general significativamente más prolongada que la quimioterapia sola

OlympiAD: Study Design



EMBRACA: Study Design

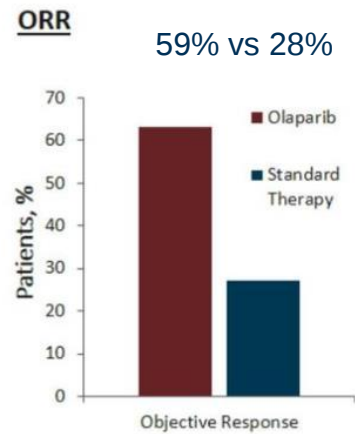
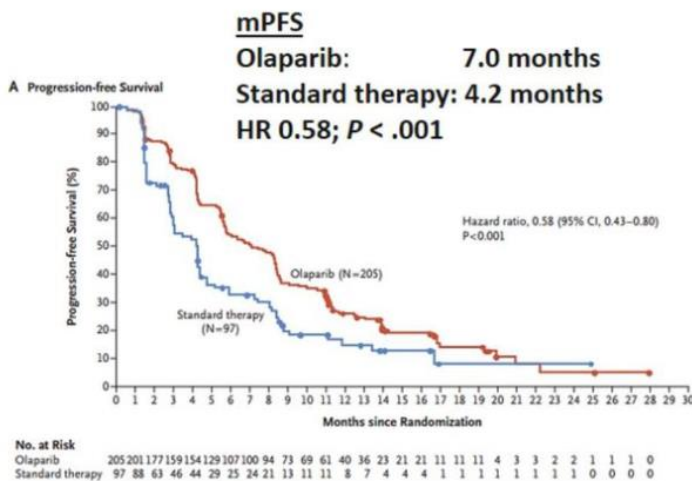


No mas de 3 líneas, taxano o antraciclinas

N Engl J Med 2017;377:523-533 DOI: 10.1056/NEJMoa1706450

N Engl J Med 2018;379:753-763 DOI: 10.1056/NEJMoa1802905

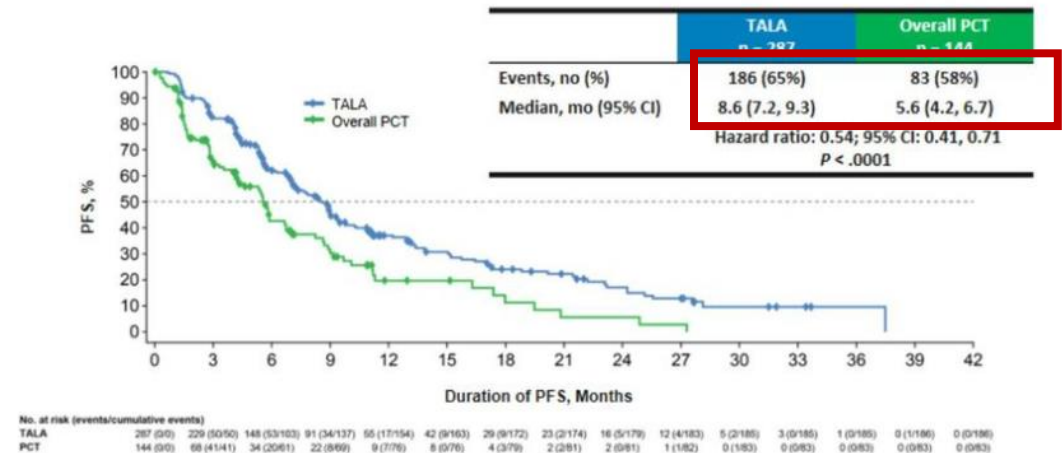
OlympiAD: Olaparib Improves mPFS and ORR



El riesgo de progresión de la enfermedad o muerte fue un 42% menor con la monoterapia con olaparib

N Engl J Med 2017;377:523-533 DOI: 10.1056/NEJMoa1706450
N Engl J Med 2018;379:753-763 DOI: 10.1056/NEJMoa1802905

EMBRACA Primary Endpoint: PFS by Blinded Central Review



1-year PFS: 37% vs 20%
Median follow-up time: 11.2 months

ORR fue talazoparib 62,6% frente a 27,2%.

