



18^{as} Jornadas HITOS
ONCOLÓGICOS: LO MEJOR DE 2023

Madrid, 22 y 23 de noviembre de 2023

Actualización en el tratamiento del cáncer de mama triple negativo metastásico

Fernando Moreno

Hospital Clínico San Carlos

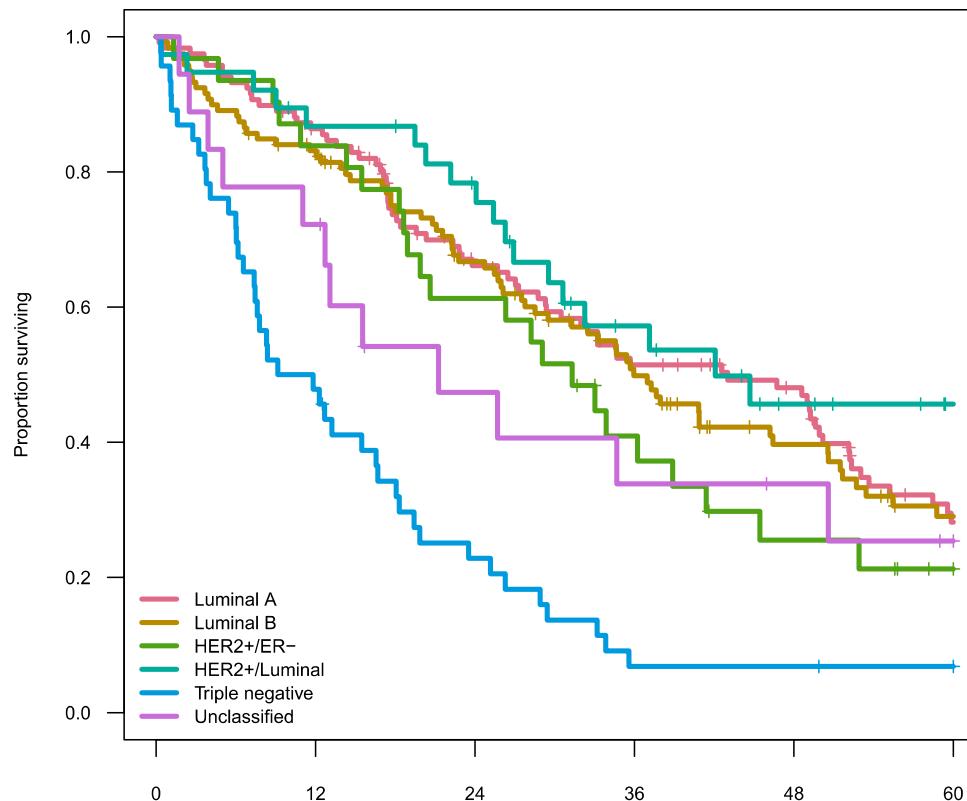
Conflictos de interés

- Consultancy/speaker fees from Novartis, Roche, Pfizer, Astra Zeneca, Daichi-Sankyo, Gilead, Exact Sciences, Seagen
- Institution research funding from Pfizer
- Travel support from Pfizer, Pierre Fabre

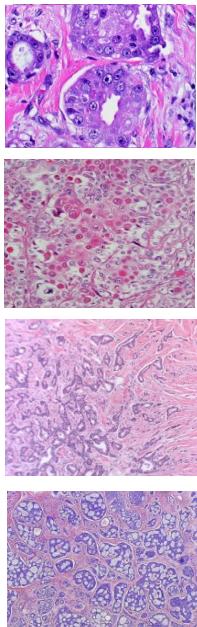


Long-term treatment survival in metastatic breast cancer

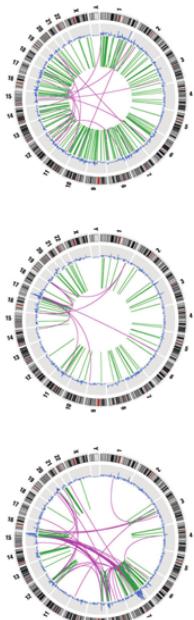
MBC managed at Uppsala University during 2009–2016



Histology

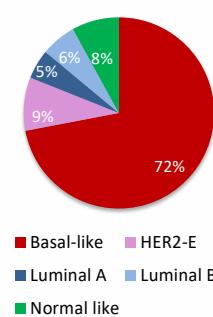


Mutation profile

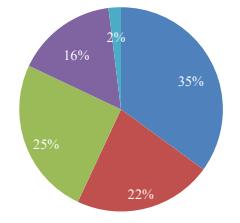


Gene expression

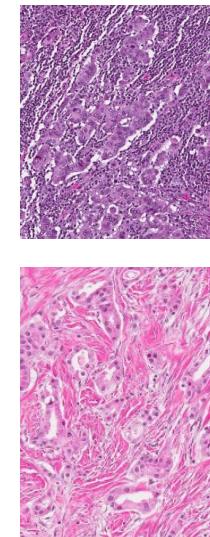
Subtipo Intrínseco PAM50



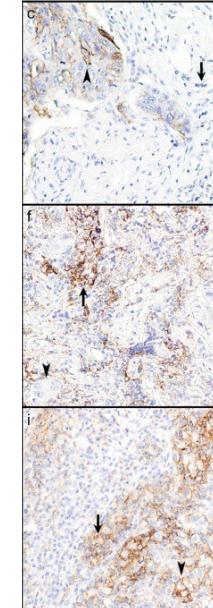
Clasificación de Burstein



Tumor Stromal TILs

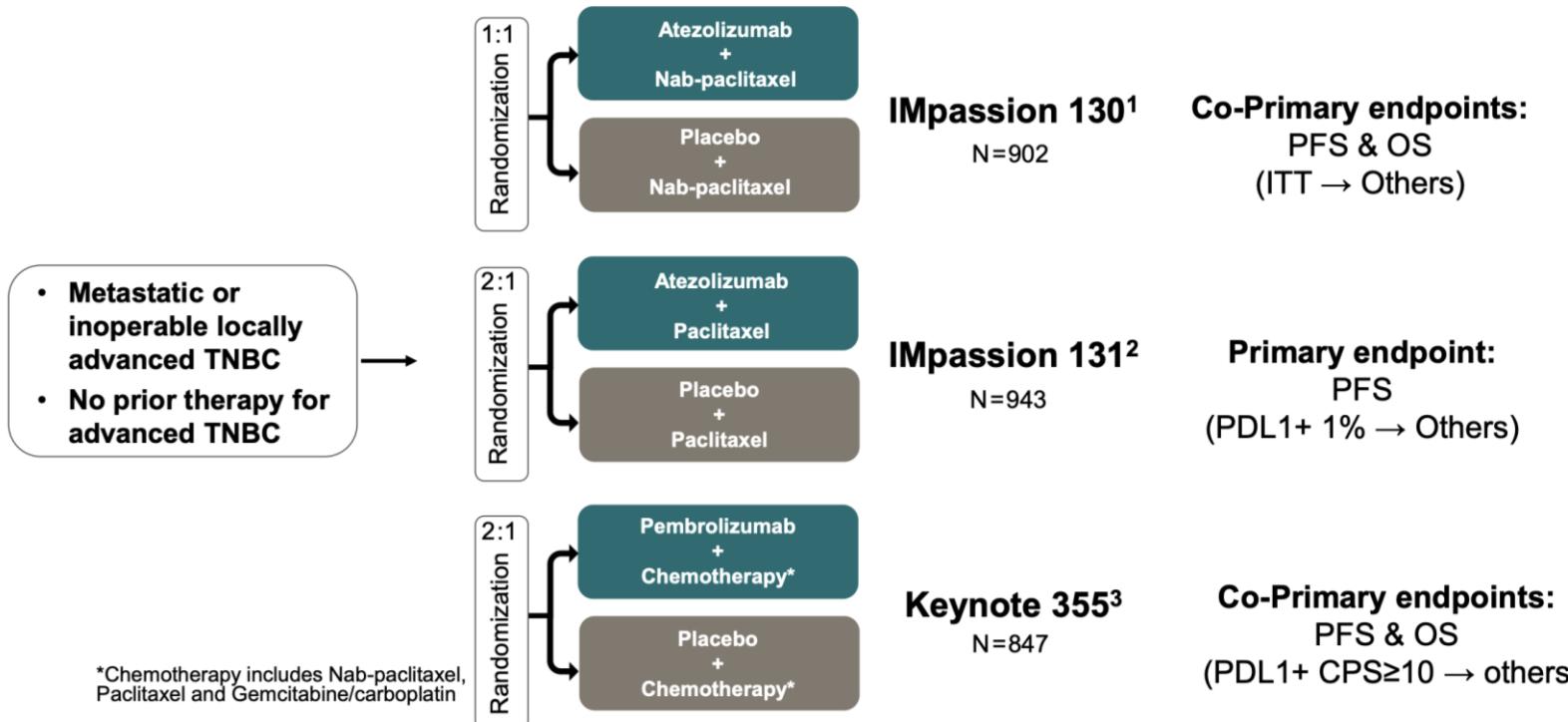


PD-L1 Expression



Immunotherapy

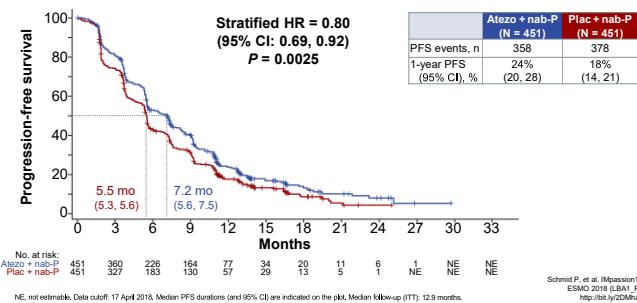
Immune Checkpoint Inhibitors: Randomized Phase III Trials: Design



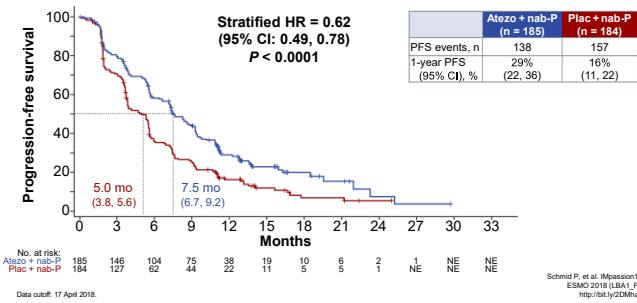
ICIs: Progression Free Survival

IMpassion 130

PFS in the ITT population

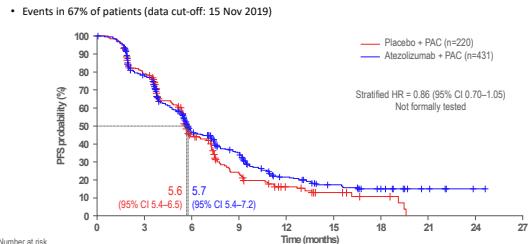


PFS PD-L1+ (IC \geq 1%)

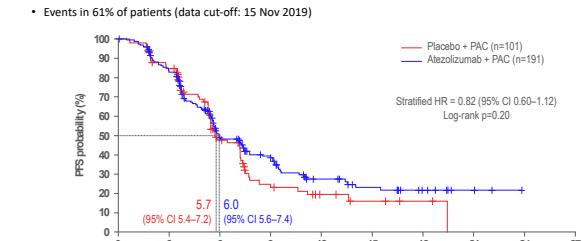


IMpassion 131

PFS in the ITT population
(Not formally tested)

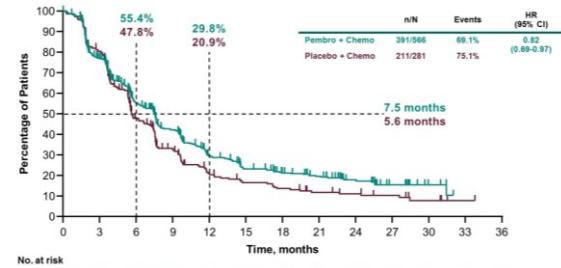


PFS PD-L1+ (IC \geq 1%)

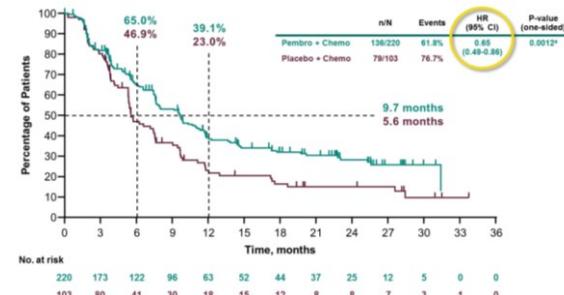


Keynote 355

PFS in the ITT population
(Not formally tested)



