Inside the Issue: Optimizing the Management of Metastatic BRCA-Negative, Triple-Negative Breast Cancer

A CME/MOC-Accredited Live Webinar

Monday, September 11, 2023
5:00 PM – 6:00 PM ET

Faculty

Hope S Rugo, MD
Tiffany A Traina, MD, FASCO

Moderator

Neil Love, MD

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Faculty

Hope S Rugo, MD
Professor of Medicine
Winterhof Family Professor of Breast Cancer
Director, Breast Oncology and Clinical Trials Education
Medical Director, Cancer Infusion Services
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
San Francisco, California

Tiffany A Traina, MD, FASCO
Vice Chair, Department of Medicine
Section Head
Triple-Negative Breast Cancer Clinical Research Program
Associate Attending Physician
Breast Medicine Service
Memorial Sloan Kettering Cancer Center
Associate Professor
Weill Cornell Medical College
New York, New York

Moderator
Neil Love, MD
Research To Practice

Commercial Support

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Dr Love — Disclosures

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Consultancy/Advisory Support	Daiichi Sankyo Inc, Napo Pharmaceuticals Inc, Puma Biotechnology Inc, Viatris
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, F Hoffmann-La Roche Ltd, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Lilly, Merck, Novartis, OBI Pharma Inc, Pfizer Inc, Pionyr Immunotherapeutics, Sermonix Pharmaceuticals, Stemline Therapeutics Inc, Taiho Oncology Inc, Veru Inc
Travel Support to Academic Meetings	AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Merck

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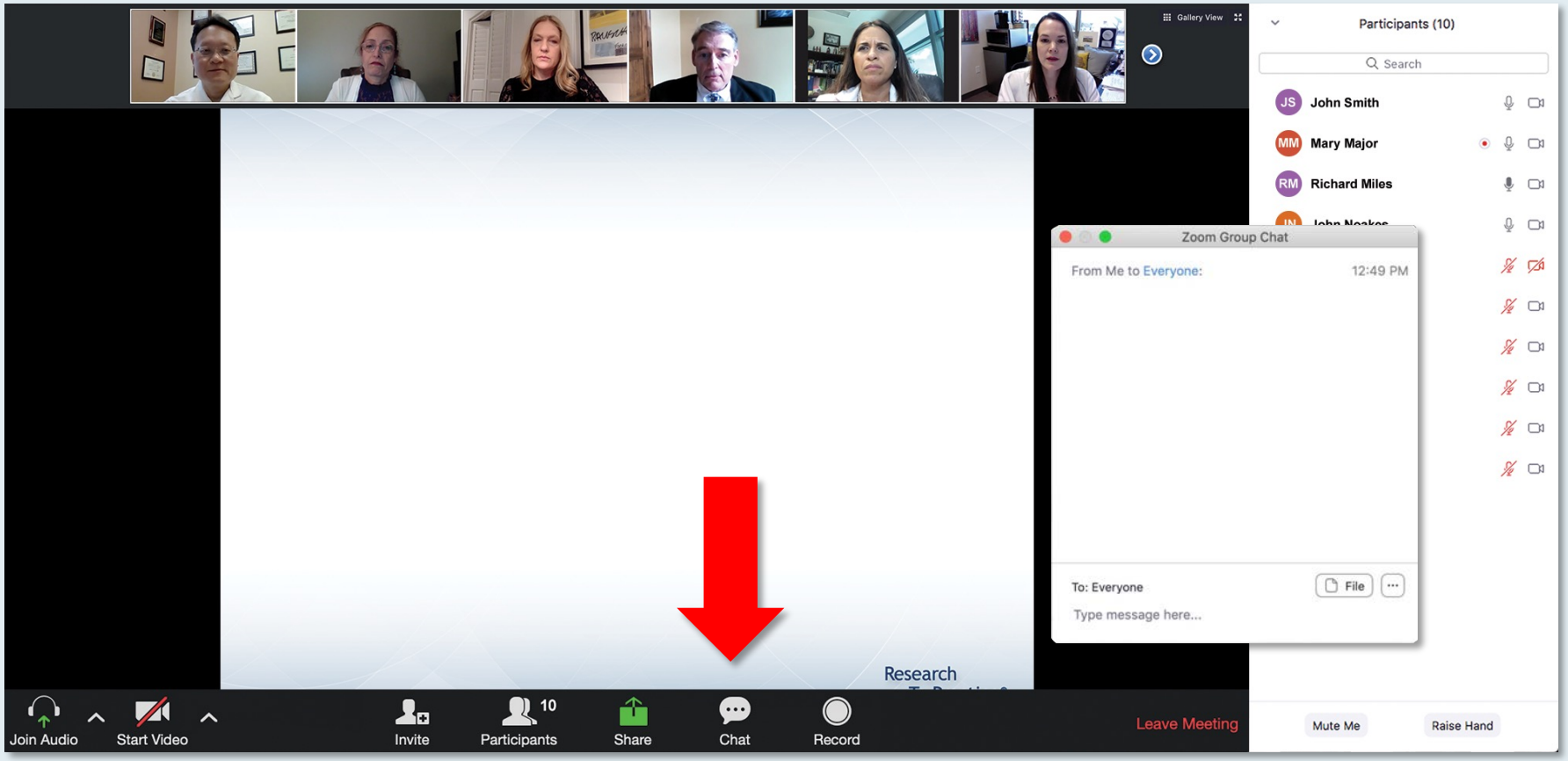
Dr Traina — Disclosures

Consulting or Advisory Role	AstraZeneca Pharmaceuticals LP, Biotheranostics Inc, Daiichi Sankyo Inc, Exact Sciences Corporation, G1 Therapeutics Inc, GE Healthcare, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Hengrui Therapeutics Inc, Merck, Novartis, Pfizer Inc, Stemline Therapeutics Inc, TerSera Therapeutics LLC
Research Funding (to Institution)	Astellas, AstraZeneca Pharmaceuticals LP, Ayala Pharmaceuticals, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Pfizer Inc

We Encourage Clinicians in Practice to Submit Questions



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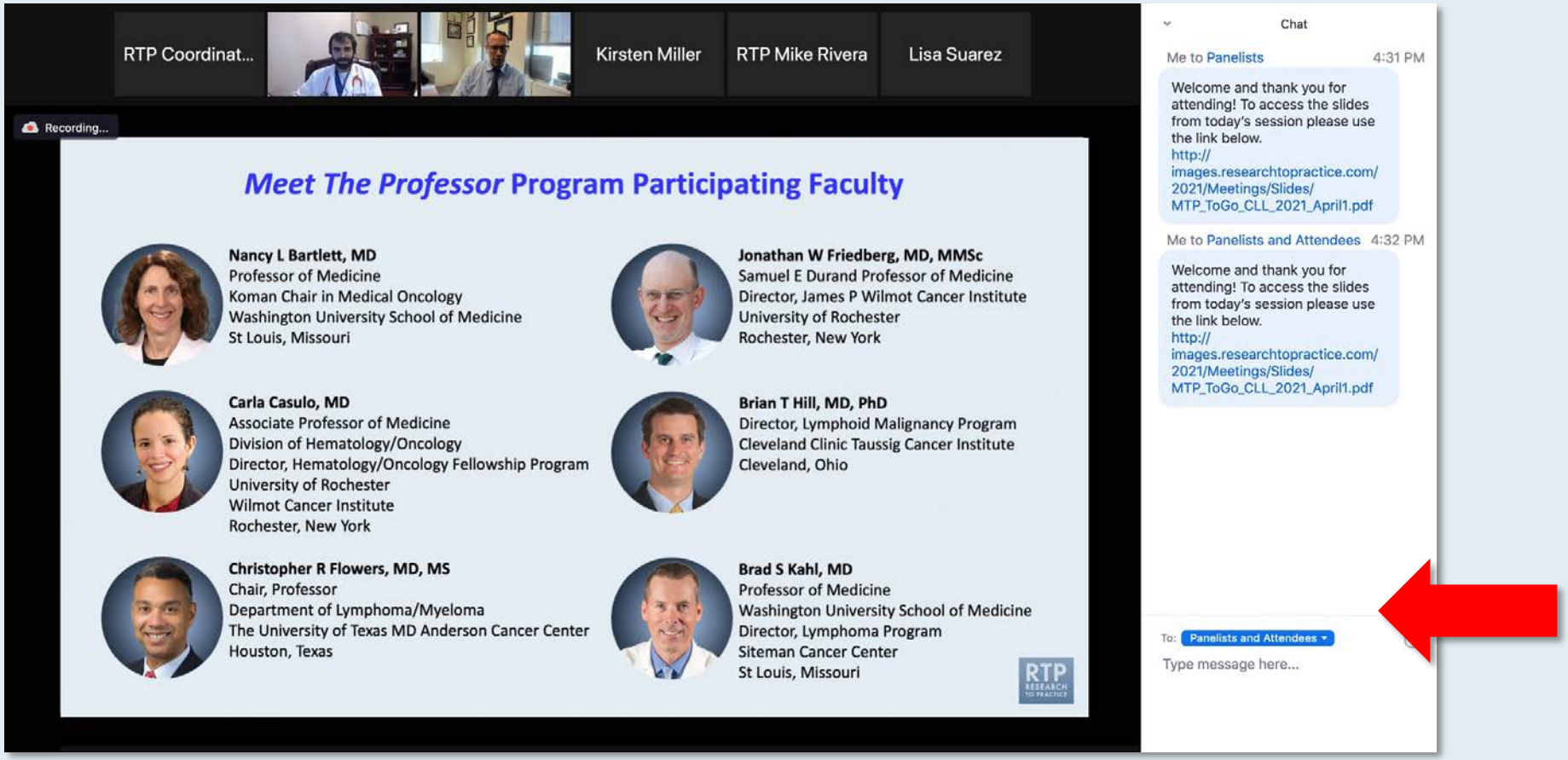

