Fred Hutch Cancer Center

# Metastatic Breast Cancer

**Natasha B. Hunter, M.D.**
Assistant Professor, University of Washington
UW CME Comprehensive Hematology & Oncology Review

# Disclosures

I have no relevant financial interests to disclose.

# Learning objectives

- To review the appropriate diagnostic workup for metastatic breast cancer (MBC)
- To review current guidelines for the treatment and monitoring of metastatic breast cancer
- To understand recent key developments in drugs to treat MBC

# Lecture structure

- Case based
- NCCN-guideline focused
- Emphasis on standard therapies

# Locally recurrent disease: Case 1

60 year-old patient with a history of stage IIIA ER/PR+, HER2-negative breast cancer treated 6 years prior with neoadjuvant anthracycline-based chemotherapy, lumpectomy with sentinel lymph node biopsy (SLNB), radiation and 5 years of an aromatase inhibitor, presents with an expanding mass near her lumpectomy scar. Biopsy demonstrates invasive ductal carcinoma with similar histology to her prior tumor. Your next step is:

A) Mastectomy with SLNB
B) Mastectomy with axillary lymph node dissection (ALND)
C) Chemotherapy
D) A and C
E) B and C

# Locally recurrent disease: Case 1

- Answer: B Mastectomy with ALND
  - Actual real first step: Probably restaging
  - Patients with prior mastectomy should undergo surgical resection (if possible) and radiation to the chest wall and supraclavicular area (if the chest wall was not previously irradiated). Benefit of repeat SLN biopsy after mastectomy is unknown, but not encouraged.
  - Patients with prior breast-conserving surgery and radiation therapy with prior SLNB: NCCN panel consensus recommendation is mastectomy and a level I/II axillary dissection.

# Locally recurrent disease: A case for chemotherapy?

- CALOR trial (Lancet 2014): Studied effect of chemotherapy after complete resection in patients with isolated locoregional recurrence
- Adjuvant chemotherapy improved DFS and OS. Five-year OS 88% vs. 76%, *P* .024 in chemo vs non-chemo group.
- Benefit of adjuvant chemotherapy was only significant in hormone-receptor **negative** disease: DFS = 67% versus 35% for ER negative disease; DFS = 70% versus 69% in ER-positive disease, (HR, 0.94; 95% CI, 0.47–1.89).

Aebi S, Gelber S, Anderson SJ, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. Lancet Oncol 2014;15:156-163

# Diagnosis and workup: Case 2

A 56 yo postmenopausal woman presents with a self-detected R breast lump. Diagnostic mammogram demonstrates a 4 cm R breast mass at 3:00, N+8. MRI shows a 5.1 cm unifocal mass, and three suspicious-appearing axillary lymph nodes. Biopsy reveals grade 2 invasive lobular carcinoma, ER+ (95%), PR+ (75%), HER2 1+. She is otherwise healthy, takes no prescribed meds; ROS reveals sciatica x 2 months. She inquires about next steps. You advise:

A) Neoadjuvant chemotherapy with ddAC/T

B) Surgical resection with SLNB

C) PET scan

D) Biopsy to evaluate extent of disease

E) CT C/A/P and bone scan

# Diagnosis and workup: Staging

- Answer: E.
  - **Previous NCCN guidance**: “For patients presenting with disease confined to the breast (stage I to II) the NCCN Panel does not recommend routine systemic imaging in the absence of signs or symptoms suspicious for metastatic disease. According to the panel, additional tests may be considered in patients who present with locally advanced (T3 N1-3 M0) disease and in those with signs or symptoms suspicious for metastatic disease.”

# Diagnosis and workup: Staging

- Answer: E.

  **New NCCN guidance:** [R]outine systemic imaging is *not* indicated for patients with early-stage breast cancer *in the absence* of signs/symptoms of metastatic disease. Recommendations for additional metastatic workup should be performed for those patients with signs or symptoms suspicious for metastatic disease, based on lack of evidence to demonstrate any benefits with metastatic workup in early-stage disease.

# Diagnosis and workup: Imaging

- Why not a PET?
  - The non-diagnostic CT scans used for PET under-evaluate the lungs and the liver compared with contrast-enhanced diagnostic CT scans.
  - FDG PET/CT is optional, may be most helpful when other imaging is equivocal or suspicious.

# Diagnosis and workup: Case 2, con't

The patient undergoes CT C/A/P and bone scan, which reveal multiple lesions in liver, the largest measuring 2 cm,  and diffuse metastases to the spine and axial skeleton. The patient endorses lower back pain x 2 months which you suspect corresponds to an L3 lesion. She inquires about next steps. You advise:

A) Initiate treatment with a CDK 4/6 inhibitor and endocrine therapy
B) MRI spine w/ referral to radiation oncology for RT to L3
C) Liver biopsy
D) L3 biopsy

# Diagnosis and workup: Biopsy

- Answer: C, Liver biopsy
  - –Metastatic disease should be biopsied at first presentation or at first recurrence in order to confirm the diagnosis and determine tumor histology and molecular profile.
  - –Soft tissue tumor biopsy preferred over bone sites as demineralization procedures can degrade proteins and DNA needed for IHC, FISH and molecular assays. For clinical (non-board exam) purposes, request EDTA decalcification if possible to avoid this issue – this process is somewhat slower, but preserves proteins and nucleotides.

# Diagnosis and workup: Markers

- IHC and FISH: **ER, PR and HER2 status** (primary and metastatic sites can be discordant), **PDL1**.
- Molecular markers for MBC with clinical significance (*not* standard or recommended for early-stage disease): **PIK3CA, AKT, PTEN, TMB, ERBB2**. Rare but useful if found: **MSI, NTRK, RET fusion, high tumor mutational burden (TMB)**. Possible future significance: FGFR2, others.
- Genetic testing: **Germline BRCA1/2** mutations should be assessed in all patients with recurrent or metastatic breast cancer as positive results have implications for therapy

