Triple-Negative Breast Cancer: Updates on Treatment of Early- and Late-Stage Disease

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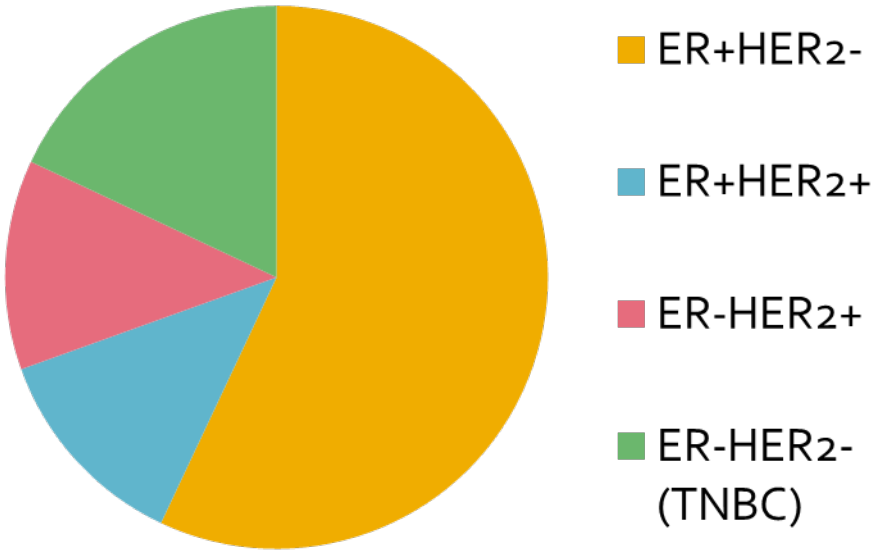
Learning Objectives

- To understand the biology of triple-negative breast cancer (TNBC) and unique features of systemic treatment in early- and late-stage disease
- To summarize clinical trial results for novel agents including IO in neoadjuvant and metastatic setting

Triple Negative Breast Cancer

- Estrogen receptor (ER) negative (< 1% cells positive)
- Progesterone receptor (PR) negative (< 1% cells positive)
- Negative HER2 over-expression (IHC 0-1+ or FISH ratio < 2)

- ER + 65-80%
- HER2 + 25%
- Triple-negative 10-20%

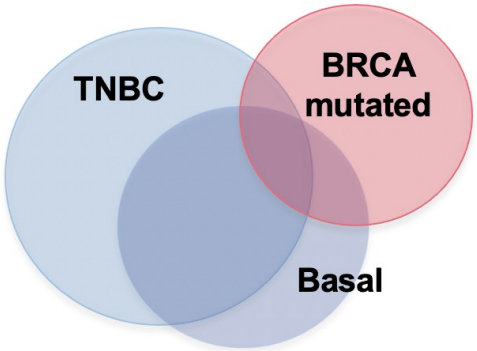


Perou CM et al Nature 2000, Bauer KR Cancer 2007, ER/PR ASCO-CAP guidelines 2010, HER2 ASCO-CAP guidelines 2013

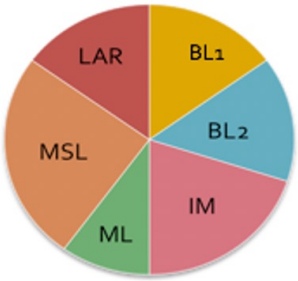
TNBC Subtyping to Characterize Heterogeneity

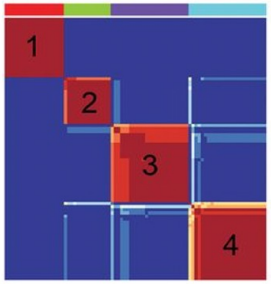
Basal-like molecular subtype[1]

- **Intrinsic subtype**
- **ER/PR/HER2- EGFR expressed**
- **Basal cytokeratins expressed**



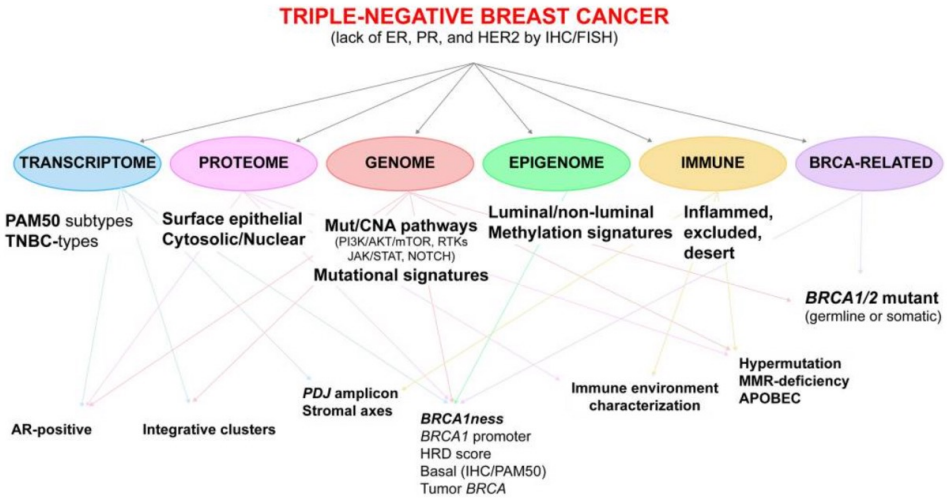
TNBCtype[2]





RNA and DNA profiling

TNBC Subtypes[3]
LAR (luminal androgen receptor)
MES (mesenchymal)
BLIS (basal-like immunosuppressed)
BLIA (basal-like immune-activated)



[1]Perou et al Nature 2000 [2]Lehmann et al JCI 2011, [3]Burstein et al CCR 2015, Garrido-Castro Cancer Disc 2019

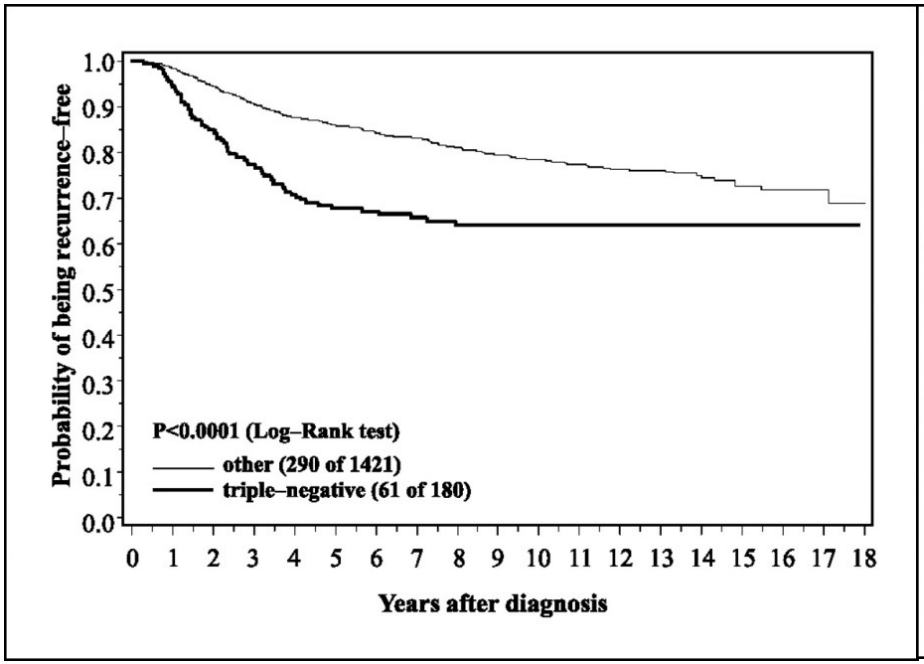
None of this heterogeneity is as yet actionable, except for BRCA mutation

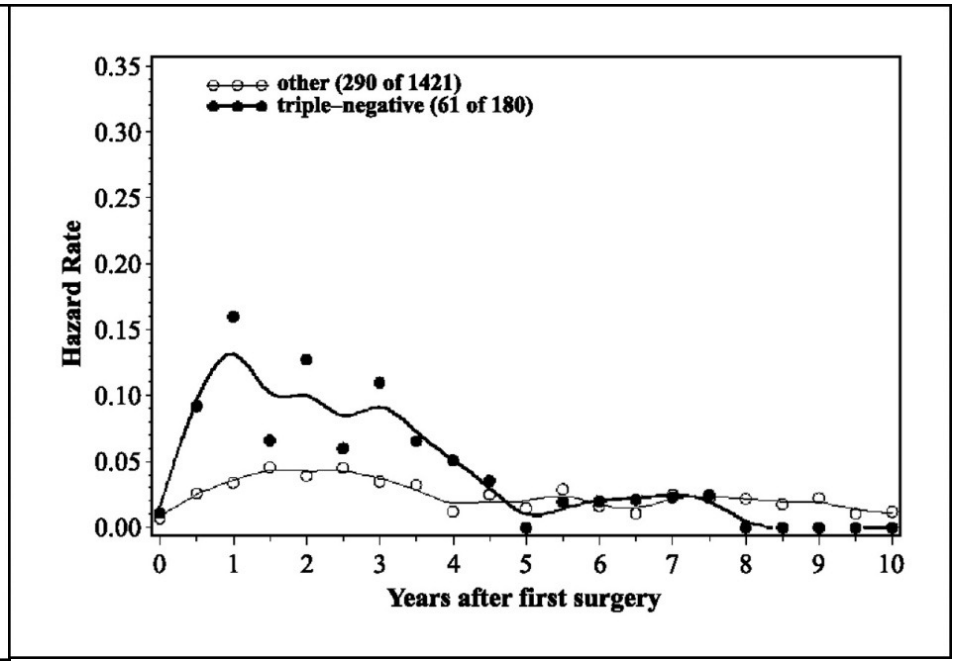
TNBC Clinical Characteristics

- Aggressive, early recurrences (within 5 years), increased risk of brain metastases
- More likely in young women (~20%) and in African and African-American women (3-fold)
- Higher likelihood of BRCA1 mutations
- Increased use of neoadjuvant chemotherapy (with IO); adjuvant capecitabine
- PARPi for BRCA/PALB2; chemo/IO for PDL-1+; ADCs (Sacituzumab; T-DXd)

