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COMPREHENSIVE
CANCER CENTER

Breast Cancer Management in North Carolina: Updates for 2020

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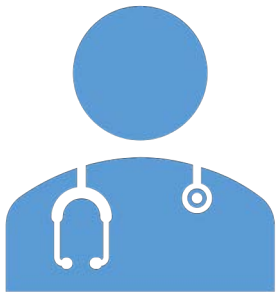

Objectives

- Recognize the options for adjuvant therapy in early stage HER2+ breast cancer
- Describe the role of genomic assays in determining adjuvant treatment for early stage hormone receptor-positive (HR+) breast cancer
- Define the options for treating metastatic HER2+ breast cancer

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Focal Points

- Review updates in neoadjuvant and adjuvant treatment for early stage breast cancer
  - Chemotherapy de-escalation for HER2+
  - Addition of immunotherapy in triple negative
  - Use of genomic assays in HR+
- Discuss management of metastatic breast cancer (MBC)
  - Role of locoregional therapy in MBC
  - Therapeutic options for HER2+
  - Therapeutic options for triple negative
- Our approach to breast cancer care during COVID-19 pandemic

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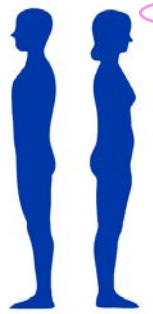
Epidemiology

Cases diagnosed per year

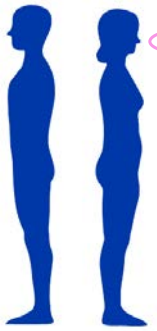
Prostate	19%
Lung & bronchus	14%
Colon & rectum	9%
Urinary bladder	7%
Melanoma of skin	6%
Kidney & renal pelvis	5%
Non-Hodgkin lymphoma	5%
Oral cavity & pharynx	4%
Leukemia	4%
Liver & intrahepatic bile duct	4%
All other sites	22%



30%	Breast
13%	Lung & bronchus
7%	Colon & rectum
7%	Uterine corpus
5%	Thyroid
4%	Melanoma of skin
4%	Non-Hodgkin lymphoma
3%	Pancreas
3%	Leukemia
3%	Kidney & renal pelvis
21%	All other sites

Cancer deaths per year

Lung & bronchus	26%
Prostate	9%
Colon & rectum	8%
Pancreas	7%
Liver & intrahepatic bile duct	6%
Leukemia	4%
Esophagus	4%
Urinary bladder	4%
Non-Hodgkin lymphoma	4%
Kidney & renal pelvis	3%
All other sites	24%



25%	Lung & bronchus
14%	Breast
8%	Colon & rectum
7%	Pancreas
5%	Ovary
4%	Uterine corpus
4%	Leukemia
3%	Liver & intrahepatic bile duct
3%	Non-Hodgkin lymphoma
3%	Brain & other nervous system
24%	All other sites

In the United States, breast cancer is the most commonly diagnosed female cancer, and the second most common cause of cancer death in women.

Cancer Facts and Figures 2019. American Cancer Society. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2019.html.

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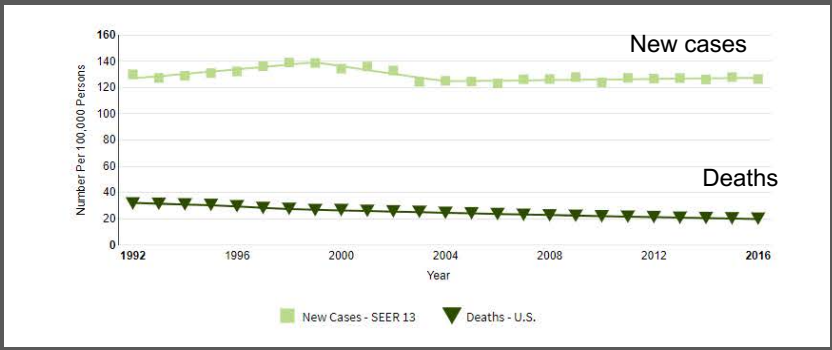
The North Carolina Department of Health and Human Services estimates that there will be more than 9,000 new cases of invasive breast cancer in NC in 2020.



5-year Overall Survival for Breast Cancer

89.9%

2009-2015

https://schs.dph.ncdhhs.gov/schs/CCR/proj20site.pdf, https://seer.cancer.gov/statfacts/html/breast.html

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Neoadjuvant and Adjuvant Systemic Therapy

HER2-positive breast cancer

- Patients with a tumor size >1 cm should receive a combination of **chemotherapy plus HER2-directed therapy** (trastuzumab +/- pertuzumab, IV monoclonal antibodies)
  - Given over 4-5 months
  - HER2-directed therapy cuts the risk of recurrence in half
  - Risk of cardiotoxicity with trastuzumab (~2%)

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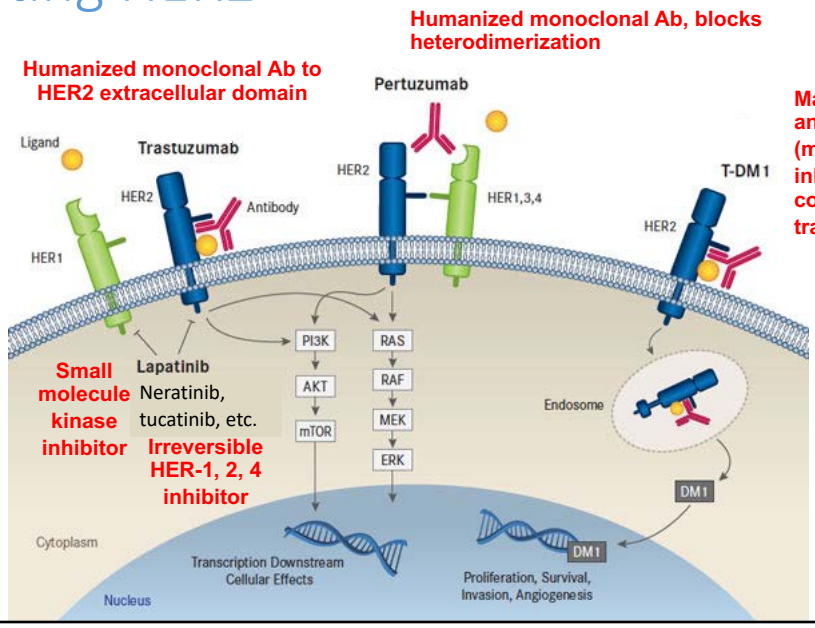
Targeting HER2



Slide courtesy of Dr. Lisa Carey

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Neoadjuvant and Adjuvant Systemic Therapy

HER2-positive breast cancer

- **Chemotherapy plus HER2-directed therapy** (trastuzumab +/- pertuzumab, "HP") for 4-5 months
- Increasingly, given in the **neoadjuvant (pre-surgical) setting**
  - Same goal of systemic control of micrometastatic disease
  - May enable breast conservation for those who are not otherwise eligible
  - Enables you to assess response at time of surgery
  - Adapt adjuvant HER2-directed therapy depending on response (HP vs TDM1)

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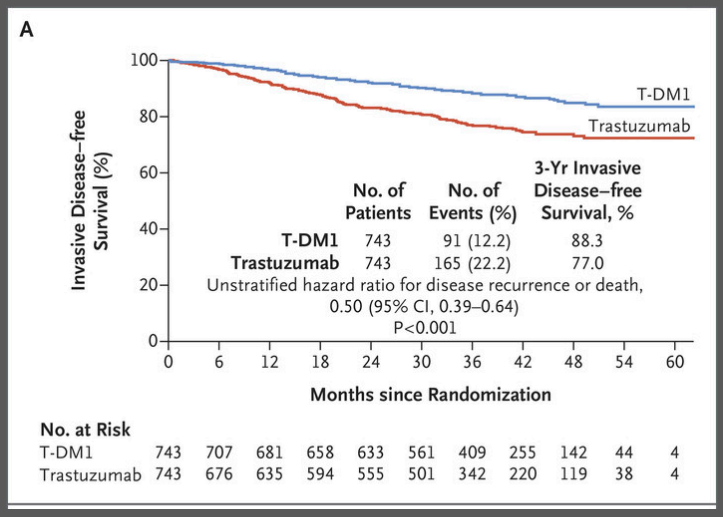
KATHERINE Trial



G von Minckwitz et al. N Engl J Med 2019;380:617-628.