# Somatic mutations with associated therapies

**Biomarkers Associated with FDA-Approved Therapies**

| Breast Cancer Subtype | Biomarker | Detection | FDA-Approved Agents | NCCN Category of Evidence | NCCN Category of Preference |
|---|---|---|---|---|---|
| HR-positive/ HER2-negative[w] | *PIK3CA* activating mutation | NGS, PCR (Blood or tumor tissue if blood negative) | Alpelisib + fulvestrant[x] | Category 1 | Preferred second- or subsequent-line therapy |
| HR-positive/ HER2-negative[y] | *PIK3CA or AKT1* activating mutations or *PTEN* alterations | NGS, (Blood or tumor tissue if blood negative) | Capivasertib + fulvestrant[y] | Category 1 | Preferred second- or subsequent-line therapy in select patients[y] |
| HR-positive/ HER2-negative[z] | *ESR1* mutation | NGS, PCR (Tumor tissue or blood) | Elacestrant[z] | Category 2A | Other recommended regimen |
| Any | Germline *BRCA1* or *BRCA2* mutation | Germline sequencing | Olaparib<br>Talazoparib | Category 1 | Preferred |
| Any | *NTRK* fusion | FISH, NGS, PCR (Tumor tissue or blood) | Larotrectinib[aa]<br>Entrectinib[aa]<br>Repotrectinib[bb] | Category 2A[bb] | Useful in certain circumstances |
| Any | MSI-H/dMMR | IHC, NGS, PCR, (Tumor tissue) | Pembrolizumab[cc,dd]<br>Dostarlimab-gxly[ee] | Category 2A | |
| Any | TMB-H (≥10 mut/Mb) | NGS (Tumor tissue or blood) | Pembrolizumab[cc,dd] | Category 2A | |
| Any | *RET*-fusion | NGS (Tumor tissue or blood) | Selpercatinib[ff] | Category 2A | |

# Treatment: Case 2, con't

This patient's biopsy of her largest liver mass returns with the same histology as index tumor (ER/PR+, HER2-). Molecular analysis reveals a PIK3CA mutation. You advise:

A) Tamoxifen

B) CDK 4/6 inhibition plus endocrine therapy

C) Alpelisib plus fulvestrant

D) Capecitabine

# Treatment: First line therapy for HR+ disease

- Answer: B, CDK4/6 inhibition plus endocrine therapy.
  - –Aromatase inhibitor in combination with CDK4/6 inhibition is a preferred first-line treatment.
  - –Trials of all three medications in this class have demonstrated improved PFS and OS over AI alone: MONALEESA-2 and -7 (ribociclib), PALOMA-2 (palbociclib), MONARCH-3 (abemaciclib).
  - –Only MONALEESA 7 looked at premenopausal patients, but all these agents are given to young patients along with ovarian suppression or BSO.

# Treatment for HR+ MBC: CDK4/6 inhibitors

- All CDK 4/6 inhibitors exhibit hematologic toxicities (neutropenia, leukopenia), GI toxicities, elevated LFTs, increased risk of pulmonary embolism
- Ribociclib: QTc prolongation, administration requires cardiac monitoring
- Abemaciclib: Higher incidence of all-grade and grade 3/4 gastrointestinal toxicities, seems to have some blood/brain barrier penetration, is given continuously, and can be given as monotherapy.

Sammons SL et al, Curr Cancer Drug Targets. 2017 Sep; 17(7): 637–649.

# Treatment for HR+ MBC: Other first-line therapies

- Fulvestrant monotherapy. (Improved time to progression was seen with fulvestrant compared to anastrazole, FIRST study)
- Fulvestrant + AI (mixed trial results, FACT and SoFEA)
- Fulvestrant + CDK4/6 inhibitor
- Monotherapy with endocrine agents

Ellis MJ, Llombart-Cussac A, Feltl D, et al. J Clin Oncol 2015;33:3781-3787.
Bergh J, Jonsson PE, Lidbrink EK, et al. J Clin Oncol. 2012;30:1919-1925
Johnston SR, Kilburn LS, Ellis P, et al. Lancet Oncol 2013;14:989-998.

# Treatment: Case 2, con't

Nine months later, scans reveal that the patient's tumor has progressed, demonstrating enlarging mediastinal nodes and new bone metastases. Depending on the the patient's PS and tumor characteristics, as a next line of therapy you could choose:

A) Fulvestrant monotherapy

B) Exemestane + everolimus

C) Targeted therapy

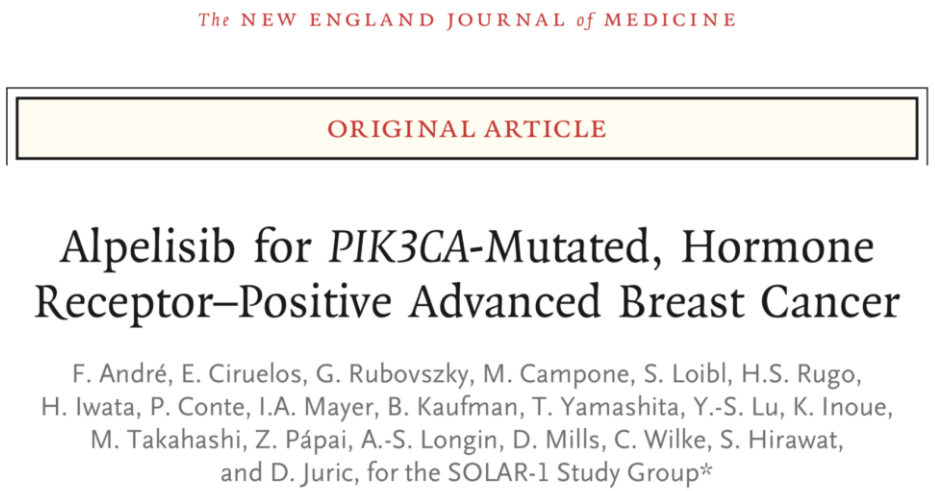
D) Any of the above

# Treatment: Case 2, con't

- Answer: D, any of the above. Acceptable second line regimens for HR+ MBC include:
  - Fulvestrant monotherapy
  - Fulvestrant + CDK 4/6 inhibitor
  - Exemestane + everolimus
  - Targeted therapy when appropriate. In this patient, many would choose a targeted therapy given her PIK3CA mutation.

