Il carcinoma mammario metastatico triplo negativo

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Declaration of Interests

Emilia Montagna

Institutional financial interests with commercial entities:

- Novartis
- Pierre fabre

- **No personal financial interests with any commercial entity**

Agenda

- Introduction
- Highlights in the treatment of mTNBC
- Take home messages

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Some definitions

- TNBC is an heterogeneous entity
  - Histologic
  - Biologic
  - Microenvironmental

- TNBC is 60-80% basal like
- Basal like is 70% TNBC

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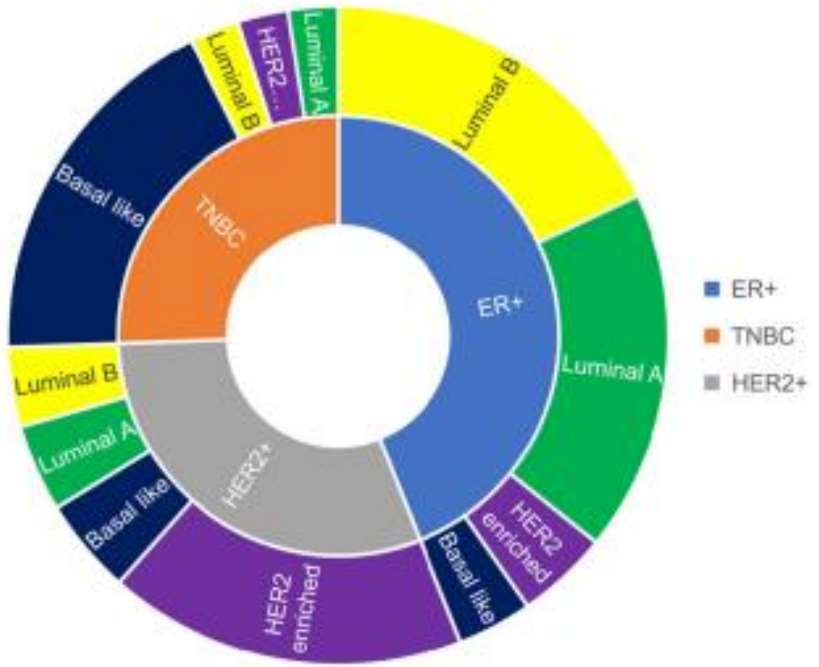
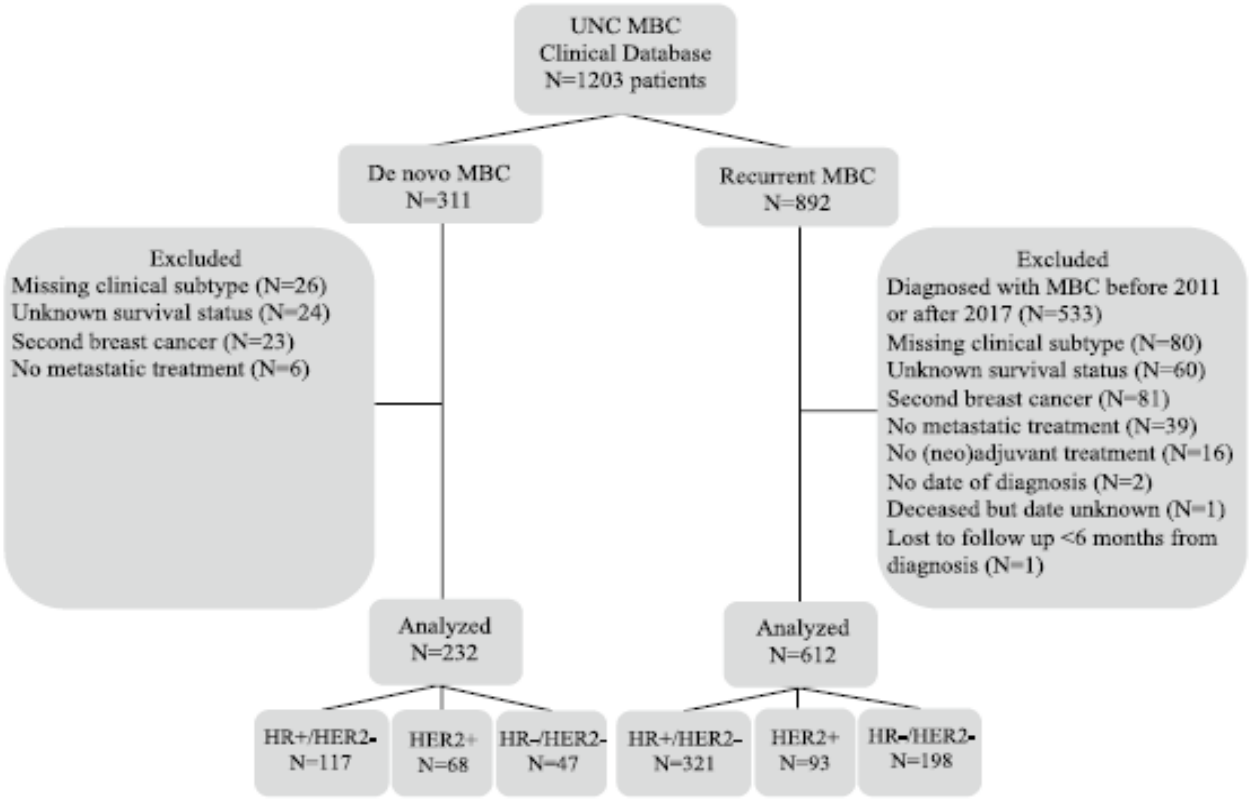


Fig. 1 Intrinsic molecular subtypes of breast cancer. Within each clinical subtype there are multiple molecular subtypes. ER endocrine receptor; TNBC triple negative breast cancer; HER2 Human Epidermal Growth Factor Receptor 2.

Zagami et Carey, NPJ Breast Cancer 2022

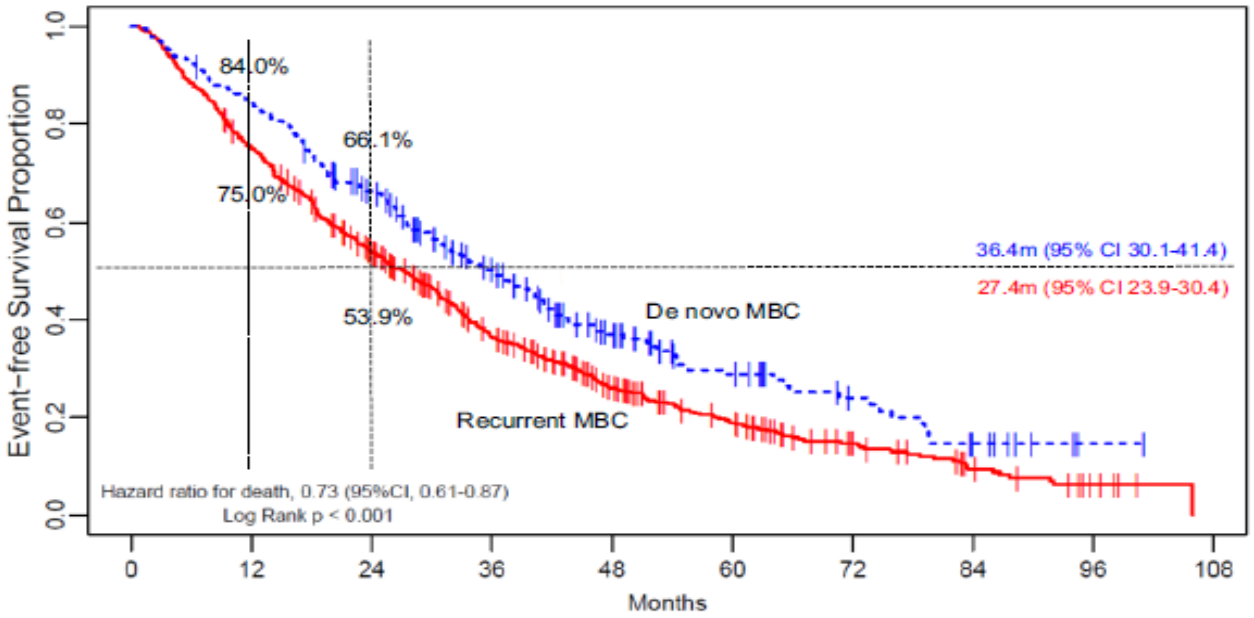
MBC de novo vs recurrent

Fig. 1 Consort diagram. *UNC* University of North Carolina, *MBC* metastatic breast cancer, *HR* hormone receptor; *HER2* human epidermal growth factor receptor 2



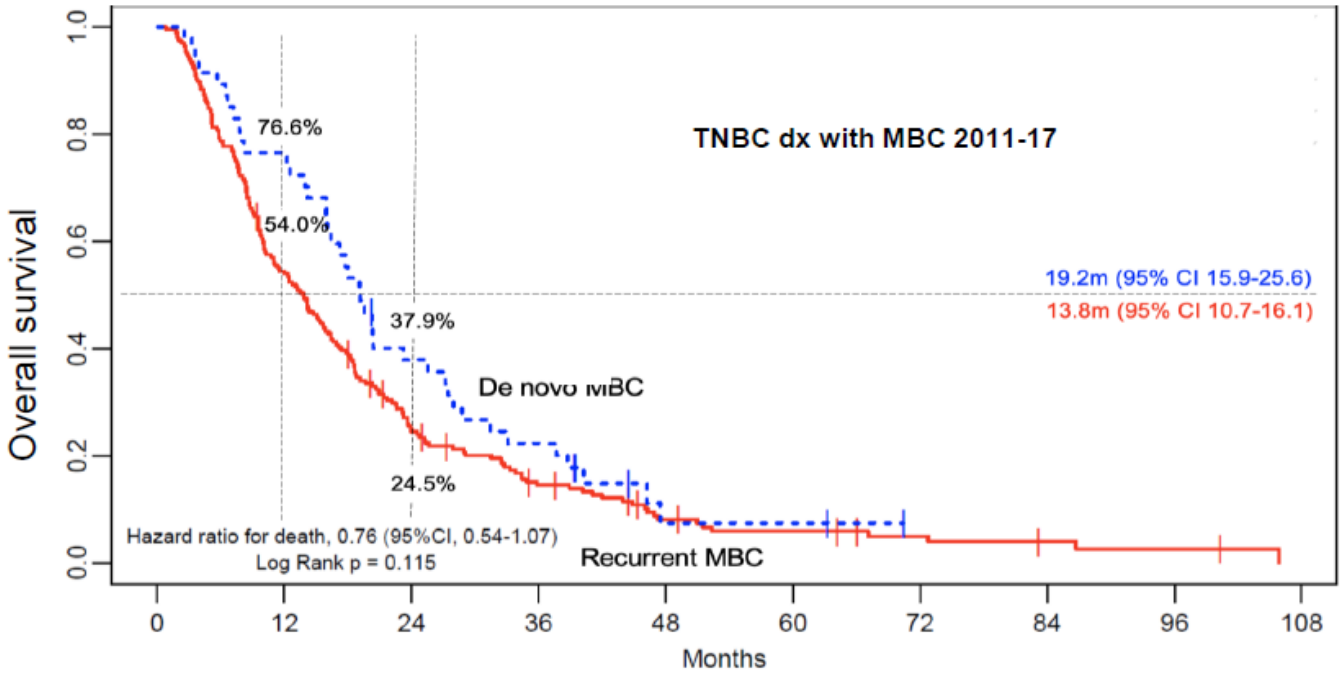
Survival in MBC

Fig. 2 Overall survival among entire metastatic breast cancer study population by *de novo* or recurrent status. Estimates of overall survival were from Kaplan–Meier curves and tests of differences by two-sided log-rank test. Black-dashed line = *de novo* metastatic breast cancer. Gray solid line = recurrent metastatic breast cancer



No. at Risk									
Recurrent MBC	612	456	307	184	106	65	34	16	5
De novo MBC	232	194	145	93	51	30	18	8	1

Outcomes of Metastatic TNBC (Diagnosed with Metastasis 2011-2017)



Overall survival ~ 1.5y

Anticipate an increase in the *de novo* % as adjuvant Rx reduces recurrence rates (~5% ↑ during this timeframe)

Significant risk factors for OS in multivariable analysis of 844 MBC pts treated at UNC

Factor	Impact on survival
De novo disease	37% better
Age ≥ 50	40% worse
Black (vs White)	60% worse
TNBC (vs HR+ HER2-)	**70% worse**
Tumor size (T3-4 vs 1-2)	30% worse
Grade 3 (vs 1/2)	90% worse
> 1 site	45% worse

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Few years ago…

Current Treatment Options for Metastatic TNBC

- Sequential single-agent chemotherapy is the preferred approach for most pts with metastatic TNBC
  - Combination chemotherapy can be used for pts requiring more rapid response but does not improve OS

Taxanes	Anthracyclines	Antimetabolites	Other Microtubule Inhibitors	Platinum Agents
Paclitaxel	Doxorubicin	Capecitabine	Vinorelbine	Carboplatin
Nab-paclitaxel	Pegylated liposomal doxorubicin	Gemcitabine	Eribulin	Cisplatin
Docetaxel	Epirubicin		Ixabepilone	

- Patients should generally remain on a regimen until best response, disease progression, or significant toxicity

