Breast Cancer: Updates, Advances, and New Treatment Options

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August 6, 2022

Disclosure of Conflicts of Interest

Antoinette R. Tan, MD, MHSc, FACP has the following financial relationships to disclose:

- Consultant: Astra-Zeneca, Genentech/Roche, Immunomedics, Novartis
- Grant Research Support: Daiichi-Sankyo, Merck, Pfizer

Outline

- Adjuvant therapy of high-risk, early-stage triple-negative breast cancer
- Treatment of metastatic triple-negative breast cancer
- New treatment option for metastatic HER2-low breast cancer

FDA Drug Approvals for Breast Cancer, 2021-2022

- 4/7/21: Sacituzumab govitecan for metastatic TNBC who have received 2 or more prior systemic therapies, at least one of them for metastatic disease

- 7/6/21: Pembrolizumab for high-risk, early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery

- 10/12/21: Abemaciclib with endocrine therapy (tamoxifen or an aromatase inhibitor) for adjuvant treatment with HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%

FDA Drug Approvals for Breast Cancer, 2021-2022

- 3/11/22: Olaparib for adjuvant treatment of germline BRCA-mutated HER2-negative high-risk, early breast cancer treated with neoadjuvant or adjuvant chemotherapy

- 5/4/22: Fam-trastuzumab deruxtecan for metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy

Changing Landscape in Breast Cancer Therapy

- Breast cancer treatment has undergone major breakthroughs
- Chemotherapy has been the mainstay for treatment of triple-negative breast cancer
- The results of recent clinical trials show the benefit of combining chemotherapy and immunotherapy in both the early stage and advanced setting for triple-negative breast cancer
- Targeted therapies i.e. PARP inhibitors, demonstrate significant clinical benefit for BRCA-mutated, HER2-negative breast cancer
- HER2-low is now a targetable subset of breast cancer

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Triple-Negative Breast Cancer (TNBC)

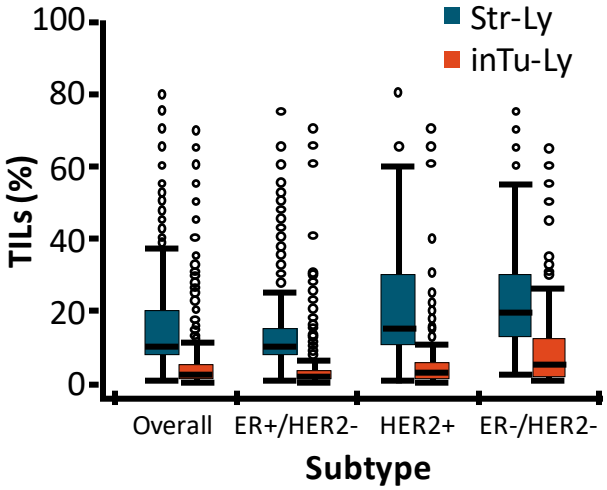
- TNBC accounts for 15%-20% of breast cancers
- At diagnosis
  - Majority of tumors are grade 3 and highly proliferative
  - Majority are diagnosed at Stage II or Stage III
- Associated with early recurrences
- Neoadjuvant chemotherapy (NAC) is the current SOC treatment approach for early-stage disease
- Patients who experience pCR following NAC have longer EFS and OS; however increased risk for disease recurrence and death remains
- High unmet need for novel therapies that can augment effectiveness of chemotherapy
- Strong rationale for combination of immunotherapy and chemotherapy in TNBC

Amedos M, et al. Ther Adv Med Oncol 2012; 4: 195-210; Cortazar P, et al. Lancet 2014; 384:164-72

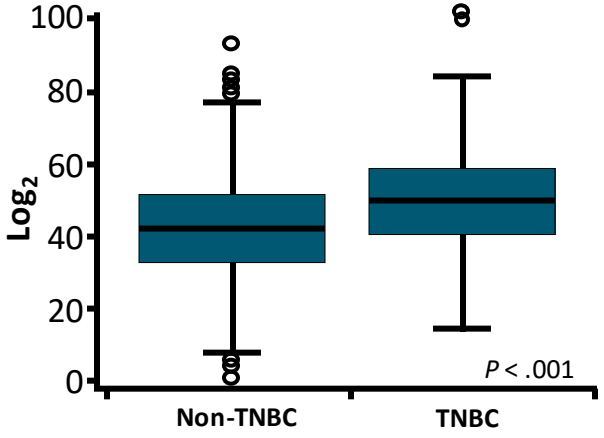
Courtesy of P Schmid, ESMO Virtual Plenary 2021

Immune Checkpoint Inhibition in TNBC: Rationale

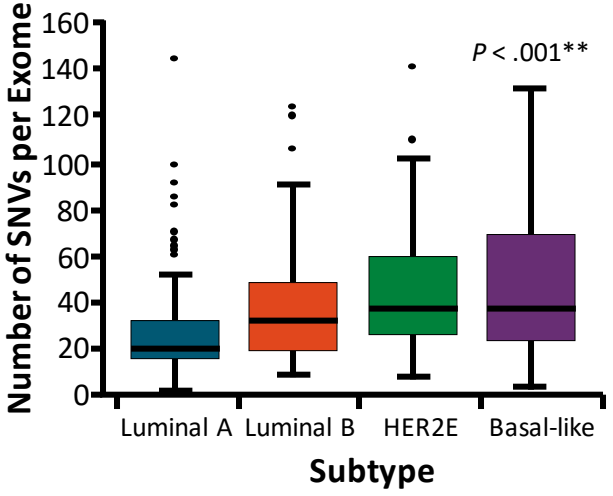
Tumor-Infiltrating Lymphocytes[1]



PD-L1 Expression[2]



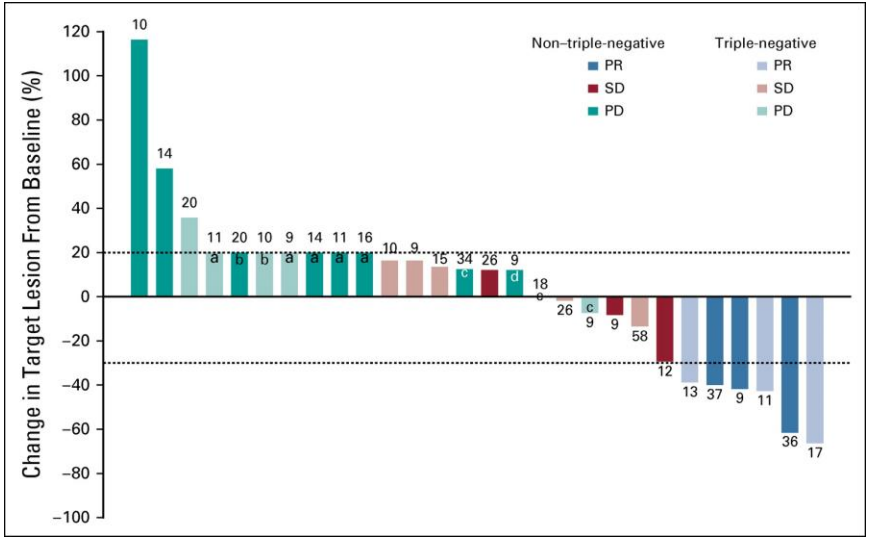
Nonsynonymous Mutations[3]



1. Loi S, et al. J Clin Oncol 2013;31:860-7 2. Mittendorf E, et al. Cancer Immunol Res 2014;2:361-70 3. Luen S, et al. Breast 2016;29:241-50

Pembrolizumab in Metastatic Breast Cancer with High TMB (ASCO Tapur Study)

- 10% of metastatic breast cancer with high TMB
- High TMB defined as ≥ 9 Mut/Mb
- Overall response rate was 21%
- Disease control rate of 37% (10/28)
- Median PFS was 10.6 weeks
- Median OS was 30.6 weeks



Alva A, et al. J Clin Oncol 2021;39: 2442-2451

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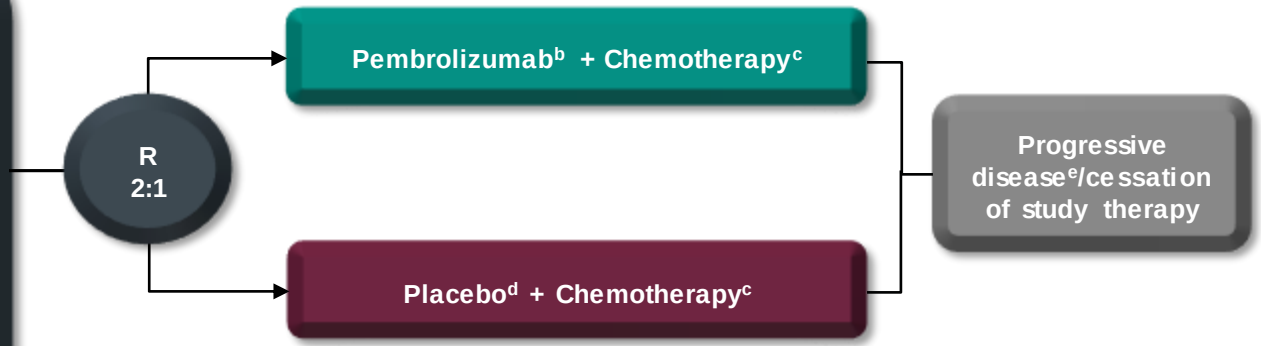
Pembrolizumab in Triple-Negative Breast Cancer

- Pembrolizumab monotherapy showed durable antitumor activity and manageable safety in metastatic TNBC[1-4]
  - Improved clinical responses in patients with higher PD-L1 expression[4]
  - Responses to pembrolizumab more durable than those to chemotherapy[4]
- Pembrolizumab plus chemotherapy showed promising antitumor activity and manageable safety in early TNBC[5-8]
  - Statistically significant and clinically meaningful improvement in EFS with neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab versus chemotherapy alone in KEYNOTE-522[7,8]
- Prior analyses from KEYNOTE-355[9] showed that the addition of pembrolizumab to chemotherapy resulted in a statistically significant and clinically meaningful improvement in PFS versus chemotherapy alone for the first-line treatment of PD-L1–positive (CPS ≥10) metastatic TNBC
- Based on the PFS results from KEYNOTE-355[9], pembrolizumab plus chemotherapy was approved by the US FDA for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10)

1. Nanda R et al. J Clin Oncol 2016;34:2460-7. 2. Adams S et al. Ann Oncol 2019;30:397-404. 3. Adams S et al. Ann Oncol 2019;30:405-11. 4. Cortes J et al. Ann Oncol 2019; 30(suppl 5):v851-v934. 5. Schmid P et al. Ann Oncol 2020;31:569-81. 6. Nanda R et al. JAMA Oncol 2020; 6:676-84. 7. Schmid P et al. N Engl J Med 2020;382:810-21 8.Schmid P et al ESMO Virtual Plenary, July 15-16, 2021. 9. Cortes J et al. Lancet 2020;396:1817-28

KEYNOTE-355 Study Design (NCT02819518)

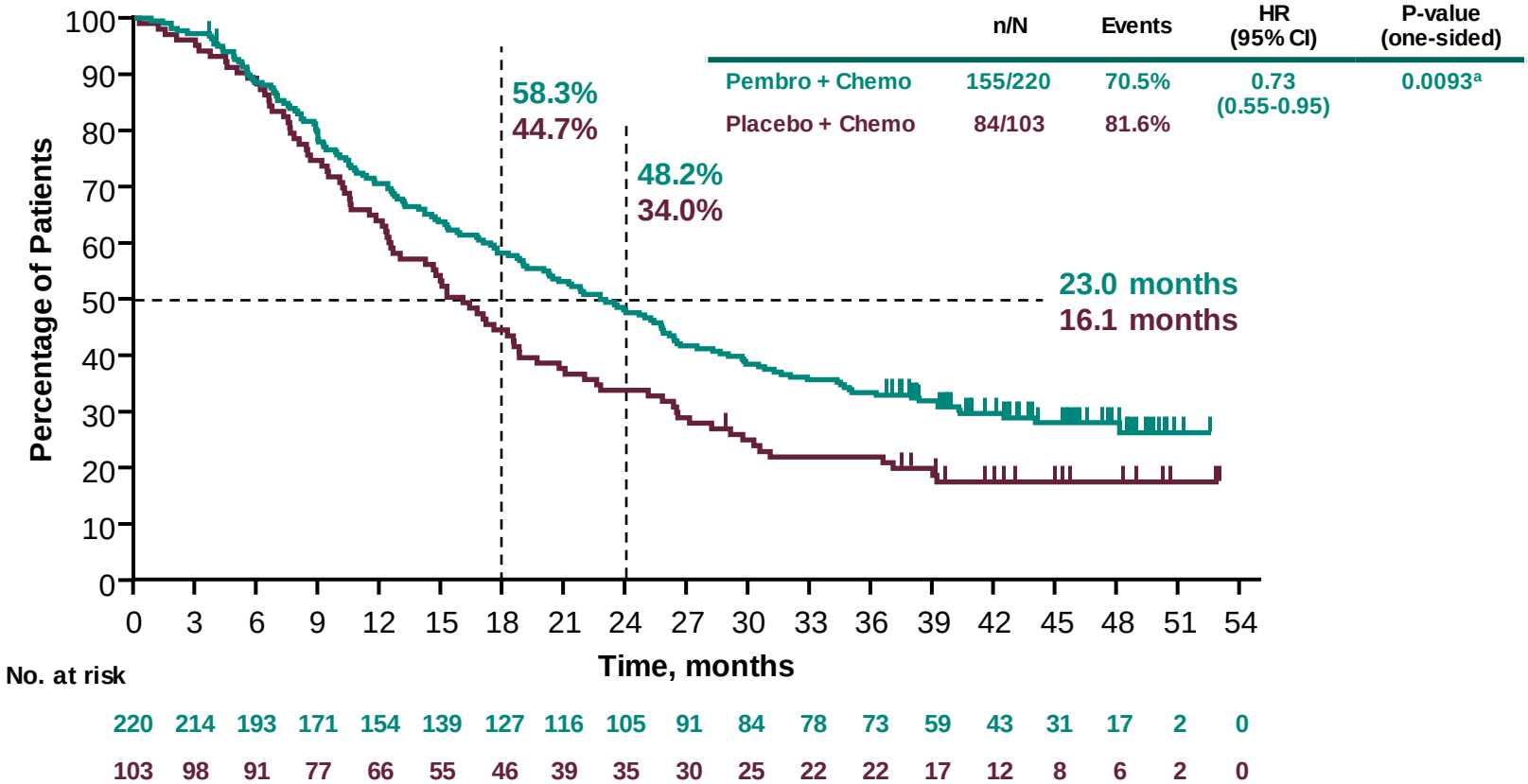
Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression[a]
- Previously untreated locally recurrent inoperable or metastatic TNBC
- De novo metastasis or completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease