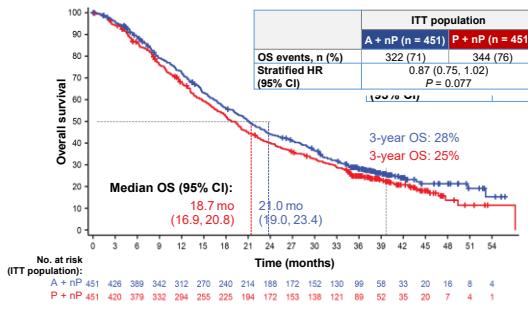
PFS PD-L1+ (CPS \geq 10)



ICIs: Overall Survival

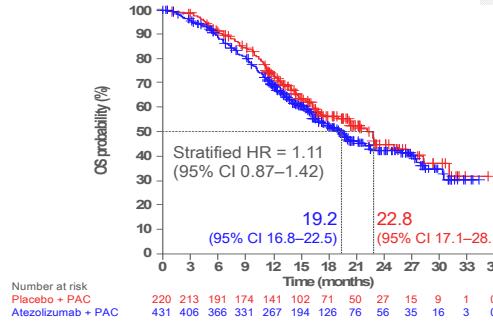
IMpassion 130

OS in the ITT population X



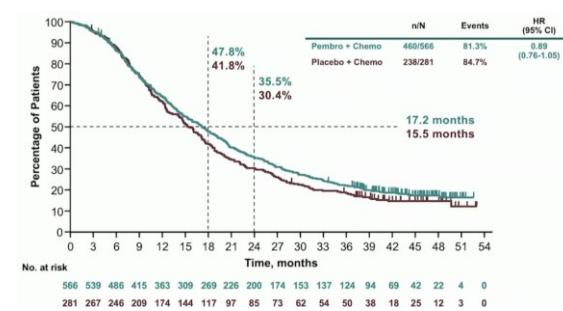
IMpassion 131

OS in the ITT population X

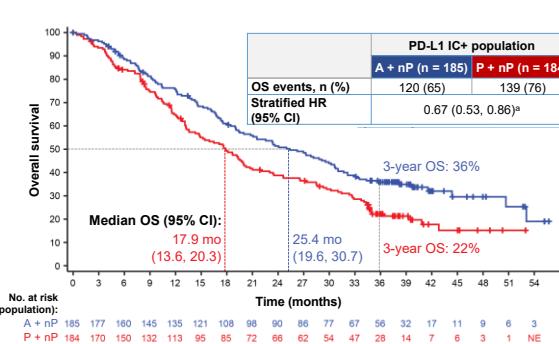


Keynote 355

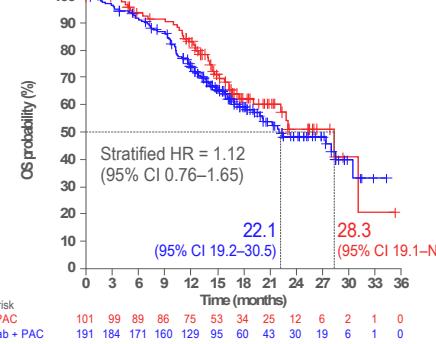
OS in the ITT population X



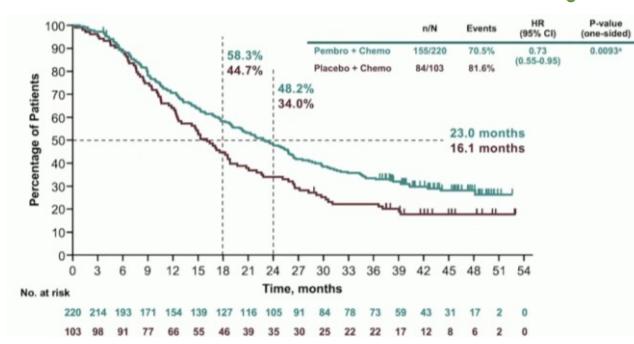
OS PD-L1+ (IC ≥ 1%) Not formally tested ✓

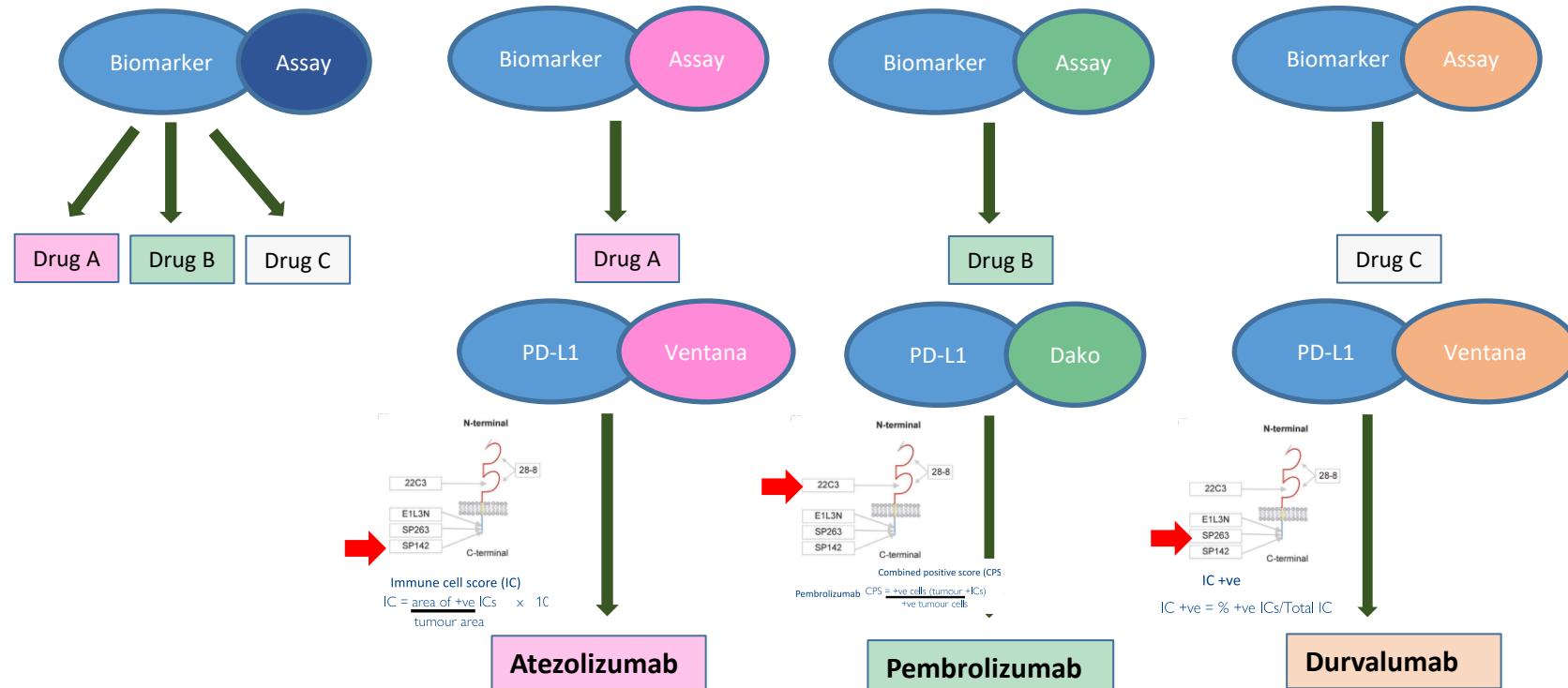


OS PD-L1+ (IC ≥ 1%) X



OS PD-L1+ (CPS ≥ 10) ✓

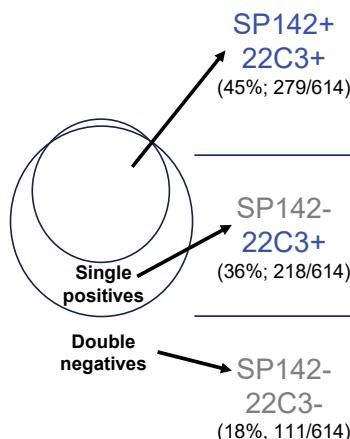
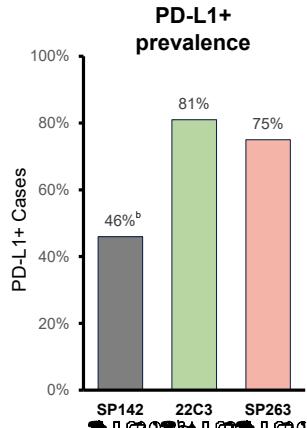




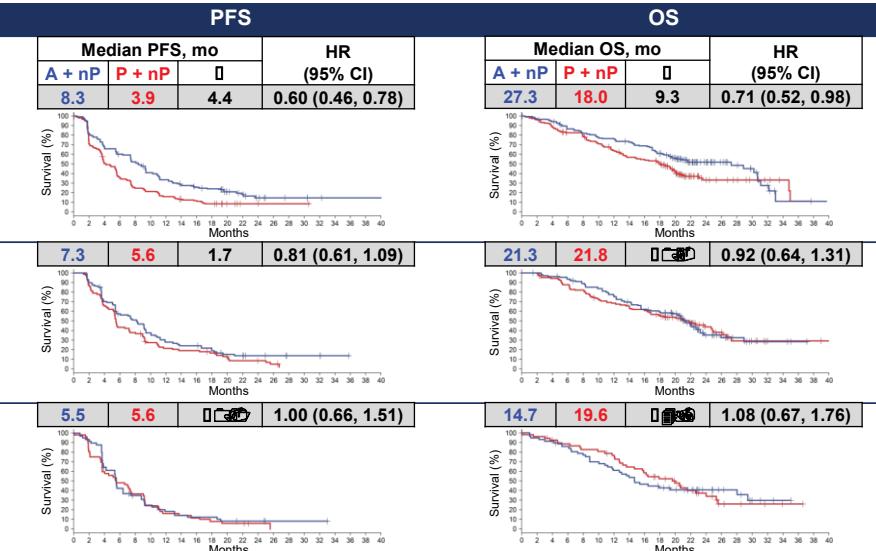


Performance of PD-L1 IHC assays in metastatic TNBC: post hoc analysis of IMpassion130

PD-L1 IHC assays: prevalence and analytical concordance



Clinical outcomes in subpopulations defined by SP142 (IC 1%) and 22C3 (CPS1)



- With overall percentage agreements of 64% (22C3) the analytical concordance was subpar (< 90%) and the assays are not equivalent
- The clinical benefit in 22C3+ and SP263+ subgroups was driven by the SP142+ subgroup

ICIs: Lessons learned from Phase III trials

Atezolizumab
+
nab-paclitaxel

- Improvement in PFS ($\Delta 2.5\text{-}3.9$ months)
- Improvement in OS ($\Delta 7.6\text{-}6.9$ months)



OS should be the goal of ICIs trials

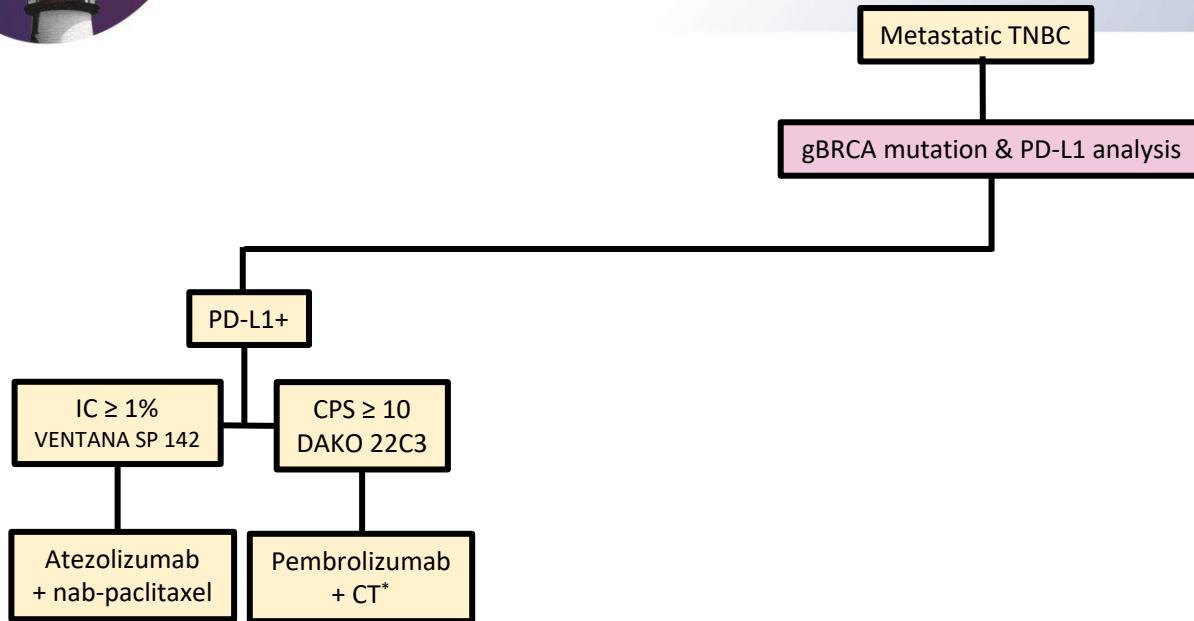
Pembrolizumab
+
Chemotherapy

- Limited to PD-L1 + population
(IC $\geq 1\%$ -Atezo; CPS ≥ 10 -pembro)



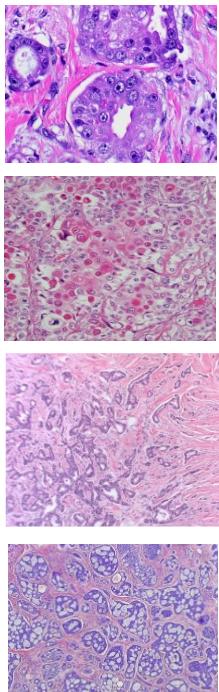
PD-L1 is predictive and should be tested
to choose first line treatment in advanced
TNBC

Biomarker analysis are needed!