ZeichnerSB, et al. Breast Cancer (Auckl). 2016

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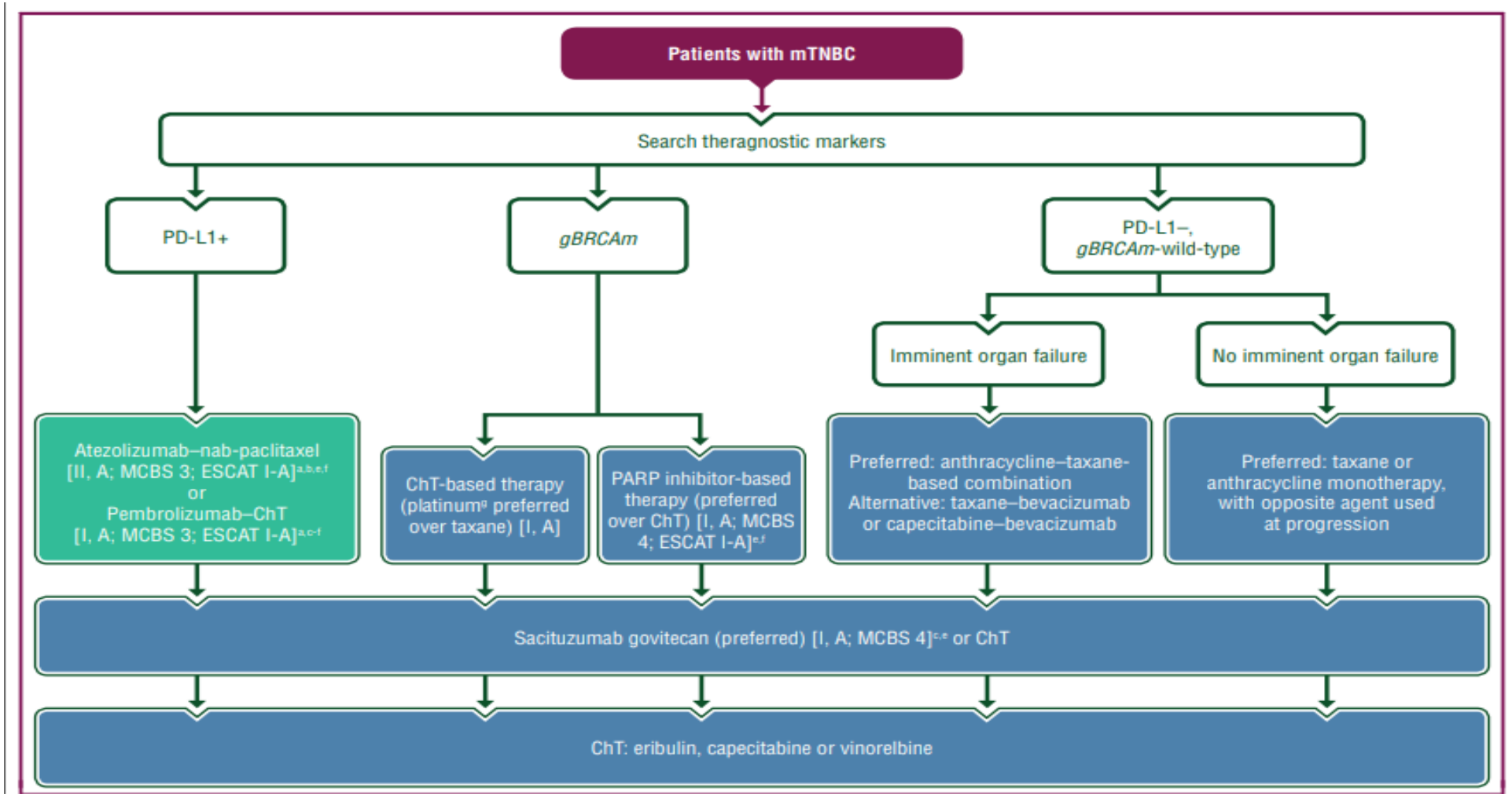

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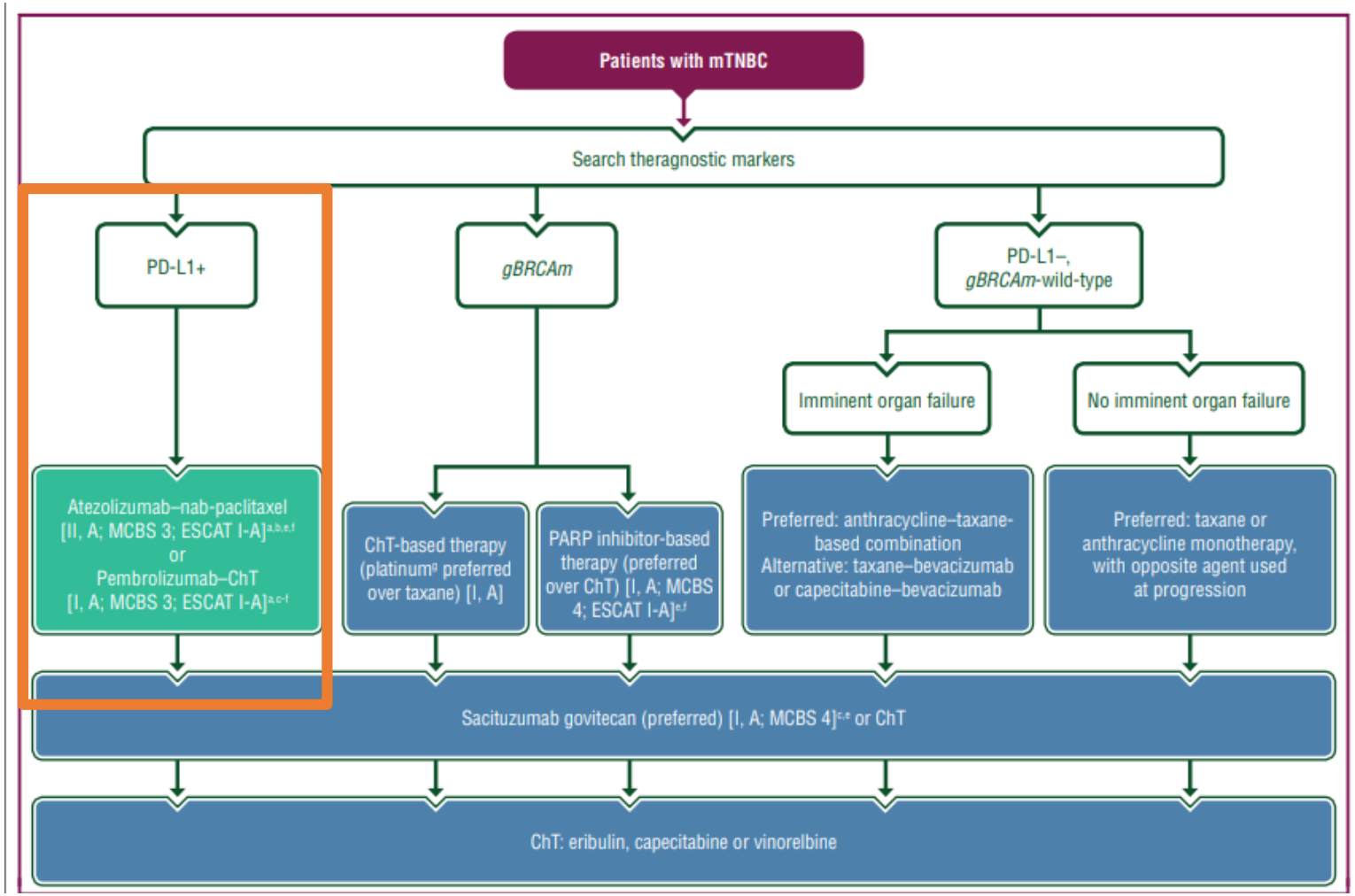

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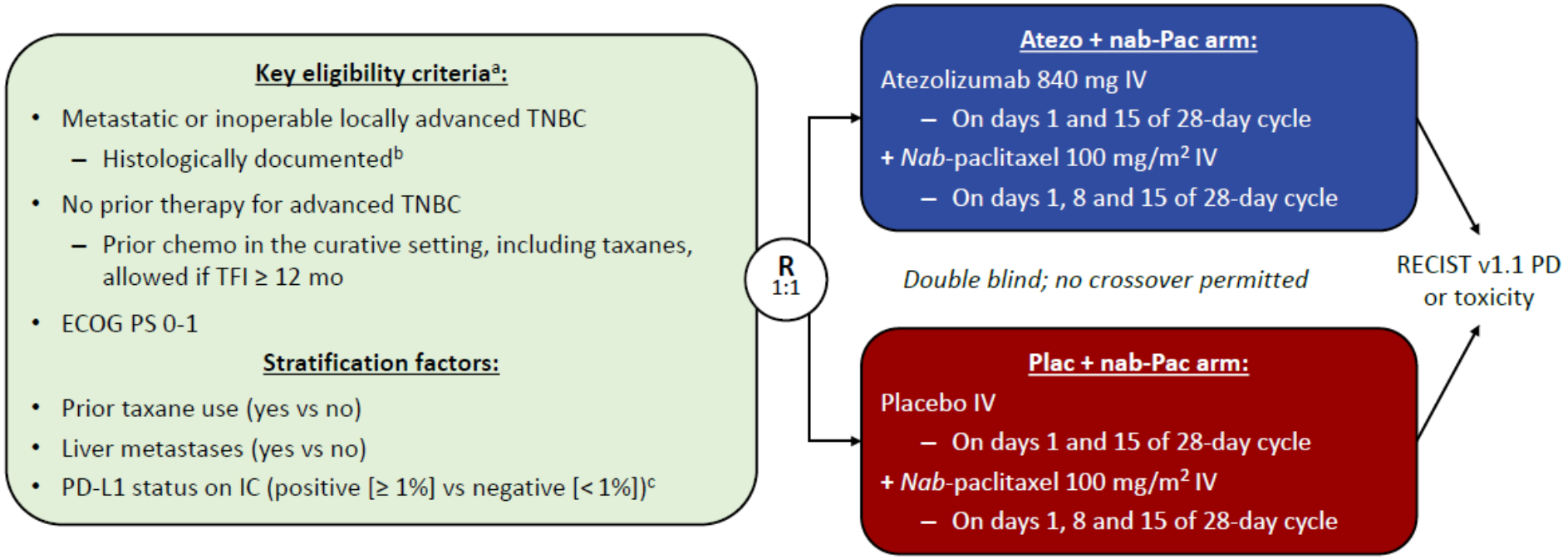
IMpassion130 (Phase III) – Study Design (TNBC metastatic disease)



- Co-primary endpoints were **PFS** and **OS** in the **ITT and PD-L1+ populations**[d].
- Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated.

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Emens et al, ESMO 2020

IMpassion130 – Study Population

Characteristic	Atezo + nab-Pac (N = 451)	Plac + nab-Pac (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)
Female, n (%)	448 (99%)	450 (100%)
Race, n (%)[a]		
White	308 (68%)	301 (67%)
Asian	85 (19%)	76 (17%)
Black/African American	26 (6%)	33 (7%)
Other/multiple	20 (4%)	26 (6%)
ECOG PS, n (%)[b,c]		
0	256 (57%)	270 (60%)
1	193 (43%)	179 (40%)
Prior (neo)adjuvant treatment, n (%)	284 (63%)	286 (63%)
Prior taxane	231 (51%)	230 (51%)
Prior anthracycline	243 (54%)	242 (54%)

Characteristic	Atezo + nab-Pac (N = 451)	Plac + nab-Pac (N = 451)
Metastatic disease, n (%)	404 (90%)	408 (91%)
No. of sites, n (%)[d]		
0-3	332 (74%)	341 (76%)
≥ 4	118 (26%)	108 (24%)
Site of metastatic disease, n (%)		
Lung	226 (50%)	242 (54%)
Bone	145 (32%)	141 (31%)
Liver	126 (28%)	118 (26%)
Brain	30 (7%)	31 (7%)
Lymph node only[d]	33 (7%)	23 (5%)
PD-L1+ (IC), n (%)	185 (41%)	184 (41%)

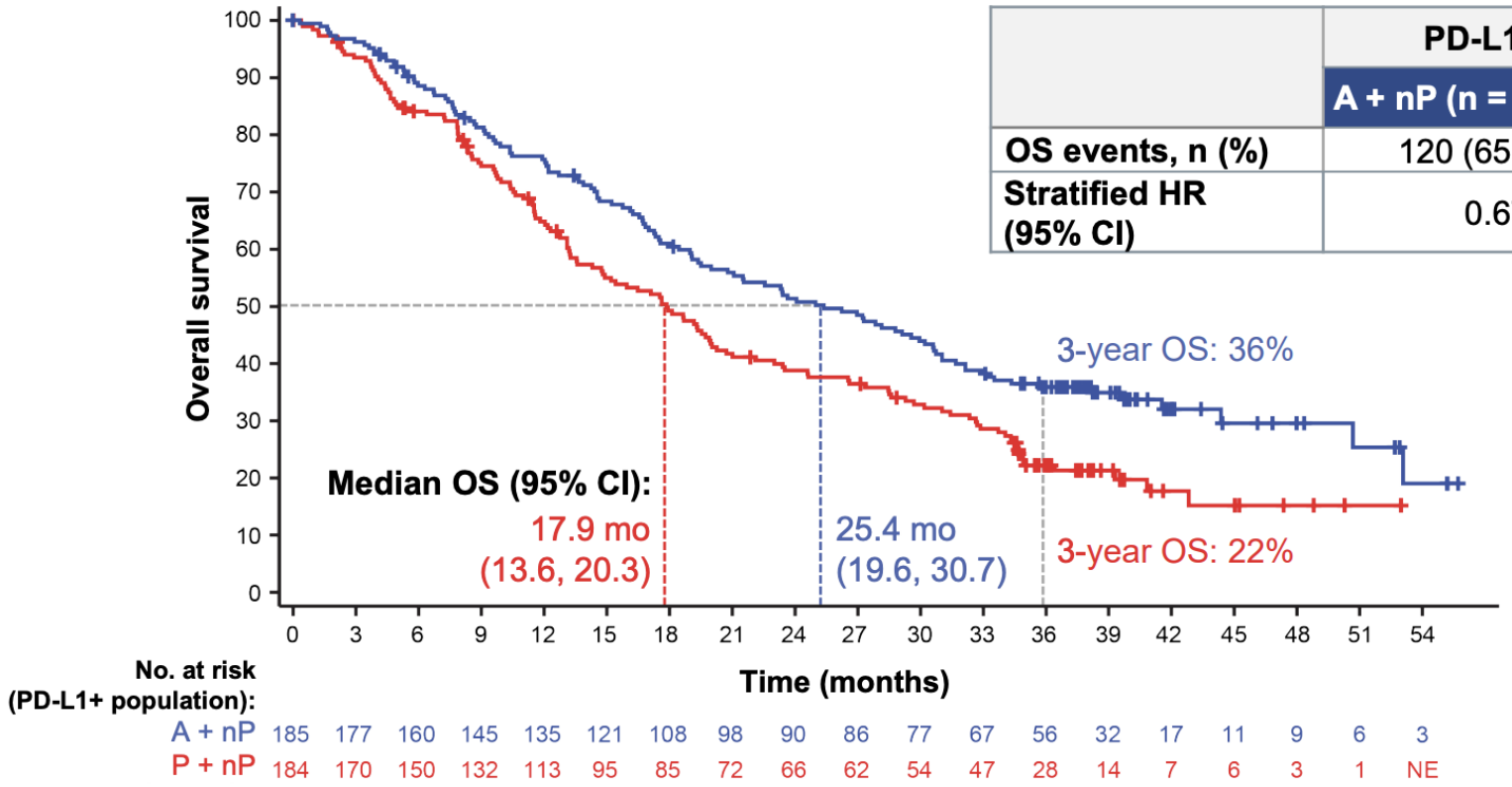
Data cutoff: 17 April 2018. [a] Race was unknown in 12 patients in the Atezo + nab-Pac arm and 15 in the Plac + nab-Pac arm. [b] Of n = 450 in each arm. [c] ECOG PS before start of treatment was 2 in 1 patient per arm. [d] Of n = 450 in the Atezo + nab-Pac arm and n = 449 in the Plac + nab-Pac arm arm.