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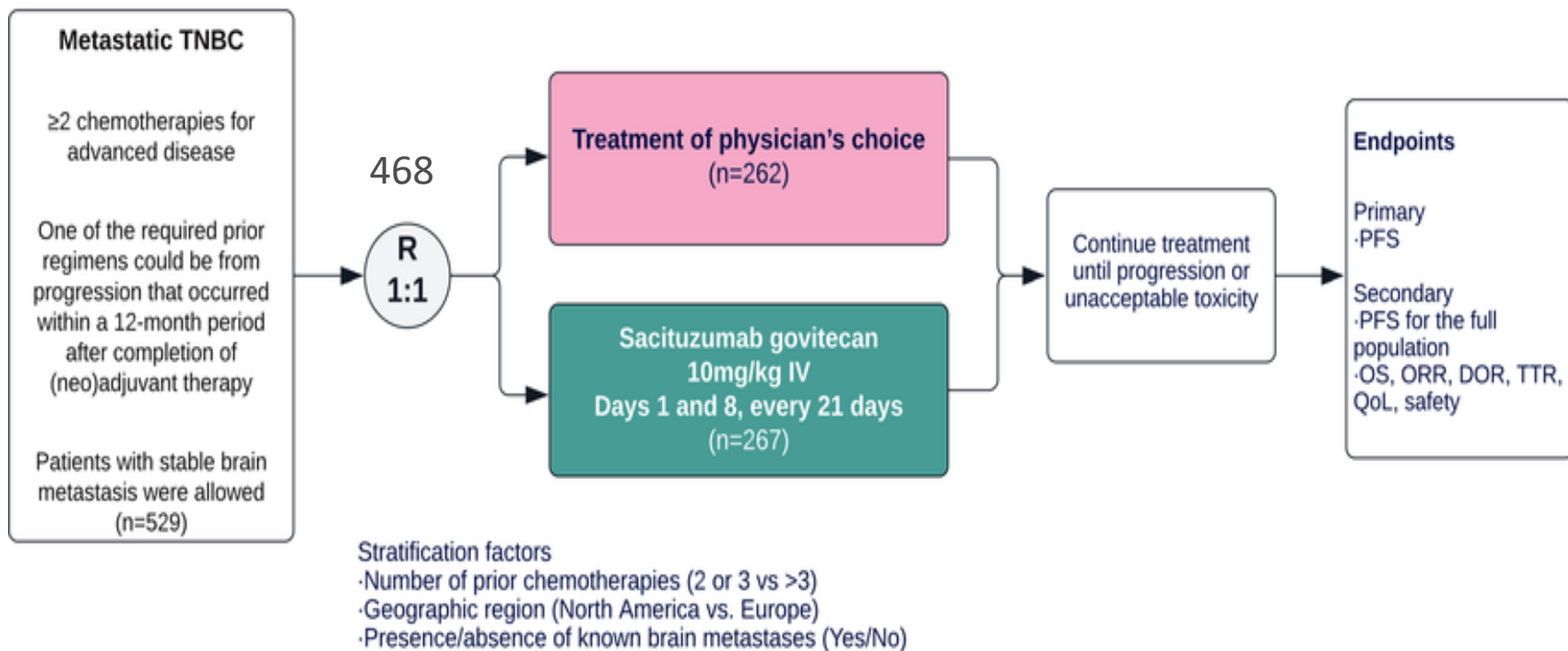
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Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents BINV-Q (6)
	Any	Systemic chemotherapy BINV-Q (5)

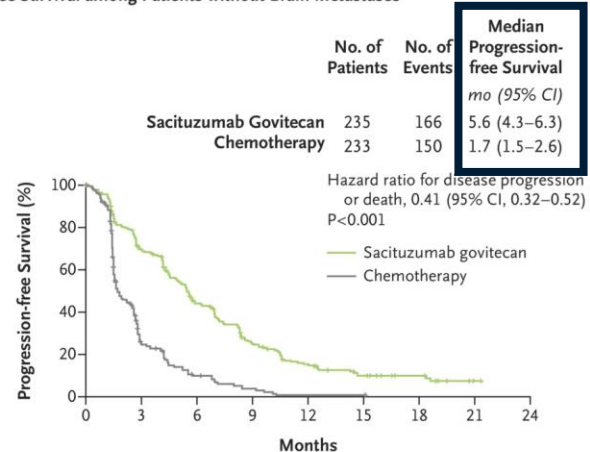
ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC