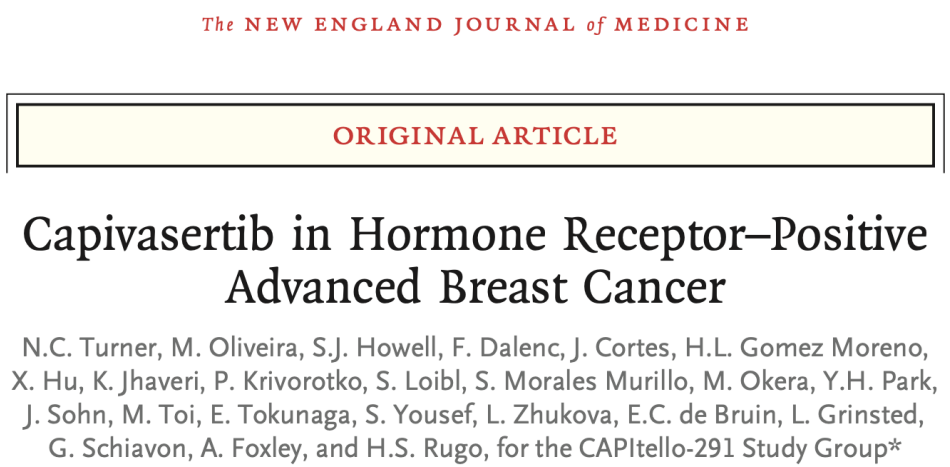
# Second line therapy for HR+ MBC: Targeted agents

- *PIK3CA* mutations: ~40% of patients with hormone-receptor positive, HER2-negative breast cancer
- PFS=11.0 months in the alpelisib–fulvestrant group, vs. 5.7 months in the placebo–fulvestrant group
- FDA approval: May 24, 2019, along with approval for companion diagnostic
- For ER/PR+ patients with advanced breast cancer following progression on or after endocrine-based treatment
- Common SEs: Rash, hyperglycemia, diarrhea



# Second line therapy for HR+ MBC: Targeted agents

- Study enrolled 708 patients with ER+, HER2- MBC, progressing on first-line endocrine therapy. 289 had AKT pathway-altering mutations (PIK3CA, AKT1, PTEN)
- PFS=7.2 months in capivasertib–fulvestrant group vs 3.6 months in placebo group. Similar results for AKT-altered subgroup.
- FDA approval: Nov 16, 2023, for ER/PR+ MBC with PIK3CA, AKT1 and PTEN mutations following progression on or after endocrine-based treatment
- Common SEs: Rash, diarrhea



# Treatment: Case 2, con't

Over the course of the next three years, the patient progresses through alpelisib + fulvestrant, and capecitabine, and is currently receiving Enhertu (remember that her tumor was HER2 1+). She presents to the ED with shortness of breath, and is found to have a new pleural effusion with pleural thickening. You see her in the hospital, and she asks if any targeted therapy is still available to her. You offer:

A. Paclitaxel
B. Sacituzumab govitecan
C. Evaluation for Enhertu-induced ILD
D. A or B

# Visceral crisis in ER+ MBC

Answer: A or B. ILD presents with b/l infiltrates, generally not with effusions or pleural changes. But important to keep in mind with Enhertu therapy!

| HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory | | |
|---|---|---|
| **Setting** | **Subtype/Biomarker** | **Regimen** |
| **First Line** | No germline *BRCA1/2* mutation[b] | Systemic chemotherapy see BINV-Q (5) |
| | Germline *BRCA1/2* mutation[b] | PARPi (olaparib, talazoparib)[c] (Category 1, preferred) |
| **Second Line** | HER2 IHC 1+ or 2+/ISH negative[d] | Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred) |
| | Not a candidate for fam-trastuzumab deruxtecan- nxki | Sacituzumab govitecan[f] (Category 1, preferred) |
| | | Systemic chemotherapy see BINV-Q (5) |
| **Third Line and beyond** | Any | Systemic chemotherapy see BINV-Q (5) |
| | Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H) | Targeted agents see BINV-Q (6) |

# Sacituzumab govitecan in ER+ MBC

- Sacituzumab: ADC linking an anti-Trop-2 antibody to a topoisomerase I inhibitor
- FDA approves in Feb 2023 for patients with metastatic breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.

## Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial

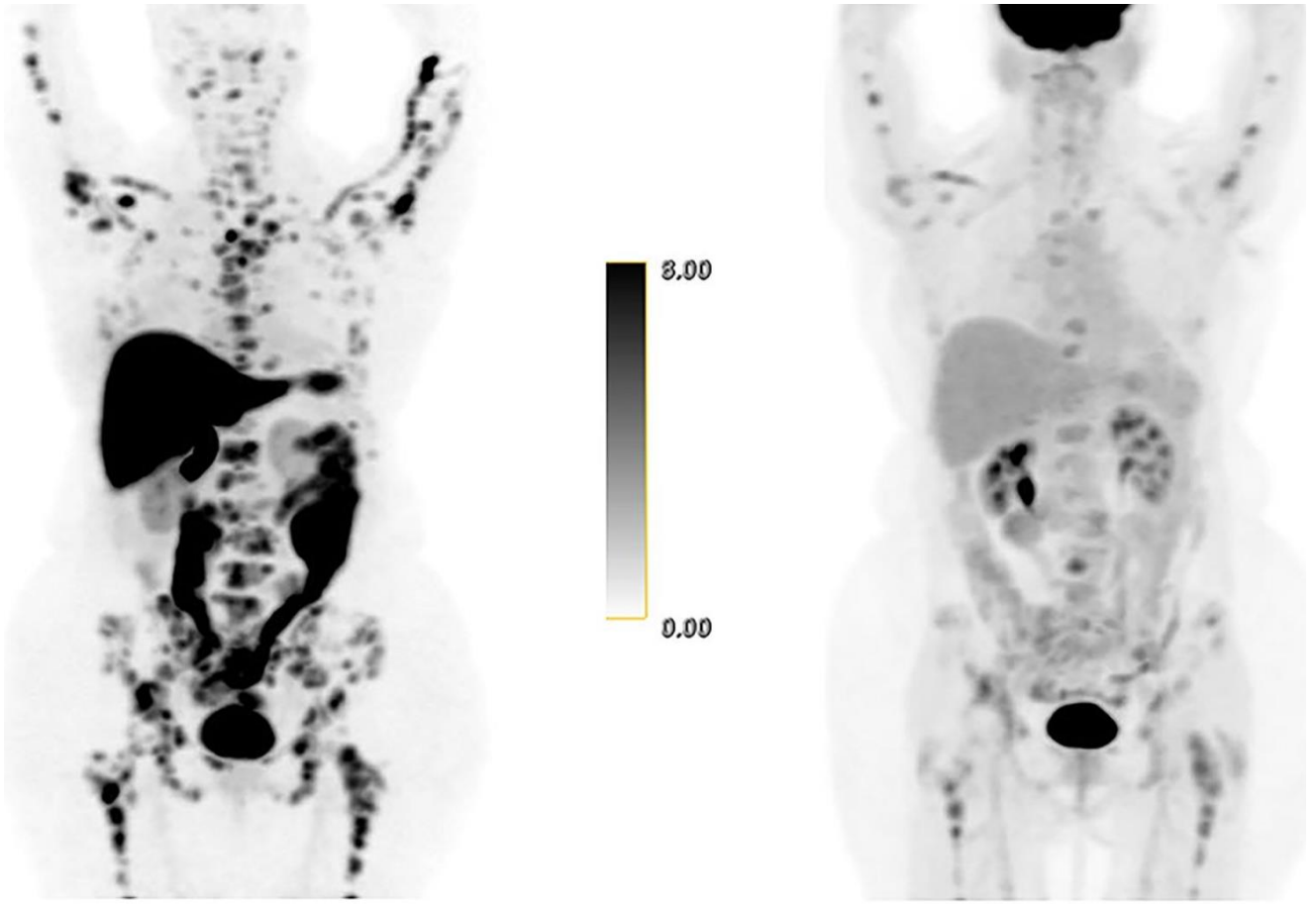
*Hope S Rugo*, Aditya Bardia*, Frederik Marmé, Javier Cortés, Peter Schmid, Delphine Loirat, Olivier Trédan, Eva Ciruelos, Florence Dalenc, Patricia Gómez Pardo, Komal L Jhaveri, Rosemary Delaney, Theresa Valdez, Hao Wang, Monica Motwani, Oh Kyu Yoon, Wendy Verret, Sara M Tolaney*