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Neoadjuvant and Adjuvant Systemic Therapy

HER2-positive breast cancer

- **HER2-directed therapy continues for <u>1 year</u>**
  - Pathologic complete response (pCR): Trastuzumab +/- pertuzumab
  - No pCR: TDM1 (per KATHERINE trial)

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Neoadjuvant and Adjuvant Systemic Therapy

HER2-positive breast cancer

- **Chemotherapy plus HER2-directed therapy (trastuzumab +/- pertuzumab, IV monoclonal antibodies)**
- Does everyone need aggressive chemotherapy as the HER2 partner (e.g. neoadjuvant TCHP)?
- Are there some patients who don't need chemotherapy at all and would do well with HER2-directed therapy alone?

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Neoadjuvant and Adjuvant Systemic Therapy

HER2-positive breast cancer

- **Does everyone need aggressive chemotherapy as the HER2 partner (e.g. neoadjuvant TCHP)?**
  - Adjuvant paclitaxel and trastuzumab (APT) trial
  - Phase II study
  - HER2-positive breast cancer with tumors 3 cm or smaller and negative nodes
  - Adjuvant weekly paclitaxel (80 mg/m2) with trastuzumab for 12 weeks, followed by trastuzumab for 9 months
  - Primary end point was disease-free survival (DFS)

SM Tolaney, et al. Journal of Clinical Oncology 2019 371868-1875. DOI: 10.1200/JCO.19.00066

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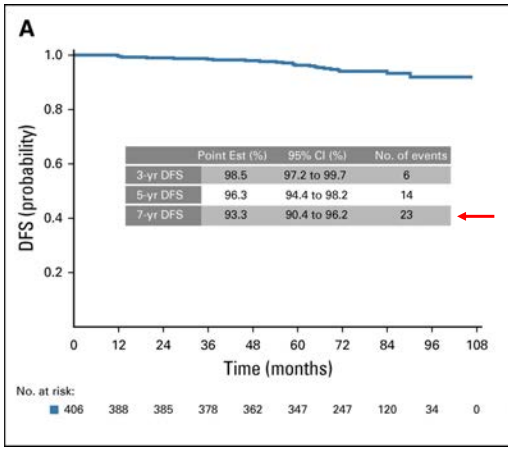
Disease-free survival (DFS). (A) Kaplan-Meier plot of DFS in the intention-to-treat population.



Published in: Sara M. Tolaney; Hao Guo; Sonia Pernas; William T. Barry; Deborah A. Dillon; Lauren Ritterhouse; Bryan P. Schneider; Fei Shen; Kit Fuhrman; Michele Baltay; Chau T. Dang; Denise A. Yardley; Beverly Moy; P. Kelly Marcom; Kathy S. Albain; Hope S. Rugo; Mathew J. Ellis; Iuliana Shapira; Antonio C. Wolff; Lisa A. Carey; Beth Overmoyer; Ann H. Partridge; Clifford A. Hudis; Ian E. Krop; Harold J. Burstein; Eric P. Winer; *Journal of Clinical Oncology* 2019 371868-1875.
DOI: 10.1200/JCO.19.00066

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Neoadjuvant and Adjuvant Systemic Therapy

HER2-positive breast cancer

- **Does everyone need aggressive chemotherapy as the HER2 partner (e.g. neoadjuvant TCHP)?**
  - No
  - HER2-positive breast cancer with tumors 2 cm or smaller and node-negative
  - Adjuvant weekly paclitaxel (80 mg/m2) with trastuzumab for 12 weeks, followed by trastuzumab for 9 months

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Neoadjuvant and Adjuvant Systemic Therapy

HER2-positive breast cancer

- **Chemotherapy plus HER2-directed therapy (trastuzumab +/- pertuzumab, IV monoclonal antibodies)**
- Are there some patients who don't need chemotherapy at all and would do well with HER2-directed therapy alone?

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Areas of Investigation in HER2+ Breast Cancer

- Can HER2-directed therapy without chemotherapy be used in some patients?
  - **ATOP trial** at UNC: T-DM1 in the adjuvant setting for older patients (age ≥ 60) with HER2-positive breast cancer
    - Patients who are ineligible for or decline to receive chemotherapy + HER2-directed therapy
    - Can still receive radiation and endocrine therapy when indicated
    - Primary end point is disease-free survival

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Neoadjuvant and Adjuvant Systemic Therapy

Triple negative (ER/PR negative and HER2 negative) breast cancer, TNBC

- Recommend chemotherapy in patients tumor size ≥ 0.5 cm
  - Generally treat with **multidrug chemotherapy**
  - Often given in the **neoadjuvant (pre-surgical) setting** rather than adjuvant setting
    - Try to down-stage the axilla
    - Enable easier surgery (i.e. make eligible for lumpectomy if not initially)
    - Assess response to therapy to allow adaption of adjuvant therapy (similar to HER2+ paradigm)

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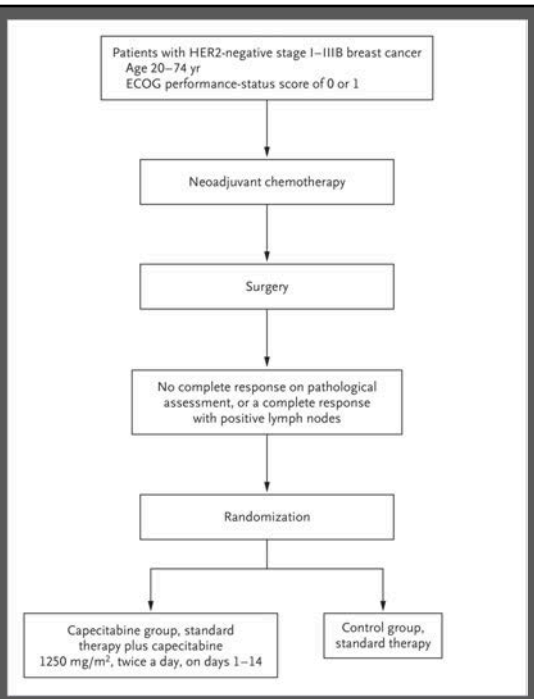
CREATE-X Trial



Masuda N et al. N Engl J Med 2017;376:2147-2159.