NCT02574455



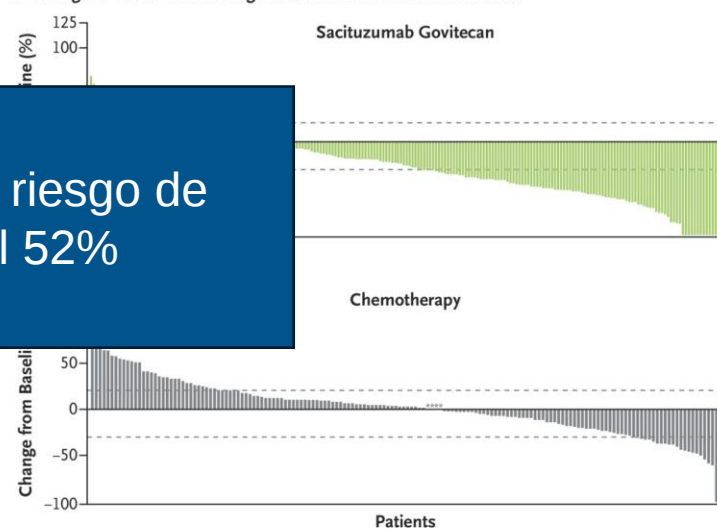
N Engl J Med 2021;384:1529-1541 DOI: 10.1056/NEJMoa2028485

A Progression-free Survival among Patients without Brain Metastases

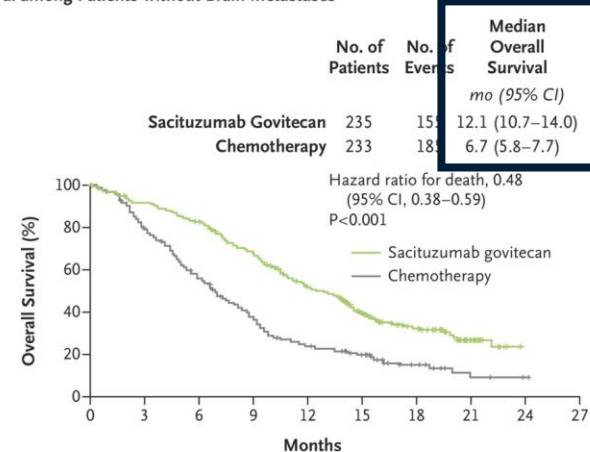


No. at Risk								
Sacituzumab govitecan	235	154	91	49	28	15	9	1
Chemotherapy	233	39	14	5	1	1	0	0

C Change in Tumor Size among Patients without Brain Metastases

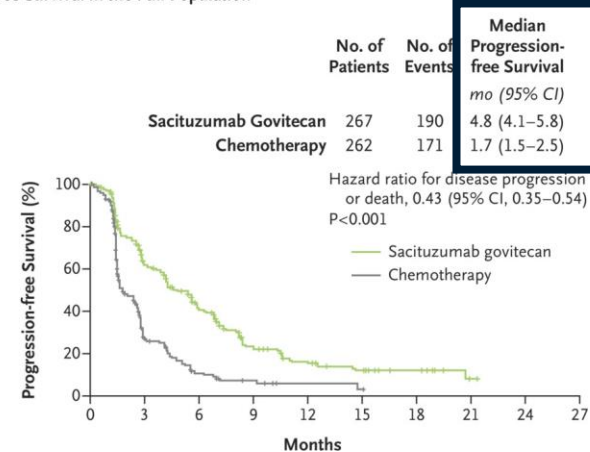


B Overall Survival among Patients without Brain Metastases



No. at Risk								
Sacituzumab govitecan	235	214	190	153	107	70	37	13
Chemotherapy	233	173	117	74	45	30	11	3