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

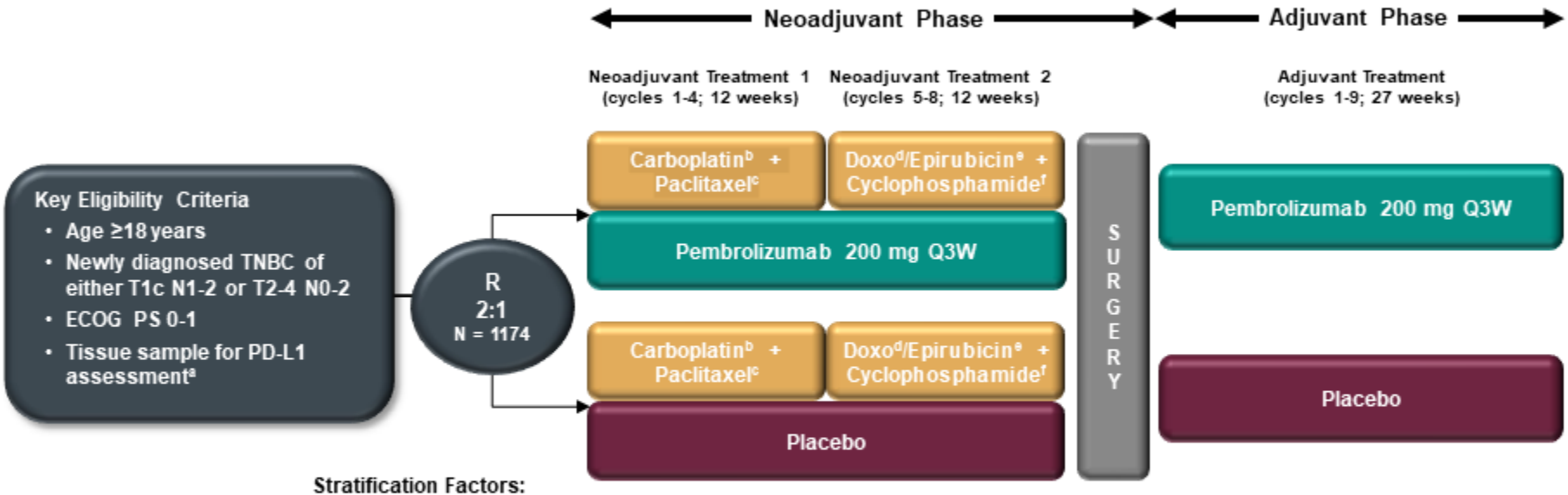
[a]Based on a newly obtained tumor sample from a locally recurrent inoperable or metastatic site (an archival tumour sample was used with permission from the study sponsor if a new tumor biopsy was not obtainable). [b]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W). [c]Chemotherapy dosing regimens 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. [d]Normal saline. [e]Treatment may be continued until confirmation of progressive disease.

Overall Survival: PD-L1 CPS ≥10



[a]Prespecified *P* value boundary of 0.0113 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m² QW.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

Baseline Characteristics, ITT Population

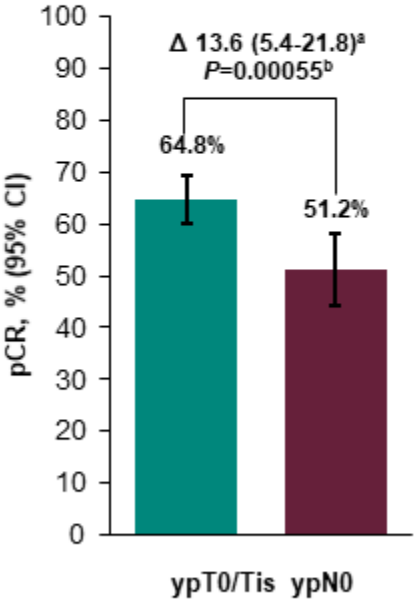
Characteristic, n (%)	All Subjects, N = 1174	
	Pembro + Chemo N = 784	Pbo + Chemo N = 390
Age, median (range), yrs	49 (22-80)	48 (24-79)
ECOG PS 1	106 (13.5)	49 (12.6)
PD-L1–positive[a]	656 (83.7)	317 (81.3)
Carboplatin schedule		
QW	449 (57.3)	223 (57.2)
Q3W	335 (42.7)	167 (42.8)
Tumor size		
T1/T2	580 (74.0)	290 (74.4)
T3/T4	204 (26.0)	100 (25.6)
Nodal involvement		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)

[a]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Data cutoff date: March 23, 2021.

Prior Analyses of KEYNOTE-522

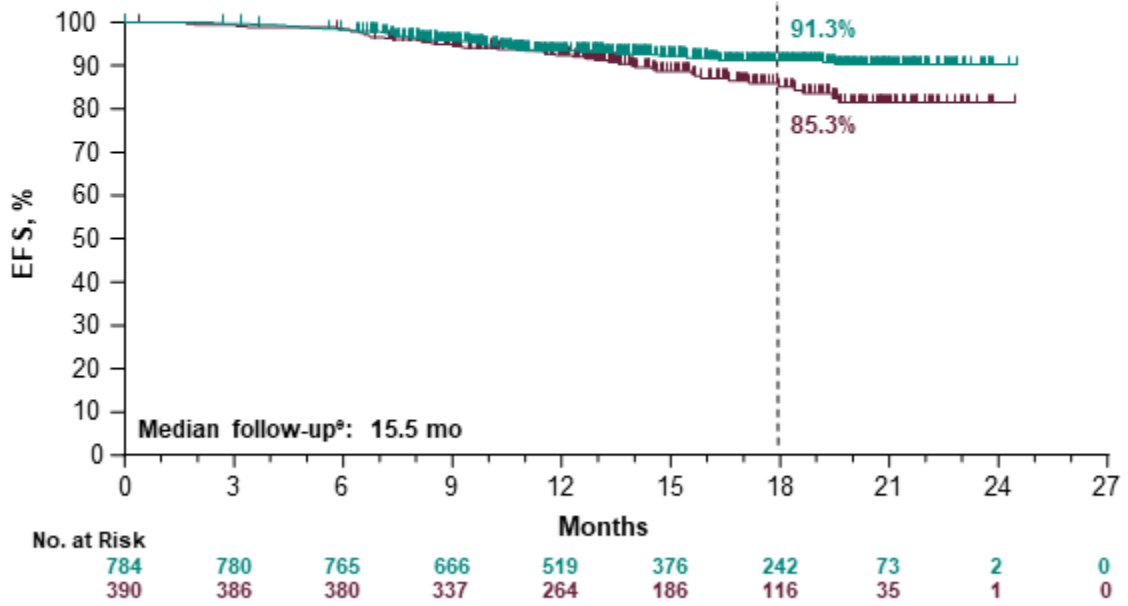
Primary pCR Endpoint at IA1[1]

Pembro + Chemo (N = 401)
Pbo + Chemo (N = 201)



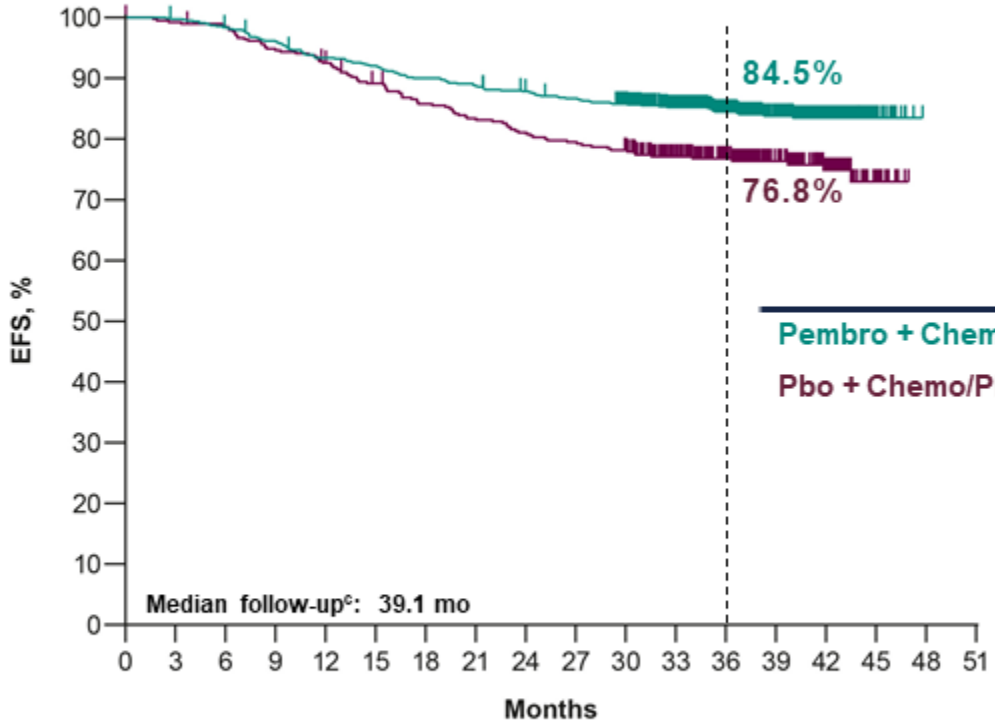
First EFS Analysis at IA2[1]

	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	7.4%	0.63[c] (0.43-0.93)	0.0089[d]
Pbo + Chemo/Pbo	11.8%		



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]Prespecified *P*-value boundary for significance of 0.003 was crossed; data cutoff date: September 24, 2018. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary for significance of 0.000051 not reached at this analysis. [e]Defined as the time from randomization to the date of death or data cutoff date of April 24, 2019, if the patient was alive. 1. Schmid P, et al. *N Engl J Med* 2020;382:810-21.

Statistically Significant and Clinically Meaningful EFS at IA4



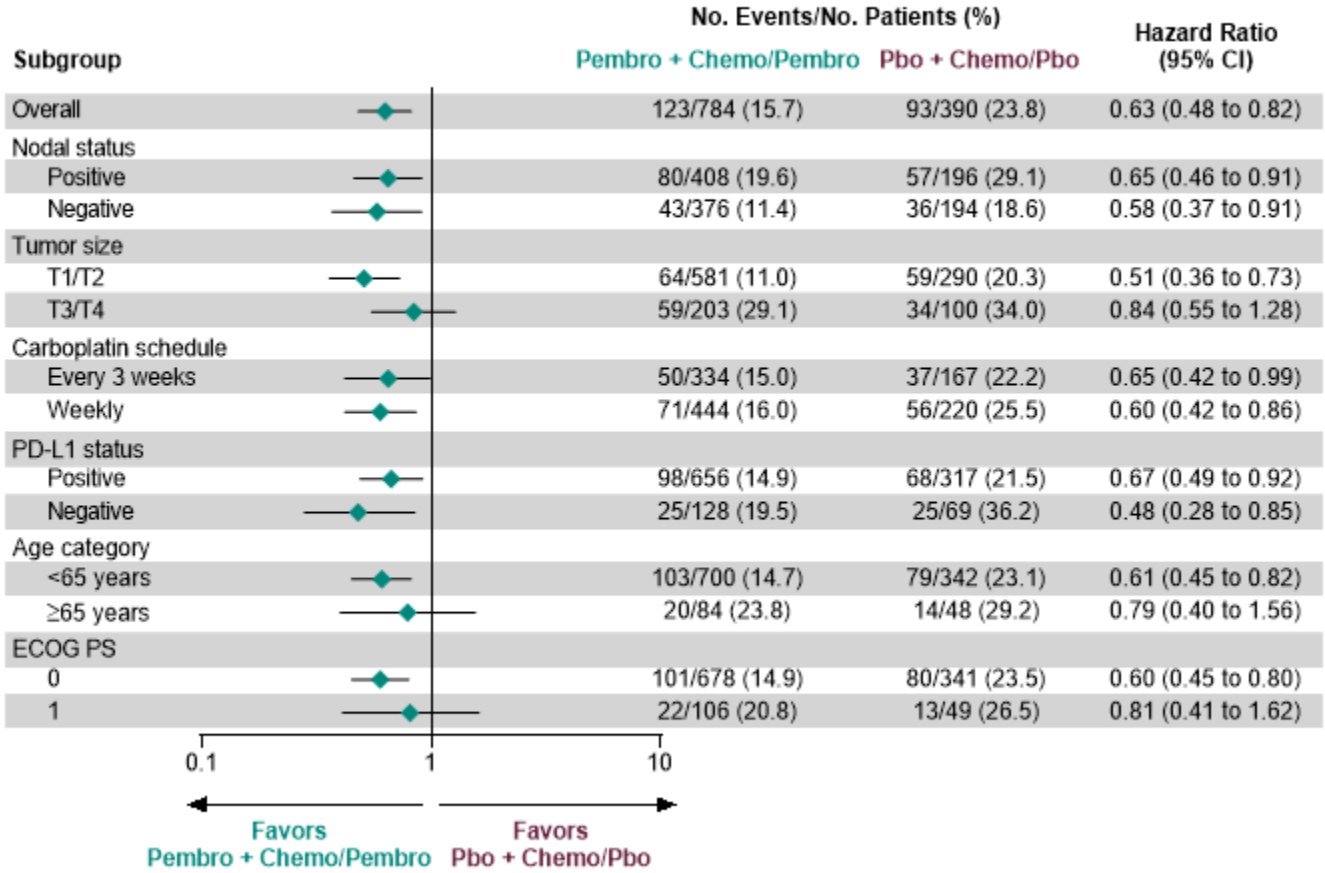
	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

No. at Risk

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

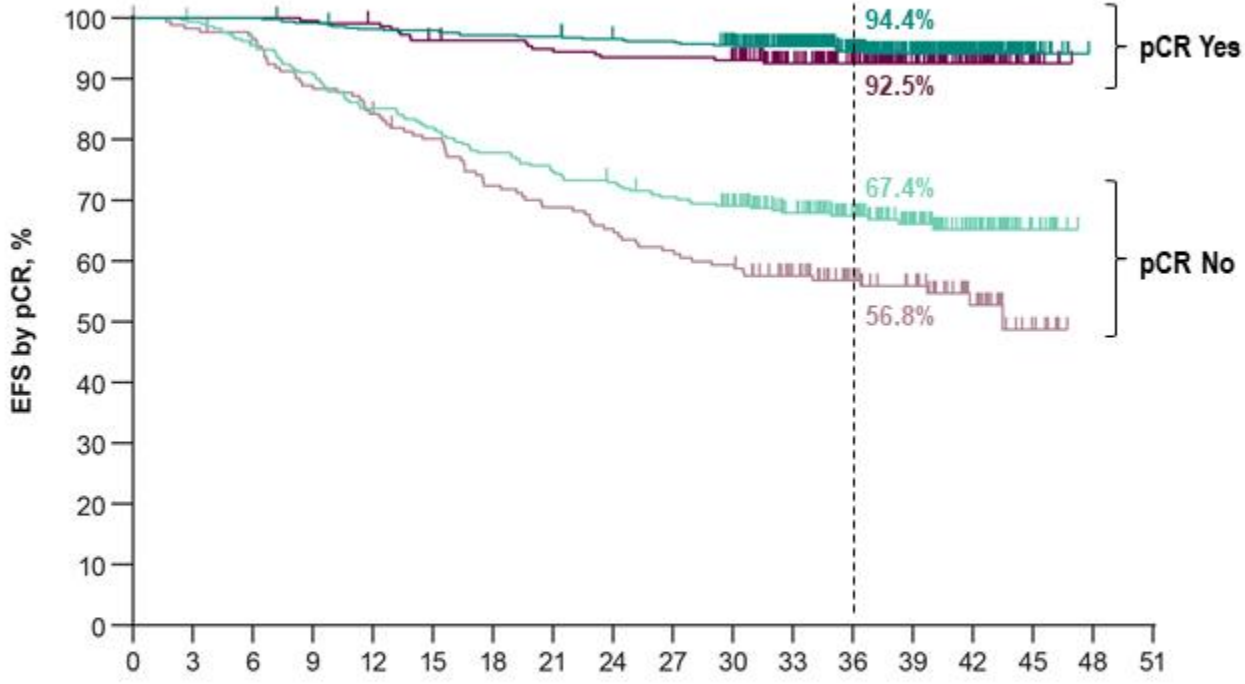
[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00517 reached at this analysis.
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

EFS in Patient Subgroups



For overall population and PD-L1 subgroups, analyses based on Cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4), and frequency of carboplatin (once weekly vs once every 3 weeks); for other subgroups, analysis based on unstratified Cox model. Data cutoff date: March 23, 2021.