Increased early risk of recurrence in TNBC compared to other subtypes

Rates of Distant Recurrence in TNBC





Clinical Cancer Research

Dent R et al. Clin Cancer Res 2007;13:4429-4434

Patients treated at the HBBC in Toronto, ON, Canada
From 1987-1997
Database review

BRCA Mutations and TNBC

- Incidence of BRCA1/2 mutations in TNBC 11-37% compared to 1-7% in all patients with breast cancer
- NCCN guidelines
  - Early stage TNBC any age – BRCA testing
  - High risk disease to guide adjuvant rx with Olaparib
  - Metastatic breast cancer
- ASCO-CAP guidelines changed in 2010 defining ER/PR negative as < 1% positive (previously low-positive 1-9% was negative)
- ER/PR low positive breast cancer may have similar risk of BRCA mutation as ER/PR negative (MDACC, Sanford et al. Cancer 2015)

Early-Stage TNBC

Neoadjuvant and Adjuvant Therapy

Neo/Adjuvant Chemotherapy Regimens TNBC

- **When to give chemo (NCCN guidelines)**:
  - Tumor > 1 cm or node + - Chemotherapy is recommended
  - Tumor 0.6cm – 1.0 cm, pN1mi –Chemotherapy should be considered
  - Tumor <0.6 cm, pN0 – chemotherapy may be given in selected cases

- **Preoperative (neoadjuvant) v. adjuvant chemotherapy**
  - T2+ tumor (> 2 cm) or node + preoperative is favored
  - Chemotherapy before or after surgery results in equivalent long-term outcomes for an individual regimen in breast cancer.

(Citron et al. Intergroup C9741 CALGB 9741. JCO 2003, Jones et al. TC v. AC US Oncology 9735, JCO 2009)

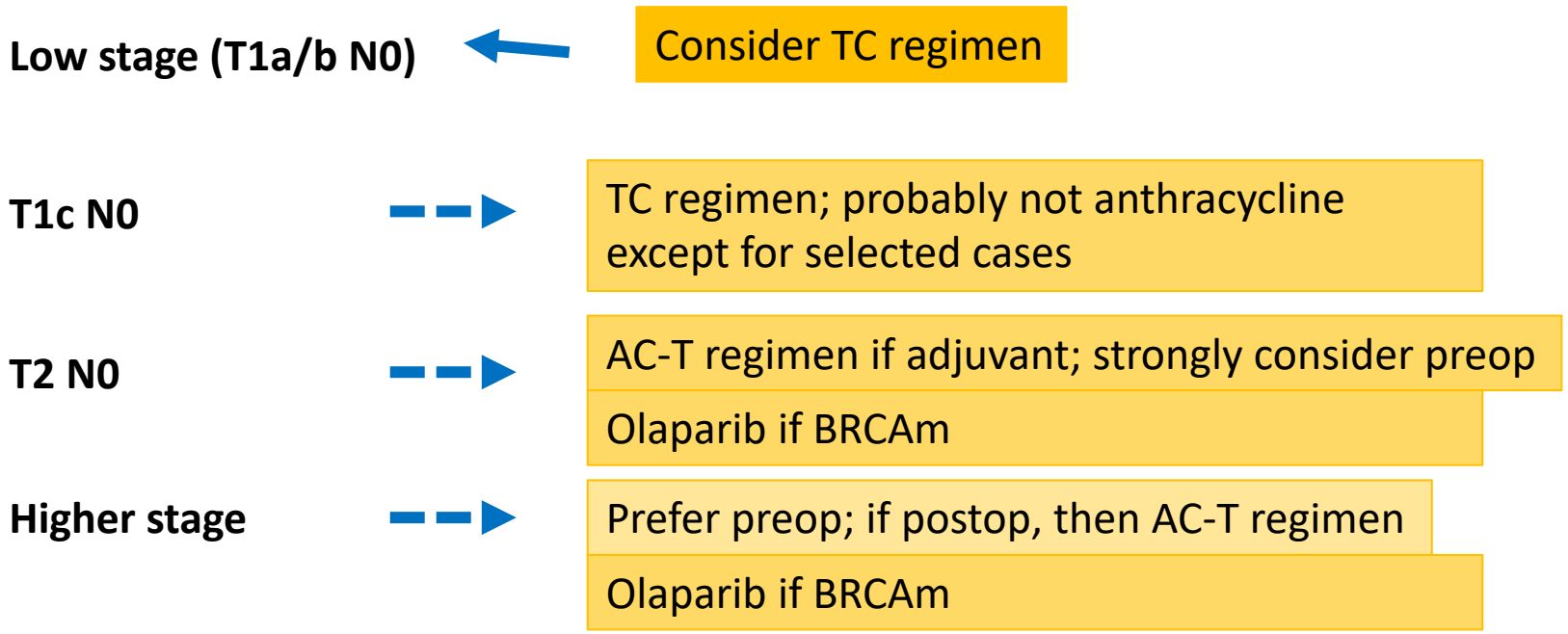
Advantages of Preoperative Chemotherapy in TNBC: Why Give?

- **Must use:**
  - Inoperable tumors (including inflammatory, matted nodes, N3, T4, etc) M0
  - Operable large primary tumor relative to breast – pt desires breast conservation

- **Recommended to consider:**
  - Node-positive possibility to become node-negative with preop systemic therapy
  - T2+ or node-positive: eligible for IO therapy

- **Benefits:**
  - Facilitates breast conservation, render inoperable operable
  - ***IO therapy only approved in the neoadjuvant setting***
  - Prognostic information in TNBC (and HER2+) based on pCR v. residual disease
  - Allow tailoring adjuvant therapy (TNBC and HER2+) if no pCR
  - Allows time for genetic testing, plan reconstruction
  - Allow SLNBx if positive axilla cleared with preop therapy

CURRENT MANAGEMENT APPROACH for TNBC: Adjuvant



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ORIGINAL REPORT

Anthracyclines in Early Breast Cancer: The ABC Trials—USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology)

Joanne L. Blum, Patrick J. Flynn, Greg Yothers, Lina Asmar, Charles E. Geyer Jr, Samuel A. Jacobs, Nicholas J. Robert, Judith O. Hopkins, Joyce A. O'Shaughnessy, Chau T. Dang, Henry Leonidas Gómez, Louis Fehrenbacher, Svetislava J. Vukelja, Alan P. Lyss, Devchand Paul, Adam M. Brufsky, Jong-Hyeon Jeong, Linda H. Colangelo, Sandra M. Swain, Eleftherios P. Mamounas, Stephen E. Jones, and Norman Wolmark

- High risk node-negative or node-positive
- HER2-negative breast cancer
- Randomized to TC x 6 v. TaxAC
- Primary endpoint: iDFS
- Designed to prove noninferiority of TC x 6 compared to TaxAC
- 4-year iDFS improved with TaxAC
- OS data immature
- No BRCA reported