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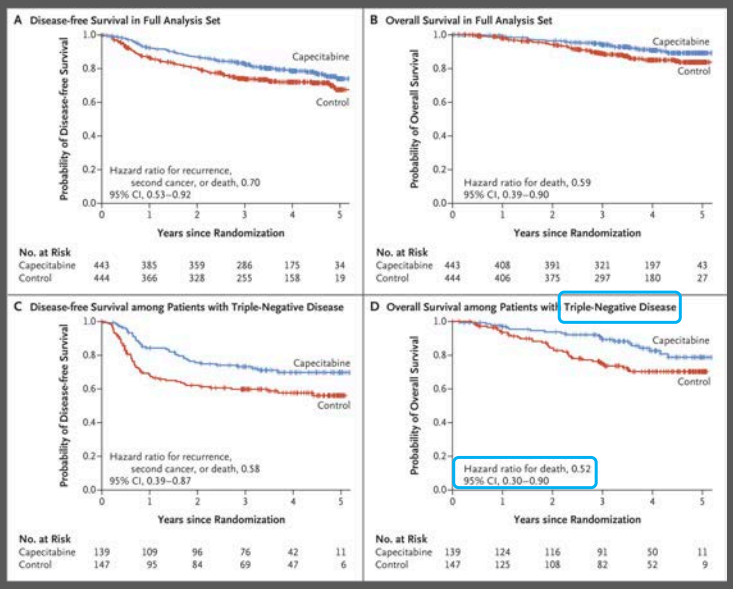
CREATE-X Trial



Masuda N et al. N Engl J Med 2017;376:2147-2159.

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Neoadjuvant and Adjuvant Systemic Therapy

Triple negative (ER/PR negative and HER2 negative) breast cancer, TNBC

- pCR after neoadjuvant chemotherapy -> No additional systemic therapy
- Residual disease (no pCR) following neoadjuvant chemotherapy -> Treat with 6 months of adjuvant capecitabine

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Neoadjuvant and Adjuvant Systemic Therapy

Triple negative (ER/PR negative and HER2 negative) breast cancer

- Does the addition of immunotherapy to neoadjuvant chemotherapy improve outcomes in early stage triple negative breast cancer?

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ORIGINAL ARTICLE FREE PREVIEW

Pembrolizumab for Early Triple-Negative Breast Cancer

Peter Schmid, M.D., Javier Cortes, M.D., Lajos Pusztai, M.D., Heather McArthur, M.D., Sherko Kümmel, M.D., Jonas Bergh, M.D., Carsten Denkert, M.D., Yeon Hee Park, M.D., Rina Hui, Ph.D., Nadia Harbeck, M.D., Masato Takahashi, M.D., Theodoros Foukakis, M.D., et al., for the KEYNOTE-522 Investigators*

- Triple-negative breast cancer
- Newly diagnosed, previously untreated, non-metastatic (tumor stage T1c, nodal stage N1-2, or tumor stage T2-4, nodal stage N0-2) disease
- Randomized to:

Control group	Paclitaxel Carboplatin **Placebo** For 12 weeks	Followed by	Doxorubicin or Epirubicin Cyclophosphamide **Placebo** For 12 weeks
Intervention group	Paclitaxel Carboplatin **Pembrolizumab** For 12 weeks		Doxorubicin or Epirubicin Cyclophosphamide **Pembrolizumab** For 12 weeks

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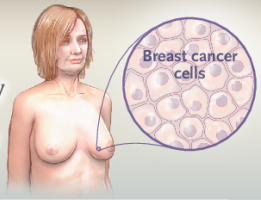
Pembrolizumab for Triple-Negative Breast Cancer

RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

1174 Patients with previously untreated triple-negative breast cancer



	Neoadjuvant Pembrolizumab + chemotherapy, followed by surgery and adjuvant pembrolizumab (N=784)	Neoadjuvant Placebo + chemotherapy, followed by surgery and adjuvant placebo (N=390)
Pathological complete response at time of surgery	64.8%	51.2%
	Difference, 13.6 percentage points; 95% CI, 5.4–21.8; P<0.001	
Event-free survival	91.3% (95% CI, 88.8–93.3)	85.3% (95% CI, 80.3–89.1)
	HR for an event or death, 0.63; 95% CI, 0.43–0.93	
Grade ≥3 adverse events	76.8%	72.2%

P. Schmid et al. 10.1056/NEJMoa1910549

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Adverse Events during the Neoadjuvant Phase at the Second Interim Analysis.*

P Schmid et al. N Engl J Med 2020;382:810-821.

Table 3. Adverse Events during the Neoadjuvant Phase at the Second Interim Analysis.*

Event	Pembrolizumab–Chemotherapy (N=781)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	777 (99.5)	633 (81.0)	389 (100.0)	295 (75.8)
Treatment-related adverse event†	773 (99.0)	600 (76.8)	388 (99.7)	281 (72.2)
Nausea	490 (62.7)	26 (3.3)	246 (63.2)	5 (1.3)
Alopecia	471 (60.3)	14 (1.8)	220 (56.6)	8 (2.1)
Anemia	430 (55.1)	142 (18.2)	215 (55.3)	58 (14.9)
Neutropenia	365 (46.7)	270 (34.6)	183 (47.0)	129 (33.2)
Fatigue	321 (41.1)	27 (3.5)	147 (37.8)	6 (1.5)
Diarrhea	230 (29.4)	17 (2.2)	92 (23.7)	5 (1.3)
Elevated alanine aminotransferase level	199 (25.5)	41 (5.2)	96 (24.7)	9 (2.3)
Vomiting	199 (25.5)	18 (2.3)	85 (21.9)	6 (1.5)
Asthenia	191 (24.5)	25 (3.2)	99 (25.4)	9 (2.3)
Constipation	185 (23.7)	0	82 (21.1)	0
Decreased neutrophil count	185 (23.7)	146 (18.7)	112 (28.8)	90 (23.1)
Rash	170 (21.8)	7 (0.9)	59 (15.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	82 (21.1)	4 (1.0)
Adverse event of interest‡	304 (38.9)	101 (12.9)	71 (18.3)	7 (1.8)
Infusion reaction	132 (16.9)	20 (2.6)	43 (11.1)	4 (1.0)
Hypothyroidism	107 (13.7)	3 (0.4)	13 (3.3)	0
Hyperthyroidism	36 (4.6)	2 (0.3)	4 (1.0)	0
Severe skin reaction	34 (4.4)	30 (3.8)	4 (1.0)	1 (0.3)
Adrenal insufficiency	18 (2.3)	10 (1.3)	0	0

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Neoadjuvant and Adjuvant Systemic Therapy

Triple negative (ER/PR negative and HER2 negative) breast cancer

- Does the addition of immunotherapy to neoadjuvant chemotherapy improve outcomes in early stage triple negative breast cancer?
  - Improves pCR
  - Do not yet know if improves event-free survival (prelim findings are promising)
  - Small but real risk of immune-related toxicity with significant implications for the patient

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Areas of Investigation in Triple Negative Breast Cancer

- Does the addition of immunotherapy to chemotherapy improve outcomes in triple negative breast cancer?
  - **SWOG1418 trial** at UNC: Adjuvant pembrolizumab vs observation in patients with residual invasive disease > 1 cm or positive lymph nodes after neoadjuvant chemotherapy
    - May receive adjuvant capecitabine prior to enrollment
    - Must enroll within 35 days of completion of adjuvant capecitabine

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Adjuvant Systemic Therapy

Hormone receptor-positive breast cancer (i.e. ER and/or PR ≥ 1%)

- Endocrine (anti-estrogen) therapy for all

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Historical Perspective: 2000 NIH Consensus Conference

- "Because adjuvant polychemotherapy **improves survival**, it should be recommended to the **majority of women** with localized breast cancer **regardless of nodal, menopausal, or hormone receptor status**."
- Bottom line: Tumor > 1cm, give chemo

Adjuvant Therapy for Breast Cancer. NIH Consensus Statement 2000 November 1-3; 17(4): 1-23.