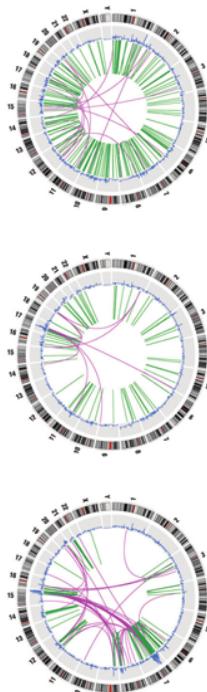




Histology

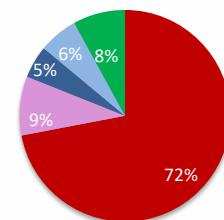


Mutation profile



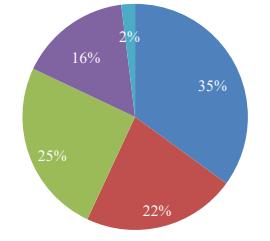
Gene expression

Subtipo Intrínseco PAM50



- Basal-like ■ HER2-E
- Luminal A ■ Luminal B
- Normal like

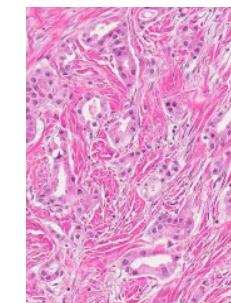
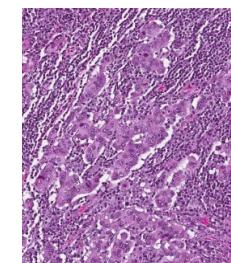
Clasificación de Burstein



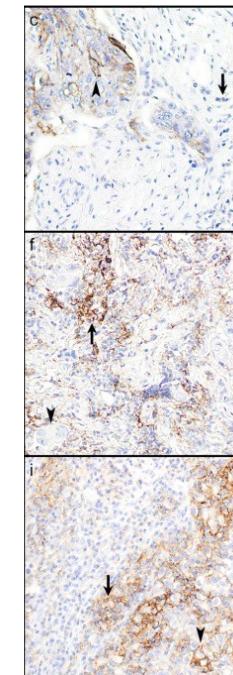
- BL1 ■ BL2 ■ IM ■ LAR ■ No clasificado

PARP inhibitors

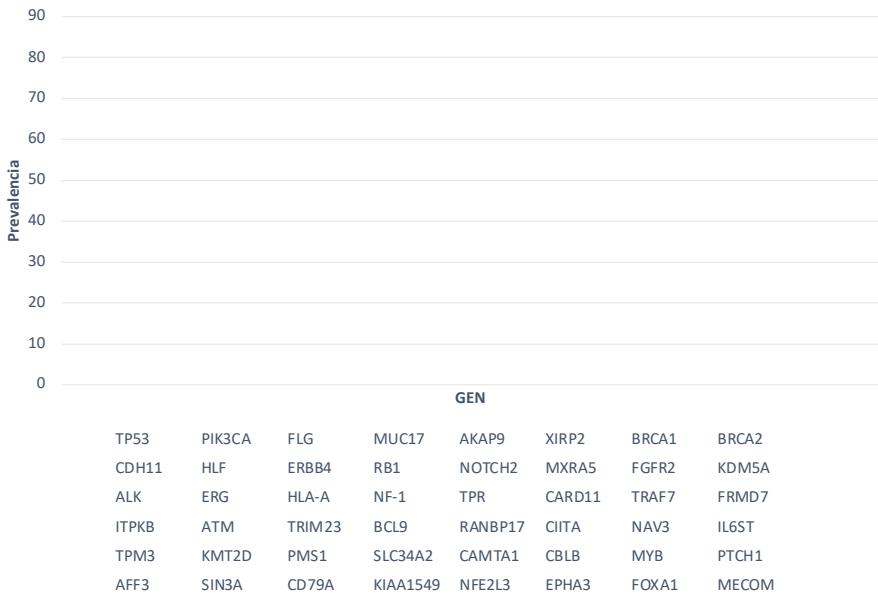
Tumor Stromal TILs



PD-L1 Expression



Somatic mutations in basal-like BC



- High heterogeneity
- TP53 mutations (~85%) → Not actionable
- PIK3CA/AKT1/PTEN alterations ~35%

Ipatasertib: Phase II (LOTUS)

: Phase III (IPATunity 130)

Capivasertib: Phase II (PAKT)

: Phase III Capitello 290

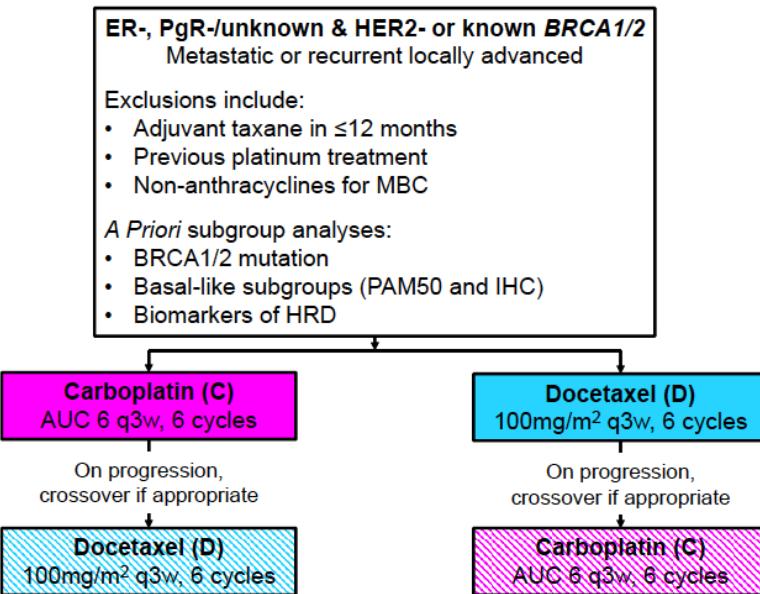
- BRCA 1/2 function loss ~20%

: OLYMPIA

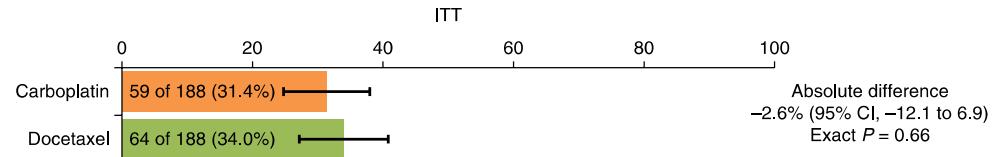
: EMBRACA

TNT Trial: Carboplatin in *BRCA1/2*-mutated and TNBC

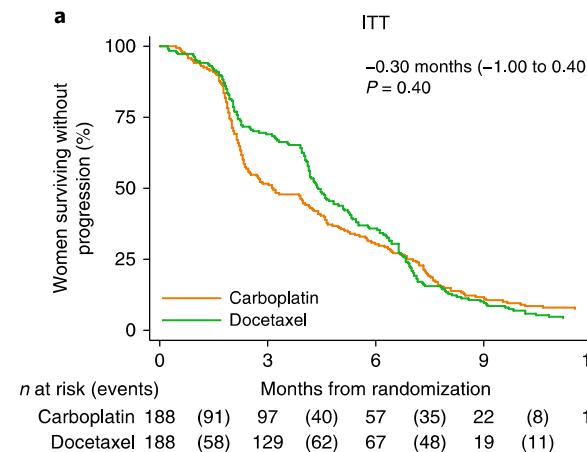
Design



Response Rate (ITT)



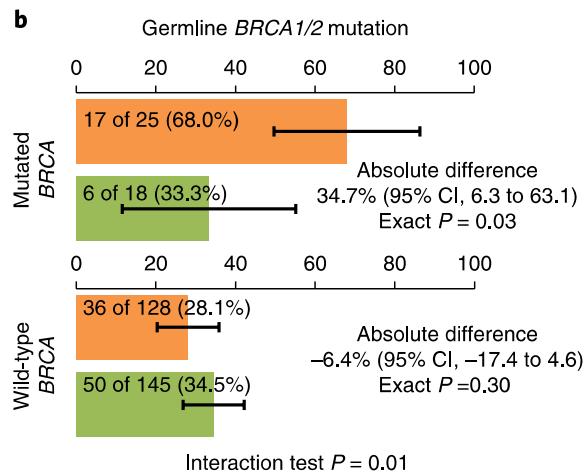
Progression-free Survival (ITT)



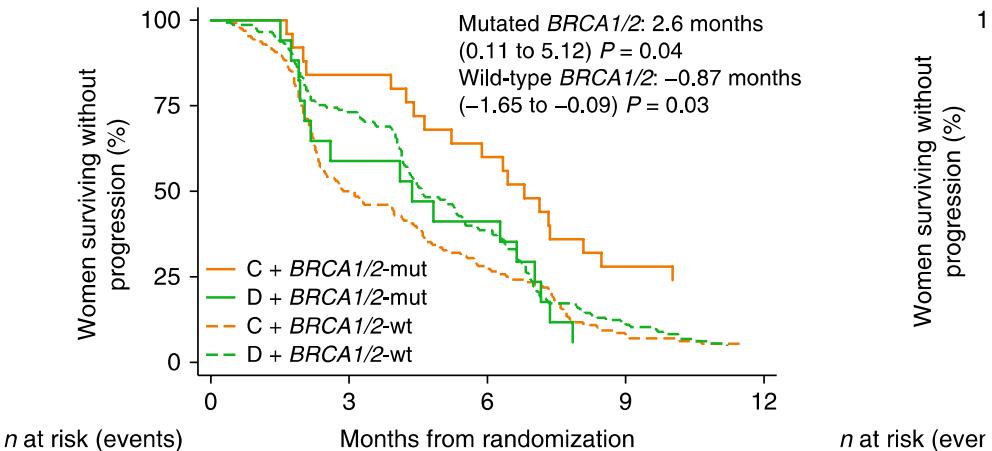


TNT Trial: Carboplatin in *BRCA1/2*-mutated and TNBC

ORR according to BRCA mutation

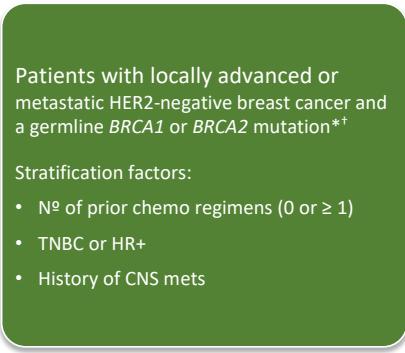


PFS according to BRCA mutation



PARP inhibitors Phase III Trials: Design

EMBRACA (n = 431)



Talazoparib
1 mg PO daily

Physician's choice of therapy (PCT)[‡]:
capecitabine,
eribulin, gemcitabine,
or vinorelbine