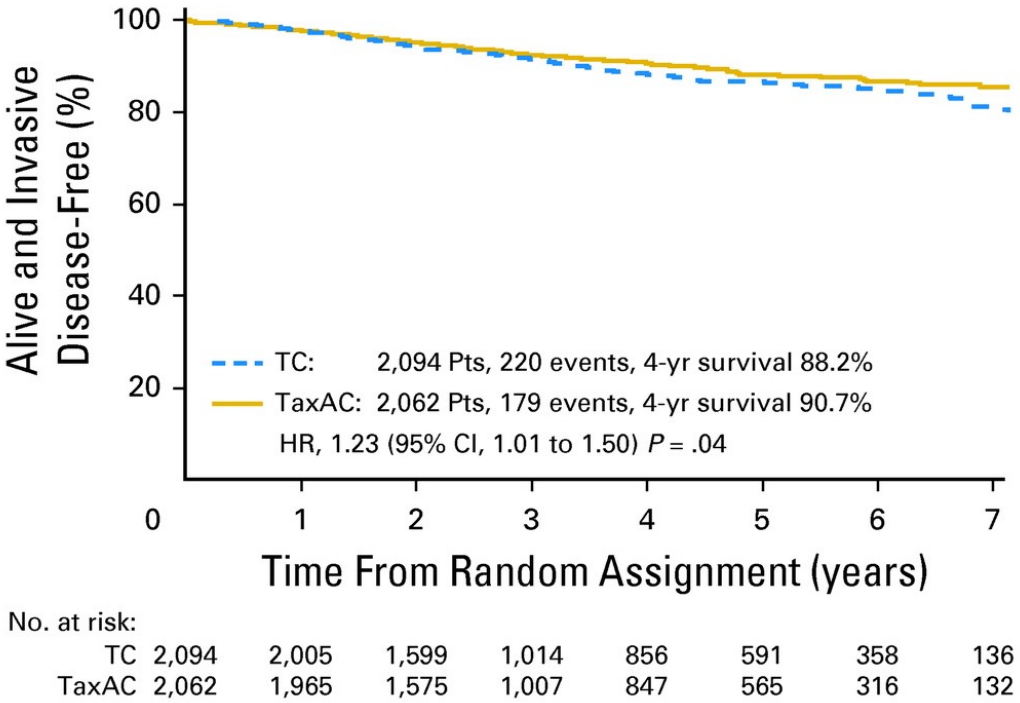


Table 3. IDFS by Hormone and Nodal Status

Status	No. of Patients		No. of Events		4-Year IDFS (%)		4-Year IDFS Δ (%)	HR (95% CI)
	TaxAC	TC	TaxAC	TC	TaxAC	TC		
HR negative								
Node negative	459	488	37	52	89.5	87.0	2.5	1.31 (0.86 to 1.99)
1-3 positive nodes	153	119	21	28	85.5	74.6	10.9	1.58 (0.90 to 2.79)
≥ 4 positive nodes	42	40	11	16	71.8	60.8	11.0	1.34 (0.62 to 2.91)
HR positive								
Node negative	358	378	29	22	91.5	94.2	−2.7	0.69 (0.39 to 1.19)
1-3 positive nodes	771	789	46	53	94.3	92.3	2.0	1.14 (0.77 to 1.69)
≥ 4 positive nodes	279	280	35	49	87.2	81.4	5.8	1.46 (0.95 to 2.26)

Abbreviations: HR, hormone receptor; IDFS, invasive disease-free–survival; TaxAC, doxorubicin and cyclophosphamide regimens with a taxane; TC, docetaxel and cyclophosphamide.

- In subset analysis, more benefit from TaxAC in patients with TNBC compared to HR + and in node-positive compared to node-negative
- Absolute benefit 2.5% in node-negative TNBC and -2.7 in node-negative HR+

- Risk of anthracycline-induced cardiomyopathy – Symptomatic heart failure in 1-2% of patients treated with a cumulative doxorubicin dose 240-360 mg/m^2. AC = 60 mg/m^2 each dose x 4 = 240 mg/m^2. Also rarely secondary leukemia (5 cases TaxAC v. O TC.

- Risk factors for anthracycline-induced cardiotoxicity include cumulative dose, age, preexisting cardiac risk factors, radiation, other cardiotoxic agents

Hershman et al Oncology 2009-Anthracycline-induced cardiomyopathy

CURRENT MANAGEMENT APPROACH for TNBC: Preoperative

TCb/pembro → AC/pembro ← Stage II/III; no contraindications

Controversies:

- No data for use of this regimen in the adjuvant setting
- Should T2N0 be included? Do they have a high enough risk to warrant toxicity?
- Is carboplatin required? Can other regimens be used with IO therapy?
- Is the adjuvant pembrolizumab needed for those who achieved pCR?

Post-surgical systemic therapy following preop therapy for TNBC

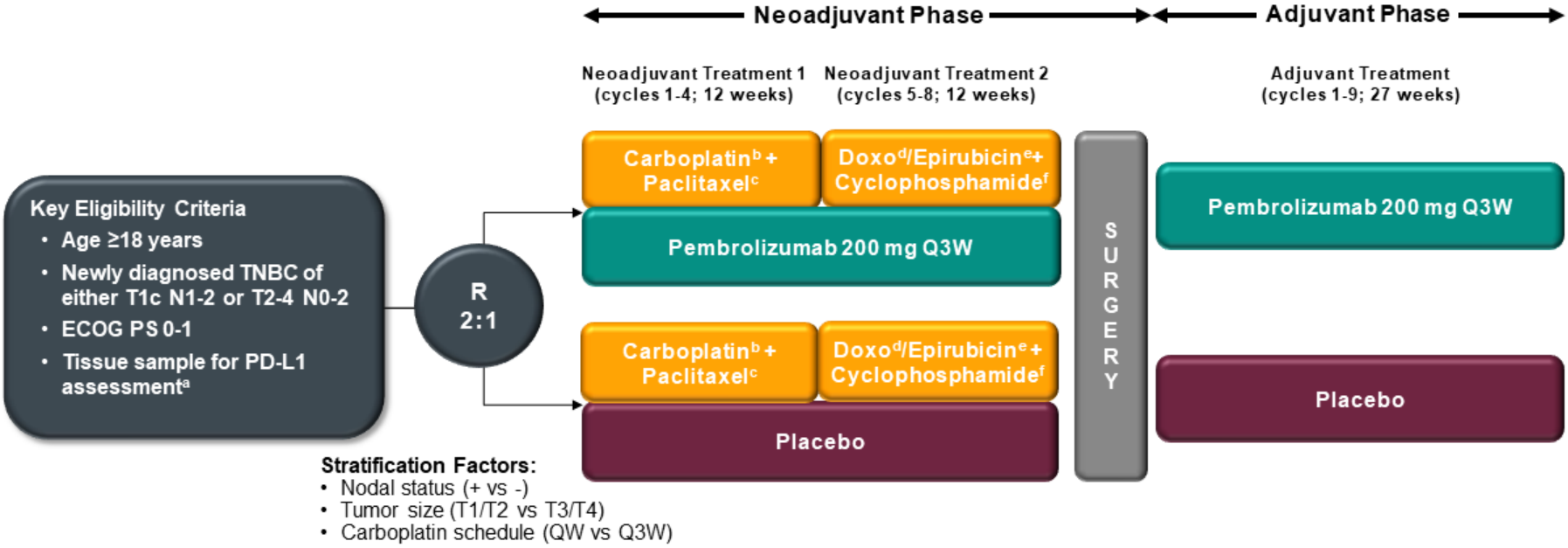
Post-surgical systemic therapy following preop therapy for TNBC

Pembrolizumab to complete a year	If IO given preop
Capecitabine for 8 cycles	If ≥ ypT1 or N1
Olaparib for a year	If BRCAm and ≥ ypT1 or N1

Controversies:

- No data for combined use of these agents in the adjuvant setting
- Is pembrolizumab needed for those who achieved pCR?

KEYNOTE-522 Study Design (NCT03036488)



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/m^2 QW.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Schmid KN522 ESMO 2019

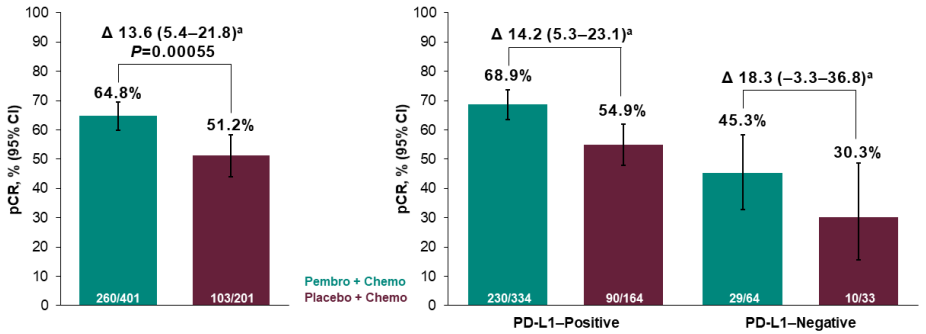
Baseline Characteristics, ITT Population

Characteristic, n (%)	All Subjects, N = 1174	
	Pembro + Chemo N = 784	Placebo + 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: April 24, 2019.

Schmid KN522 ESMO 2019

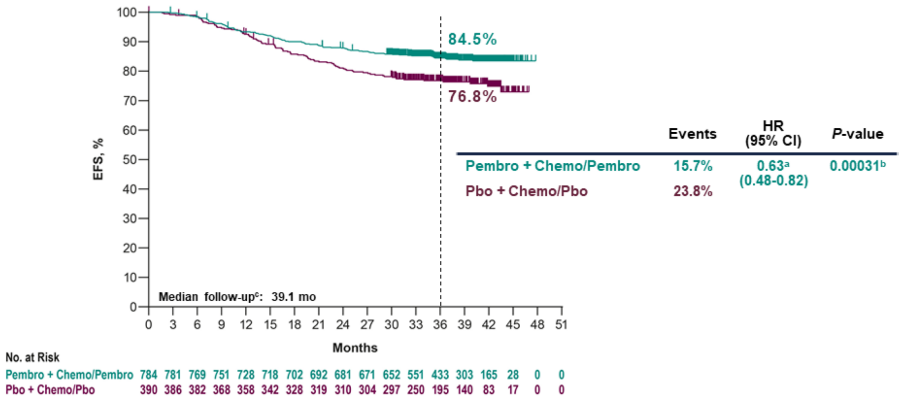
Pathological Complete Response at IA1



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]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: September 24, 2018.