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Adjuvant Systemic Therapy

Hormone receptor-positive breast cancer (i.e. ER and/or PR ≥ 1%)

- Endocrine (anti-estrogen) therapy for all
- If > 0.5 cm and node-negative:
  - Send tumor for genomic assay to help determine if chemotherapy is indicated

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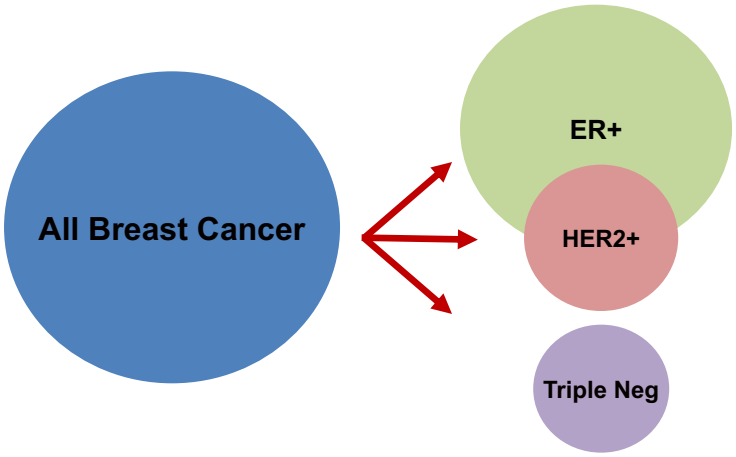
Clinical Subsets



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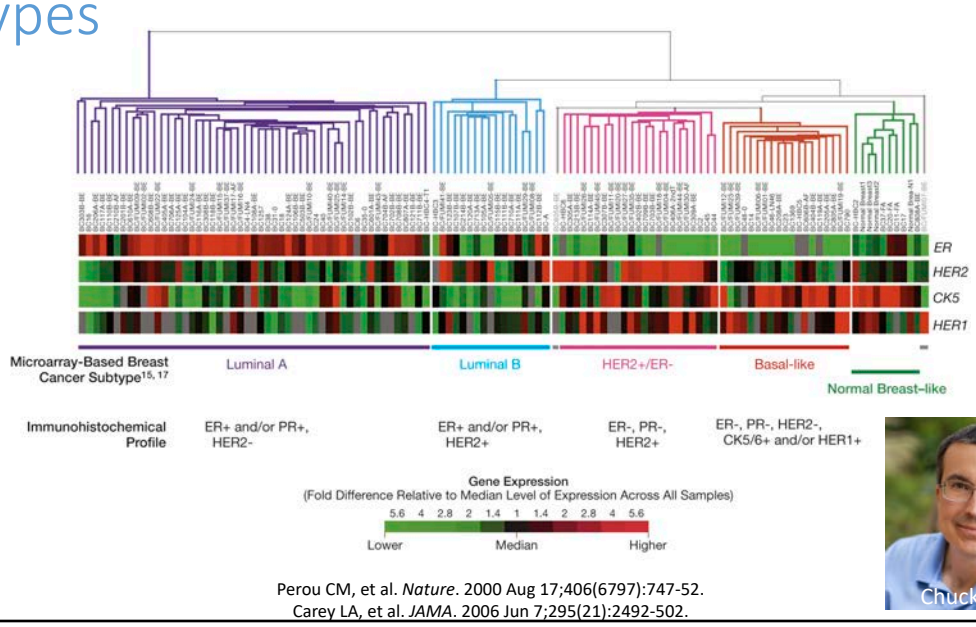
Breast Cancer - Multiple Distinct Subtypes



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Perou CM, et al. *Nature*. 2000 Aug 17;406(6797):747-52.
Carey LA, et al. *JAMA*. 2006 Jun 7;295(21):2492-502.

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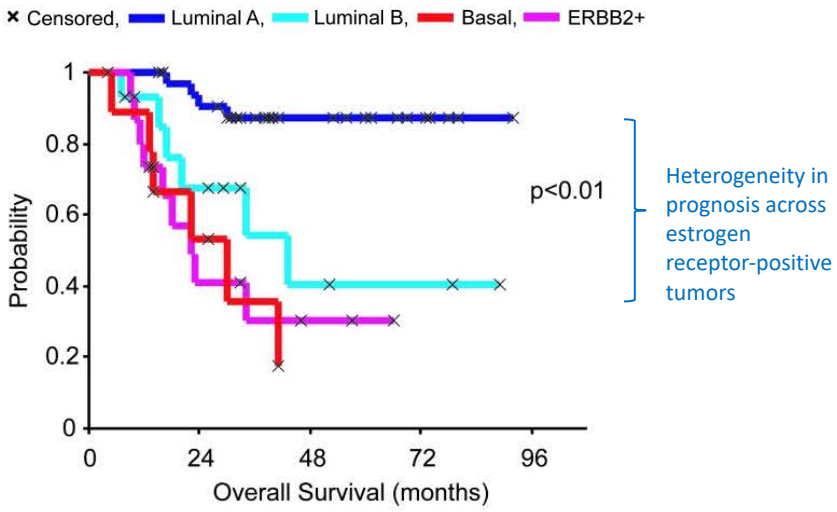
Breast Cancer Subtypes and Prognosis



Heterogeneity in prognosis across estrogen receptor-positive tumors

Sorlie T, et al. *Proc Natl Acad Sci USA*. 2003;100:8418-8423. PMID: 12829800.

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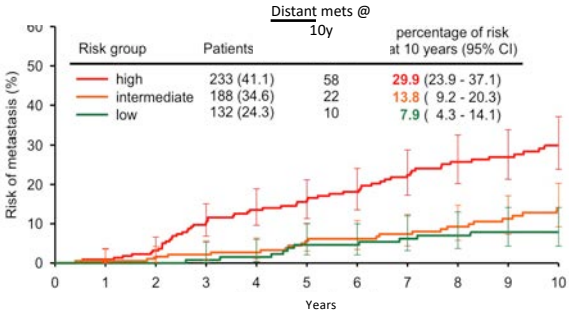
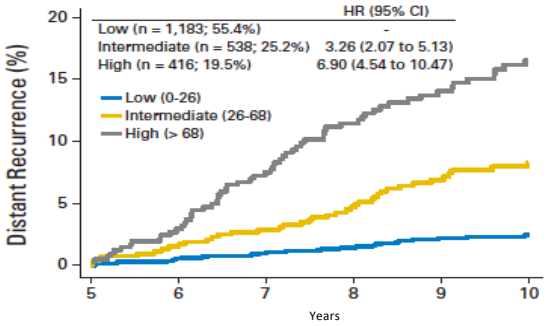
Prosigna™ (Commercial Intrinsic Subtype)

Nielsen TO et al, CCR 2010; Gnant M et al, Ann Oncol 2014; Sestak I et al JCO 2014.



Why give chemo if genetically low risk?



Which patients have higher risk of late recurrence? *Longer duration of endocrine therapy in these*

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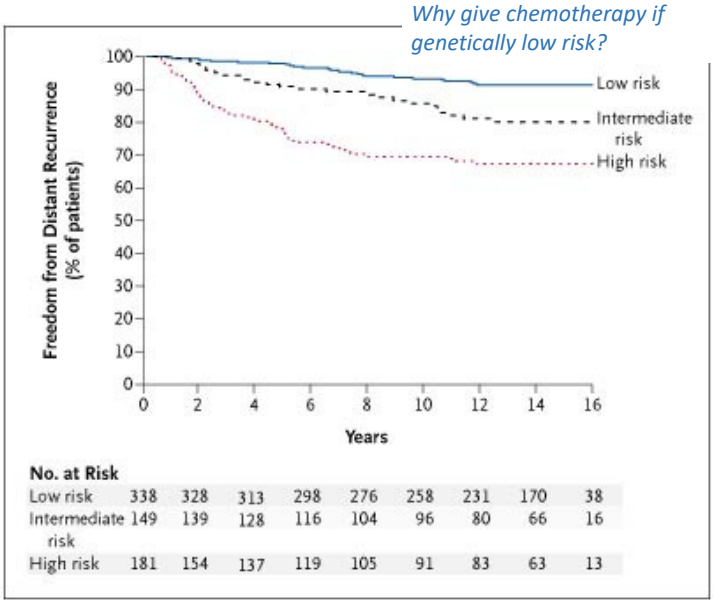
Oncotype Dx Recurrence Score™

Paik S et al. N Engl J Med 2004;351:2817-2826.