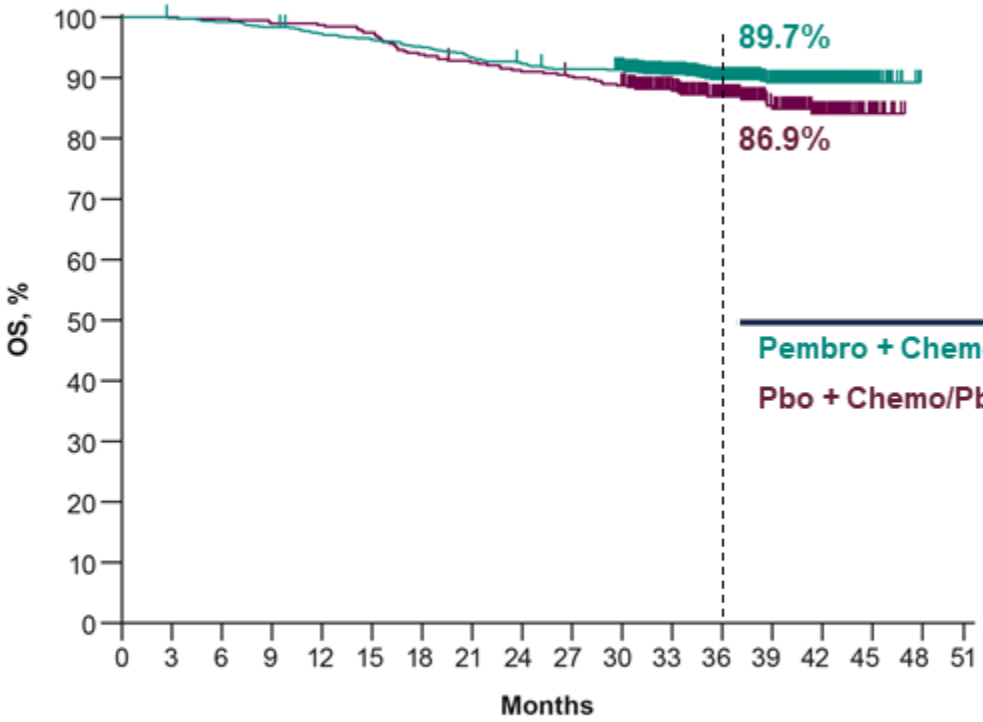
EFS by pCR (ypT0/Tis ypN0)



No. at Risk																		
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Data cutoff date: March 23, 2021.

Overall Survival



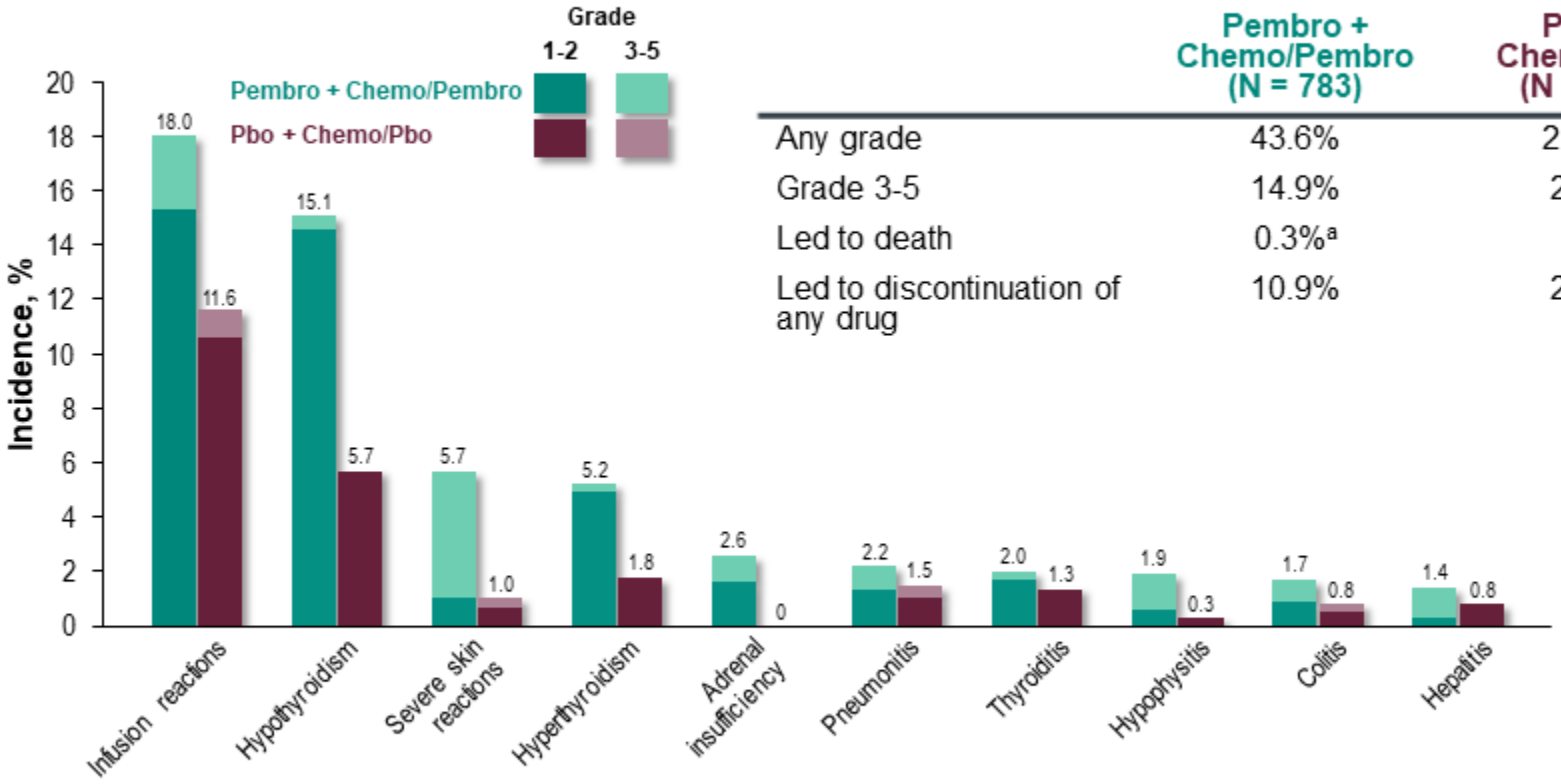
	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	10.2%	0.72[a] (0.51-1.02)	0.03214[b]
Pbo + Chemo/Pbo	14.1%		

No. at Risk

Pembro + Chemo/Pembro	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Pbo + Chemo/Pbo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00086 not reached at this analysis.
Data cutoff date: March 23, 2021.

Immune-Mediated AEs and Infusion Reactions in Combined Phases



	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

[a]1 patient from pneumonitis and 1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: March 23, 2021.

KEYNOTE-522 Questions

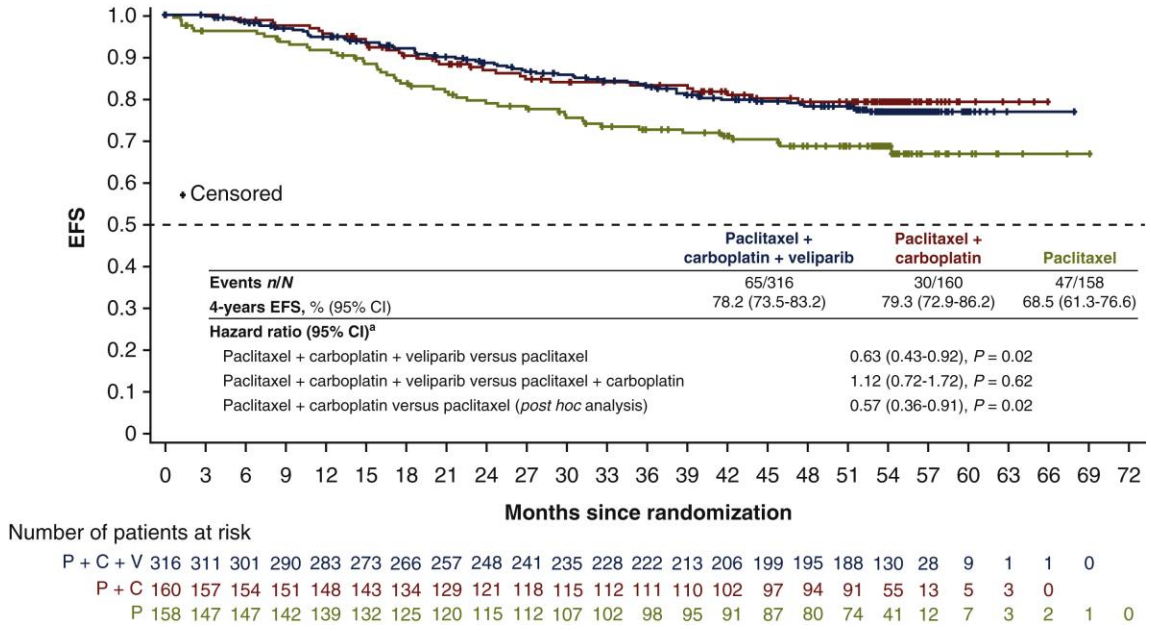
- Four agent chemotherapy backbone: needed for all?
  - Role of carboplatin as part of NAC

- Adjuvant therapy for residual disease
  - Capecitabine and pembrolizumab?
  - Phase II trial in MBC, n = 30 : Grade 3 or higher adverse events occurring in at least 10% of patients were an elevation in alkaline phosphatase, hand-foot syndrome, anemia and lymphopenia. Adverse events similar to capecitabine monotherapy

- Pembrolizumab maintenance in pCR

Shah A, et al. J Immunother Cancer 2020; 8:e000173

BrighTNess Phase III Trial: Adding Carboplatin with or without Veliparib to NAC in TNBC



Improvement in pCR with the addition of carboplatin was associated with long-term EFS benefit with a manageable safety profile; adding veliparib did not impact EFS.

Geyer CE, et al. Ann Oncol 2022; 33:384-394

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Maintenance Question

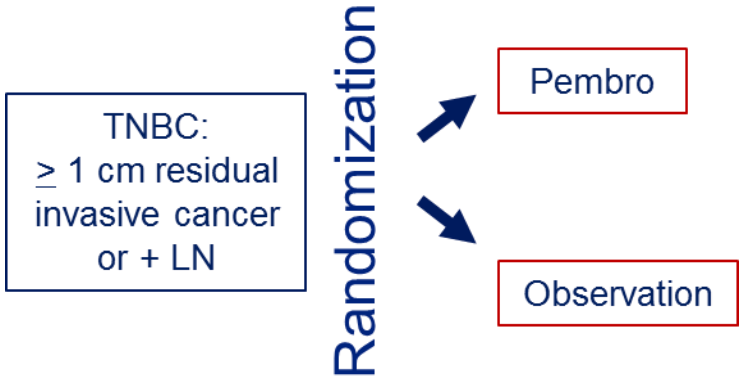
- KN-522 subjects completed 1 year of pembrolizumab regardless of pathologic response
- Excellent outcomes for pCR in pembrolizumab/control arm
- Trials to address pembrolizumab maintenance question are needed

Residual Disease After NAC: Role of Checkpoint Inhibitor

Adjuvant checkpoint inhibitor trials

Trial	N	Intervention
A-BRAVE	335	Avelumab x 1 yr vs. observation
IMPASSION030	2300	Weekly paclitaxel, DDAC (or EC) +/- atezolizumab x 1 yr

SWOG S1418: Residual disease



Primary Endpoint: IDFS Overall and PD-L1+

Adams S, et al. JAMA Oncol 2019; 5: 1205-1214

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Other Practical Considerations

- Every 2-weeks AC (Dose-dense) vs every 3 weeks AC and reverse sequence
- Adjuvant radiation therapy concomitant with pembrolizumab vs sequential radiotherapy with adjuvant pembrolizumab
- Administering pembrolizumab every 6 weeks
- Monitor blood cortisol at baseline, prior to surgery, and as clinically indicated

AC, doxorubicin and cyclophosphamide

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PARP Inhibitor Trials in BRCA-Mutated Metastatic Breast Cancer: OlympiAD

Patient Population

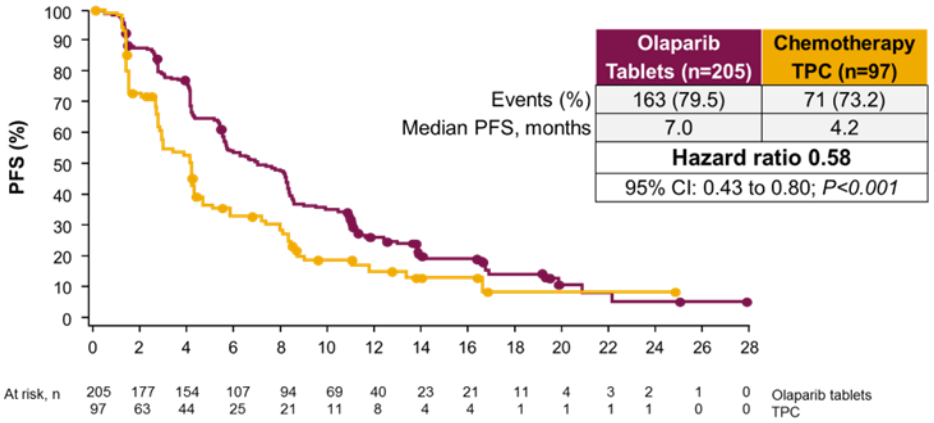
- HER2– MBC
  - ER+ and/or PR+ or
  - TNBC
- Deleterious or suspected deleterious g*BRCA*m
- ≤2 prior chemotherapy lines in metastatic setting
- Prior anthracycline and taxane
- HR+ patients who have progressed on ≥1 endocrine therapy, or not suitable
- If patients had received platinum
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