Emens et al, ESMO 2020

IMpassion130 – Final OS analysis

OS in the PD-L1 IC+ population

	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR (95% CI)	0.67 (0.53, 0.86)[a]	



+7.5-mo median OS improvement

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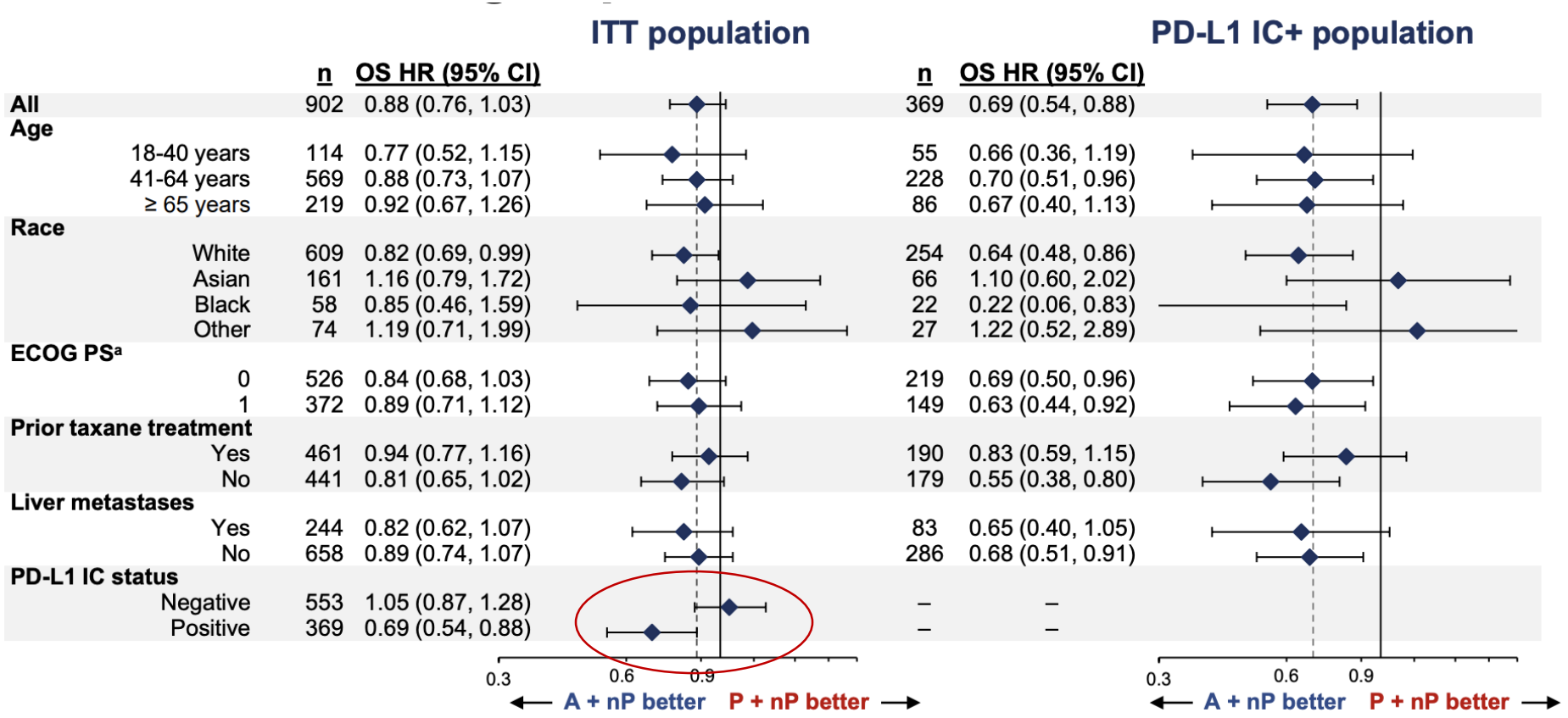
IMpassion130 – Final OS analysis



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IMpassion130 – Safety

AESI, n (%)[a]	Plac + nab-Pac (n = 438)		Atezo + nab-Pac (n = 452)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hepatitis (all)	62 (14.2%)	13 (3.0%)	69 (15.3%)	23 (5.1%)
Hepatitis (diagnosis)	7 (1.6%)	1 (0.2%)	10 (2.2%)	6 (1.3%)
Hepatitis (lab abnormalities)	58 (13.2%)	12 (2.7%)	62 (13.7%)	17 (3.8%)
Hypothyroidism	19 (4.3%)	0	78 (17.3%)	0
Hyperthyroidism	6 (1.4%)	0	20 (4.4%)	1 (0.2%)
Adrenal insufficiency	0	0	4 (0.9%)	1 (0.2%)
Pneumonitis	1 (0.2%)	0	14 (3.1%)	1 (0.2%)
Colitis	3 (0.7%)	1 (0.2%)	5 (1.1%)	1 (0.2%)
Pancreatitis*	0	0	2 (0.4%)	1 (0.2%)
Diabetes mellitus	2 (0.5%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Other AESI (Rash)	114 (26.0%)	2 (0.5%)	154 (34.1%)	4 (0.9%)

There were no reported events of Guillian-Barre syndrome, Hypophysitis, Myasthenia Gravis or Myocarditis

*Enzyme elevations only

Emens et al, ESMO 2020

New for Italian patients with MBC

MENU

Agenzia Italiana del Farmaco

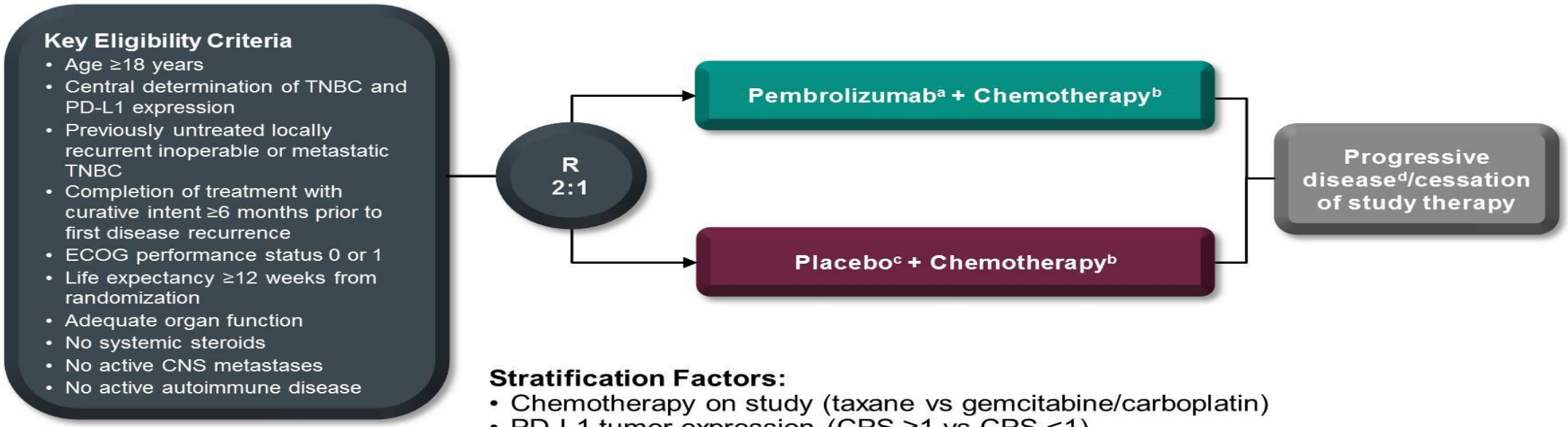
Home > Prezzi e Rimborso > Registri farmaci sottoposti a monitoraggio > Attivazione web e pubblicazione schede di monitoraggio - Registro KEYTRUDA - CAR

Attivazione web e pubblicazione schede di monitoraggio - Registro KEYTRUDA - CARCINOMA MAMMARIO

Si informano gli utenti dei Registri dei Farmaci sottoposti a Monitoraggio che, a seguito della pubblicazione della Determina AIFA nella GU n. 166 del 18/07/2023, a partire dal 19/07/2023 è possibile utilizzare, in regime di rimborsabilità SSN, il medicinale KEYTRUDA per la seguente indicazione terapeutica:

- *Keytruda, in associazione a chemioterapia, è indicato nel trattamento del carcinoma mammario triplo negativo localmente ricorrente non resecabile o metastatico negli adulti il cui tumore esprime PD-L1 con un CPS ≥ 10 e che non hanno ricevuto una precedente chemioterapia per malattia metastatica (vedere paragrafo 5.1).*

KEYNOTE-355 Study Design (NCT02819518)

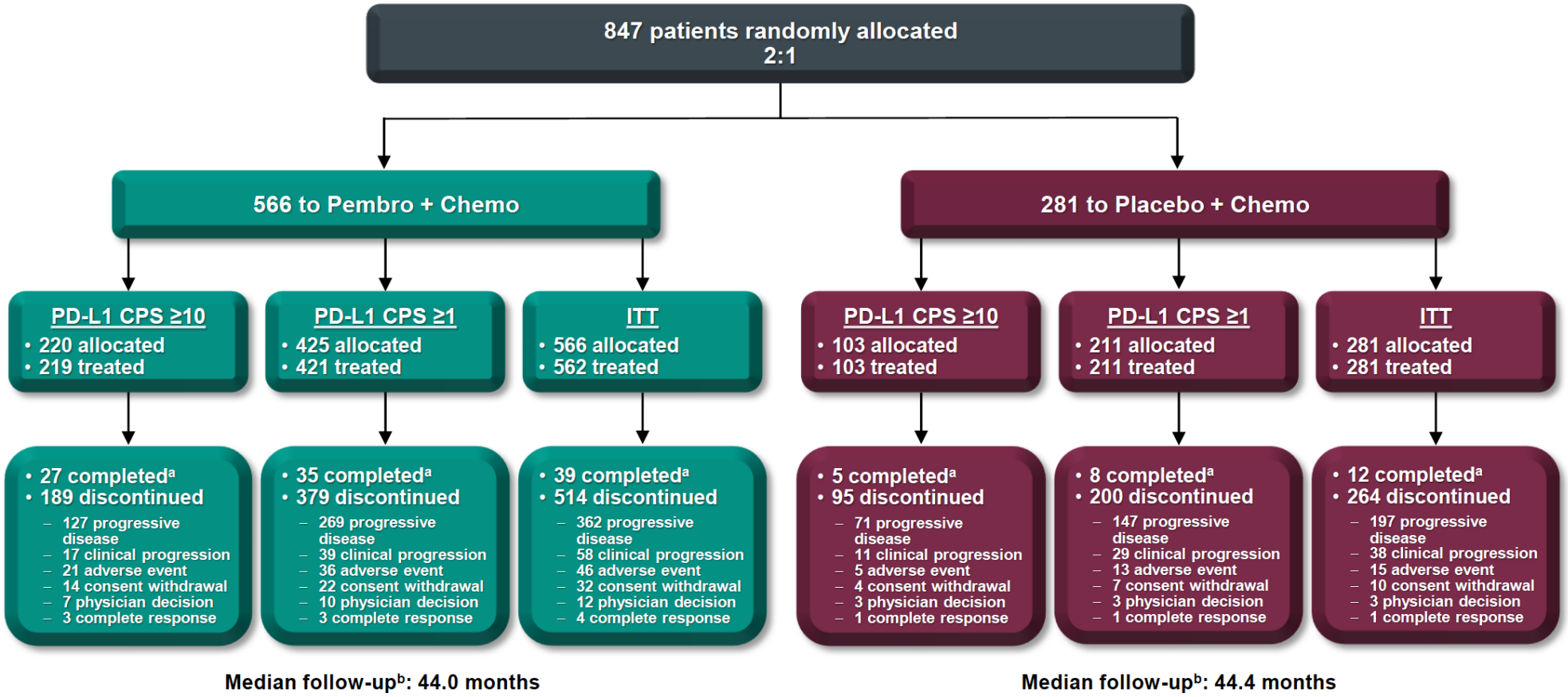


Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

[c]Normal saline
[d]Treatment 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