Why give chemotherapy if genetically low risk?



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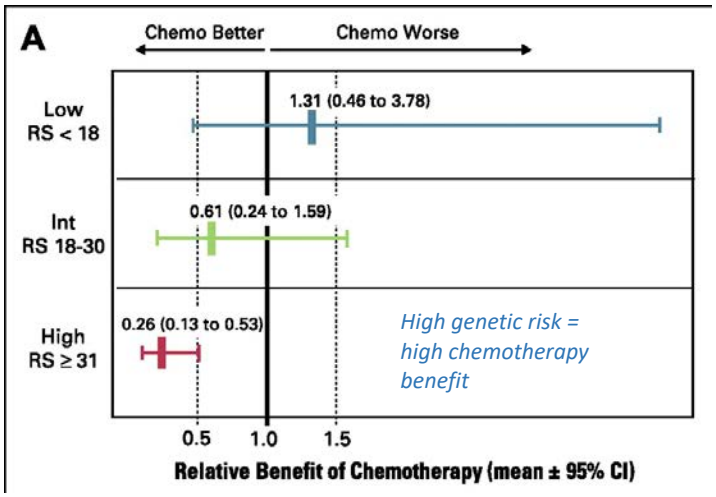
Oncotype Dx Recurrence Score™

Paik S et al. JCO 2006; 24:3726-3734.



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Adjuvant Systemic Therapy

Hormone receptor-positive breast cancer (i.e. ER and/or PR ≥ 1%)

- Endocrine (anti-estrogen) therapy for all
- In node-negative, HR+ breast cancers, > 0.5 cm
  - Send tumor for genomic assay to help determine if chemotherapy is indicated
    - **Only if patient is eligible for / would consider chemotherapy**

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Adjuvant Systemic Therapy

Hormone receptor-positive breast cancer (i.e. ER and/or PR ≥ 1%)

- What about use of genomic assays in HR+, node-positive tumors?

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Adjuvant Systemic Therapy

- HR+, node-positive tumors
  - At UNC, all HR+, node-positive receive adjuvant chemotherapy
  - RxPONDER study (ET +/- chemo) is ongoing, awaiting these results
  - MINDACT showed that patients with high clinical risk (i.e. node-positive tumors) and low genetic risk (i.e. low risk on genomic assay) still benefit from chemotherapy
    - Especially true in premenopausal women
    - Some question of whether it is the chemo itself vs ovarian suppression caused by the chemo
    - Can you optimize endocrine therapy and forego chemo in some patients?
    - Need prospective, randomized, controlled trial to determine this
    - For now, we treat these patients with chemo and do not order genomic assays

https://clinicaltrials.gov/ct2/show/NCT01272037
Cardoso F, et al. *N Engl J Med* 2016; 375:717-729/ DOI: 10.1056/NEJMoa1602253.

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Metastatic Breast Cancer (MBC)

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Role of locoregional treatment in MBC

- Stage IV patients with intact primary tumor (e.g. no prior surgery or radiation) were registered, treated with optimal systemic therapy based on patient and tumor characteristics
- Those who did not progress during 4-8 months of optimal systemic therapy were randomized to locoregional therapy (LRT) for the intact primary tumor or no LRT
- The primary endpoint was overall survival (OS), with locoregional disease control as a secondary endpoint.
- Locoregional treatment of intact primary tumor does not improve overall survival or health-related quality of life in MBC

Khan SA, et al. *J Clin Oncol* 38: 2020 (suppl; abstr LBA2).

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Role of locoregional treatment in MBC

- 390 patients enrolled and received optimal systemic therapy
  - Of these, 256 eligible patients were randomized to continued systemic tx +/- LRT
  - No significant difference in 3-year OS (68.4% in LRT arm vs. 67.9% systemic tx alone arm, HR = 1.09, 90% CI: 0.80, 1.49)
  - No significant difference in progression-free survival (p = 0.40)
  - Locoregional recurrence/progression was significantly higher in the systemic treatment alone arm (3-year rate 25.6% vs 10.2%)
  - Health-related quality of life measured by FACT-B Trial Outcome Index was significantly worse at 18 months in those who received LRT
  - KEY POINT: Locoregional treatment of intact primary tumor does not improve overall survival or health-related quality of life in MBC

Khan SA, et al. *J Clin Oncol* 38: 2020 (suppl; abstr LBA2).

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Metastatic: HER2+

- First-line: Docetaxel, trastuzumab, pertuzumab (THP)
- Second-line: ado-trastuzumab emtansine (TDM1)

Giordano SH, et al. *J Clin Oncol*. 2014; doi:10.1200/JCO.2013.54.0948.

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Metastatic: HER2+

- First-line: Docetaxel, trastuzumab, pertuzumab (THP)
- Second-line: ado-trastuzumab emtansine (TDM1)
- Third-line:
  - Tucatinib (Tukysa) – combined with trastuzumab and capecitabine
  - Fam-trastuzumab deruxtecan-nxki (Enhertu)
  - Clinical trial

Giordano SH, et al. *J Clin Oncol*. 2014; doi:10.1200/JCO.2013.54.0948.

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ORIGINAL ARTICLE FREE PREVIEW

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

Rashmi K. Murthy, M.D., Sherene Loi, M.D., Alicia Okines, M.D., Elisavet Paplomata, M.D., Erika Hamilton, M.D., Sara A. Hurvitz, M.D., Nancy U. Lin, M.D., Virginia Borges, M.D., Vandana Abramson, M.D., Carey Anders, M.D., Philippe L. Bedard, M.D., Mafalda Oliveira, M.D., et al.

KEY ELIGIBILITY CRITERIA:
- Metastatic HER2+ breast cancer
- Previously treated with trastuzumab, pertuzumab, and TDM1
- ECOG PS 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not requiring immediate local therapy
  - Previously treated progressing brain metastases not requiring immediate local therapy
  - No evidence of brain metastases

R (2:1)

N = 410

Tucatinib + trastuzumab + capecitabine (21-day cycle)

Tucatinib 300 mg po BID
+
Trastuzumab 6 mg/kg IV q3w (loading dose 8 mg/kg on C1D1)
+
Capecitabine 1000 mg/m2 po BID (Days 1-14)

N = 202

Placebo + trastuzumab + capecitabine (21-day cycle)

Placebo
+
Trastuzumab 6 mg/kg IV q3w (loading dose 8 mg/kg on C1D1)
+
Capecitabine 1000 mg/m2 po BID (Days 1-14)

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HER2CLIMB – Tucatinib for HER2+ MBC

- Primary end point: progression-free survival (PFS)
- Secondary end points: overall survival, progression-free survival among patients with brain metastases, confirmed objective response rate, and safety

Murthy RK, et al. N Engl J Med 2020; 382:597-609.