Randomized 2:1 (N=302)

- **Olaparib tablets 300 mg BID**
- **Chemotherapy TPC**
  - Capecitabine
  - Eribulin
  - Vinorelbine

Treat until progression

Primary Endpoint	Secondary Endpoints
PFS (RECIST 1.1, BICR)	• OS • Time to second progression or death • ORR • Global HRQoL (EORTC-QLQ-C30) • Safety and tolerability



	Olaparib Tablets (n=205)	Chemotherapy TPC (n=97)
Events (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
Hazard ratio 0.58		
95% CI: 0.43 to 0.80; *P<0.001*		

Robson M, et al N Engl J Med 2017;377:523-533

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PARP Inhibitor Trials in BRCA-Mutated Metastatic Breast Cancer: EMBRACA

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†

Stratification factors:

- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

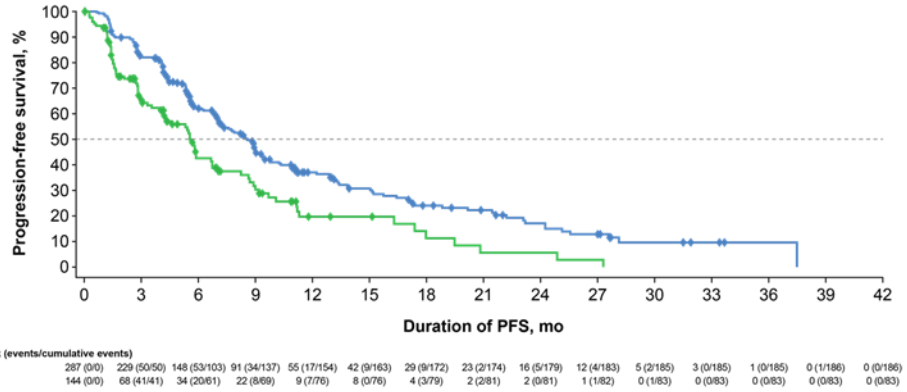
R 2:1

Talazoparib
1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

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

Phase 3, international, open-label study randomized 431 patients in 16 countries and 145 sites



Litton JK, et al N Engl J Med. 2018;379:753-763

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OlympiA Study Rationale and Background

- There is evidence that inhibition and trapping of PARP1 on DNA results in synthetic lethality with loss of function of BRCA1 and BRCA2 proteins and homologous recombination DNA repair

- Stage II/III *BRCA1/2* mutation associated breast cancers require chemotherapy with or without endocrine therapy but can have significant residual risk of recurrence despite multi-agent chemotherapy

- The PARP1 inhibitor olaparib had demonstrated high response rates in proof of concept studies, now with FDA approvals based on progression free survival in *BRCA1/2* associated breast, ovarian, prostate, and pancreatic cancer

- The role of olaparib as an adjuvant therapy in any gBRCAm malignancy is untested and OlympiA sought to examine this in high recurrence risk early breast cancer

Fong PC, et al. N Engl J Med 2009;361:123-34; Tutt A, et al. Lancet 2010; 376:235-44; Audeh WM, et al. Lancet 2010; 376:245-51; Robson M, et al. N Engl J Med 2017; 377:523-533; Moore K, et al. N Engl J Med 2018; 379: 2495-2505; Golan T, et al. N Engl J Med 2019; 381:317-327; Hussain M, et al. N Engl J Med 2020; 383:2345-2357

OLYMPIA: TRIAL SCHEMA

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III breast cancer or lack of PathCR to NACT

Neoadjuvant group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant chemotherapy → **Surgery** → **+/- Radiotherapy**

Adjuvant group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → **≥ 6 cycles Adjuvant chemotherapy** → **+/- Radiotherapy**

Olaparib
300 mg twice daily for 1 year

1:1 randomisation
N = 1836

Placebo
twice daily for 1 year

Presented at ASCO 2021
Presented at SABCS 2021
Primary endpoint
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary endpoints
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health-related QoL
- Safety

Stratification factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent adjuvant therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd adjuvant chemotherapy

Hormone receptor-positive defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

OLYMPIA: PATIENT CHARACTERISTICS

	Olaparib (N = 921)	Placebo (N = 915)
Age, years, median (interquartile range)	**42** (36–49)	**43** (36–50)
BRCA gene affected in germline		
BRCA1	657 (**71.3%**)	670 (**73.2%**)
BRCA2	261 (**28.3%**)	239 (**26.1%**)
BRCA1 and *BRCA2*	2 (0.2%)	5 (0.5%)
BRCA testing available		
Local and central BRCA result*	590 (**64.1%**)	585 (**63.9%**)
Local testing only	90 (9.8%)	96 (10.5%)
Central Myriad testing only	240 (26.1%)	234 (25.6%)
No local or central Myriad testing available	1 (0.1%)	0 (0.0%)
Primary breast cancer surgery		
Mastectomy	698 (**75.8%**)	673 (**73.6%**)
Conservative surgery only	223 (24.2%)	240 (26.2%)
Missing	0 (0.0%)	2 (0.2%)

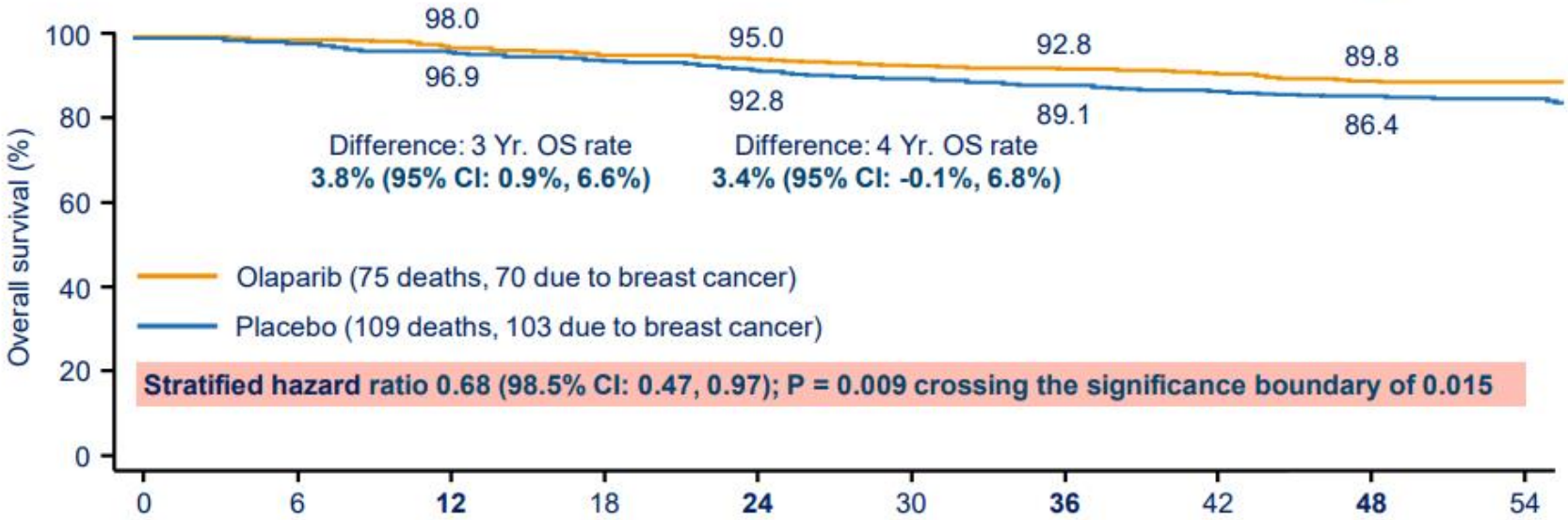
*Local/Central discordant results: Olaparib 13 (2.2%), Placebo 10 (1.7%), Total 23 (2.0%)

OLYMPIA: PATIENT CHARACTERISTICS

	Olaparib (N = 921)	Placebo (N = 915)
Hormone receptor status*		
ER and/or PgR positive ≥ 1% / HER2-negative†	168 (**18.2%**)	157 (**17.2%**)
Triple negative breast cancer‡	751 (**81.5%**)	758 (**82.8%**)
Menopausal status (female only)		
Premenopausal	572/919 (62.2%)	553/911 (60.7%)
Postmenopausal	347/919 (37.8%)	358/911 (39.3%)
Prior chemotherapy		
Adjuvant (ACT)	461 (**50.1%**)	455 (**49.7%**)
Neoadjuvant (NACT)	460 (**49.9%**)	460 (**50.3%**)
Anthracycline and taxane regimen	871 (**94.6%**)	849 (**92.8%**)
Neo(adjuvant) platinum-based therapy	247 (**26.8%**)	238 (**26.0%**)
Concurrent endocrine therapy (ER and/or PgR positive only)	146/168 (86.9%)	146/157 (93.0%)

*Defined by local test results
†Following a protocol amendment in 2015, the first patient with hormone receptor–positive disease was enrolled in December 2015
‡Two patients are excluded from the summary of the triple negative breast cancer subset because they do not have confirmed HER2–negative status

SECOND OVERALL SURVIVAL INTERIM ANALYSIS - OS IA 2 (ITT)

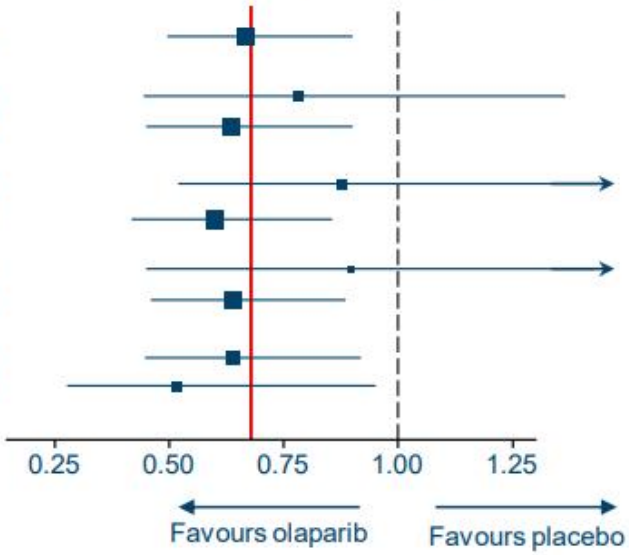


No. at risk										
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

98.5% confidence intervals are shown for the hazard ratio because P < 0.015 is required for statistical significance

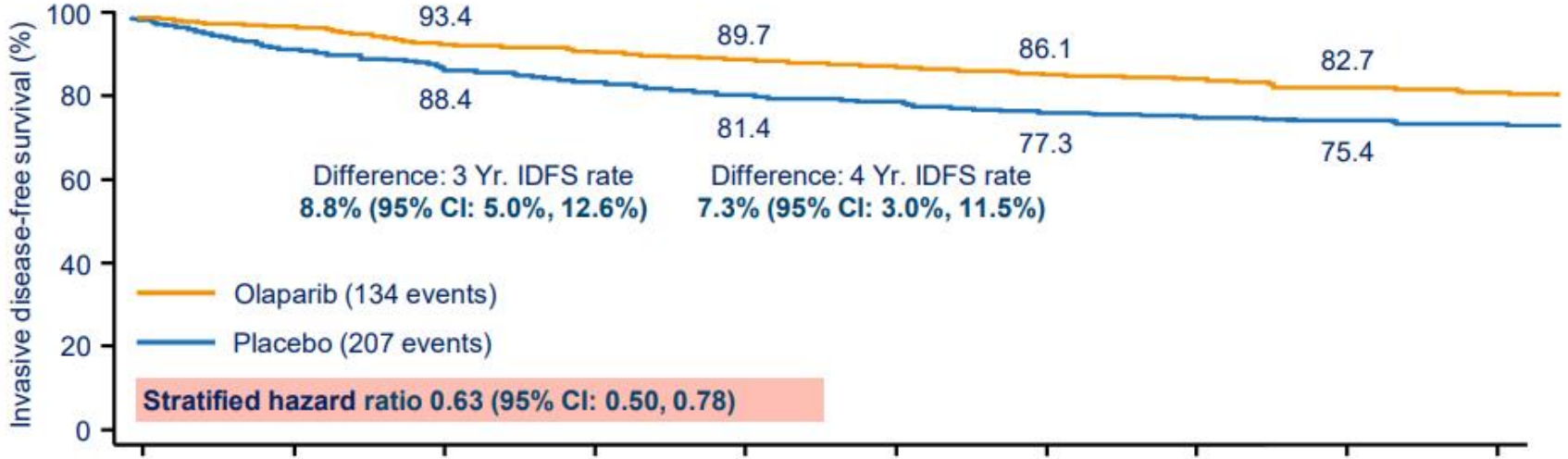
SUBGROUP ANALYSIS OF OS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)	P value for heterogeneity
	No. of patients who died /total no.			
All patients	75 / 921	109 / 915	0.678 (0.503, 0.907)	NA
Prior chemo				0.543
Adjuvant	22 / 461	28 / 455	0.783 (0.444, 1.365)	
Neoadjuvant	53 / 460	81 / 460	0.638 (0.449, 0.900)	
Prior platinum				0.236
Yes	27 / 247	29 / 238	0.882 (0.520, 1.491)	
No	48 / 674	80 / 677	0.601 (0.417, 0.855)	
HR status				0.381
HR+/HER2-	16 / 168	17 / 157	0.897 (0.449, 1.784)	
TNBC	59 / 751	92 / 758	0.640 (0.459, 0.884)	
BRCA				0.845
BRCA1	49 / 579	75 / 588	0.643 (0.446, 0.918)	
BRCA2	16 / 235	28 / 216	0.521 (0.276, 0.951)	
BRCA1/2 both	0 / 2	0 / 3	NC	



All subgroup hazard ratio point estimates are < 1 and confidence intervals include the hazard ratio for olaparib treatment effect in the overall ITT population