**Summary**

**Background** Sacituzumab govitecan demonstrated significant progression-free survival benefit over chemotherapy in the phase 3 TROPiCS-02 trial in patients with pretreated, endocrine-resistant hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+ and HER2–) metastatic breast cancer with limited treatment options. Here, we report the protocol-specified final analysis of overall survival and endpoints by trophoblast cell-surface antigen 2 (Trop-2) expression and other variables.

# Is my patient endocrine-refractory?

- Generally a clinical determination: Patient progresses through all the available classes of endocrine therapy.
- 2023: FDA approves flouro-estradiol F-18 (FES) PET for patients with ER+ disease, to predict responsiveness to endocrine therapy. Now incorporated into NCCN guidelines.




**FES PET** **FDG PET**

# Treatment: Case 3

45-year-old woman with a history of stage IIIB, ER/PR negative, HER2+ breast cancer presents with metastatic recurrence to liver and bone three years out from curative therapy. Liver biopsy reveals histology similar to her original tumor. Her performance status is ECOG 0-1. You recommend:

A) HER2 directed monotherapy
B) Taxane + trastuzumab
C) Taxane + trastuzumab and pertuzumab

# Treatment: Case 3

- **Answer: C, Taxane + trastuzumab and pertuzumab.**

CLEOPATRA: Compared efficacy and safety of docetaxel + trastuzuma/pertuzumab versus docetaxel + trastuzumab/placebo as first-line treatment women with HER2-positive metastatic breast cancer. The addition of pertuzumab resulted in improvement in PFS (median, 18.5 versus 12.4 months. At 30 months: Statistically significant improvement in OS for pertuzumab-containing regimen.

Baselga J, Cortes J, Kim SB, et al. N Engl J Med 2012;366:109- 119.

# Treatment for HER2+ MBC: Which taxane?

- PERUSE study: Patients with advanced HER2-positive breast cancer received docetaxel, paclitaxel or nab-paclitaxel with trastuzumab + pertuzumab: Median PFS comparable among agents.
- Paclitaxel demonstrated more neuropathy (31% vs. 16%) than docetaxel, but less febrile neutropenia (1% vs. 11%) and mucositis (14% vs. 25%).
- NCCN recommends a taxane plus pertuzumab and trastuzumab in first line: Docetaxel + HP is a category 1, paclitaxel + HP is a category 2A recommendation.

# Case 3, con't

Patient does well w/ THP, transitions to HP only. She receives HP injections. She does so well she lengthens her interval of scans to every 4-5 months. However, just over 2 years later, tumor markers rise, scan demonstrates e/o progression, new disease in her LNs. Next steps?

# Case 3, con't

TDM-1: Antibody-drug conjugate, trastuzumab to the microtubule-inhibitory agent DM1 (Support for first line: MARIANNE study. Has activity and is often used in second line: EMILIA trial)