KEYNOTE 355 – Study Population allocation



Rugo et al, ESMO 2021

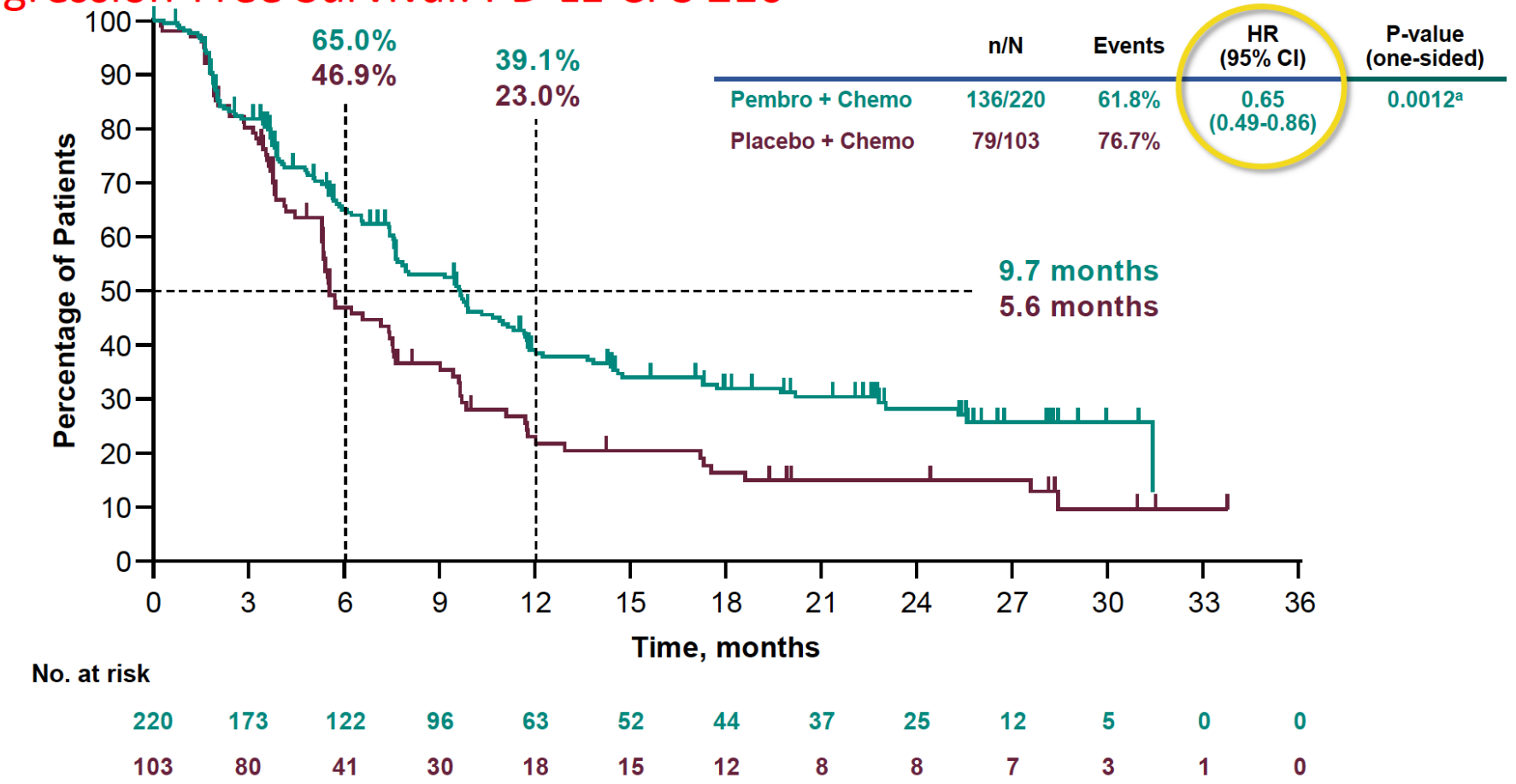
KEYNOTE 355 – Study Population allocation

Characteristic, n (%)	All Subjects, N = 847	
	Pembro + Chemo N = 566	Placebo + Chemo N = 281
Age, median (range), yrs	53 (25-85)	53 (22-77)
ECOG PS 1	232 (41.0)	108 (38.4)
PD-L1–positive CPS ≥1	425 (75.1)	211 (75.1)
PD-L1–positive CPS ≥10	220 (38.9)	103 (36.7)
Chemotherapy on study		
Taxane	255 (45.1)	127 (45.2)
Gemcitabine/Carboplatin	311 (54.9)	154 (54.8)
Prior same-class chemotherapy		
Yes	124 (21.9)	62 (22.1)
No	442 (78.1)	219 (77.9)
Disease-free interval		
de novo metastasis	168 (29.7)	84 (29.9)
<12 months	125 (22.1)	50 (17.8)
≥12 months	270 (47.7)	147 (52.3)

Rugo et al, ESMO 2021

KEYNOTE 355 - Outcomes

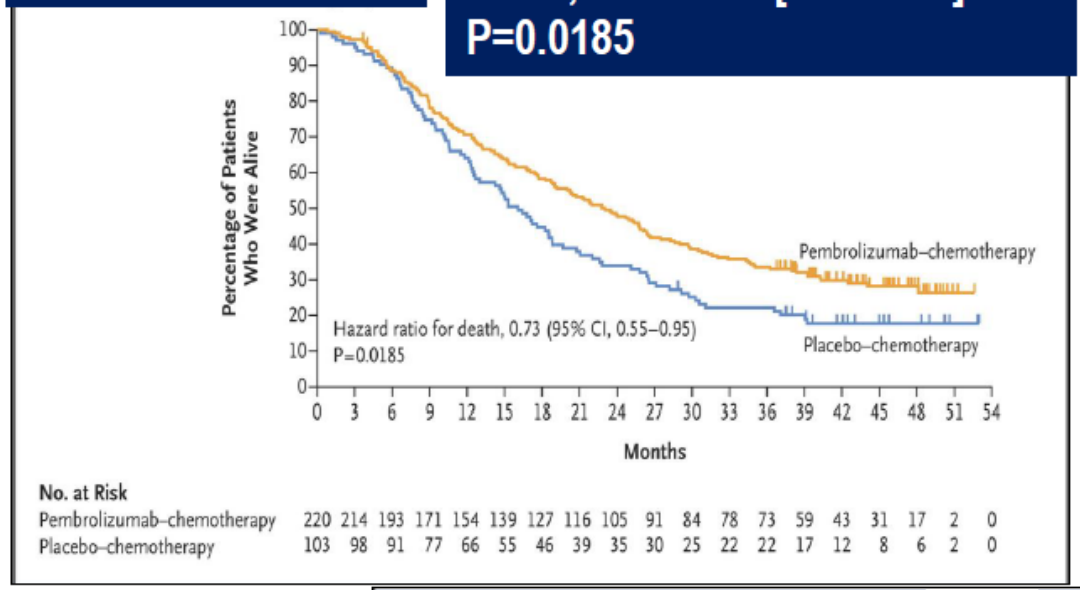
Progression-Free Survival: PD-L1 CPS ≥10



Presented By Javier Cortes at TBD

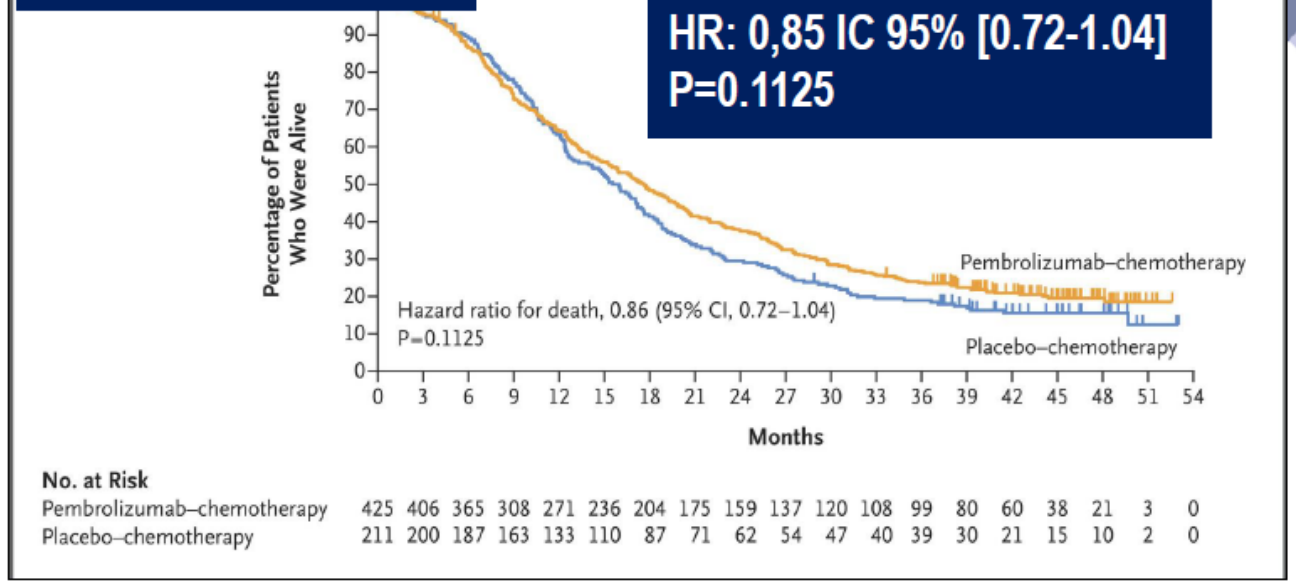
CPS-10 Subgroup

OS: 23 vs 16.1 months
HR: 0,73 IC 95% [0.55-0.95]
P=0.0185



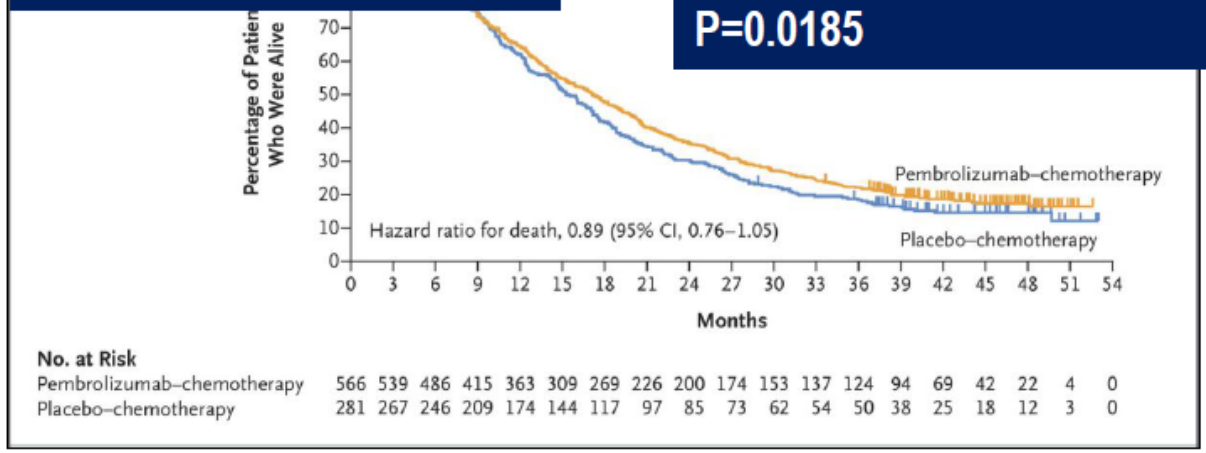
CPS-1 Subgroup

OS: 17.6 vs 16 months
HR: 0,85 IC 95% [0.72-1.04]
P=0.1125



Intention to treat Population

OS: 17.2 vs 15.5 months
HR: 0,789 IC 95% [0.76-1.05]
P=0.0185



[Cortes et al, 2022]

IMMUNOTHERAPY

PEMBROLIZUMAB

KEYNOTE 355
(First line treatment with Pembrolizumab-CT in advanced and mTNBC)

ATEZOLIZUMAB

IM PASSION 130
(First line treatment with Atezoluzimab-Nab Paclitaxel in mTNBC)

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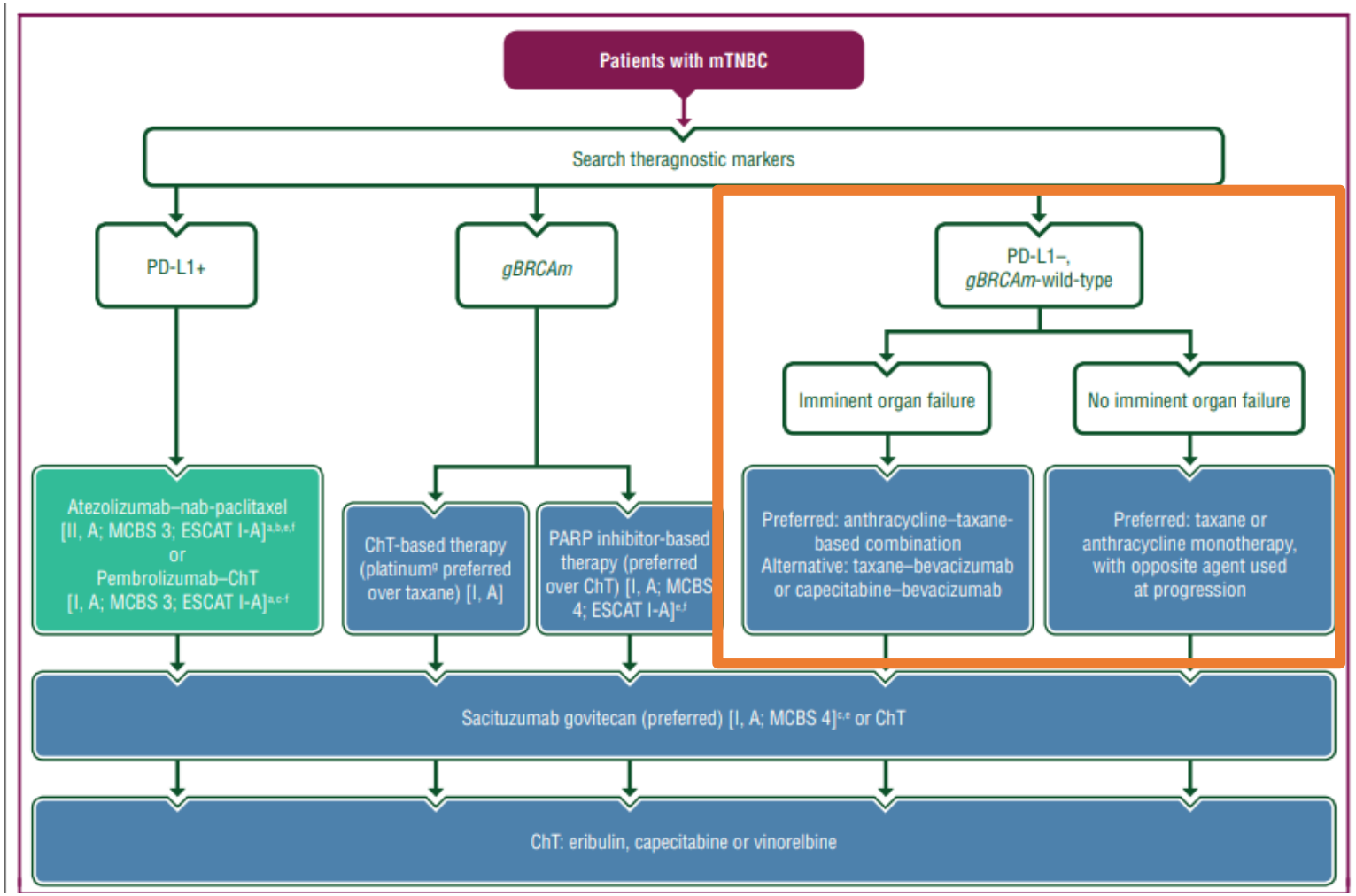