D Progression-free Survival in the Full Population



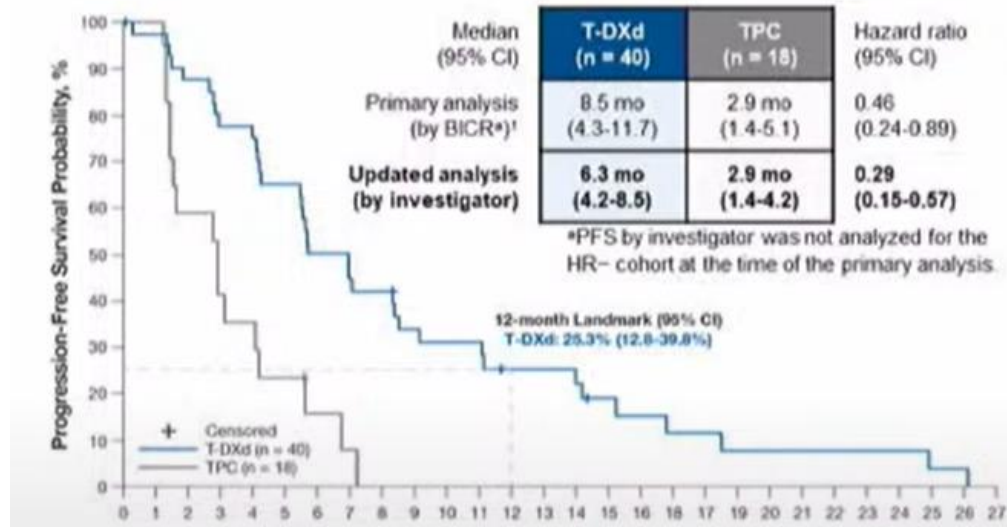
No. at Risk								
Sacituzumab govitecan	267	145	82	38	23	14	8	1
Chemotherapy	262	41	13	6	2	1	0	0

Reducción del riesgo de muerte del 52%

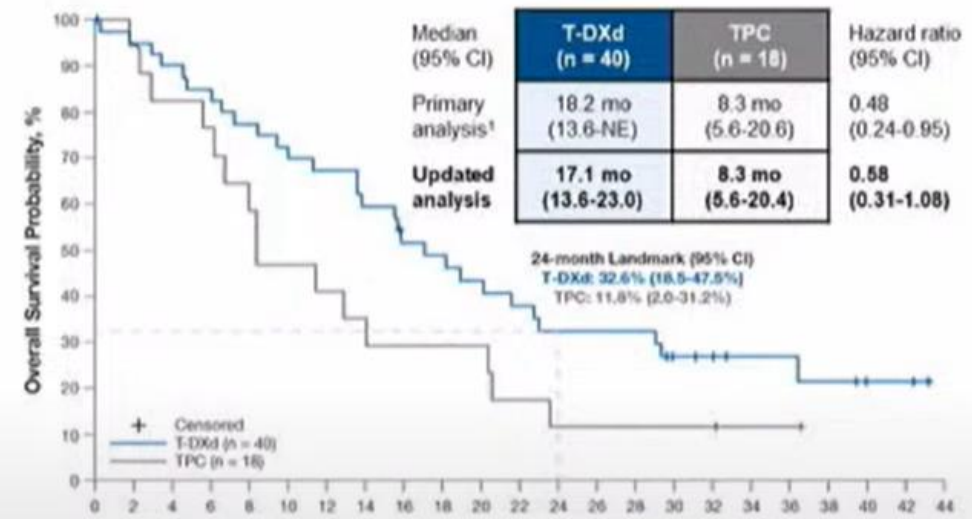
Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

DESTINY BR04: 58 patients with TNBC (HER2-low)

