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

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A NATIONAL CANCER INSTITUTE-DESIGNATED CONSORTIUM COMPREHENSIVE CANCER CENTER

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WOMEN'S CANCER
DEVELOPMENTAL THERAPEUTICS

Learning Objectives

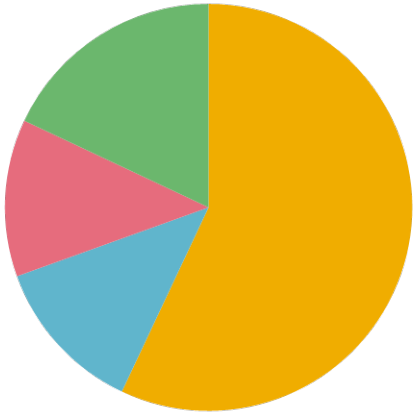
- To understand the biology of triple-negative breast cancer (TNBC) and unique features of systemic treatment in early- and late-stage disease
- To summarize recent treatment advanced including IO in neoadjuvant and metastatic setting

Biologic Breast Cancer Subtypes

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

Traditional Subtypes

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



Modern Subtypes

ER+HER2- → ~60% HER2 low

ER+HER2+

ER-HER2+

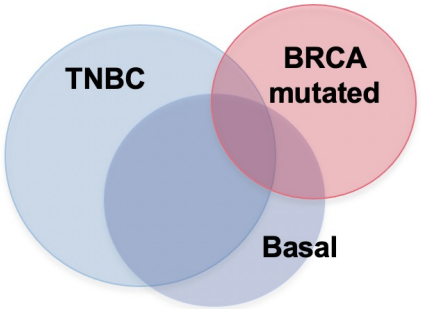
ER-HER2- (TNBC) → ~40% HER2 low

Perou CM et al Nature 2000, Bauer KR Cancer 2007, ER/PR ASCO-CAP guidelines 2020, HER2 ASCO-CAP guidelines 2023, Tarantino P et al JCO 2020

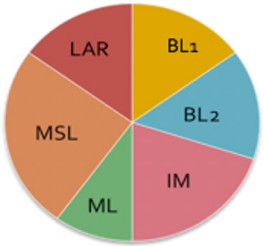
TNBC Subtyping to Characterize Heterogeneity

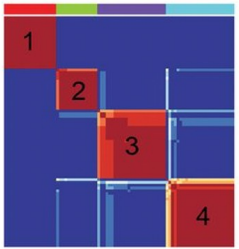
Basal-like molecular subtype[1]

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



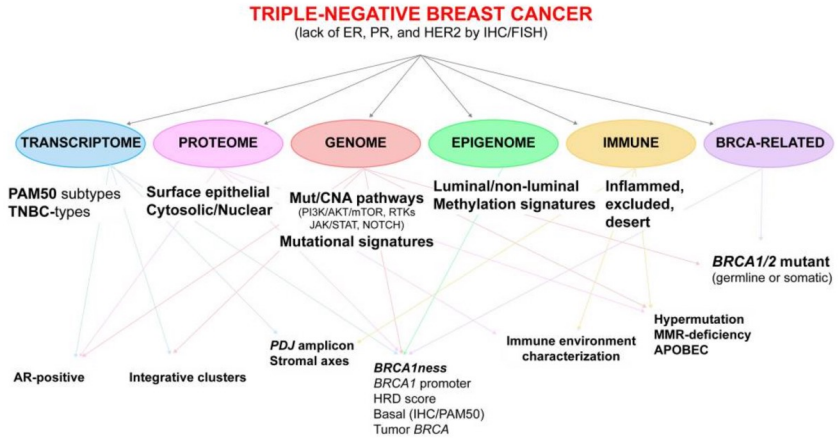
TNBCtype[2]





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

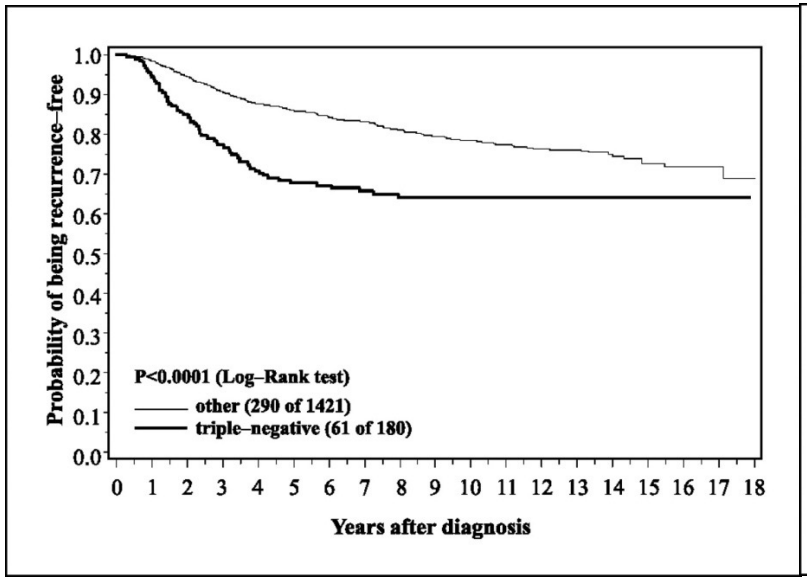
- Actionable Update: HER2 low subtype – trastuzumab deruxtecan