Primary endpoint

- Progression-free survival by RECIST by blinded central review

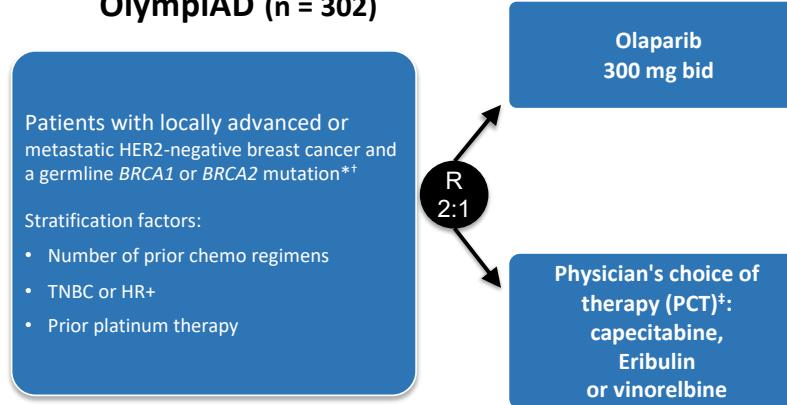
Key secondary efficacy endpoints

- Overall survival (OS)
- ORR by investigator
- Safety

Exploratory endpoints

- Duration of response (DOR) for objective responders
- Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)

OlympiAD (n = 302)



Olaparib
300 mg bid

Physician's choice of therapy (PCT)[‡]:
capecitabine,
Eribulin
or vinorelbine

Primary endpoint

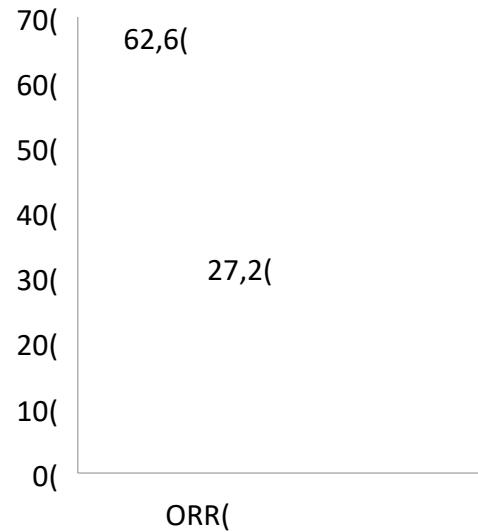
- Progression-free survival by RECIST by independent review

Secondary endpoints

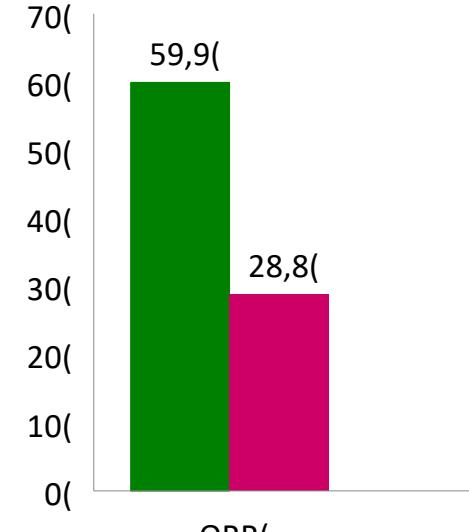
- Overall survival (OS)
- PFS2
- ORR by investigator
- Safety and tolerability
- Quality of life (QoL; EORTC QLQ-C30,)
- PFS, PFS2 and OS based on Myriad gBRCAm status

Objective Response Rate

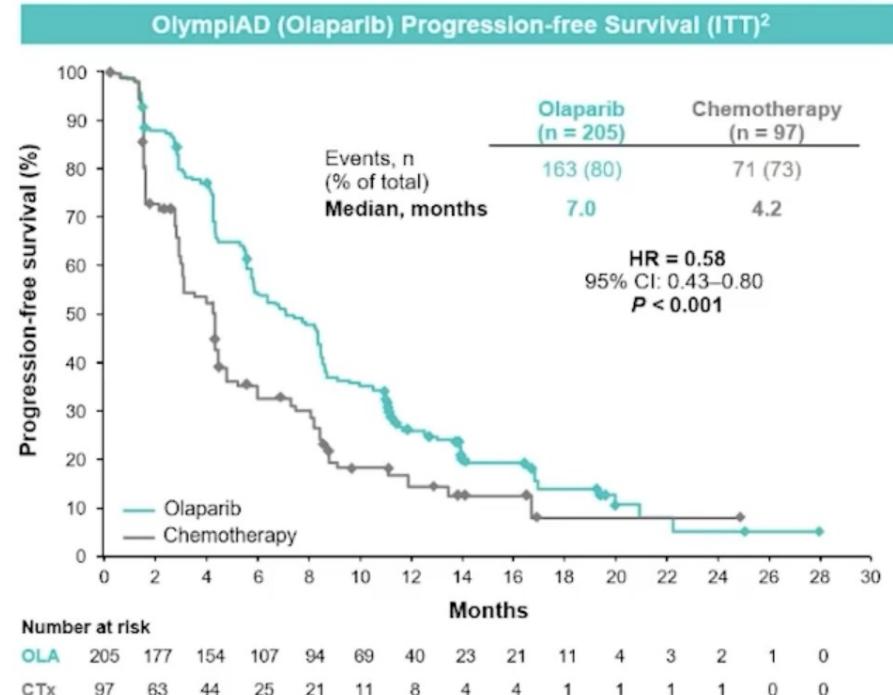
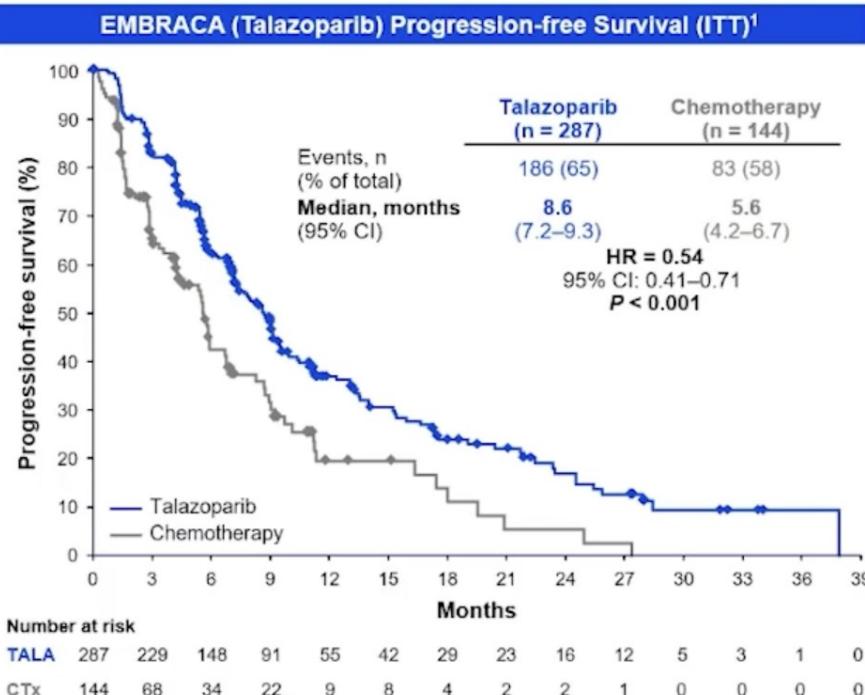
EMBRACA
ORR (mensurable disease)



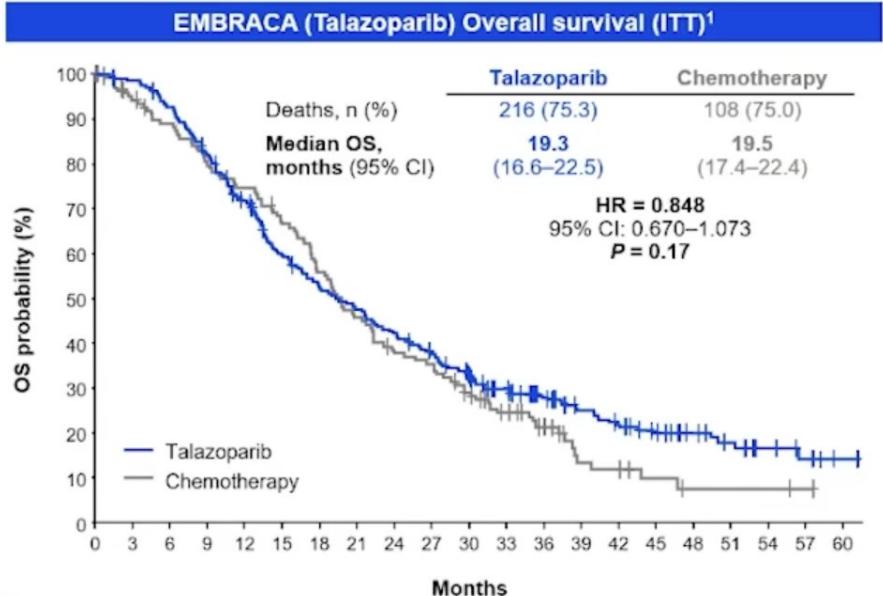
OlympiAD
ORR (mensurable disease)



