HIGHLIGHTS
nel Setting Metastatico

Triplo Negativo

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Gemelli

GIM
Gruppo Italiano Mammella

DISCLOSURE

Personal financial interests

- **Consultant or advisor:** Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD,, Menarini

- **Speaker honoraria:** Astra Zeneca, Roche, Lilly, Novartis, Gilead, Pfizer, Daiichi Sankyo Exact Sciences

- **Travel support:** Astra Zeneca, Gilead

- **Research support (to the Institution):** Astra Zeneca, Roche

- **Member** of the national council of the Italian Society of Medical Oncology (AIOM)

Thoughts from Research to Clinical Practice Today in*'BJClub'*

- ✗ **Comportamento del TN nell'ultimo 20ennio**
- ✗ **Lo standard di cura**
- ✗ **Dopo la I linea il mantenimento.....ovaio = mammella?**
- ✗ **ADCs e la loro 'postazione'....dove, come....e quel che sarà**
- ✗ **News in Biomarcatori**

Real-world clinical and survival outcomes of pts with early relapsed TNBC from the ESME cohort

All diagnoses between 2008 and 2020

Women with mTNBC, with a history of localized of stage up to III TNBC (N = 3, 449)

- Did not receive or missing data on the neo/adjuvant CT (n = 1,115)
- No available end date of last neo/adjuvant treatment (n = 408)

Women receiving systemic therapy for metastatic breast cancer previously treated with neo/adjuvant anthracycline and/or taxane chemotherapy for stage I-III with a known end date (N = 1, 926)

TNBC patients were defined using the threshold of 10% for HR expression

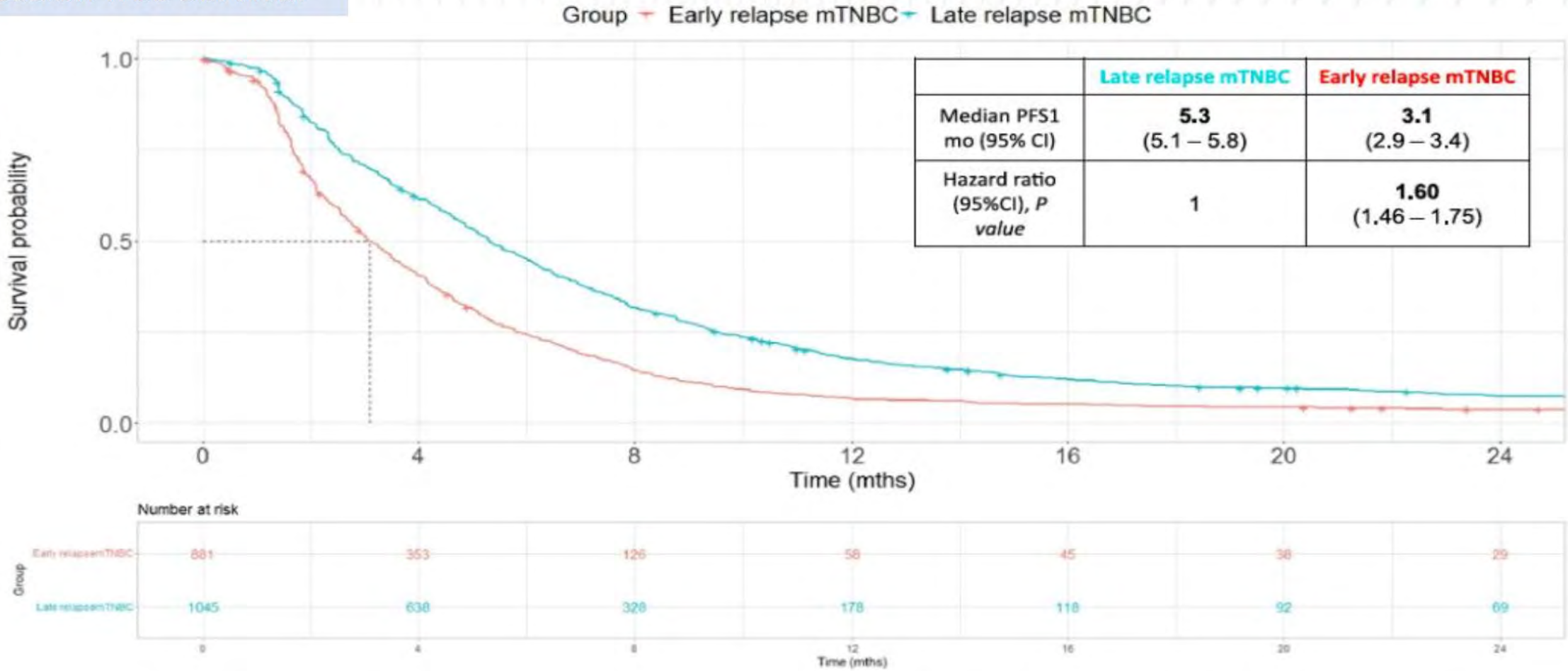
Patient with Early relapse TNBC
(<12 mths from the end of neo/adjuvant treatment)
(N = 881)

Patients with Late relapse TNBC
(≥12 mths from the end of neo/adjuvant treatment)
(N = 1, 045)

Grinda T, et al. Eur J Cancer 2023;189:112935.

Real-world clinical and survival outcomes of pts with early relapsed TNBC from the ESME cohort

Progression free survival

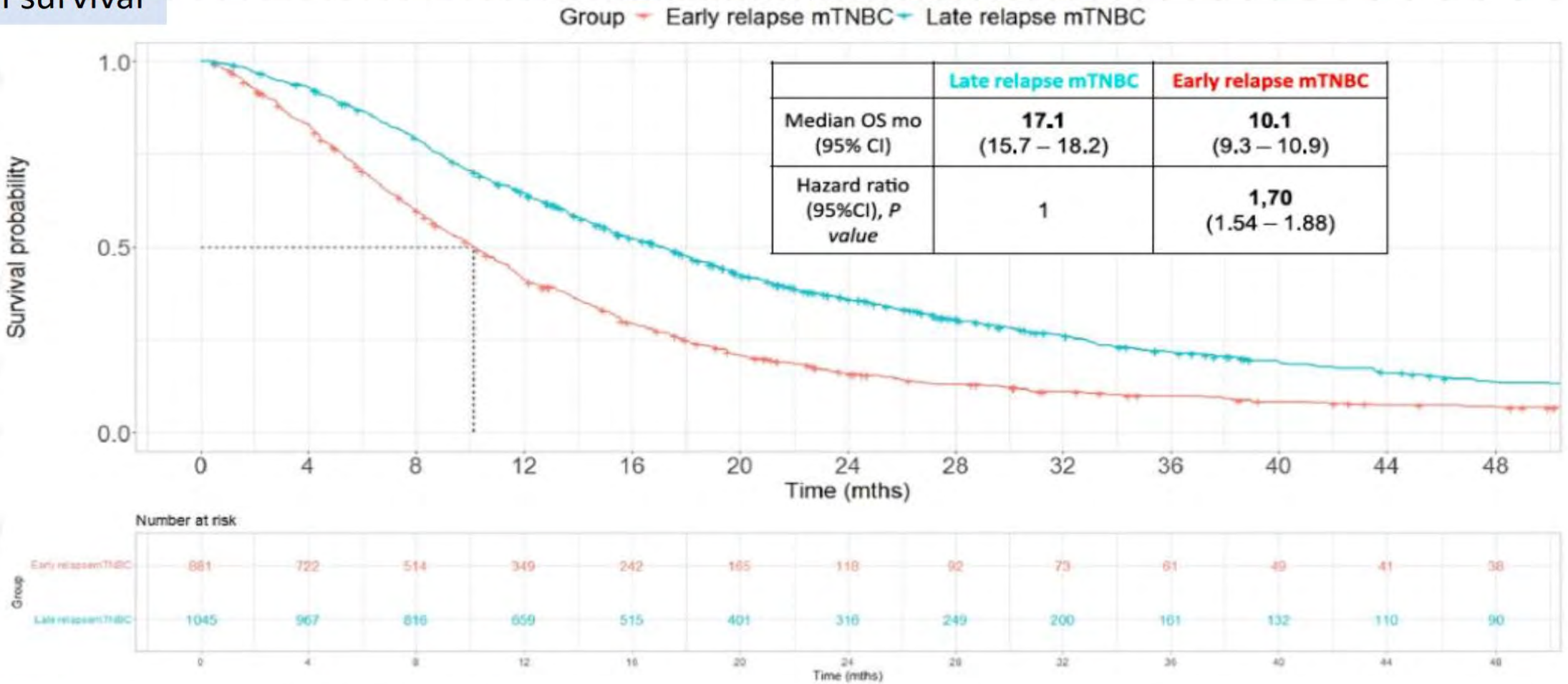


	Late relapse mTNBC	Early relapse mTNBC
Median PFS1 mo (95% CI)	**5.3** (5.1 – 5.8)	**3.1** (2.9 – 3.4)
Hazard ratio (95%CI), *P value*	1	**1.60** (1.46 – 1.75)

Grinda T, et al. Eur J Cancer 2023;189:112935.

Real-world clinical and survival outcomes of pts with early relapsed TNBC from the ESME cohort

Overall survival

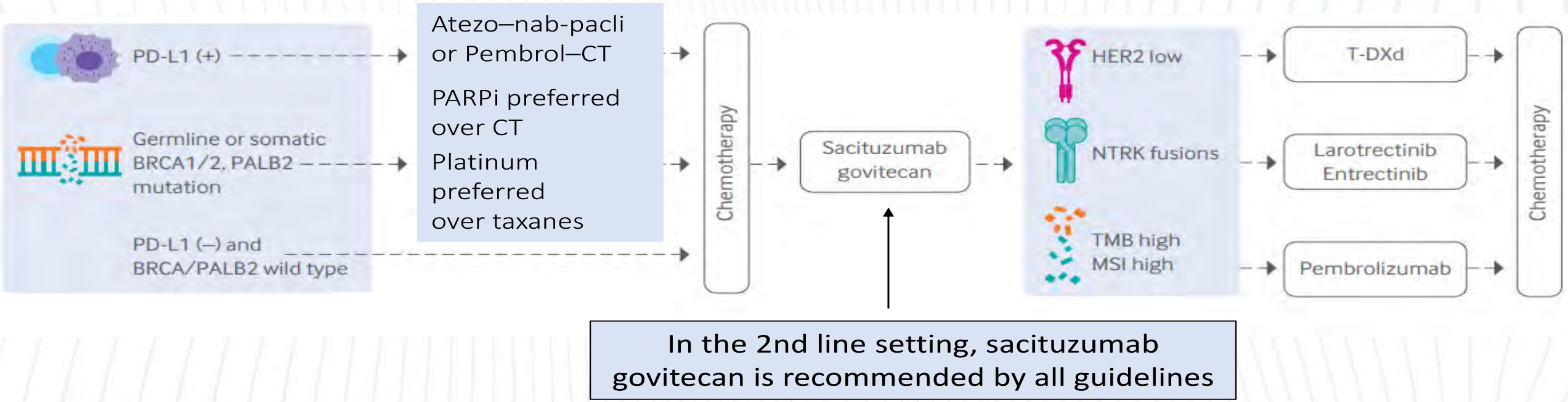


	Late relapse mTNBC	Early relapse mTNBC
Median OS mo (95% CI)	**17.1** (15.7 – 18.2)	**10.1** (9.3 – 10.9)
Hazard ratio (95%CI), *P value*	1	**1,70** (1.54 – 1.88)

Grinda T, et al. Eur J Cancer 2023;189:112935.