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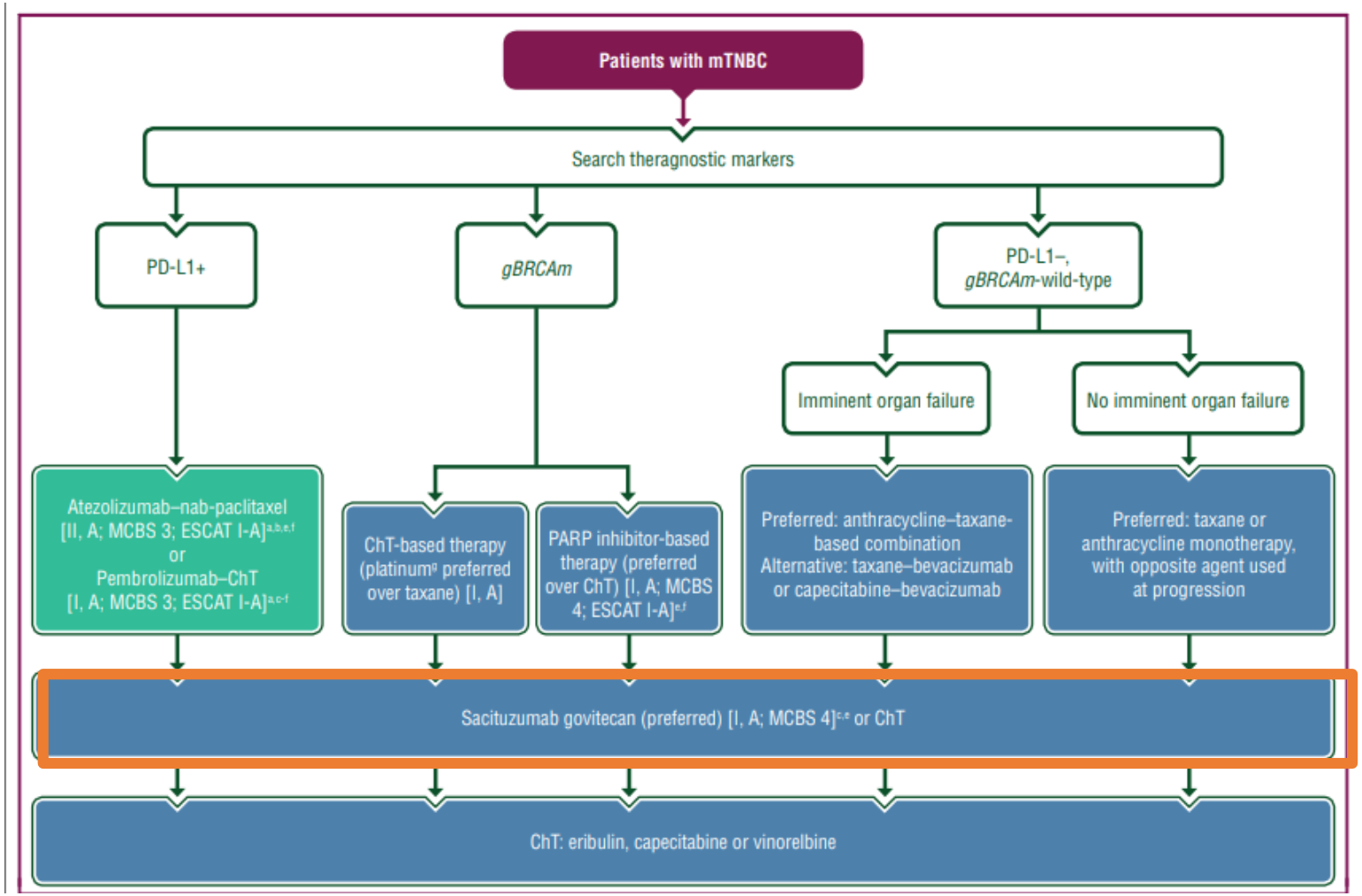

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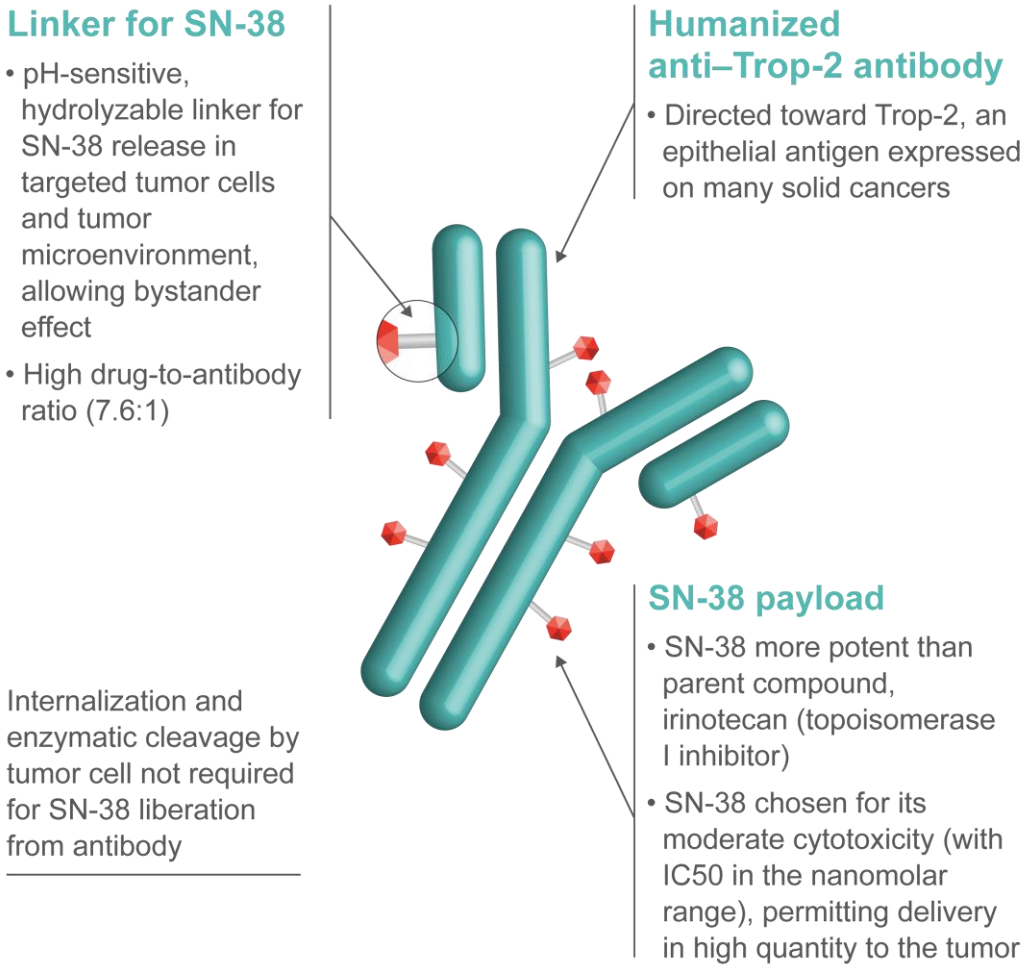
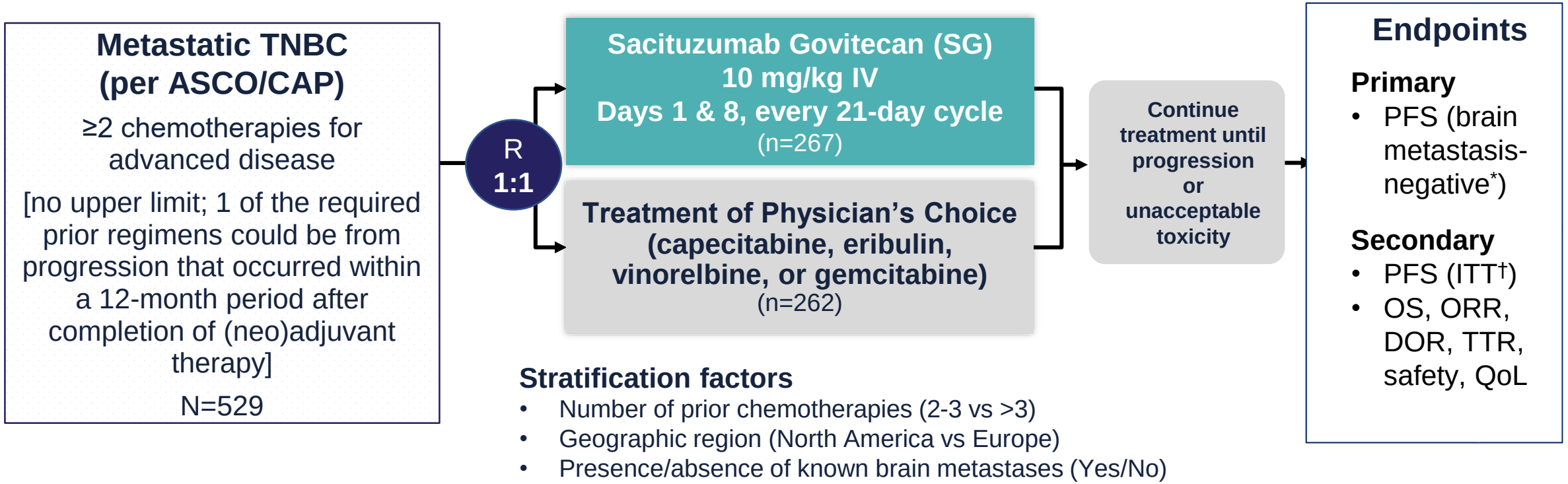
Sacituzumab Govitecan

Sacituzumab Govitecan Antibody-Drug Conjugate



Trop-2, trophoblast cell surface antigen 2.

ASCENT Study Design



Stratification factors

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

Adapted **from *N Engl J Med*. Bardia A,** Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. Vol. 384, pp 1529-1541. Copyright ©2022 Massachusetts Medical Society. Reused with permission from Massachusetts Medical Society.

*PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis.

†The ITT population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; ITT, intention-to-treat; IV, intravenous; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TNBC, triple-negative breast cancer; TTR, time to response.

1. Bardia A, et al. Presented at ASCO 2022 (abstract ID #1071). Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC): Final results from the Phase 3 ASCENT study.

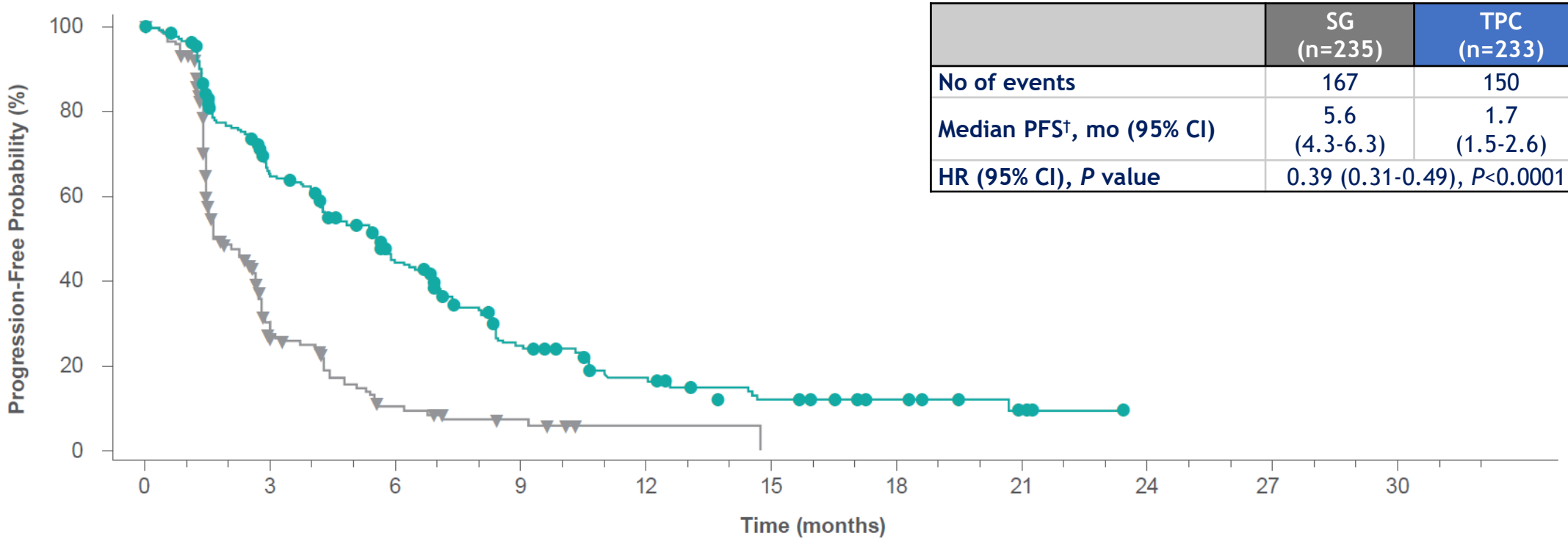
GILEAD | Oncology

Demographics and Baseline Characteristics (BMNeg Population)

	SG (n=235)	TPC (n=233)
Female, n (%)	233 (99)	233 (100)
Median age at study entry, y (range)	54.0 (29-82)	53.0 (27-81)
Race, n (%)		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other	10 (4)	15 (6)
ECOG performance status, n (%)		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
TNBC at initial breast cancer diagnosis, n (%)	165 (70)	157 (67)
Number of prior chemotherapies, n (%)		
2-3	166 (71)	164 (70)
>3	69 (29)	69 (30)
Median prior systemic regimens*, n (range)	4.0 (2-17)	4.0 (2-14)
Previous use of checkpoint inhibitors, n (%)	67 (29)	60 (26)
Setting of prior systemic therapies, n (%)		
Adjuvant	140 (60)	129 (55)
Neoadjuvant	113 (48)	111 (48)
Metastatic	226 (96)	231 (99)
Locally advanced disease	8 (3)	4 (2)
***BRCA1/2* mutational status, n (%)**		
Negative	133 (57)	125 (54)
Positive	16 (7)	18 (8)
Unknown	86 (37)	90 (39)

*Anticancer regimens refer to any treatment regimen that was used to treat breast cancer in any setting.
BRCA, breast cancer gene; BMNeg, brain metastases-negative; ECOG, Eastern Cooperative Oncology Group; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice; y, year.
1. Bardia A, et al. Presented at ASCO 2022 (abstract ID #1071). Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC): Final results from the Phase 3 ASCENT study.