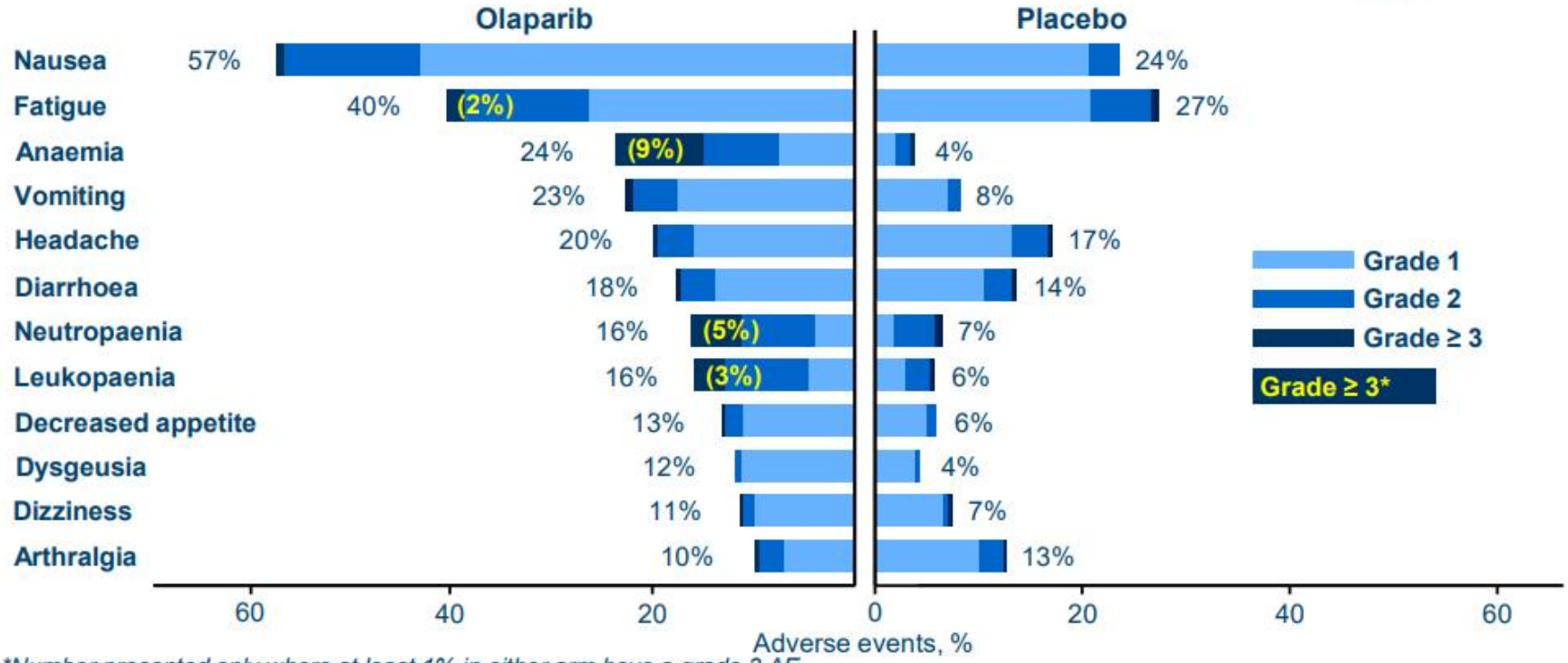
ANALYSIS OF IDFS (ITT) AT OS IA2



No. at risk

Olaparib	921	825	777	738	694	603	495	382	293	204
Placebo	915	807	765	715	656	571	459	370	293	187

ADVERSE EVENTS OF ANY GRADE ≥ 10%



*Number presented only where at least 1% in either arm have a grade 3 AE

OlympiA Questions

- TNBC with residual disease
  - Capecitabine or olaparib or sequence?
    - OlympiAD data would support adjuvant olaparib over capecitabine; olaparib “outperformed” in terms of ORR vs treatment of physician’s choice (59.9% vs 28.8%)
  - Combine pembrolizumab with olaparib?

- HR+ Eligible Patients
  - Calculate CPS + EG score
  - Abemaciclib or olaparib or sequence?

CPS (clinical and post-treatment pathological stage) +EG (estrogen receptor status and grade)

Atrium Health

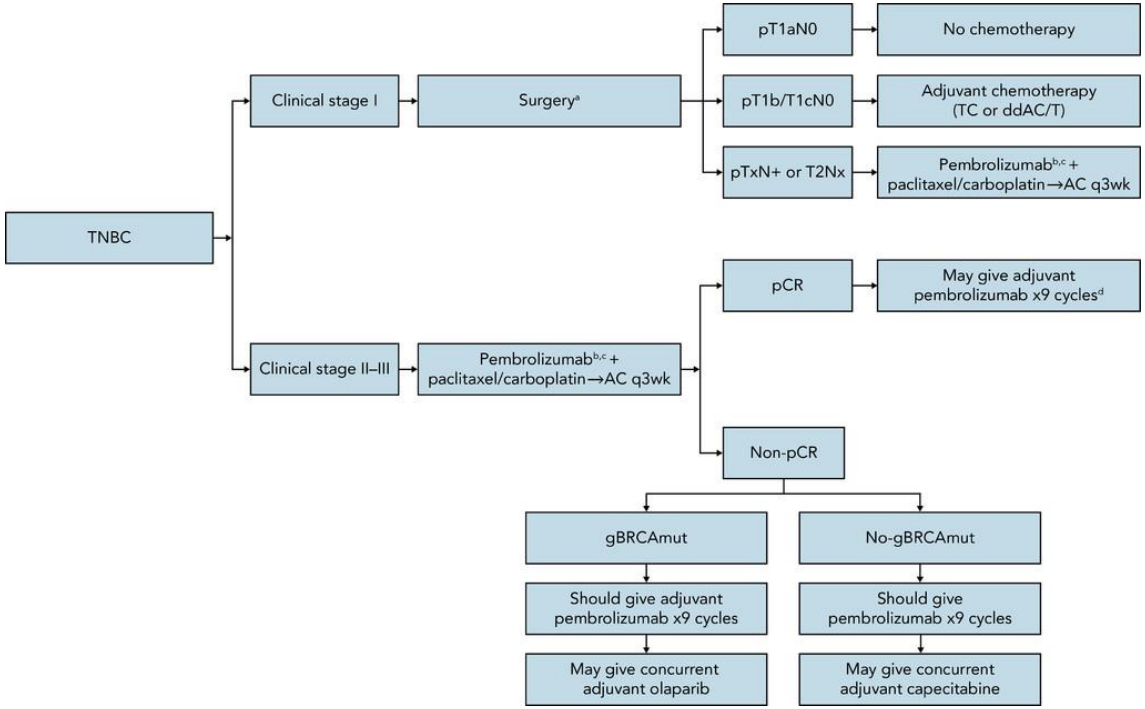
PARP Inhibition and Checkpoint Blockade in Metastatic Breast Cancer

Trial	BRCA1/2 mutation	Drugs	Selection	N	ORR	DCR
MEDIOLA	Germline	Olaparib and durvalumab	Max of 2 lines of chemotherapy	30	63% 1 CR, 18 PRs	50% at 28 weeks
TOPACIO	Germline	Niraparib and pembrolizumab	Max of 2 lines of chemotherapy	47	21% 5 CRs, 5 PRs	49%

MEDIOLA trial: Grade ≥ 3 AEs were anemia (12%), neutropenia (9%), and pancreatitis (6%)
TOPACIO trial: Grade ≥ 3 AEs were anemia (18%), thrombocytopenia (15%), and fatigue (7%); grade ≥3 immune-related AEs was 4%; no new safety signals reported

Domchek SM, et al. Lancet Oncol. 2020;21:1155-1164; Vinayak S, et al. JAMA Oncol. 2019;5:1132-1140

Practical Guidance in Integrating Chemoimmunotherapy in Early-Stage TNBC



Santa-Maria CA, et al. J Natl Compr Canc Netw 2022: 20: 738-744

Atrium Health

Treatment of Metastatic Triple-Negative Breast Cancer – What to Know in 2022

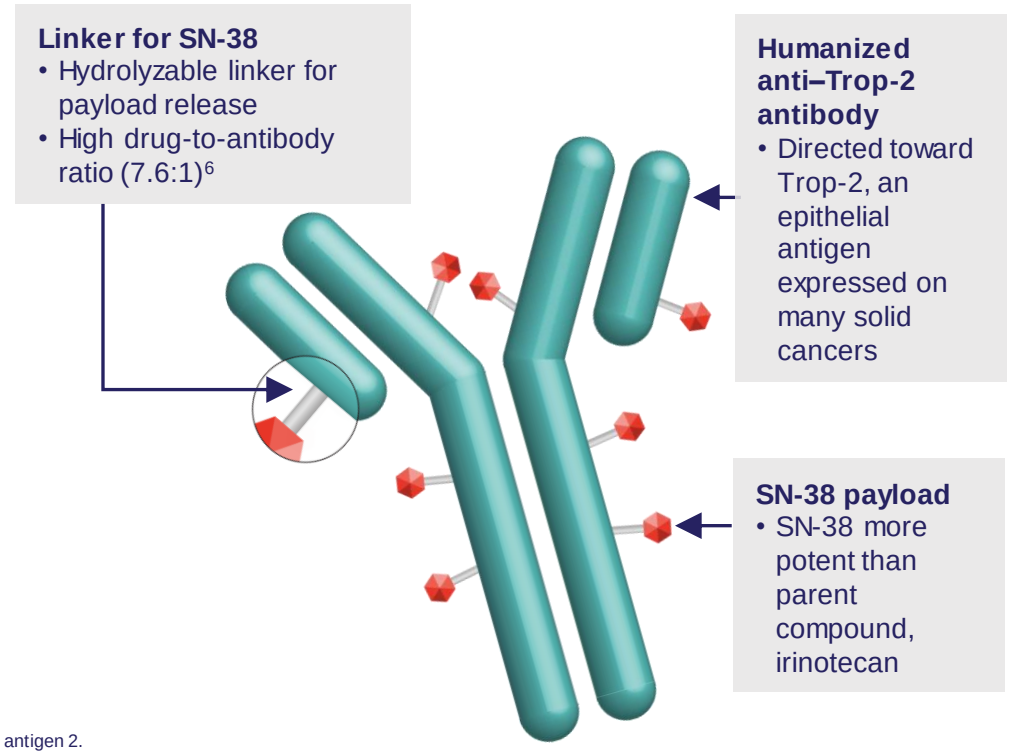
- *BRCA1/2* germline sequencing
- PD-L1 expression
  - 22C3 PharmDX assay scored by CPS ≥ 10 (Combined Positive Score)
- Other molecularly targeted aberrations
  - NTRK fusion positive (<1% of MBC)
  - TMB-High (<10% of TNBC)
  - MSI-H, dMMR (<2% of TNBC)

NTRK, Neurotrophic Tyrosine Receptor Kinase; TMB, Tumor mutational burden-high; MSI-H, Microsatellite instability-high; dMMR, mismatch repair deficient

Atrium Health

Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed ADC

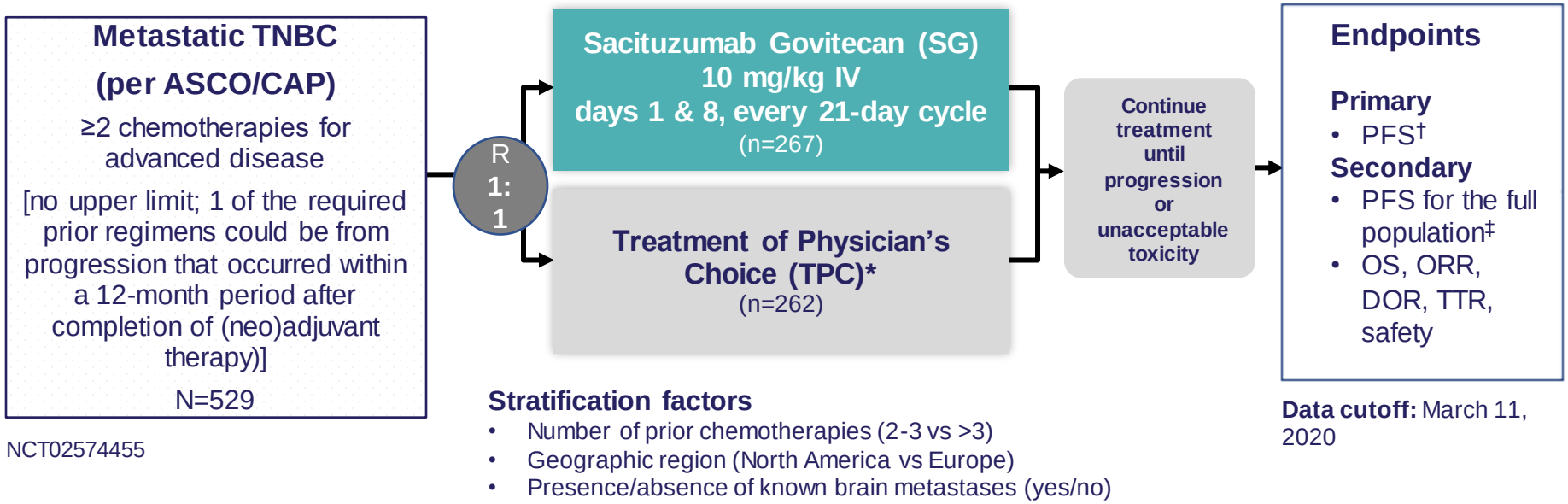
- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and fast-track designation in metastatic urothelial cancer[7]



ADC, antibody–drug conjugate; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Vidula N et al. *J Clin Oncol.* 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One.* 2014;9(5):e96993. 3. Goldenberg DM et al. *Expert Opin Biol Ther*. 2020 Aug;20(8):871-885. 4. Nagay ama A et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 5. Cardillo TM et al. *Bioconjugate Chem* 2015;26:919-931. 6. Goldenberg DM et al. *Oncotarget*. 2015;6:22496-224512. 7. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020.