PFS



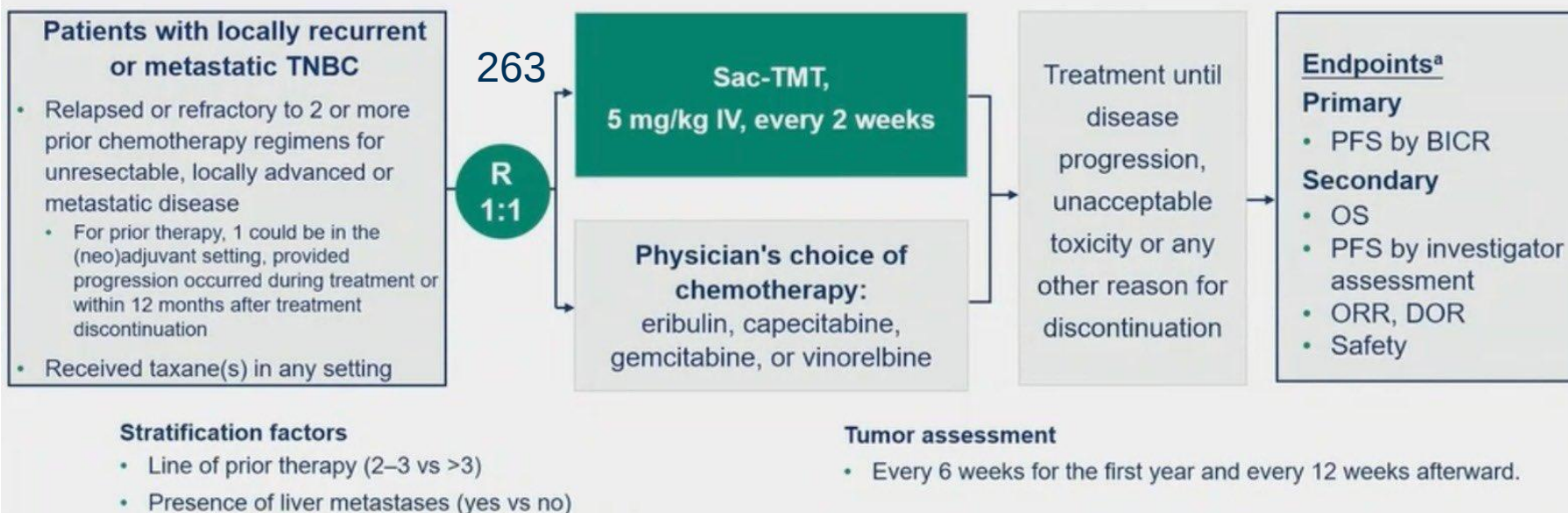
OS



2022 Jul 7;387(1):9-20. doi: 10.1056/NEJMoa2203690

OptiTROP-Breast01: Randomized, Controlled, Open-Label Phase III Study (NCT05347134)