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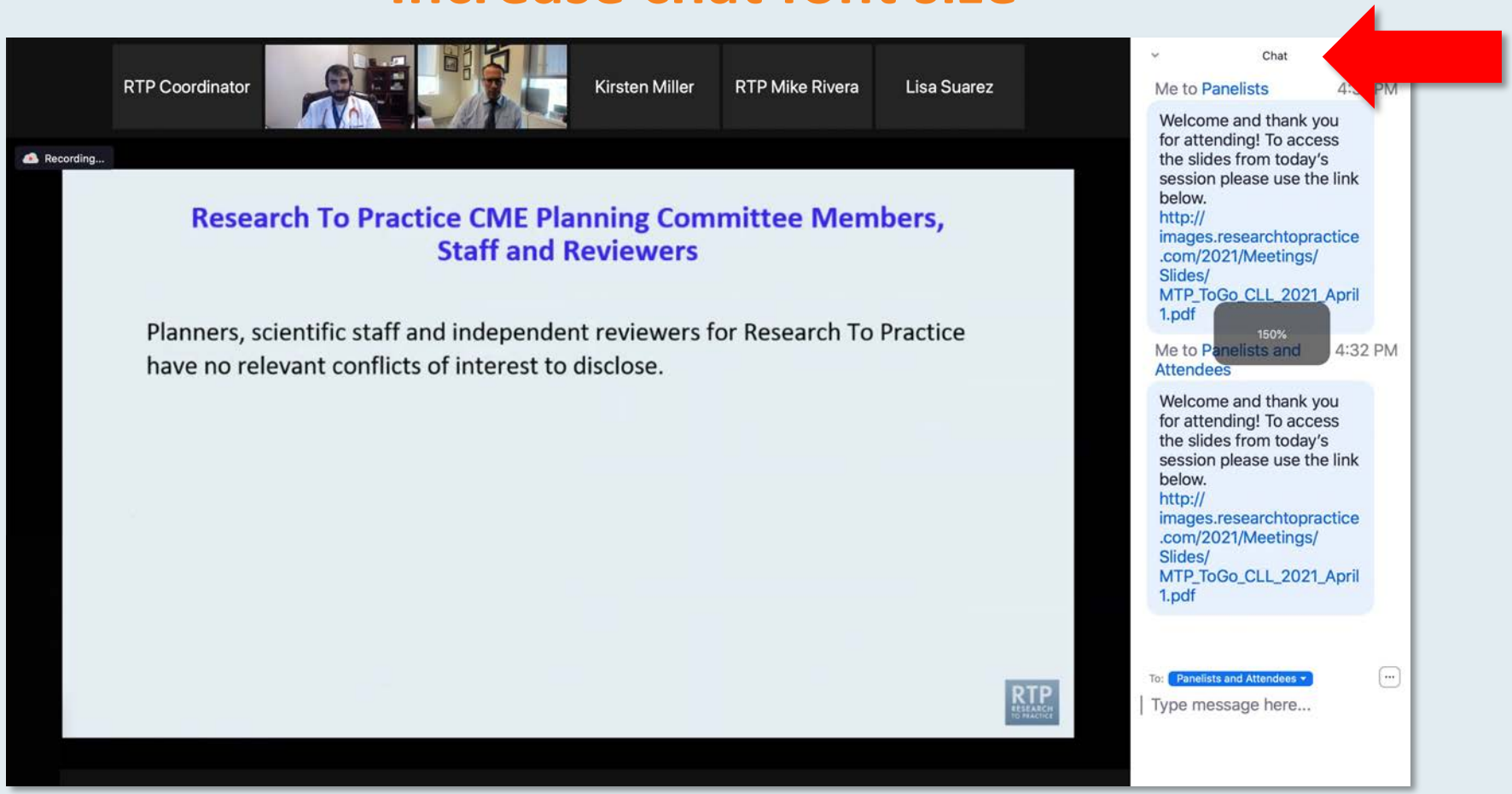

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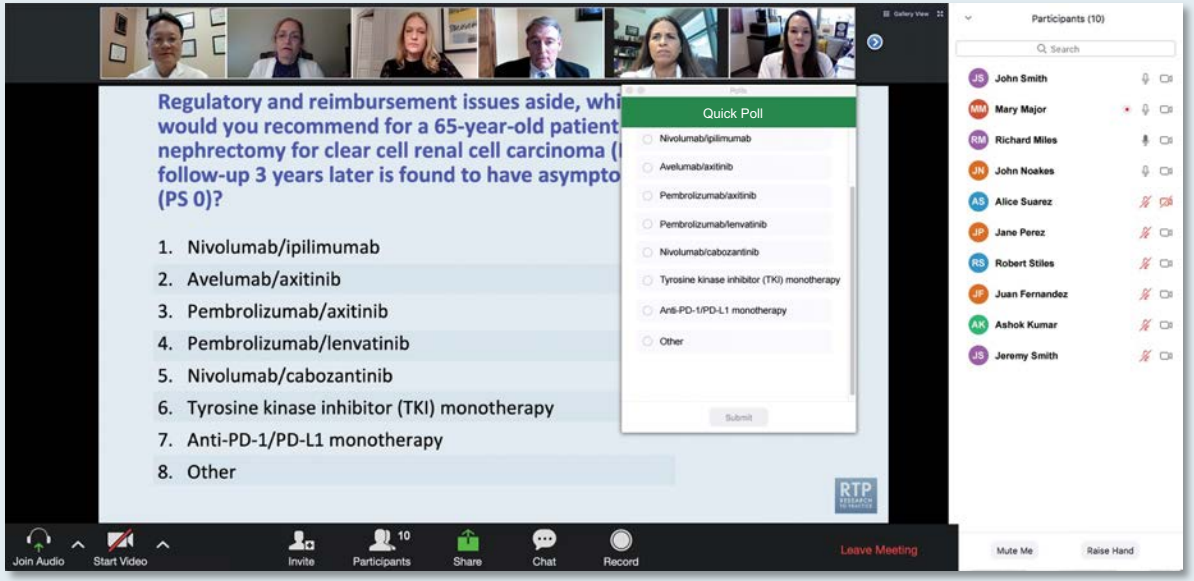

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Special Edition — Key Presentations on Breast Cancer from the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting

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UT SOUTHWESTERN MEDICAL CENTER

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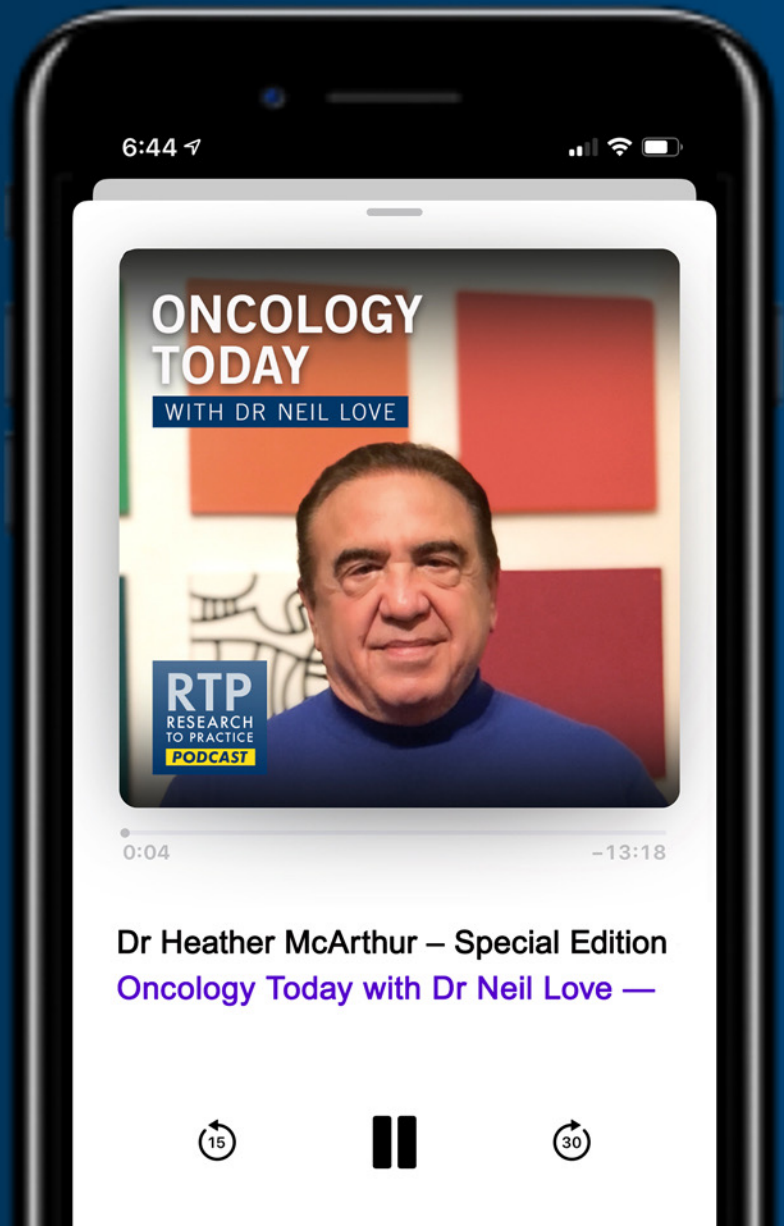

Meet The Professor

Optimizing the Management of Ovarian Cancer

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Optimizing the Management of Acute Myeloid Leukemia and Myelodysplastic Syndromes

Tuesday, September 19, 2023
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Practical Perspectives: Investigators Discuss Current Management and Actual Cases of Relapsed/Refractory Metastatic Colorectal Cancer

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J Randolph Hecht, MD

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Inside the Issue: Integrating Targeted and Immunotherapy into the Management of Localized Non-Small Cell Lung Cancer

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John V Heymach, MD, PhD

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What Clinicians Want to Know About the Management of Relapsed/Refractory Mantle Cell Lymphoma