Standard treatment of mTNBC

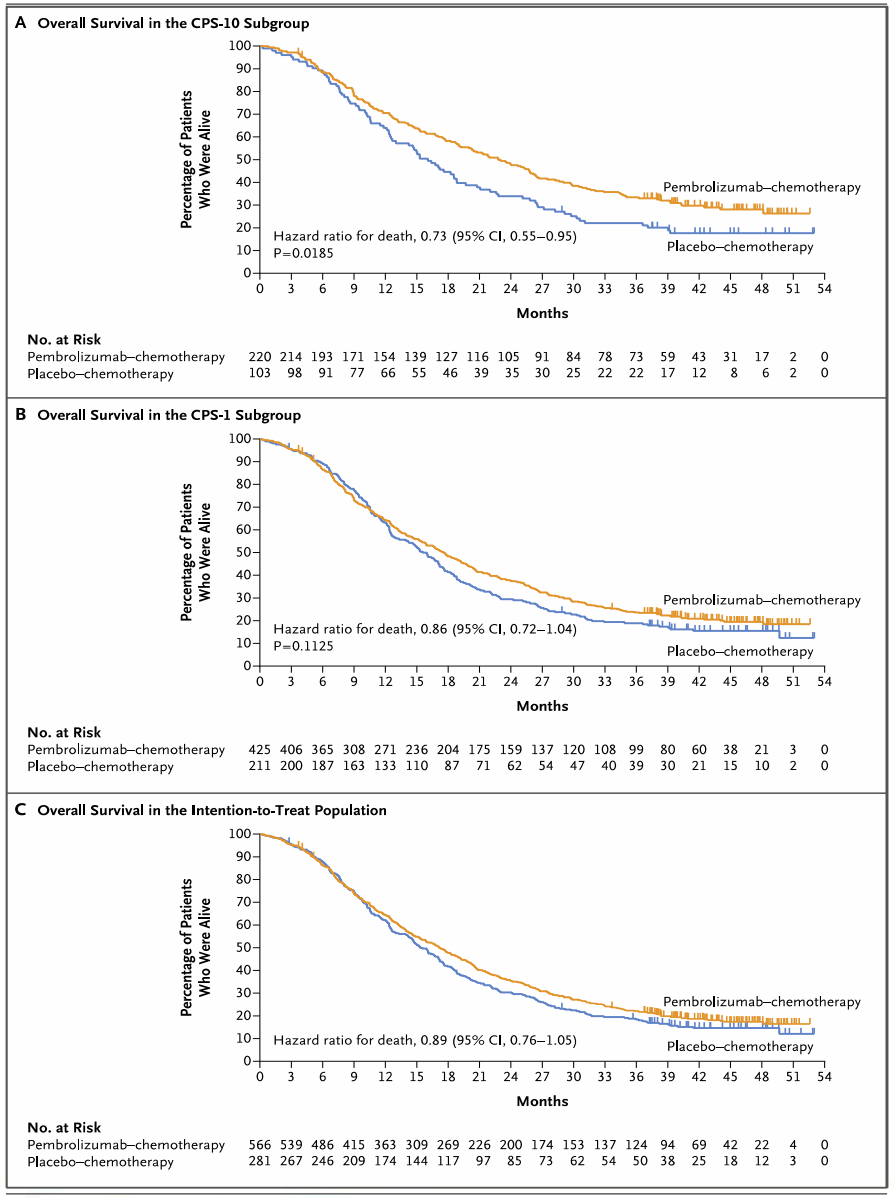
A shift from an empiric “pick a chemotherapy drug from a list” approach to a biomarker driven method of drug selection



In the 2nd line setting, sacituzumab govitecan is recommended by all guidelines

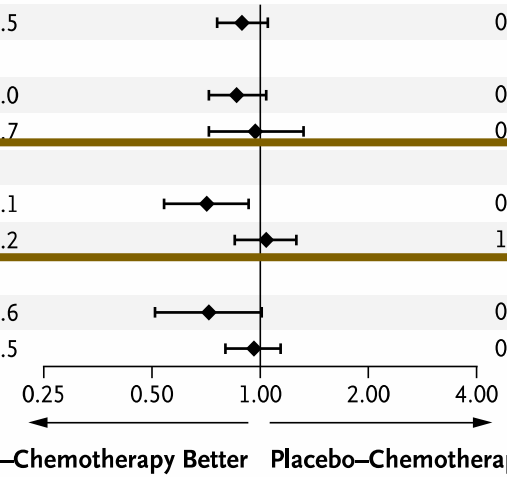
Modified from Leon-Ferre RA, Goetz MP. BMJ 2023;381:e0716

The ERA of Immunotherapy - Keynote 355



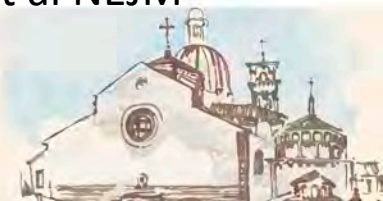
Overall Survival in Subgroups According to PD-L1 CPS Status at Baseline

Subgroup	No. of Patients	Median Overall Survival: Pembrolizumab–chemotherapy (mo)	Median Overall Survival: Placebo–chemotherapy (mo)	Hazard Ratio for Death (95% CI)
Overall	847	17.2	15.5	0.89 (0.76–1.05)
PD-L1 CPS cutoff of 1				
CPS ≥1	636	17.6	16.0	0.86 (0.72–1.04)
CPS <1	211	16.2	14.7	0.97 (0.72–1.32)
PD-L1 CPS cutoff of 10				
CPS ≥10	323	23.0	16.1	0.71 (0.54–0.93)
CPS <10	524	14.7	15.2	1.04 (0.85–1.26)
PD-L1 CPS cutoff of 20				
CPS ≥20	204	24.0	15.6	0.72 (0.51–1.01)
CPS <20	643	15.9	15.5	0.96 (0.80–1.14)



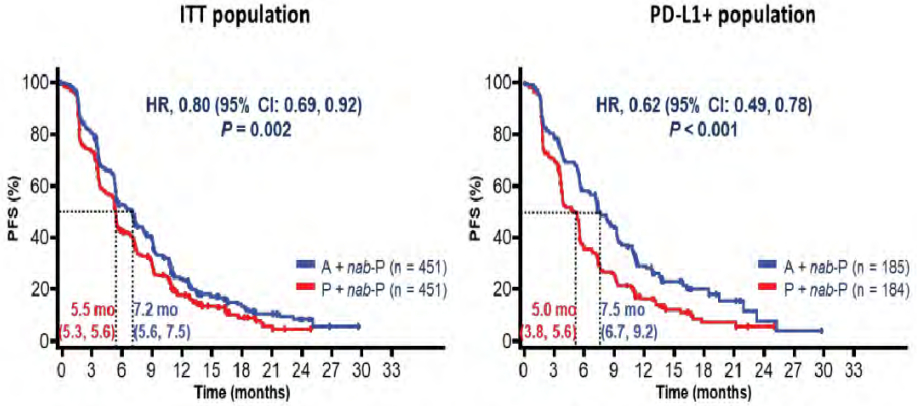
vantaggio di sopravvivenza di 7 mesi e riduzione del rischio di morte del 30%

Cortes et al NEJM

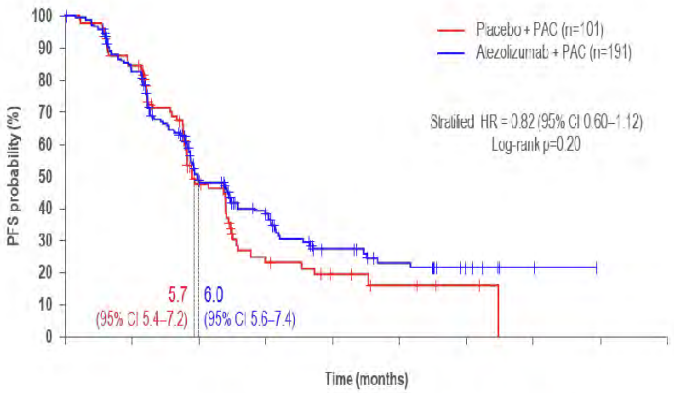


Randomized phase III studies with chemotherapy & PD1/PDL1 inhibitors: Key efficacy results

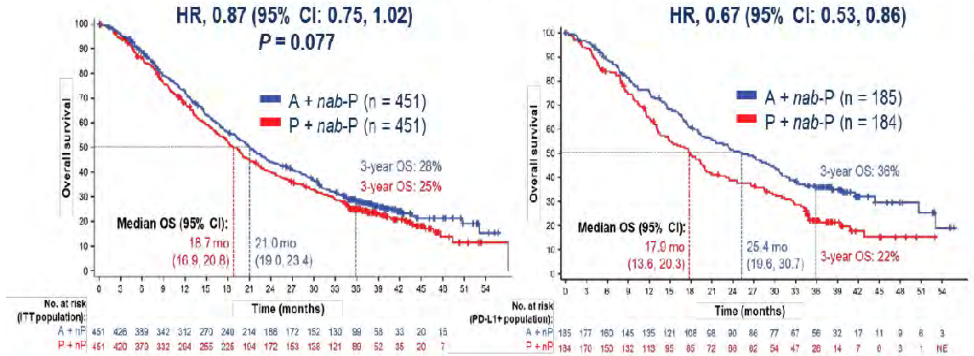
Impassion 130: PFS[1]



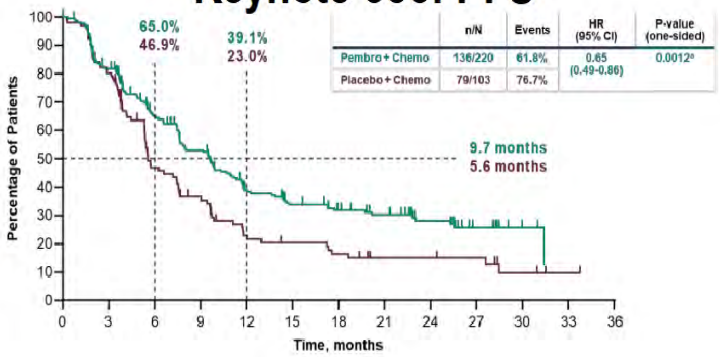
Impassion 131: PFS[3]



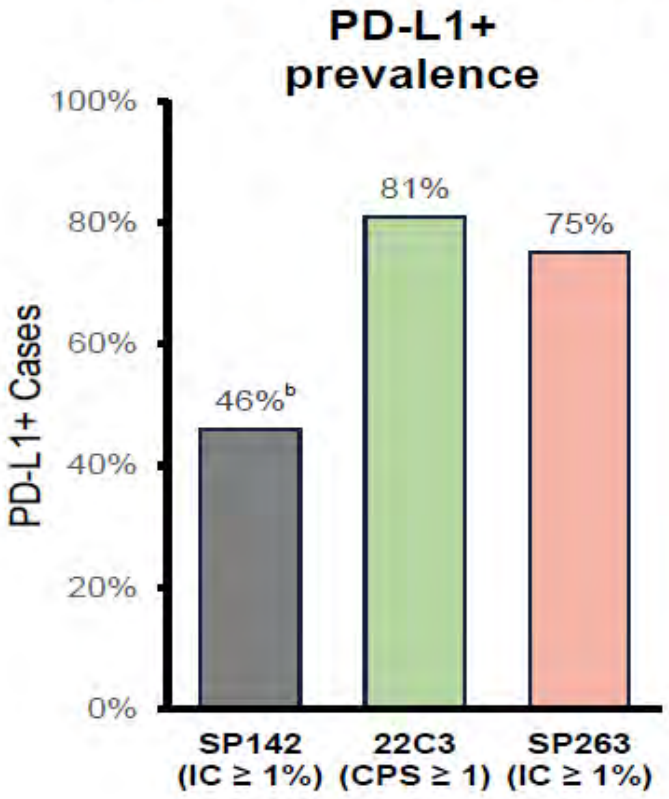
Impassion 130: Final OS[2]

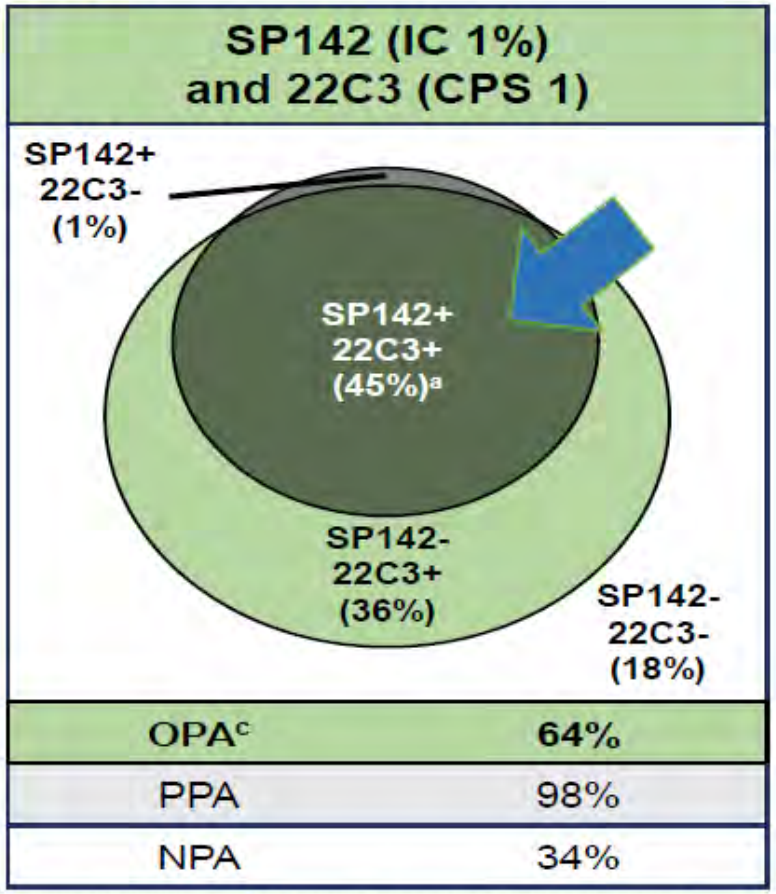


Keynote 355: PFS[4]

