Il carcinoma mammario metastatico triplo negativo

Emilia Montagna
Istituto Europeo di Oncologia
Milano

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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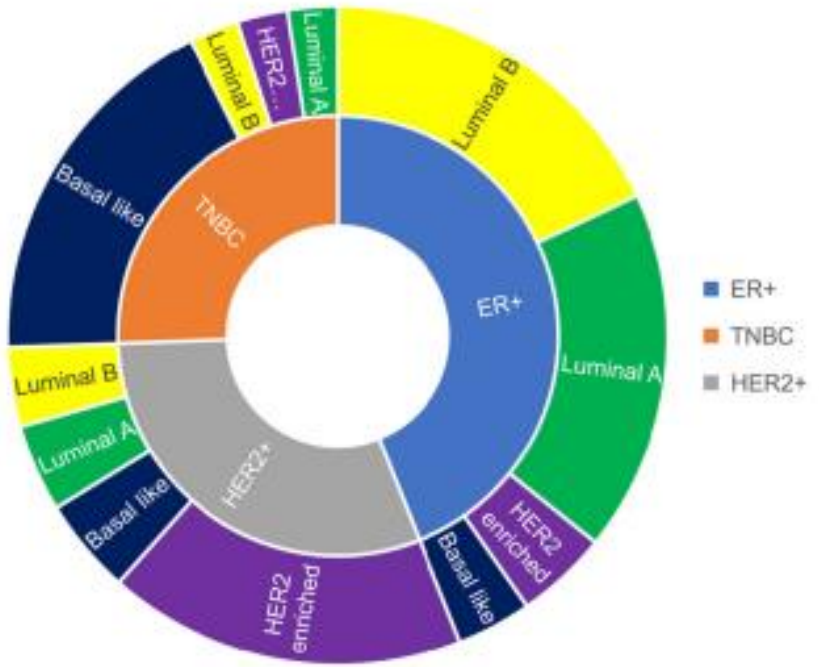
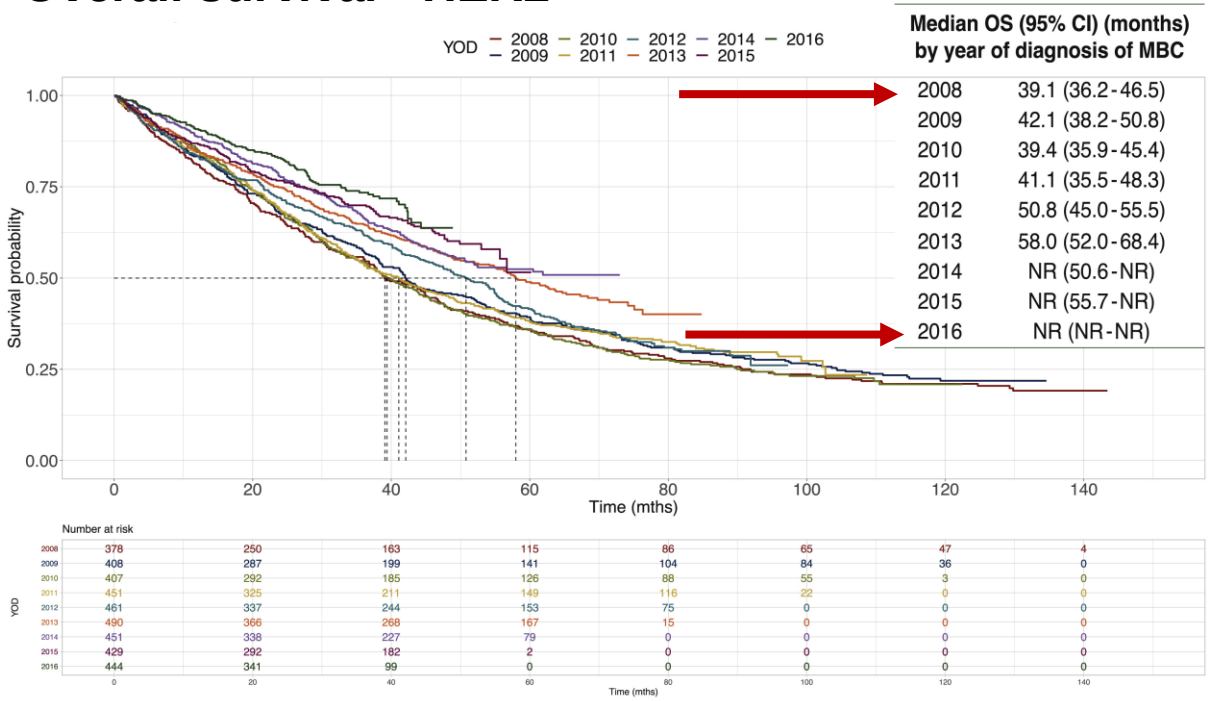


Fig. 1 Intrinsic molecular subtypes of breast cancer. Within each clinical subtype there are multiple molecular subtypes. ER endocrine receptor; TNBC triple negative breast cancer; HER2 Human Epidermal Growth Factor Receptor 2.

Zagami et Carey, NPJ Breast Cancer 2022

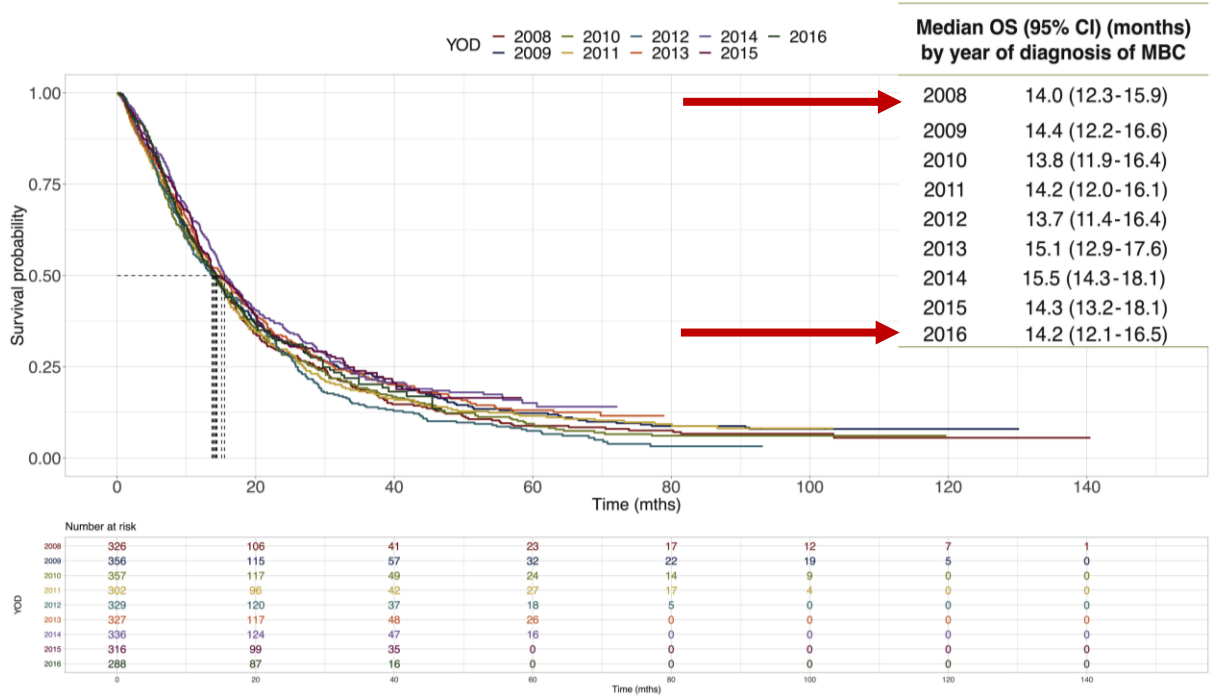
No major survival improvements for tnbc in the last decade

Overall survival - HER2+



Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	39.1 (36.2-46.5)
2009	42.1 (38.2-50.8)
2010	39.4 (35.9-45.4)
2011	41.1 (35.5-48.3)
2012	50.8 (45.0-55.5)
2013	58.0 (52.0-68.4)
2014	NR (50.6-NR)
2015	NR (55.7-NR)
2016	NR (NR-NR)

Overall survival - TNBC



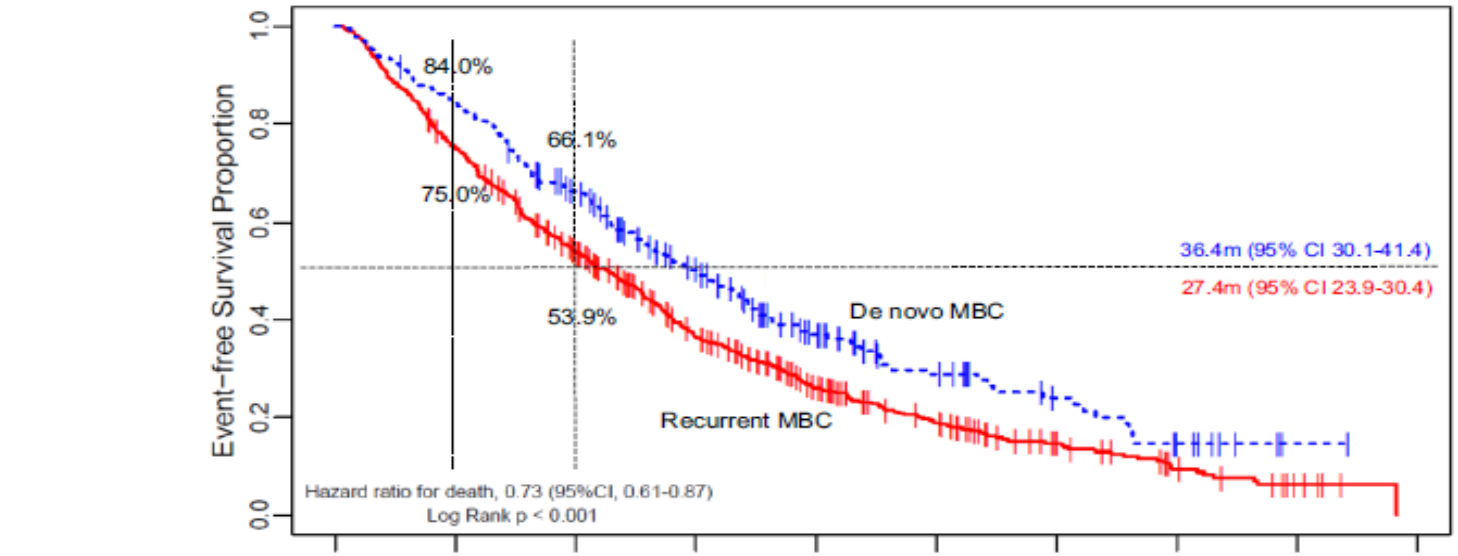
Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	14.0 (12.3-15.9)
2009	14.4 (12.2-16.6)
2010	13.8 (11.9-16.4)
2011	14.2 (12.0-16.1)
2012	13.7 (11.4-16.4)
2013	15.1 (12.9-17.6)
2014	15.5 (14.3-18.1)
2015	14.3 (13.2-18.1)
2016	14.2 (12.1-16.5)

Median overall survival of TNBC from the onset of metastasis is <18 months

Grinda, ESMO Open 2021

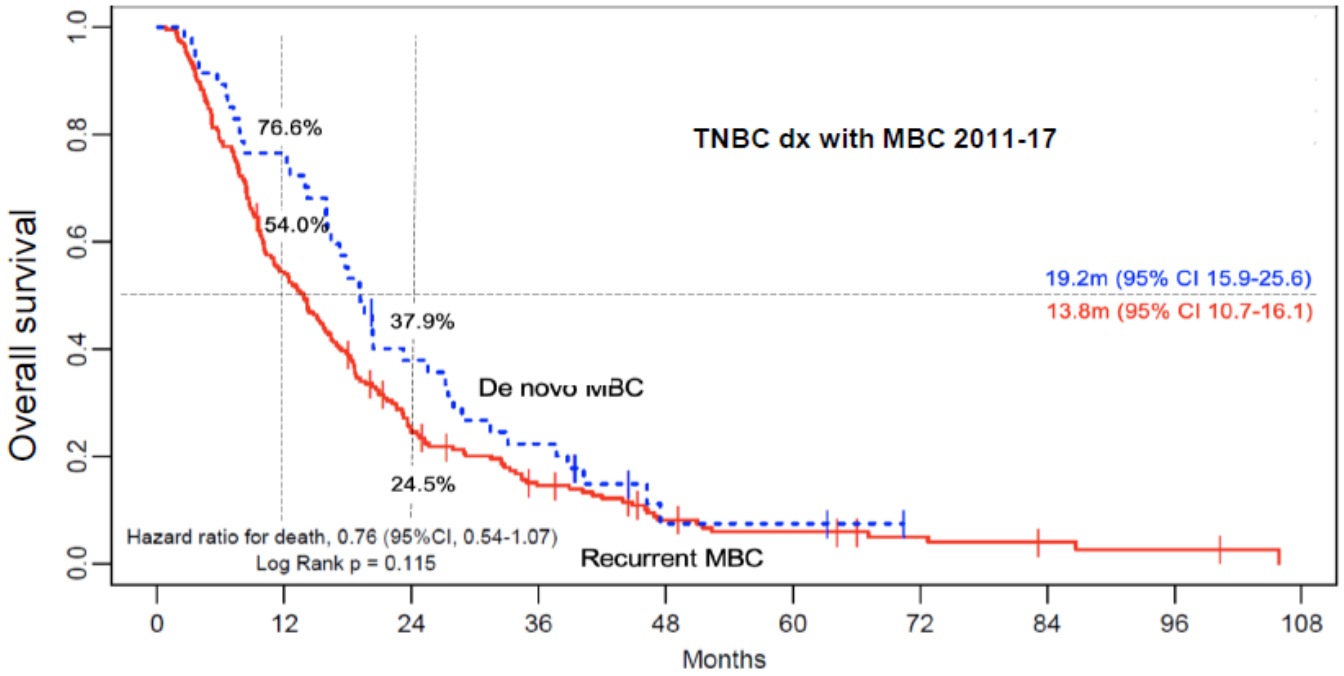
Survival in MBC de novo vs recurrent

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

Relapse in TNBC

- Approximately half of all patients developing metastatic TNBC following standard (neo)adjuvant CT experience relapse within 12 months of completing CT[1,2]
- Early relapsing TNBC is a biologically and clinically distinct entity[3]:
  - Aggressive, intrinsically resistant to standard therapies[4]
  - More common in younger patients with large primary tumours without *BRCA* alterations[1,2]

Rapidly relapsing TNBC represents one of our most challenging clinical situations

[1]Grinda T, et al. Eur J Cancer 2023; [2]Kim H, et al. Cancers (Basel) 2021;
[3]Zhang Y, et al. BMC Cancer 2021; [4]Karaayvaz M, et al. Nat Commun 2018

IMPASSION132 (NCT03371017) TRIAL DESIGN

Double-blind placebo-controlled randomised phase 3 trial

- **Unresectable locally advanced/ metastatic TNBC**
- **Prior anthracycline and taxane for early TNBC**
- **Disease progression <12 months after last treatment with curative intent for early TNBC[a]**
- **No prior CT for advanced TNBC**
- **Known PD-L1 status (SP142)**

R 1:1

Carboplatin/gemcitabine or capecitabine[b] + atezolizumab 1200 mg q3w

Treatment continued until disease progression or unacceptable toxicity

Carboplatin/gemcitabine or capecitabine[b] + placebo q3w

Stratification factors:

- Visceral (lung and/or liver) metastases
- CT backbone
- PD-L1 status (during all-comer enrolment)

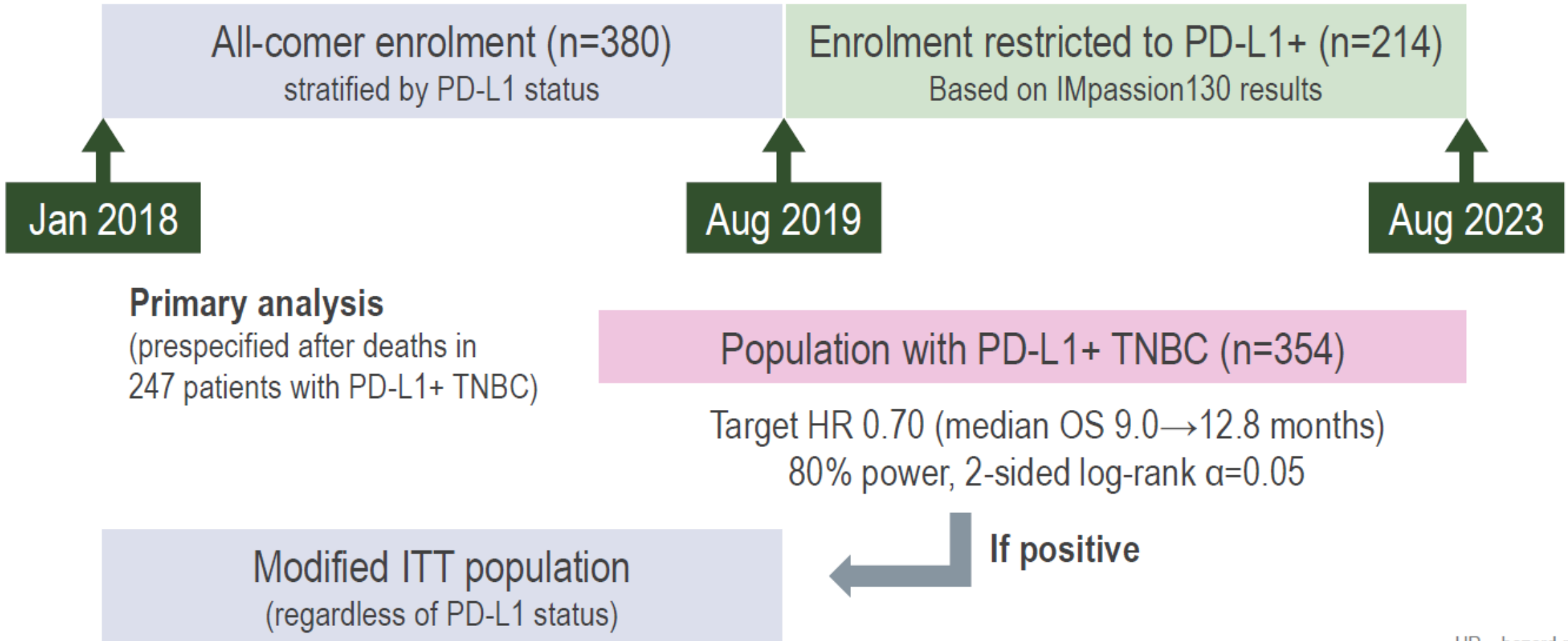
Primary endpoint:

- OS (hierarchical testing: PD-L1+ TNBC[c] then, if positive, modified ITT population[d])

[a]Last dose of any (neo)adjuvant CT regimen or primary breast surgery after neoadjuvant CT, whichever occurred last.
[b]Investigator-selected CT: gemcitabine 1000 mg/m^2 + carboplatin AUC 2 mg/mL/min days 1 & 8 q21d, or capecitabine 1000 mg/m^2 bid days 1–14 q21d (mandatory if platinum pretreated). [c]PD-L1–expressing immune cells covering ≥1% of the tumour area by VENTANA SP142 PD-L1 assay.
[d]All-comer patients randomised before August 2019 protocol amendment.

ITT = intention to treat;
OS = overall survival

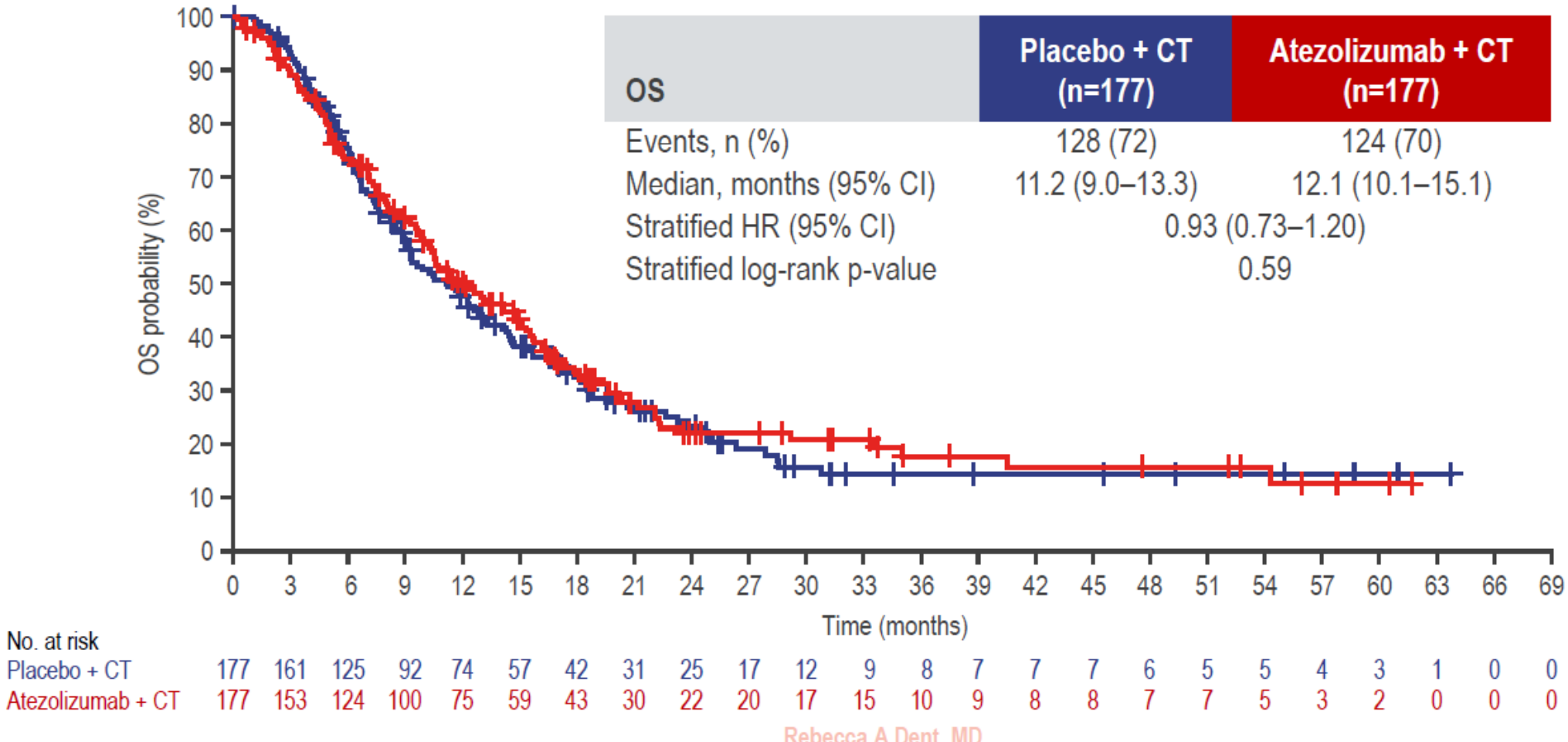
PATIENT POPULATIONS AND STATISTICAL DESIGN



HR = hazard ratio

PRIMARY ENDPOINT: OS (PATIENTS WITH PD-L1+ TNBC)

No significant improvement in OS with atezolizumab (median follow-up: 9.8 months)



OS	Placebo + CT (n=177)	Atezolizumab + CT (n=177)
Events, n (%)	128 (72)	124 (70)
Median, months (95% CI)	11.2 (9.0–13.3)	12.1 (10.1–15.1)
Stratified HR (95% CI)	0.93 (0.73–1.20)	
Stratified log-rank p-value	0.59	

No. at risk																								
Placebo + CT	177	161	125	92	74	57	42	31	25	17	12	9	8	7	7	7	6	5	5	4	3	1	0	0
Atezolizumab + CT	177	153	124	100	75	59	43	30	22	20	17	15	10	9	8	8	7	7	5	3	2	0	0	0

Rapidly relapsing TNBC remains a critical research priority and clinical unmet need

- Combining atezolizumab with CT for PD-L1-positive TNBC relapsing <12 months after last CT or surgery for early TNBC did not significantly improve outcomes versus CT alone
  - Median OS ~10 months, consistent with real-world data[1]
  - Lack of benefit from immune checkpoint inhibition is consistent with KEYNOTE-355 subgroup analyses in patients with recurrence 6–12 months after last CT[2]
- No new safety signals
- These patients have a dismal prognosis and represent a high unmet need
  - Prior therapy may trigger a variety of resistance mechanisms (translational research warranted)
  - Novel therapies and trial designs are urgently required for this treatment-resistant population
- These data highlight the importance of recognising TNBC heterogeneity, especially in the first-line setting

[1]Grinda T, et al. Eur J Cancer 2023; [2]Cortes J, et al. NEJM 2022

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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
⓾ Paclitaxel ⓾ Nab-paclitaxel ⓾ Docetaxel	⓾ Doxorubicin ⓾ Pegylated liposomal doxorubicin ⓾ Epirubicin	⓾ Capecitabine ⓾ Gemcitabine	⓾ Vinorelbine ⓾ Eribulin ⓾ Ixabepilone	⓾ Carboplatin ⓾ Cisplatin

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

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

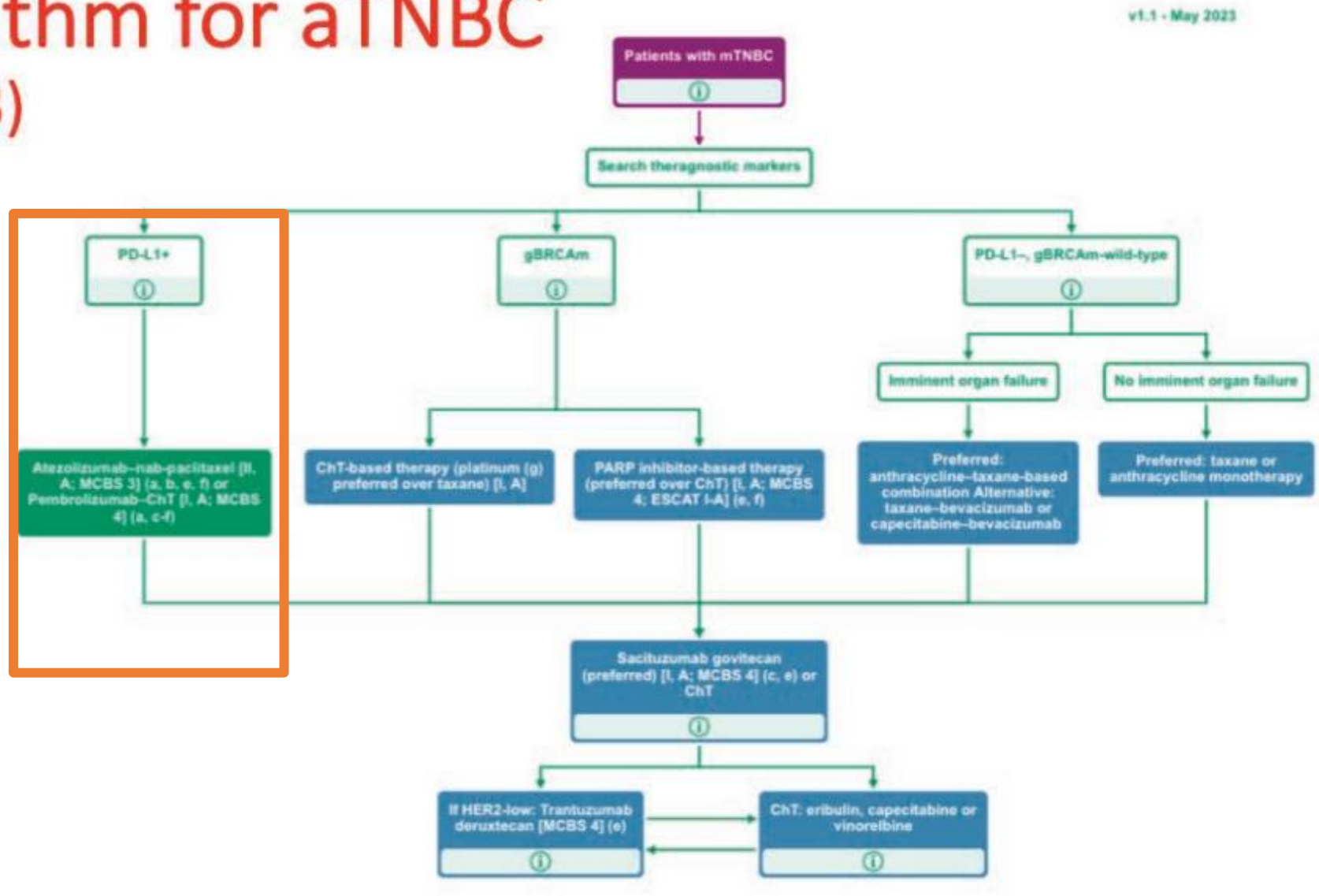
Treatment algorithm for aTNBC
(Living ESMO GLs 2023)

TNBC

PD-L1 pos : ca 40%

BRCA1/2 mut: 10-12%

HER2-low : ca 40%



What site should I test for PD-L1?