5

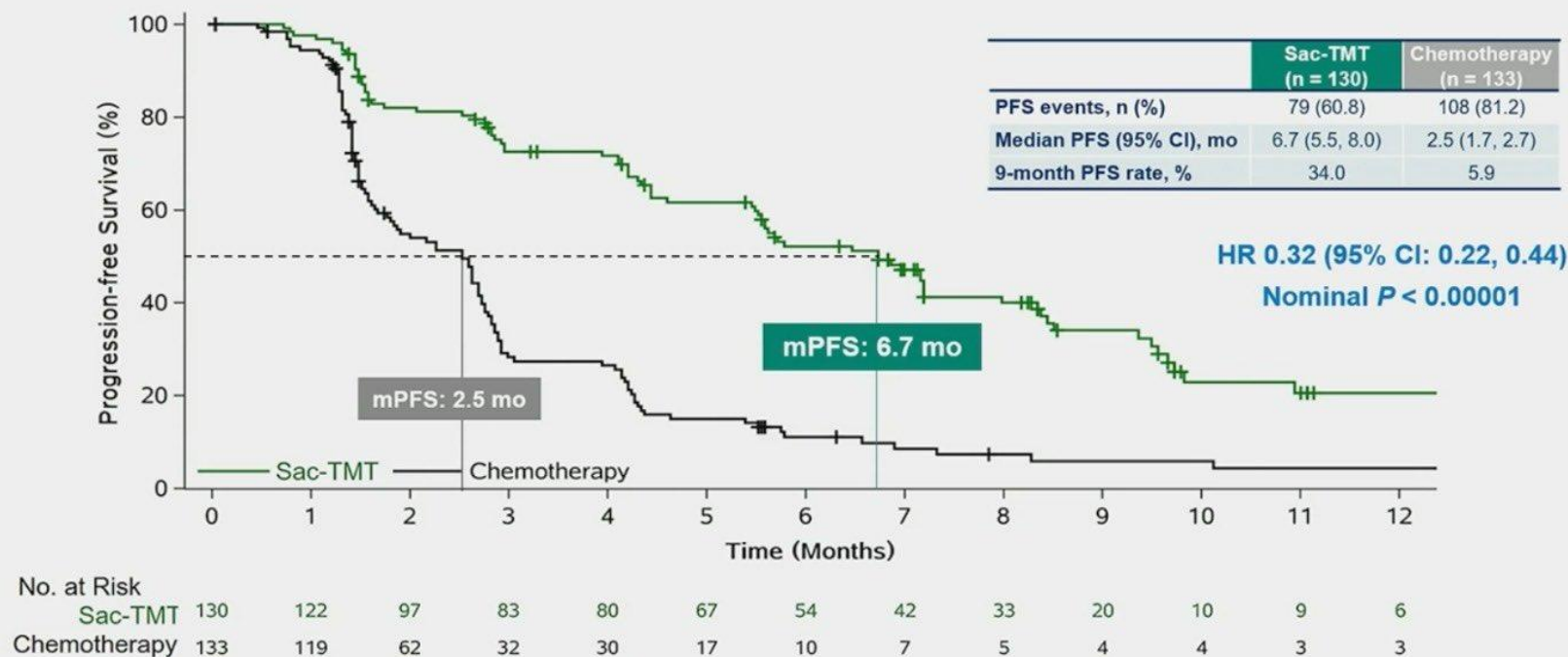


^aTumor response was assessed using RECIST version 1.1.

BICR, blinded independent central review; DOR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer.

Progression-Free Survival by BICR (Final Analysis)

Sac-TMT significantly improved PFS over chemotherapy with a 68% lower risk of disease progression or death.



• PFS by investigator assessment (secondary endpoint): Median 6.5 vs 2.6 mo; HR 0.32 (95% CI: 0.24, 0.44)

Data cutoff: Nov 30, 2023; the protocol-specified final analysis of PFS. Median follow up was 10.4 months.
BICR, blinded independent central review; CI, confidential interval; HR, hazard ratio; mPFS, median progression-free survival.

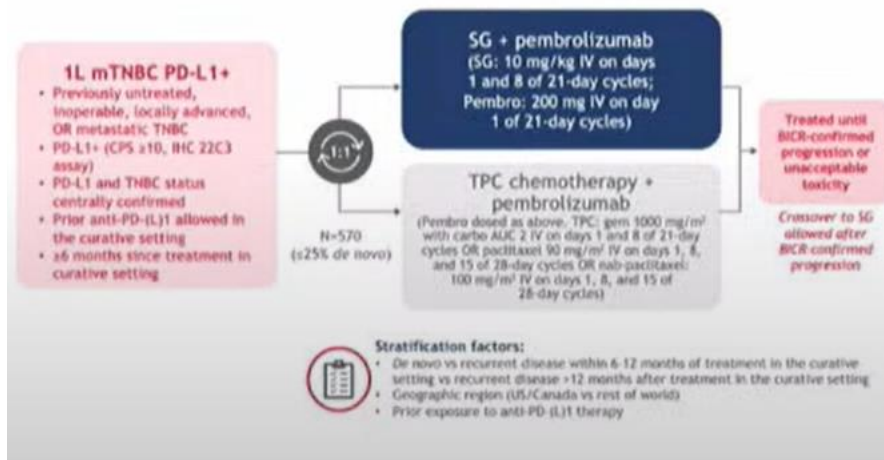
Disminuyó el riesgo de progresión o muerte en un 68%.