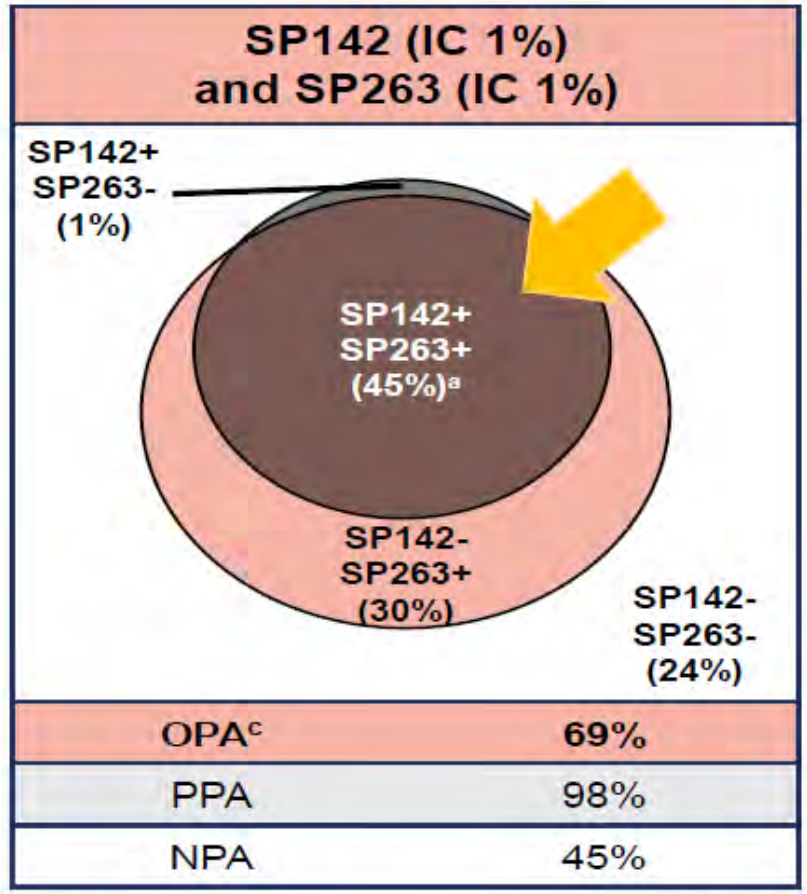


PD-L1 IHC assays: prevalence and analytical concordance





OPA[c]	64%
PPA	98%
NPA	34%



OPA[c]	69%
PPA	98%
NPA	45%

NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement.
[a] > 97% of SP142+ samples included in 22C3+ or SP263+ samples. [b] Compared with 41% in ITT (Schmid, *New Engl J Med* 2018).
[c] ≥ 90% OPA, PPA ***and*** NPA required for analytical concordance.

Rugo et al. Abstract 6571
IMpassion130 PD-L1 IHC
https://bit.ly/30OmOqz

The Choice of IL IC

DFS

Companion

Patients and Tumor Burden

Patient's Age

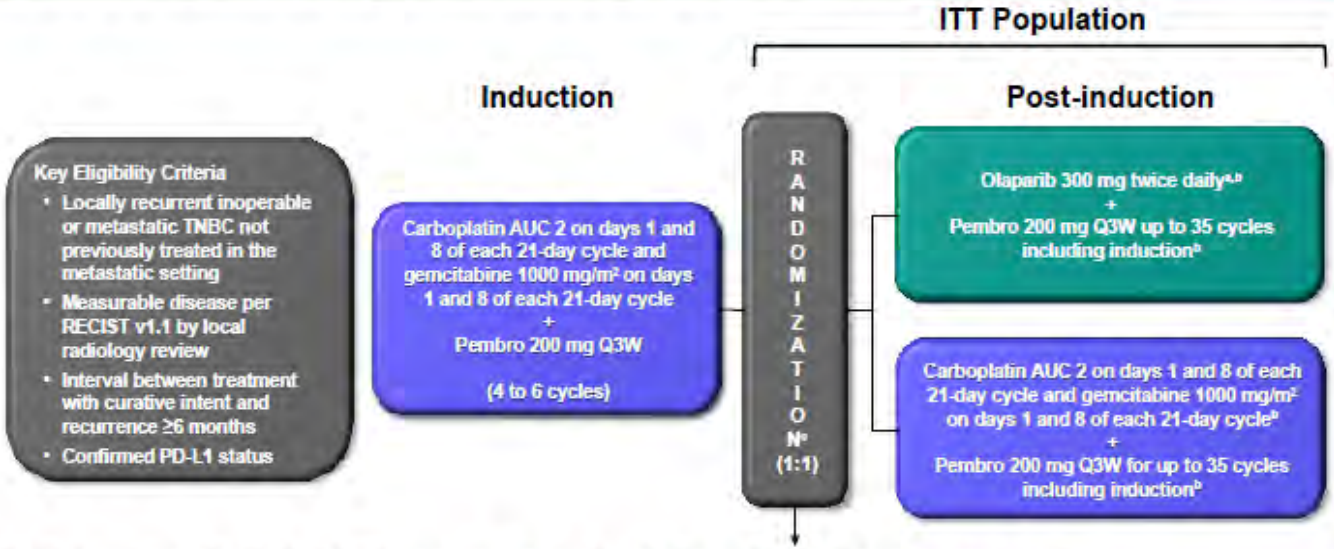
Immunotherapy at Home : Is it the Same Sound

Supplementary Table 4. Comparison between outcomes of the patients in Anastase real life and Impassion130 studies

Patient number	ANASTASE real life study 52	IMPASSION 130 study 185
Overall objective response, n (%) [95%CI]	22 **(42.3)** [28.9– 55.7]	109 **(58.9)** [51.5–66.1]
Complete Response, n (%)	3 (5.8)	19 (10.3)
Partial Response, n (%)	19 (36.5)	90 (48.6)
Stable Disease, n (%)	10 (19.2)	38 (20.5)
Progressive Disease, n (%)	16 (30.8)	31 (16.8)
Patients who had missing data or could not be evaluated, n (%)	4 (7.7)	7 (3.8)
median Duration of Response (95% CI); months	12.7 (4.1–21.4)	8.5 (7.3-9.7)
median Cycle to Best Response (95% CI); months	3.0 (1–7)	NR
median TTD (95% CI); months	5.0 (2.8-7.1)	NR
median TNT-D (95% CI); months	8.1 (5.5-10.7)	NR
median PFS (95% CI); months	6.3 (95% CI 3.9-8.7)	7.5 (95% CI 6.7-9.2)

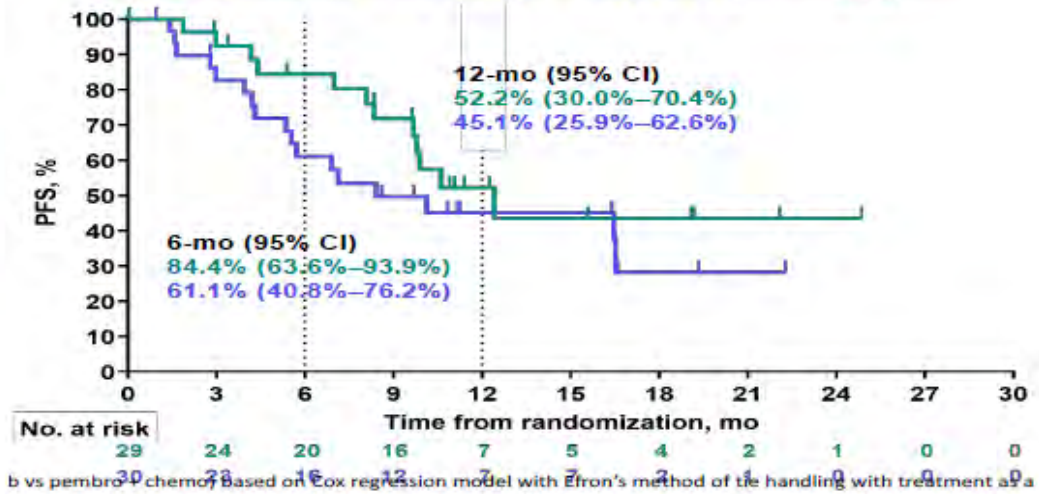
Fabi et al, NPJ BC 2023

KEYLYNK-009 (NCT04191135): Study Design



tBRCAm Population

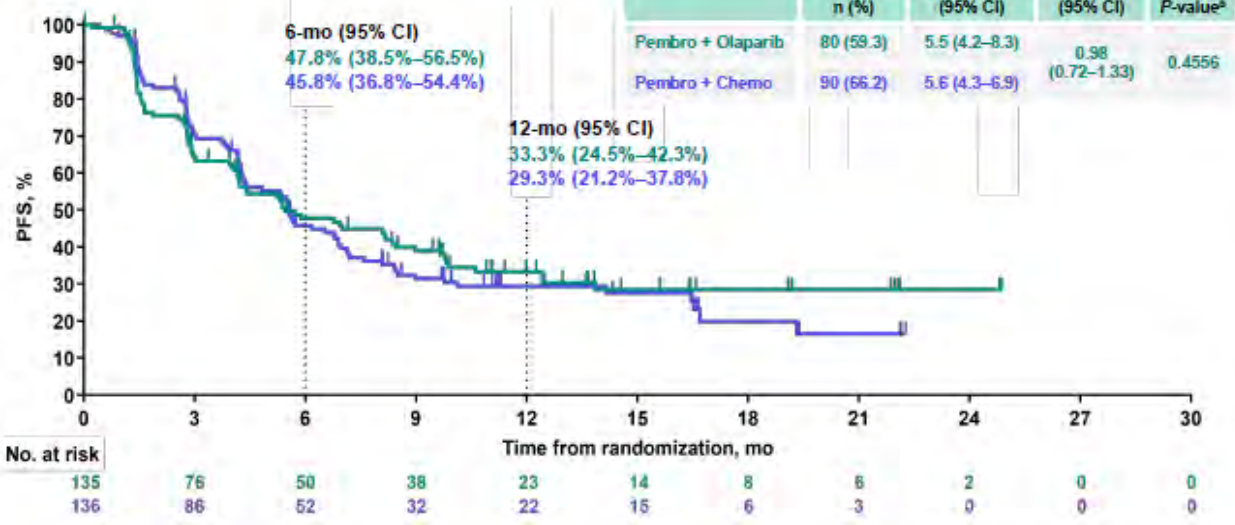
	Events, n (%)	Median, mo (95% CI)	HR[b] (95% CI)
Pembro + Olaparib	12 (41.4)	12.4 (8.3–NR)	0.70 (0.33–1.48)
Pembro + Chemo	17 (56.7)	8.4 (5.4–NR)	



b vs pembro + chemo based on Cox regression model with Efron's method of tie handling with treatment as a

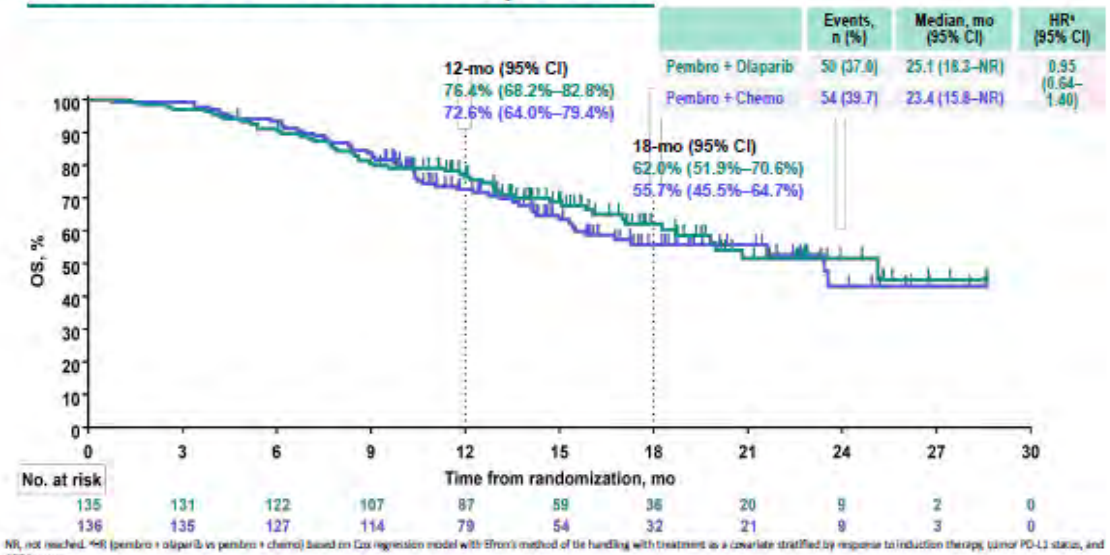
PFS per RECIST v1.1 by BICR: ITT Population