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7:15 AM – 8:15 AM ET

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Komal Jhaveri, MD

Prostate Cancer

8:15 AM – 9:15 AM ET

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Lymphoma

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Ann S LaCasce, MD, MMSc

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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Associate Professor
Weill Cornell Medical College
New York, New York

Moderator
Neil Love, MD
Research To Practice

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Associate Professor
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Attending Physician
Massachusetts General Hospital
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Melinda Telli, MD
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Stanford Cancer Institute
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Chief, Division of Breast Oncology
Associate Director, Susan F Smith Center for Women's Cancers
Senior Physician
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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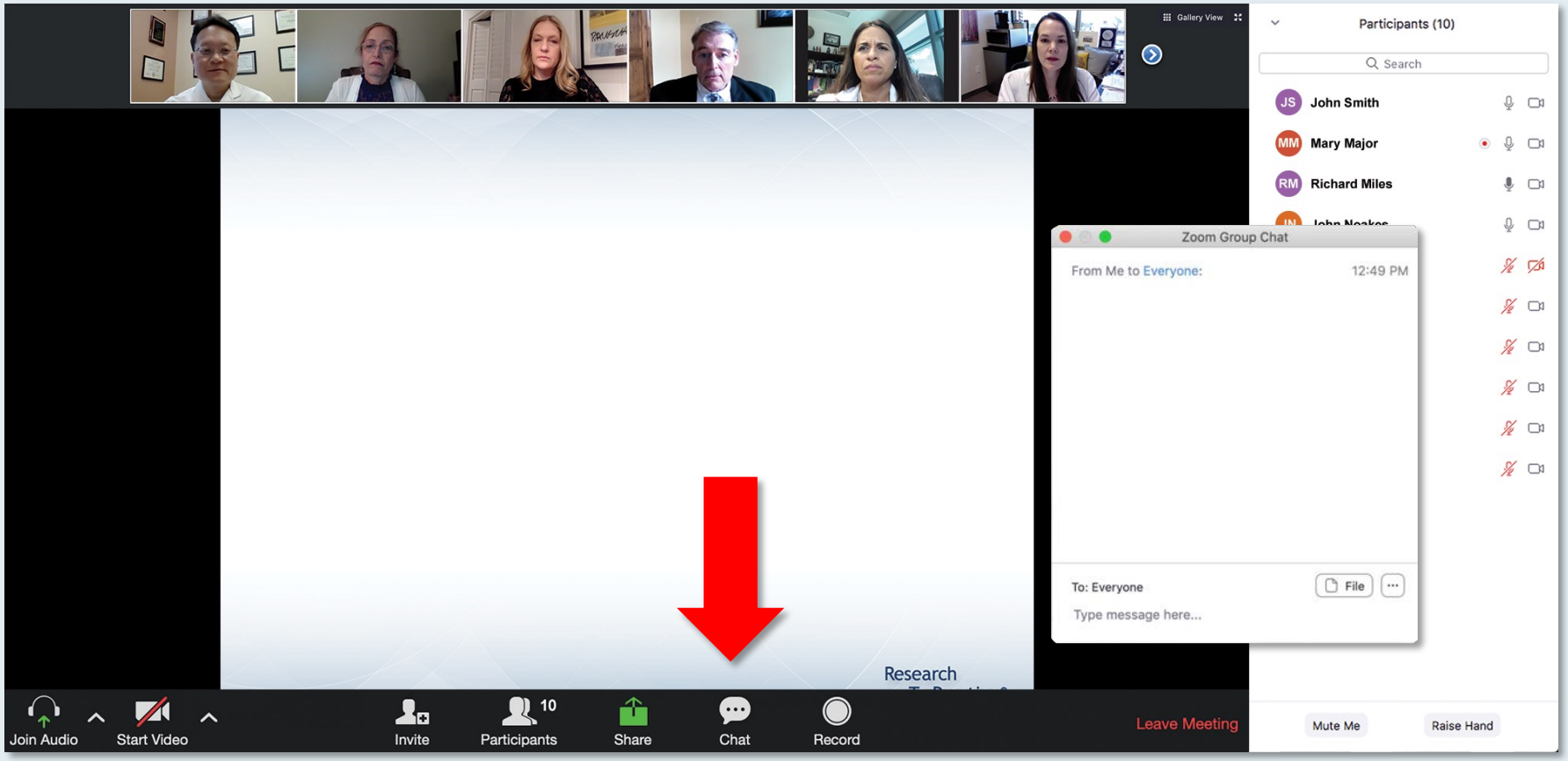

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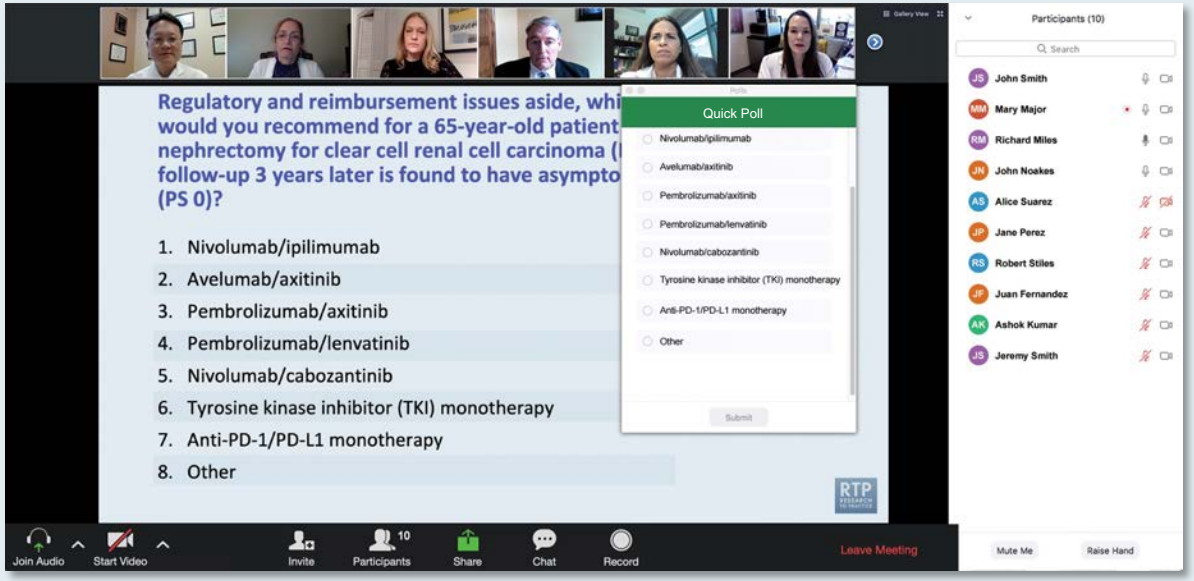

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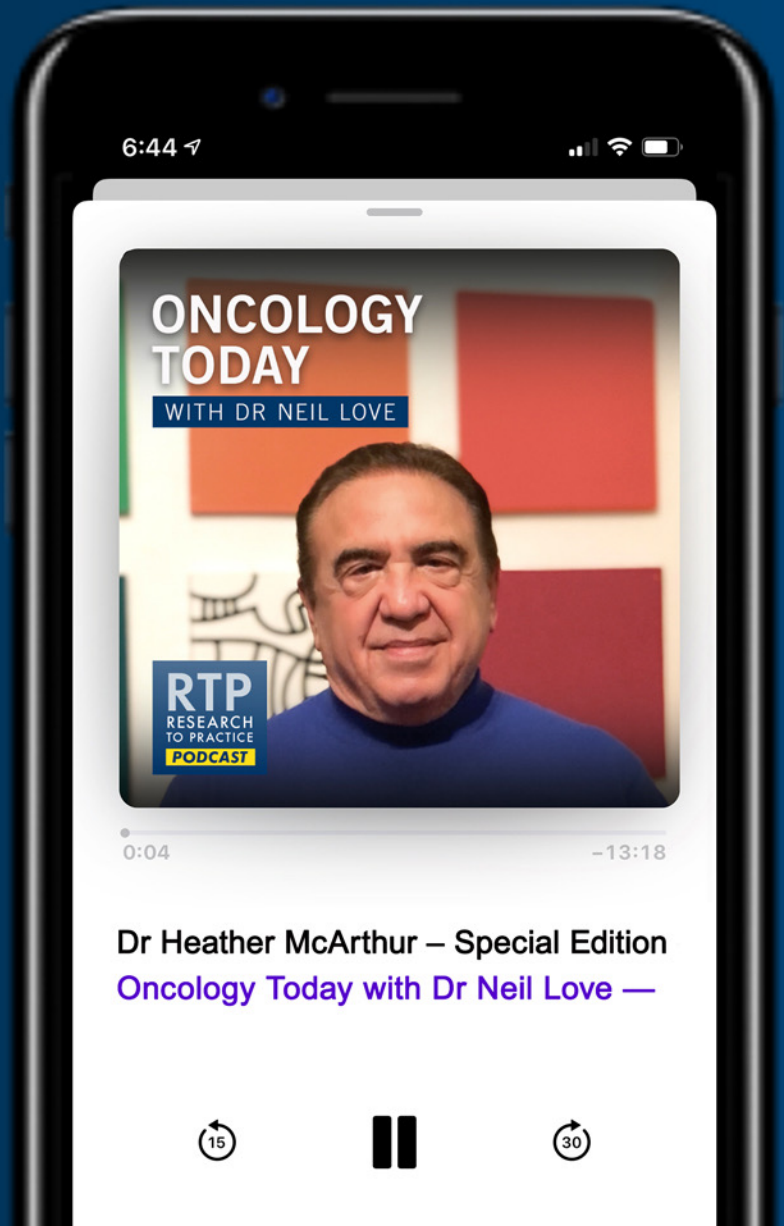

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Memorial Sloan Kettering Cancer Center

Biomarker-Based Decision-Making for Patients with BRCA-wildtype mTNBC

Tiffany A. Traina, MD FASCO
Associate Attending, Breast Medicine Service
Vice Chair, Department of Medicine
Section Head, TNBC Clinical Research Program
Memorial Sloan Kettering Cancer Center
Associate Professor, Weill Cornell Medicine
September 2023

UCSF Helen Diller Family Comprehensive Cancer Center

Current and Future Role of Non-Biomarker-Based Strategies for Patients with BRCA-Negative mTNBC: Focus on TROP2 ADCs

Hope S. Rugo, MD
Professor of Medicine
Director, Breast Oncology and Clinical Trials Education
University of California San Francisco Comprehensive Cancer Center

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Key Data Sets

Tiffany A Traina, MD, FASCO

- Hugo RS et al. KEYNOTE-355: Final results from a randomized, double-blind phase III study of first-line pembrolizumab + chemotherapy vs placebo + chemotherapy for metastatic TNBC. ESMO 2021;Abstract LBA16.
- Cortes J et al. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. *N Engl J Med* 2022;387(3):217-26.
- Tung NM et al. TBCRC 048: Phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. *J Clin Oncol* 2020 December 20;38(36):4274-82.
- Sammons SL et al. DORA: A phase II, multicenter, international, non-comparator study of olaparib (O) +/- durvalumab (D) as a chemotherapy-free maintenance strategy in platinum treated advanced triple-negative breast cancer (aTNBC). SABCS 2022;Abstract PD11-12.
- Modi S et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med* 2022 July 7;387(1):9-20.