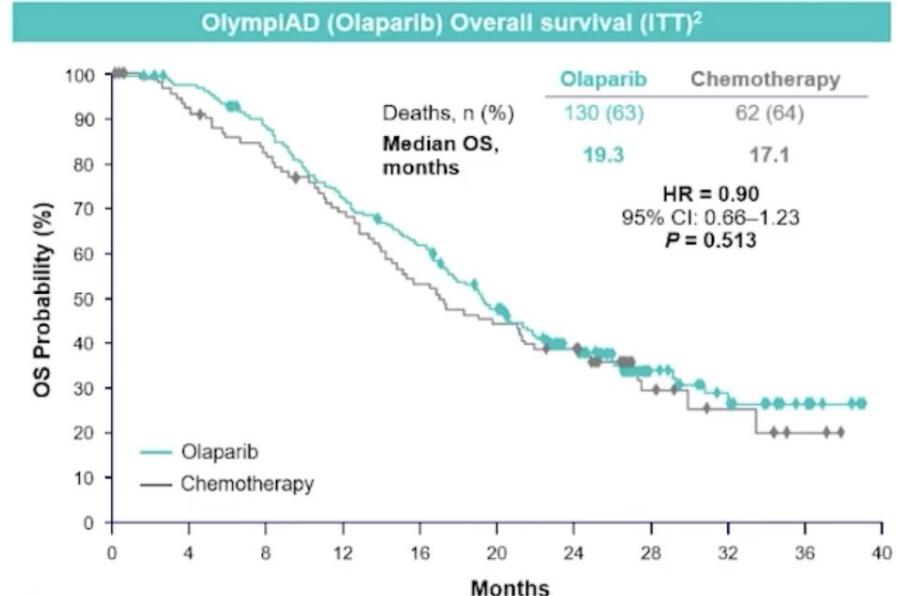
Progression-free Survival



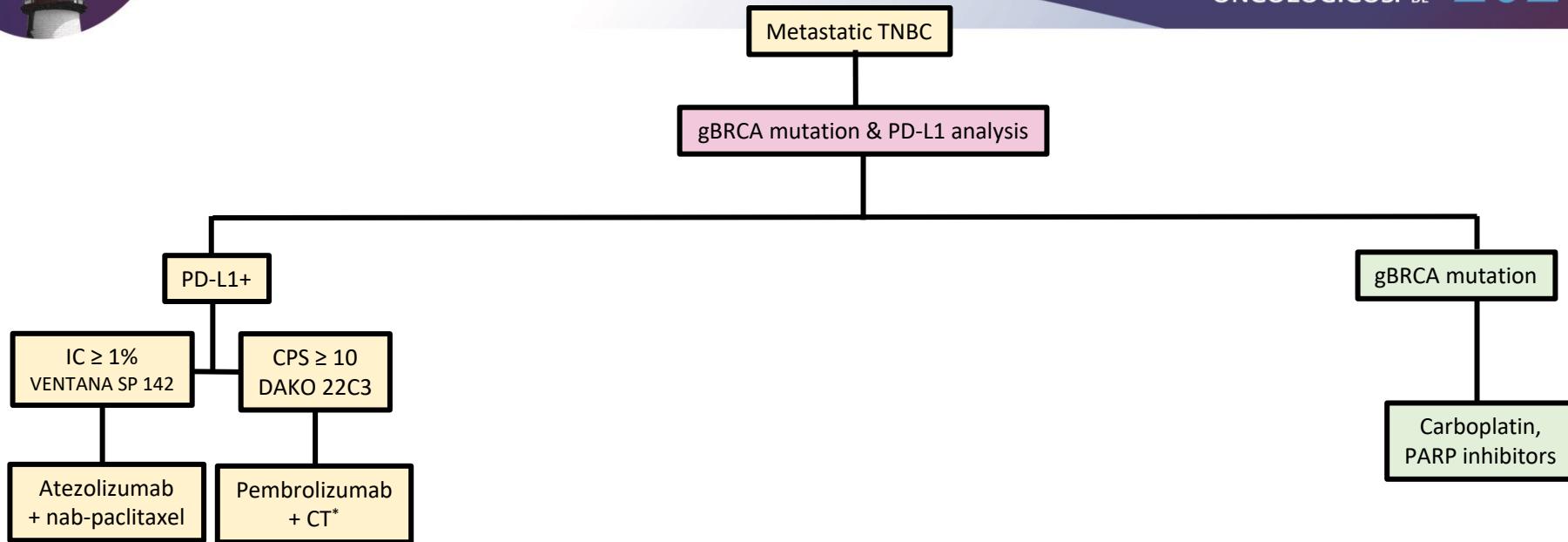
Overall Survival

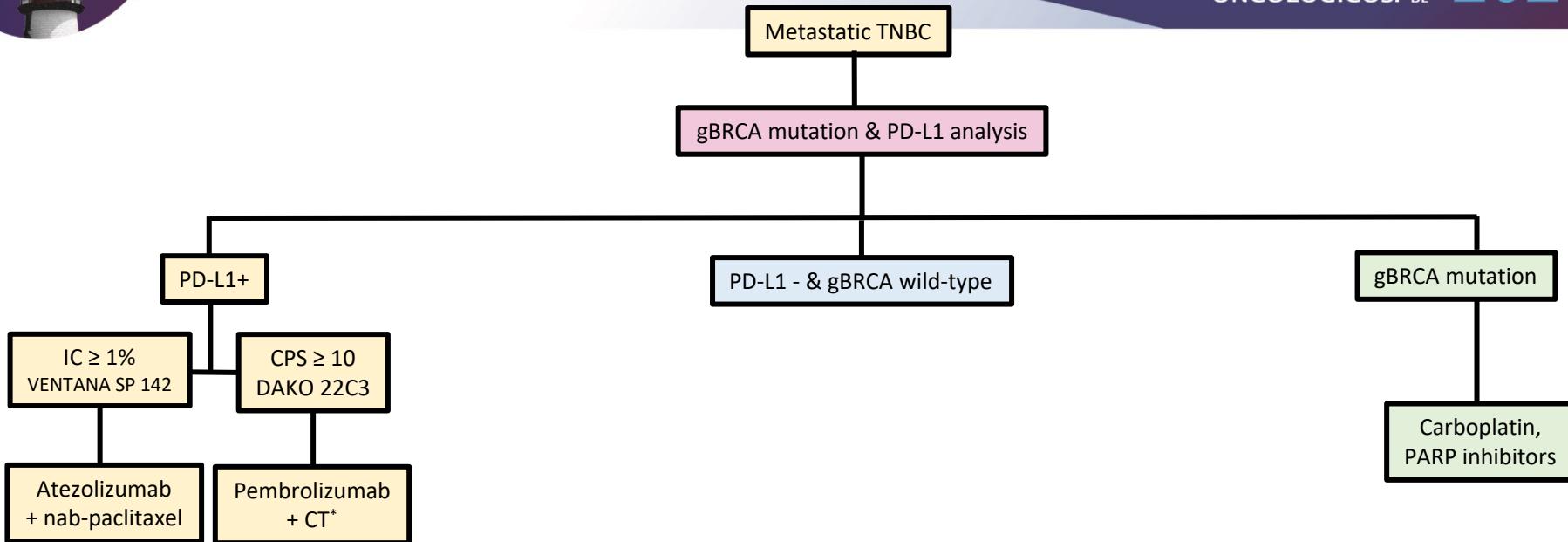


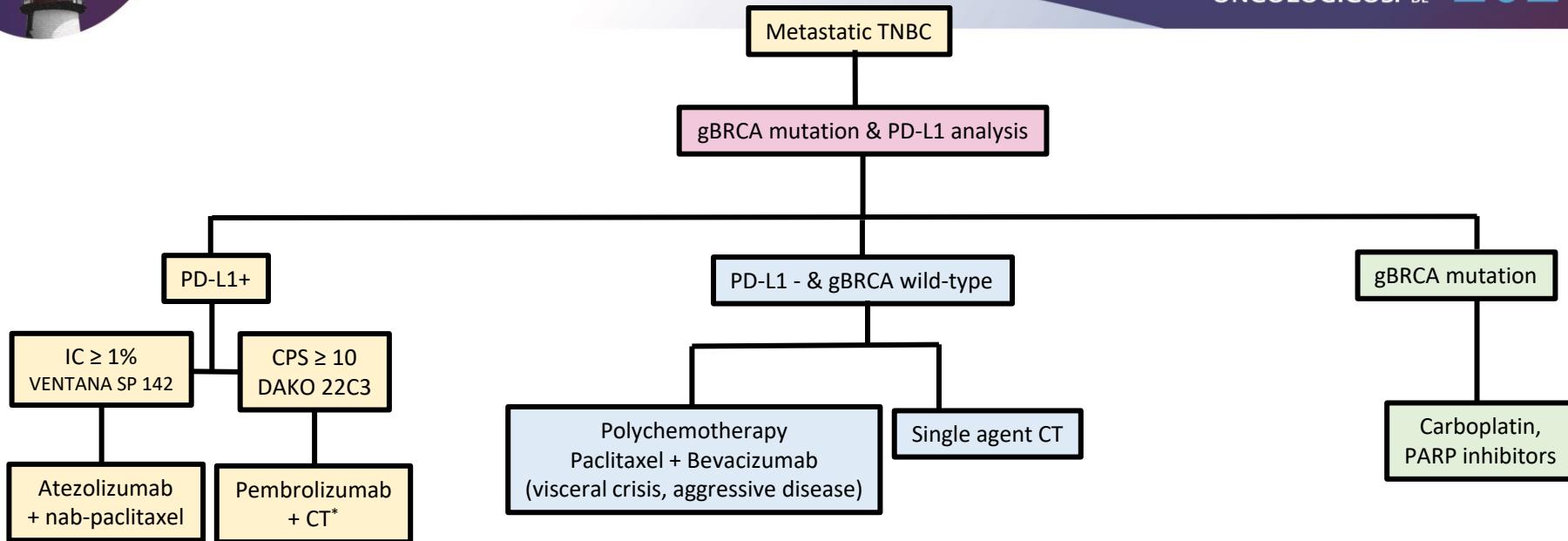
Number at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
TAL	287	280	264	232	199	163	143	128	113	101	85	68	54	41	35	27	20	15	9	6	2
CTx	144	125	116	105	96	86	71	58	48	44	34	25	18	8	7	4	2	2	1	0	0

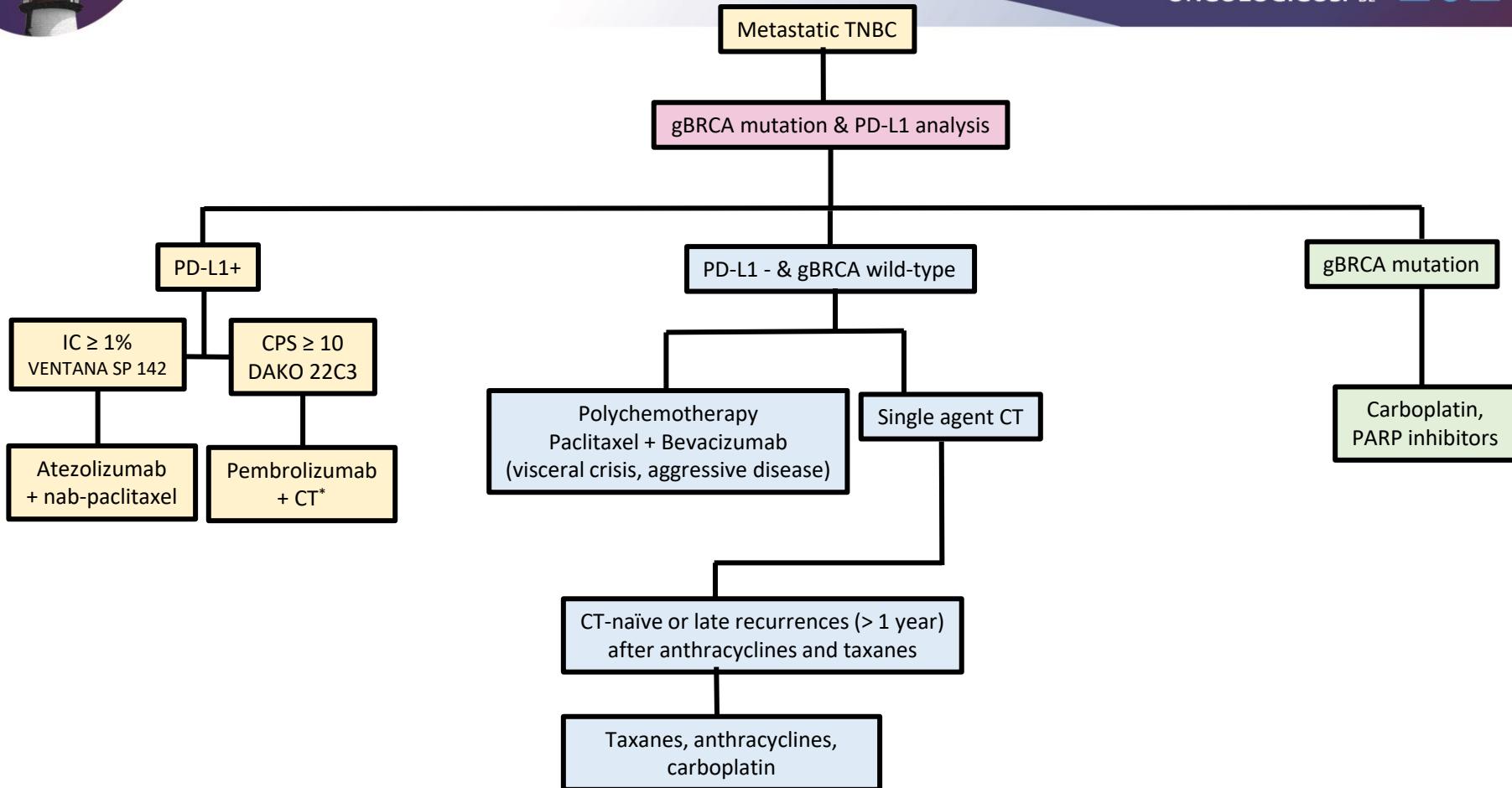


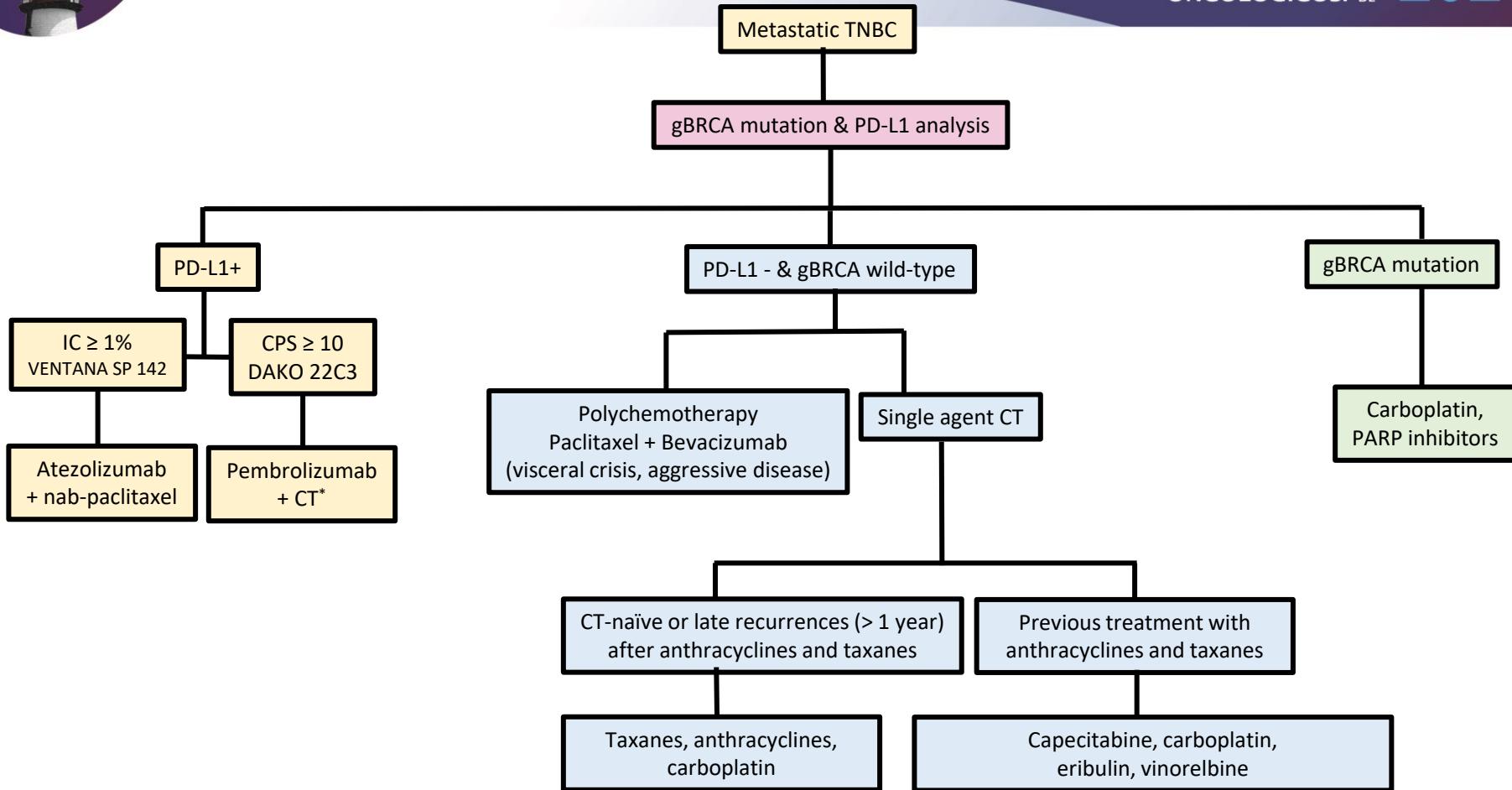
Number at risk	0	4	8	12	16	20	24	28	32	36	40
OLA	205	199	178	146	124	92	55	23	11	6	0
CTx	97	85	74	62	48	40	30	15	5	2	0