Journal for ImmunoTherapy of Cancer

Comparison of PD-L1 protein expression between primary tumors and metastatic lesions in triple negative breast cancers

Mariya Rozenblit,[1] Richard Huang,[2] Natalie Danziger,[2] Priti Hegde,[2] Brian Alexander,[2] Shakti Ramkissoon,[2,3] Kim Blenman ,[1] Jeffrey S Ross,[2,4] David L Rimm ,[1,5] Lajos Pusztai[1]

- Higher % of PD-L1 IC + primary 63.7% vs. metastastic 42.2%
- Lower positivity rates in liver (17.4%), skin (23.8%) and bone (16.7%) metastasis

IMMUNOTHERAPY

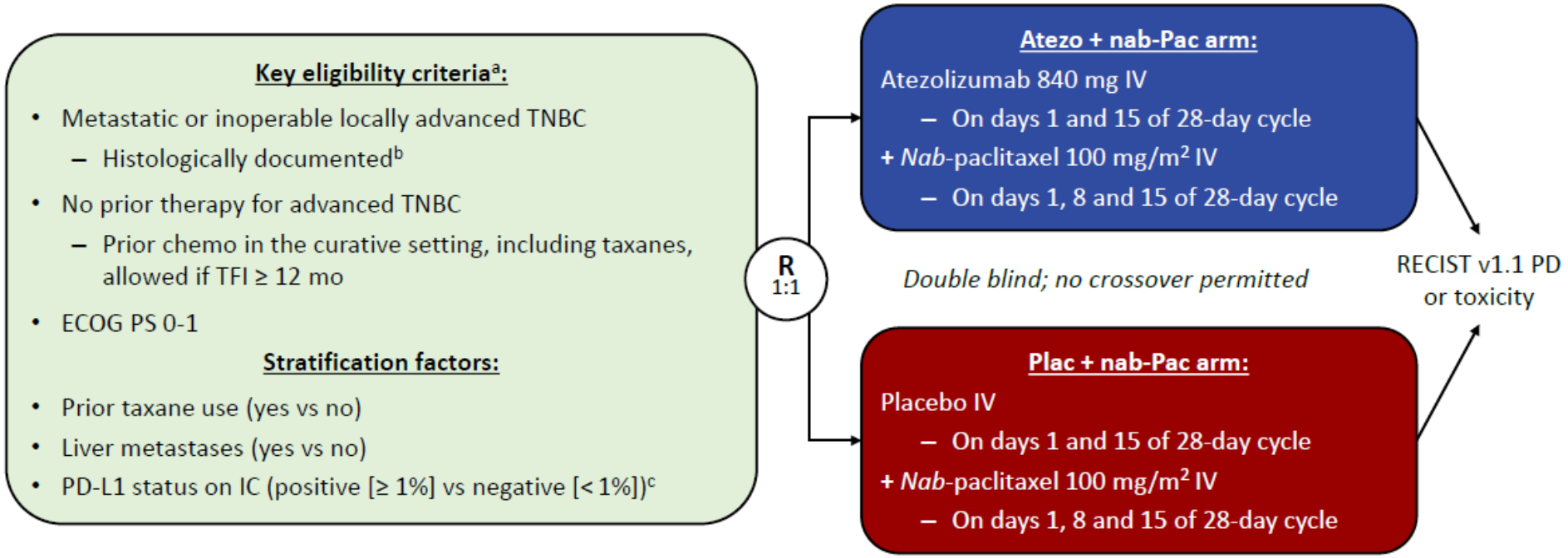
PEMBROLIZUMAB

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)

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

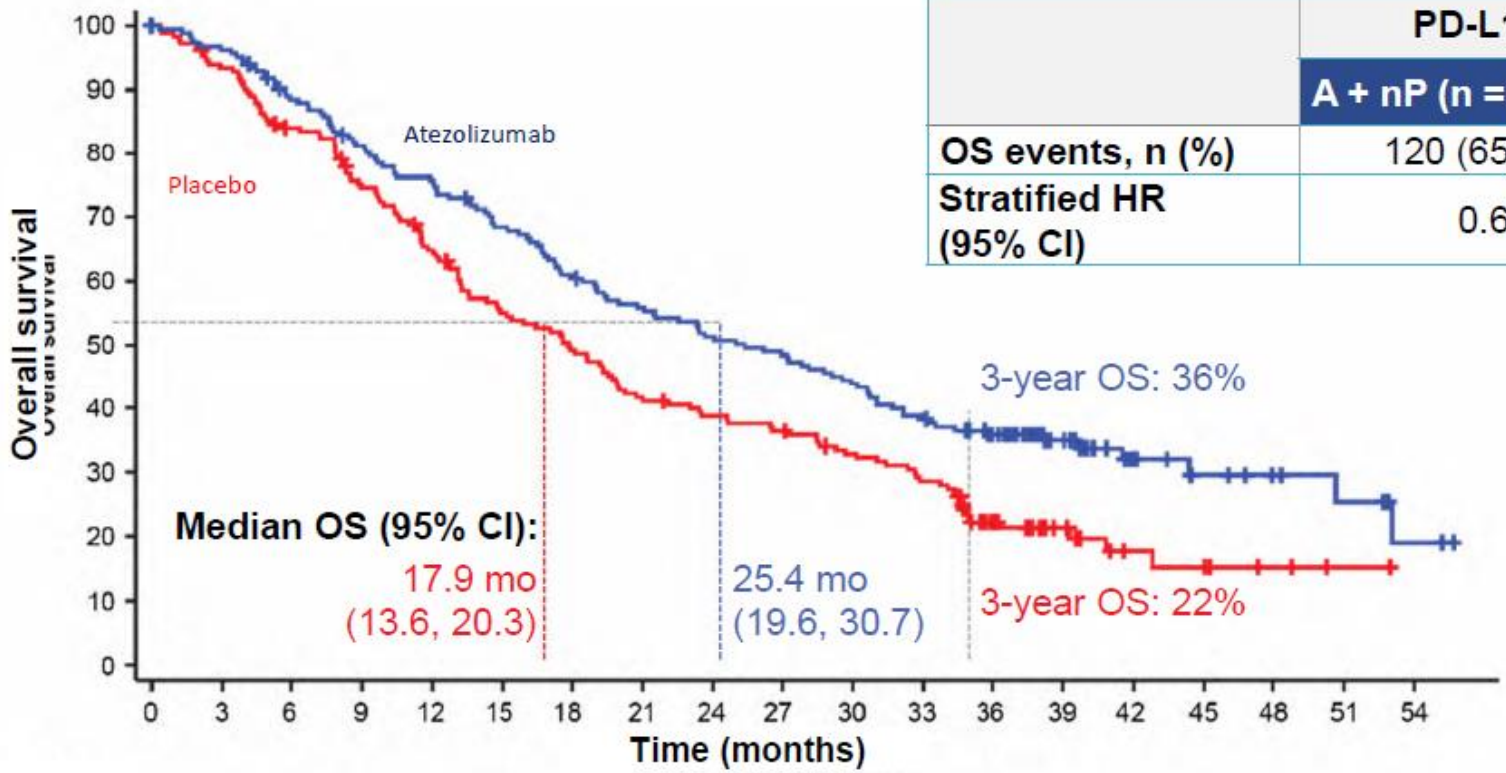


- Co-primary endpoints were **PFS** and **OS** in the **ITT and PD-L1+ populations**[d].
- Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated.

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

OS in the PD-L1 IC+ population

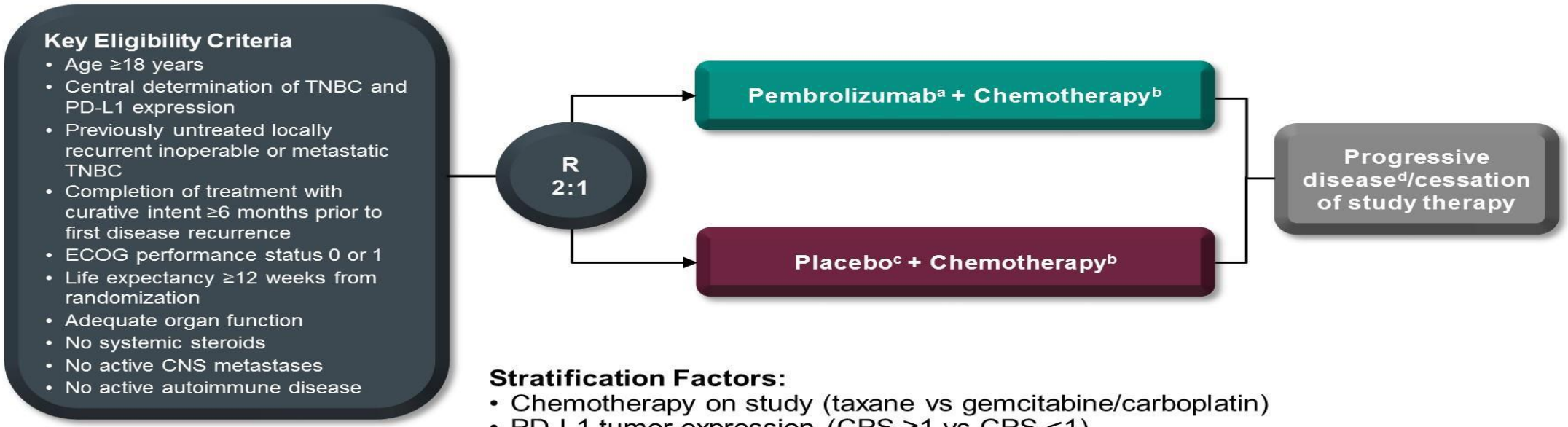


	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR (95% CI)	0.67 (0.53, 0.86)[a]	

Emens LA. Annals of Oncology 2021

Emens LA. IMpassion130 ESMO 2020

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

Presented By Javier Cortes at TBD

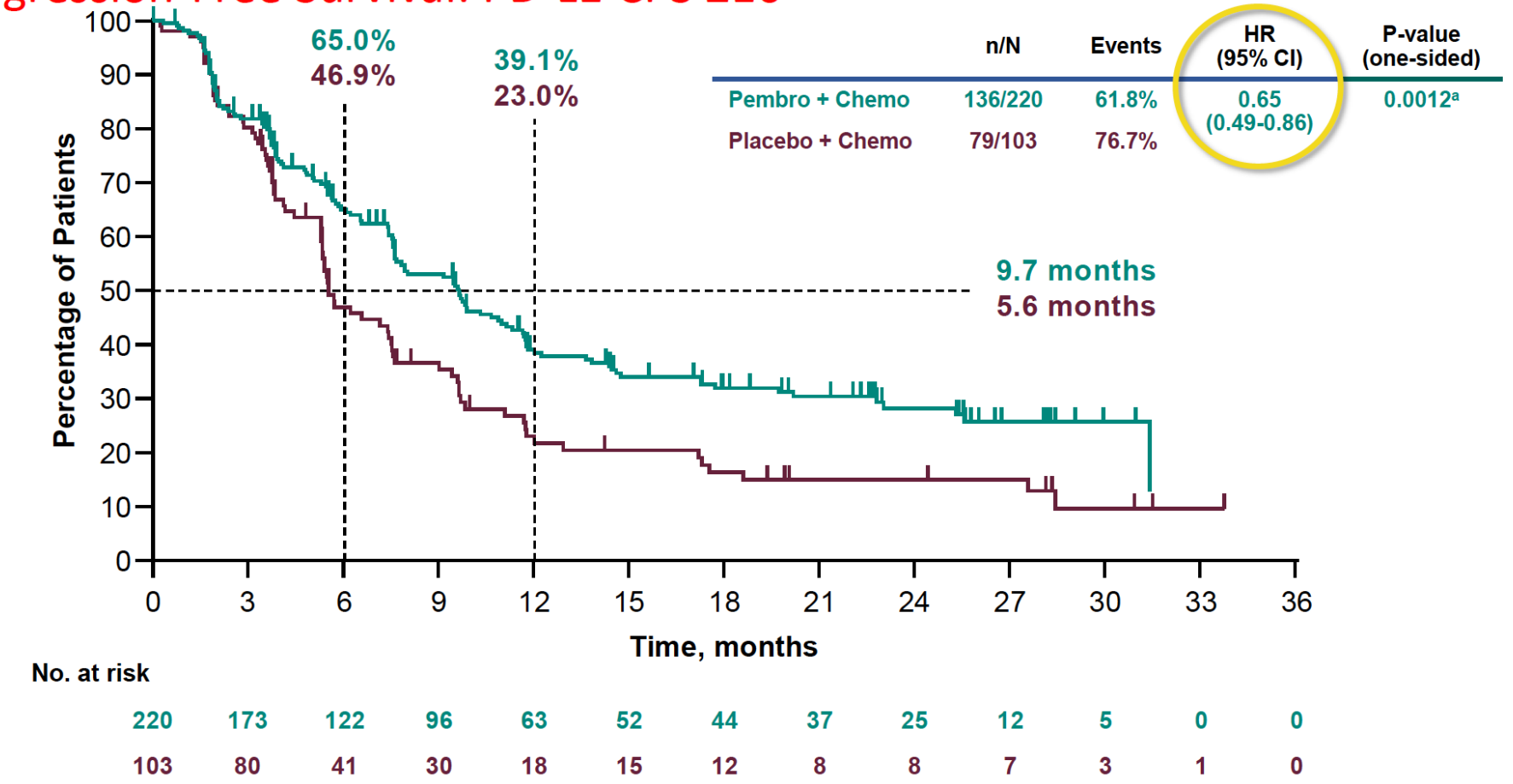
Baseline Characteristics, ITT

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 (Nab-paclitaxel or paclitaxel)	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	167 (29.5)	84 (29.9)
<12 months	126 (22.3)	50 (17.8)
≥12 months	270 (47.7)	147 (52.3)

Cortes J et al. The Lancet 2020

KEYNOTE 355 - Outcomes

Progression-Free Survival: PD-L1 CPS ≥10



	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	136/220	61.8%	0.65 (0.49-0.86)	0.0012[a]
Placebo + Chemo	79/103	76.7%		

No. at risk

220	173	122	96	63	52	44	37	25	12	5	0	0
103	80	41	30	18	15	12	8	8	7	3	1	0

Presented By Javier Cortes at TBD

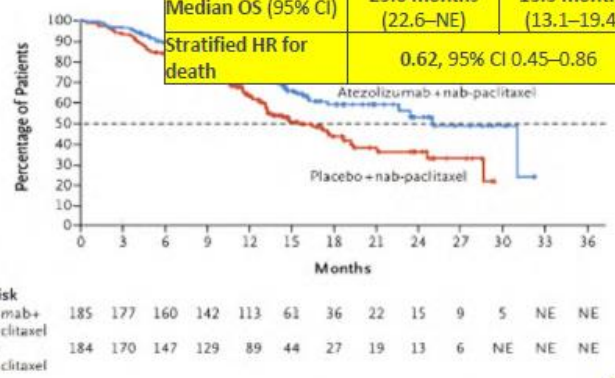
Improvement in Overall Survival with IO

1L

IMpassion130[1,2]	IMpassion131[2]	KEYNOTE-355[3]
Atezolizumab + nab-paclitaxel vs. placebo + nab-paclitaxel	Atezolizumab + paclitaxel vs. placebo + paclitaxel	Pembrolizumab + ChT vs. placebo + ChT

OS in PD-L1-positive patients

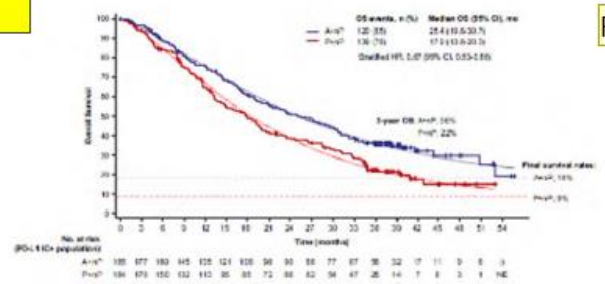
	Atezolizumab + nab-Paclitaxel (N = 185)	Placebo + nab-Paclitaxel (N = 184)
Median OS (95% CI)	25.0 months (22.6–NE)	15.5 months (13.1–19.4)
Stratified HR for death	0.62, 95% CI 0.45–0.86	