Key Data Sets

Tiffany A Traina, MD, FASCO (continued)

- Mosele F et al. Trastuzumab deruxtecan in metastatic breast cancer with variable HER2 expression: The phase 2 DAISY trial. *Nat Med* 2023 August;29(8):2110-20.
- Schmid P et al. Trastuzumab deruxtecan (T-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic hormone receptor-negative (HR-), HER2-low breast cancer: Updated results from BEGONIA, a phase 1b/2 study. SABCS 2022;Abstract PD11-08.
- Bardia A. Datopotamab deruxtecan (Dato-DXd), a TROP2-directed antibody-drug conjugate (ADC), for triple-negative breast cancer (TNBC): Preliminary results from an ongoing phase 1 trial. *Ann Oncol* 2021;32(Suppl 2):60-78;Abstract LBA4.
- Schmid P et al. Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): Updated results from BEGONIA, a phase 1b/2 study. SABCS 2022;Abstract PD11-09.

Key Data Sets

Tiffany A Traina, MD, FASCO (continued)

- Krop I et al. Results from the phase 1/2 study of patritumab deruxtecan, a HER3-directed antibody-drug conjugate (ADC), in patients with HER3-expressing metastatic breast cancer (MBC). ASCO 2022;Abstract 1002.
- Jhaveri K et al. Latest findings from the breast cancer cohort in SUMMIT — A phase 2 'basket' trial of neratinib + trastuzumab + fulvestrant for HER2-mutant, hormone receptor-positive, metastatic breast cancer. SABCS 2021;Abstract PD1-05.
- Dent R et al. Double-blind placebo (PBO)-controlled randomized phase III trial evaluating first-line ipatasertib (IPAT) combined with paclitaxel (PAC) for PIK3CA/AKT1/PTEN-altered locally advanced unresectable or metastatic triple-negative breast cancer (aTNBC): Primary results from IPATunity130 Cohort A. SABCS 2020;Abstract GS3-04.
- Schmid P et al. Mature survival update of the double-blind placebo-controlled randomised phase II PAKT trial of first-line capivasertib plus paclitaxel for metastatic triple-negative breast cancer. SABCS 2020;Abstract PD1-11.

Key Data Sets

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- Bardia A et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med* 2021 April 22;384(16):1529-41.
- Bardia A et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. *N Engl J Med* 2019 February 21;380(8):741-51.
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Key Data Sets

Hope S Rugo, MD (continued)

- Rugo HS et al. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. *NPJ Breast Cancer* 2022 August 29;8(1):98.
- Loibl S et al. Health-related quality of life in the phase III ASCENT trial of sacituzumab govitecan versus standard chemotherapy in metastatic triple-negative breast cancer. *Eur J Cancer* 2023 January;178:23-33.
- Meric-Bernstam F et al. Phase 1 TROPION-PanTumor01 study evaluating datopotamab deruxtecan (Dato-DXd) in unresectable or metastatic hormone receptor-positive/HER2-negative breast cancer (BC). SABCS 2022;Abstract PD13-08.
- Rainey N et al. A phase 2 randomized study of magrolimab combination therapy in adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC): ELEVATE-TNBC. Abstract TPS1130.

Agenda

INTRODUCTION: “Isn’t oncology depressing?”

MODULE 1: Checkpoint inhibitors

MODULE 2: Antibody-drug conjugates

MODULE 3: HER2-low disease

MODULE 4: Other agents under development

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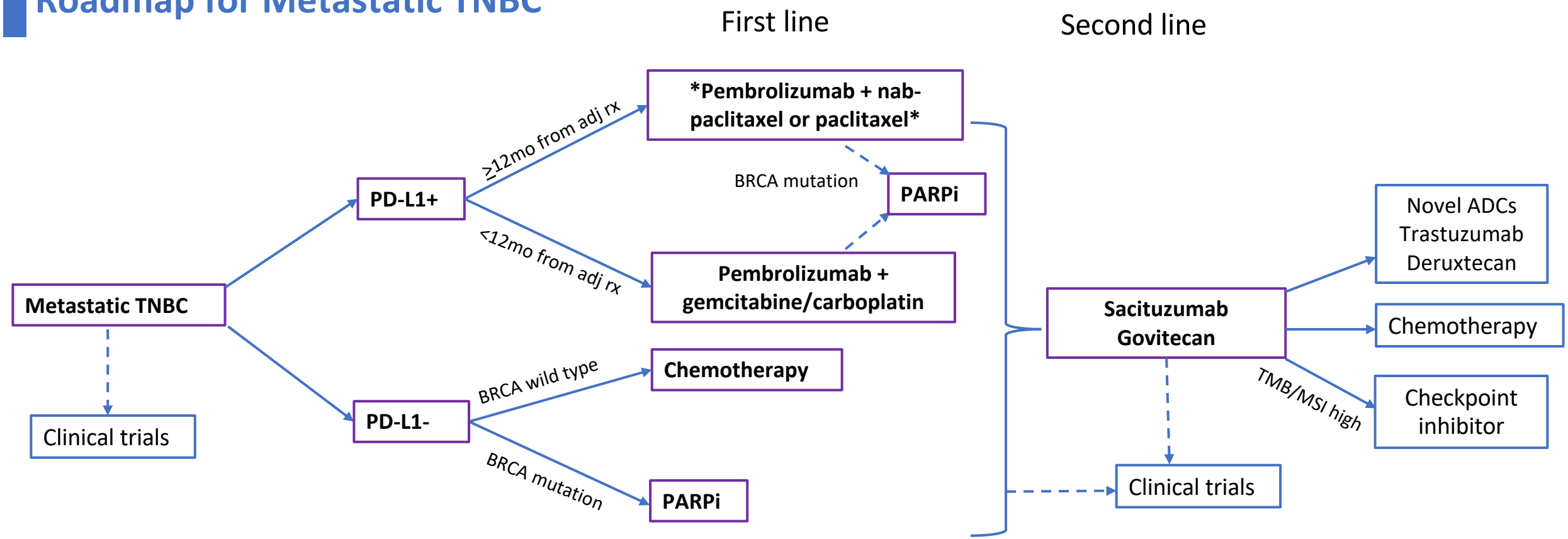
RTP
RESEARCH
TO PRACTICE

Roadmap for Metastatic TNBC



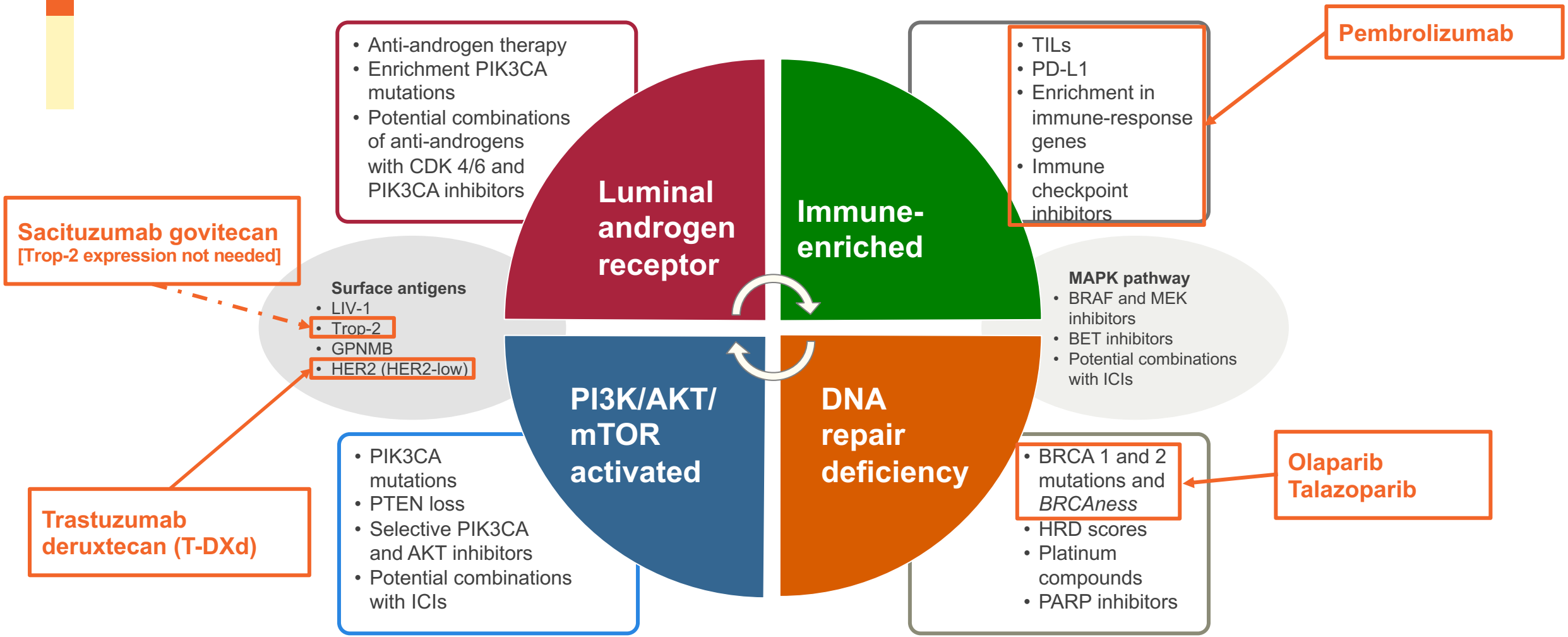
**Pembrolizumab (CPS) or atezolizumab ex US (SP142), nab-paclitaxel only*)

PARPi: PARP inhibitor (olaparib, talazoparib)

Always consider clinical trials at each decision point

Courtesy of Hope S Rugo, MD

Biomarker-Driven Therapies Are a Reality



Marra A, et al. *NPJ Breast Cancer*. 2020;6:54.