	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)	P-value[a]
Pembro + Olaparib	80 (59.3)	5.5 (4.2–8.3)	0.98 (0.72–1.33)	0.4556
Pembro + Chemo	90 (66.2)	5.6 (4.3–6.9)		



Estimates of OS: ITT Population

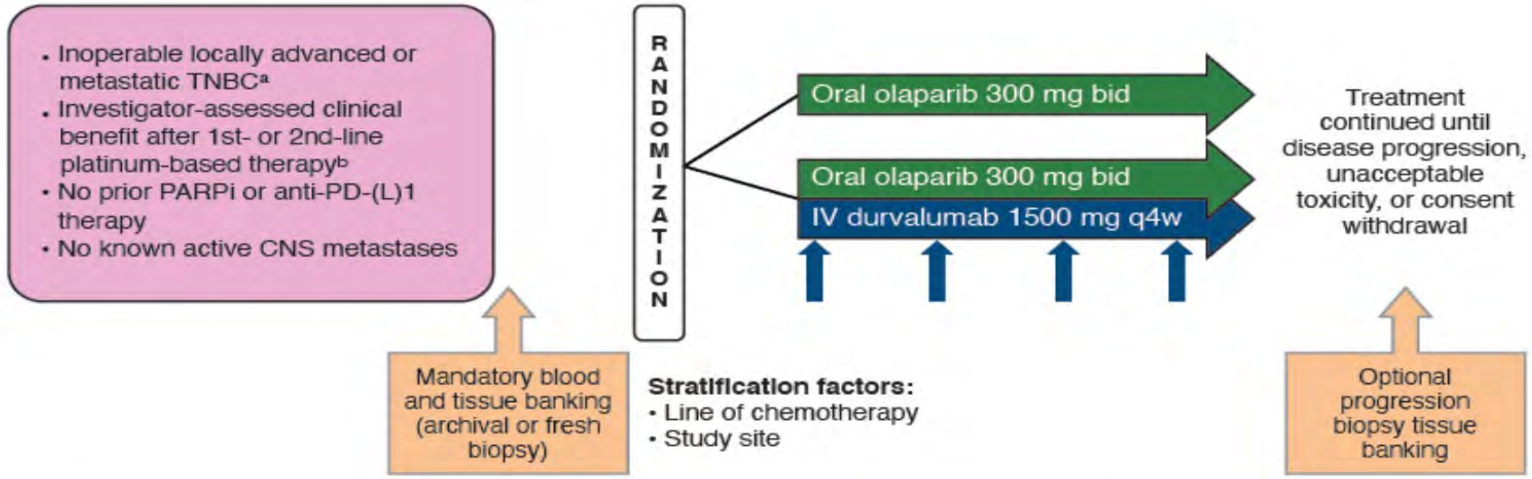
	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	50 (37.0)	25.1 (18.3–NR)	0.95 (0.64–1.40)
Pembro + Chemo	54 (39.7)	23.4 (15.8–NR)	



NR, not reached. [a]R (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy, tumor PD-L1 status, and BRCA status.

DORA: Maintenance trial of olaparib +/- durvalumab in mTNBC

Can we use platinum sensitivity as a "biomarker" to identify pts who can benefit from PARPi +/- IO



- PFS in olaparib (O=4 months) and olaparib+durvalumab (O+D=6.1 months) arms was longer than historical control (2 months)
- Durable disease control (O=52.2% and O+D= 68.2%) with chemo-free maintenance tx in subset of pts with non-gBRCA altered TNBC
  - Small pt numbers but support hypothesis of platinum sensitivity as an enrichment strategy

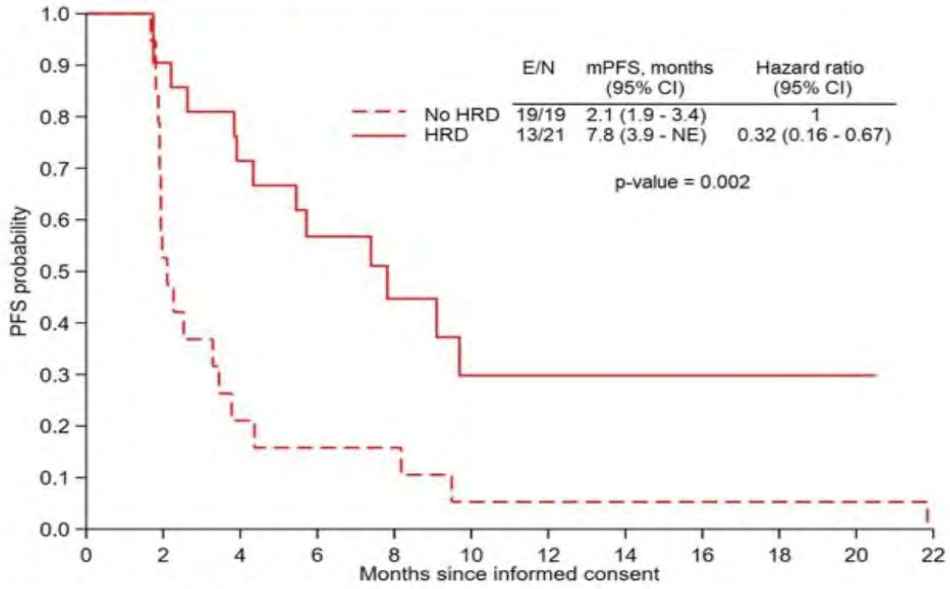
Sammons S et al. SABCS 2022 PD11-12

DORA: HRD status

HRD testing in tissue using oncoReveal™ HRD panel# and *BRCA1* & *RAD51C* methylation panel

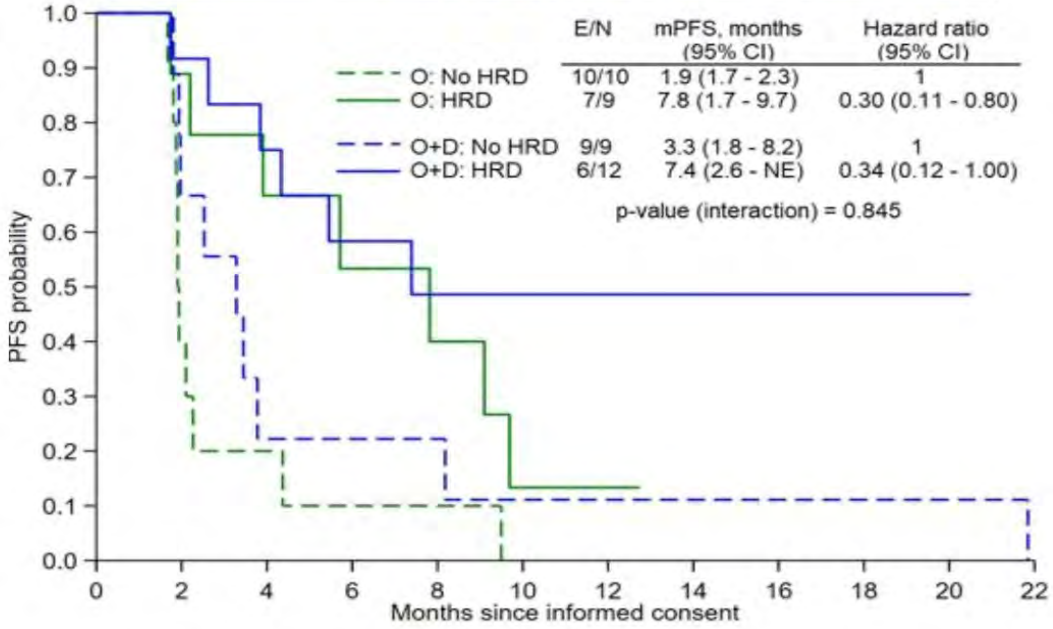
HRD = Any mutation in HR related genes, or *BRCA1*, *RAD51C* promoter methylation (n=21)

PFS longer on maintenance therapy in presence of HR alteration



HRD set – includes all patients treated with maintenance olaparib +/- durvalumab

The association between PFS and presence of HR alteration did not vary by type of maintenance therapy



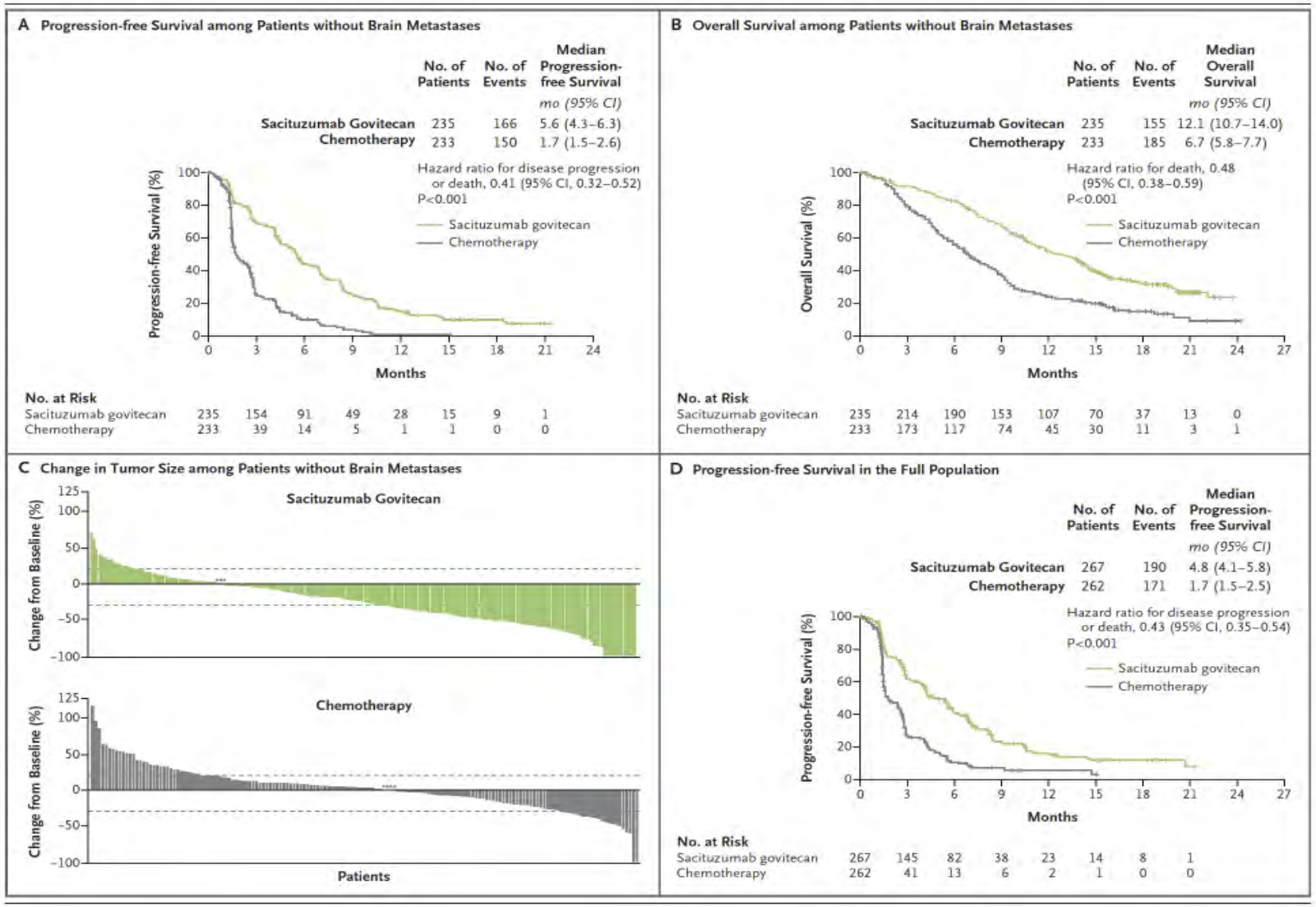
*Olaparib- TBCRC 048 & Talazoparib- Gruber