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



NCT02574455

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

Data cutoff: March 11, 2020

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †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 full 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; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

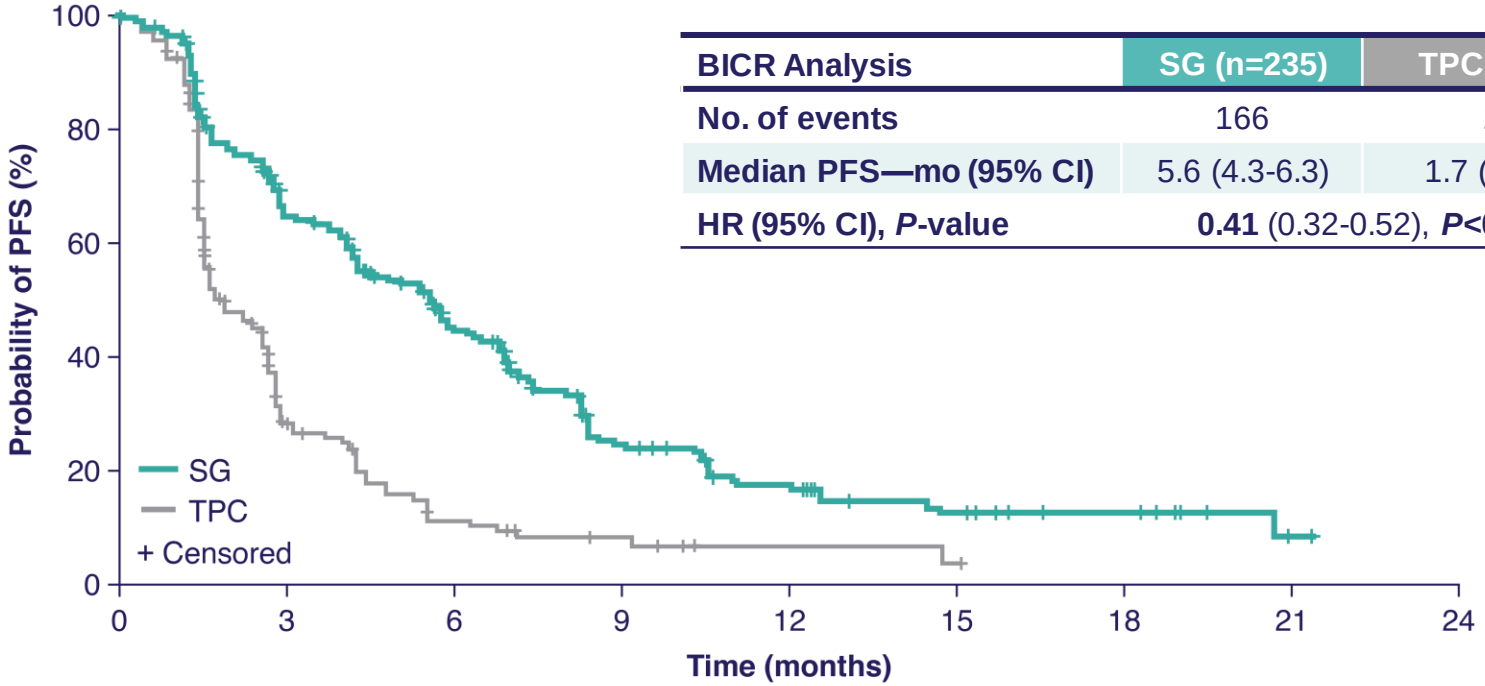
Demographics and Patient Characteristics

	SG (n=235)	TPC (n=233)
Female—no. (%)	233 (99)	233 (100)
Median age—yr (range)	54 (29-82)	53 (27-81)
Race or ethnic group—no. (%)		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG PS—no. (%)		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
BRCA 1/2 mutational status—no. (%)		
Positive	16 (7)	18 (8)
Negative	133 (57)	125 (54)
Unknown	86 (37)	90 (39)
TNBC at initial diagnosis*		
Yes	165 (70)	157 (67)
No	70 (30)	76 (33)

	SG (n=235)	TPC (n=233)
Previous anticancer regimens† —median no. (range)	4 (2-17)	4 (2-14)
Most common previous chemotherapy—no. (%)		
Taxane‡	235 (100)	233 (100)
Anthracycline§	191 (81)	193 (83)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Previous PARP inhibitor—no. (%)	17 (7)	18 (8)
Previous use of checkpoint inhibitors—no. (%)	67 (29)	60 (26)
Most common sites of disease‖—no. (%)		
Lung only	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Bone	48 (20)	55 (24)

Brain metastases-negative population.
*Patients on study either had TNBC at initial diagnosis or had hormone receptor-positive disease that converted to hormone-negative at time of study entry. †Anticancer regimens refer to any treatment regimen that was used to treat breast cancer in any setting ‡Includes: Paclitaxel, paclitaxel albumin, and docetaxel. §Includes: Doxorubicin, daunorubicin, epirubicin, and variations of those treatment names. ‖Based on independent central review of target and non-target lesions.
BRCA, breast cancer gene; ECOG PS, Eastern Cooperative Oncology Group performance status; PARP, poly-ADP ribose polymerase; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

Progression-Free Survival (BICR Analysis)



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

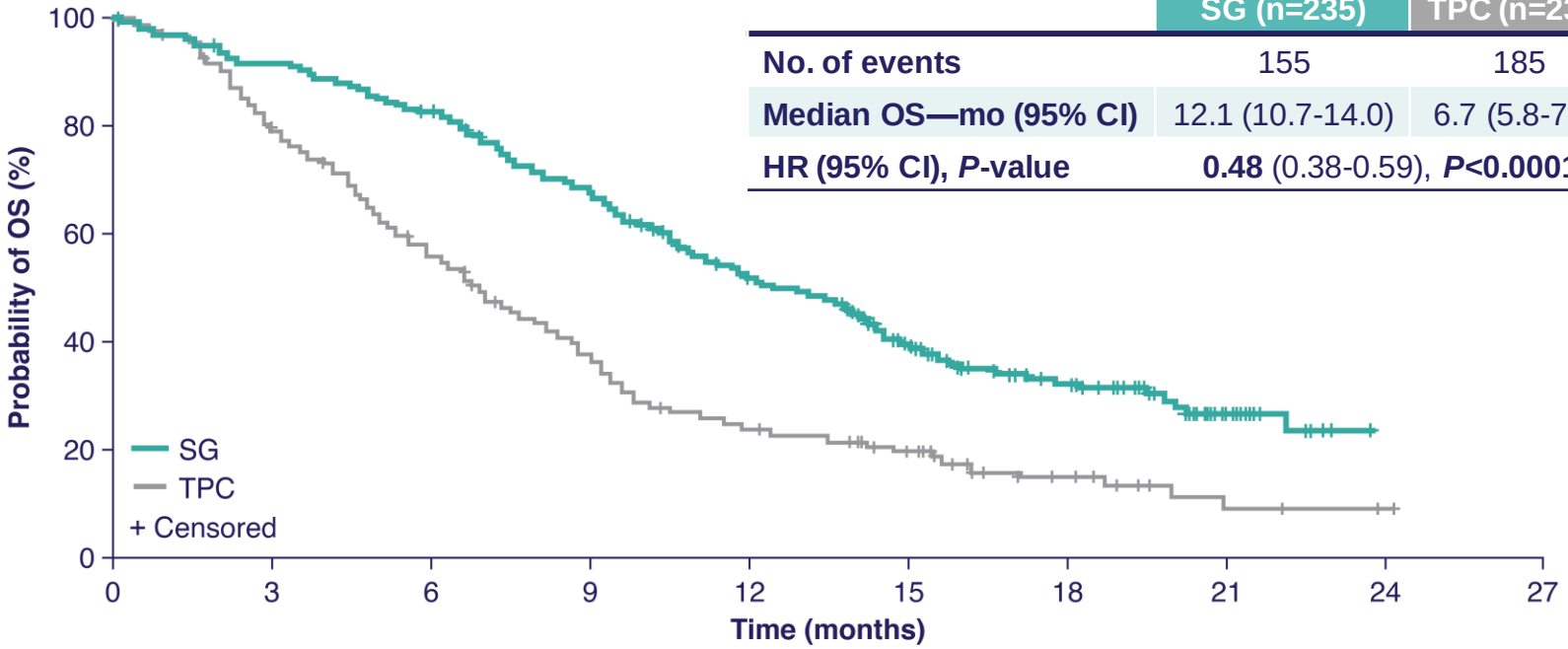
Number of patients at risk

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

Primary endpoint (PFS) assessed by independent central review in the brain metastases-negative population, as pre-defined in the study protocol.
Secondary endpoint (PFS) assessed in the full population (brain metastases-positive and -negative) and PFS benefit was consistent (HR=0.43 [0.35-0.54], *P*<0.0001).
BICR, blind independent central review; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Overall Survival

	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

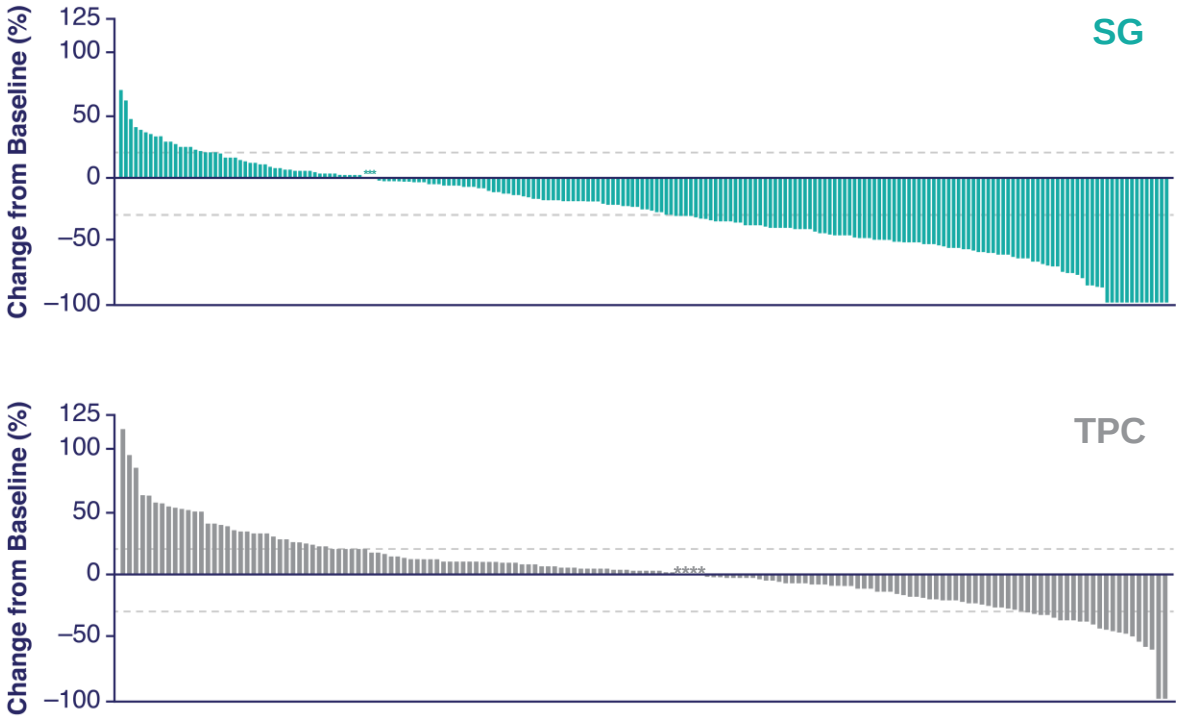


Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

Assessed by independent central review in the brain metastases-negative population.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Overall Response and Best Percent Change From Baseline in Tumor Size



	SG (n=235)	TPC (n=233)
ORR—no. (%)	**82 (35)**	**11 (5)**
***P*-value**	**<0.0001**	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	**105 (45)**	**20 (9)**
***P*-value**	**<0.0001**	
Median DOR—mo (95%CI)	**6.3 (5.5–9.0)**	**3.6 (2.8–NE)**
***P*-value**	**0.057**	

Assessed by independent central review in brain metastases-negative population.
*Denotes patients who had a 0% change from baseline in tumor size.
BICR, blind independent central review; CBR, clinical benefit rate (CR + PR + SD ≥6 mo); CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TTR, time to response.

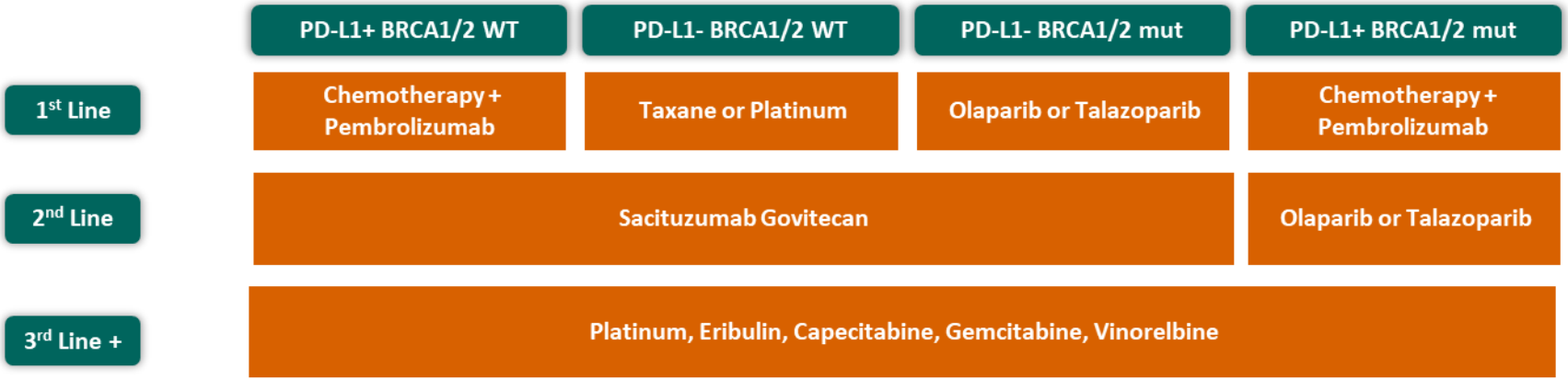
TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	**Neutropenia†**	**63**	**46**	**17**	**43**	**27**	**13**
	Anemia‡	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	**Diarrhea**	**59**	**10**	**0**	12	<1	0
	Nausea	**57**	**2**	**<1**	**26**	**<1**	**0**
	Vomiting	29	1	<1	10	<1	0
Other	**Fatigue**	**45**	**3**	**0**	**30**	**5**	**0**
	Alopecia	**46**	**0**	**0**	**16**	**0**	**0**

- Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%)
  - G-CSF usage was 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
- No severe cardiovascular toxicity, no grade >2 neuropathy or grade >3 interstitial lung disease with SG
- No treatment-related deaths with SG; 1 treatment-related death (neutropenic sepsis) with TPC
- AEs leading to treatment discontinuation were low for SG and TPC: 4.7% and 5.4%
- Patients received a median of 7 treatment cycles of SG, with a median treatment duration of 4.4 months (range, 0.03-22.9)

*Patients may report more than 1 event per preferred term. AEs were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. †Combined preferred terms of 'neutropenia' and 'decreased neutrophil count'. ‡Combined preferred terms of 'anemia' and 'decreased hemoglobin'. §Combined preferred terms of 'leukopenia' and 'decreased white blood cell count'.
G-CSF, granulocyte-colony stimulating factor; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related AE.