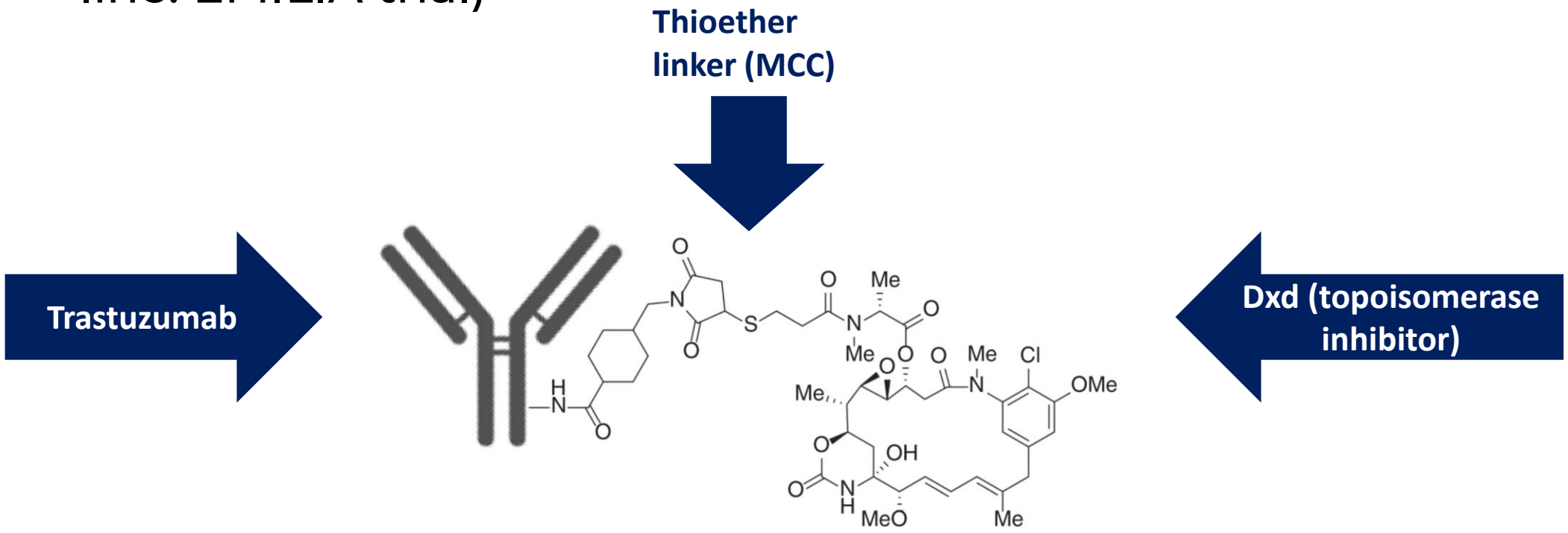
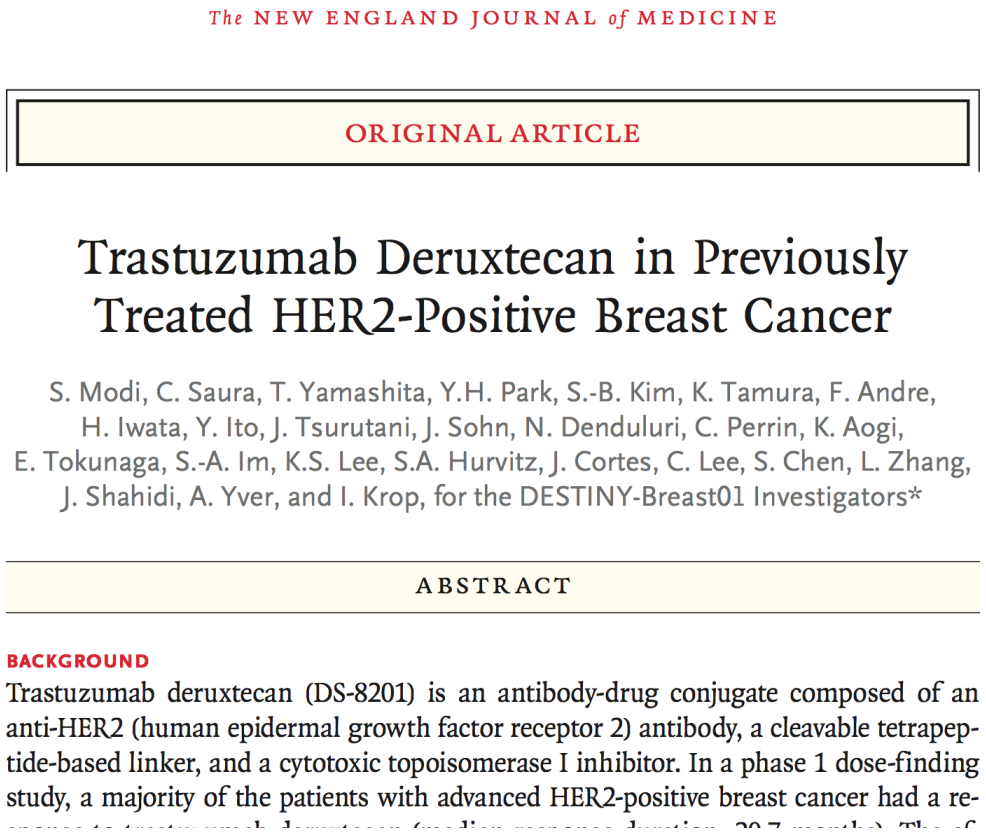



Image: *British Journal of Cancer* volume 122, pages 603–612 (2020)

# Newer agents for HER2+ MBC: Trastuzumab deruxtecan

- DESTINY-Breast01: Patients with HER2 positive disease previously treated with trastuzumab, untreated or symptomatic brain metastases excluded.
- Primary endpoint was overall response rate: 60.9% (95% CI, 53.4 to 68.0), of which 6.0% had a complete response. Disease control rate was 97.3% (95% CI, 93.8 to 99.1).



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

ABSTRACT

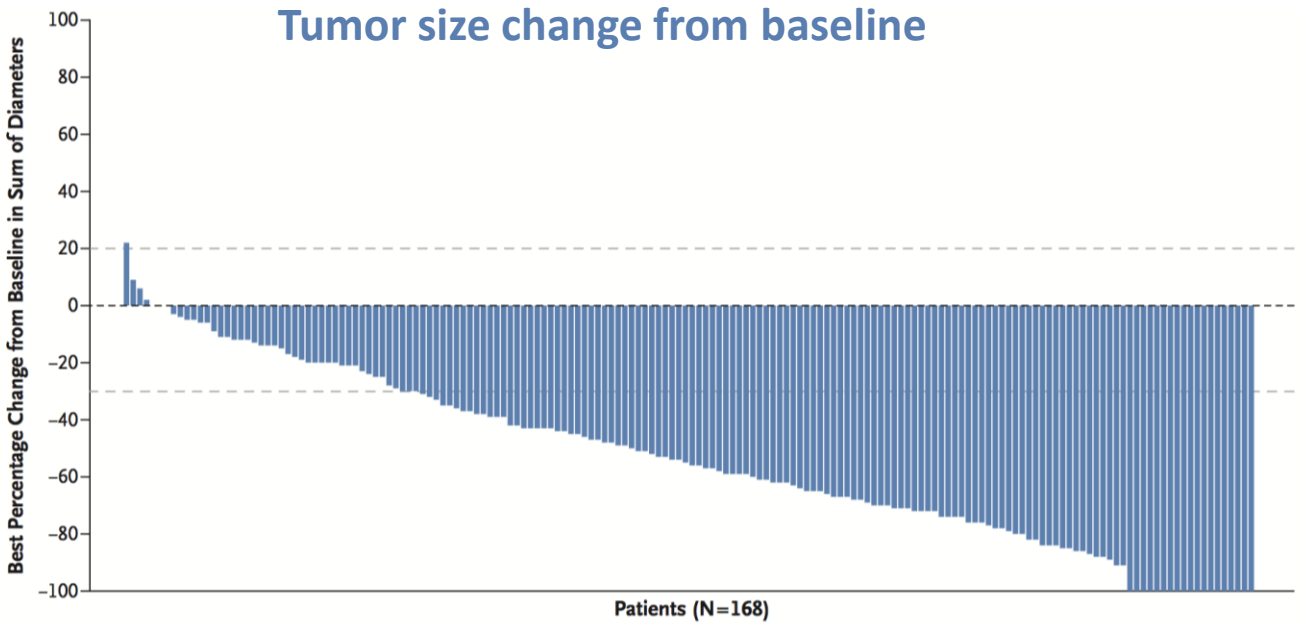
**BACKGROUND**

Trastuzumab deruxtecan (DS-8201) is an antibody-drug conjugate composed of an anti-HER2 (human epidermal growth factor receptor 2) antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor. In a phase 1 dose-finding study, a majority of the patients with advanced HER2-positive breast cancer had a re-

Modi S et al. N Engl J Med 2020;382:610-21.