Tan TJ et al. ESMO BC 4MO

Phase III ASCENT Trial Comparing Sacituzumab Govitecan to Chemotherapy in Metastatic TNBC

<u>April 2020</u>: Granted accelerated FDA approval

<u>April 2021</u>: Granted full FDA approval

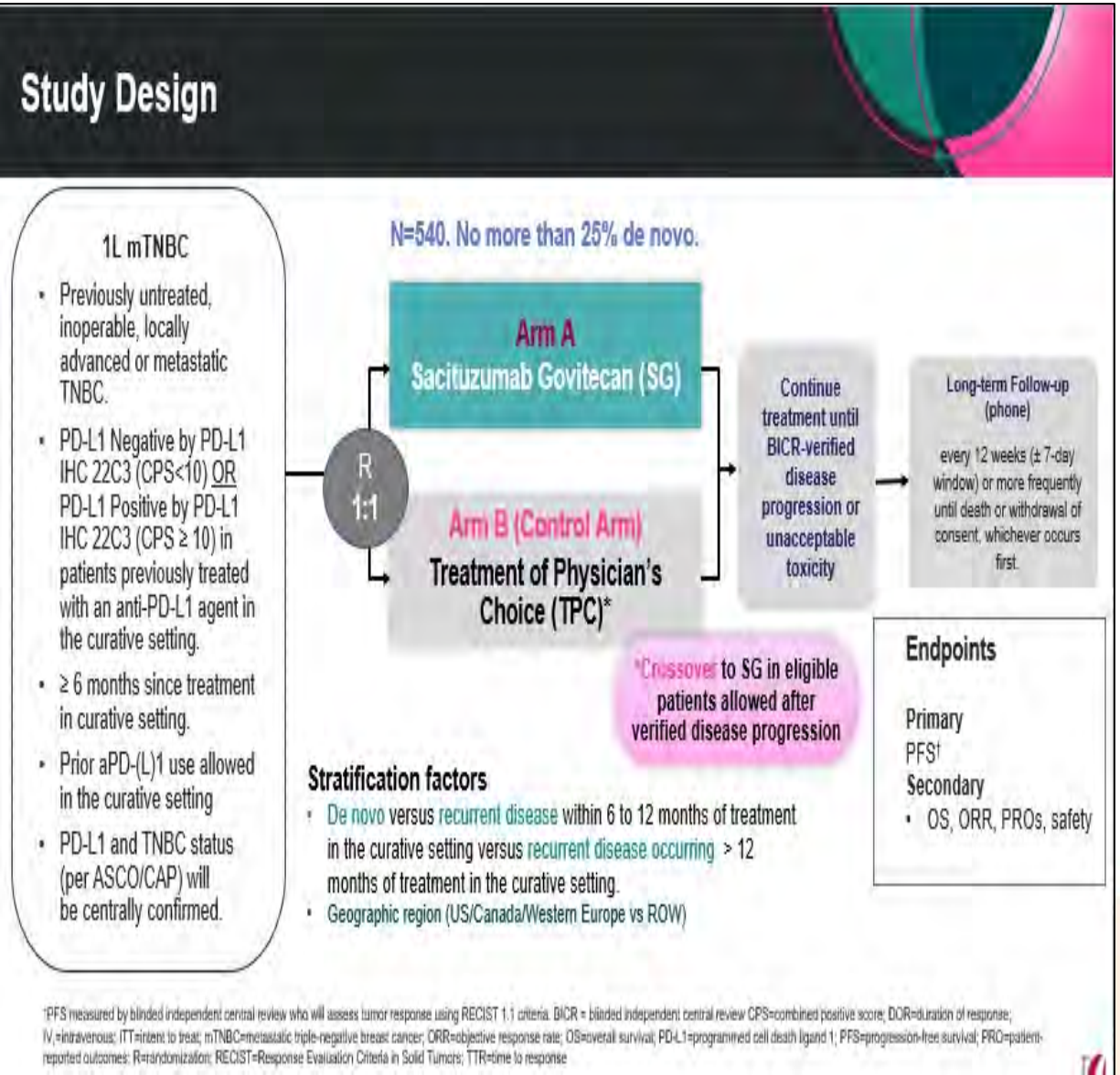


Bardia A, et al. NEJM 2021; 384:1529-41

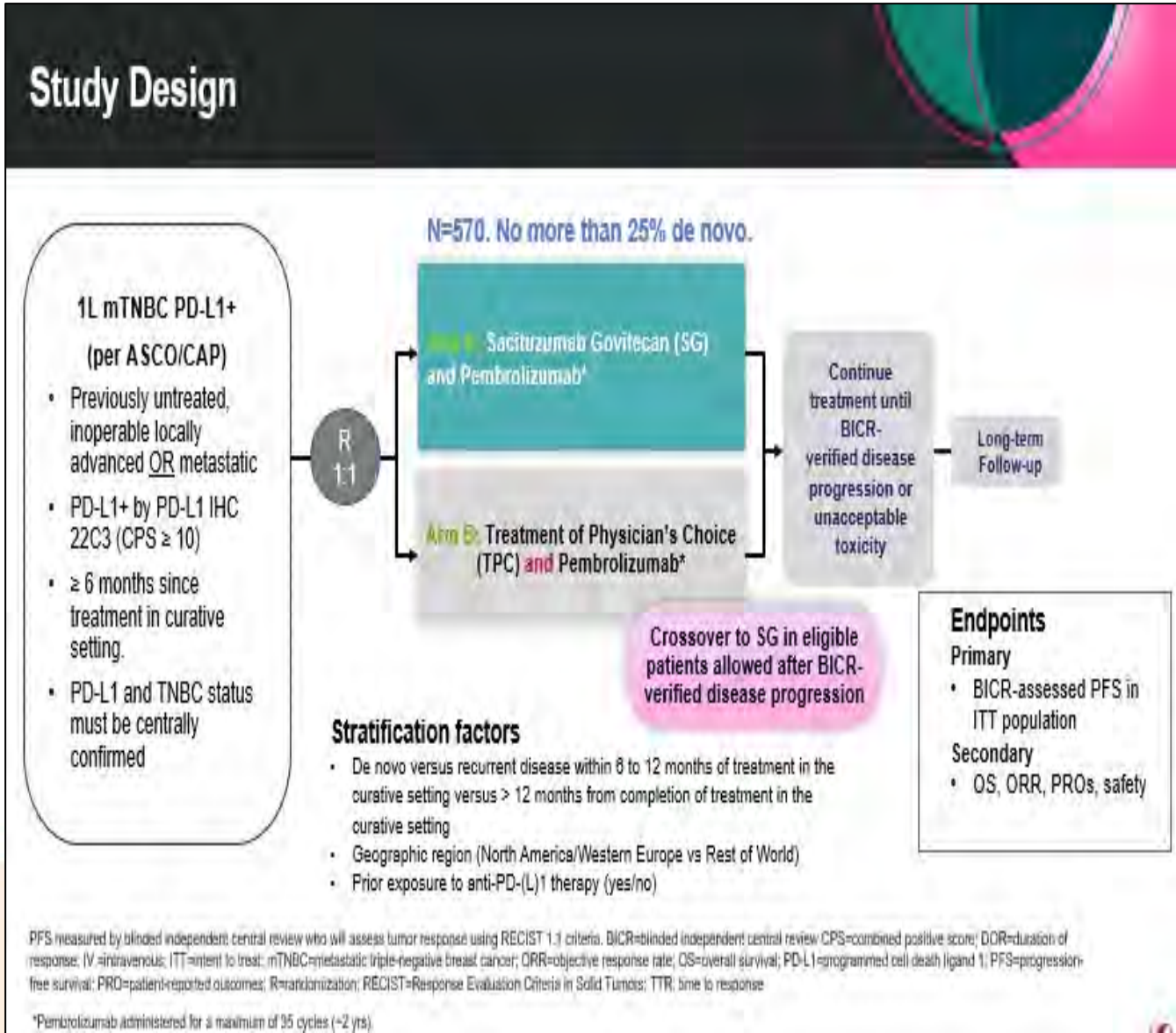
WHAT ELSE ???

First line treatment combinations, does one size fits all?

ASCENT 03

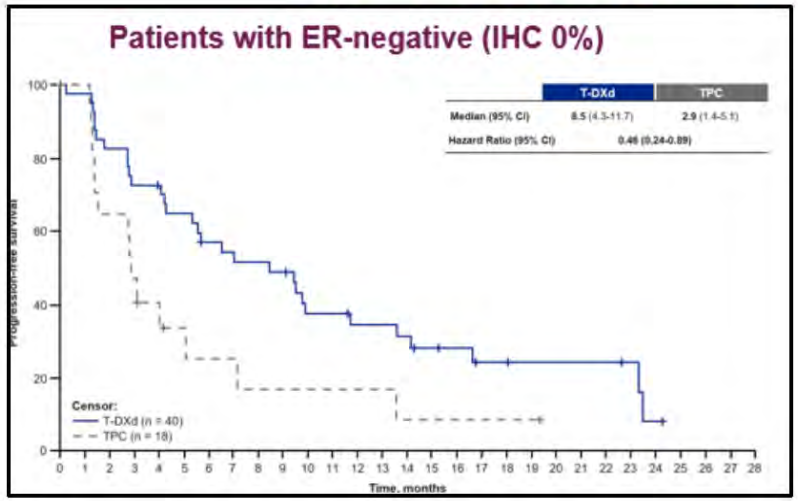


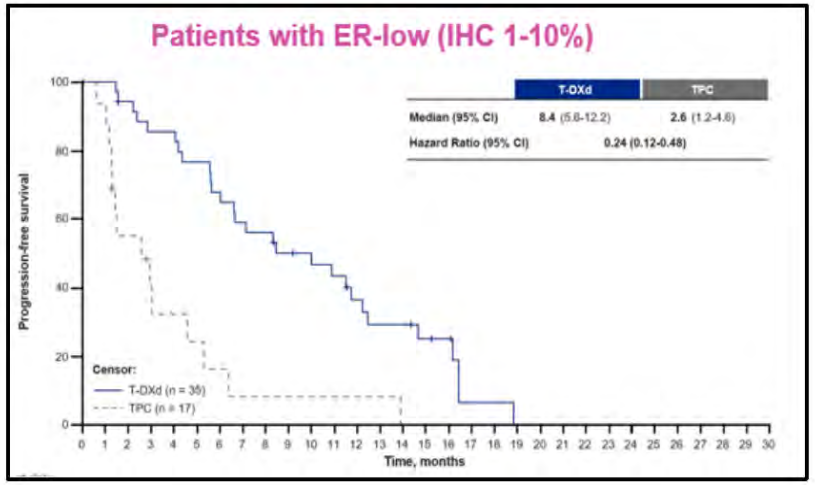
ASCENT 04



DESTINY Breast04: Subgroup analysis in ER-low/HER2-low MBC

ER-negative (IHC 0%)		ER-low (IHC 1-10%)	
T-DXd (n = 40)	TPC (n = 18)	T-DXd (n = 35)	TPC (n = 17)





	ER-Low (IHC 1-10%)		ER-negative (IHC 0%)	
	T-DXd	TPC	T-DXd	TPC
ORR	57.9%	5.9%	50.0%	6.7%
PFS (months)	8.4	2.6	8.5	2.9
OS (months)	20	10.2	18.2	8.3