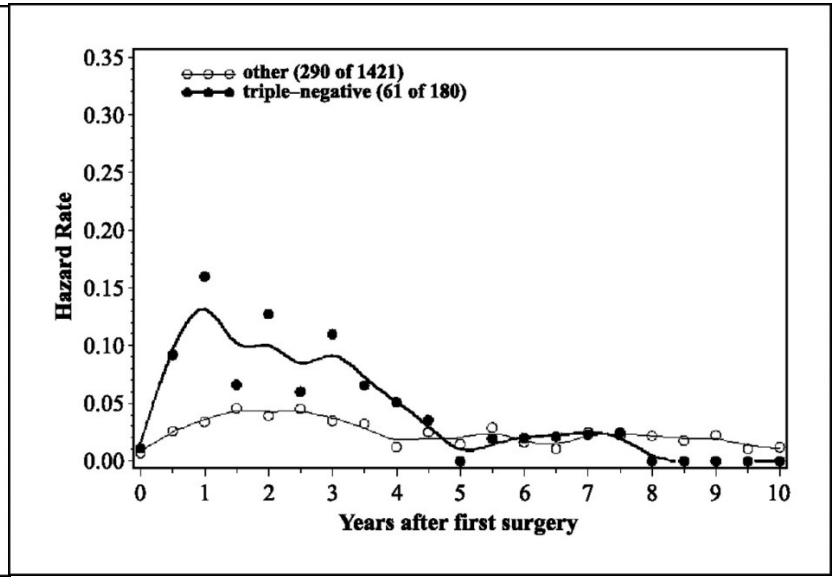
TNBC Clinical Characteristics

- Historically, aggressive breast cancer subtype with higher risk of recurrence, limited treatment options (chemotherapy) and inferior survival
- Early recurrence (within 3-5 years), more visceral disease (brain, lung)
- **Clinical outcomes are improving**
- Neoadjuvant chemotherapy in early-stage disease incorporating IO and adjuvant capecitabine
- Targeted (PARPi for BRCA-mutated), IO + chemo in PD-L1-positive, TROP2 ADC (Sacituzumab govitecan), HER2-low trastuzumab deruxtecan

Marra et al NPJ 2020, Chan et al JOP 2018, Lyons et al Br Ca Met and Drug Res 2019

Distant Recurrence in TNBC: 3-5 years



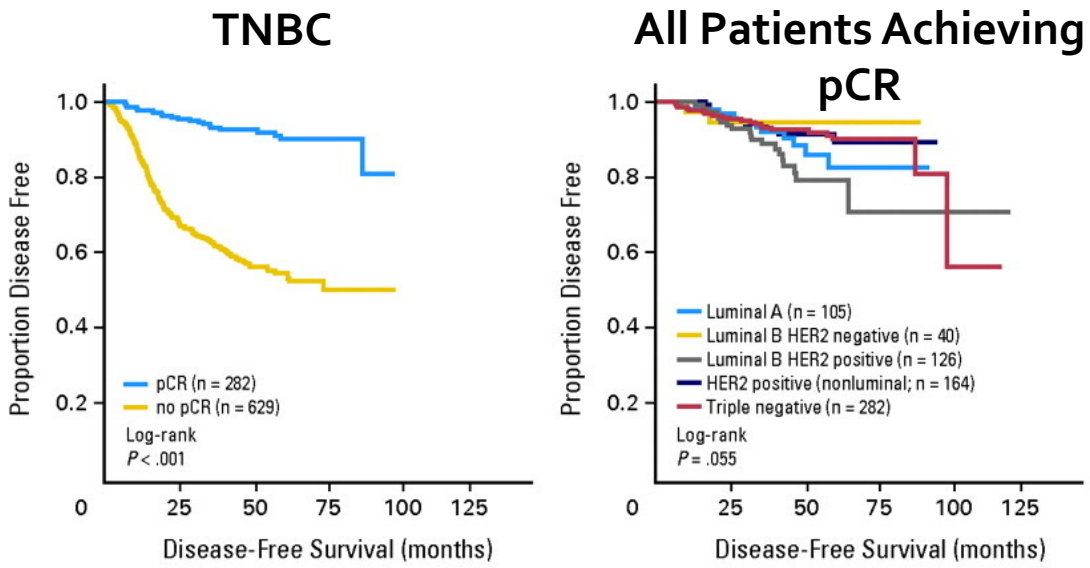


Clinical Cancer Research

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

Prognostic Impact of pCR on DFS in TNBC



4,193 patients treated with neoadjuvant anthracycline-taxane-based chemotherapy
TNBC subtype pCR ypTo/is ypNo (35.8%)

Gunter von Minckwitz et al. JCO 2012;30:1796-1804

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Unique Risk Factors for TNBC

- **Young women**
  - Mean age at diagnosis 53 years TNBC v. 57.7 years other ER or HER2 positive; Canada (Dent et al CCR 2007)
  - ~ 20% of breast cancer is TNBC in women under 45; US SEER (Dolle et al Cancer Epi Bio Prev 2009)
- **African-American women**
  - Threefold increased risk of TNBC in African-American and African Women (Boyle Annals of Oncology 2012)
  - 14-40% of breast cancers are TNBC (Carey et al JAMA 2006, Bauer et al Cancer 2007,)
- **BRCA1 mutation carriers**

Early-Stage TNBC

Neoadjuvant and Adjuvant Therapy

Preoperative Chemotherapy: ≥ T2 or ≥ N1 TNBC Why is this important?

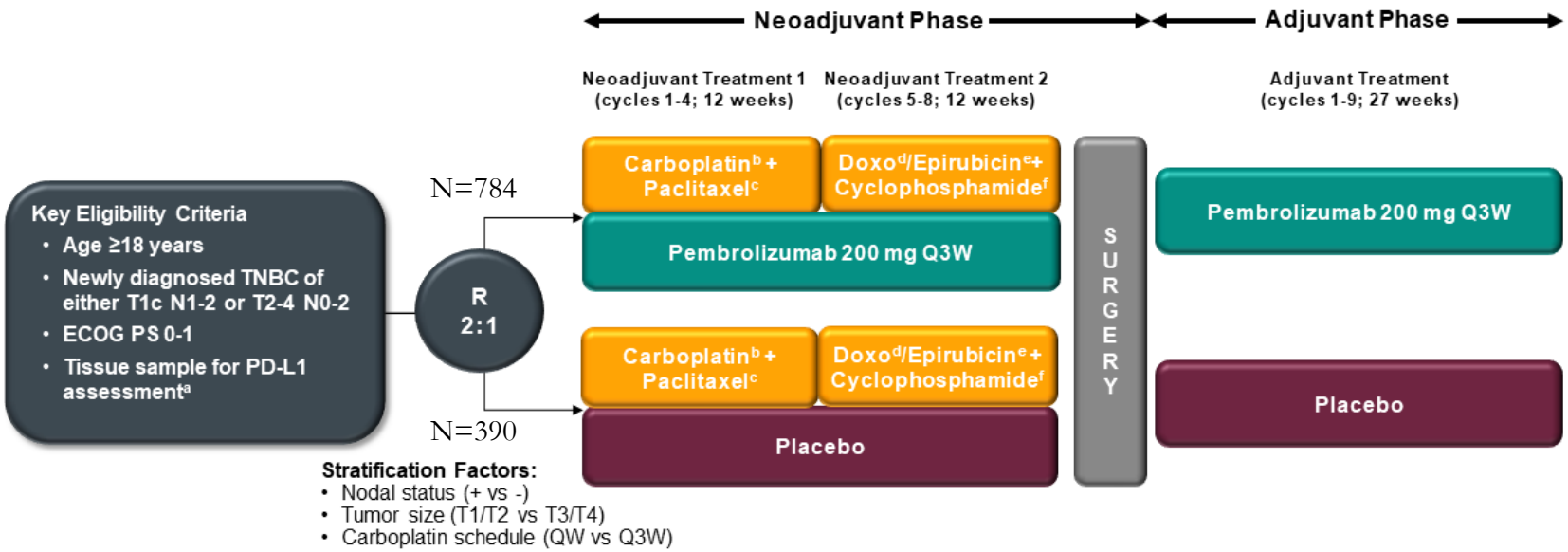
- Most patients with early stage TNBC are Stage II or III at diagnosis (>60%) and candidates for preop chemo