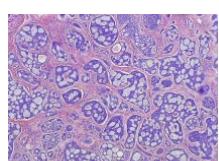
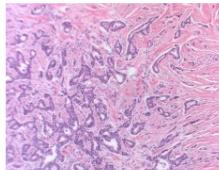
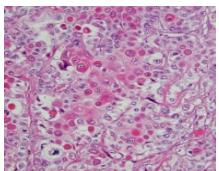
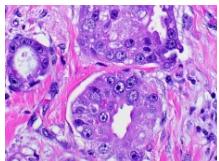




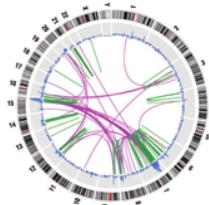
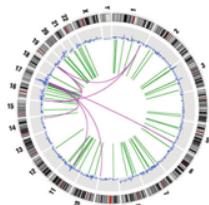
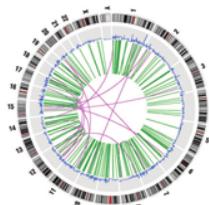




Histology

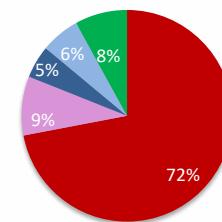


Mutation profile



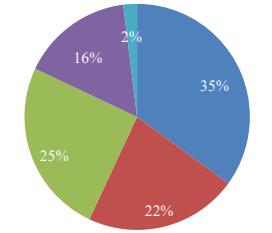
Gene expression

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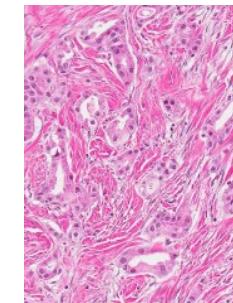
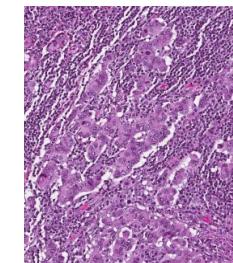
- Basal-like ■ HER2-E
- Luminal A ■ Luminal B
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Clasificación de Burstein

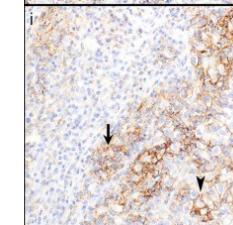
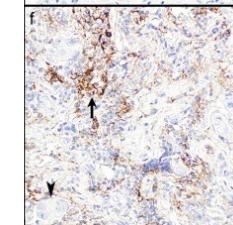
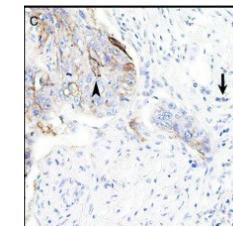


- BL1 ■ BL2 ■ IM ■ LAR ■ No clasificado

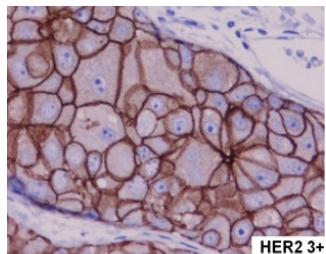
Tumor Stromal TILs



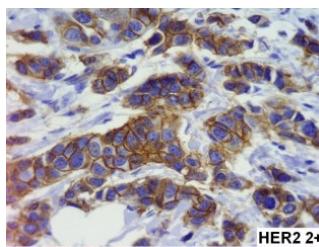
PD-L1 Expression



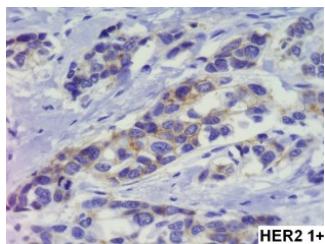
ADCs



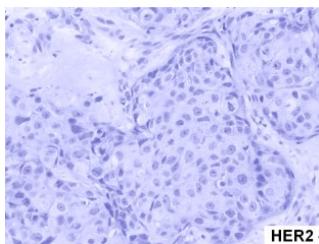
HER2 3+



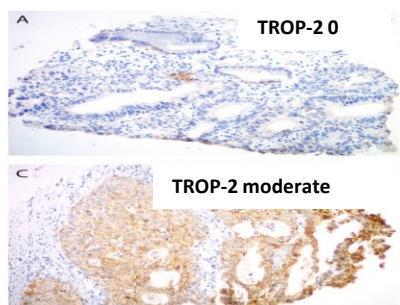
HER2 2+



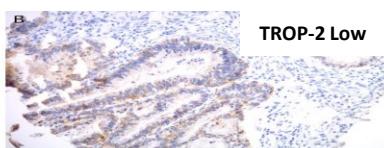
HER2 1+



HER2 -



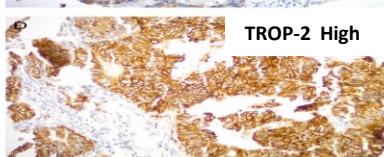
TROP-2 0



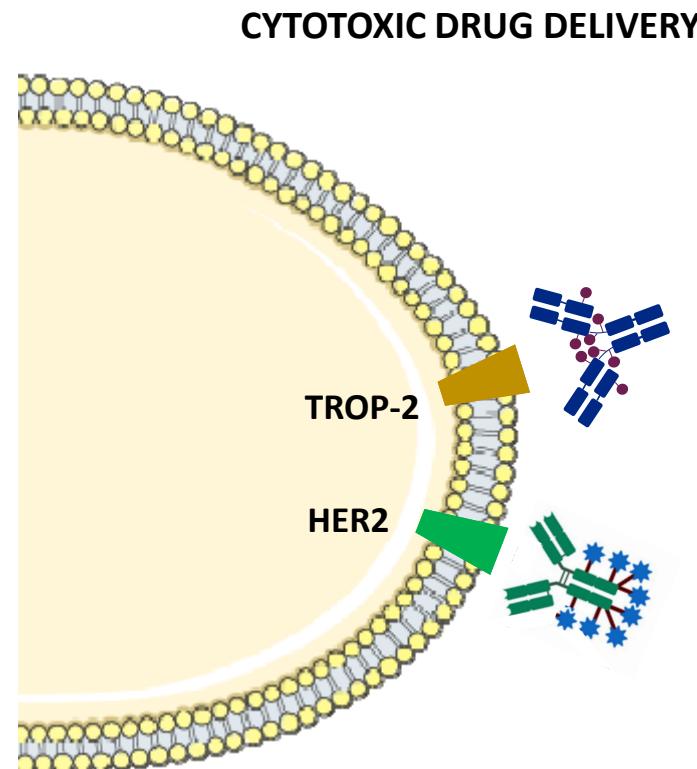
TROP-2 Low



TROP-2 moderate



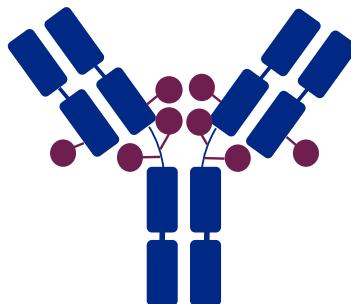
TROP-2 High



Modificado de: Tarantino P. Expert Opinion on Biological Therapy 2020

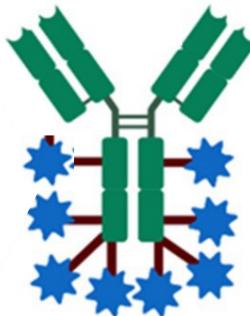
Trastuzumab deruxtecan

(T-DXd)



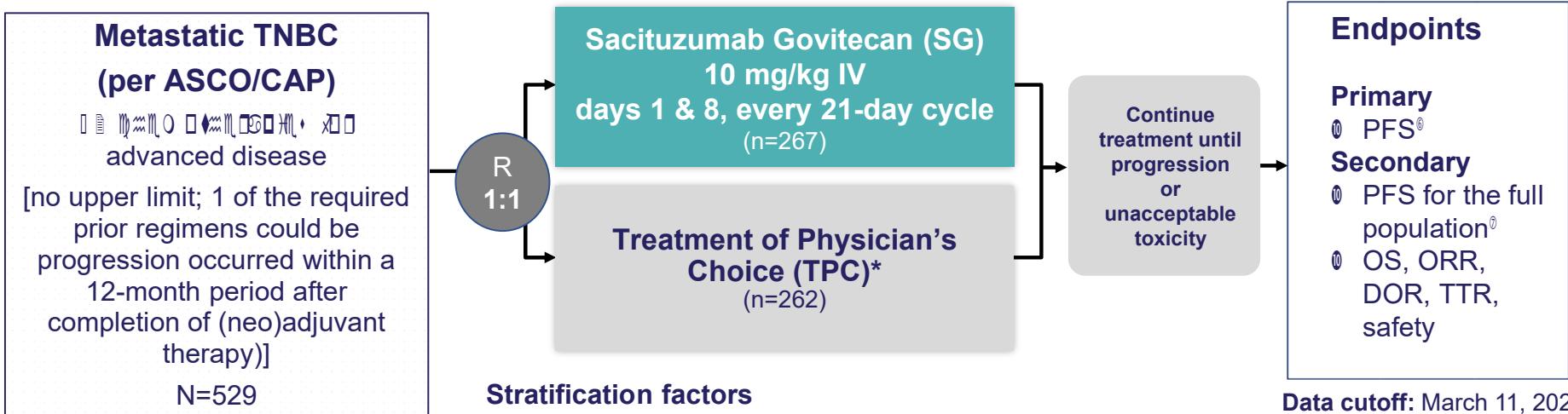
Sacituzumab Govitecan

(SG)



ADC Attributes	T-DXd	Sacituzumab Govitecan
Target	HER2	Trop2
Payload MoA	Exatecan derivative Topoisomerase I inhibitor	SN 38 Topoisomerase I Inhibitor
Drug-to-antibody ratio	~8:1	7.6
Tumor-selective cleavable linker?	Yes	Yes
Evidence of bystander anti-tumor effect?	Yes	Yes