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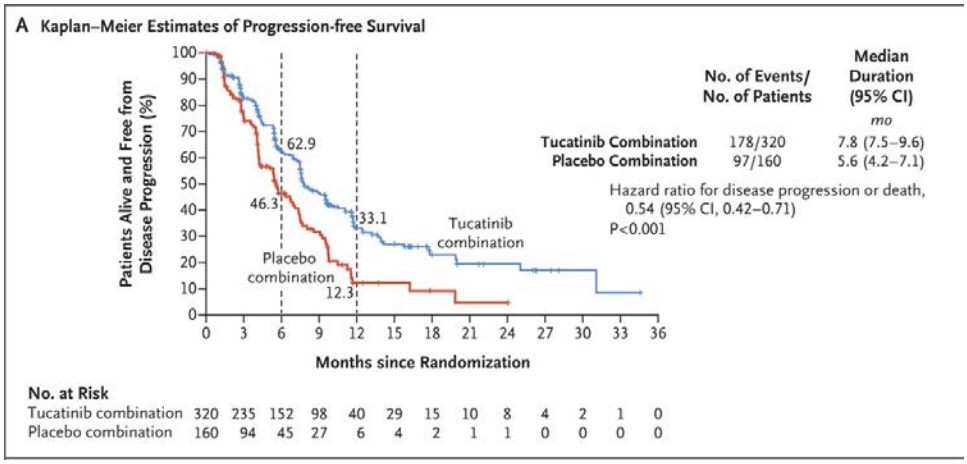
HER2CLIMB – Tucatinib for HER2+ MBC



Murthy RK, et al. N Engl J Med 2020; 382:597-609.

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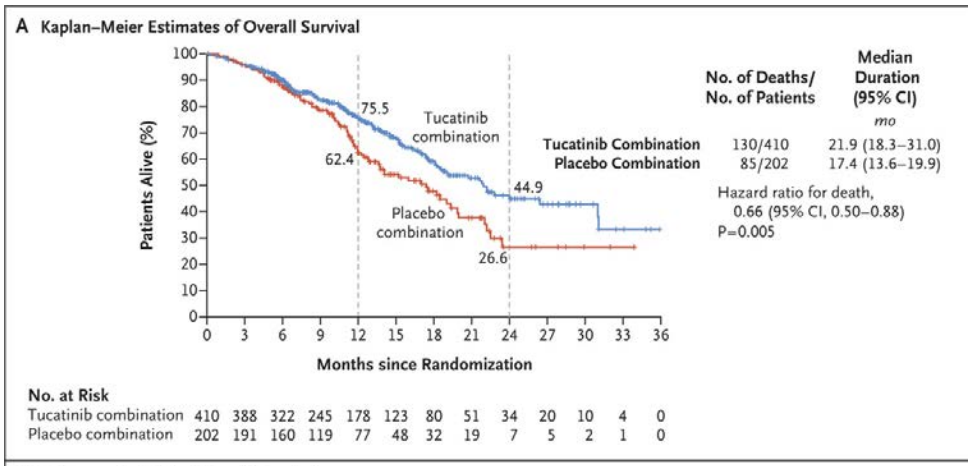
HER2CLIMB – Tucatinib for HER2+ MBC



Murthy RK, et al. N Engl J Med 2020; 382:597-609.

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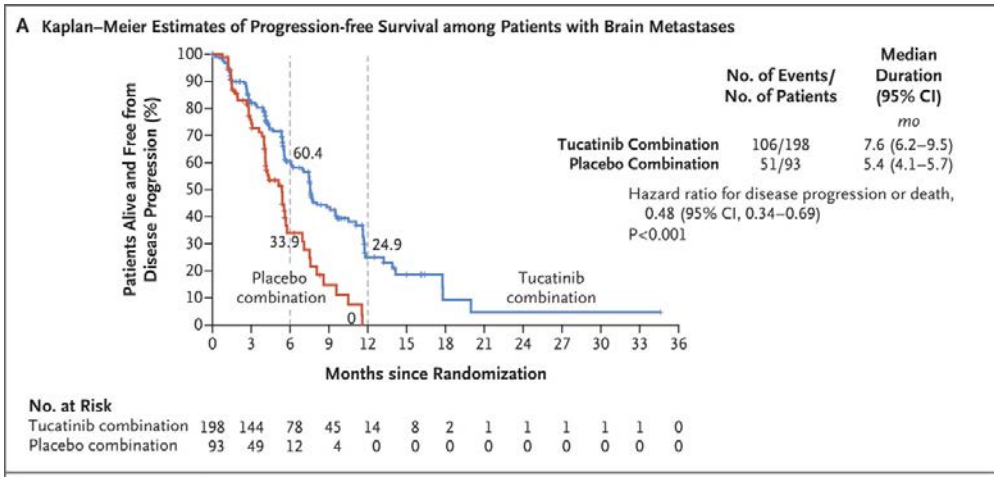
HER2CLIMB – Tucatinib for HER2+ MBC



Murthy RK, et al. N Engl J Med 2020; 382:597-609.

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HER2CLIMB – Tucatinib for HER2+ MBC

Table 2. Most Common Adverse Events.*

Event	Tucatinib-Combination Group (N=404)		Placebo-Combination Group (N=197)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	401 (99.3)	223 (55.2)	191 (97.0)	96 (48.7)
Diarrhea	327 (80.9)	52 (12.9)	105 (53.3)	17 (8.6)
PPE syndrome	256 (63.4)	53 (13.1)	104 (52.8)	18 (9.1)
Nausea	236 (58.4)	15 (3.7)	86 (43.7)	6 (3.0)
Fatigue	182 (45.0)	19 (4.7)	85 (43.1)	8 (4.1)
Vomiting	145 (35.9)	12 (3.0)	50 (25.4)	7 (3.6)
Stomatitis	103 (25.5)	10 (2.5)	28 (14.2)	1 (0.5)
Decreased appetite	100 (24.8)	2 (0.5)	39 (19.8)	0
Headache	87 (21.5)	2 (0.5)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	86 (21.3)	18 (4.5)	22 (11.2)	1 (0.5)
Alanine aminotransferase increased	81 (20.0)	22 (5.4)	13 (6.6)	1 (0.5)

* Listed are adverse events that were reported in at least 20% of the patients in the tucatinib-combination group. Safety analyses included all the patients who received at least one dose of any trial drug or placebo. Data are reported according to preferred terms in the *Medical Dictionary for Regulatory Activities*, version 22.0. PPE denotes palmar–plantar erythrodysesthesia.

Murthy RK, et al. N Engl J Med 2020; 382:597-609.

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Metastatic: HER2+

- First-line: Docetaxel, trastuzumab, pertuzumab (THP)
- Second-line: ado-trastuzumab emtansine (TDM1)
- Third-line:
  - Tucatinib (Tukysa) – combined with trastuzumab and capecitabine
    - Especially in the setting of brain metastases

Giordano SH, et al. *J Clin Oncol*. 2014; doi:10.1200/JCO.2013.54.0948.