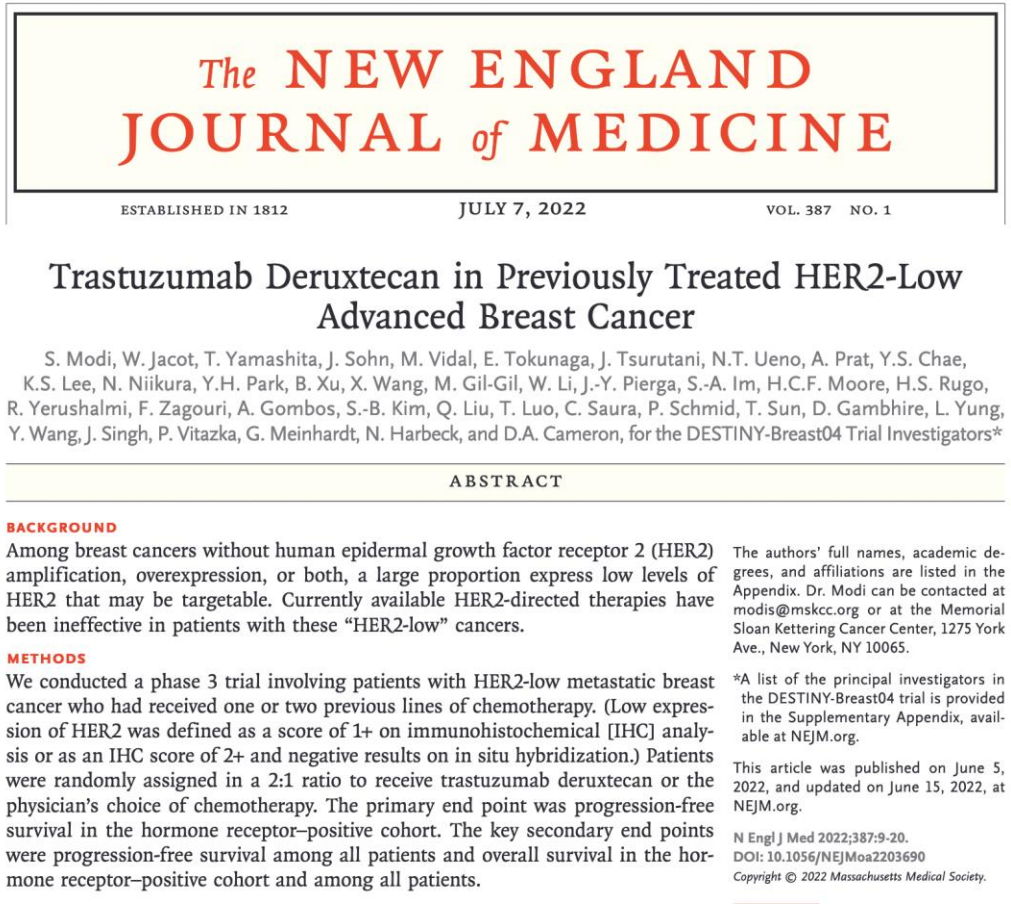
# Trastuzumab deruxtecan (T-DXt)

- FDA grants accelerated approval in Dec. 2019 for patients with HER2+ disease after two prior lines of therapy
- 13.6% of patients developed interstitial lung disease, leading to at least four deaths. Agent is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).



# T-DXt in “HER2 low” disease

- DESTINY-Breast04: T-DXt vs. physician’s choice of chemotherapy in patients with low HER2 expression.
- 52.3% overall response vs. 16.3% in the control, with 12 patients in the T-DXt group achieving a complete response.
- Improved longer progression-free survival and overall survival
- Aug 2022: FDA approves T-DXt for ”HER2 low” subtype (IHC 1+ or 2+/ISH negative)



The NEW ENGLAND JOURNAL of MEDICINE

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*

ABSTRACT

BACKGROUND

Among breast cancers without human epidermal growth factor receptor 2 (HER2) amplification, overexpression, or both, a large proportion express low levels of HER2 that may be targetable. Currently available HER2-directed therapies have been ineffective in patients with these “HER2-low” cancers.

METHODS

We conducted a phase 3 trial involving patients with HER2-low metastatic breast cancer who had received one or two previous lines of chemotherapy. (Low expression of HER2 was defined as a score of 1+ on immunohistochemical [IHC] analysis or as an IHC score of 2+ and negative results on in situ hybridization.) Patients were randomly assigned in a 2:1 ratio to receive trastuzumab deruxtecan or the physician’s choice of chemotherapy. The primary end point was progression-free survival in the hormone receptor–positive cohort. The key secondary end points were progression-free survival among all patients and overall survival in the hormone receptor–positive cohort and among all patients.

The authors’ full names, academic degrees, and affiliations are listed in the Appendix. Dr. Modi can be contacted at modis@mskcc.org or at the Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065.

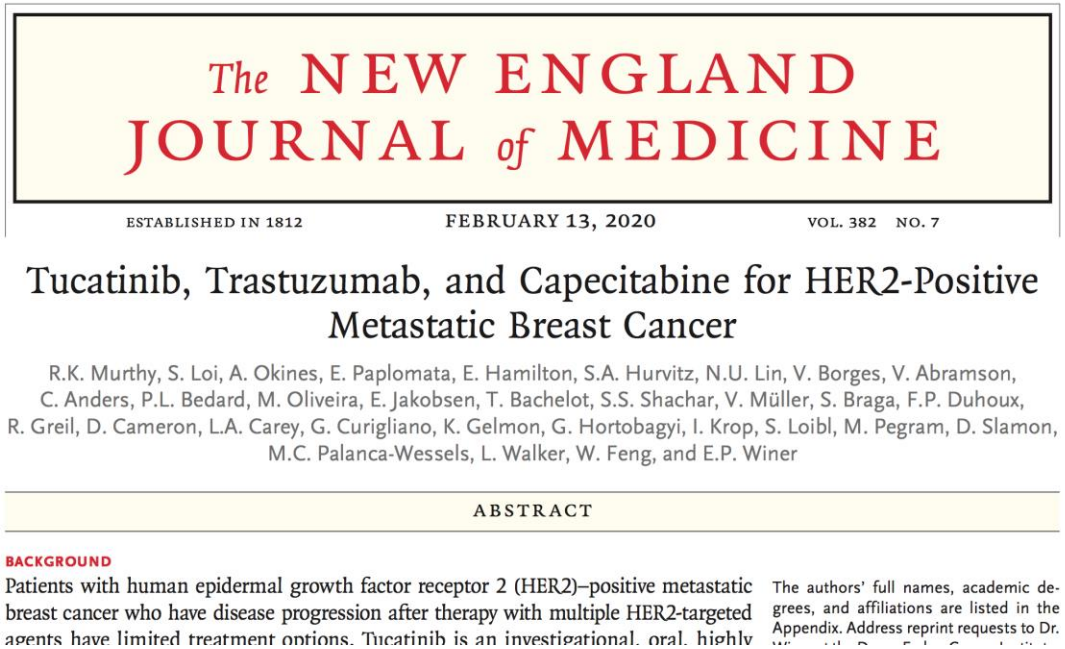
*A list of the principal investigators in the DESTINY-Breast04 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 5, 2022, and updated on June 15, 2022, at NEJM.org.