RL0

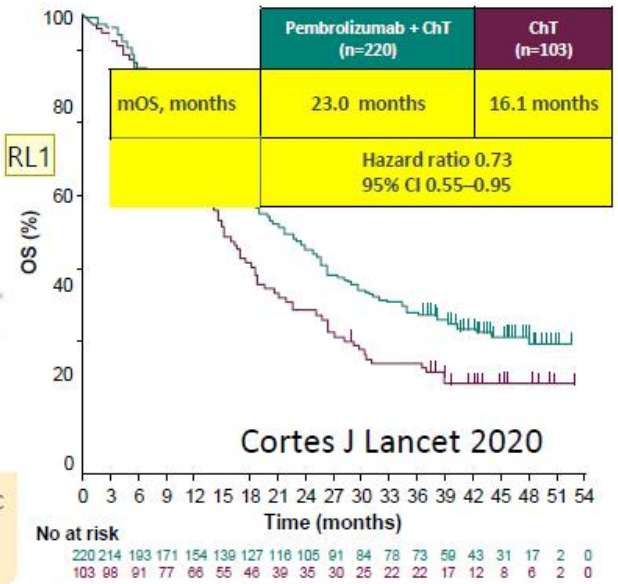
On 27 August 2021, Roche voluntarily withdrew the FDA accelerated approval of atezolizumab plus nab-paclitaxel in the 1L mTNBC setting for patients whose tumours express PD-L1 because of the negative PFS results from the IMpassion131 post-marketing requirement study.[4] This decision only impacts the mTNBC indication in the US

OS in PD-L1-positive patients[3]



OS in patients with PD-L1 CPS ≥10[3]

	Pembrolizumab + ChT (n=220)	ChT (n=103)
mOS, months	23.0 months	16.1 months
	Hazard ratio 0.73 95% CI 0.55–0.95	



RL1

Cortes J Lancet 2020

1. Schmid P, et al. *N Engl J Med* 2. Emens L, et al. *Ann Oncol*. 2021 3. Rugo H, et al. Presented at ESMO 2021

Toxicities with IO & chemotherapy
Immune-Mediated Adverse Events

IMpassion 130[1]

G≥3 AESI: 9%

AE (medical concept), n (%)[a]	Atezolizumab + nab-paclitaxel (n = 460)		Placebo + nab-paclitaxel (n = 430)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Hepatitis (diagnosis)[b]	11 (2)	7 (2)	7 (2)	1 (< 1)
Hypothyroidism	54 (12)	0	15 (4)	0
Hyperthyroidism	22 (5)	1 (< 1)	5 (1)	0
Adrenal insufficiency	6 (1)	1 (< 1)	0	0
Pneumonitis	18 (4)	2 (< 1)	1 (< 1)	0
Colitis	7 (2)	2 (< 1)	3 (1)	1 (< 1)
Pancreatitis	2 (< 1)	1 (< 1)	0	0
Diabetes mellitus	1 (< 1)	1 (< 1)	3 (1)	2 (< 1)
Hypophysitis	1 (< 1)	1 (< 1)	0	0
Myositis	2 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)
Rash	165 (35)	5 (1)	112 (26)	2 (< 1)
Severe cutaneous reactions	4 (1)	1 (< 1)	3 (1)	0

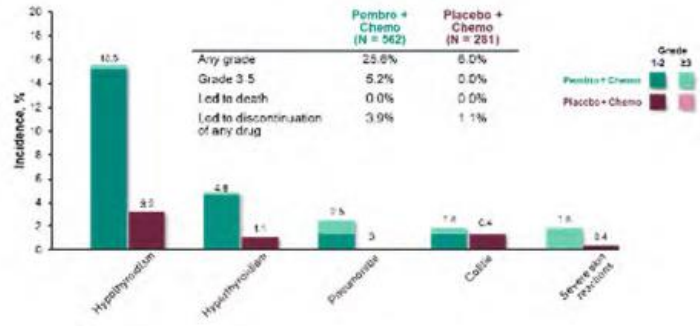
IMpassion 131[2]

G≥3 AESI: 10.2%

Immune-mediated AEs by medical concept, n (%)	Placebo + PAC (n=210)		Atezo + PAC (n=431)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Hepatitis (diagnosis)[a]	1 (0.5)	0	7 (1.6)	2 (0.5)
Pneumonitis	2 (0.9)	0	16 (3.7)	3 (0.7)
Hypothyroidism	9 (4.1)	0	56 (12.9)	0
Hyperthyroidism	0	0	22 (5.1)	0
Diabetes mellitus	2 (0.9)	2 (0.9)	4 (0.9)	3 (0.7)
Adrenal insufficiency	0	0	2 (0.5)	0
Infusion-related reactions	8 (3.7)	0	14 (3.2)	2 (0.5)
Pancreatitis	1 (0.5)	1 (0.5)	6 (1.4)	5 (1.4)
Colitis	2 (0.9)	2 (0.9)	3 (0.7)	1 (0.2)
Rash	67 (30.7)	2 (0.9)	137 (31.8)	4 (0.9)
Ocular inflammatory toxicity	1 (0.5)	0	4 (0.9)	0
Severe cutaneous reactions	3 (1.4)	0	1 (0.2)	0
Myositis	0	0	2 (0.5)	0

Keynote 355

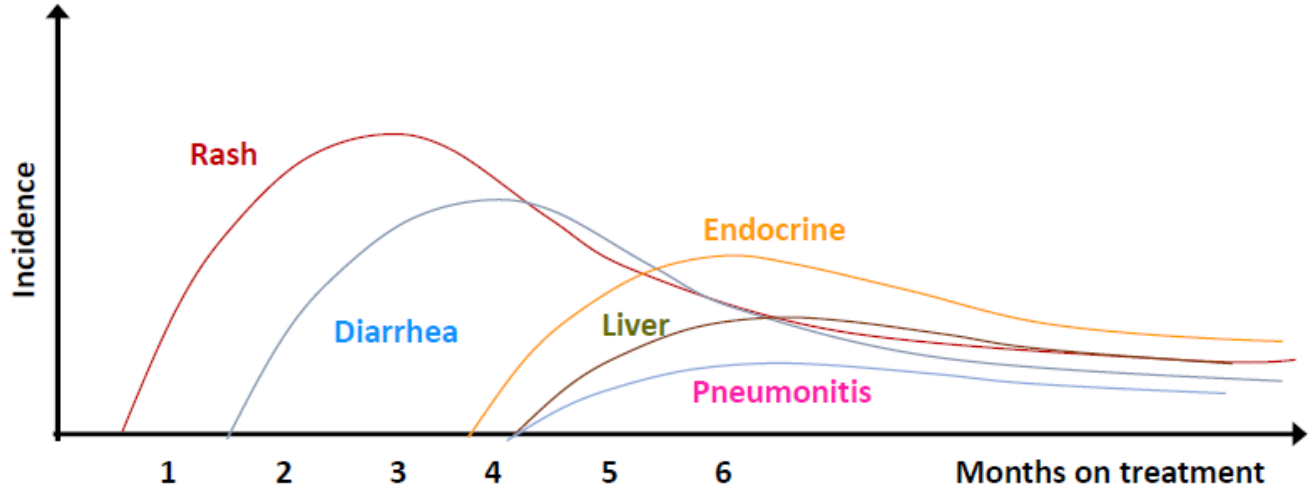
G≥3 AESI: 5.2%



1.Emens LA, et al, ESMO 2020; Miles D, et al. ESMO 2020

Toxicities With Immune Checkpoint Inhibitors

- Timing can be highly variable
- irAE can occur months or even a year after the end of treatment
- Time course might be even more variable with novel combinations

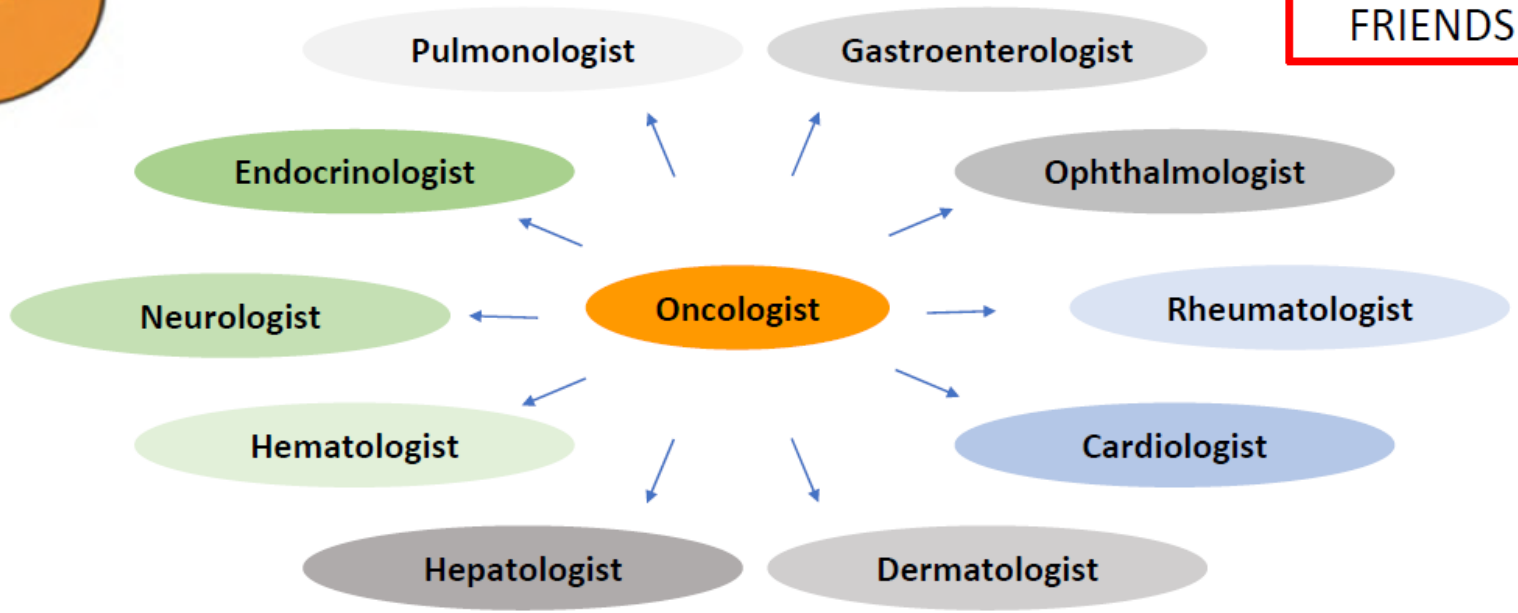


KFP0

Multidisciplinary Management Coordinated by Oncologist

TREAT

TALK TO YOUR FRIENDS!



Must learn from each other and feedback and follow up!

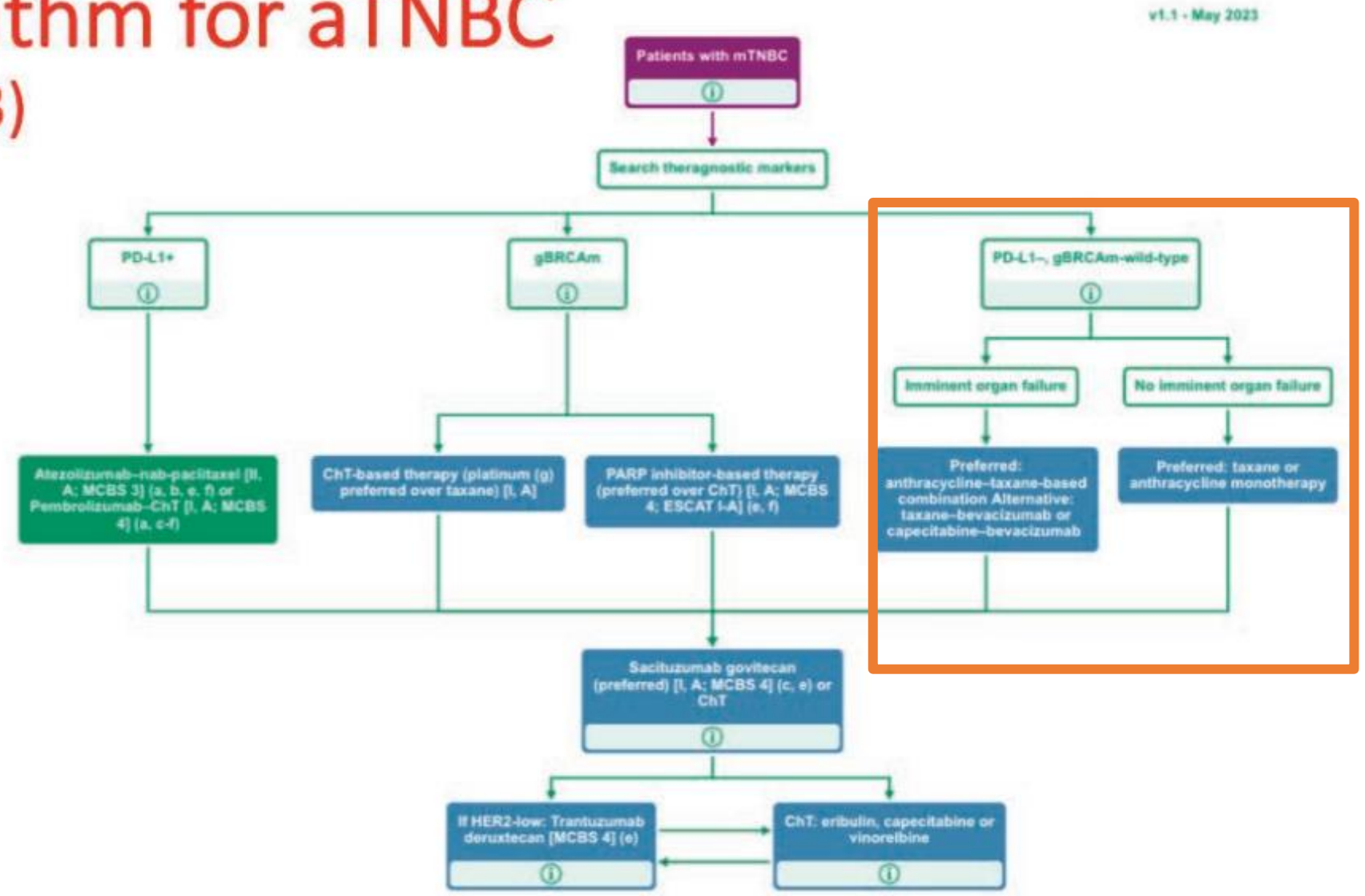
Treatment algorithm for aTNBC
(Living ESMO GLs 2023)