Schmid KN522 ESMO Virtual Plenary 2021

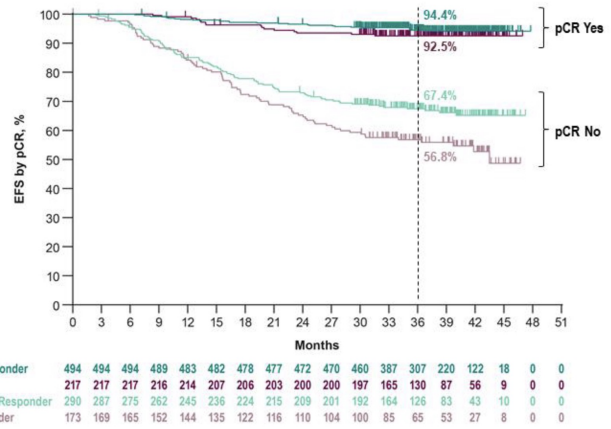
Statistically Significant and Clinically Meaningful EFS at IA4



[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.

Schmid KN522 ESMO Virtual Plenary 2021

EFS by pCR (ypT0/Tis ypN0)



Data cutoff date: March 23, 2021.

KEYNOTE-522 Conclusions

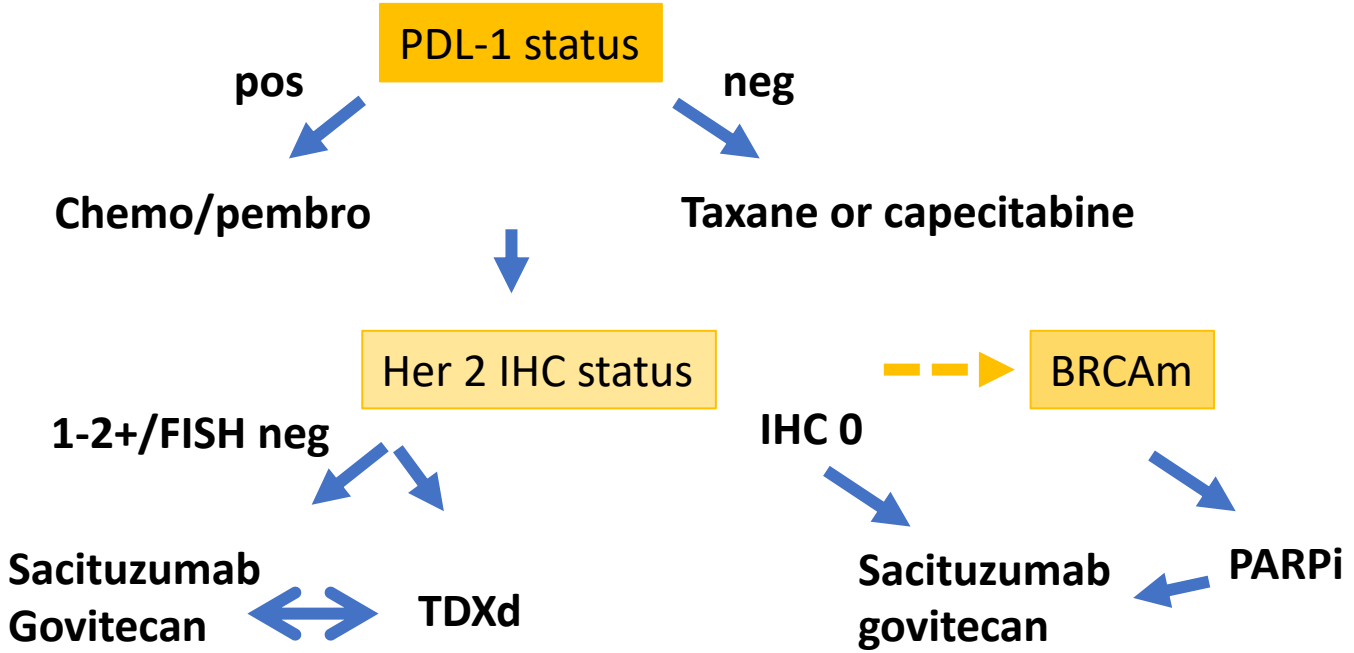
- The addition of pembrolizumab to platinum-containing neoadjuvant chemotherapy improves pCR and EFS in patients with TNBC regardless of PD-L1 status.
- FDA Approval was granted July 27, 2021
- The safety profile was consistent with known profiles of individual agents
- Future trials will likely evaluate de-escalation strategies for patients with T2N0 disease similar to trials in HER2+ breast cancer

Metastatic TNBC-Historic Perspective

- **Retrospective multicenter review 111 TNBC patients**
  - 14 % presented with de novo metastatic disease
  - Median distant disease-free interval 18 mos
  - Median survival 13.3 mos (up to 19 mos in some trials)
  - First line therapy 11.9 weeks
  - Second line therapy 9 weeks
  - Third-line therapy 4 weeks
  - Only 50 % received 3rd line therapy

Kassam et al Clinical Breast Cancer 2009

CURRENT MANAGEMENT APPROACH for TNBC: Metastatic

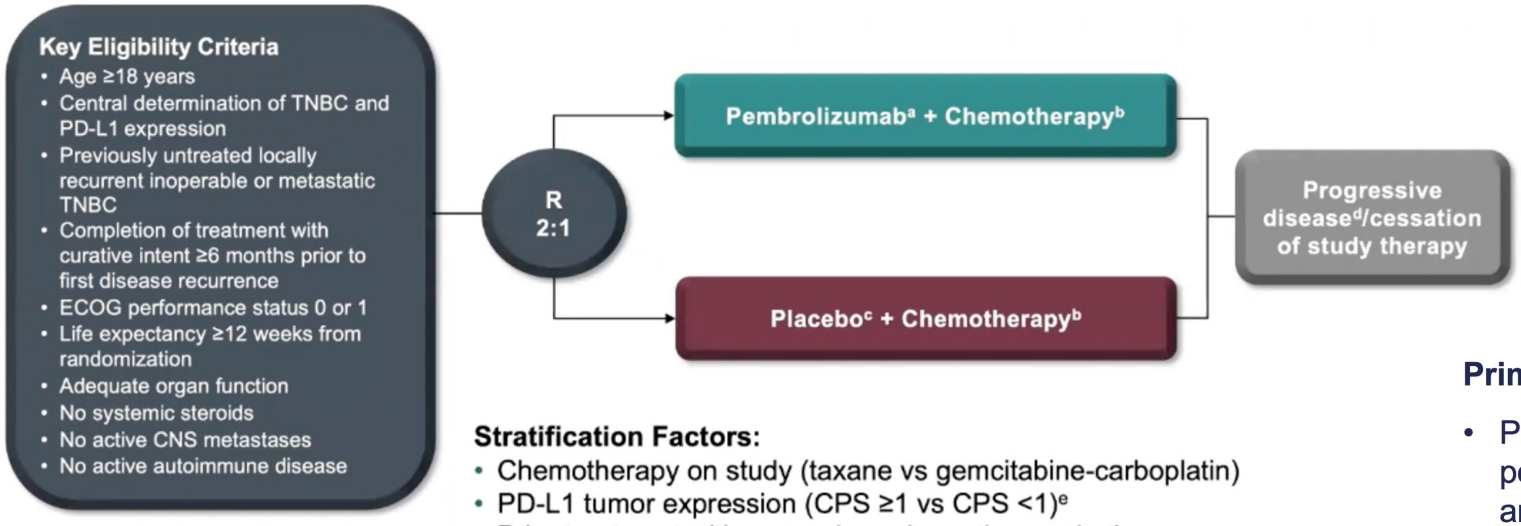


Later regimens
Single agent chemotherapy: Eribulin, etc
Targeted approaches: MSI-H, TMB-H, Her2m, AKT1m, NTRK fusion, other mutations

Controversies:

- **Will IO therapy be useful if received IO therapy in the neoadjuvant setting?**
- **Will IO therapy be at all useful in later line therapy?**
- **For TNBC Her2 1-2+/F-, should SG or TDXd be first? Since both have topo I inhibitor, they will have some cross-resistance. Will TROP2 become a biomarker of importance?**

KEYNOTE-355: Phase III randomized study of pembro + chemo (paclitaxel, nab-paclitaxel or carbo/gem) v. placebo + chemo



Stratification Factors:

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

Primary Endpoints:

- PFS in PD-L1-positive (CPS ≥ 10 and CPS ≥ 1) and ITT
- OS in PD-L1-positive (CPS ≥ 10 and CPS ≥ 1) and ITT

[a]Pembrolizumab 200 mg IV Q3W.
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m² IV on days 1, 8, and 15 every 28 days.
Paclitaxel 90 mg/m² IV on days 1, 8, and 15 every 28 days.
Gemcitabine 1000 mg/m²/carboplatin AUC 2 on days 1 and 8 every 21 days.

[c]Normal saline.
[d]Treatment may be continued until confirmation of progressive disease.
[e]PD-L1 CPS at cutoff 10 was not a stratification factor.