- Benefits:
  - Facilitates breast conservation, render inoperable operable
  - Prognostic information in TNBC (and HER2+) based on pCR v. residual disease
  - Allow tailoring adjuvant therapy in TNBC (and HER2+) if no pCR
  - Allows time for genetic testing, plan reconstruction
  - Possibly allow for SLNBx in N1 if positive axilla cleared clinically with preop therapy

Preferred Regimen: KEYNOTE-522 – carboplatin paclitaxel weekly x 12 weeks followed by doxorubicin cyclophosphamide every 3 weeks x 4 cycles with pembrolizumab x 1 year

NCCN guidelines 4.2023

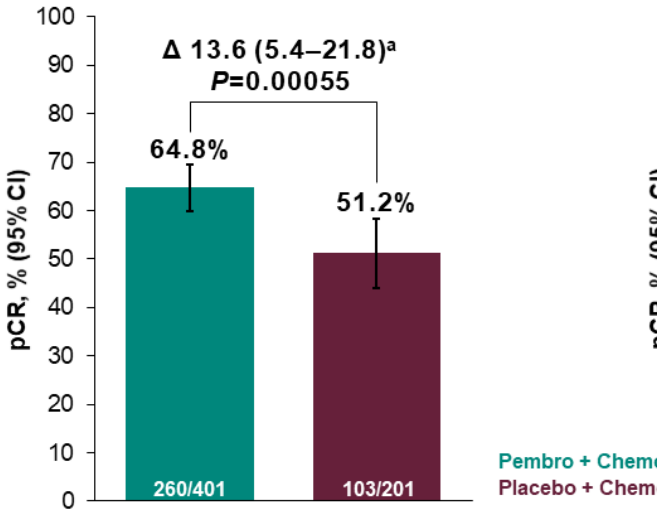
KEYNOTE-522 Study Design (NCT03036488)



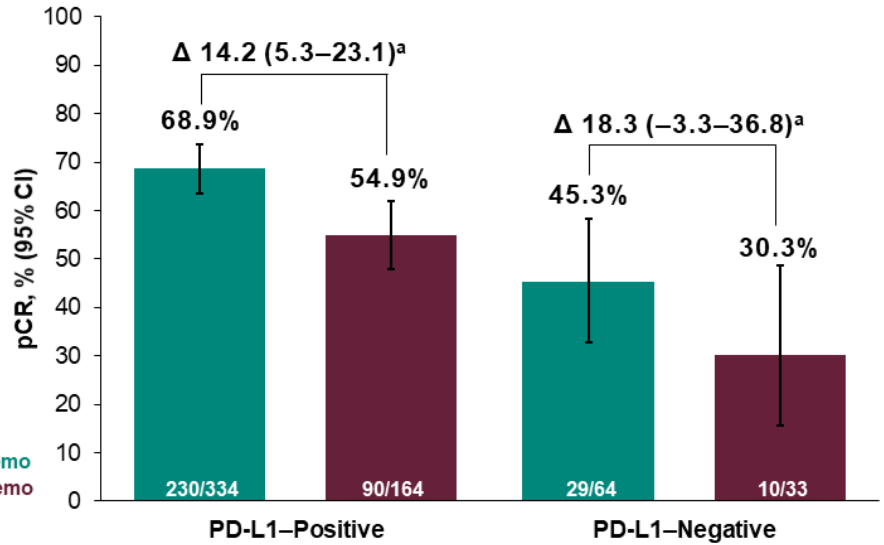
- Primary Endpoints
  - pCR (ypT0/Tis ypN0) assessed by local pathologist in ITT population[a]
  - Event-free survival (EFS) assessed by investigator in ITT population