Progression-Free Survival* (BMNeg Population)



	SG (n=235)	TPC (n=233)
No of events	167	150
Median PFS†, mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	0.39 (0.31-0.49), *P*<0.0001	

No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
SG	235	222	166	134	127	104	81	63	54	37	33	24	22	17	16	13	11	10	8	6	5	3	1	1	0
TPC	233	178	77	34	31	18	11	8	6	5	3	1	1	1	1	0	0	0	0	0	0	0	0	0	0

*PFS is defined as the time from the date of randomization to the date of the first radiological disease progression or death due to any cause, whichever comes first. †Median PFS is from Kaplan-Meier estimate. CI for median is computed using the Brookmeyer-Crowley method. Stratified log-rank test and stratified Cox regression adjusted for stratification factors: number of prior chemotherapies and region.
BMNeg, brain metastasis-negative; CI, confidence intervals; HR, hazard ratio; PFS, progression free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Bardia A, et al. Presented at ASCO 2022 (abstract ID #1071). Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC): Final results from the Phase 3 ASCENT study.

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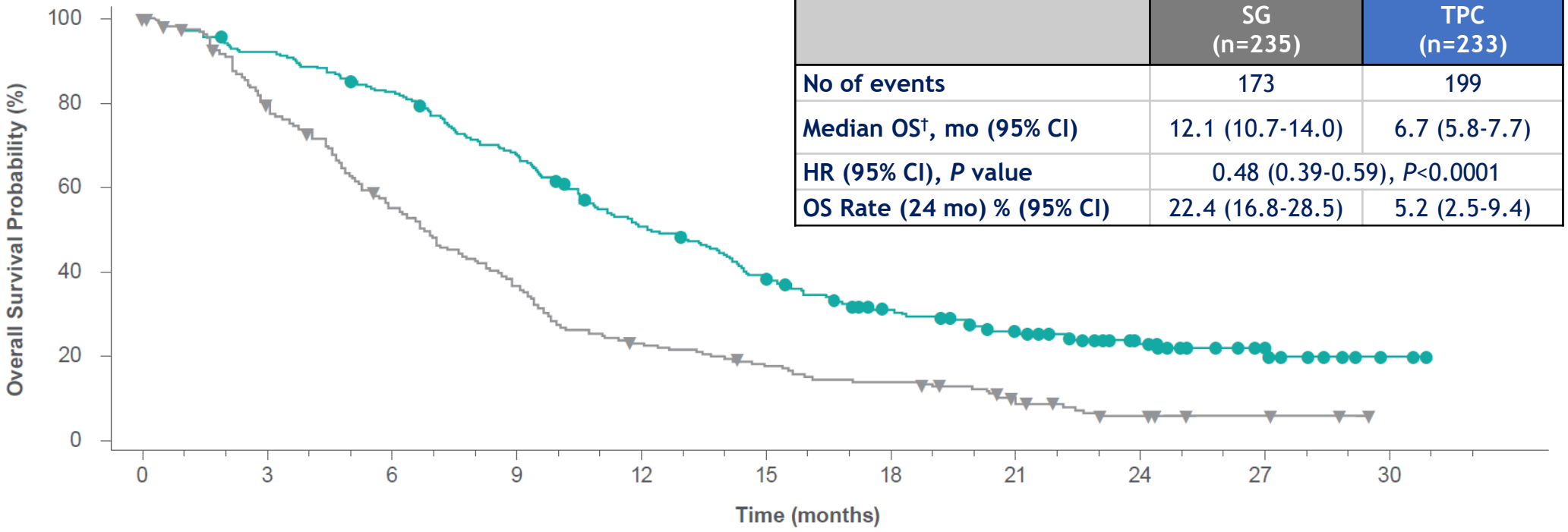
Overall Survival* (BMNeg Population)

	SG (n=235)	TPC (n=233)
No of events	173	199
Median OS†, mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	0.48 (0.39-0.59), *P*<0.0001	
OS Rate (24 mo) % (95% CI)	22.4 (16.8-28.5)	5.2 (2.5-9.4)



No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
SG	235	228	220	214	206	197	191	177	164	156	140	122	113	105	97	85	74	65	59	56	46	40	35	30	25	17	14	11	7	4	2
TPC	233	214	200	173	156	134	117	101	90	77	58	53	47	44	40	35	30	28	27	24	22	13	11	7	6	4	3	3	2	1	0

*OS is defined as the time from date of randomization to the date of death from any cause. Patients without documentation of death are censored on the date they were last known to be alive. †Median OS is from Kaplan-Meier estimate. CI for median was computed using the Brookmeyer-Crowley method. Stratified log-rank test and stratified Cox regression adjusted for stratification factors: number of prior chemotherapies and region.
BMNeg, brain metastasis-negative; CI, confidence intervals; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Bardia A, et al. Presented at ASCO 2022 (abstract ID #1071). Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC): Final results from the Phase 3 ASCENT study.

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Response Rates* (BMNeg Population)

	SG (n=235)	TPC (n=233)
ORR, n (%)	82 (35)	11 (5)
P-Value	*P*<0.0001	
Best overall response, n (%)		
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR, n (%)	105 (45)	20 (9)
P-Value	*P*<0.0001	
Median DOR, mo (95% CI)	6.3 (5.5-7.9)	3.6 (2.8-NE)
Median TTR, mo (range)	1.5 (0.7-10.6)	1.45 (1.3-4.2)

*Denominator for percentages is the number of patients in the Brain Metastasis Negative Population. †P-value is based on Cochran-Mantel-Haenszel test. ‡Objective Response is defined as the best confirmed overall response of either CR or PR. The best overall response is derived based on independent review assessed tumor response at each tumor assessment according to RECIST 1.1. Responses of CR and PR are confirmed no less than 4 weeks later. SD requires a minimum duration of 6 weeks to be classified as SD. §Clinical benefit rate (CBR) is defined as the percentage of patients with a confirmed best overall response of CR or PR, and SD with a duration of at least 6 months. ‖Only patients achieving CR or PR are included in the analysis of DOR and TTR. Median DOR is from Kaplan-Meier estimate. CI for median is computed using the Brookmeyer-Crowley method.

BMNeg, brain metastasis-negative; CBR, clinical benefit rate; CI, confidence intervals; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PR, partial response; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TTR, time to response.

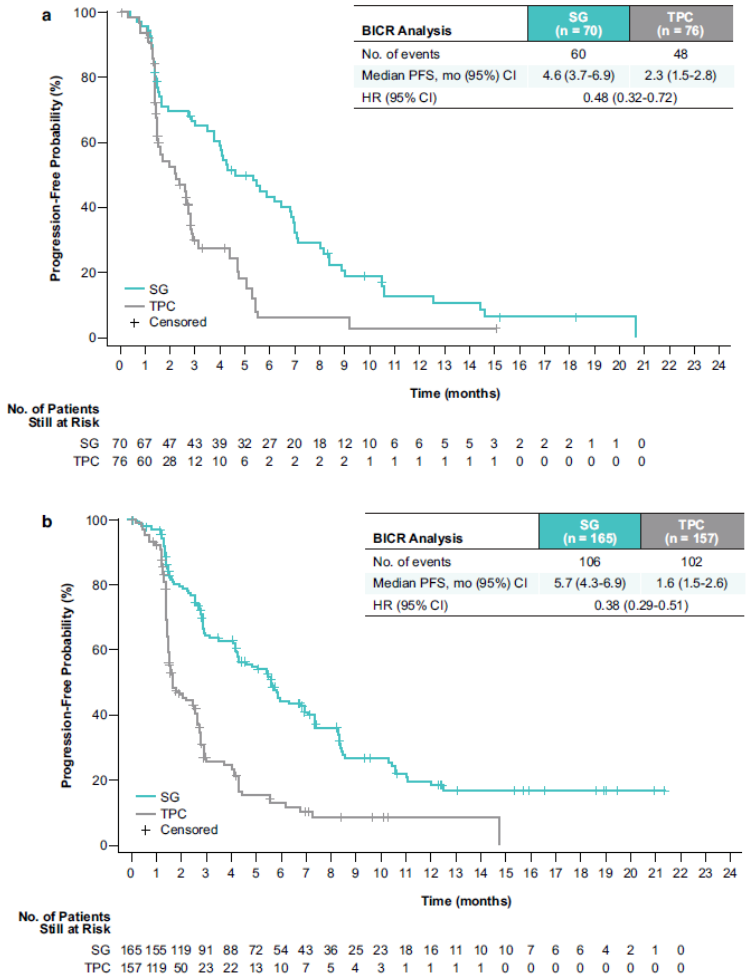
1. Bardia A, et al. Presented at ASCO 2022 (abstract ID #1071). Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC): Final results from the Phase 3 ASCENT study.

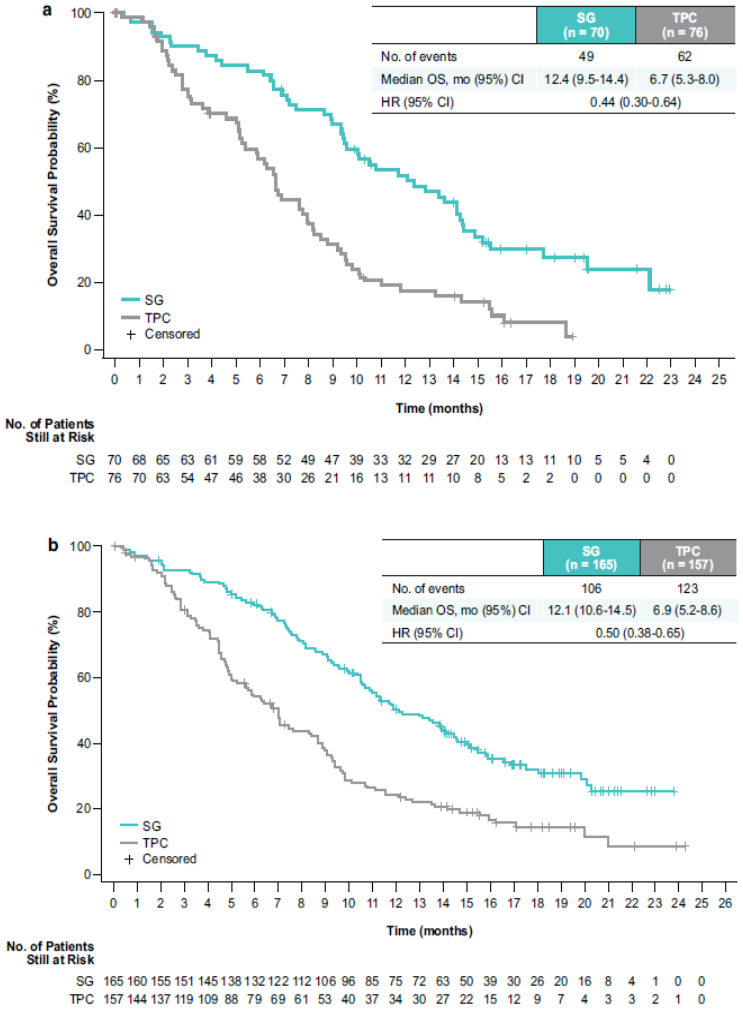
TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=258)			TPC (n=224)		
TRAE*		All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	Neutropenia†	163 (63)	88 (34)	45 (17)	96 (43)	45 (20)	29 (13)
	Anemia	89 (35)	20 (8)	0	53 (24)	11 (5)	0
	Febrile Neutropenia	15 (6)	12 (5)	3 (1)	5 (2)	4 (2)	1 (<1)
	White blood cell count decreased	33 (13)	18 (7)	2 (1)	22 (10)	9 (4)	2 (1)
Gastrointestinal	Diarrhea	153 (59)	28 (11)	0	27 (12)	1 (<1)	0
	Nausea	147 (57)	6 (2)	1 (<1)	59 (26)	1 (<1)	0
	Vomiting	75 (29)	3 (1)	1 (<1)	23 (10)	1 (<1)	0
Other	Fatigue	115 (45)	8 (3)	0	68 (30)	12 (5)	0
	Alopecia	119 (46)	0	0	35 (16)	0	0

*Treatment-emergent adverse event is defined as an adverse event with start date on or after the date of first dose of study treatment and up to 30 days after date of last dose of study treatment. AEs were classified according to the MedDRA systems of preferred terms (version 22.1). †Combined neuropenia and neutrophil count decreased.
SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment related adverse event.
1. Bardia A, et al. Presented at ASCO 2022 (abstract ID #1071). Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC): Final results from the Phase 3 ASCENT study.