Courtesy of Tiffany A Traina, MD, FASCO

Memorial Sloan Kettering Cancer Center

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RTP
RESEARCH
TO PRACTICE

Key Data Sets

Tiffany A Traina, MD, FASCO

- Hugo RS et al. **KEYNOTE-355**: Final results from a randomized, double-blind phase III study of first-line **pembrolizumab + chemotherapy vs placebo + chemotherapy** for metastatic TNBC. ESMO 2021;Abstract LBA16.
- Cortes J et al. **Pembrolizumab plus chemotherapy** in advanced triple-negative breast cancer. *N Engl J Med* 2022;387(3):217-26.
- Sammons SL et al. **DORA**: A phase II, multicenter, international, non-comparator study of **olaparib (O) +/- durvalumab (D)** as a chemotherapy-free maintenance strategy in platinum treated advanced triple-negative breast cancer (aTNBC). SABCS 2022;Abstract PD11-12.

Case – Dr Traina: mTNBC 1L chemo/immunotherapy

62yo germline wildtype
2019 cT2N0 ER 30% HER2 neg BC
Neo weekly paclitaxel c/b allergy → changed to weekly nab-paclitaxel but had clinical progression after 5 doses
Changed to ddAC x4
6/2019 Left total mastectomy + SNB → IDC 2mm, mod diff, 0/2LN neg. ypT1aN0
Adjuvant Capecitabine x 6 months

November 2020
Elevated tumor markers prompted imaging with CT CAP: mediastinal lymphadenopathy ranging in size from 2.1 to 3.4 cm
12/2020 Endobronchial biopsy of LN = PD IDC TNBC PDL1 CPS>10
1/19/21 While in screening for 1st line clinical trial, MRI brain detected multiple CNS metastases with edema

- s/p VP shunt insertion and WBXRT

2/23/21 Begin gemcitabine, carboplatin and pembrolizumab

- CR on first set of scans!

8/26/21 Gemcitabine discontinued in setting of thrombocytopenias. Continued on Carboplatin q3 weeks and Pembro

12/2022 Carbo/Pembro dose held due to traumatic C1 and wrist fracture after a fall, requiring neurosurgery for spinal stabilization 12/26/22.

Resumed Carbo/Pembro Jan 2023

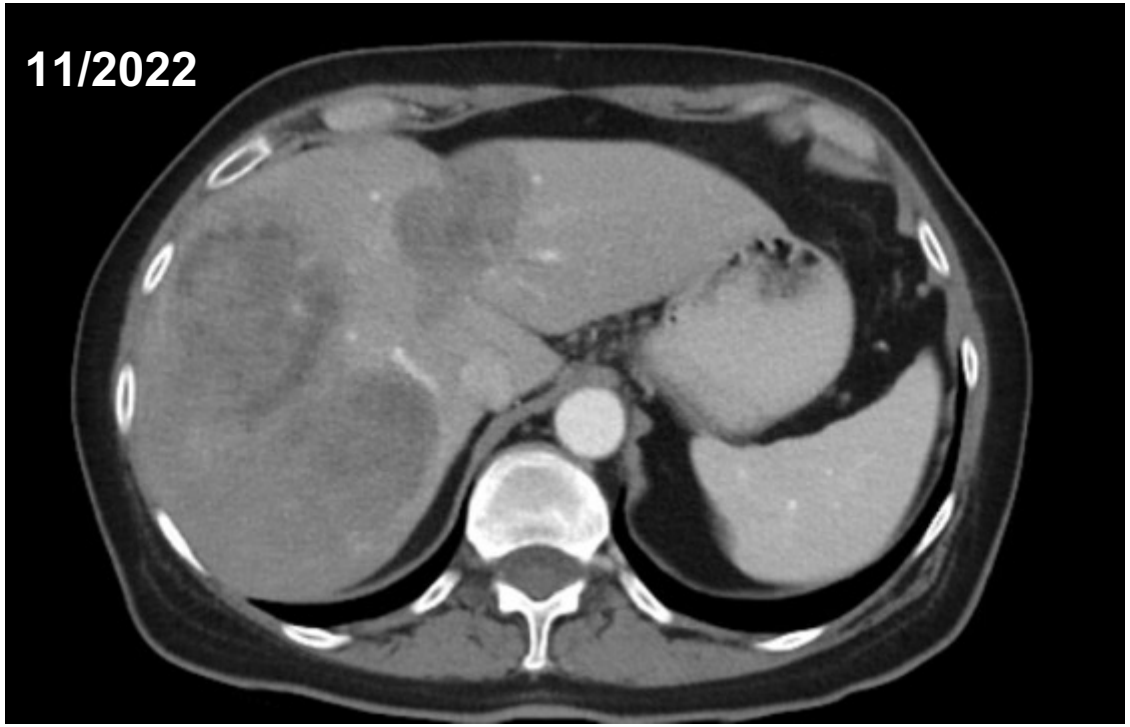
June 2023 Remains NED on imaging! Now continues on Pembrolizumab alone

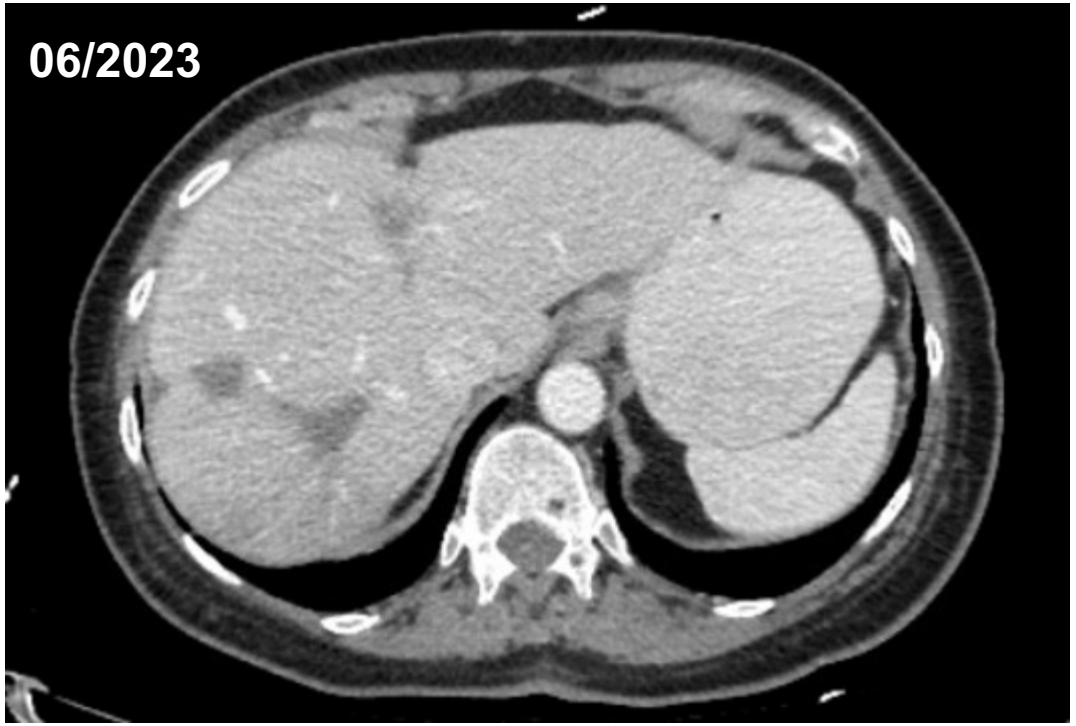
Case – Dr Traina: mTNBC 1L chemo/immunotherapy