Pathological Complete Response at IA1

Primary Endpoint: ypT0/Tis ypN0

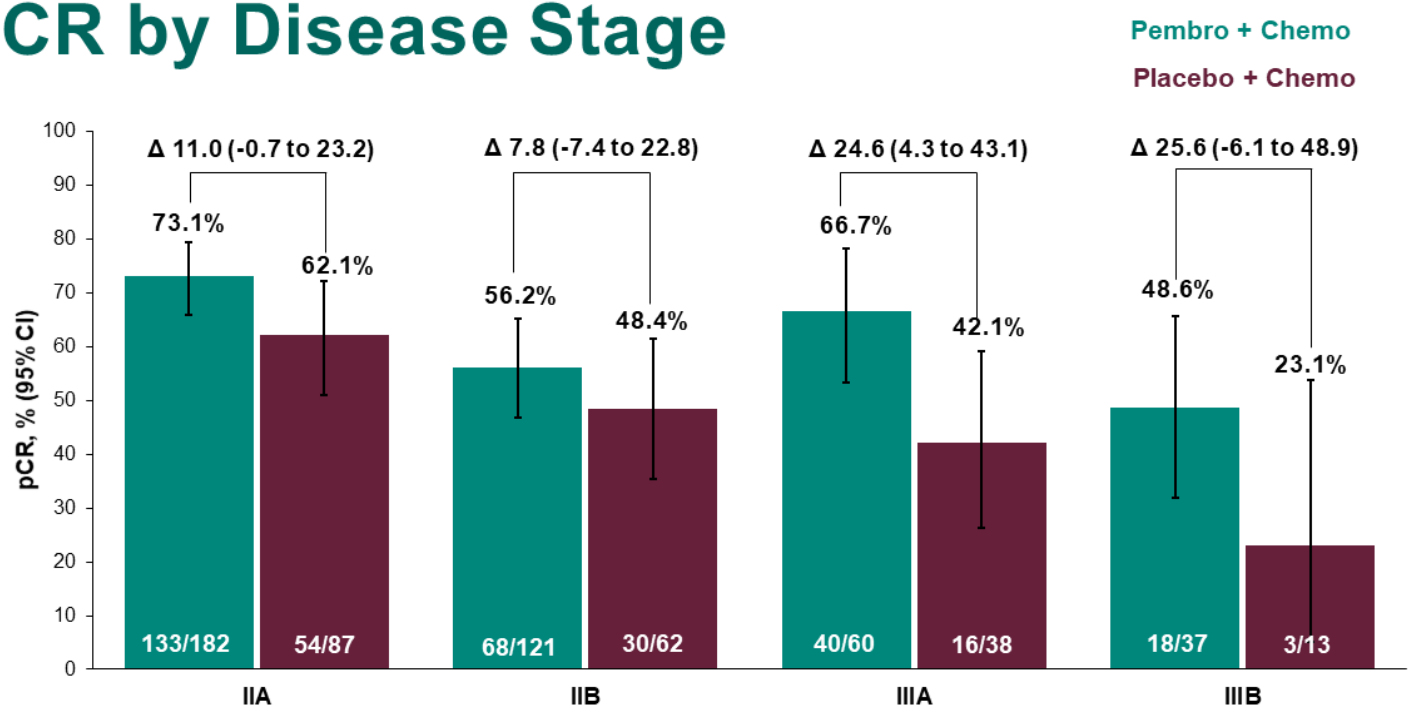


By PD-L1 Status[b]: ypT0/Tis ypN0



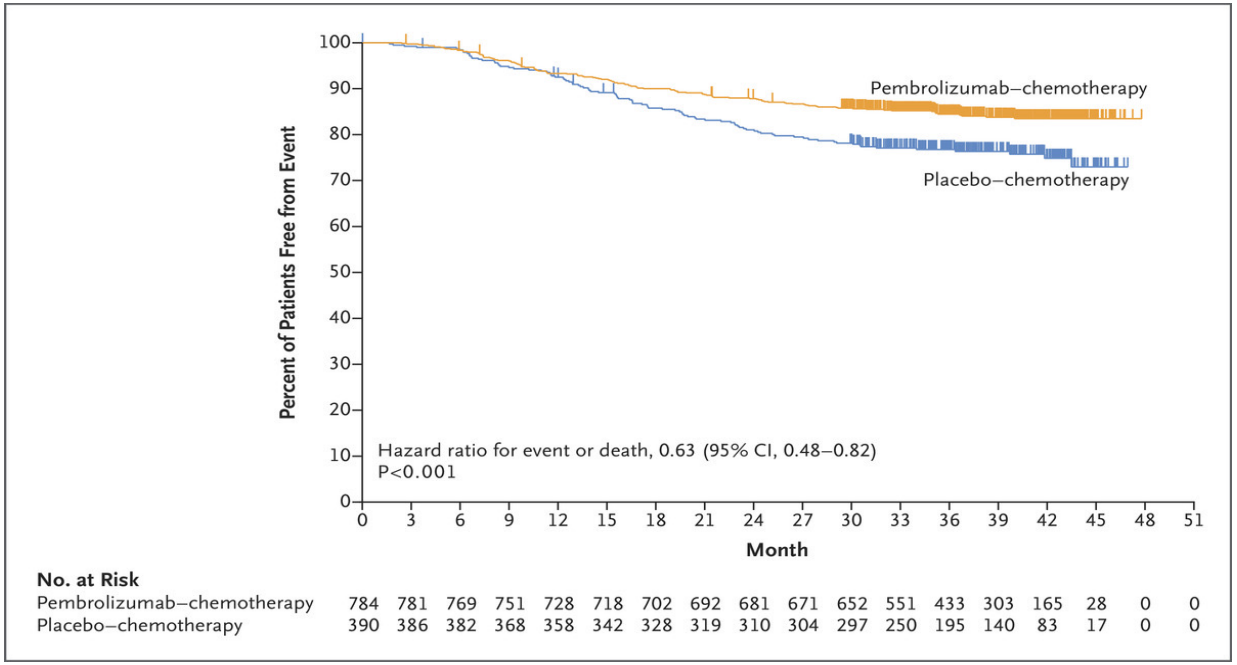
[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Data cutoff date: September 24, 2018.

pCR by Disease Stage



Post-hoc analysis. Estimated treatment difference based on unstratified Miettinen & Nurminen method. Data cutoff date: September 24, 2018.

KEYNOTE-522: Kaplan–Meier Estimates of Event-free Survival According to Treatment Group (Intention-to-Treat Population



Event-free survival at 36 mos

Pembro 84.5%
Placebo 76.8%

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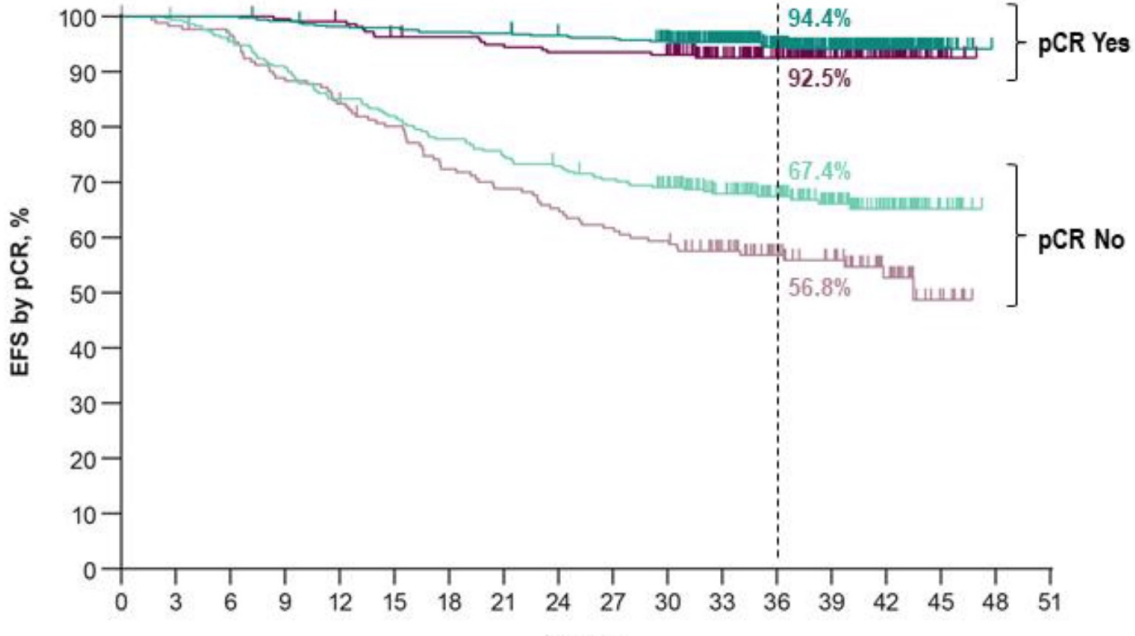
Schmid et al NEJM 2022