N Engl J Med 2022;387:9-20.
DOI: 10.1056/NEJMoa2203690

# Newer agents for HER2+ MBC: Tucatinib

- HER2CLIMB: Tucatinib + trastuzumab + capecitabine
- Patients with HER2+ disease with progression on two prior lines of therapy
- PFS for Tucatinib combo vs. placebo combo 7.8 vs. 5.6 months ($p<0.001$)
- FDA approval in April 2020 for use after ONE prior line of therapy



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

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

R.K. Murthy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer

ABSTRACT

BACKGROUND

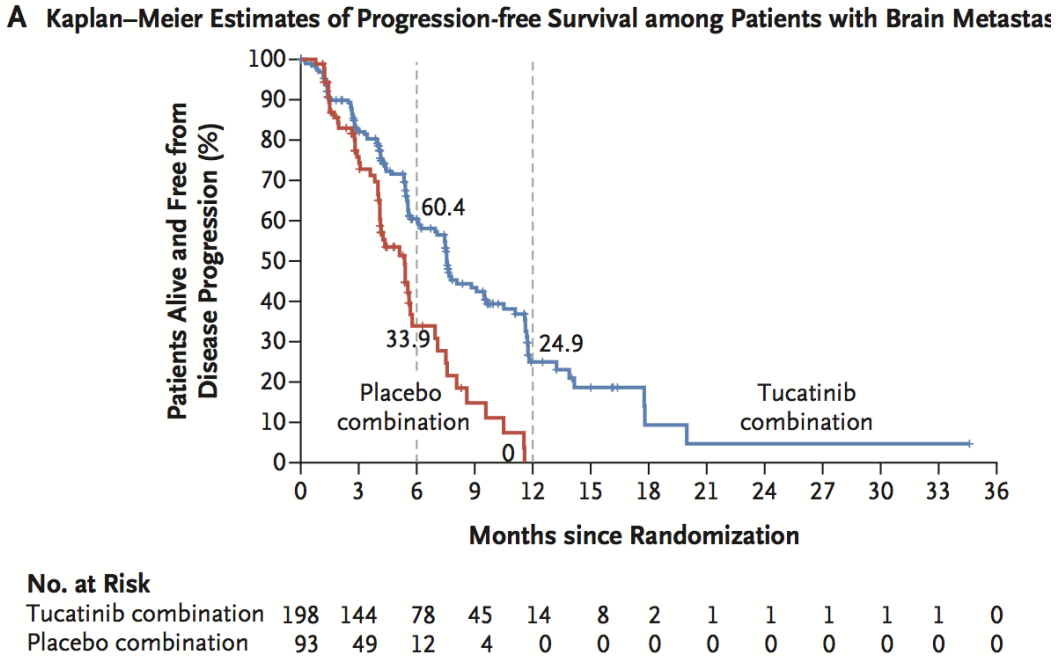
Patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer who have disease progression after therapy with multiple HER2-targeted agents have limited treatment options. Tucatinib is an investigational, oral, highly

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr.

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

# Tucatinib in patients with CNS disease

- Patients with brain metastases included unless in need of immediate treatment. Patients with untreated brain mets >2 cm enrolled with approval from the medical monitor.
- Patients with leptomeningeal disease were excluded.
- Risk of CNS progression reduced by 68% in patients with brain metastases, with a median CNS-PFS of 9.9 vs 4.2 months.




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

# Newer agents in HER2+ MBC: Margetuximab

- SOPHIA trial: median OS 21.6 months with margetuximab vs 19.8 with trastuzumab, and investigator-assessed PFS showed 29% relative risk reduction favoring margetuximab
- FDA approves in Dec 2020 in combination with chemo for patients with HER2+ MBC who have received ≥2 lines of HER2 directed therapy, at least one for metastatic disease

JAMA Oncology | Original Investigation

## Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer

### A Phase 3 Randomized Clinical Trial

Hope S. Rugo, MD; Seock-Ah Im, MD, PhD; Fatima Cardoso, MD; Javier Cortés, MD, PhD; Giuseppe Curigliano, MD, PhD; Antonino Musolino, MD, PhD, MSc; Mark D. Pegram, MD; Gail S. Wright, MD; Cristina Saura, MD, PhD; Santiago Escrivá-de-Michelino De Laurentiis, MD, PhD; Christelle Levy, MD; Ursa Brown-Glaberman, MD; Jean-Marc Ferrero, MD; Maaike de Bo Sung-Bae Kim, MD, PhD; Katarína Petráková, MD, PhD; Denise A. Yardley, MD; Orit Freedman, MD, MSc; Erik H. Jakobsen, Rinat Yerushalmi, MD; Peter A. Fasching, MD; Jeffrey L. Nordstrom, PhD; Ezio Bonvini, MD; Scott Koenig, MD, PhD; Suttor Shengyan Hong, PhD; Edwin P. Rock, MD, PhD; William J. Gradishar, MD; for the SOPHIA Study Group

**IMPORTANCE** ERRB2 (formerly HER2)–positive advanced breast cancer (ABC) remains typically incurable with optimal treatment undefined in later lines of therapy. The chimeric antibody margetuximab shares ERBB2 specificity with trastuzumab but incorporates an engineered Fc region to increase immune activation.