50

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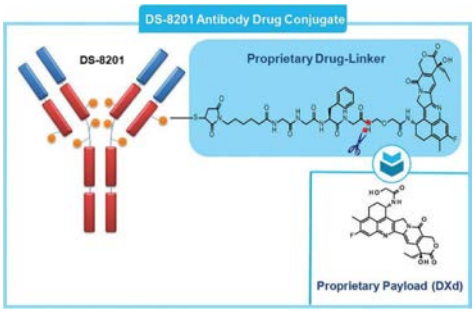
  - Fam-trastuzumab deruxtecan-nxki (Enhertu)



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

Shanu Modi, M.D., Cristina Saura, M.D., Ph.D., Toshinari Yamashita, M.D., Yeon Hee Park, M.D., Sung-Bae Kim, M.D., Ph.D., Kenji Tamura, M.D., Ph.D., Fabrice Andre, M.D., Ph.D., Hiroji Iwata, M.D., Ph.D., Yoshinori Ito, M.D., Junji Tsurutani, M.D., Ph.D., Joohyuk Sohn, M.D., Ph.D., Neelima Denduluri, M.D., et al., for the DESTINY-Breast01 Investigators*

DESTINY-Breast01, phase II trial

- Metastatic HER2+ breast cancer
- Previously received TDM1
- Primary end-point: overall response rate (ORR)
- Secondary endpoints: disease-control rate, clinical-benefit rate, duration of response, PFS, and safety.

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Trastuzumab deruxtecan (DESTINY-Breast01)

- 184 patients
- Median of six previous treatments (heavily pretreated group)
- Assigned to receive 5.4 mg/kg (established recommended dose)
- ORR 60.9% (95% confidence interval [CI], 53.4 to 68.0)
- Median duration of follow-up was 11.1 months (range, 0.7 to 19.9)

Modi S, et al. N Engl J Med 2020; 382:610-621, DOI: 10.1056/NEJMoa1914510.

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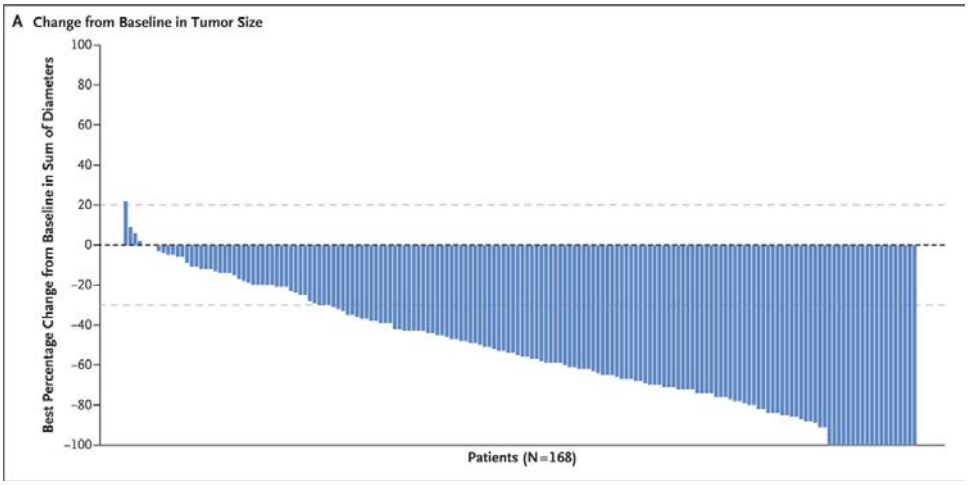
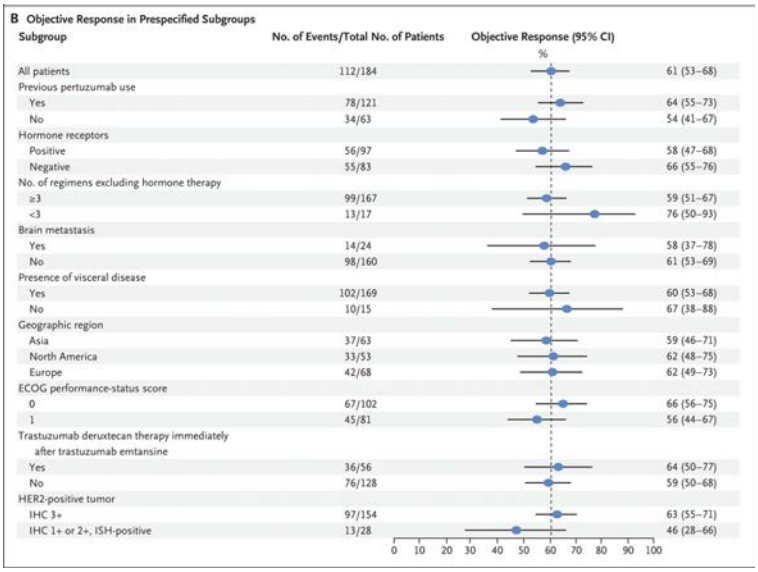
Trastuzumab deruxtecan (DESTINY-Breast01)



Modi S, et al. N Engl J Med 2020; 382:610-621, DOI: 10.1056/NEJMoa1914510.

54

Trastuzumab deruxtecan (DESTINY-Breast01)



Modi S, et al. N Engl J Med 2020; 382:610-621, DOI: 10.1056/NEJMoa1914510.

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Trastuzumab deruxtecan (DESTINY-Breast01)

Table 2. Adverse Events in the Overall Population of 184 Patients.*

Adverse Events	Any Grade	Grade 3	Grade 4
	number of patients (percent)		
Any adverse event†	183 (99.5)	89 (48.4)	7 (3.8)
Nausea	143 (77.7)	14 (7.6)	0
Fatigue	91 (49.5)	11 (6.0)	0
Alopecia	89 (48.4)	1 (0.5)	0
Vomiting	84 (45.7)	8 (4.3)	0
Constipation	66 (35.9)	1 (0.5)	0
Decreased neutrophil count‡	64 (34.8)	36 (19.6)	2 (1.1)
Decreased appetite	57 (31.0)	3 (1.6)	0
Anemia§	55 (29.9)	15 (8.2)	1 (0.5)
Diarrhea	54 (29.3)	5 (2.7)	0
Decreased white-cell count¶	39 (21.2)	11 (6.0)	1 (0.5)
Decreased platelet count‖	39 (21.2)	7 (3.8)	1 (0.5)
Headache	36 (19.6)	0	0
Cough	35 (19.0)	0	0
Abdominal pain**	31 (16.8)	2 (1.1)	0
Decreased lymphocyte count††	26 (14.1)	11 (6.0)	1 (0.5)
Adverse events of special interest			
Interstitial lung disease‡‡	25 (13.6)	1 (0.5)	0
Prolonged QT interval	9 (4.9)	2 (1.1)	0
Infusion-related reaction	4 (2.2)	0	0
Decreased left ventricular ejection fraction§§	3 (1.6)	1 (0.5)¶¶	0

Modi S, et al. N Engl J Med 2020; 382:610-621, DOI: 10.1056/NEJMoa1914510.

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Metastatic: HER2+

- First-line: Docetaxel, trastuzumab, pertuzumab (THP)
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- Third-line:
  - Tucatinib (Tukysa) – combined with trastuzumab and capecitabine
    - Especially in the setting of brain metastases
  - Fam-trastuzumab deruxtecan-nxki (Enhertu)
    - Monitor carefully for interstitial lung disease
  - Clinical trial

Giordano SH, et al. *J Clin Oncol*. 2014; doi:10.1200/JCO.2013.54.0948.

57

Metastatic: Triple negative

- First-line:

P Schmid et al. N Engl J Med 2018;379:2108-2121.

58

Metastatic: Triple negative

- First-line: chemotherapy +/- immunotherapy
  - Need to evaluate PD-L1 on tumor
    - PD-L1 negative: Treat with single-agent chemotherapy
    - PD-L1 positive (≥1%): Treat with atezolizumab (checkpoint inhibitor, immunotherapy) and nab-paclitaxel (Abraxane, chemotherapy) – IMpassion130

P Schmid et al. N Engl J Med 2018;379:2108-2121.