Analysis of patients with or without TNBC at initial diagnosis (ASCENT study)



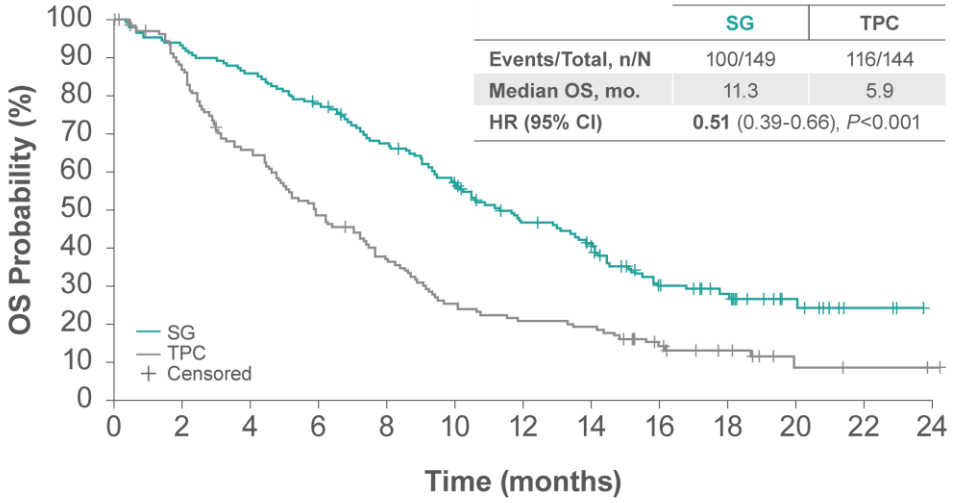


Patient without TNBC at initial diagnosis had improved clinical outcomes and a manageable safety profile with SG

O'Shaughnessy J BCRT 2022

Results Overall Survival according HER2 status (ASCENT)

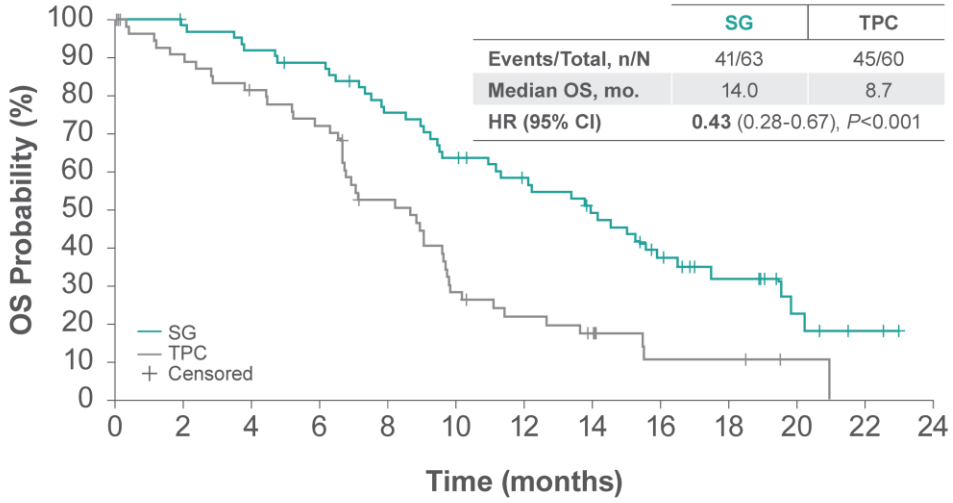
A



No. of Patients Still at Risk

SG, HER2 IHC0	149	139	128	115	98	80	62	52	29	22	11	4	0
TPC, HER2 IHC0	144	118	88	64	48	33	27	25	15	9	3	2	1

B

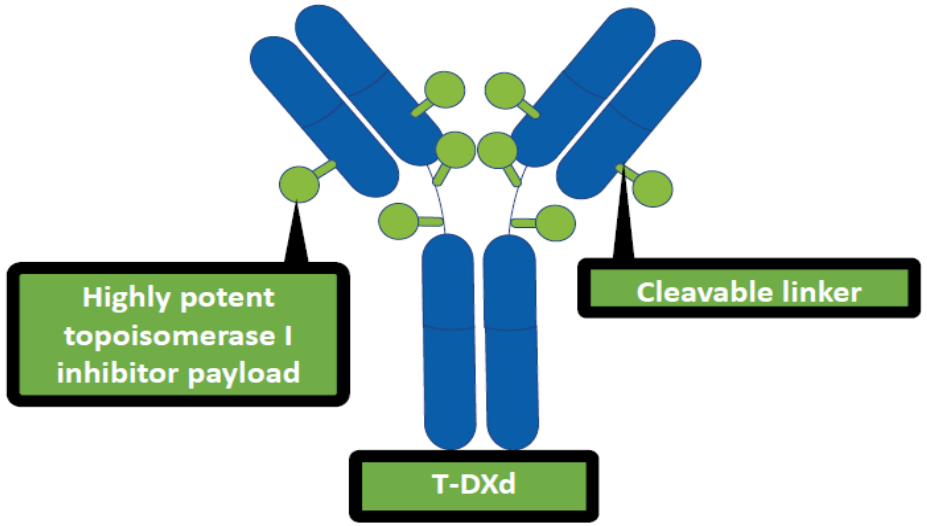


No. of Patients Still at Risk

SG, HER2-Low	63	61	57	54	45	38	32	26	17	10	5	2	0
TPC, HER2-Low	60	49	43	38	26	14	10	7	3	3	1	0	0

[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice

Trastuzumab deruxtecan

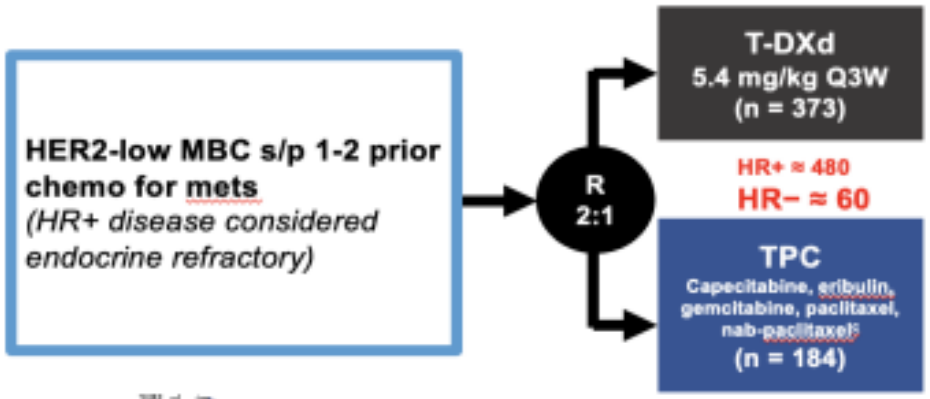


- Anti-HER2 antibody
- Cleavable linker
- Deruxtecan Topo-1i payload
- High DAR

FDA-approved in 2nd line HER2+
Phase III in "HER2-low" (IHC 1+, 2+/FISH-neg) = DESTINY Breast 04

Modi S et al, NEJM 2022

Destiny breast-04

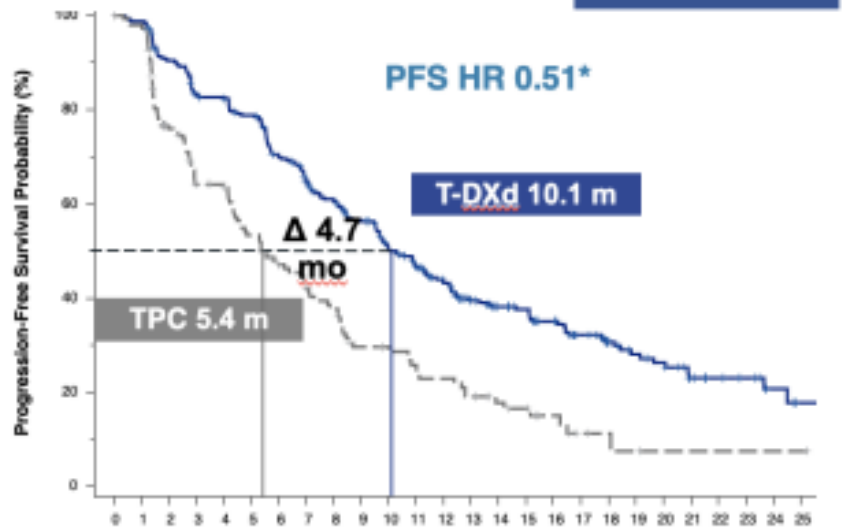


Primary endpoint
- PFS in HR+

Key secondary endpoints
- PFS in all pts
- OS (HR+ and all patients)

Hierarchical testing

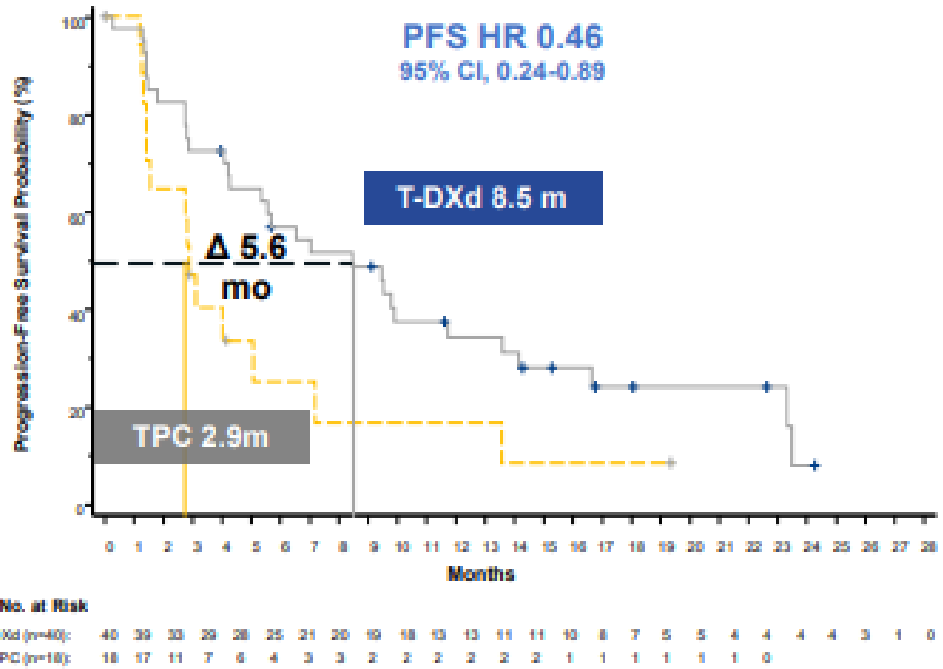
PFS in HR+ ↓ PFS in all patients ↓ OS in HR+ (until positive read out) ↓ OS in all patients

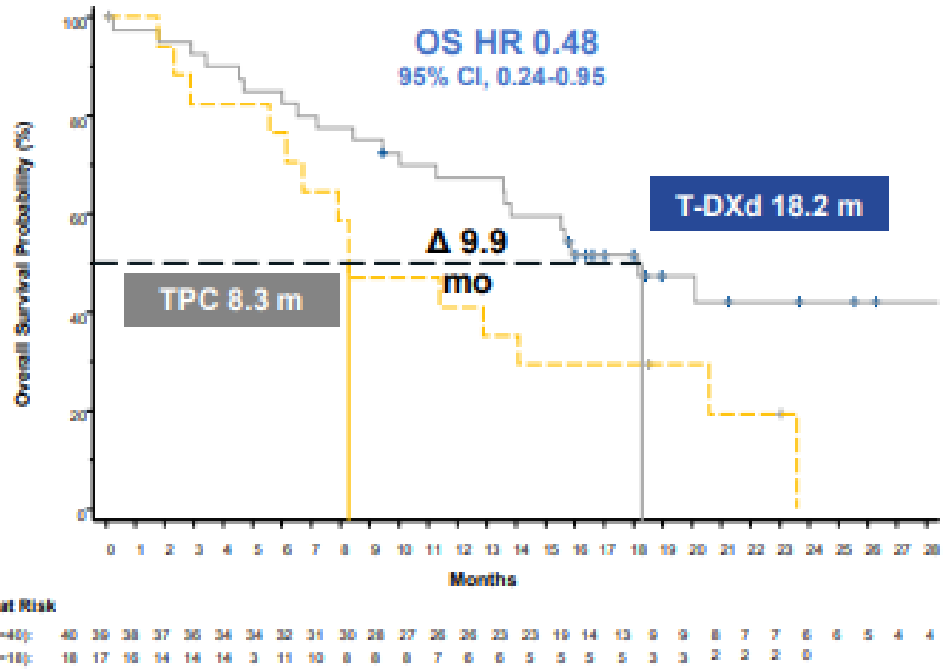


- **Met endpoints in HR+, all pts, OS (immature)**
- **No difference between 1+ and 2+**
- **Toxicity:**
  - **myelosuppression (all lines), GI (nausea, diarrhea mostly gr1), LFT ↑, fatigue, alopecia**
  - **ILD 12% (1% fatal), LVEF ↓ 4% (0.5% CHF)**

Modi et al, NEJM 2022

TNBC subset (10% of population)





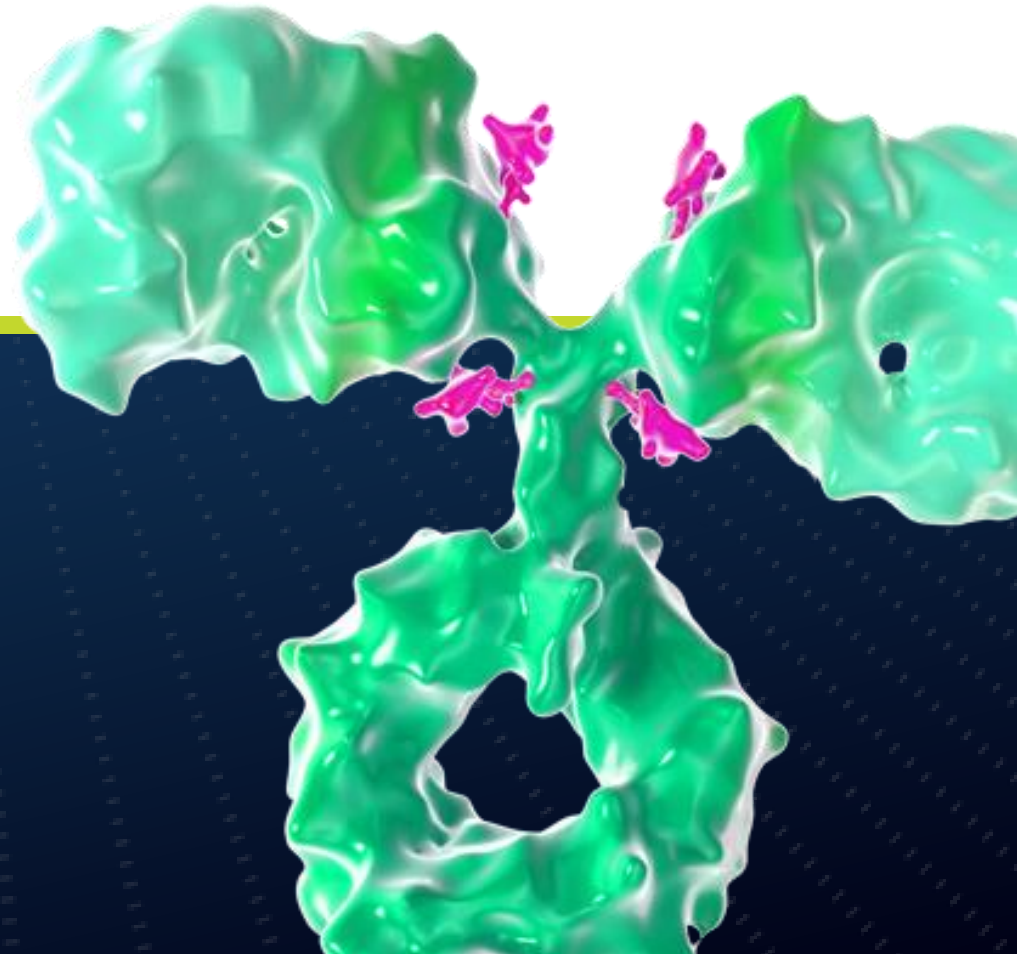
Exploratory subset, few patients. Similar effect as seen in HR+ disease.