# Treatment for HER2+ MBC: Other regimens

- H + paclitaxel +/- carboplatin, docetaxel, vinorelbine, capecitabine
- Lapatinib + capecitabine or trastuzumab
- HER2 directed agents + anthracycline and cyclophosphamide contraindicated (27% rate of cardiac dysfunction)

# Treatment for HER2+ MBC: In summary…

| HR-Positive or -Negative and HER2-Positive[j,k] | |
|---|---|
| **Setting** | **Regimen** |
| **First Line[l]** | Pertuzumab + trastuzumab + docetaxel (Category 1, preferred) |
| | Pertuzumab + trastuzumab + paclitaxel (preferred) |
| **Second Line[n]** | Fam-trastuzumab deruxtecan-nxki[m] (Category 1, preferred) |
| **Third Line** | Tucatinib + trastuzumab + capecitabine[n] (Category 1, preferred) |
| | Ado-trastuzumab emtansine (T-DM1)[o] |
| **Fourth Line and Beyond (optimal sequence is not known)[p]** | Trastuzumab + docetaxel or vinorelbine |
| | Trastuzumab + paclitaxel ± carboplatin |
| | Capecitabine + trastuzumab or lapatinib |
| | Trastuzumab + lapatinib (without cytotoxic therapy) |
| | Trastuzumab + other chemotherapy agents[q,r] |
| | Neratinib + capecitabine |
| | Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) |
| | Additional Targeted Therapy Options see BINV-Q (6) |

# Treatment for HER2+ MBC: What about HR+ disease?

- PERTAIN trial: Postmenopausal women assigned to first-line pertuzumab plus trastuzumab and an AI or trastuzumab plus an AI, with a ~3 month improvement in PFS for triplet combo
- If patient is treated initially with chemotherapy and trastuzumab plus pertuzumab, and the chemotherapy is stopped, endocrine therapy may be added.
- NCCN includes other chemo-free trastuzumab combinations (e.g., fulvestrant or tamoxifen), but should be considered only after chemotherapy plus HER2-directed therapy, or in some patients with indolent disease

# Treatment: Case 4

A 58-year-old woman presents with a 6 cm clinically node positive breast tumor. Biopsy demonstrates a high-grade invasive ductal carcinoma, ER/PR/HER2 negative. Staging scans demonstrate liver involvement, which biopsy shows to be metastatic disease. NGS of her tumor reveals a high tumor mutational burden (TMB). What therapy will you select in the first line for her?

A) Atezolizumab
B) Sacituzumab
C) Pembrolizumab
D) Avelumab

# Treatment: Case 4

Answer: C, Pembrolizumab.

TMB ≥9 mutations/megabase supports treatment with the immune checkpoint inhibitor pembrolizumab, in combination with chemotherapy.

# Rise and fall of atezolizumab

- IMpassion 130: Atezolizumab plus nab-paclitaxel vs. placebo plus nab-paclitaxel in patients with treatment-naïve TNBC. PFS advantage and a trend toward better OS.
- March 2019: FDA granted accelerated approval for atezolizumab + nab-paclitaxel in the first line for patients with PD-L1 expressing tumors.
- Aug. 2021: TNBC indication withdrawn after IMPASSION 131 results demonstrated no PFS or OS advantage

# Sacituzumab govitecan in mTNBC

- Median overall survival was 12.1 months vs 6.7 with chemotherapy
- Objective response 35% with sacituzumab govitecan vs 5% with chemo for mTNBC.
- FDA approval in April 2021 for patients with mTNBC who have received ≥2 lines of chemo, at least in one in metastatic setting (approval in ER+ disease came later).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

A. Bardia, S.A. Hurvitz, S.M. Tolaney, D. Loirat, K. Punie, M. Oliveira, A. Brufsky, S.D. Sardesai, K. Kalinsky, A.B. Zelnak, R. Weaver, T. Traina, F. Dalenc, P. Aftimos, F. Lynce, S. Diab, J. Cortés, J. O'Shaughnessy, V. Diéras, C. Ferrario, P. Schmid, L.A. Carey, L. Gianni, M.J. Piccart, S. Loibl, D.M. Goldenberg, Q. Hong, M.S. Olivo, L.M. Itri, and H.S. Rugo, for the ASCENT Clinical Trial Investigators*

ABSTRACT

**BACKGROUND**

Patients with metastatic triple-negative breast cancer have a poor prognosis. Sacituzumab govitecan is an antibody–drug conjugate composed of an antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2), which is expressed in the majority of breast cancers, coupled to SN-38 (topoisomerase I inhibitor) through a proprietary hydrolyzable linker.

# Treatment for mTNBC: Chemotherapeutic agents

- Taxanes (paclitaxel), anthracyclines (doxorubicin and liposomal doxorubicin), anti-metabolites (capecitabine and gemcitabine), microtubule inhibitors (eribulin and vinorelbine), platinum agents
- Single agent chemotherapy → Lower response rates and time to progression, but multi-agent chemo → more toxicity and no overall survival benefit.

# Treatment for mTNBC: Case 5

A 46 year-old woman with a BRCA1 mutation transfers care to you. She breast cancer metastatic to her lungs, pleura, liver, and mediastinum, ER/PR/HER2 neg. Her disease has progressed on paclitaxel. PDL1 is negative. She feels well, has few symptoms, is still working. What do you recommend next?

A) Capecitabine
B) Olaparib
C) Ixabepilone
D) Atezolizumab + nab paclitaxel

# Treatment for mTNBC: BRCA mutations

- Answer: B, Olaparib
  - –OlympiAD trial (NEJM 2017): Among patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation, olaparib monotherapy provided a significant benefit over standard therapy
  - –Median progression-free survival was 2.8 months longer, risk of disease progression or death was 42% lower with olaparib monotherapy than with standard therapy.
  - –FDA has approved olaparib and talazoparib in advanced breast, ovarian, fallopian tube, peritoneal, and pancreatic cancer for patients with germline BRCA mutations.
  - **–NOTE: TNBC is more common among patients with BRCA mutations, but Olaparib is approved for patients with germline mutations and ANY subtype of breast cancer**

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

# Other treatment considerations: Bone metastases

- In patients with bone metastases, bisphosphonate treatment is associated with fewer skeletal-related events (SREs), fewer pathologic fractures, and lower need for radiation and surgery to treat pain.
- No impact on OS
- Dosing can be Q4 vs Q12 weeks w/ no significant difference in SREs in multiple trials. Reminder: Q6 months is nonmetastatic dosing for osteoporosis.

# Role for surgery and radiation

- Multiple studies demonstrating no survival advantage for resection of breast tumor in setting of metastatic disease (exception: Turkish Federation MF07-01 trial, but groups were arguably not well balanced)
- Palliative role for surgery in case of painful breast tumors, impending fractures.
- Palliative role for radiation in pain control, stabilization of bone tumors, treatment of CNS disease

# Principles of monitoring MBC

- Monitoring includes periodic assessment of symptoms, physical exam, lab tests, imaging, and blood biomarkers
- Same imaging modality should be used consistently to allow “apples to apples” monitoring
- Optimal frequency of testing is uncertain
- Frequency of monitoring can be reduced in patients who have long-term stable disease. Tumor markers can be used to guide scan intervals

# Thank you!