TNBC

PD-L1 pos : ca 40%

BRCA1/2 mut: 10-12%

HER2-low : ca 40%



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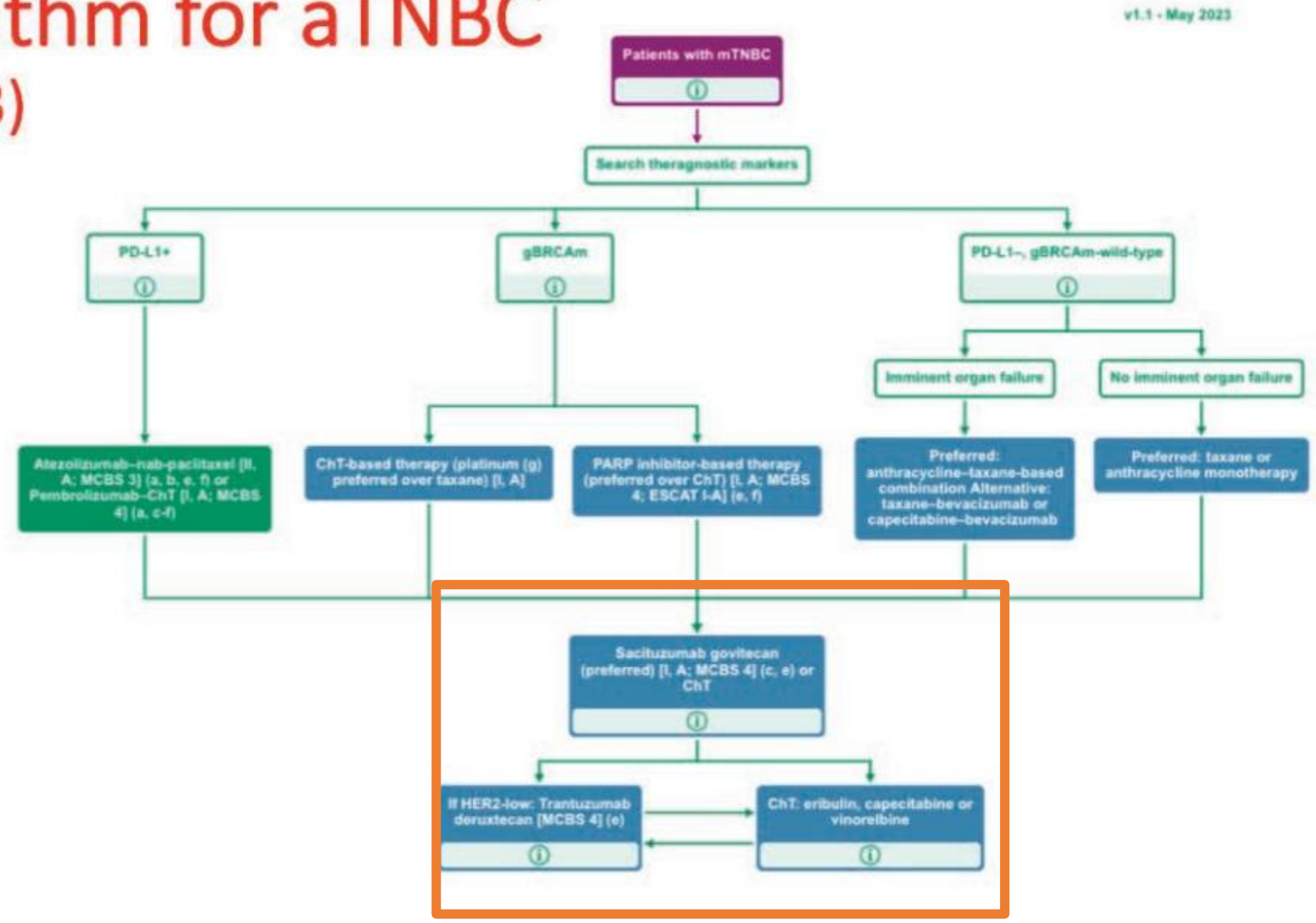
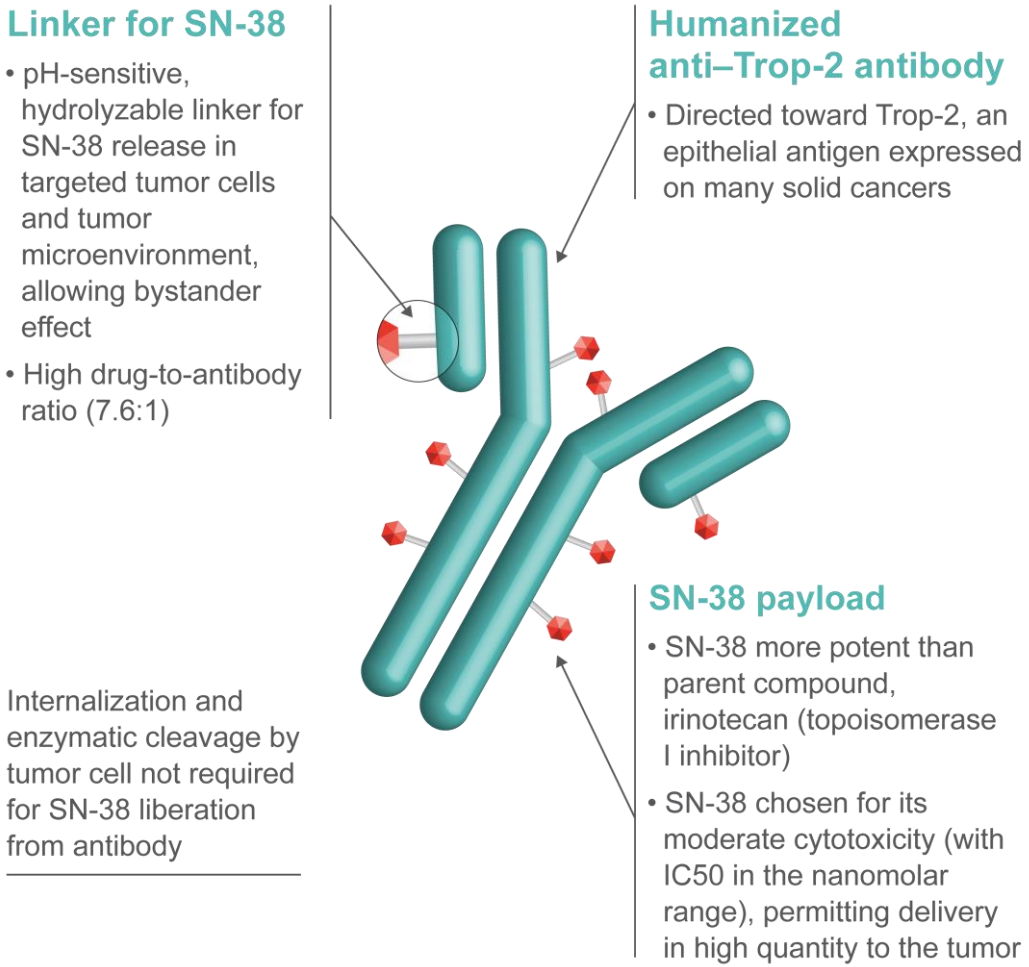


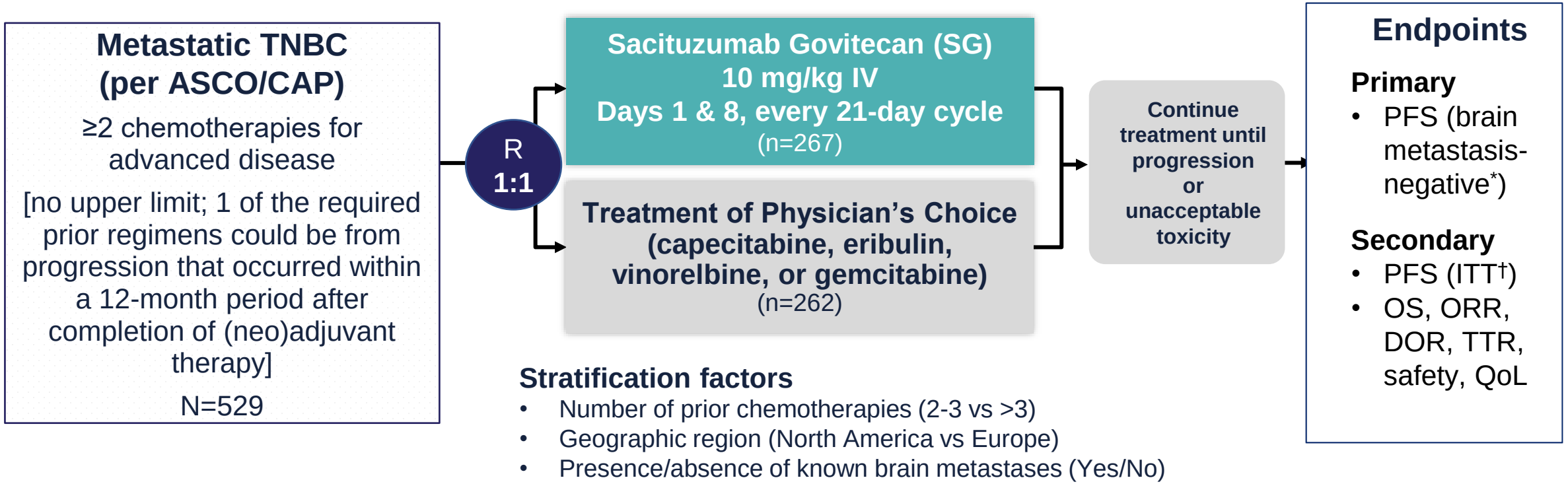
Sacituzumab Govitecan

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.

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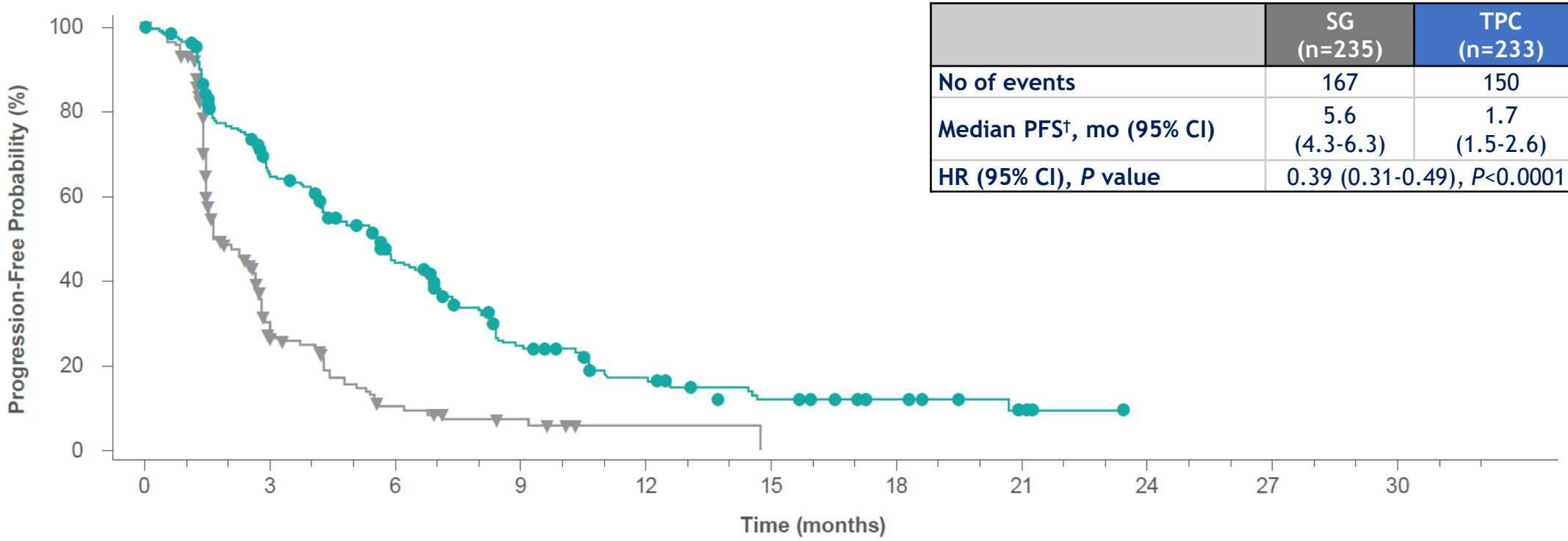
Progression-Free Survival* (BMNeg Population)



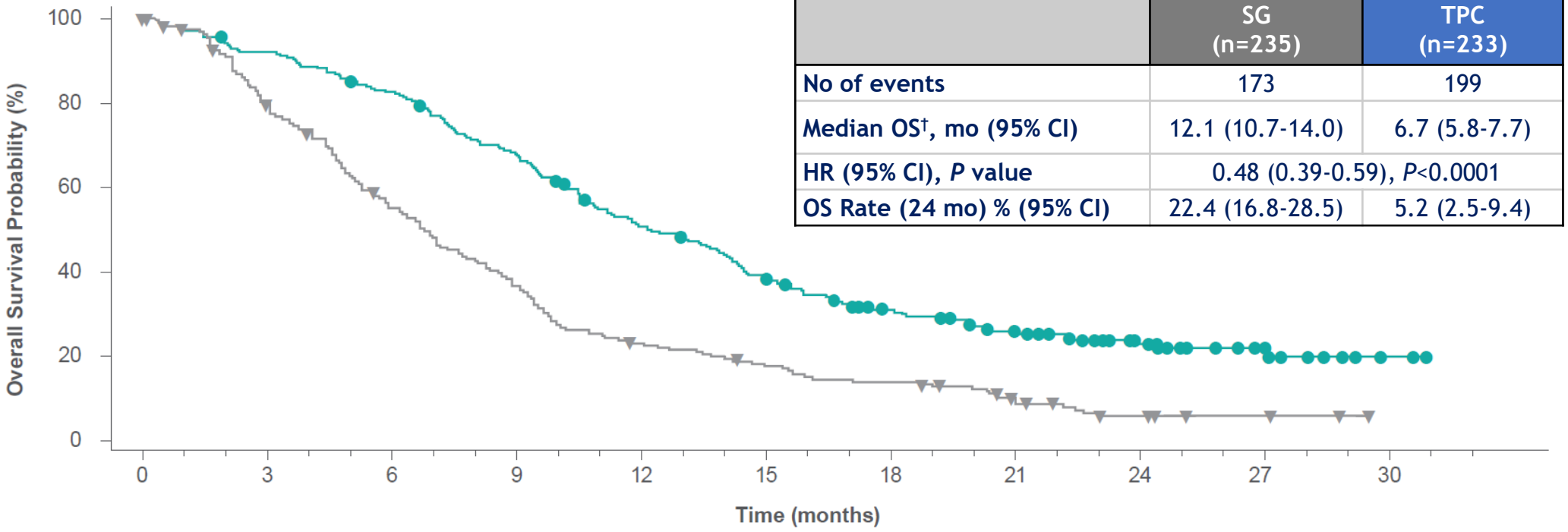
	SG (n=235)	TPC (n=233)
No of events	167	150
Median PFS†, mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	0.39 (0.31-0.49), *P*<0.0001	

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.