ER-low MBC derived similar benefit from T-DXd compared to triple negative MBC

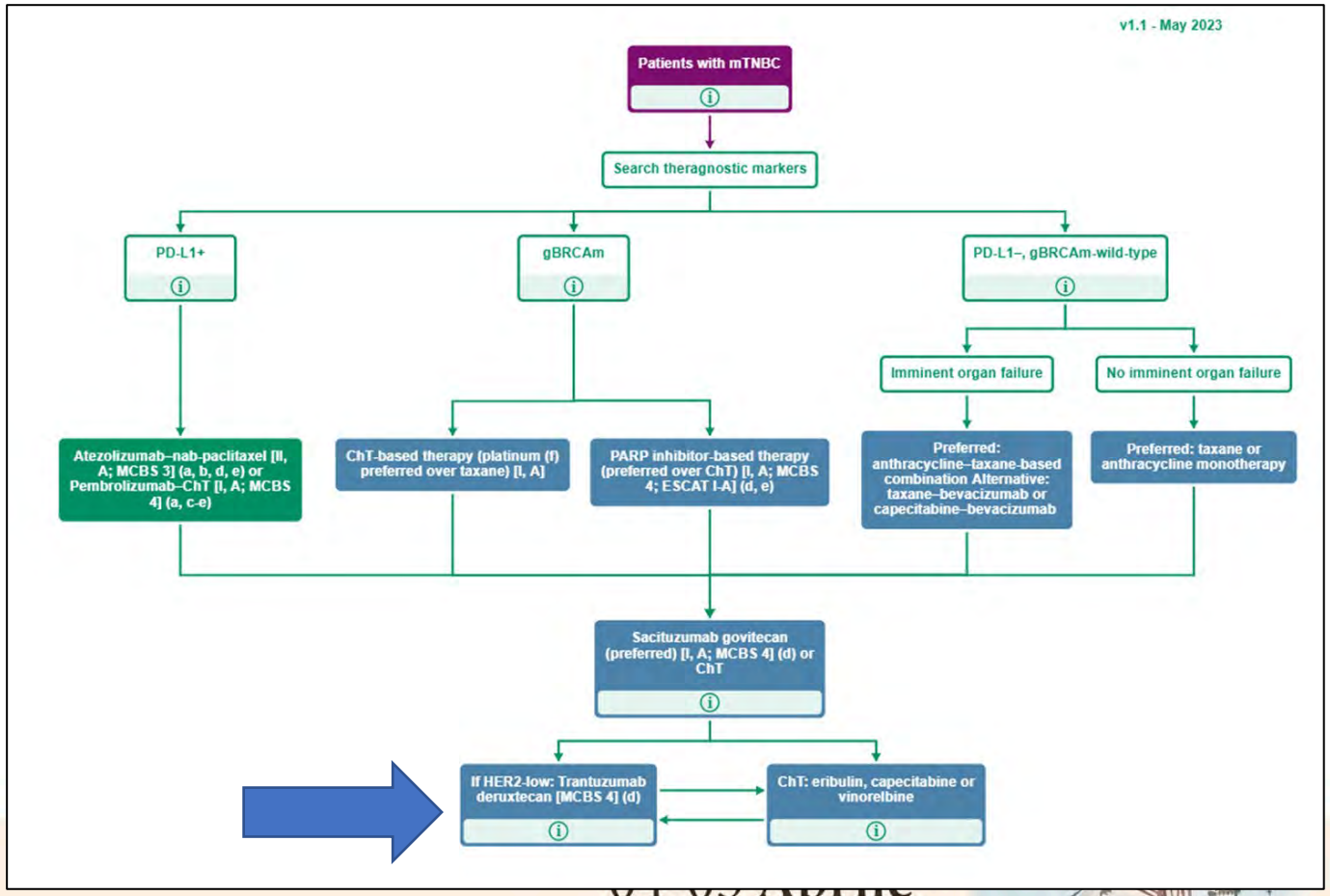
Cameron D et al. ESMO BC Abstr 192M

Sustained remarkable OS benefit with T-DXd in HER2-low (HR-)

Only on T-DXd, some patients had prolonged disease control

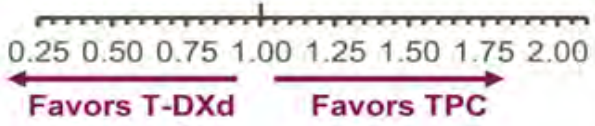
The consistent results across all endpoints (ORR, mDoR, PFS, and OS) establish the role of T-DXd in TN HER2-low mBC

Current limitations
- Exploratory analysis
- Only 58 patients



Patient's perspective: QoL benefit of T-DXd vs TPC

		Median (95% CI) TDD, months		Hazard Ratio (95% CI)	*P* Value[d]
		T-DXd (n = 331)	TPC (n = 163)		
EORTC QLQ-C30	Global health status/QoL[a]	11.4 (8.8-16.3)	7.5 (5.9-9.5)	0.69 (0.52-0.92)	0.0096
	Pain symptoms	16.4 (13.1-21.5)	6.1 (4.2-7.5)	0.40 (0.30-0.54)	<0.0001
	Physical functioning[b]	16.6 (11.3-21.5)	7.5 (4.9-9.5)	0.53 (0.40-0.70)	<0.0001
	Emotional functioning[b]	19.2 (16.3-24.5)	10.5 (7.1-NE)	0.69 (0.50-0.96)	0.0266
	Social functioning[b]	12.8 (10.4-15.2)	6.0 (4.4-7.7)	0.59 (0.45-0.77)	0.0001
	Fatigue[c]	11.1 (7.2-12.4)	4.5 (3.1-6.2)	0.61 (0.47-0.79)	0.0002
	Nausea and vomiting[c]	5.7 (3.8-8.4)	9.3 (7.5-17.1)	1.46 (1.09-1.96)	0.0128
EORTC QLQ-BR23	Arm symptoms[b]	14.4 (11.9-23.0)	8.7 (5.6-NE)	0.62 (0.45-0.85)	0.0027
	Breast symptoms[b]	NE (24.7-NE)	NE (NE-NE)	0.71 (0.50-1.01)	0.1008
EQ-5D-5L	VAS[b,c]	12.0 (9.9-15.2)	6.8 (4.9-11.4)	0.73 (0.54-0.97)	0.0288



Longer T-DXd exposure does not increase toxicity
No new cases of ILD/pneumonitis since the primary analysis

The BEGONIA Study (NCT03742102)

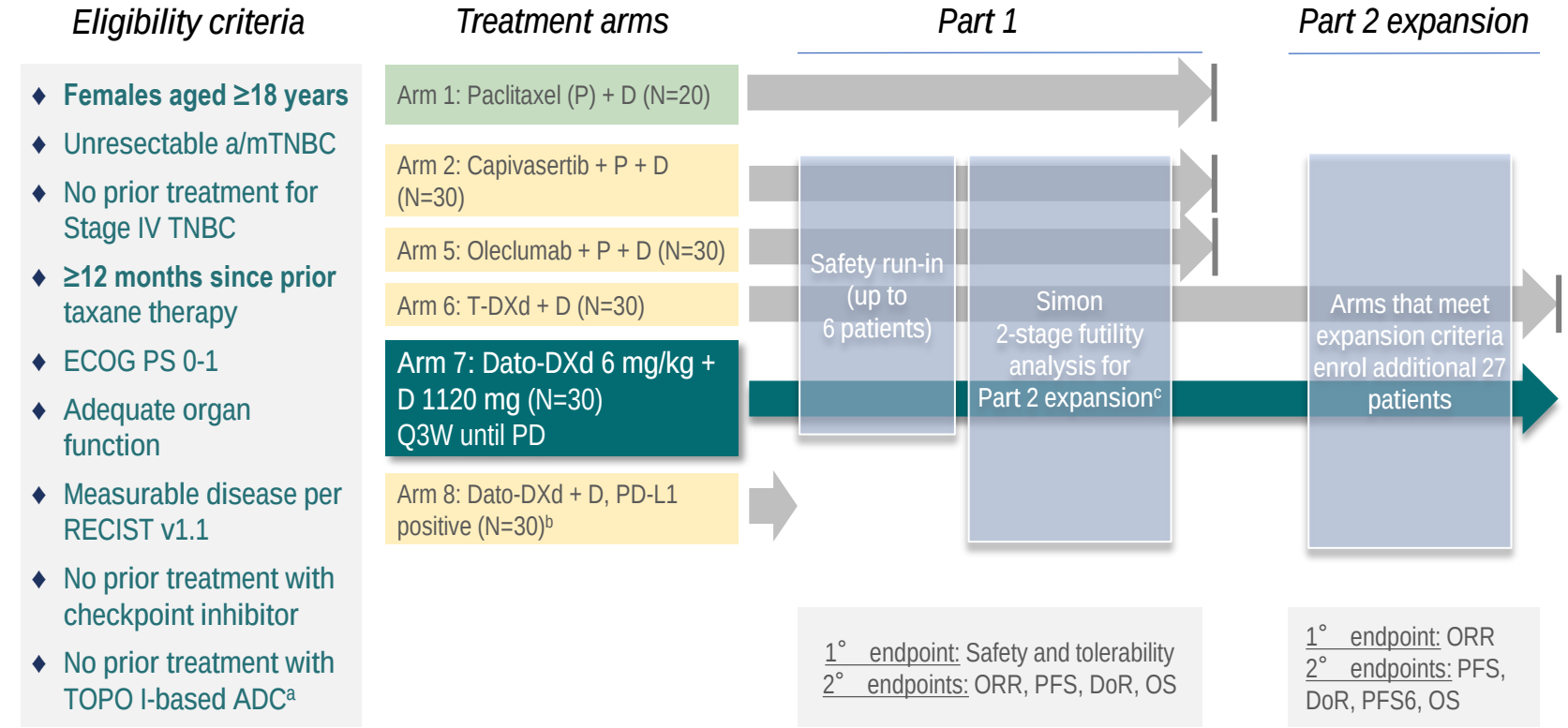
Rationale

- Immune checkpoint inhibitors + chemotherapy is the standard of care for patients with PD-L1 positive a/mTNBC; still, most progress within a year (median PFS ~9–10 months)[1,2]
- BEGONIA is evaluating combinations of durvalumab (D), an anti–PD-L1 antibody, with other novel therapies in first-line a/mTNBC
- Dato-DXd is a TROP2-directed ADC with a TOPO I inhibitor payload and a tumour-selective cleavable linker[3]
- At median 7.2 months follow-up, ORR was 74% for patients treated with Dato-DXd + D in BEGONIA[4]

Study Design

Eligibility criteria

- **Females aged ≥18 years**
- Unresectable a/mTNBC
- No prior treatment for Stage IV TNBC
- **≥12 months since prior** taxane therapy
- ECOG PS 0-1
- Adequate organ function
- Measurable disease per RECIST v1.1
- No prior treatment with checkpoint inhibitor
- No prior treatment with TOPO I-based ADC[a]



Updated results with median 11.7 months of follow-up for patients from Parts 1 and 2 treated with Dato-DXd + D in BEGONIA Arm 7

[a]ADC cohort-specific criteria. [b]Currently enrolling; a safety run-in will not occur for this arm as Dato-DXd + D was already evaluated and found to be tolerable with no dose-limiting toxicities reported. [c]Novel treatment combinations may enter Part 2 expansion if confirmed ORR is at least 57%.

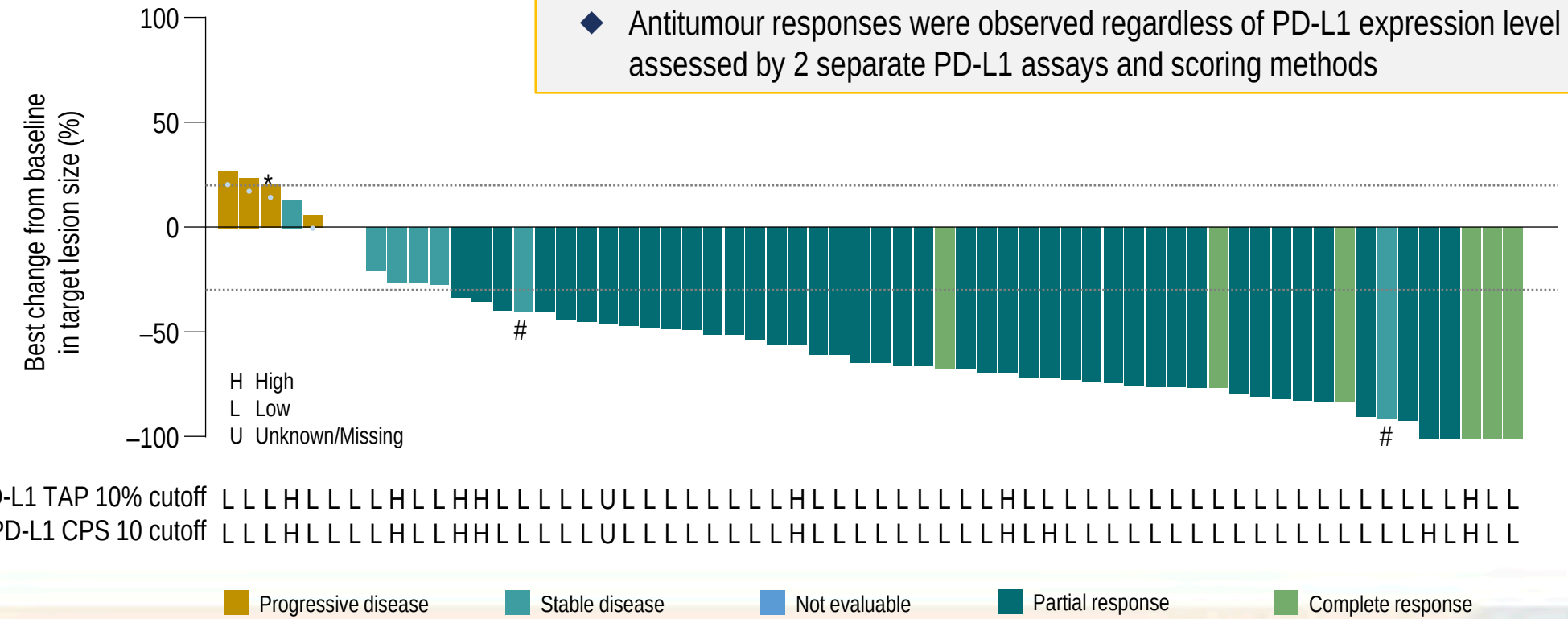
1. Cortes J. et al. *Lancet.* 2020;396(10265):1817-1828. 2. Emens LA, et al. *J Natl Cancer Inst.* 2021;113(8):1005-1016. 3. Bardia A, et al. Presented at SABCS 2022. P6-10-03. 4. Schmid P, et al. Presented at SABCS 2022. PD11-09.