EFS by pCR (ypT0/Tis ypN0)

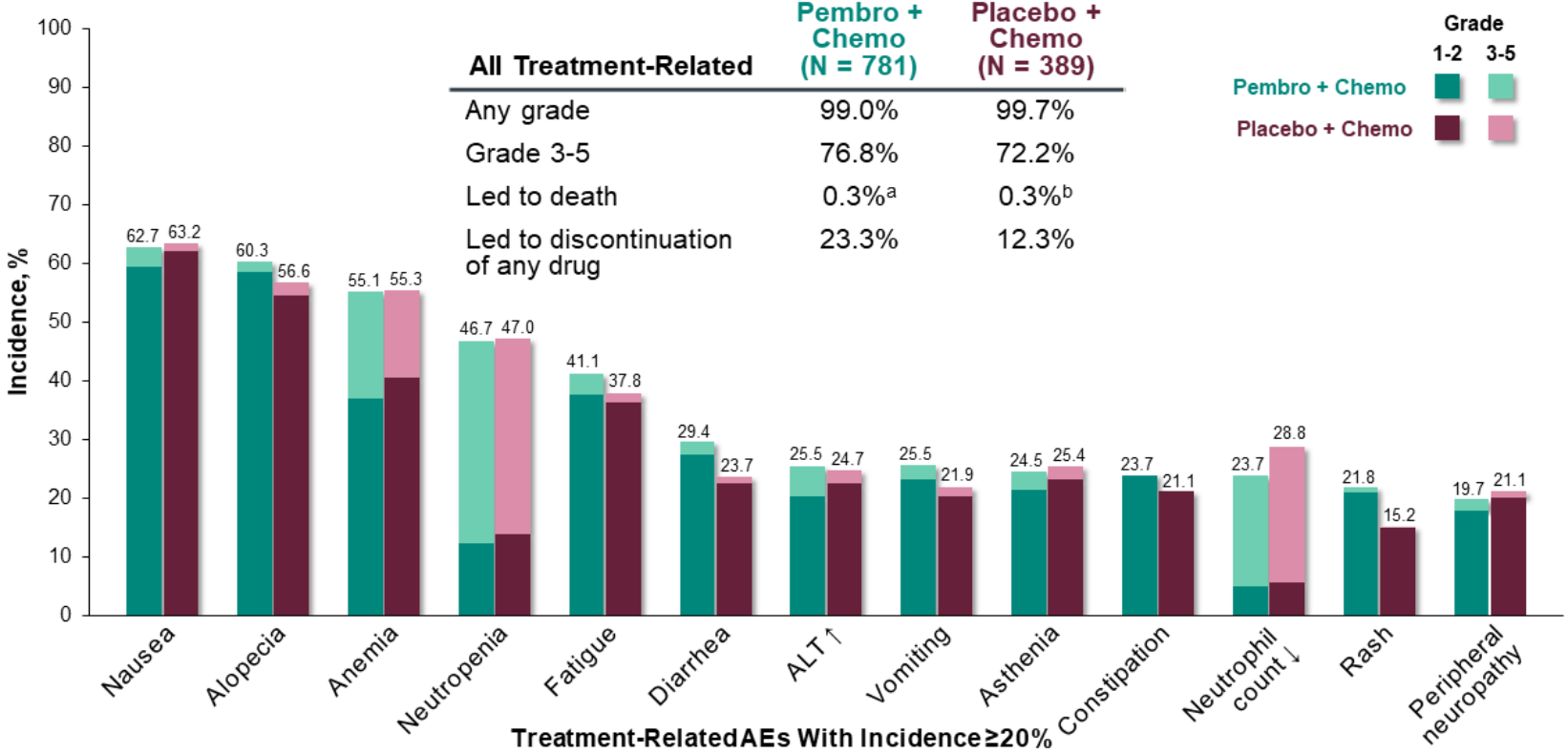


No. at Risk																		
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	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.

Treatment-Related AEs in Neoadjuvant Phase: IA2

All Treatment-Related	Pembro + Chemo (N = 781)	Placebo + Chemo (N = 389)
Any grade	99.0%	99.7%
Grade 3-5	76.8%	72.2%
Led to death	0.3%[a]	0.3%[b]
Led to discontinuation of any drug	23.3%	12.3%



[a]1 patient from sepsis and multiple organ dysfunction syndrome; 1 patient from pneumonitis. [b]1 patient from septic shock. Data cutoff date: April 24, 2019.

Neoadjuvant Chemotherapy Summary

- The addition of pembrolizumab to platinum-containing neoadjuvant chemotherapy improves pCR and EFS in patients with T2+ or node + TNBC regardless of PD-L1 status.
- The safety profile is consistent with known profiles of individual agents, including alopecia, fatigue, cytopenias, diarrhea. Autoimmune tox with rash and hypothyroid relatively common. Other autoimmune tox much less common.
- Trials to evaluate de-escalation strategies for patients with T2NoMo disease are needed.
- For patients with T1cNoMo, neoadjuvant chemotherapy with AC-T or carboplatin/docetaxel x 6 cycles OR proceed to surgery depending on multi-disciplinary team discussion.