59

Metastatic: Triple negative

- First-line: Chemotherapy +/- immunotherapy
- Second-line: Chemotherapy
  - Often use capecitabine
- Third-line: Sacituzumab govitecan-hziy (antibody-drug conjugate)

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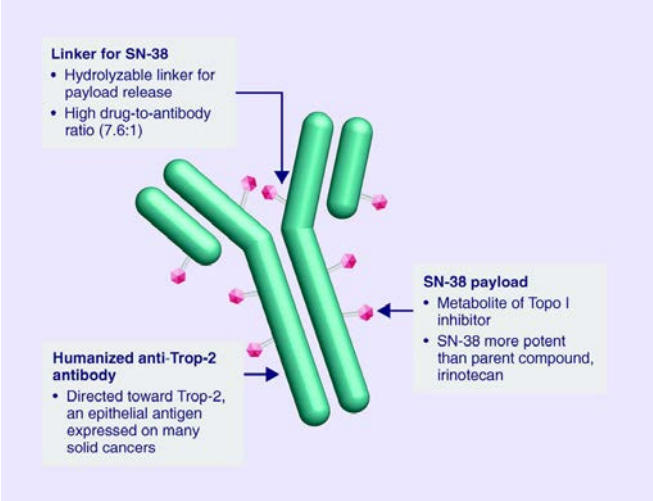
Sacituzumab govitecan-hziy



Future Medicine. 2020 Mar. doi:10.2217/fon-2020-0163

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer

Aditya Bardia, M.D., Ingrid A. Mayer, M.D., Linda T. Vahdat, M.D., M.B.A., Sara M. Tolaney, M.D., M.P.H., Steven J. Isakoff, M.D., Ph.D., Jennifer R. Diamond, M.D., Joyce O'Shaughnessy, M.D., Rebecca L. Moroose, M.D., Alessandro D. Santin, M.D., Vandana G. Abramson, M.D., Nikita C. Shah, M.D., Hope S. Rugo, M.D., et al.

- 108 patients with metastatic TNBC
- At least 2 prior therapies
- Sacituzumab govitecan-hziy 10 mg/kg IV on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxic effects
- End points: safety; the objective response rate; the duration of response; the clinical benefit rate (defined as a complete or partial response or stable disease for at least 6 months); progression-free survival; and overall survival

62

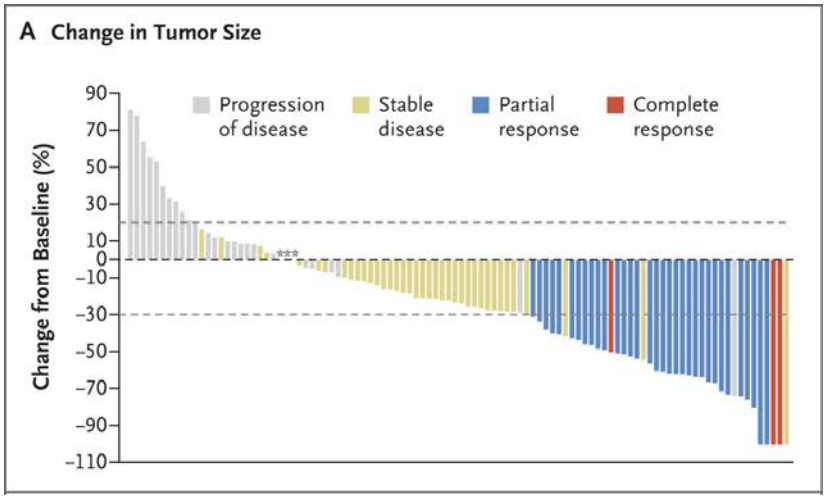
Sacituzumab govitecan-hziy (IMMU-132-01 trial)

- Median of 3 previous therapies (range, 2 to 10)
- 4 deaths during treatment
- 2.8% discontinued treatment due to adverse events (AEs)
- Grade 3 or 4 AEs in ≥ 10% of patients: anemia, neutropenia

A Bardia et al. N Engl J Med 2019;380:741-751.

63

Sacituzumab govitecan-hziy (IMMU-132-01 trial)



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64

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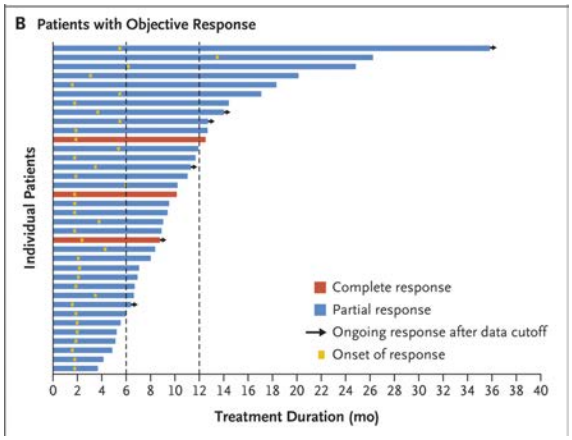

A Bardia et al. N Engl J Med 2019;380:741-751.

65

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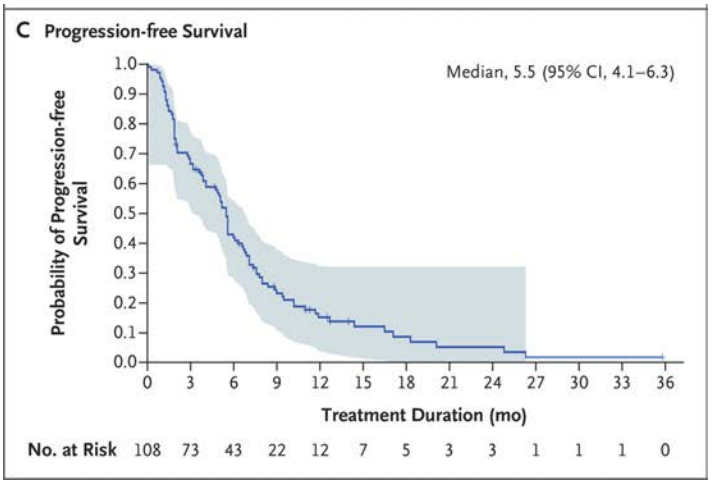

A Bardia et al. N Engl J Med 2019;380:741-751.

66

Metastatic: Triple negative

- First-line: Chemotherapy +/- immunotherapy
- Second-line: Chemotherapy
  - Often use capecitabine
- Third-line: Sacituzumab govitecan-hziy (antibody-drug conjugate)
  - Generally well-tolerated
  - Manage cytopenias with transfusion, growth factor support when needed

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Areas of Investigation in Metastatic Triple Negative Breast Cancer

- Does the addition of immunotherapy to sacituzumab improve outcomes in metastatic, PDL1-negative, triple negative breast cancer?
  - **DF-HCC 20-166 Sacituzumab Govitecan (IMMU-132) +/-pembro (pending)**

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

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Our approach to breast cancer care in the setting of the COVID-19 pandemic

- Use of more neoadjuvant endocrine therapy to delay surgery
- Delayed initiation of CDK 4/6 inhibitor
  - Doing this less, now that we know pandemic will last months not weeks
- Telemedicine
  - Non-neoadjuvant patients
  - New patients – initial visit via video, in-person prior to tx initiation, especially if neoadjuvant or metastatic
  - Second opinions
  - Access to care – smartphone availability, distance to travel
  - Different platforms, Doximity working best

ASCO Special Report: A Guide to Cancer Care Delivery During the COVID-19 Pandemic. May 19, 2020.
https://www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-Guide-Cancer-COVID19.pdf
Sheng, JY, et al. DOI: 10.1200/OP.20.00364 *JCO Oncology Practice.*

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