BEGONIA Arm 7: Dato-DXd + Durvalumab

Antitumour Responses in 1L a/mTNBC

Confirmed ORR was 79% (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods



Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%). PD-L1 expression was assessed by 1) immunohistochemistry using the VENTANA PD-L1 (SP263) Assay with expression defined as the percentage of the tumour area populated by tumour or immune cells with membranous staining (TAP), or 2) immunohistochemistry using the 22C3 antibody with expression defined as the number of PD-L1–staining tumour cells, lymphocytes, and macrophages, divided by the total number of viable tumour cells, multiplied by 100 (CPS). *If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with PD as best overall response. #Unconfirmed response.

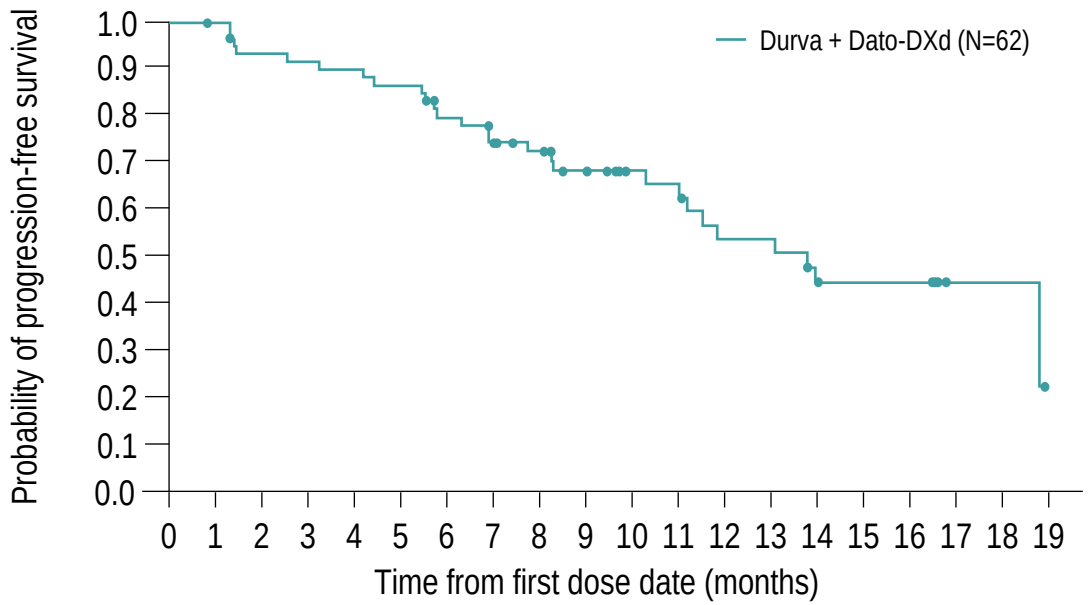
1L, first line; a/m TNBC, advanced/metastatic triple–negative breast cancer; CI, confidence interval; CPS, combined positive score; CR, complete response; Dato-DXd, datopotamab deruxtecan; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PR, partial response; TAP, tumour area positivity.

Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Progression-Free Survival and Duration of Response

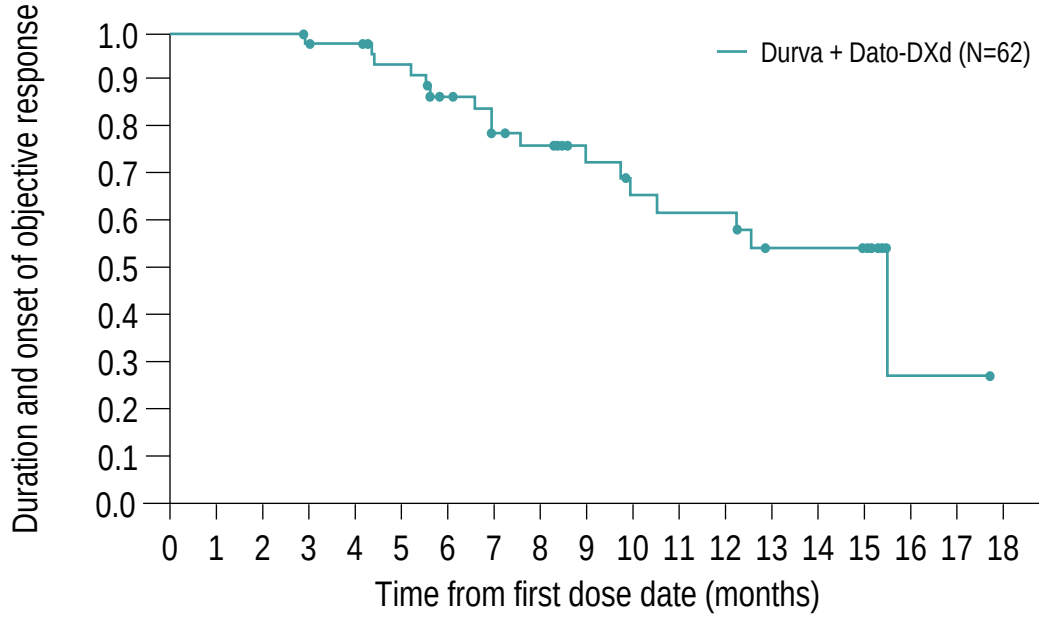
Median PFS was **13.8** months (95% CI, 11.0–NC)



Number of patients at risk

Durva + Dato-DXd	62	61	56	55	54	52	45	40	37	32	24	23	18	18	14	13	13	2	2	0

Median DoR was **15.5** months (95% CI, 9.92–NC)



Number of patients at risk

Durva + Dato-DXd	49	49	49	47	46	42	35	30	28	21	18	17	17	13	13	12	1	1	0

Kaplan-Meier analysis was performed. Circles indicate censored observations.

CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; NC, not calculable; PFS, progression-free survival.

Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Adverse Events

Most frequently reported adverse events (≥15%) (N=62)

AE preferred term	Any grade, n (%)	Grade 3/4, n (%)
Nausea	40 (65)	0
Stomatitis	40 (65)	7 (11)
Alopecia	31 (50)	0
Constipation	29 (47)	1 (2)
Fatigue	28 (45)	1 (2)
Rash	20 (32)	0
Vomiting	16 (26)	1 (2)
Amylase increased	13 (21)	11 (18)
COVID-19	13 (21)	0
Dry eye	13 (21)	0
Decreased appetite	12 (19)	1 (2)
Pruritus	10 (16)	0
Cough	10 (16)	0

- The most common AEs were gastrointestinal and generally of low grade (Table)
- Stomatitis was the most common AE leading to Dato-DXd dose reduction (11 patients)
- There were 3 (5%) adjudicated treatment-related ILD/pneumonitis events (2 grade 2 events, 1 grade 1 event)
- Limited rates of diarrhea (13% any grade, 1 grade 3 event) and neutropenia (5% any grade, 1 grade 3 event) were reported
- The most frequent AESIs for Arm 7 were stomatitis (65%), rash (32%), dry eye (21%), hypothyroidism (14.5%), and keratitis (14.5%)

AE, adverse event; AESI, adverse event of special interest; ILD, interstitial lung disease.

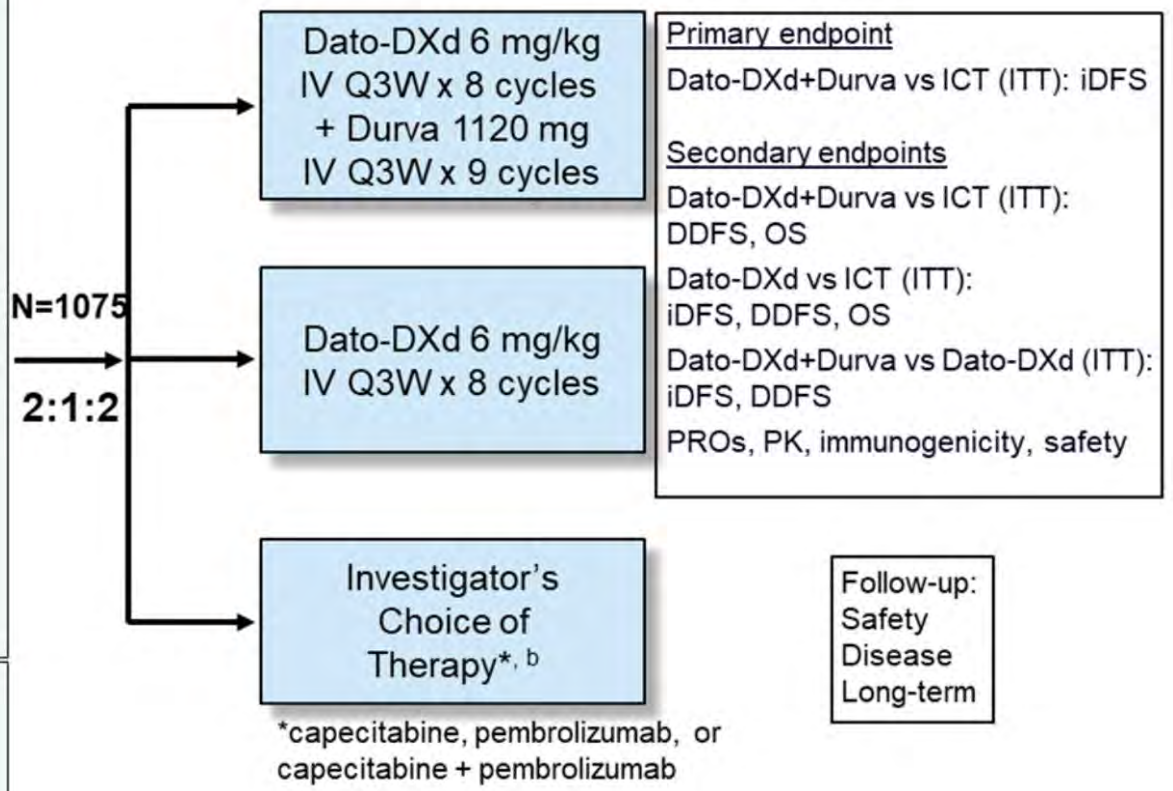
Data cutoff: 02 Feb 2023

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 in the breast and/or axillary lymph node(s) at surgical resection following neoadjuvant therapy
- No evidence of locoregional or distant relapse
- Radiotherapy (if indicated) delivered before the start of study intervention
- 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:

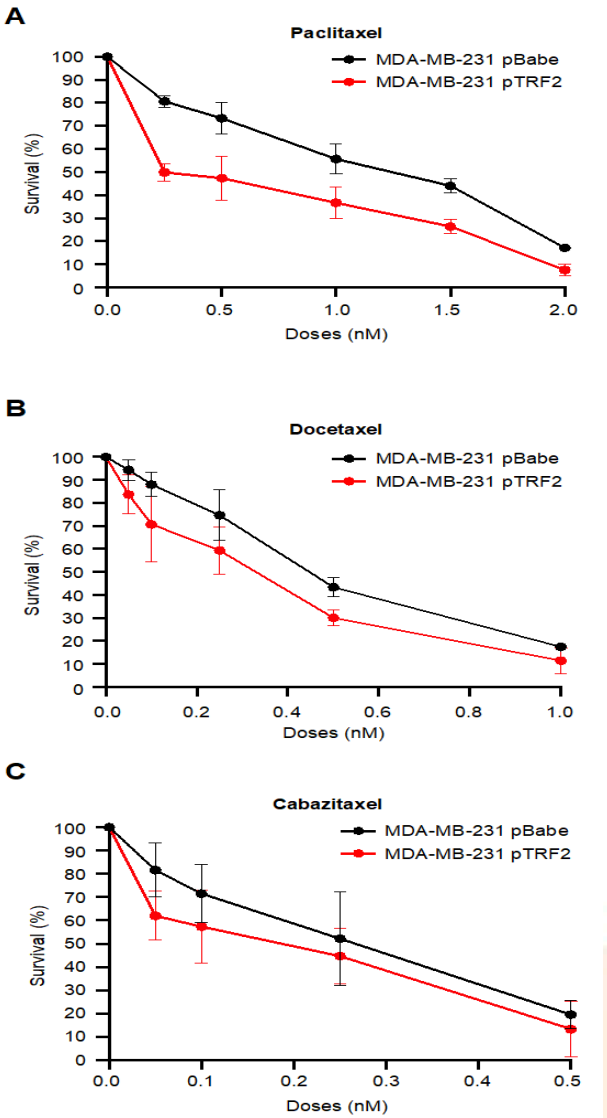
- Prior neoadjuvant pembrolizumab (Yes vs No); cap No at 40%
- Residual disease (< 1 cm vs ≥ 1 cm) [a]; cap < 1 cm at 20%
- Prior neoadjuvant platinum chemotherapy (Yes vs No)