Sharma et al CCR 2018 carboplatin docetaxel q 3 weeks x 6 pCR 55%, 3-year RFS 79%

Breast Cancer Research and Treatment (2022) 191:389–399
https://doi.org/10.1007/s10549-021-06424-z

EPIDEMIOLOGY

AC-T v. TC in Older patients with node negative TNBC

Evaluating anthracycline + taxane versus taxane-based chemotherapy in older women with node-negative triple-negative breast cancer: a SEER-Medicare study

Anna R. Schreiber[1] · Jodi Kagihara[2] · Megan Eguchi[3] · Peter Kabos[2] · Christine M. Fisher[4] · Elisabeth Meyer[3] · Elizabeth Molina[3] · Lavanya Kondapalli[5] · Cathy J. Bradley[3] · Jennifer R. Diamond[2]

Received: 23 April 2021 / Accepted: 14 October 2021 / Published online: 27 October 2021

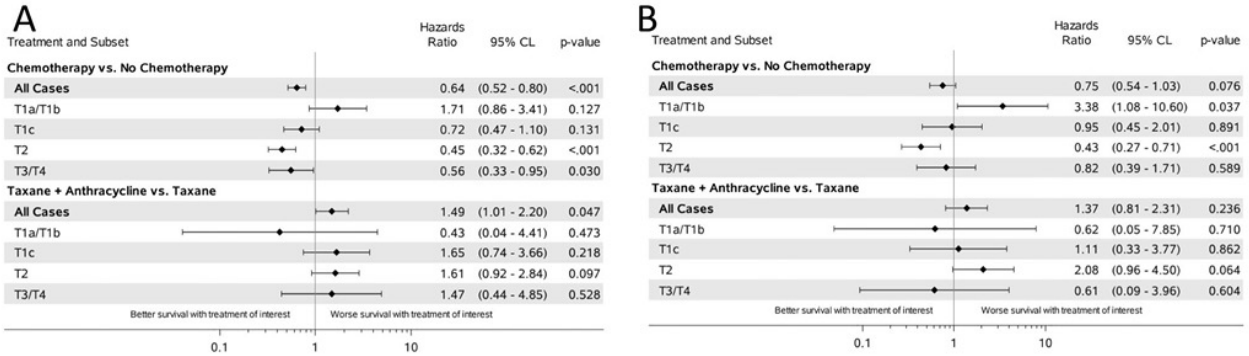


Fig. 3 Forest plots for multivariate analysis of (**A**) overall survival (OS) and (**B**) cancer-specific survival (CSS). Hazard ratios shown overall and by stage after reflecting for all other covariates

- Patients ≥ 66 yo with node-negative TNBC had inferior CSS and OS when treated with anthracycline + taxane-containing v. taxane-containing regimen
- Favor docetaxel cyclophosphamide x 4 cycles (or docetaxel carboplatin) for older pts with low risk TNBC

Additional Adjuvant Therapy for Patients with High Risk TNBC

- Adjuvant capecitabine (no pCR with preoperative chemo)
- Adjuvant Olaparib for high-risk BRCA1/2 germline mutation carriers

Adjuvant Capecitabine : s/p Neoadjuvant Chemotherapy with no pCR

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ORIGINAL ARTICLE

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

N. Masuda, S.-J. Lee, S. Ohtani, Y.-H. Im, E.-S. Lee, I. Yokota, K. Kuroi, S.-A. Im, B.-W. Park, S.-B. Kim, Y. Yanagita, S. Ohno, S. Takao, K. Aogi, H. Iwata, J. Jeong, A. Kim, K.-H. Park, H. Sasano, Y. Ohashi, and M. Toi

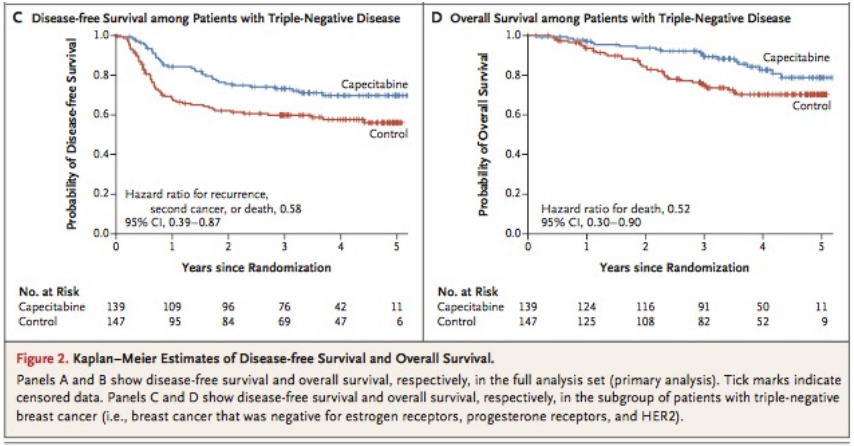

Figure 2. Kaplan–Meier Estimates of Disease-free Survival and Overall Survival.
Panels A and B show disease-free survival and overall survival, respectively, in the full analysis set (primary analysis). Tick marks indicate censored data. Panels C and D show disease-free survival and overall survival, respectively, in the subgroup of patients with triple-negative breast cancer (i.e., breast cancer that was negative for estrogen receptors, progesterone receptors, and HER2).

- CREATE-X ~900 patients HER2-negative (approx. 1/3 TNBC) residual disease after anthracycline +/- taxane chemo in Asia
- Randomized to adjuvant capecitabine x 8 cycles v. no further chemo
- Improvement in DFS and OS
- No data following KEYNOTE-522, safe to administer with pembrolizumab

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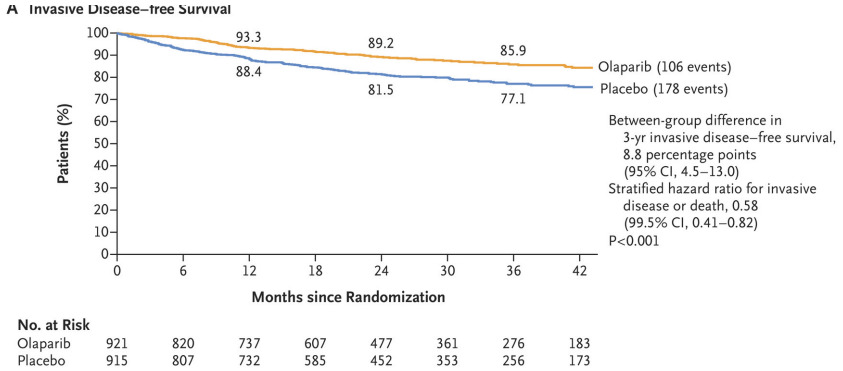
ORIGINAL ARTICLE

Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

A.N.J. Tutt, J.E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi,



- Phase III randomized, double-blind, placebo-controlled trial
- High risk, early-stage HER2-negative with BRCA1/2 germline mutation
- For TNBC – for patients with prior adjuvant chemo: node-positive or tumor 2 cm+. For prior neoadjuvant chemo: residual invasive disease
- Improvement in iDFS, dDFS and OS with adjuvant Olaparib x 1 year
- No data following KEYNOTE-522 or sequencing with capecitabine; safe to co-administer with pembrolizumab

Metastatic TNBC

Chemotherapy, immunotherapy, antibody-drug conjugates and PARPi

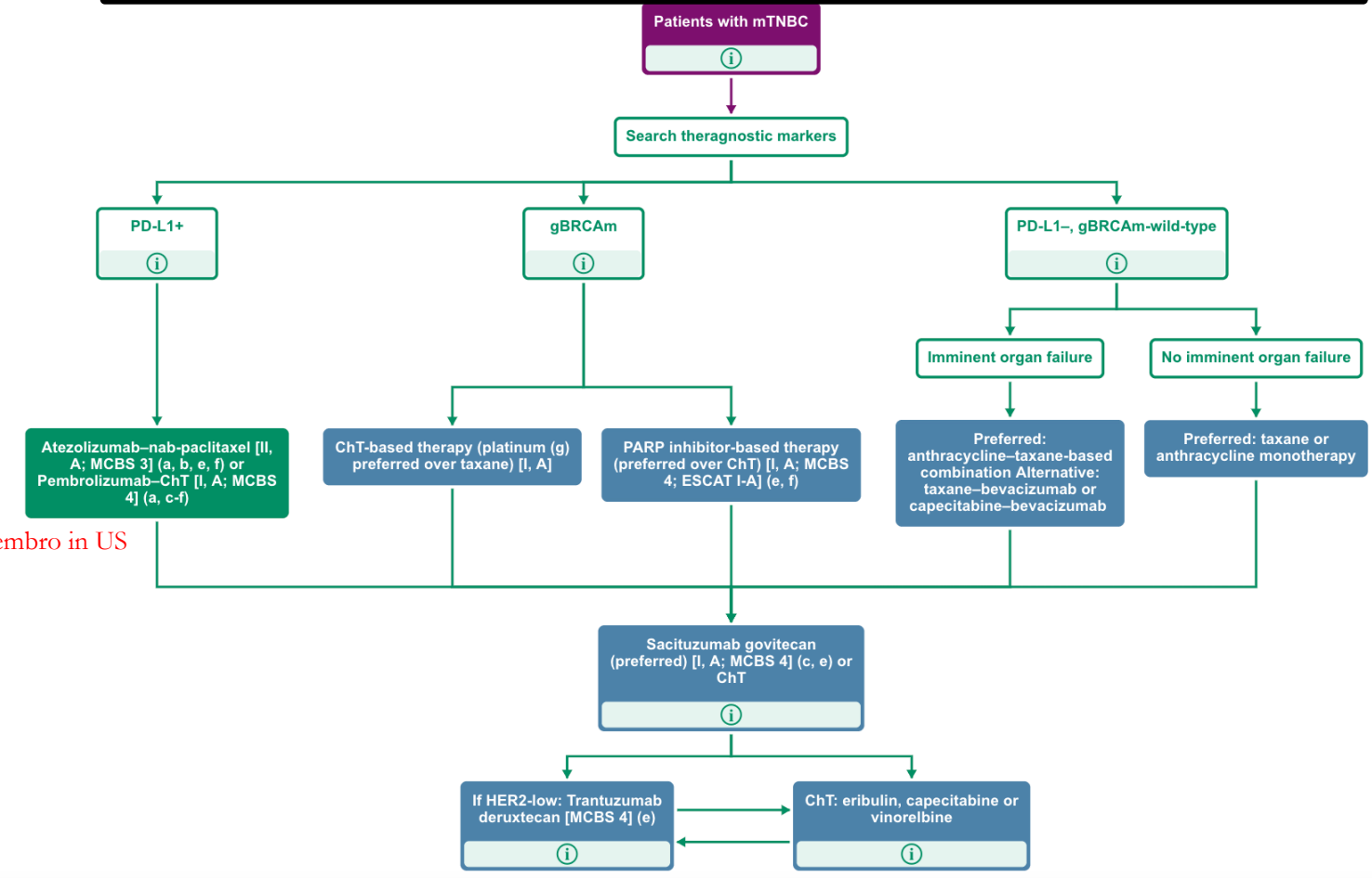
Metastatic TNBC-Historic Perspective

- **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

- **Many recent advances**
- Targeted (PARPi for BRCA-mutated), IO + chemo in PD-L1-positive, TROP2 ADC (Sacituzumab govitecan), HER2-low trastuzumab deruxtecan