ESTUDIOS EN DESARROLLO

SACITUZUMAB GOVITECAN

ASCENT-04

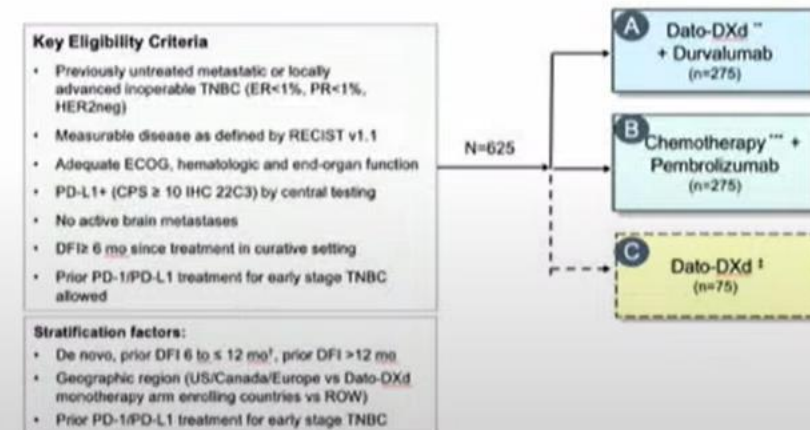
SG+ pembro vs TPC+ pembro in
1L PD-L1+ mTNBC