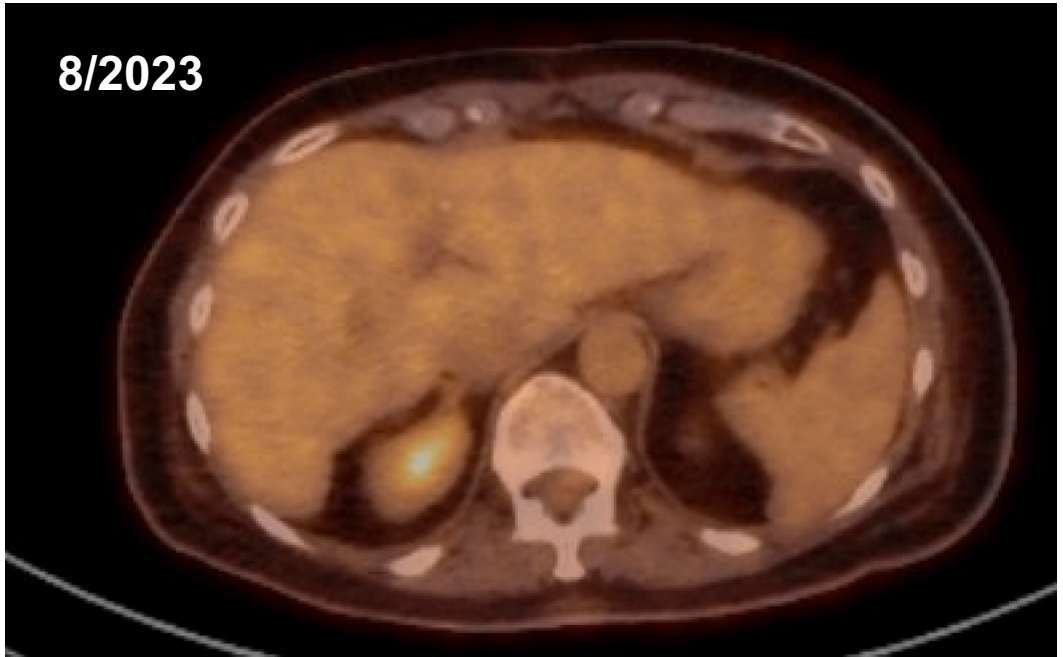
- 41yo physician underwent routine screening mammography
- April 2019: R breast IDC ER 2% PR 5% HER2 IHC 1+, right axillary core biopsy + adenocarcinoma, ER 1%, PR 5%, HER2 IHC 2+ (FISH not amplified)
- PET/CT with thoracic and portocaval adenopathy, 2 liver lesions suspicious for metastatic disease → liver biopsy confirmed ER/PR 0%, HER2 1+, AR+, PDL1+
- Germline genetics negative
- 4/2019: nab-paclitaxel and atezolizumab
- CR in liver by 10/2019, gradual improvement of adenopathy
- 10/2020 Discontinued chemotherapy, Radiated residual breast mass. Continues on atezolizumab monotherapy
- 6/2023 PET/CT remains NED!

Case – Dr Rugo: Immunotherapy for TNBC

- 72 yo woman with metastatic TNBC
- 2015 (age 65): bilateral breast cancer
  - Left breast: multifocal grade 2 IDC, largest focus 3 cm, one node with ITCs
  - ER 95%, PR negative, HER2 0, Ki67 10-15%; Oncotype 22
  - Right breast: 2mm grade 1 ILC
  - Treatment: XRT, tamoxifen x 6 years complicated by a calf DVT, then changed to anastrozole in 11/2021
- 10/2022 presented with right chest wall/axillary recurrence
  - US guided core biopsy: grade 3 IDC, ER2%, PR negative, HER2 2+/FISH NA, Ki67 25%
  - NGS:PIK3CA H1047R mutation
  - Staging scans: large chest wall mass, multiple lung nodules up to 1.5cm, and multiple liver lesions up to 8.4 cm
  - Rx: weekly paclitaxel x 2 doses, CPS found to be >10; changed to nab-paclitaxel plus pembrolizumab for cycle 2
  - 8/23: Discontinue nab-paclitaxel after 13 cycles, continue pembrolizumab alone







Courtesy of Hope S Rugo, MD

Case – Dr Traina: mTNBC with irAE

60yo woman aware of slowly growing breast mass for ~ 1 year.

- 10/2017 Bilateral mammo/US: L UOQ 5.2 cm asymmetry w/ suspicious axillary adenopathy
- Left 2:00 core bx = poorly-diff IDC, +LVI, ER <1% PR 5% HER2 2+ FISH not amplified
  L axillary LN core bx: metastatic carcinoma
- 11/30/17 CT C/A/P and Bone scan: No distant metastases
- 1/24/18 Completed neoadjuvant dd AC x4--> weekly paclitaxel/carboplatin x12
- 5/23/18 L lumpectomy and ALND: 2.5 mm residual IDC with treatment changes within 3.5 cm tumor bed with LVI, 2/5 SLN (6mm and 4mm, both without ECE, ER 20% PR 0% HER2 1+ AR 1-2%), 0/11 non-sentinel nodes.
- 7/2018 Completed breast radiation
- 7/2018 Adjuvant capecitabine x6 mo
- 7/2018 Began letrozole

Case – Dr Traina: mTNBC with irAE (cont'd)

- 8/2021 presented to local ED with chest pain and shortness of breath. CT PE negative for PE but showed new RUL mass.
- PET with RUL mass, mediastinal and hilar LN
- 9/10/2021 lung biopsy = adenocarcinoma c/w breast primary
- ER 0%, PR 0%, HER2 0, PDL1+ (CPS >10)

- 10/2021 Began 1st line nab-paclitaxel + pembrolizumab
- Complicated by severe skin toxicity including blistering, thought IO-related
- Pembrolizumab held as of November 2021. Treated with oral steroids 12/2021. Chemotherapy held as of Jan 2022.
- 12/15/2021 PET w/ decreased FDG avidity and size of RUL metastasis, resolved FDG-avid mediastinal and hilar adenopathy

Case – Dr Traina: mTNBC with irAE (cont'd)

- 4/2022 Established care at MSK
- At initial visit, patient had ECOG PS 2-3. Healing scars from prior blistering skin rash. Reported DOE and SOB at rest. Gr 3 diarrhea, non-bloody with episodes of incontinence. Decreased po intake. Requiring assistance from elderly mother and teenage children for ADLs. Admitted to hospital.
- Started high dose steroids for irAEs of presumed pneumonitis, colitis and adrenal insufficiency.
- Imaging with ground glass opacity in lungs, resolved FDG avidity. Bronchoscopy with inflammatory changes, and organizing pneumonia, no malignant cells.
- Tumor sequencing with somatic BRCA1 mutation
- Observation based on poor KPS, slow recovery from irAEs with very slow steroid taper and eventual maintenance hydrocortisone with limited volume of MBC
- 12/2022 Visual changes → MRI brain with subcm metastases s/p SRS
- 12/2022 Began olaparib off study for somatic BRCA1 mutation

A 57-year-old woman with BRCA wild-type, HRP, HER2-low (1+), de novo metastatic TNBC in the bones and chest wall. PD-L1 CPS >10. Which first-line therapy would you most likely recommend?

 Dr Rugo	Pembrolizumab/*nab* paclitaxel
 Dr Traina	Pembrolizumab/paclitaxel
 Dr Bardia	Pembrolizumab/gemcitabine/carboplatin
 Dr Brufsky	Pembrolizumab/*nab* paclitaxel
 Dr Telli	Pembrolizumab/paclitaxel
 Dr Tolaney	Pembrolizumab/paclitaxel

HRP = homologous recombination proficient; CPS = combined positive score

RTP RESEARCH TO PRACTICE

How do you typically choose between a PARP inhibitor (PARPi) and an immune checkpoint inhibitor with chemotherapy for a patient with PD-L1-positive metastatic TNBC and a BRCA mutation?

 Dr Rugo	Checkpoint inhibitor first and PARPi second based on reported survival benefits
 Dr Traina	Per NCCN, lead with checkpoint inhibitor plus chemotherapy given the survival benefit and reserve PARPi for 2nd line in that setting
 Dr Bardia	Generally start with immune checkpoint inhibitor given overall survival benefit
 Dr Brufsky	Checkpoint inhibitor and chemotherapy first, PARPi second
 Dr Telli	I generally select chemotherapy and pembrolizumab given the overall survival benefit with this combination
 Dr Tolaney	Generally, if gBRCAm, chemotherapy + PD-1 antibody first (given OS benefit) and then PARPi in second line

RTP RESEARCH TO PRACTICE

Do you generally order next-generation sequencing for your patients with metastatic TNBC?

 Dr Rugo	Yes
 Dr Traina	Yes
 Dr Bardia	Yes
 Dr Brufsky	Yes
 Dr Telli	Yes
 Dr Tolaney	Yes

NCCN Guidelines Version 3.2023
Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Specifically *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53*. See GENE-A)[a,e,f,g]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - ◊ Treatment indications
      - – To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[h,i] (See NCCN Guidelines for Breast Cancer)
      - – To aid in adjuvant treatment decisions with olaparib for high-risk,[j] HER2-negative breast cancer[h]
    - ◊ Pathology/histology
      - – Triple-negative breast cancer
      - – Multiple primary breast cancers (synchronous or metachronous)[k]
      - – Lobular breast cancer with personal or family history of diffuse gastric cancer See NCCN Guidelines for Gastric Cancer
    - ◊ Male breast cancer
    - ◊ Ancestry: Ashkenazi Jewish ancestry
  - Any age (continued):
    - ◊ Family history[l]
      - – ≥1 close blood relative[m] with ANY:
        - breast cancer at age ≤50
        - male breast cancer
        - ovarian cancer
        - pancreatic cancer
        - prostate cancer with metastatic,[n] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - – ≥3 total diagnoses of breast cancer in patient and/or close blood relatives[m]
      - – ≥2 close blood relatives[m] with either breast or prostate cancer (any grade)
- Family history of cancer only
  - An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[o]
    - ◊ If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
  - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[p]

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. In this guideline, the terms male and female refer to sex assigned at birth.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Reminder to discuss & perform germline testing!