ASCENT: A Phase 3 Study of Sacituzumab Govitecan in mTNBC

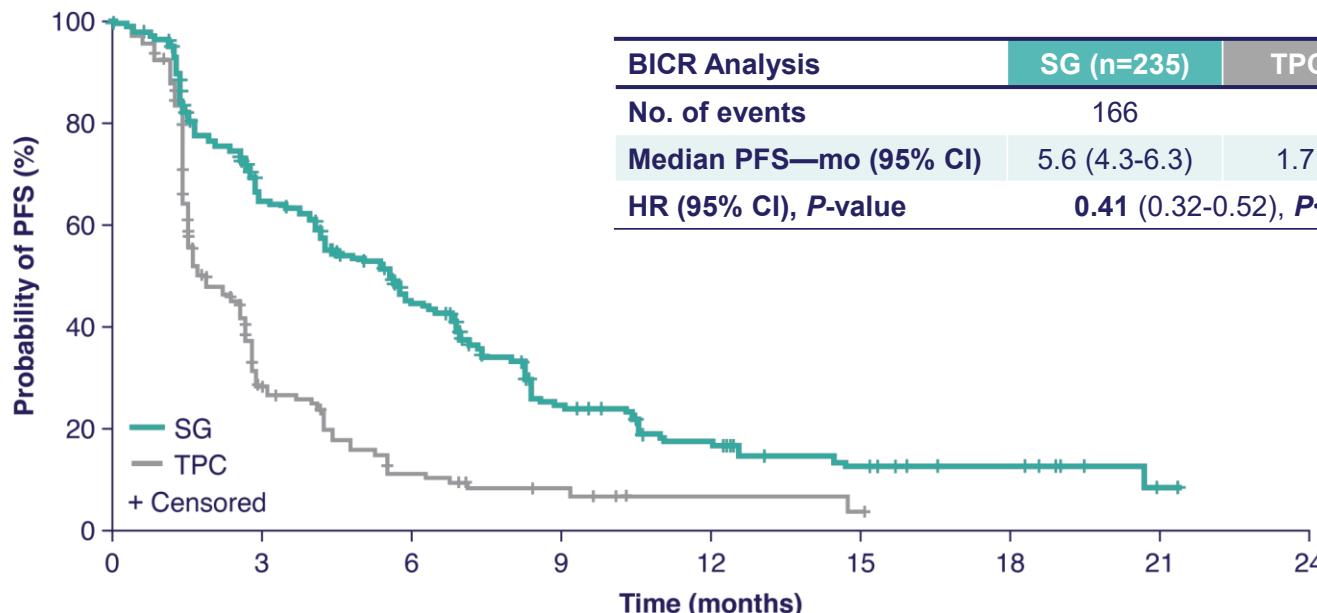


Data cutoff: March 11, 2020

Stratification factors

- ⑩ Number of prior chemotherapies (2-3 vs >3)
- ⑩ Geographic region (North America vs Europe)
- ⑩ Presence/absence of known brain metastases (yes/no)

Progression-Free Survival (BICR Analysis)

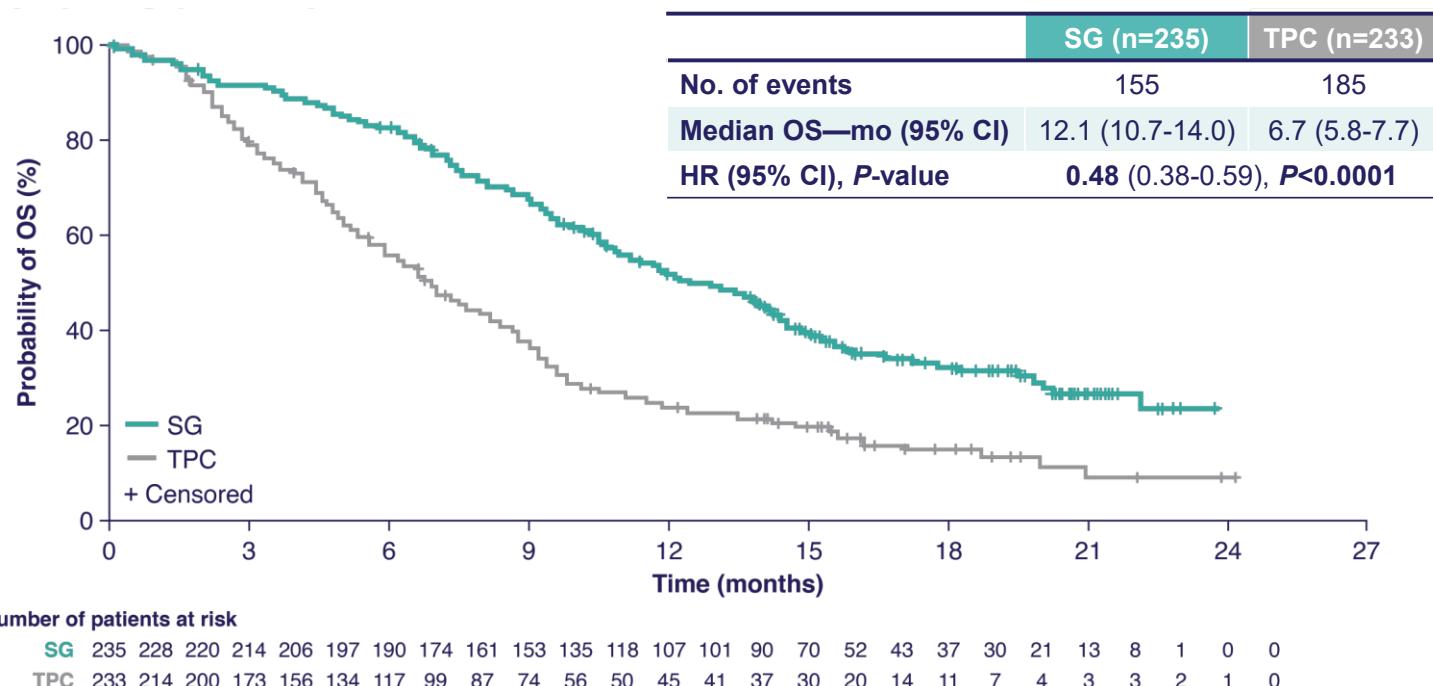


Number of patients at risk

SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	1	0	0	0	0	0	0	0	0

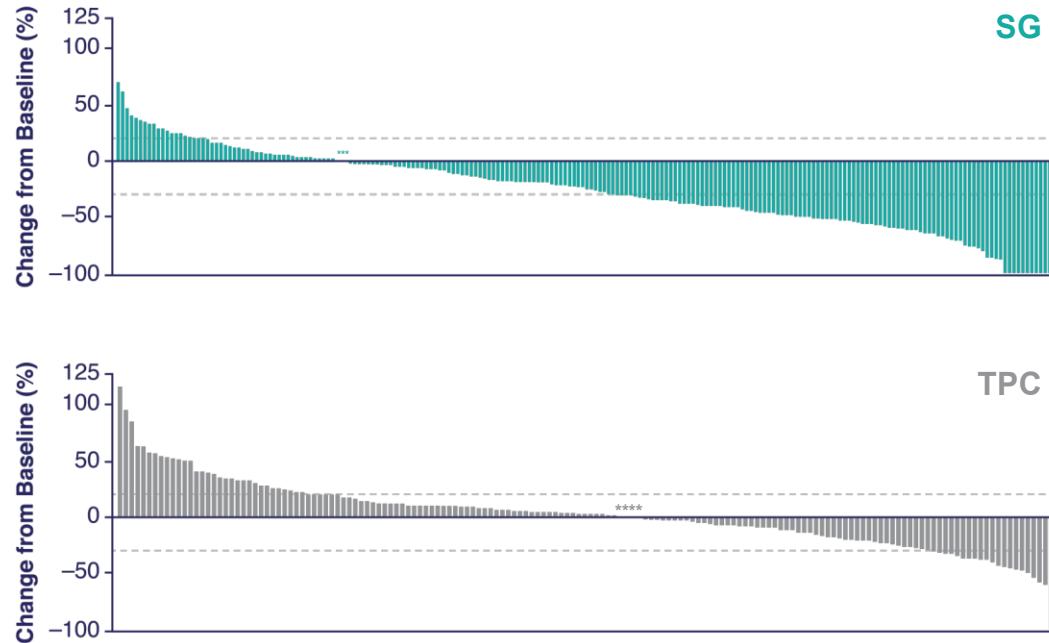


Overall Survival



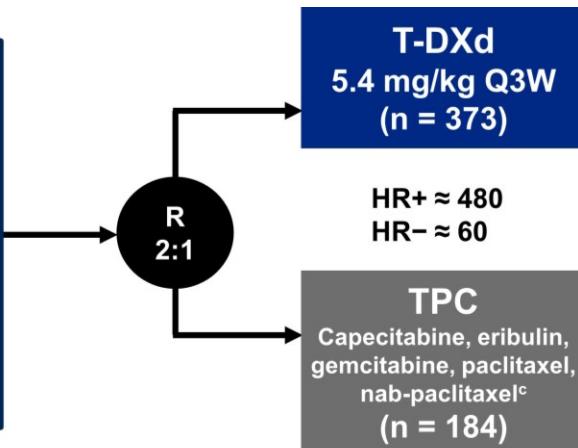
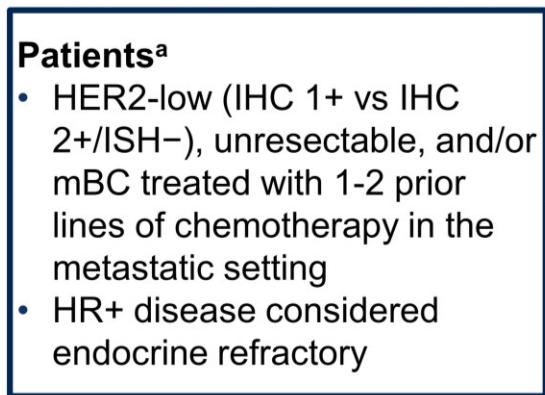


Overall Response and Best Percent Change



	SG (n=235)	TPC (n=233)
ORR no. (%)	82 (35)	11 (5)
P-value	<0.0001	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR no. (%)	105 (45)	20 (9)
P-value	<0.0001	
Median DOR mo (95%CI)	6.3 [4.0; 10.0]	3.6 [2.0; 5.0]
P-value		0.057

DESTINY-Breast04: Randomized Phase 3 Study of T-DXd for HER2-low mBC



Stratification factors

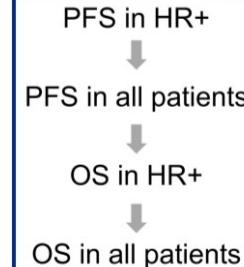
- Centrally assessed HER2 status^d (IHC 1+ vs IHC 2+/ISH-)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR-

Primary endpoint

- PFS by BICR (HR+)

Key secondary endpoints^b

- PFS by BICR (all patients)
- OS (HR+ and all patients)