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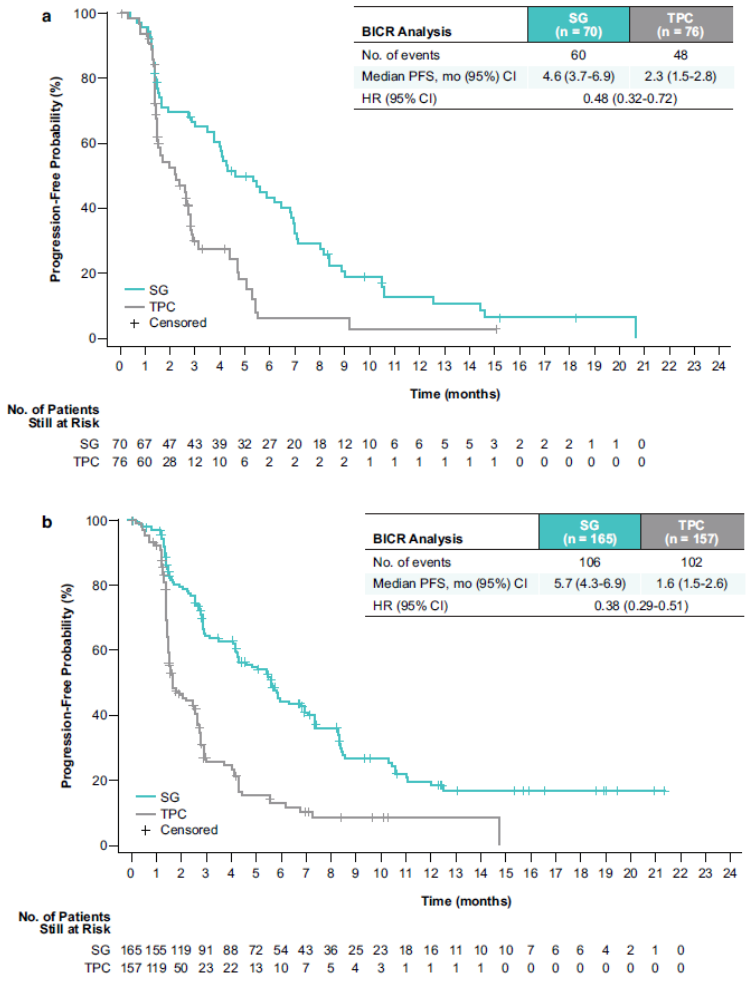
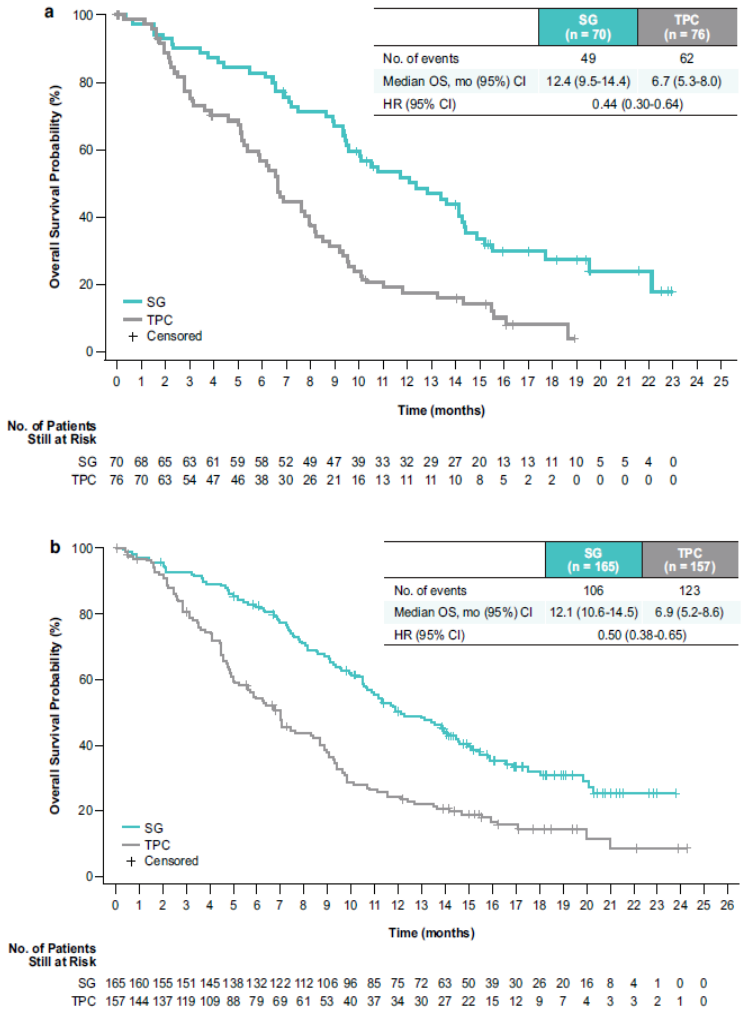
TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

		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)



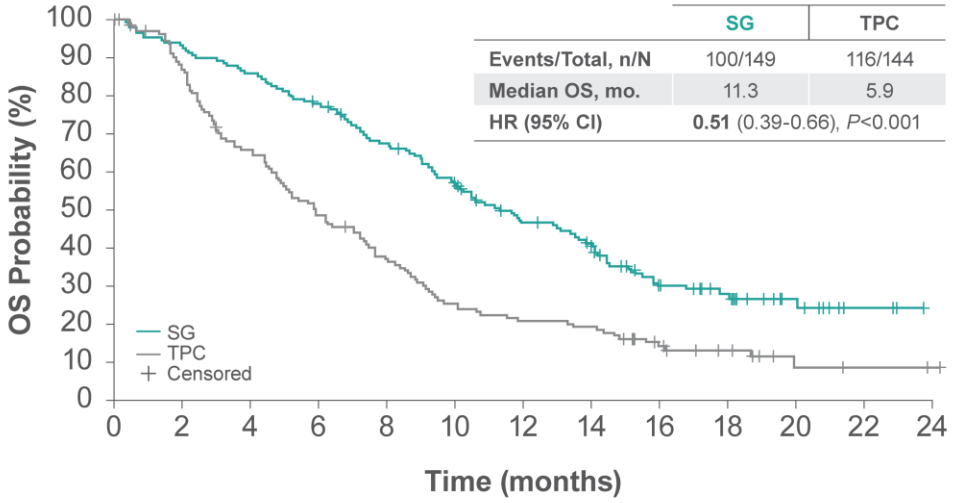


Patient without TNBC at initial diagnosis had improved clinical outcomes and a manageable safety profile with SG

O'Shaughnessy J BCRT 2022

Results Overall Survival according HER2 status (ASCENT)

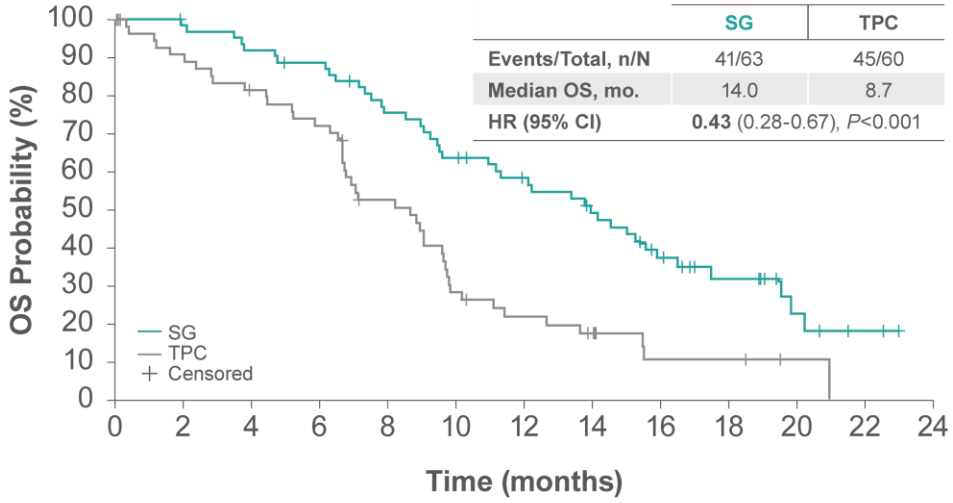
A



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

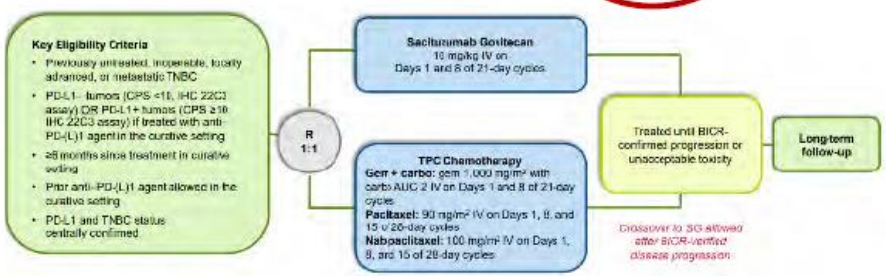
[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice

Incorporate ADCs in earlier treatment strategies and combinations

Sacituzumab Govitecan

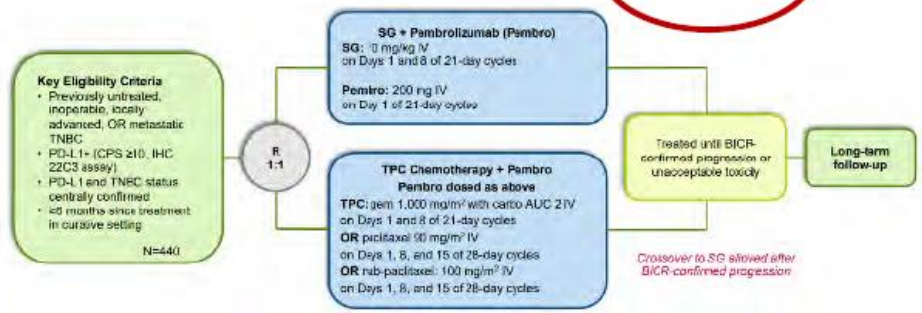
ASCENT-03 (NCT05382299)

Sacituzumab Govitecan vs TPC for 1L PDL1-



ASCENT-04 (NCT05382286)

SG + Pembro vs Pembro + CT for 1L PDL1+



1L mTNBC

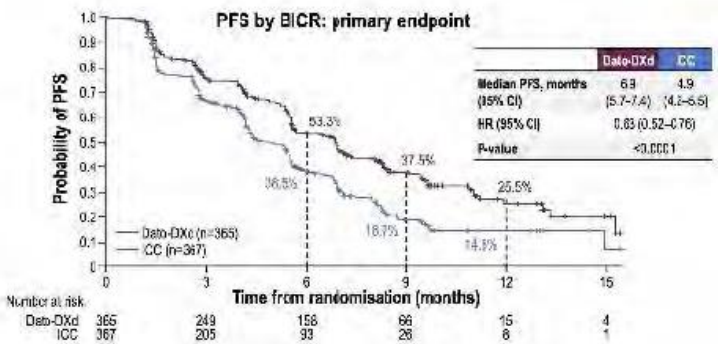
Incorporate ADCs in earlier treatment strategies

1st line Datopotamab Deruxtecan

TROPION-Breast01 Phase III trial

in HR+ HER2 low or negative

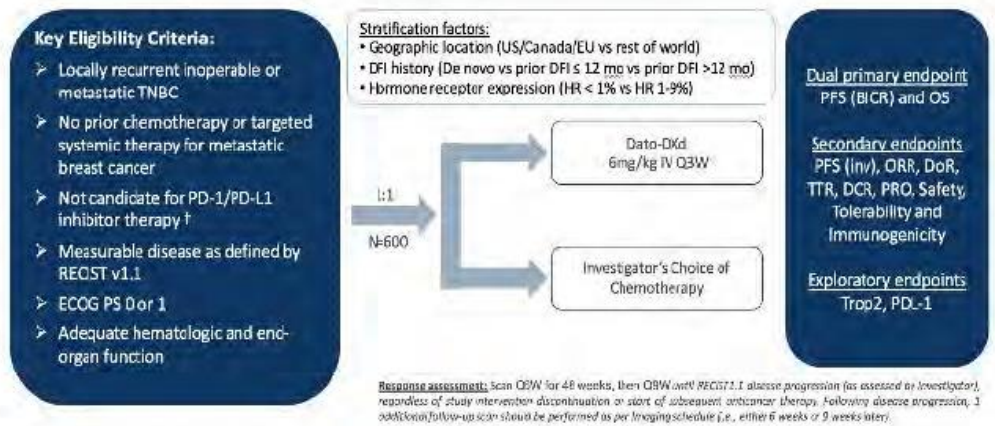
Bardia et al. ESMO 2023



Toxicity: Less ILD,
More Stomatitis

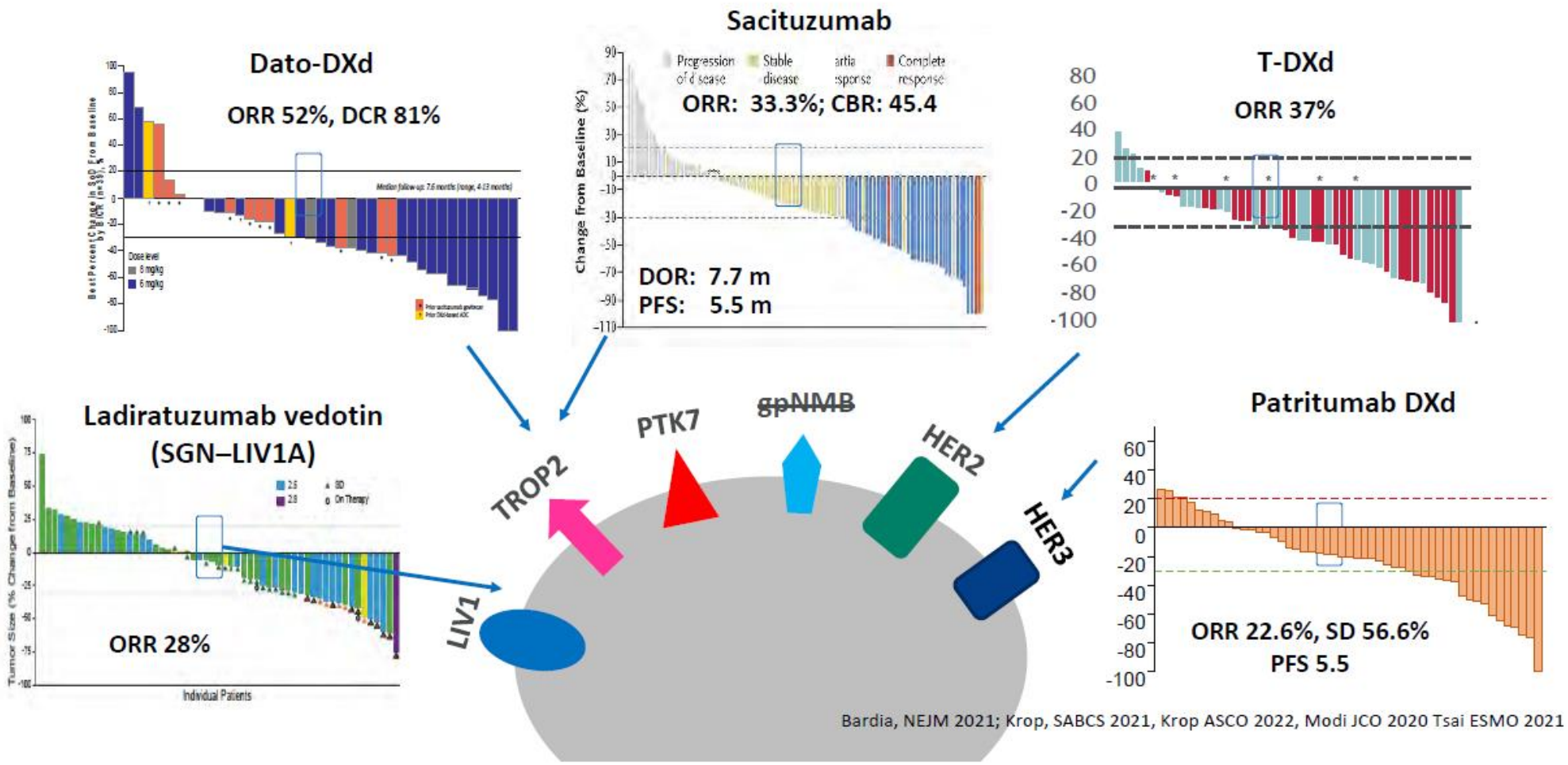
TROPION-Breast02 (NCT05374512)

Dato-DXd vs TPC 1L mTNBC not candidate for anti-PD-(L)1 therapy
Including subset of early relapsers and CNS mets