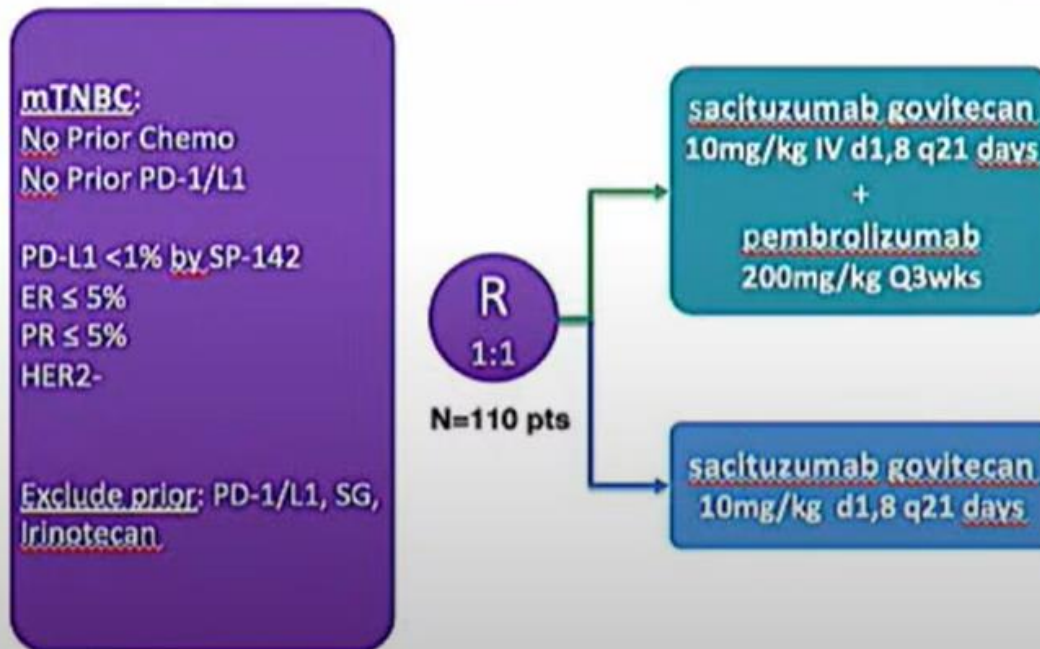
DATOPOTAMAB DERUXTECAN

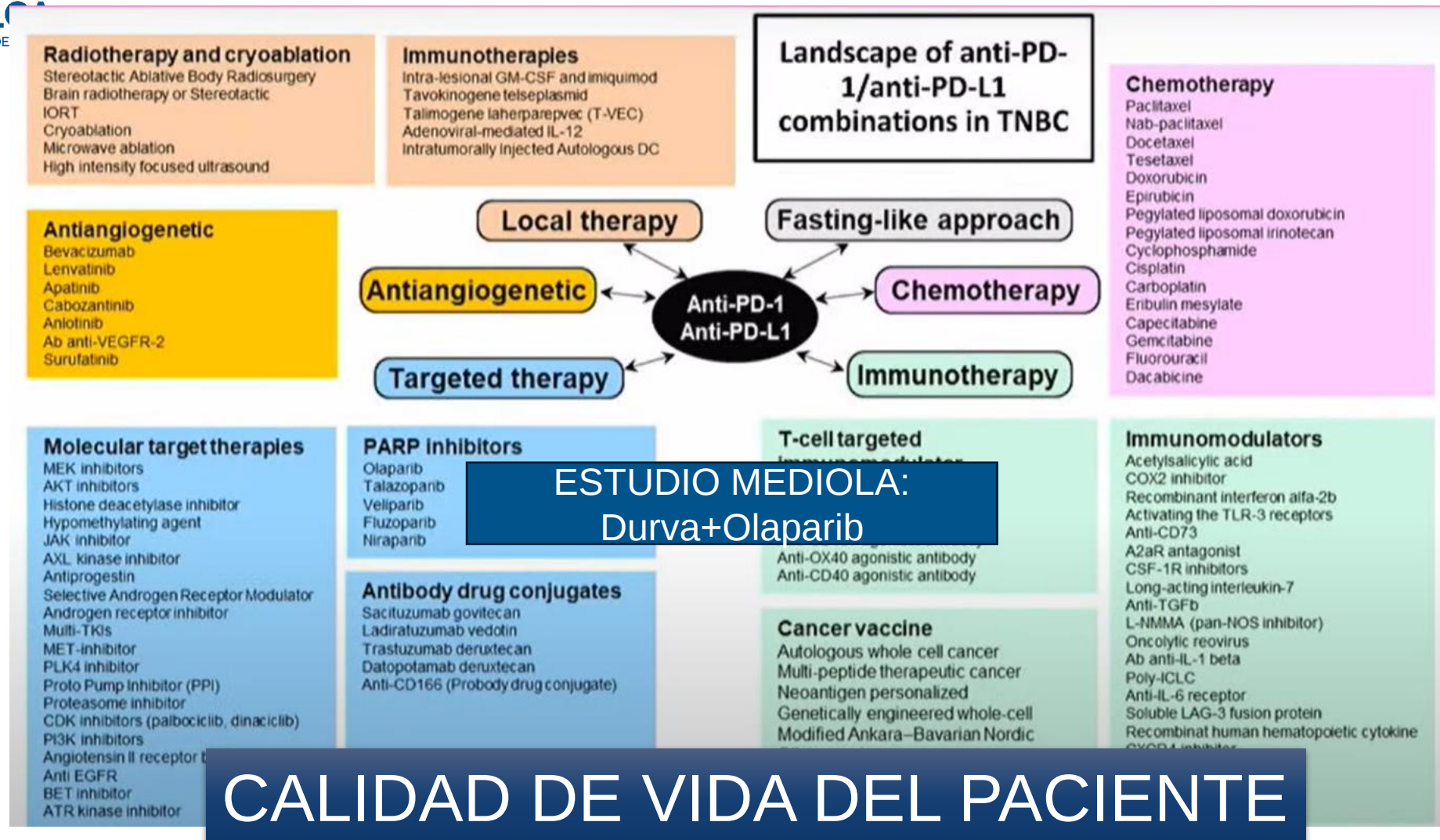
TROPION-Breast05

Dato-DXd +/- durva vs TPC + pembro in
1L PD-L1+ mTNBC



SACI IO TNBC: SG +/- pembro in PD-L1- 1L mTNBC





Bianchini G, ESMO Breast 2023

CONCLUSIONES

- La neoadyuvancia constituye una practica que mejora la sobrevida global y sobrevida libre de progresión
- El tratamiento adyuvante demuestra beneficio sobretodo en pcientes sin pCR
- En enfermedad metastásica previo a iniciar tratamiento ideal PDL1 y mutación germinal BRCA
- Inmunoterapia mas quimioterapia es una alternativa en primera línea en pacientes PDL 1 con puntaje mayor o igual a 10
- Se deben buscar alternativas en la enfermedad metastásica que mejora la sobrevida libre de progresión, hay estudios interesantes con anticuerpos conjugados (ADC)
- Pacientes con recaídas menores a 6 y 12 meses?? IMpassion 132 (negativo)



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