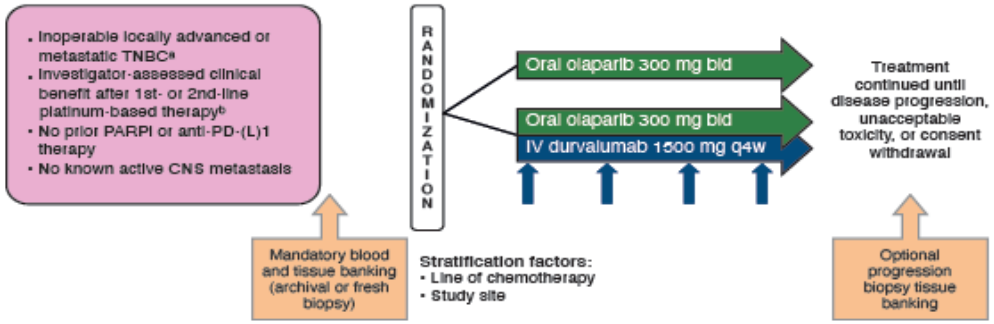
Indicated at any age with diagnosis of TNBC

Courtesy of Tiffany A Traina, MD, FASCO

Memorial Sloan Kettering Cancer Center

DORA: Ph II Olaparib +/- durvalumab as maintenance in platinum pretreated mTNBC

Figure 1. DORA maintenance trial design



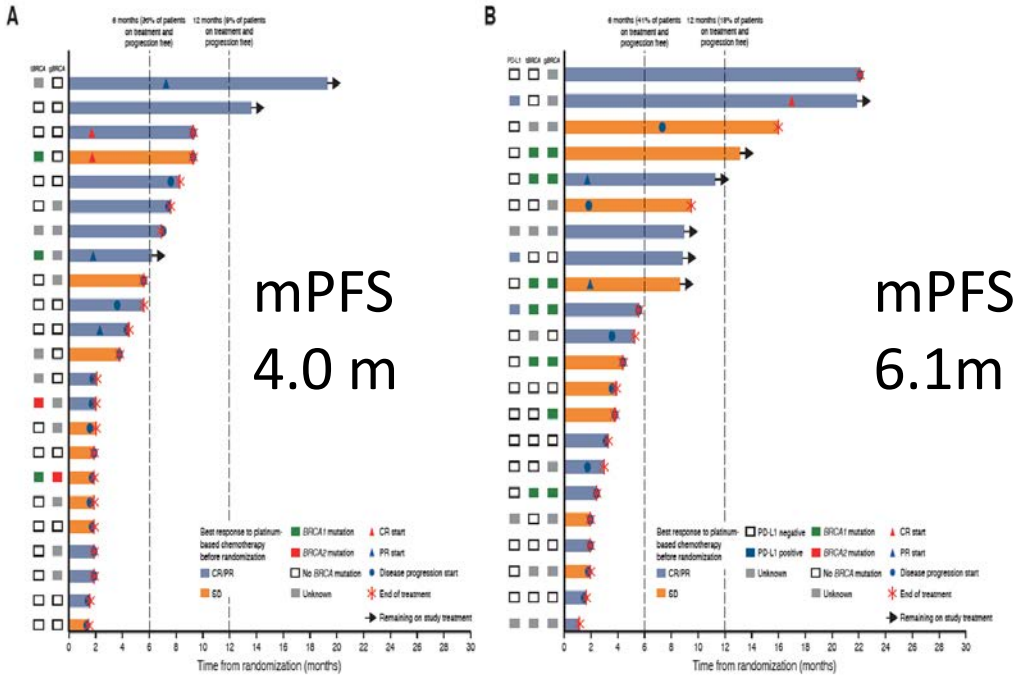
bid = twice daily; IV = intravenous; q4w = every 4 weeks. [a]Enrollment of known *gBRCA* carriers was limited to 10 patients. [b]At least three 3-weekly cycles or at least six weekly cycles.

Table 1. Baseline characteristics (ITT population)

Characteristic	Olaparib alone (n=23)	O+D combination (n=22)
Median (range) age, years	48 (35–77)	51.5 (25–72)
Most recent platinum, n (%)		
1st line	18 (78)	19 (86)
2nd line	5 (22)	3 (14)
Prior platinum regimen, n (%)		
Carboplatin	16 (70)	10 (45)
Cisplatin	7 (30)	12 (55)
Single agent	2 (9)	6 (27)
Doublet with taxane	14 (61)	9 (41)
Doublet with gemcitabine	7 (30)	7 (32)
g*BRCA* status, n (%)		
Deleterious mutation	1 (4)[a]	7 (32)[b]
No mutation detected/variant of unknown significance	13 (57)	6 (27)
Not tested[c]	9 (39)	9 (41)
DFI from initial diagnosis to advanced/metastatic TNBC, n (%)		
De novo	7 (30)	4 (18)
≤1 year	3 (13)	2 (9)
>1 year	13 (57)	16 (73)

[a]*BRCA2*. [b]All *BRCA1*. [c]*BRCA* testing is less readily available at Asian sites. DFI = disease-free interval; ITT = intent-to-treat.

Figure 2. Treatment exposure and response according to tumor characteristics: (A) Olaparib alone; (B) O+D combination therapy



mPFS 4.0 m

mPFS 6.1m

Med OS 21.7m (95% CI 7.7-NE)

Med OS 18.3m (95% CI 8.2-NE)

Sammons et al, SABCS 2022

Courtesy of Tiffany A Traina, MD, FASCO

Memorial Sloan Kettering Cancer Center

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- Carey LA et al. **Sacituzumab govitecan** as **second-line treatment** for metastatic triple-negative breast cancer-phase 3 **ASCENT study** subanalysis. *NPJ Breast Cancer* 2022 June 9;8(1):72.
- O'Shaughnessy J et al. **Analysis of patients without and with an initial triple-negative breast cancer diagnosis** in the phase 3 randomized **ASCENT** study of **sacituzumab govitecan** in metastatic triple-negative breast cancer. *Breast Cancer Res Treat* 2022 September;195(2):127-39.

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Hope S Rugo, MD (continued)

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- Loibl S et al. **Health-related quality of life** in the phase III **ASCENT** trial of **sacituzumab govitecan** versus standard chemotherapy in metastatic triple-negative breast cancer. *Eur J Cancer* 2023 January;178:23-33.

ADCs consist of numerous elements, including the monoclonal antibody, conjugated drug, and stable linker

Monoclonal antibody

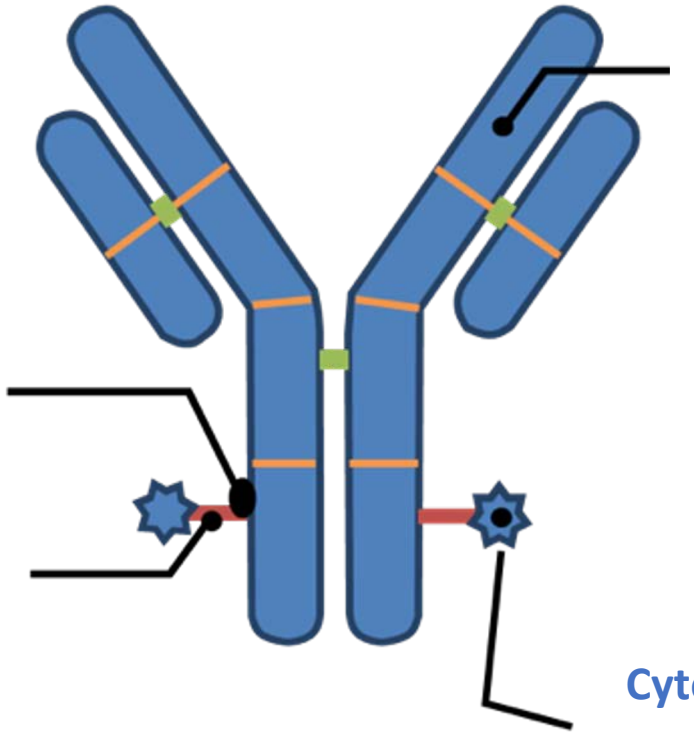
- Selective for an antigen with high copy numbers on the target tumor cell
- Internalizes in target cell
- Minimal immunogenic response

Conjugation chemistry

- Lys or Cys residue of the mAb; controls drug distribution and DAR

Stable linker

- Selectively releases drug in target cell
- Long term stability



Cytotoxic drug

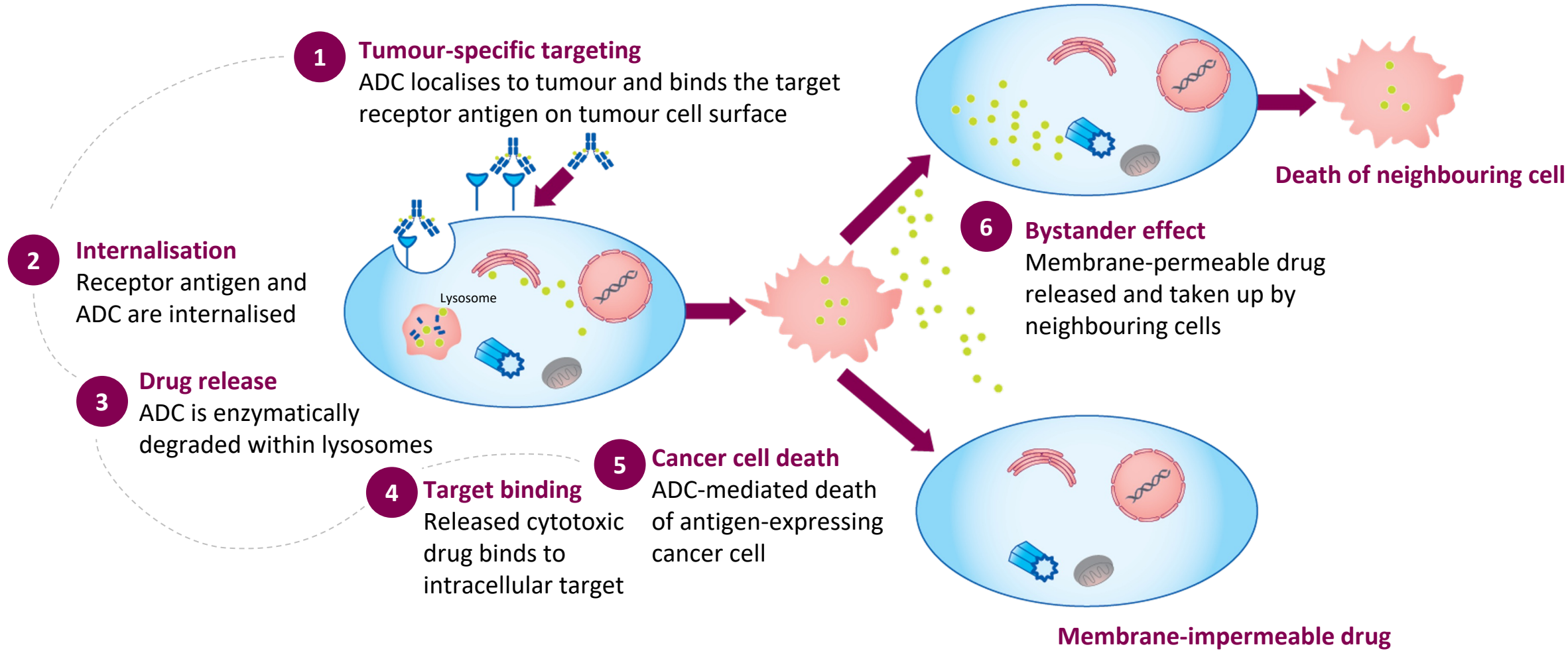
- Highly potent subnanomolar activity
- Functional groups for linking
- Lower hydrophobicity

ADC=antibody-drug conjugate; Cys=cysteine; DAR=drug:antibody ratio; Lys=lysine; mAb=monoclonal antibody.
Nakada T, et al. *Chem Pharm Bull*. 2019;67:173–185.