CPS: number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by total number of tumor cells x 100, PD-L1 IHC 22C3 PharmDx assay, archival or newly obtained FFPE central lab

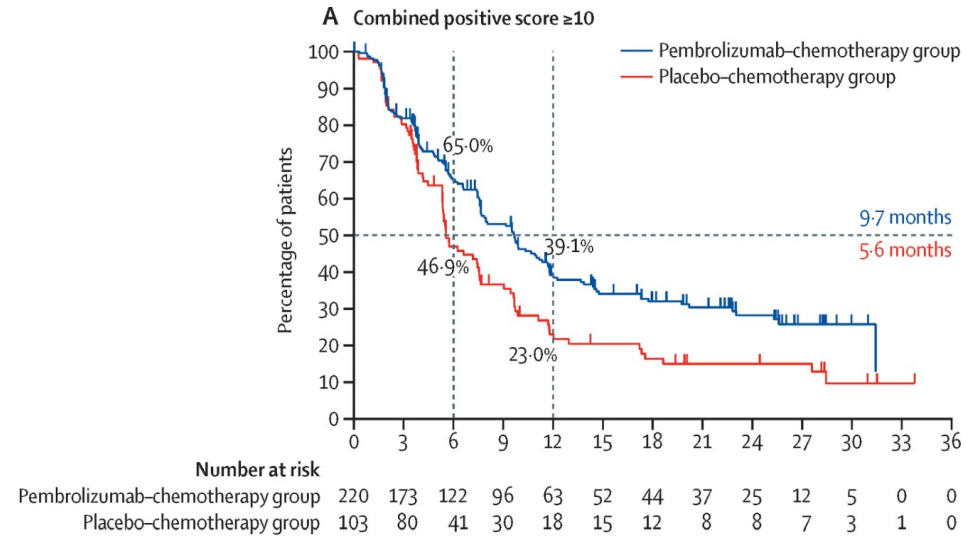
Rugo et al, SABCS 2020, Cortes et al, ASCO 2020

KEYNOTE-355 Baseline Characteristics

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		
Nab-Paclitaxel	173 (30.6)	95 (33.8)
Paclitaxel	82 (14.5)	32 (11.4)
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)

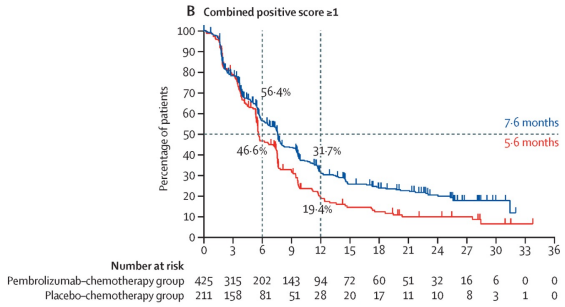
Rugo et al, SABCS 2020, Cortes et al, ASCO 2020

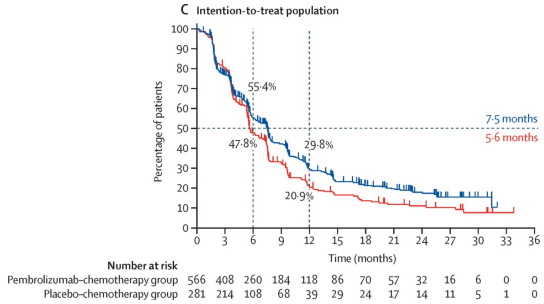
KEYNOTE-355 Progression-free survival



CPS ≥ 10

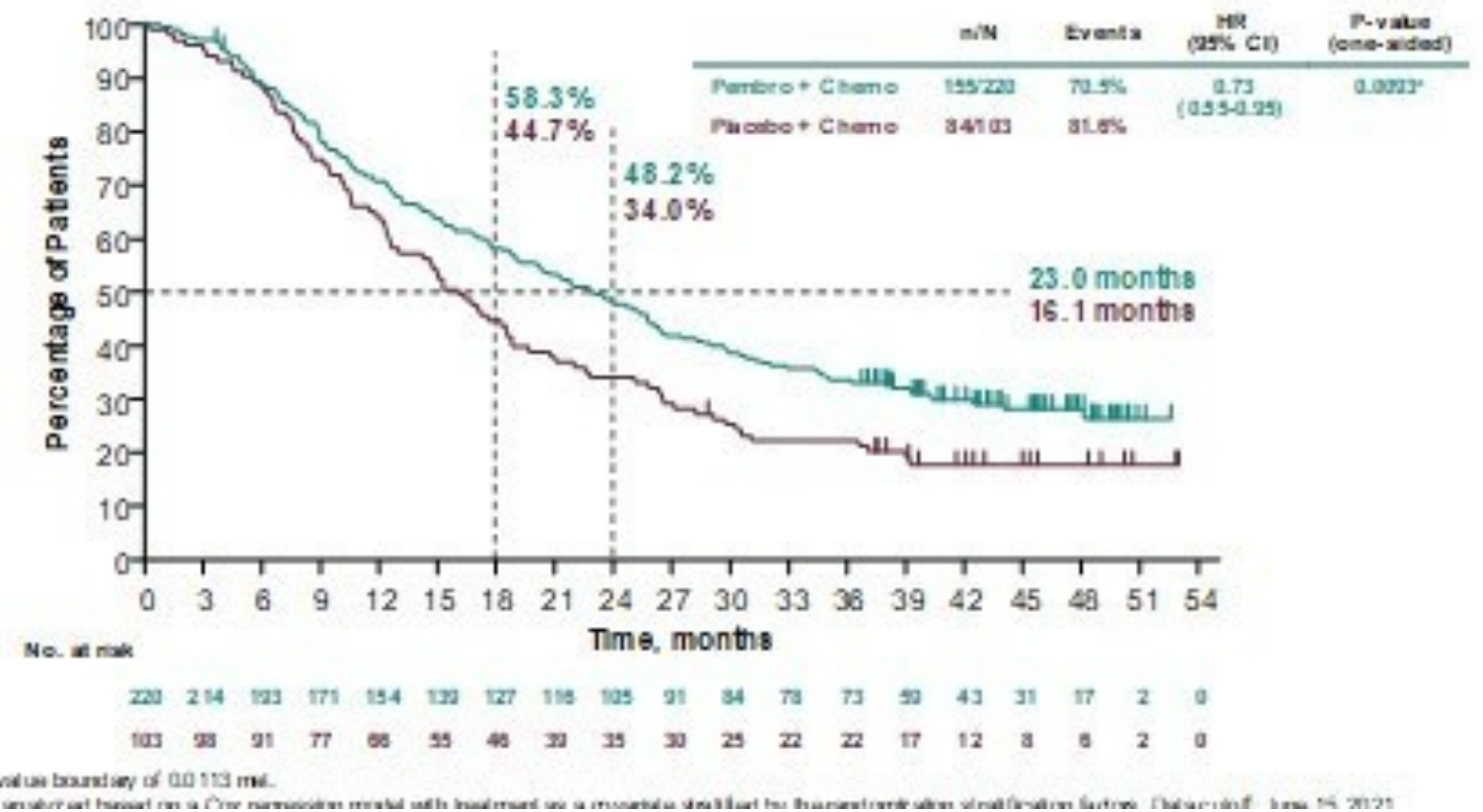
	Pembro + Chemo	PBO + Chemo
Median PFS, mos	9.7	5.6
HR = 0.65 (95% CI, 0.49-0.86) P = 0.0012		
1-yr rate of PFS	39.1%	23.0%