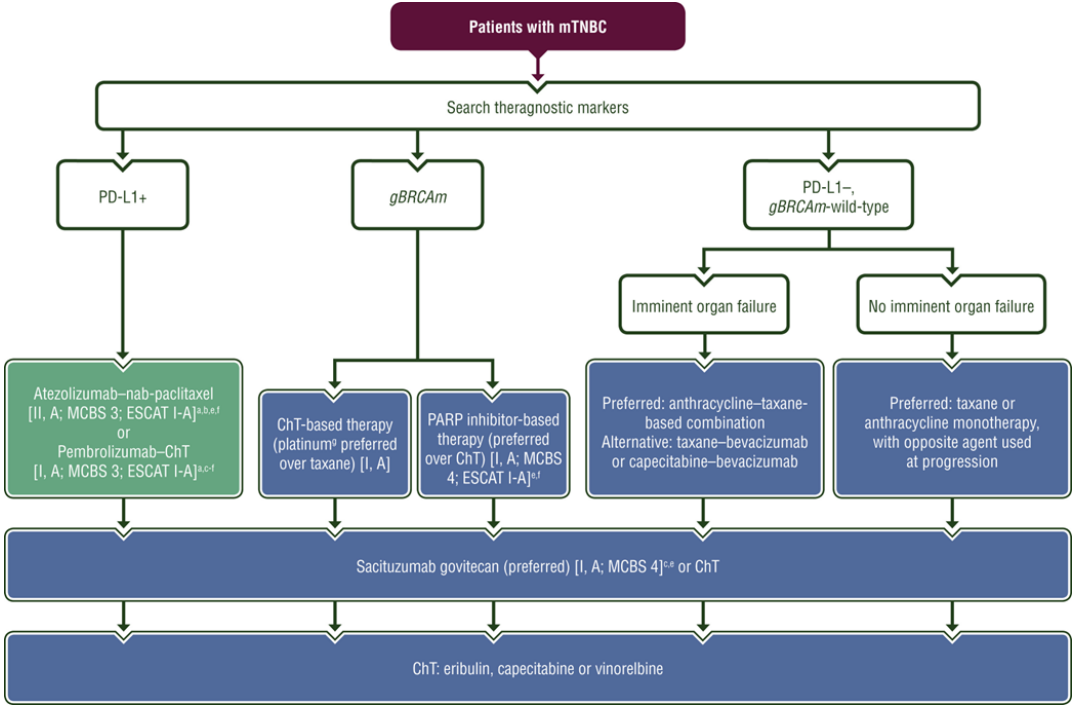
Approach to Treatment of Metastatic TNBC



Courtesy of Ian Krop, NCCN Version 4.2022

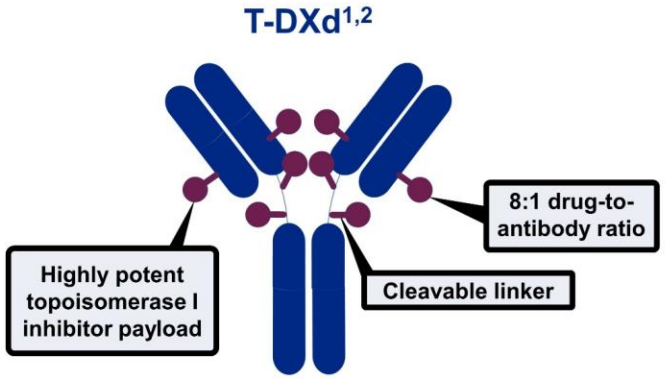
Atrium Health

ESMO Clinical Practice Guideline for Treatment of Metastatic Triple-Negative Breast Cancer

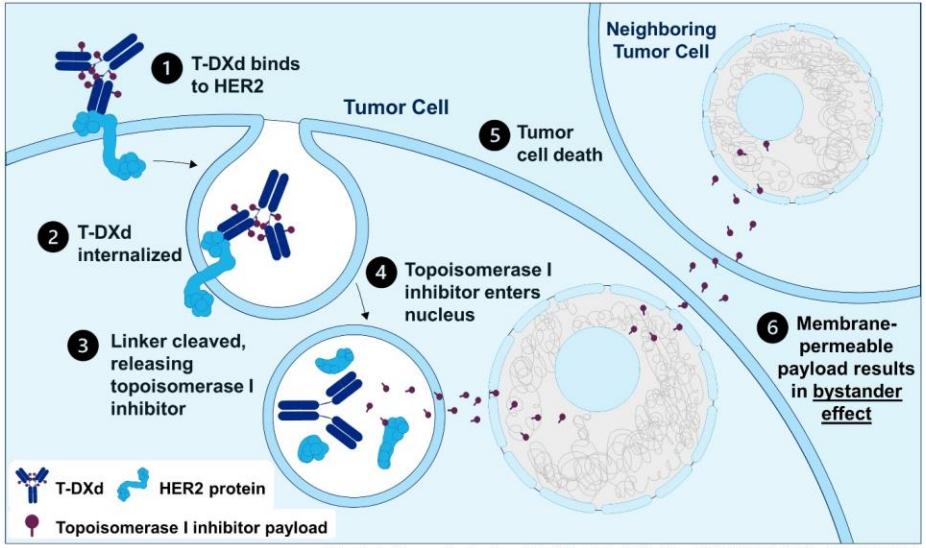


Gennari, A et al. Ann Oncol 2021; 32:1475-1495

T-DXd MOA, Bystander Effect, and Rationale for Targeting HER2-low mBC



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



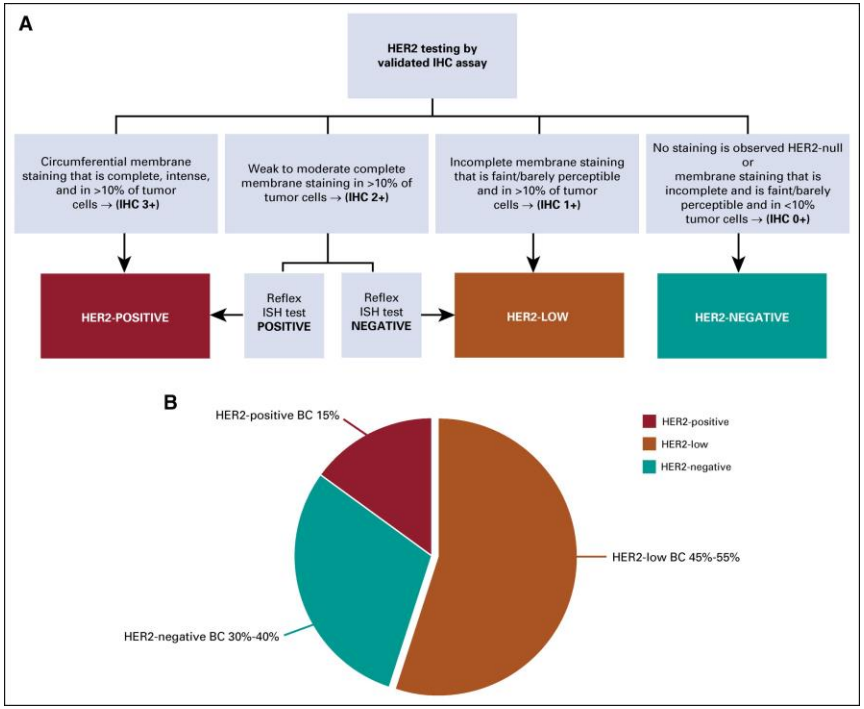
Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

- **Results from a phase 1b study have reported efficacy of T-DXd in heavily pretreated patients (N = 54) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0%[3]**

HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

1. Nakada T, et al. *Chem Pharm Bull*. 2019;67:173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097-5108. 3. Modi S, et al. *J Clin Oncol*. 2020;38:1887-1896.

Algorithm for Defining HER2-Low Breast Cancer

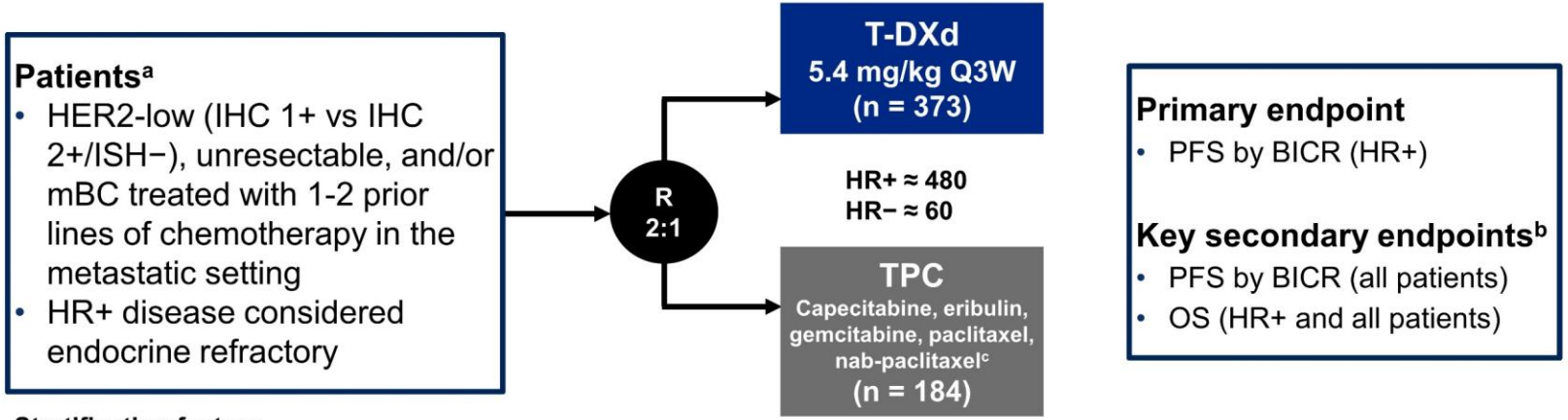


Tarantino P et al. *J Clin Oncol.* 2020;38(17): 1951-1962.

Atrium Health

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

An open-label, multicenter study (NCT03734029)



Stratification factors

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

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

Baseline Characteristics

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
Asia	128 (39)	60 (37)	147 (39)	66 (36)
North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)
ECOG performance status, %				
0	187 (56)	95 (58)	200 (54)	105 (57)
1	144 (44)	68 (42)	173 (46)	79 (43)
Hormone receptor,[a] n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes misstratified patients.

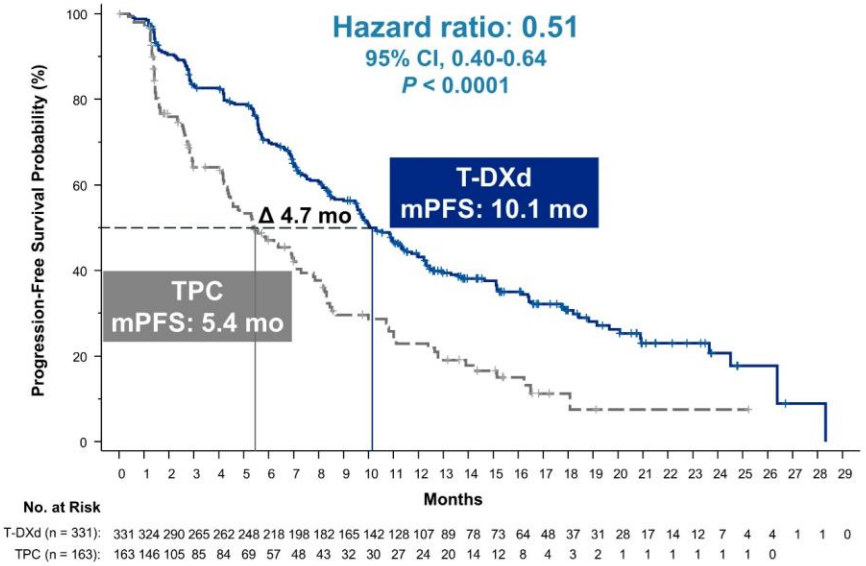
Prior Therapies

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

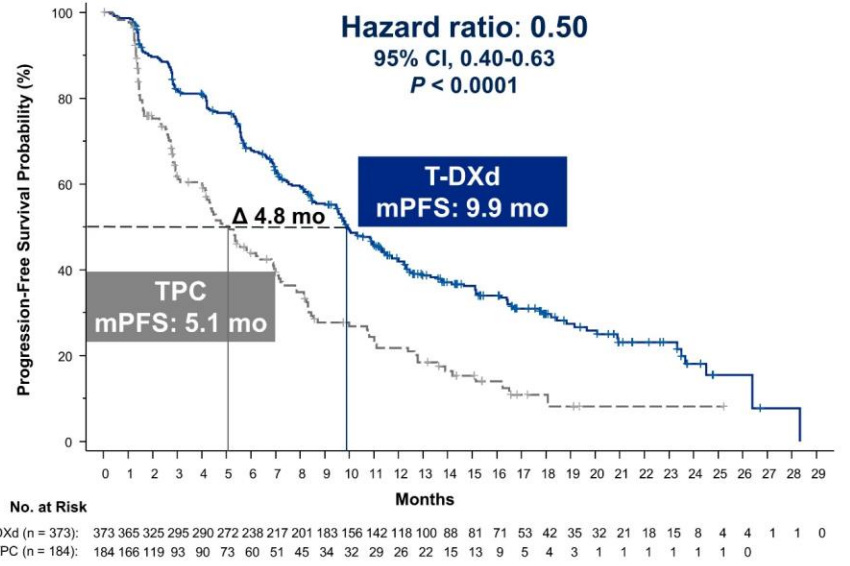
Based on derived data, which includes protocol deviations. CDK, cyclin-dependent kinase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS in HR+ and All Patients

Hormone receptor–positive



All patients

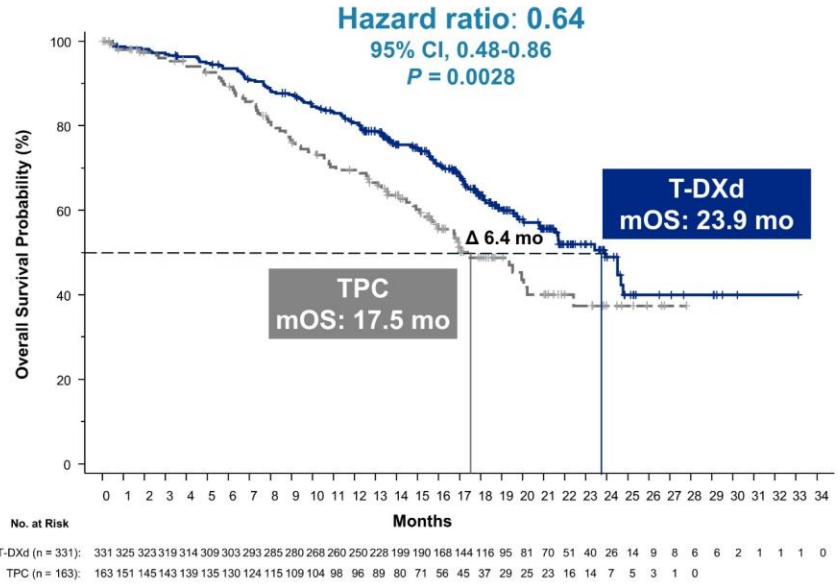


PFS by blinded independent central review.