FDA-approved August 2022 for HER2-low (regardless of HR) after 1st line.

Datopotamab Deruxtecan (Dato-DXd) in Advanced/Metastatic HER2 Negative Breast Cancer: Triple-Negative Breast Cancer Results From the Phase 1 TROPION-PanTumor01 Study

Ian Krop,[1] Dejan Juric,[2] Toshio Shimizu,[3] Anthony Tolcher,[4] Alexander Spira,[5] Toru Mukohara,[6] Aaron E. Lisberg,[7] Takahiro Kogawa,[8] Kyriakos P. Papadopoulos,[9] Erika Hamilton,[10] Senthil Damodaran,[11] Jonathan Greenberg,[12] Wen Gu,[12] Fumiaki Kobayashi,[13] Takahiro Jikoh,[13] Yui Kawasaki,[13] Funda Meric-Bernstam,[11] Aditya Bardia[2]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Department of Hematology/Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [3]National Cancer Center Hospital, Tokyo, Japan; [4]NEXT Oncology, San Antonio, TX; [5]Virginia Cancer Specialists, Fairfax, VA; [6]Department of Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [7]UCLA Jonsson Comprehensive Cancer Center, Santa Monica, CA; [8]Advanced Medical Development Center, The Cancer Institute Hospital of JFCR, Tokyo, Japan; [9]START Center for Cancer Care San Antonio, San Antonio, TX; [10]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [11]The University of Texas MD Anderson Cancer Center, Houston, TX; [12]Daiichi Sankyo, Inc, Basking Ridge, NJ; [13]Daiichi Sankyo Co, Ltd, Tokyo, Japan



Podium presentation at San Antonio Breast Cancer Symposium December 7-10, 2021.

TROPION-PanTumor01 (NCT03401385)

Phase 1 Study in Relapsed/Refractory Metastatic Solid Tumors

- Relapsed/refractory advanced/metastatic solid tumors
- Unselected for TROP2 expression[a]
- Age ≥18 (US) or ≥20 (Japan) years
- ECOG PS 0-1
- Measurable disease per RECIST version 1.1
- Stable, treated brain metastases allowed

→ NSCLC[b] (0.27 to 10 mg/kg IV Q3W)

→ TNBC[c] 8 mg/kg (n=2); 6 mg/kg (n=42)

→ HR positive/HER2 negative breast cancer[d]

→ Other tumor types (including SCLC, bladder, gastric, esophageal)

Primary Objectives

- Safety
- Tolerability

Secondary Objectives[e]

- Efficacy[f]
- Pharmacokinetics
- Antidrug antibodies

Data cutoff: July 30, 2021

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IV, intravenous; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small cell lung cancer.

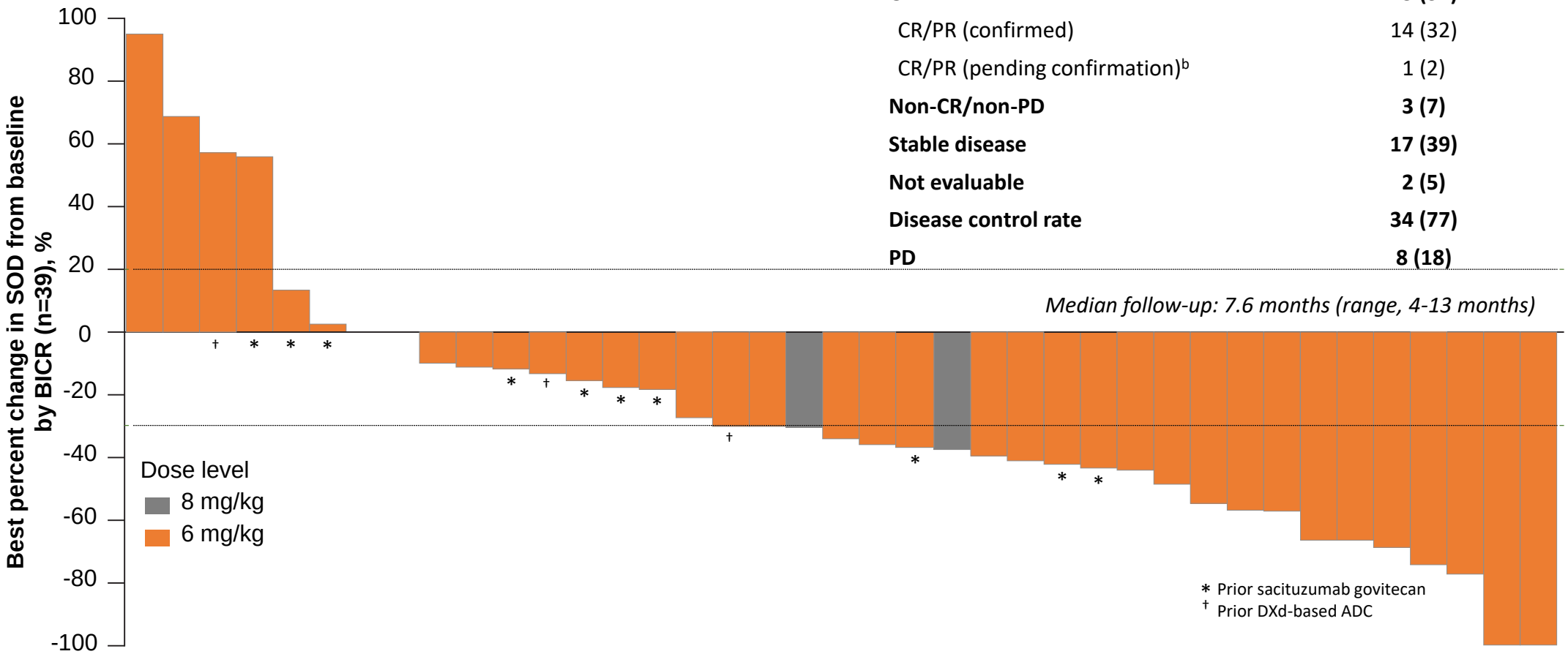
[a] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b] Results from the NSCLC cohort have been previously reported.[1,2] [c] Includes patients treated in the dose-escalation and dose-expansion portions. [d] Enrollment in the HR positive/HER2 negative cohort is now complete and data will be forthcoming. [e] Exploratory objectives include analyses of biomarkers associated with response. [f] Response assessments are based on RECIST 1.1.

1. Garon E, et al. Presented online at: IASLC 2021 World Conference on Lung Cancer; September 8-14, 2021. Abstract 156. 2. Meric-Bernstam F, et al. Presented online at: 2021 ASCO Annual Meeting; June 4-8, 2021. Abstract 9058.

Antitumor Responses by BICR

All Patients With TNBC

Patients, n (%)[a]	All patients (n=44)
ORR	**15 (34)**
CR/PR (confirmed)	14 (32)
CR/PR (pending confirmation)[b]	1 (2)
Non-CR/non-PD	**3 (7)**
Stable disease	**17 (39)**
Not evaluable	**2 (5)**
Disease control rate	**34 (77)**
PD	**8 (18)**

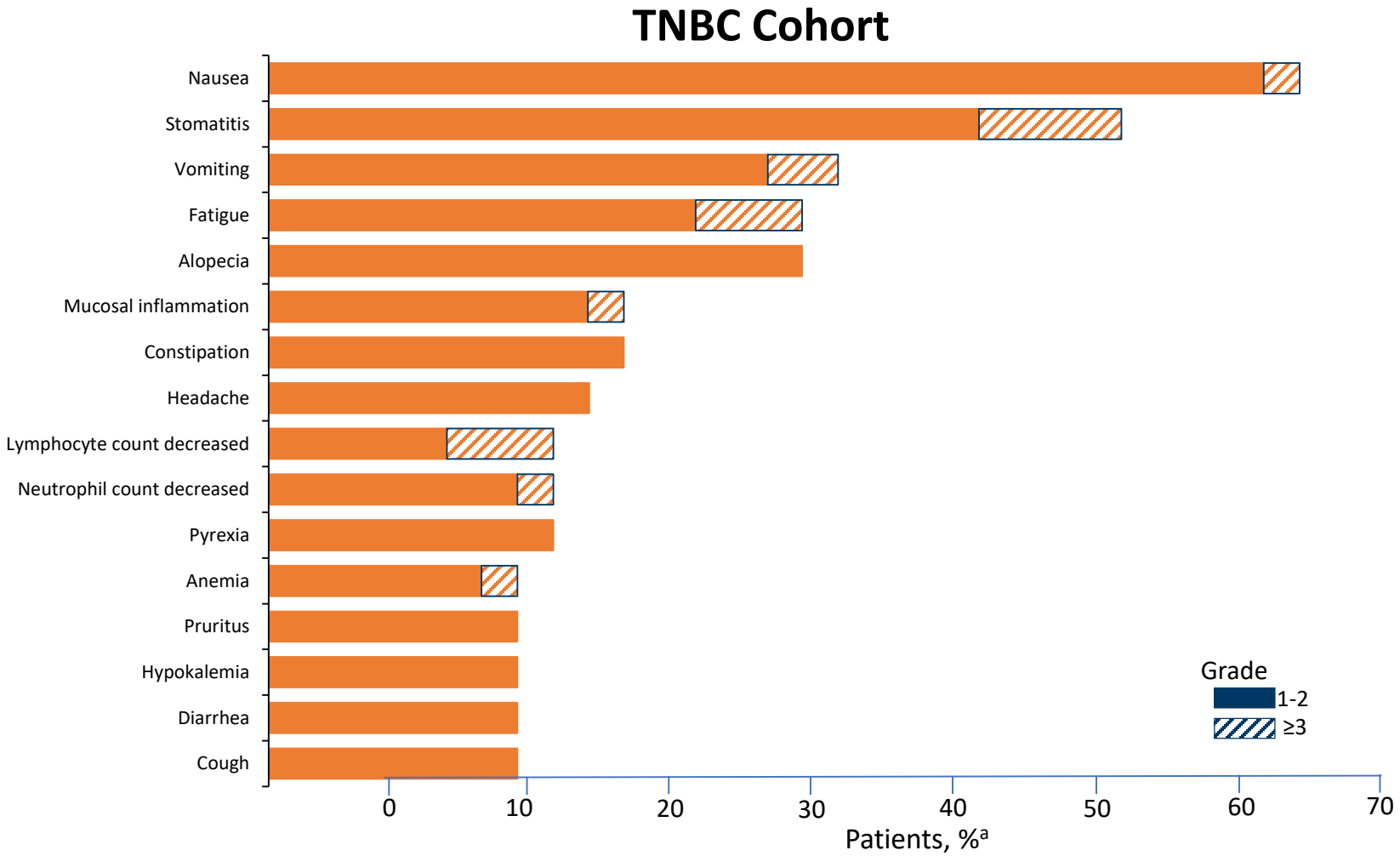


BICR, blinded independent central review; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SOD, sum of diameters.

[a] Includes response-evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. Postbaseline tumor assessments were not yet available for 2 patients at the data cutoff. Three patients were not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD. [b] Includes patients with an unconfirmed response but are ongoing treatment.

Data cutoff: July 30, 2021

Treatment-Emergent Adverse Events in ≥15% of Patients



- Most common adverse events observed were nausea and stomatitis (predominantly grade 1/2)
- Low frequency of hematologic toxicity and diarrhea
- No cases adjudicated as drug-related ILD

ILD, interstitial lung disease.
[a] n=44 patients.

Data cutoff: July 30, 2021

Agenda

- Introduction
- Highlights in the treatment of mTNBC
- Take home messages

Point of discussion LOW ER expression

- Patients with low (1-10%) ER (and PR) positive, HER2 negative ABC should not be considered for endocrine therapy exclusively.

- Patients with low (1-10%) ER (and PR) positive, HER2 negative ABC can be considered as patients with triple negative ABC, for clinical trials.

Conclusioni

- Avremo le corrispondenti opzioni di terapia nelle stesse linee di trattamento

- Imparare a prevedere la «magnitude of benefit» per ogni diversa opzione di terapia

Es paz candidate al trattamento vs responsivi al trattamento

- Costruire una sequenza terapeutica basata sulla efficacia attesa dei possibili trattamenti

GRAZIE!!