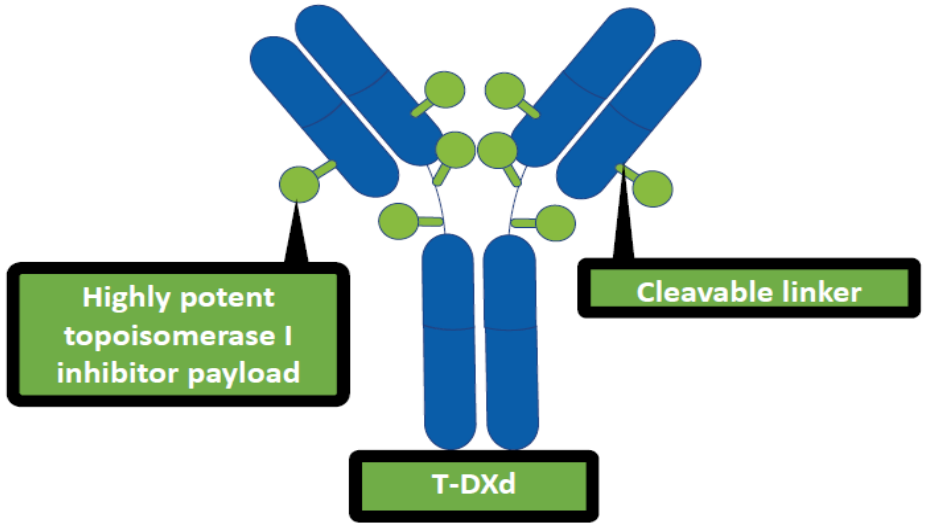
TIP Dent R et al. SABCS 2022

Targets for Antibody-Drug Conjugates in TNBC



Bardia, NEJM 2021; Krop, SABCS 2021, Krop ASCO 2022, Modi JCO 2020 Tsai ESMO 2021

Trastuzumab deruxtecan

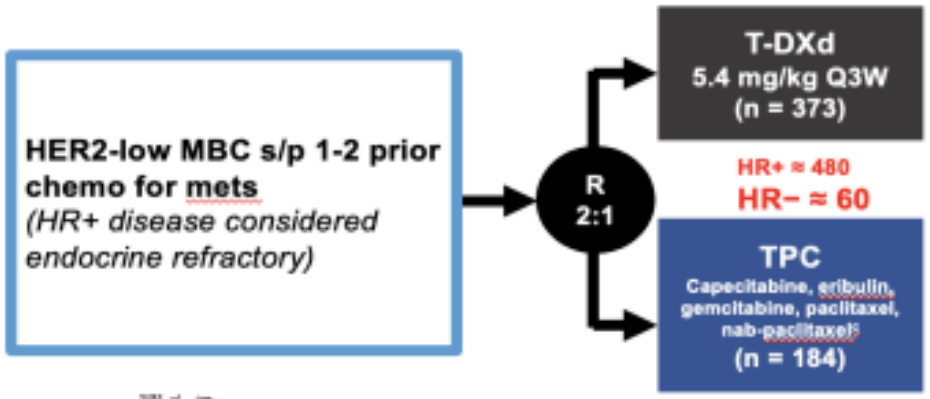


- Anti-HER2 antibody
- Cleavable linker
- Deruxtecan Topo-1i payload
- High DAR

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

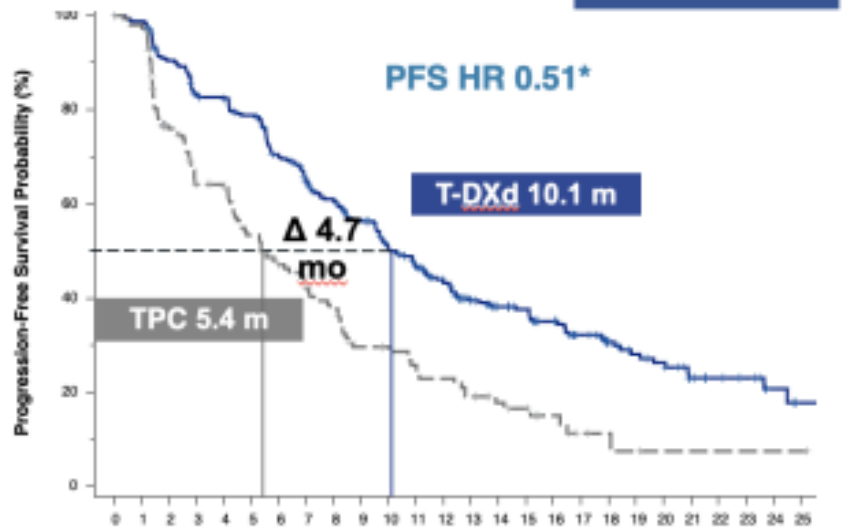


Primary endpoint
- PFS in HR+

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

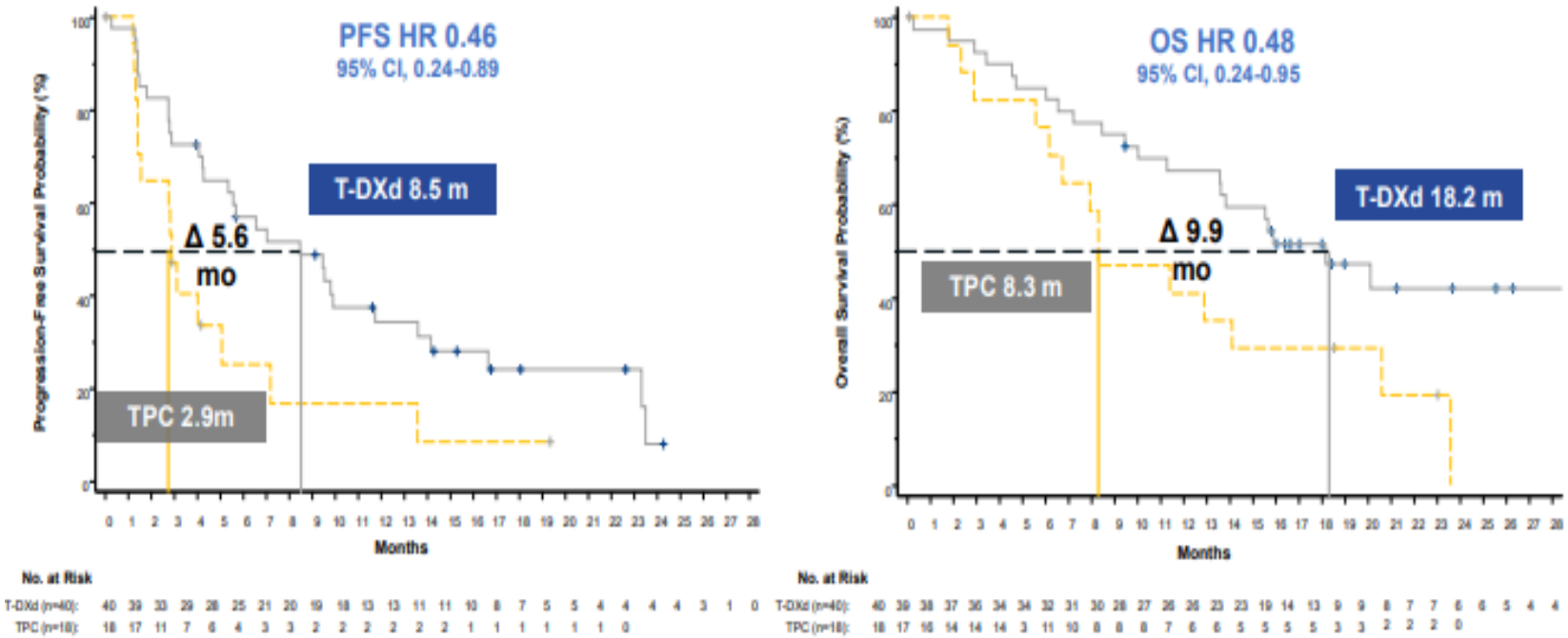


- **Met endpoints in HR+, all pts, OS (immature)**
- **No difference between 1+ and 2+**
- **Toxicity:**
  - **myelosuppression (all lines), GI (nausea, diarrhea mostly gr1), LFT ↑, fatigue, alopecia**
  - **ILD 12% (1% fatal), LVEF ↓ 4% (0.5% CHF)**

Modi et al, NEJM 2022

TNBC subset (10% of population)

INDICAZIONE in monoterapia è indicato per il trattamento di pazienti adulti con cancro della mammella HER2-low non resecabile o metastatico, che hanno ricevuto precedente chemioterapia per malattia metastatica o che hanno sviluppato recidiva della malattia durante o entro 6 mesi dal completamento della chemioterapia adiuvante.



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

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

New strategies

- Capivasertib is an oral, potent and selective inhibitor of all three AKT isoforms (AKT1/2/3),[1] recommended in combination with fulvestrant as a treatment option for patients with ER-positive/HER2-negative ABC with one or more *PIK3CA/AKT1/PTEN* tumour alterations after disease progression or recurrence following one or more prior lines of endocrine therapy[2,3]
- The PI3K/AKT signalling pathway is often overactivated in cancer,[4] promoting breast cancer cell survival and resistance to chemotherapy or endocrine therapy;[5–7] about one-third of patients with TNBC harbour *PIK3CA/AKT1/PTEN* tumour alterations[8,9]
- Preclinical data showed that combining capivasertib with paclitaxel decreased cell proliferation and increased cell death in TNBC cells with or without *PIK3CA/AKT1/PTEN* alterations (Eberlein C, et al. ESMO 2024; Poster #366P)
- The randomised, double-blind Phase 2 LOTUS (ipatasertib–paclitaxel vs placebo–paclitaxel)[10,11] and PAKT (capivasertib–paclitaxel vs placebo–paclitaxel)[12,13] trials provided rationale for a Phase 3 trial of capivasertib–paclitaxel in patients with mTNBC

CAPItello-290: Study overview

Phase 3, randomised, double-blind, placebo-controlled study (NCT03997123)

BARCELONA 2024 ESMO congress

Patients with locally advanced or mTNBC

- Men and pre-/post-menopausal women
- Eligible for taxane monotherapy
- No prior (neo)adjuvant chemotherapy within 6 months (12 months for taxanes)
- No prior systemic therapy for inoperable locally advanced or metastatic disease
- ECOG performance status 0 or 1
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumour sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1
N=812

Capivasertib–paclitaxel[a]

Placebo–paclitaxel[a]

Stratification factors:
- Visceral vs non-visceral disease
- (Neo)adjuvant chemotherapy (yes/no)
- Region[b]

- First patient randomised: July 2019
- Last patient randomised: February 2022

Dual primary endpoints

OS
- Overall population
- *PIK3CA*/*AKT1*/*PTEN*-altered population

Key secondary endpoints

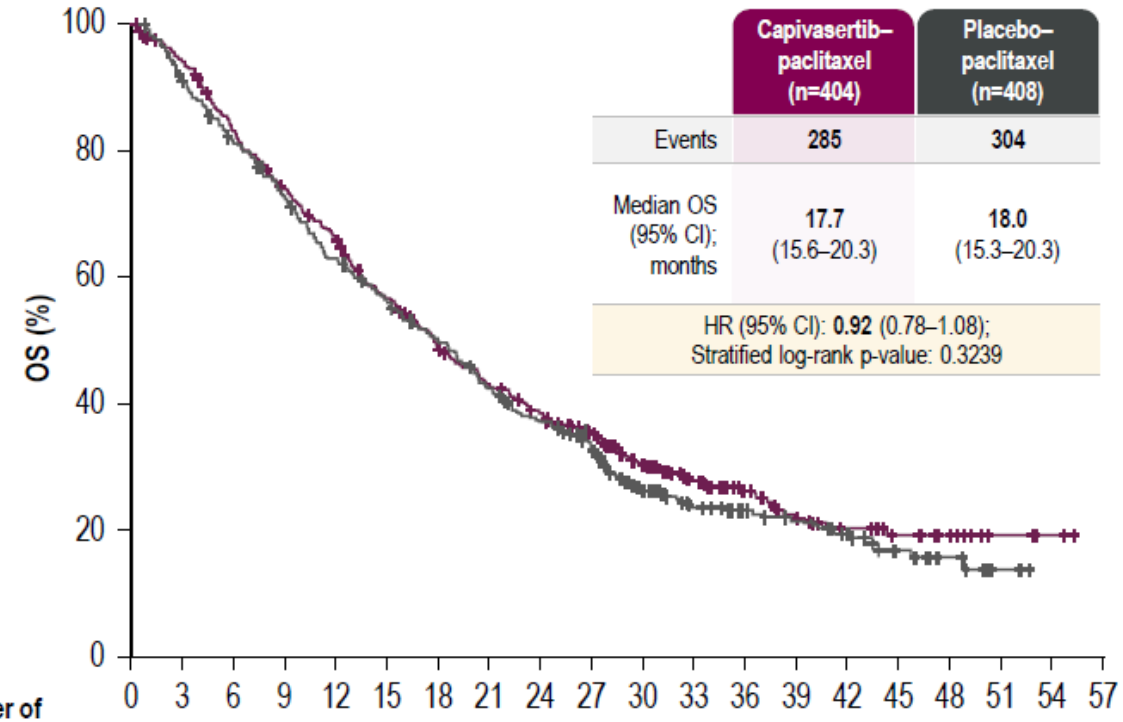
PFS
- Overall population
- *PIK3CA*/*AKT1*/*PTEN*-altered population

Safety

CAPItello-290: Dual primary endpoints: OS in the overall population and in patients with *PIK3CA/AKT1/PTEN*-altered tumours (DCO2)

No statistically significant OS difference between treatment arms in either population

Overall population



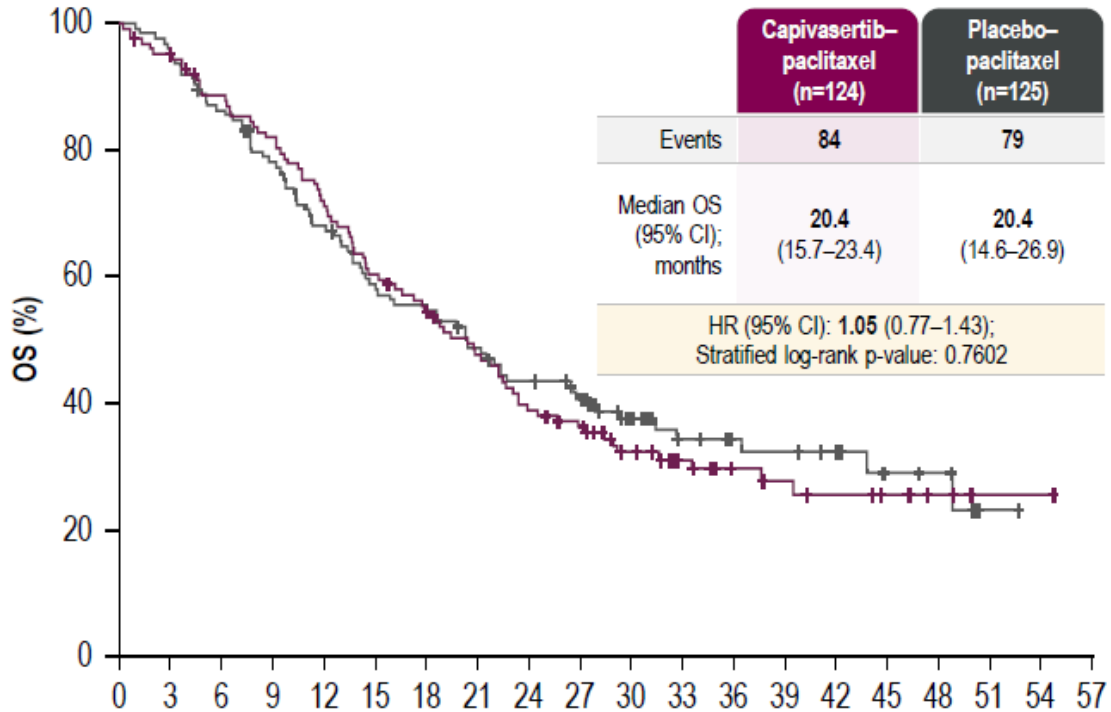
	Capivasertib–paclitaxel (n=404)	Placebo–paclitaxel (n=408)
Events	285	304
Median OS (95% CI); months	17.7 (15.6–20.3)	18.0 (15.3–20.3)