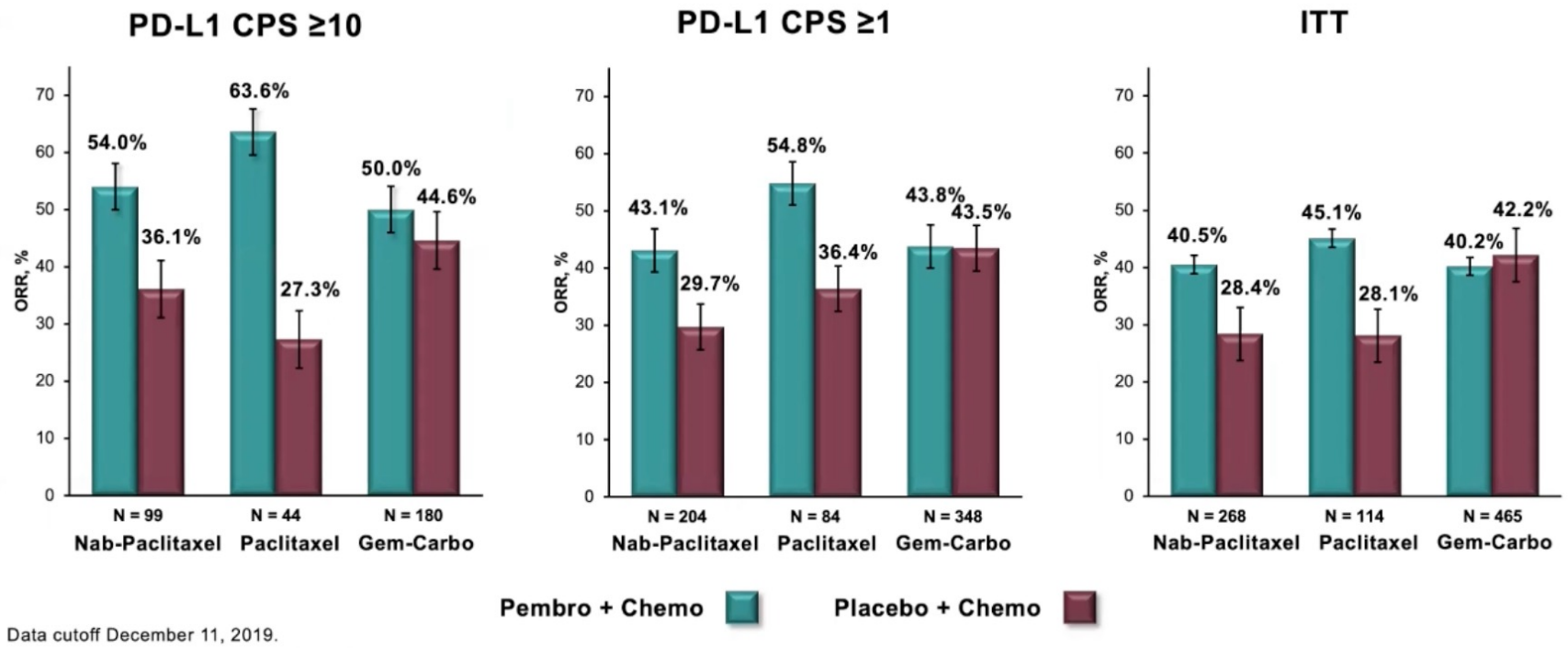
Cortes et al, Lancet 2020

Overall Survival: PD-L1 CPS ≥10



mOS pembrolizumab plus chemotherapy versus placebo plus chemotherapy (23.0 months versus 16.1 months, respectively) at a median follow-up of 44.1 months in PD-L1-positive CPS ≥ 10 (HR 0.73; 95% confidence interval 0.55–0.95; p=0.0093)

KEYNOTE-355 ORR by Chemo Partner



Data cutoff December 11, 2019.

*Trial was not powered to compared chemotherapy groups

Rugo et al, SABCS 2020

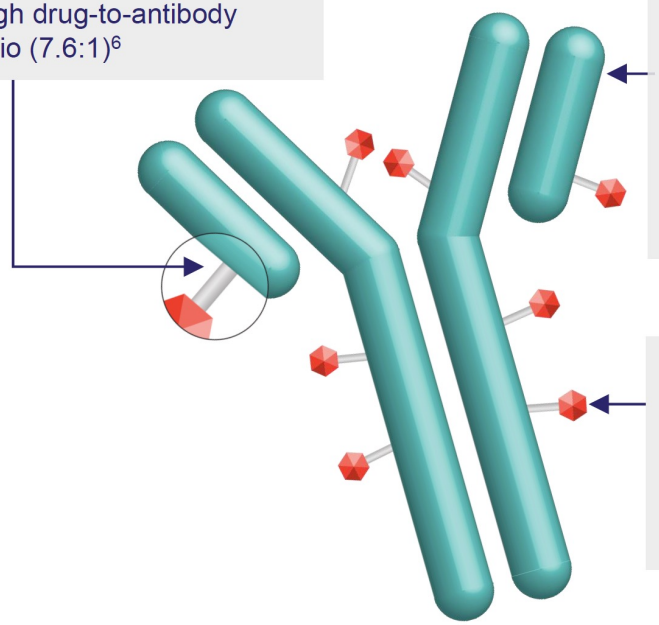
KEYNOTE-355 Conclusions

- Pembro + chemo significantly improves PFS and OS in first-line met TNBC PD-L1-positive (CPS $\geq$ 10)
- Magnitude of benefit greater for OS compared to PFS (as can be seen for IO)
- Benefit of pembro present in all chemo arms
- Granted accelerated FDA-approval 11/2020 for this indication

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]

Linker for SN-38
- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)[6]



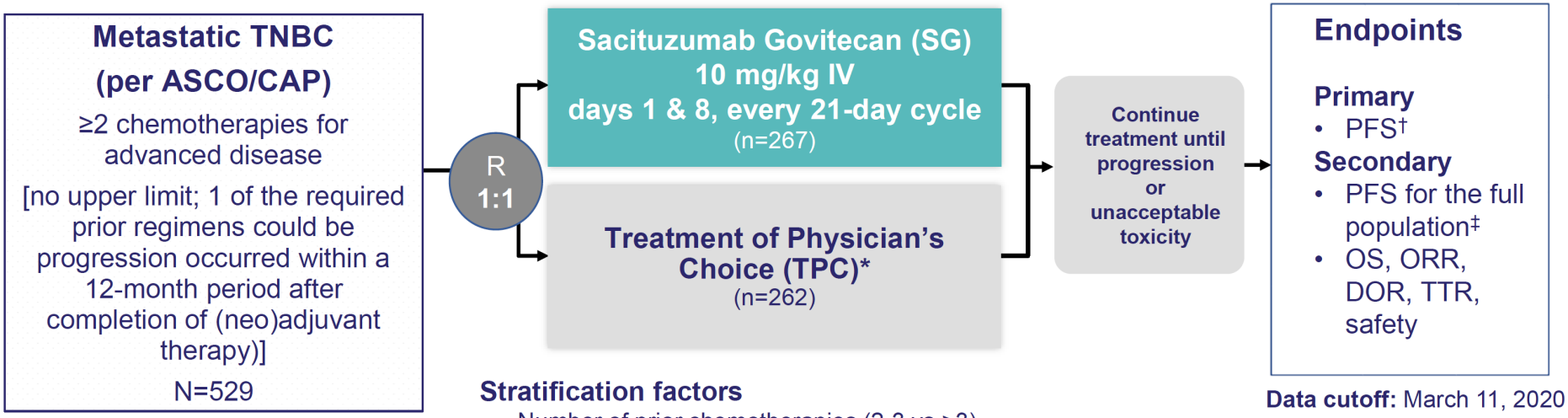
Humanized anti–Trop-2 antibody
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

SN-38 payload
- SN-38 more potent than parent compound, irinotecan

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. Nagayama 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.

SG: ASCENT trial

Demographics and Patient Characteristics

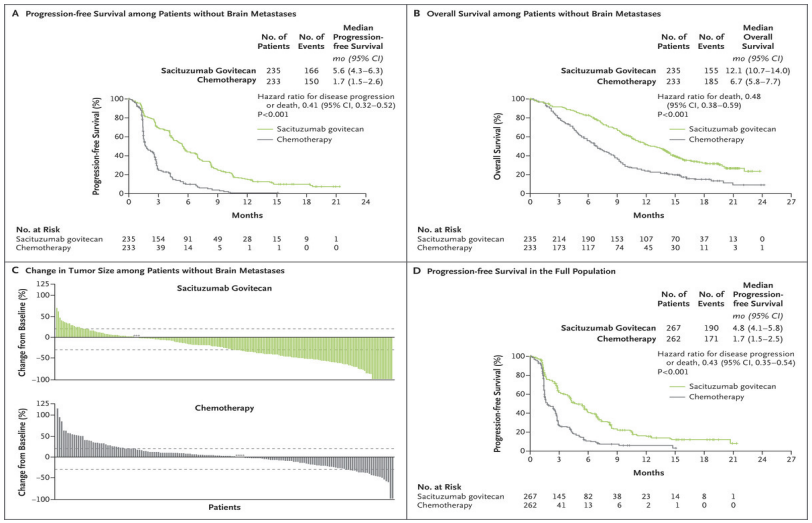
	SG (n=235)	TPC (n=233)
Female—no. (%)	233 (99)	233 (100)
Median age—yr (range)	54 (29-82)	53 (27-81)
Race or ethnic group—no. (%)		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG PS—no. (%)		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
BRCA 1/2 mutational 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.

Sacituzumab govitecan Indications and key findings

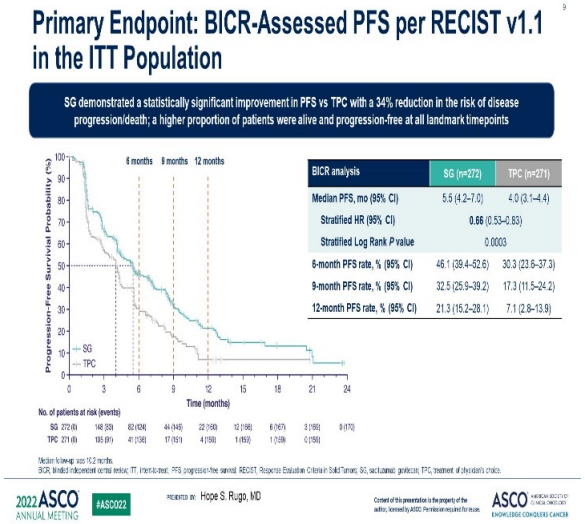
- TNBC: ASCENT trial Bardia NEJM 2021
  - Eligibility: relapsed/refractory metastatic or unresectable/locally advanced TNBC, ≥2 prior lines, prior taxane (in any setting)
  - FDA approved indication: Metastatic TNBC, ≥2 prior lines, at least one of which was for metastatic disease
  - Key findings: Improved PFS and OS with sacituzumab compared to standard chemotherapy
- ER+: TROPiCS-02 Rugo ASCO 2022
  - Eligibility: HR+/HER2- metastatic or locally recurrent inoperable disease that progressed after ≥ 1 endocrine therapy, taxane and CDK46i in any setting, ≥2 and ≤4 prior lines
  - Key finding: Improved PFS with sacituzumab compared to standard chemotherapy. OS not reported.