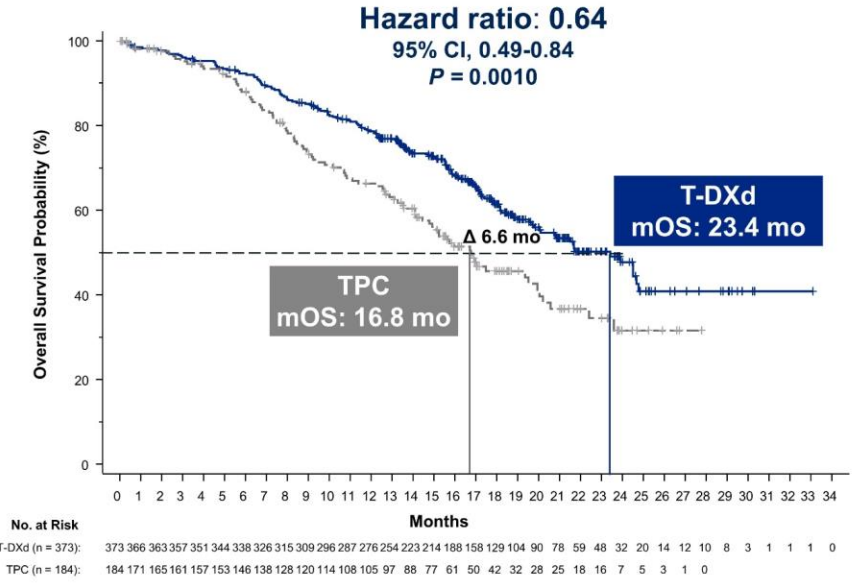
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

Hormone receptor–positive



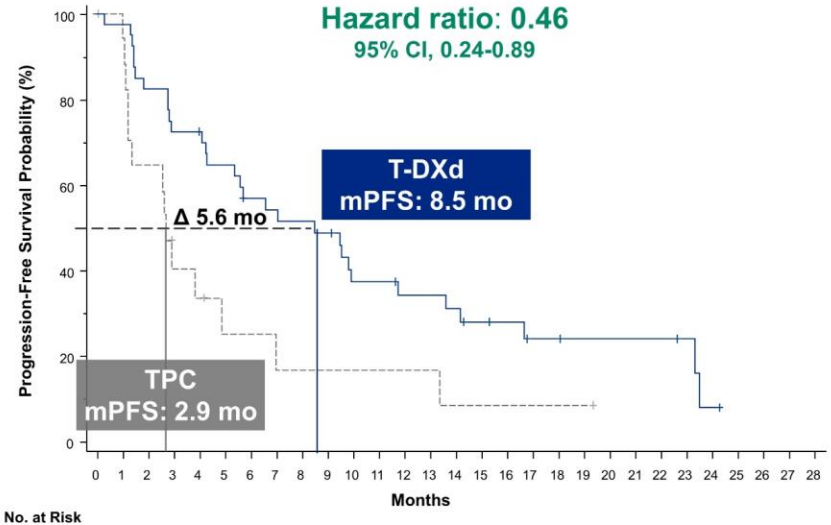
All patients



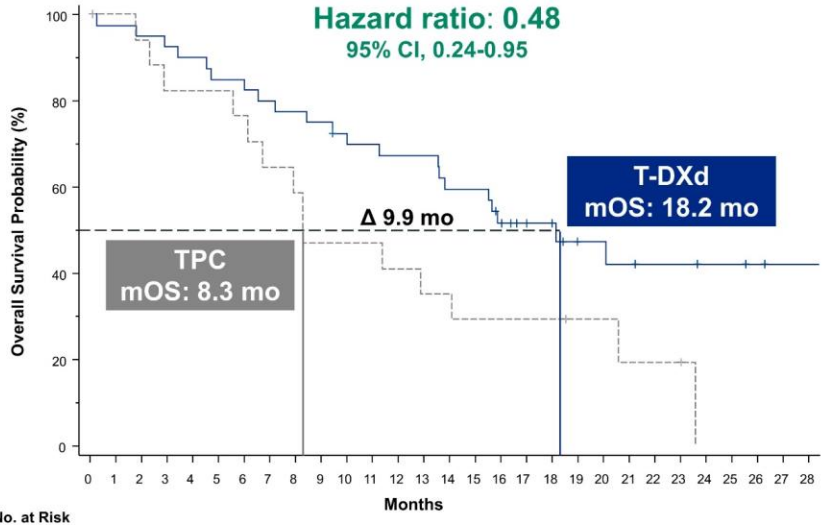
HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS and OS in HR− (Exploratory Endpoints)

PFS



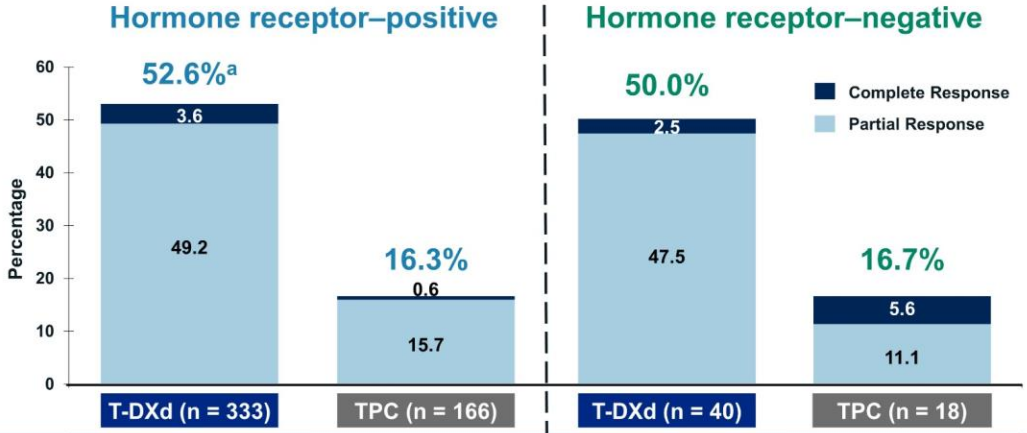
OS



HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.

Confirmed ORR

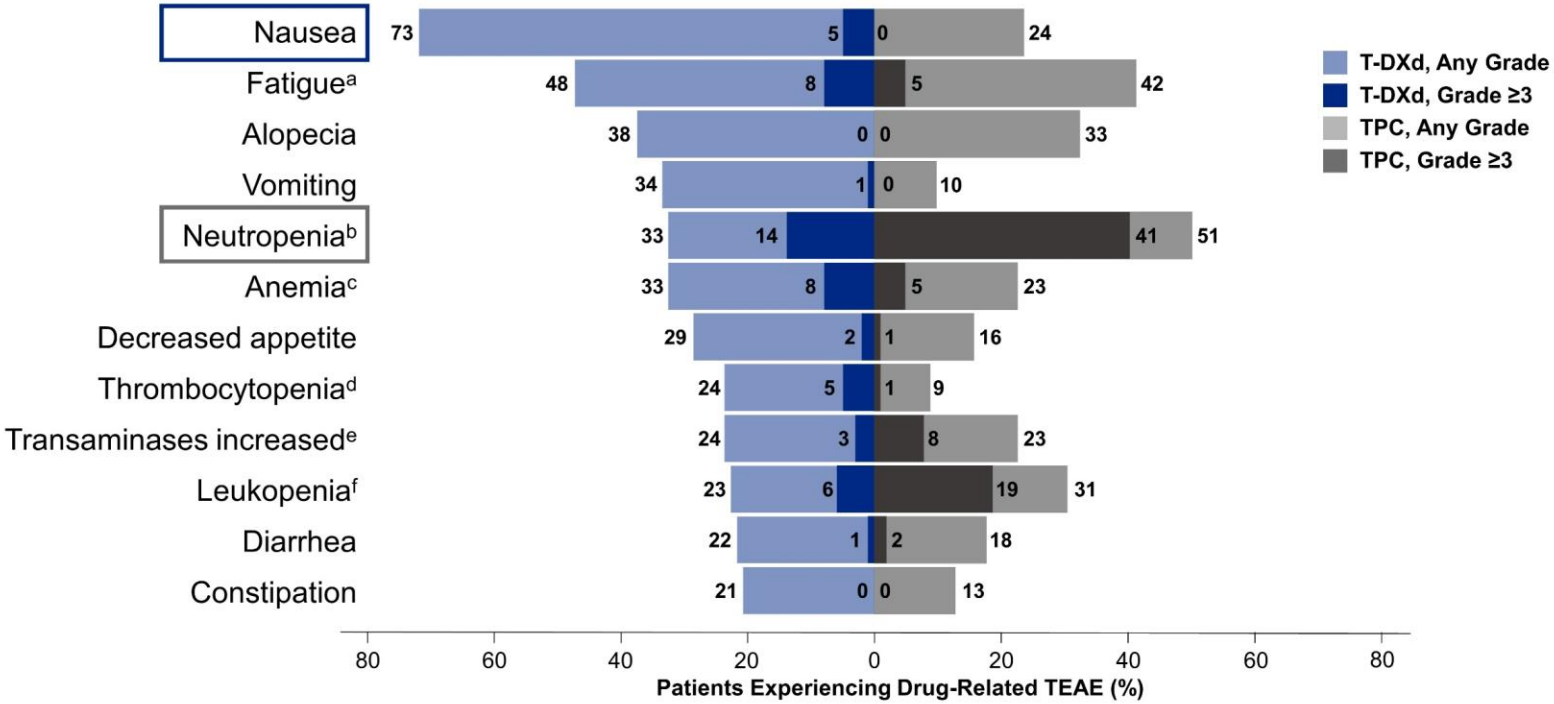
Confirmed Objective Response Rate



	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.

Drug-Related TEAEs in ≥20% of Patients



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

Left ventricular dysfunction[b]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Ejection fraction decreased						
T-DXd (n = 371)	1 (0.3)	14 (3.8)	1 (0.3)	0	0	16 (4.3)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure[c]						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to have recovered.

Critical Questions and Priorities

- What is the critical threshold of HER2 protein expression needed for antitumor activity with T-DXd?
  - DESTINY-Breast04: Outcomes were similar with a IHC score of 1+ and with a IHC score of 2+
  - Fernandez et al. *JAMA Oncol* 2022: less than 70% interrater agreement was found between ERBB2 scores of 0 and 1+ on 15 of 80 College of American Pathologists survey cases
  - DAISY trial: ORR = 30% in a cohort (n=38) HER2-negative breast cancer (HER2 IHC 0)
    - Were these tumors really 1+s?
  - Raises possibility that the level of HER2 expression required for activity of T-DXd is lower than the sensitivity of the IHC assay
  - Need – reliable, sensitive quantitative assay to assess low levels of HER2 expression
- For pathology labs only checking FISH for HER2, now need to check IHC status.

Ongoing Trials in HER2-Low Metastatic Breast Cancer

Drug/Sponsor	Compound	NCT#	Phase	Size	Regimen
T-DXd Daiichi-Sankyo/AZ DESTINY Breast-08	ADC Payload:DXd Topoisomerase I inhibitor	04556733	Ib	182	T-DXd + capecitabine T-DXd + durvalumab + paclitaxel T-DXd + capivasertib T-DXd + anastrozole T-DXd + fulvestrant
T-DXd Daiichi-Sankyo/AZ DESTINY Breast-06	ADC Payload:DXd Topoisomerase I inhibitor	04494425	III	850	TDX-d vs Treatment of Physician's Choice (capecitabine, nab-paclitaxel, or paclitaxel)
SYD985 Trastuzumab Duocarmazine Synthon ISPY-P1.01	ADC Payload: Duocarmazine	04602117	I/Ib	27	SYD985 + paclitaxel
MRG002 Shanghai Miracogen	ADC Payload:MMAE	04742153	II	66	MRG002
ARX-788 Zheijang Medicine	ADC Payload: Microtubule inhibitor (AS269)	05018678	II	54	ARX-788

DESTINY-Breast04 Trial: Take Home Points

- T-DXd is an active drug; provides a new treatment option for patients with HER2-low metastatic disease.
  - ORR 52% vs 16.3% (T-Dxd vs TPC)
  - Doubling of progression-free survival
  - A 6-month gain in overall survival
  - 12% ILD (Interstitial lung disease)
- Becomes critical to know the HER2 IHC status of a metastatic tumor, i.e. status 0, 1+ and 2+.
  - We now have a new category of breast cancer—HER2-low—the trial results redefine how we classify breast cancer and will result in significantly expanding the population of patients who can benefit from HER2-targeted therapy.
- The next steps will be studies to explore the minimum threshold of HER2 expression that will respond to T-DXd.

Atrium Health

KEYNOTE-522 Trial: Take Home Points

- Chemotherapy and pembrolizumab approved as neoadjuvant therapy for Stage II-III TNBC, followed by adjuvant pembrolizumab after surgery
  - Tumor size > 1 cm but ≤ 2 cm in diameter with nodal involvement or tumor size > 2 cm in diameter regardless of nodal involvement
- No PD-L1 testing requirement
- Most immune-mediated adverse events occurred in the neoadjuvant phase, low grade and manageable
- Improves pCR, improves EFS
- Await mature OS analysis

OlympiA Trial: Take Home Points

- Olaparib approved as adjuvant therapy for BRCA-mutated HER2-negative high-risk, early-stage breast cancer
  - Adjuvant olaparib for pts with TNBC and tumor > 2 cm or any involved axillary nodes
  - For HR+ disease, adjuvant olaparib in pts with at least 4 involved axillary lymph nodes
  - For TNBC pts who receive NAC, adjuvant olaparib for residual disease
  - For HR+ pts who receive NAC, adjuvant olaparib for residual disease a CPS + EG score ≥ 3
- Duration: 1 year therapy
- Improves DFS and OS

Atrium Health

ASCENT Trial: Take Home Points

- Sacituzumab govitecan approved for metastatic TNBC
  - Can use second-line and beyond
- Higher ORR, longer PFS, and longer OS vs physician's choice chemotherapy
- Neutropenia and diarrhea common, but manageable
  - Management with dose reduction, growth factors, and anti-diarrheals

Summary

- Integration of immunotherapy, PARP inhibitors and antibody-drug conjugates into the treatment of breast cancer marks important milestones and has changed the SOC
- Biomarkers are needed to optimally identify patients that require the addition of immune checkpoint inhibitors to chemotherapy
- Determine what other breast cancer subtypes can benefit from PARP inhibitors i.e. tumors with aberrations in the DNA repair pathways
- Need a better understanding of the appropriate use of ADCs in metastatic breast cancer, i.e. whether ADCs carrying similar payloads can be used in sequence and what is the optimal sequencing of these agents