HR (95% CI): **0.92** (0.78–1.08);
Stratified log-rank p-value: 0.3239

Number of patients at risk:

Capivasertib–paclitaxel	404	376	328	290	259	218	184	160	140	118	88	66	45	31	23	16	12	4	2	0
Placebo–paclitaxel	408	369	325	290	250	221	196	165	140	114	77	53	43	36	27	15	9	2	0	0

PIK3CA/AKT1/PTEN-altered population



	Capivasertib–paclitaxel (n=124)	Placebo–paclitaxel (n=125)
Events	84	79
Median OS (95% CI); months	20.4 (15.7–23.4)	20.4 (14.6–26.9)

HR (95% CI): **1.05** (0.77–1.43);
Stratified log-rank p-value: 0.7602

Capivasertib–paclitaxel	124	117	107	99	86	73	65	55	45	40	30	22	15	13	10	7	4	1	1	0
Placebo–paclitaxel	125	119	106	94	82	69	66	57	50	44	30	20	17	16	14	7	6	1	0	0

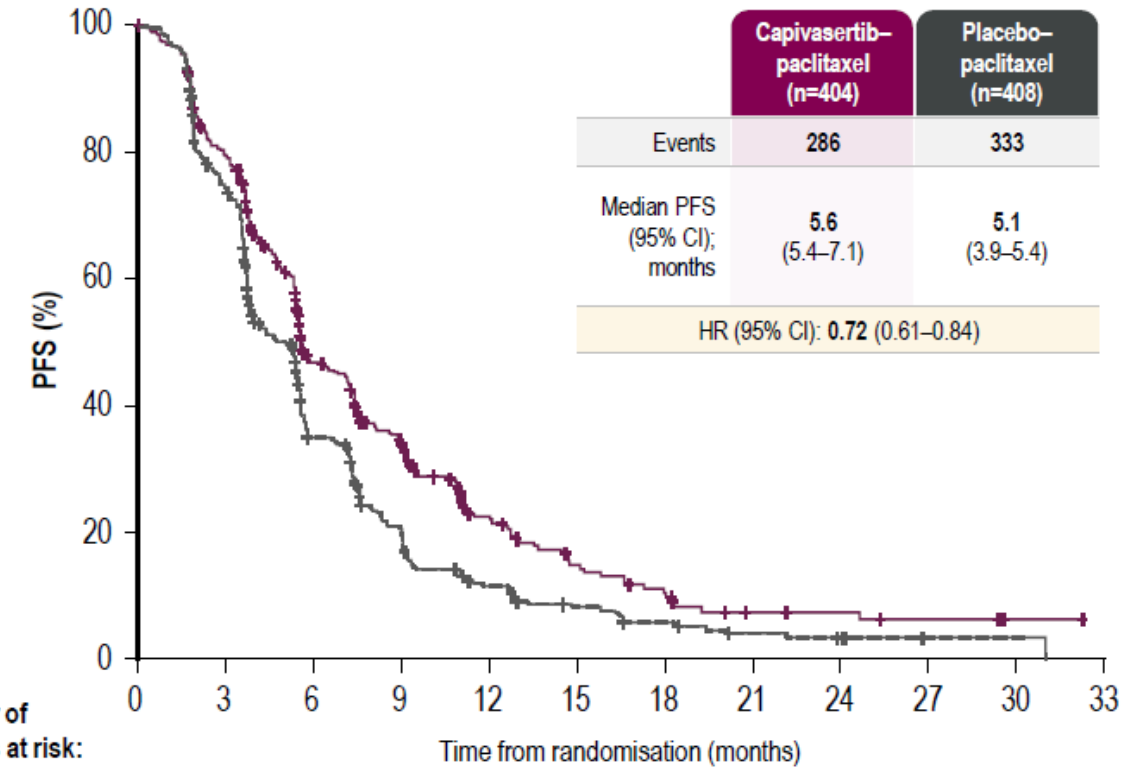
Exploratory analyses: No significant OS difference between treatments in patients with *PIK3CA/AKT1/PTEN*-non-altered tumours (n=563, hazard ratio 0.88 [95% CI 0.72–1.06]; patients with confirmed non-altered tumours [n=465], hazard ratio 0.90 [95% CI 0.73–1.11]).

Data cutoff: 18 March 2024 (DCO2). Tick marks indicate censored observations. Median (range) duration of follow-up in censored patients: Overall population: Capivasertib–paclitaxel: 31.8 (0.5–55.4) months, placebo–paclitaxel: 30.8 (0.3–52.7) months; *PIK3CA/AKT1/PTEN*-altered population: Capivasertib–paclitaxel: 32.6 (0.9–54.8) months, placebo–paclitaxel: 30.3 (3.0–52.7) months. Cox proportional hazards model stratified by (yes vs no): *PIK3CA/AKT1/PTEN*-altered (overall population only), visceral metastases, prior (neo)adjuvant chemotherapy. CI, confidence interval.

CAPItello-290: Investigator-assessed PFS (DCO1)

PFS numerically favoured capivasertib–paclitaxel over placebo–paclitaxel

Overall population

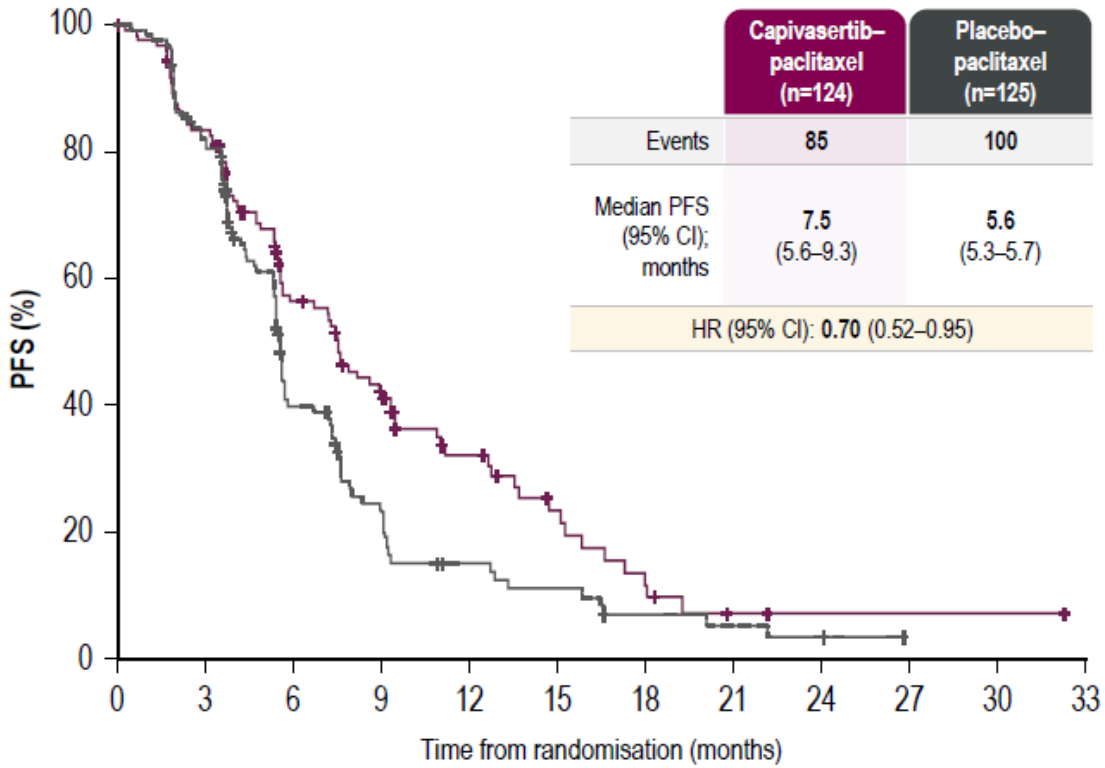


	Capivasertib–paclitaxel (n=404)	Placebo–paclitaxel (n=408)
Events	286	333
Median PFS (95% CI); months	5.6 (5.4–7.1)	5.1 (3.9–5.4)
HR (95% CI): **0.72** (0.61–0.84)		

Number of patients at risk:

Capivasertib–paclitaxel	404	302	149	96	46	24	16	7	6	4	1	0
Placebo–paclitaxel	408	289	117	59	29	17	11	6	4	1	1	0

PIK3CA/AKT1/PTEN-altered population



	Capivasertib–paclitaxel (n=124)	Placebo–paclitaxel (n=125)
Events	85	100
Median PFS (95% CI); months	7.5 (5.6–9.3)	5.6 (5.3–5.7)
HR (95% CI): **0.70** (0.52–0.95)		

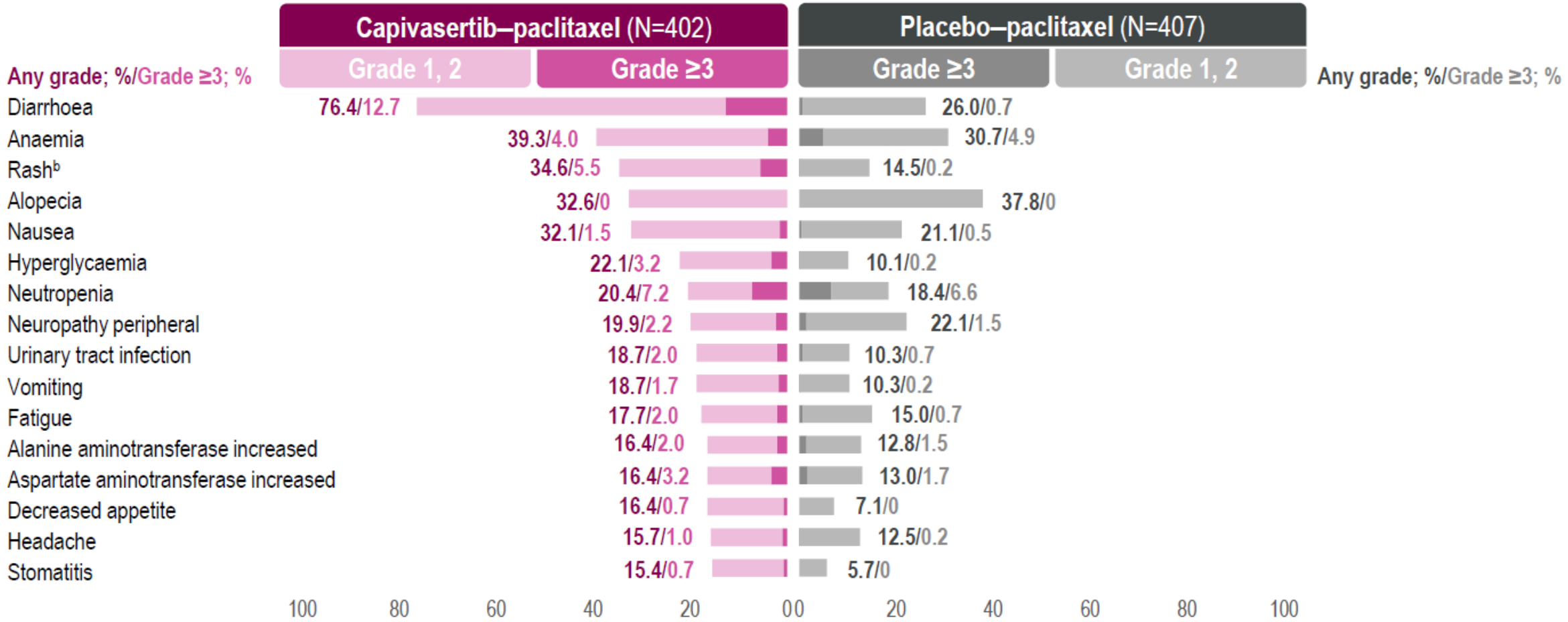
Capivasertib–paclitaxel	124	100	58	40	21	12	6	2	1	1	1	0
Placebo–paclitaxel	125	99	42	20	11	8	4	3	2	0	0	0

Exploratory analyses: Similar results favouring capivasertib–paclitaxel in patients with *PIK3CA/AKT1/PTEN*-non-altered tumours (n=563, hazard ratio 0.70 [95% CI 0.58–0.85]; patients with confirmed non-altered tumours [n=465], hazard ratio 0.77 [95% CI 0.62–0.95]).
Data cutoff: 25 May 2022 (DCO1). Tick marks indicate censored observations. Median (range) duration of follow-up in censored patients: Overall population: Capivasertib–paclitaxel: 5.6 (0.0–32.3) months, placebo–paclitaxel: 5.3 (0.0–26.8) months; *PIK3CA/AKT1/PTEN*-altered population: Capivasertib–paclitaxel: 8.9 (0.0–32.3) months, placebo–paclitaxel: 5.6 (0.0–26.8) months. Cox proportional hazards model stratified by (yes vs no): *PIK3CA/AKT1/PTEN*-altered (overall population only), visceral metastases, prior (neo)adjuvant chemotherapy.

CAPItello-290: Most frequent AEs (Safety population[a])

BARCELONA 2024 ESMO congress

Diarrhoea was the most frequent AE at any grade and Grade ≥3 in the capivasertib–paclitaxel group
The AE profile of capivasertib–paclitaxel was broadly consistent with the known profiles of the agents



Data cutoff: 18 March 2024 (DCO2). AEs occurring in ≥15.0% of patients in the capivasertib–paclitaxel group.

[a]The safety population comprised all patients who received at least one dose of study drug (paclitaxel, capivasertib, placebo). [b]Rash group term including the reported preferred terms of rash, rash macular, rash maculopapular, rash popular, rash pruritic, rash erythematous, dermatitis bullous and dermatitis exfoliative.

CAPItello-290: Conclusions

- CAPItello-290 was conducted in response to the positive data from the Phase 2 LOTUS[1,2] and PAKT[3,4] trials
- The dual primary endpoints of OS in the overall population and in patients with *PIK3CA/AKT1/PTEN*-altered tumours failed to meet the prespecified boundary for statistical significance
- In prespecified analyses, differences noted in the secondary endpoints of PFS and ORR numerically favoured capivasertib–paclitaxel over placebo–paclitaxel in the overall population and in patients with *PIK3CA/AKT1/PTEN*-altered tumours
- The safety profile of capivasertib–paclitaxel was broadly consistent with the known profiles of capivasertib and paclitaxel, with no new signals identified

CAPItello-290 did not meet the predefined threshold for improving OS in either the overall population or in patients with *PIK3CA/AKT1/PTEN*-altered tumours, although PFS numerically favoured first-line capivasertib–paclitaxel over placebo–paclitaxel in patients with mTNBC

Agenda

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

Future Directions, Challenges & Oppor

§ Many new agents in clinical development *(… D … n-02 Tropion-05…)*

§ Urgently need to understand optim … (…*TRADE-DXd trial*)

§ Need to diversify antib … nd payloads (…*Bispecific tumor-antigen, dual payloads, RNA inhibitor*

§As mor … clinical benefit, safety & tolerability will win the day

We need to keep seeking curative therapeutic strategies for mTNBC
While survival has improved, it is simply not good enough

GRAZIE!!