OS

PFS

ASCENT trial Bardia NEJM 2021



TROPiCS-02 Rugo ASCO 2022

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.

ASCENT Conclusion

- Sacituzumab govitecan compared to single-agent TPC resulted in superior ORR, PFS and OS
- Neutropenia was common and g-csf administered to ~50% of patients. Discontinuation for Aes was uncommon
- ASCENT confirmed Phase II trial and FDA full approval met TNBC with at least 2 prior systemic therapies (at least one line in metastatic setting).
- Many ongoing studies in TNBC fist line, adjuvant, ER+ and other epithelial tumors

2022 ASCO® ANNUAL MEETING

DESTINY-Breast04

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Results of DESTINY-Breast04, a randomized, phase 3 study

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June 5, 2022

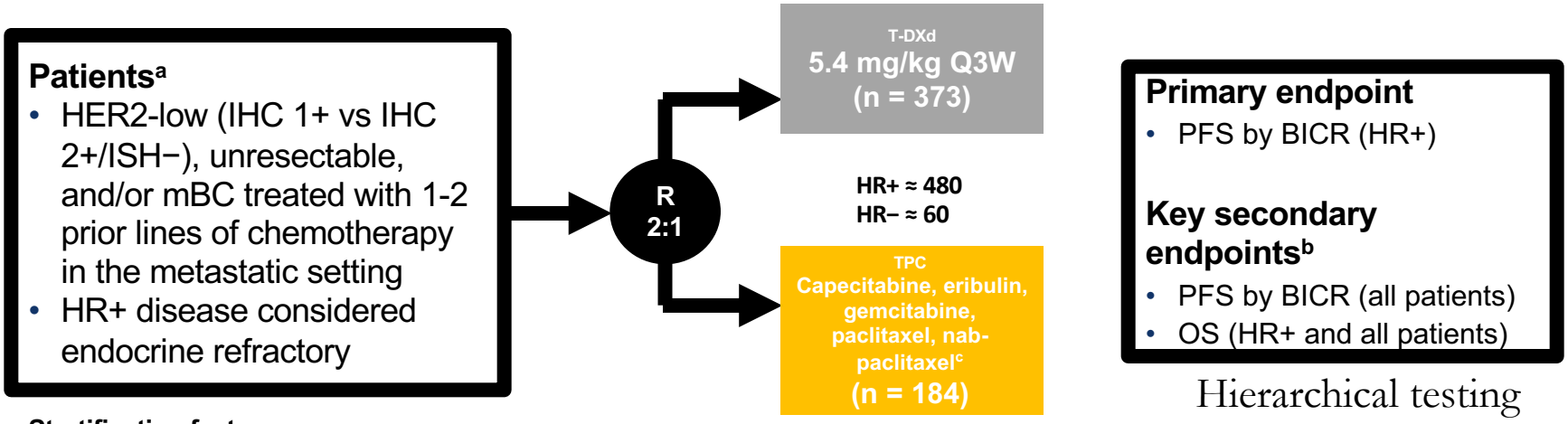
Additional authors: William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

On behalf of the DESTINY-Breast04 investigators

LBA-3

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

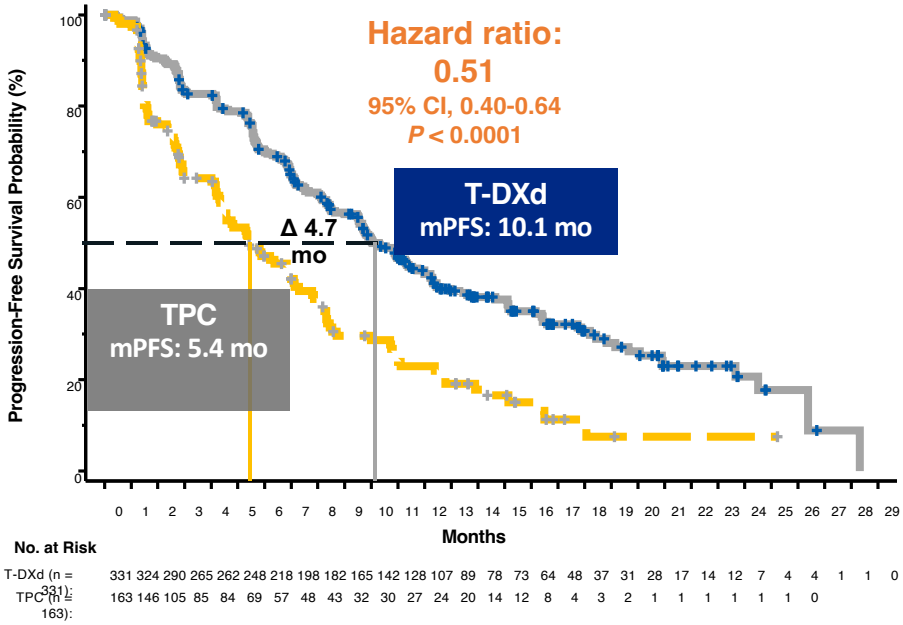
	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
Asia	128 (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.

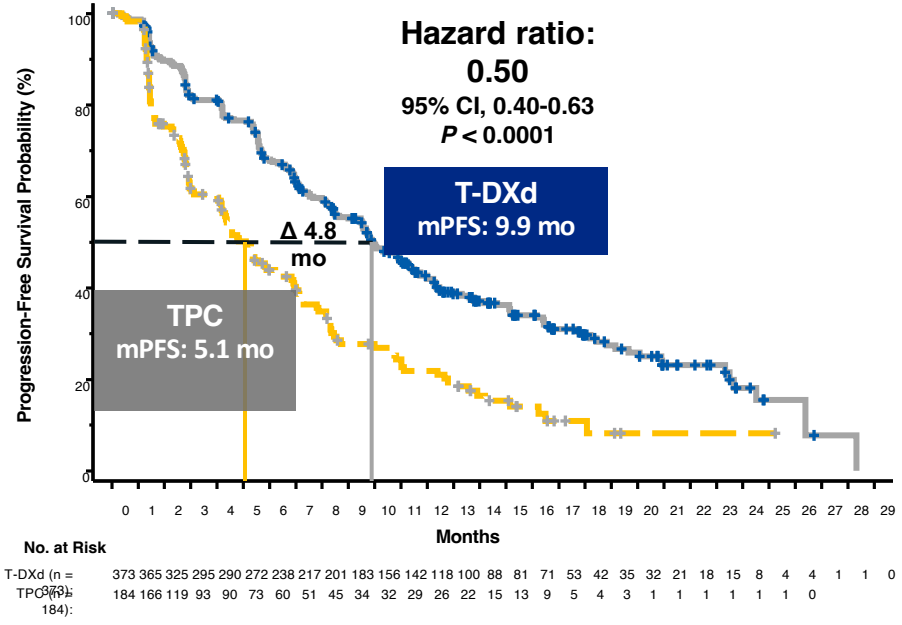
TNBC: 45 on T-DXd and 22 on TPC

PFS in HR+ and All Patients

Hormone receptor–positive



All patients

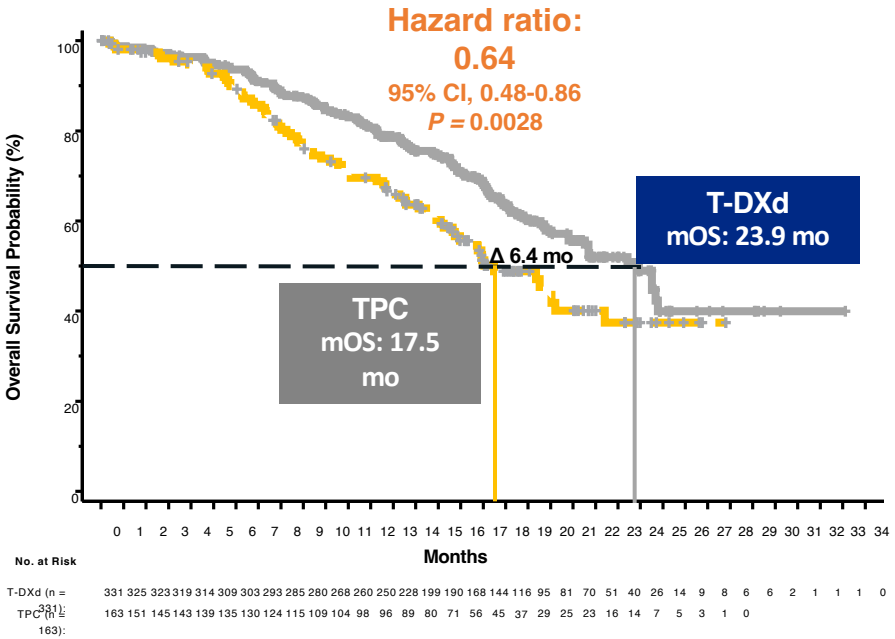


PFS by blinded independent central review.