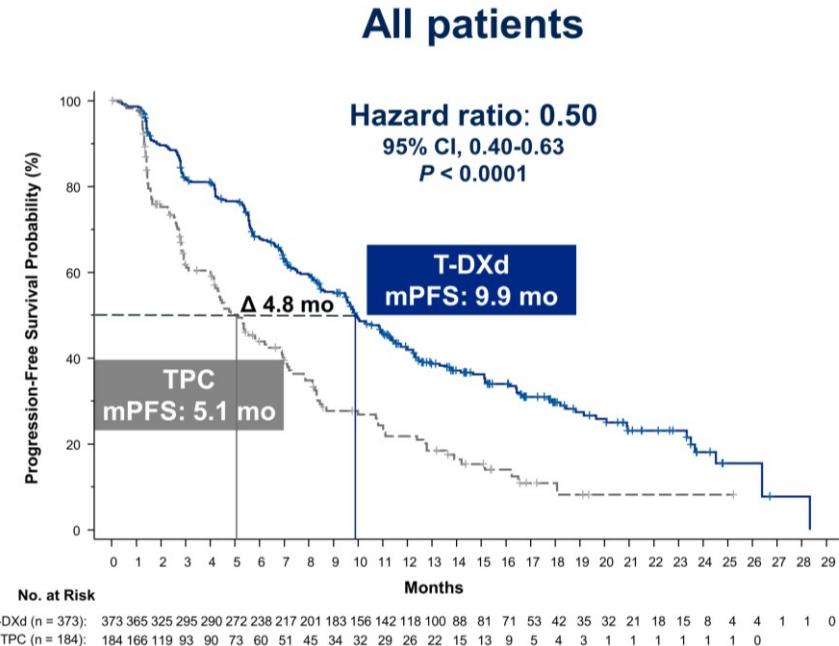




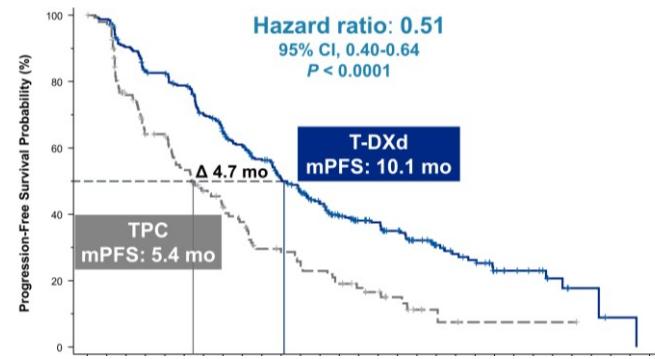
DESTINY-Breast04

18^{as} Jornadas HITOS
ONCOLÓGICOS: LO MEJOR DE 2023

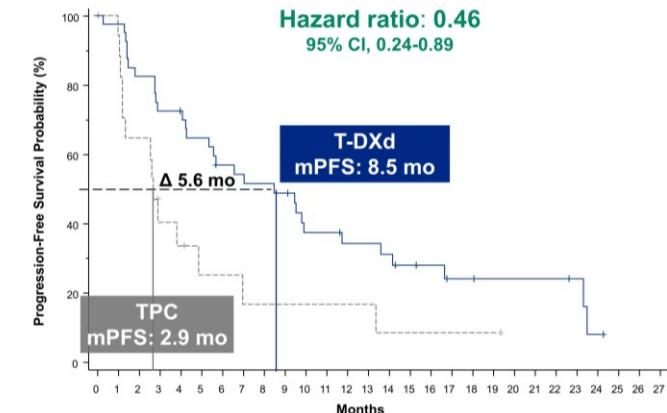
PFS in all patients, HR + & HR -



Hormone receptor-positive

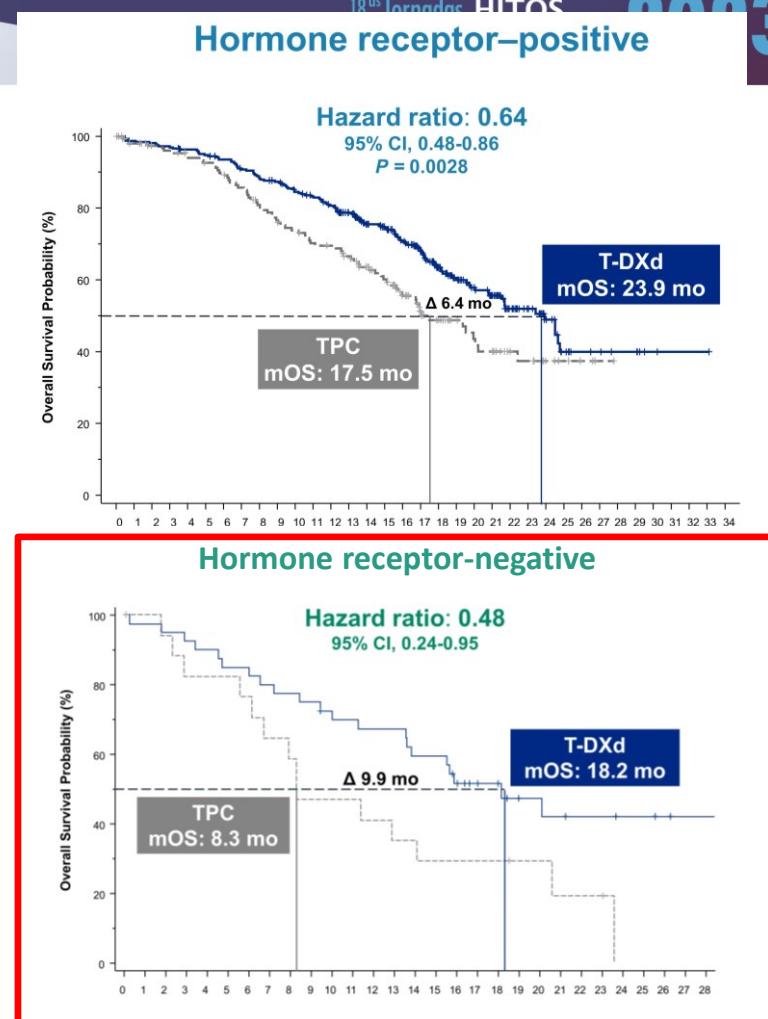
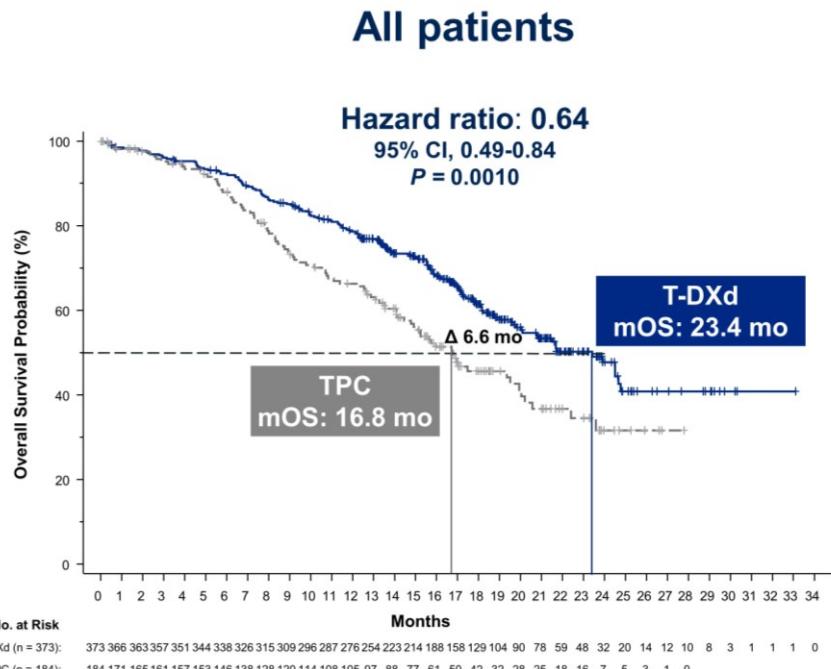


Hormone receptor-negative



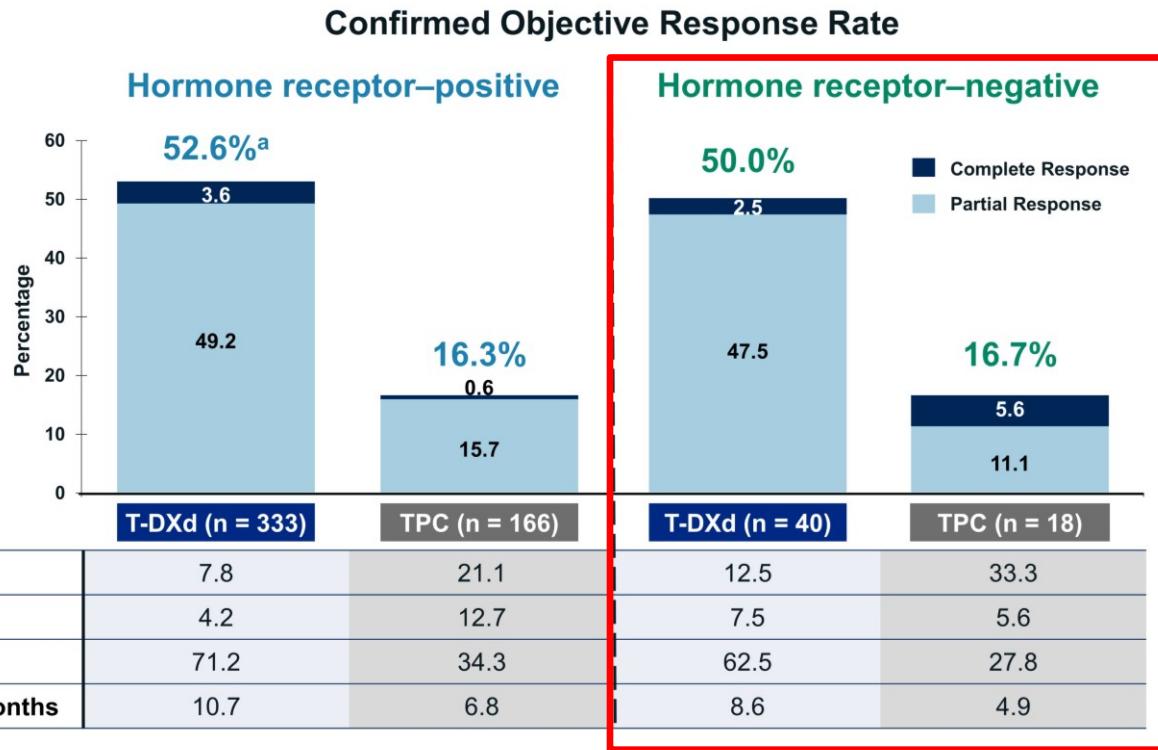


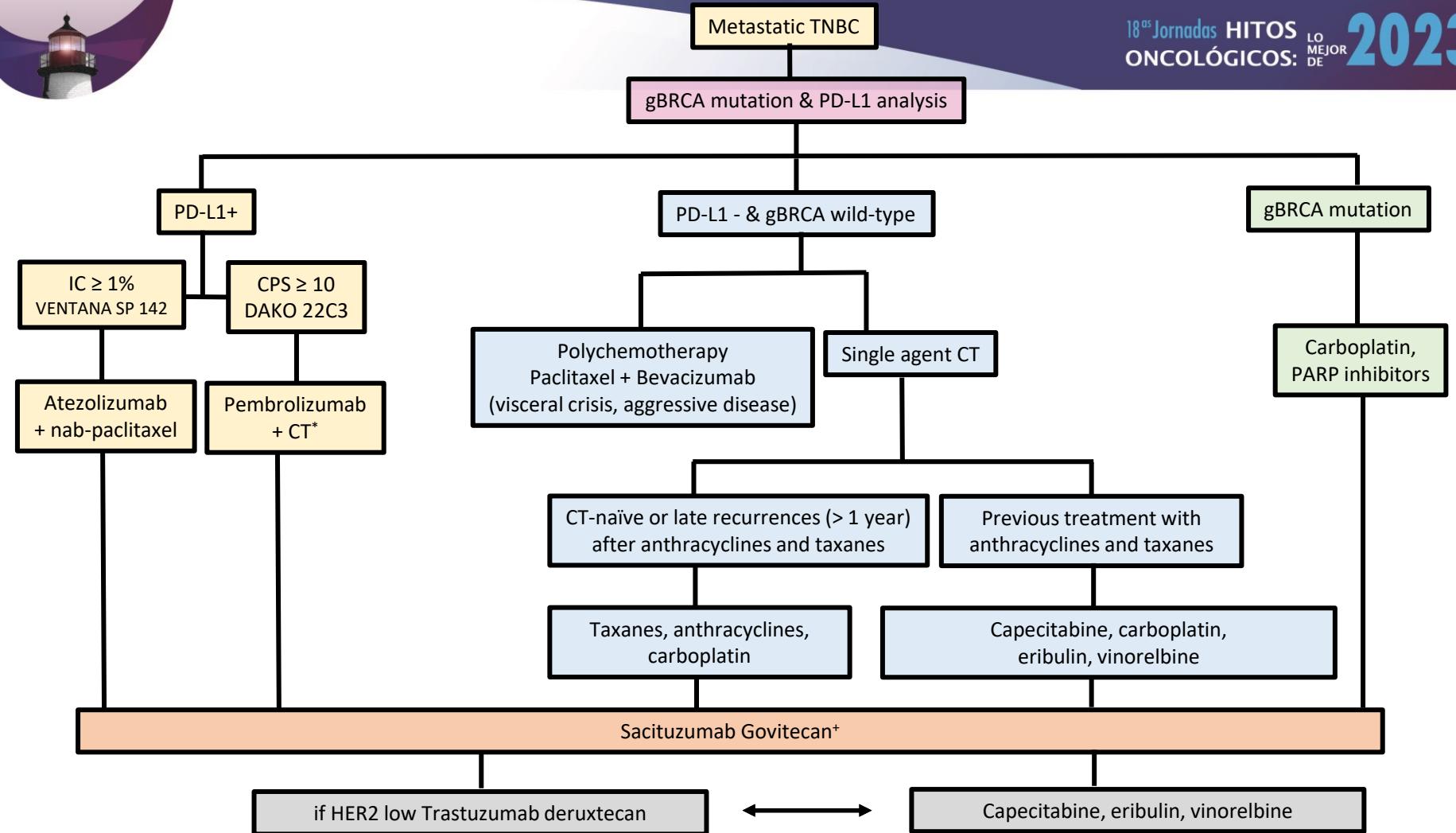
OS in all patients, HR + & HR -





Response Rate





Many questions answered

Immunotherapy

- Better biomarkers to predict for clinical benefit
- Which is the best Chemotherapy partner?
- Treatment at progression. Role of rechallenge of anti PD-1?
- Do PARP inhibitors and ADCs enhance the activity of immunotherapy?



Antibody-drug Conjugates

- Direct comparison between ADCs
- Cross-resistance between ADCs?
- Will they replace conventional chemotherapy in the first line?