Kassam et al Clinical Breast Cancer 2009

Landscape Metastatic TNBC



*only pembro in US

ESMO Guidelines 2023

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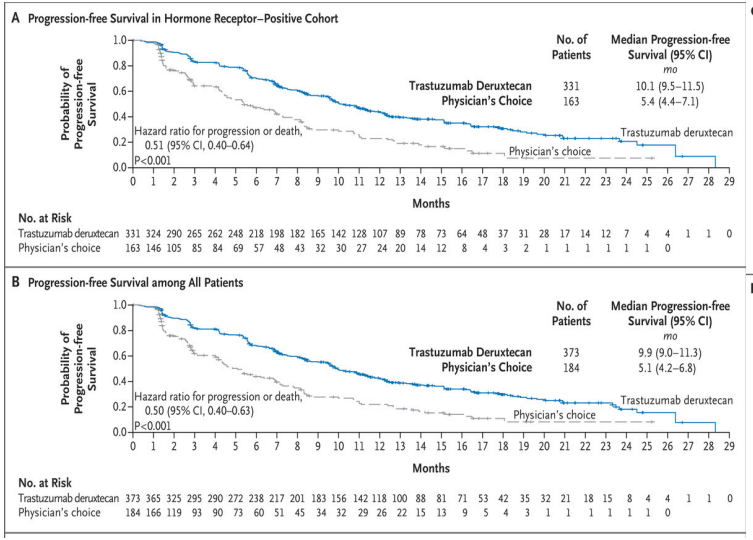
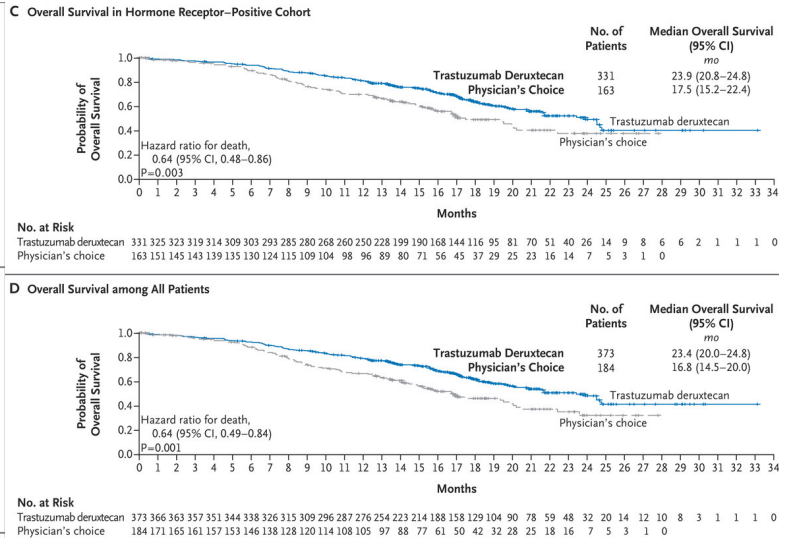
ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

- 2L and beyond
- Improvement in PFS and OS with T-DXd compared to TPC
- Small number of TNBC (~40 in T-DXd arm)
- Encourage repeat biopsy to eval for HER2 (IHC 1+ or 2+ ISH negative) as clinically feasible due to heterogeneity





2023 ASCO ANNUAL MEETING

Randomized Trial of Fixed Dose Capecitabine Compared to Standard Dose Capecitabine in Metastatic Breast Cancer: X-7/7 trial

Qamar Khan, Colleen Bohnenkamp, Taylor Monson, Holly Smith, Milind Phadnis, Vinay Raja, Manana Elia, Anne O'Dea, Gregory Crane, Mark Fesen, Lauren Nye, Maureen Sheehan, Robert Pluenneke, Raed Al-Rajabi, Joaquina Baranda, Anup Kasi, Richard McKittrick, Laura Mitchell, Stephanie LaFaver, Priyanka Sharma

PRESENTED BY: Qamar Khan, MD

X-7/7 Study Design

ELIGIBILITY

- Adult female patients with pathologically confirmed MBC
- Any prior number of chemo or endocrine therapies
- Any breast cancer subtype
- HER2+ required concurrent trastuzumab
- CrCl >50 mL/min

STRATIFICATION

- Line of chemotherapy (first or subsequent line)
- Measurable or non-measurable disease
- ER status

1:1

FD-7/7 Arm (N=80)

Capecitabine 1500 mg PO BID x7 days followed by 7-day rest

SD-14/7 Arm (N=73)

Capecitabine 1250* mg/m² PO BID x14 days followed by 7-day rest

Physician had discretion to use alternative dosing of 1000 mg/m² PO BID (N=11)

ENDPOINTS

- Primary: 3-month PFS
- Secondary: PFS, Overall Survival, Objective Response Rate, Toxicity

- CT C/A/P and bone scan every 12 weeks
- Cycles repeated every 14 (FD-7/7) or 21 (SD-14/7) days until PD, unacceptable toxicity, or delays >4 weeks
- Capecitabine toxicities were solicited at each visit

Progression Free Survival, Landmark Analysis and Objective Response Rate

PFS	FD-7/7 (N=80)	SD-14/7 (N=73)	P-value
3-month PFS	60 (76%)	55 (76%)	0.99
12-month PFS	31 (39%)	35 (50%)	0.23
24-month PFS	20 (25%)	16 (23%)	0.77
36-month PFS	8 (11%)	0	0.24

Response Rate	FD-7/7	SD-14/7	P-value
ORR	5/56 (8.9%)	9/46 (19.6%)	0.11

Toxicity

	FD-7/7 (N=80)	SD-14/7 (N=73)	P-Value
Diarrhea			
Any Grade	16 (20)	45 (61.6)	0.0039
Grade 2-4	**2 (2.5)**	**15 (20.5)**	**0.0008**
Hand Foot Syndrome			
Any Grade	22 (27.5)	39 (53.4)	0.0033
Grade 2-4	**3 (3.8)**	**11 (15.1)**	**0.0019**
Oral Mucositis			
Any Grade	3 (3.75)	20 (27.4)	0.0001
Grade 2-4	**0**	**4 (5.5)**	**0.0001**
Neutropenia			
Any Grade	30 (37.5)	31 (42.5)	0.67
Grade 2-4	**17 (21.3)**	**20 (27.4)**	0.68

Grade 3-4 toxicity:
27.4% in SD-14/7
11.3% in FD-7/7
p=0.02

Treatment Discontinuation:
28.7% in SD-14/7
7.5% in FD-7/7
p<0.0006

Dose Modification:
23.3% in SD-14/7
7.5% in FD-7/7
p=0.0063

Fixed-Dose 7/7 Capecitabine in Metastatic TNBC

- Goal for treatment of metastatic breast cancer is decrease symptoms, improve QOL and prolong survival
- **Fixed-dose 7/7 capecitabine has a favorable safety profile and equivalent efficacy compared to standard-dose and schedule in metastatic breast cancer**
- FDA Project Optimus changing focus or early drug development to identify a dose based on safety, efficacy and QOL rather than just the MTD based on DLTs in the first cycle
- **Insufficient data to apply this dose and schedule to the adjuvant setting without further clinical trial data**

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 is appropriate for many patients in the neoadjuvant setting and select patients in the metastatic setting.
- Sacituzumab govitecan and trastuzumab deruxtecan (in HER2 low) prolongs survival in previously treated patients.
- Continues to be a need for biomarker selection strategies, novel agents and combinations.