Tropion Breast 03

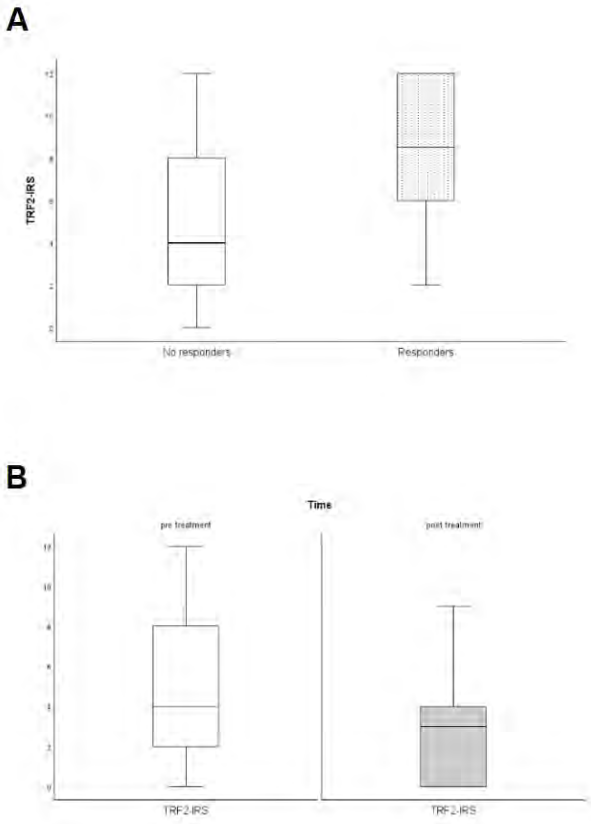
TRF2 is a novel marker of tumor response to taxane-based therapy: from mechanistic insight to clinical implications

S. Iachettini, I. Terrenato, M. Porru, S. Di Vito, A. Rizzo, C. D'Angelo, A. Di Benedetto, A. Mulè, A. Santoro, A. Palazzo, P. Fuso, A. Stoppacciaro, P. Vici, A. Fabi*, A. Biroccio*, P. Zizza*



TRF2 over-expression confers sensitivity to chemotherapy to TNBC cells *in vitro*

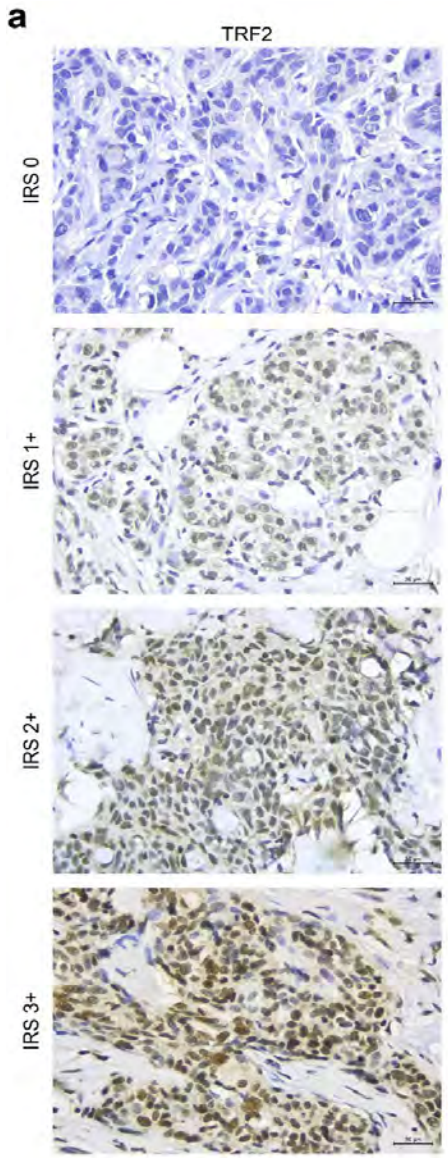
TRF2 over-expression correlates with responsiveness of TNBC patients to Taxane-based neo-adjuvant chemotherapy

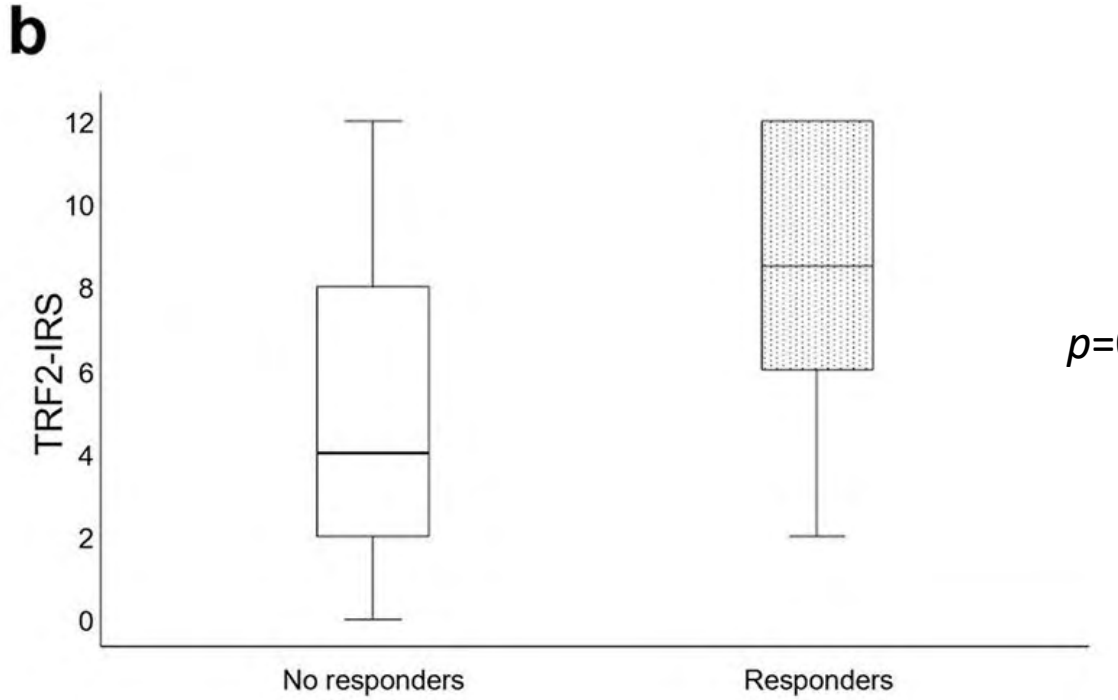


J Exp Clin Cancer Res 2024

04-05 Aprile
2024 Padova

Upregolation del PDL-1





p=0.005

median follow-up 43 months

Iachettini et al, J Exp Clin Cancer Res 2024

Overexpression of KLHL22 correlates with poor prognosis in patients with triple-negative breast cancer

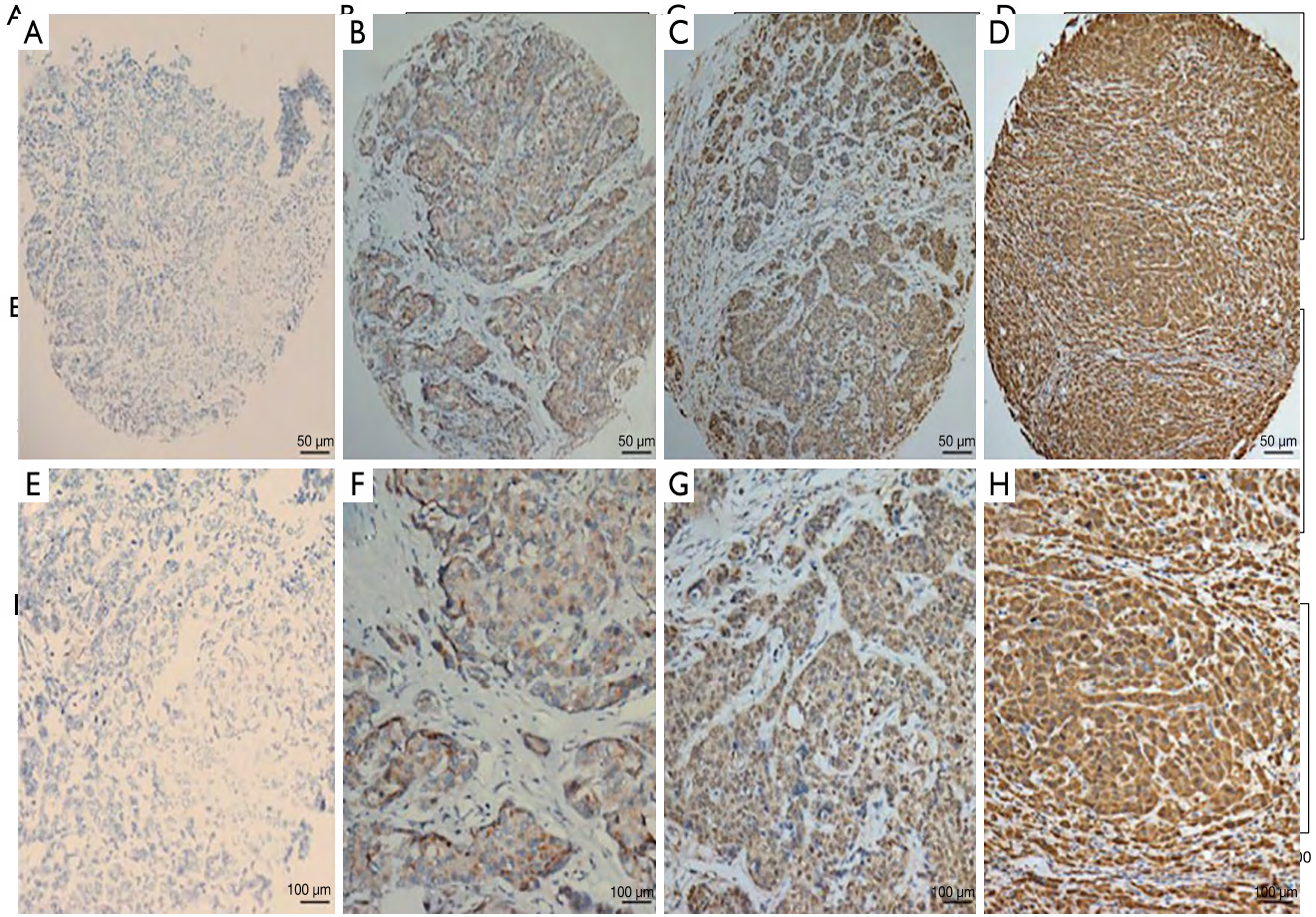


Table 3 Multivariate survival analyses of clinicopathologic variables in TNBC patients

Variable	OS			PFS		
	HR	95% CI	P value	HR	95% CI	P value
Age (>49 *vs.* ≤49) (year)	0.602	0.300–1.207	0.152	0.52	0.185–1.466	0.216
P53 (yes *vs.* no)	2.441	1.125–5.299	0.024	0.633	0.234–1.714	0.368
Tumor size (>2.5 *vs.* ≤2.5) (cm)	0.847	0.424–1.691	0.637	0.74	0.254–2.154	0.581
Clinical stage (III+IV *vs.* I+II)	4.596	2.260–9.345	<0.001	3.093	1.062–9.008	0.038
KLHL22 (high *vs.* low)	10.41	4.313–25.126	<0.001	8.493	2.210–32.642	0.002

TNBC, triple-negative breast cancer; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

- We need to keep seeking curative therapeutic strategies for advanced TNBC
  - This has proven elusive so far
  - While survival has improved, it is simply not good enough

- For all who are new to breast cancer research, there is enormous opportunity to contribute to a better future for all affected by TNBC
  - Potential for clinical impact is real and patients are depending on it

Thank you for your attention