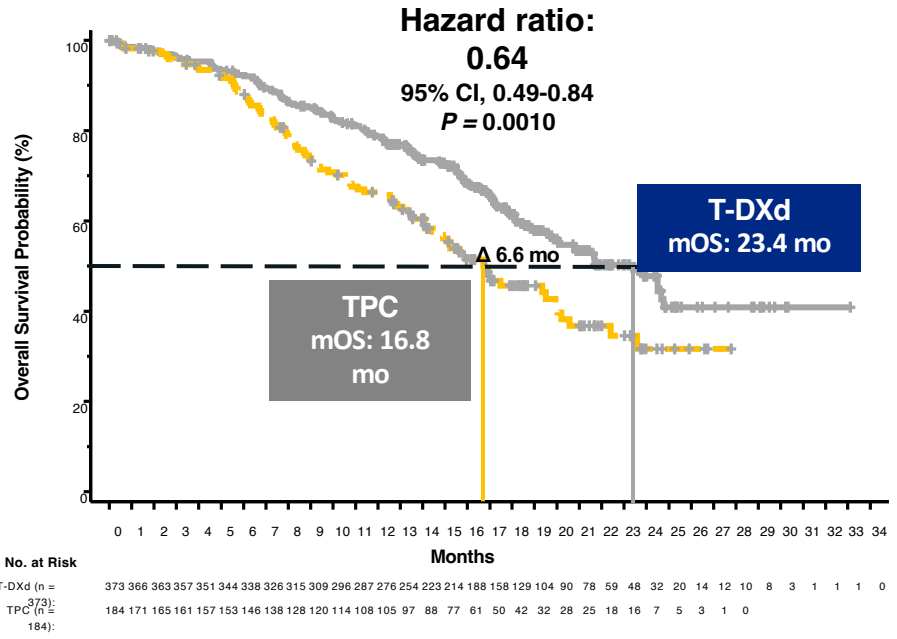
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

Hormone receptor–positive



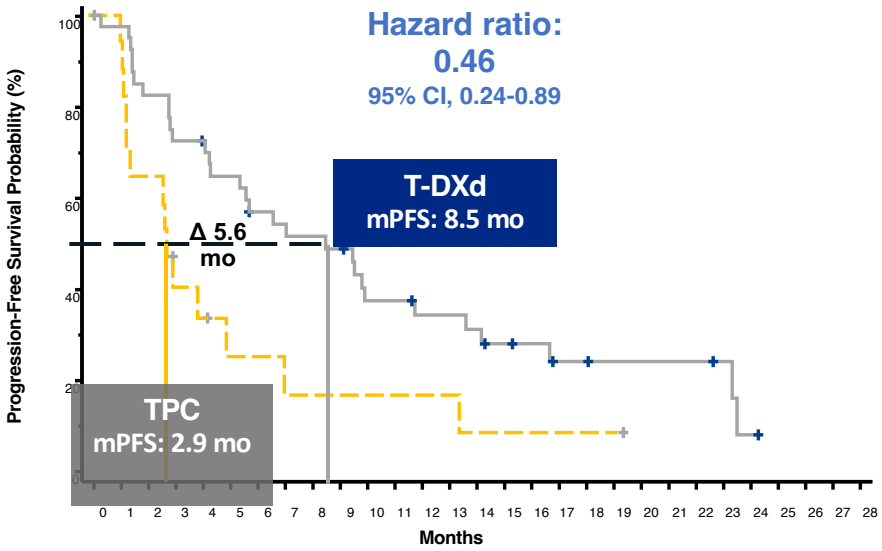
All patients



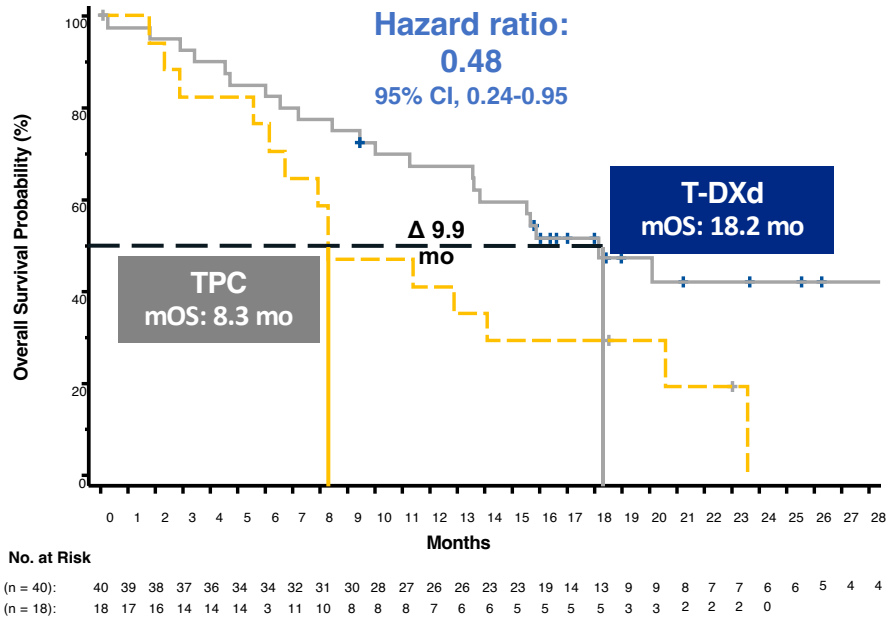
HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS and OS in TNBC (Exploratory Endpoints)

PFS



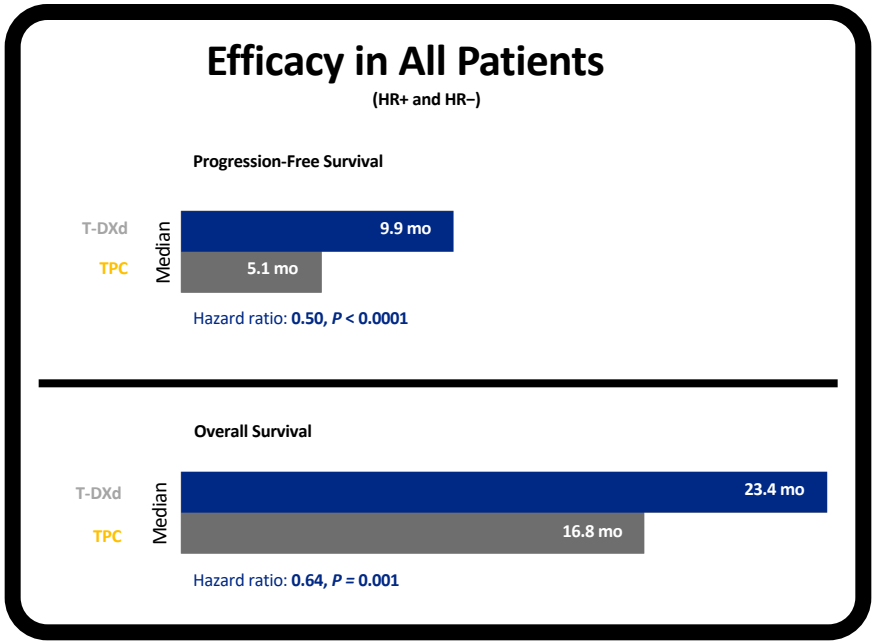
OS



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.

DESTINY-Breast04 establishes T-DXd as the new standard of care in HER2-low, HR+/HR− mBC

- T-DXd is the first HER2-targeted therapy to demonstrate unprecedented statistically significant and clinically meaningful improvement in PFS and OS versus TPC
- Similar magnitude of benefit across all subgroups, including HER2 IHC status and prior CDK4/6i use
- Safety is consistent with the known safety profile and showed an overall positive benefit-risk
- DESTINY-Breast04 establishes HER2-low (IHC 1+, IHC 2+/ISH−) mBC as a new targetable patient population, with T-DXd as a new standard of care



CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; 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; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Take Home: Trastuzumab deruxtecan in "Her2 low" MBC

- **Practice changing:** Trial has established the clinical utility of T-DXd in previously treated (at least one prior line of chemotherapy (as well as prior ET for HR+)) MBC that is Her2 1+ or Her2 2+/ISH neg
  - mPFS increased from 5.1m with TPC to 9.9m with T-DXd (HR 0.50)
  - mOS also improved: 16.8m with TPC to 23.4m with T-DXd (HR 0.64)
- Primary endpoint was mPFS in ER+/Her2 low: limited #s of TNBC (although similar results)
- Interstitial pneumonitis can be lethal (must monitor)
- "Her2 low" is heterogeneous and not a distinct subset
- Part of the effectiveness is the lack of prior exposure to topo I inhibitors – how this will interact with Sacituzumab govitecan is unknown

Conclusions

- TNBC remains an aggressive breast cancer subtype although outcomes are improving likely related to use of neoadj chemo, strategies to escalate therapy and new agents.

- Pembrolizumab + chemotherapy in PD-L1-positive. Remember to use the appropriate PD-L1-assay.

- Sacituzumab govitecan prolongs survival in previously treated patients.
- Fam-trastuzumab deruxtecan prolongs survival in previously treated patients, although sample size for TNBC small.
- Continues to be a need for biomarker selection strategies, novel agents and combinations.

QUESTIONS?