Linker Payload Disulphide bonds

Courtesy of Hope S Rugo, MD

ADC Technology Enables Tumor-Specific Targeting



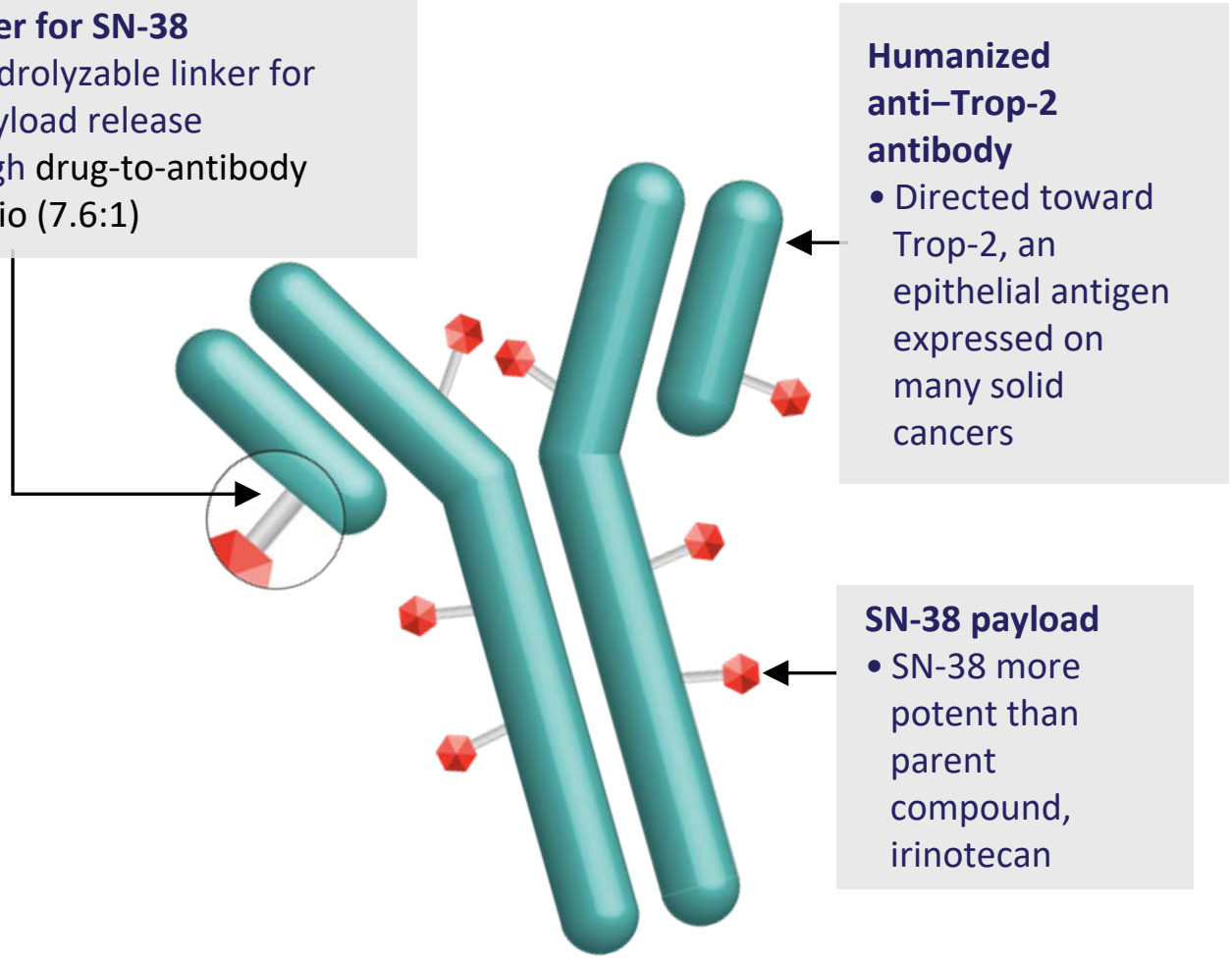
ADC=antibody-drug conjugate

1. Adapted from: Trail PA, et al. *Pharmacol Ther.* 2018;181:126–142.

Courtesy of Hope S Rugo, MD

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

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- Distinct from other ADCs
  - 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
- Accelerated FDA approval for metastatic TNBC in 2020 (now final approval), in metastatic urothelial cancer in 2021; and approved for metastatic HR+/HER2- BC in 2023.



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

Courtesy of Hope S Rugo, MD

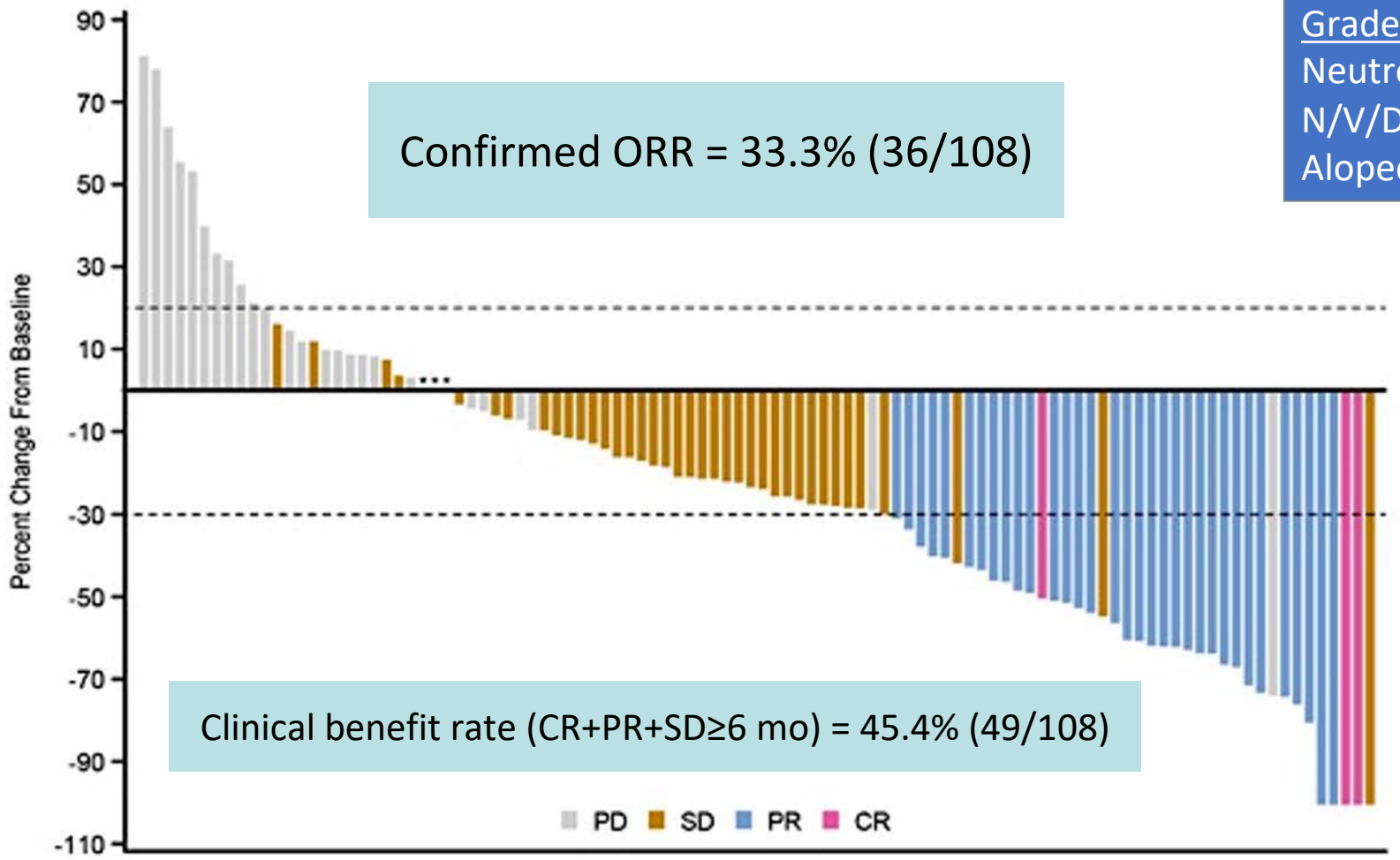
Sacituzumab Govitecan: Phase I/II Trial in mTNBC

108 patients with refractory mTNBC

Median of 3 prior lines of therapy (range 2-10) in the advanced setting

Confirmed ORR = 33.3% (36/108)

Grade 3/4 toxicity:
Neutropenia: 41%; FN 8%
N/V/D: 5/5/8%
Alopecia: 36%



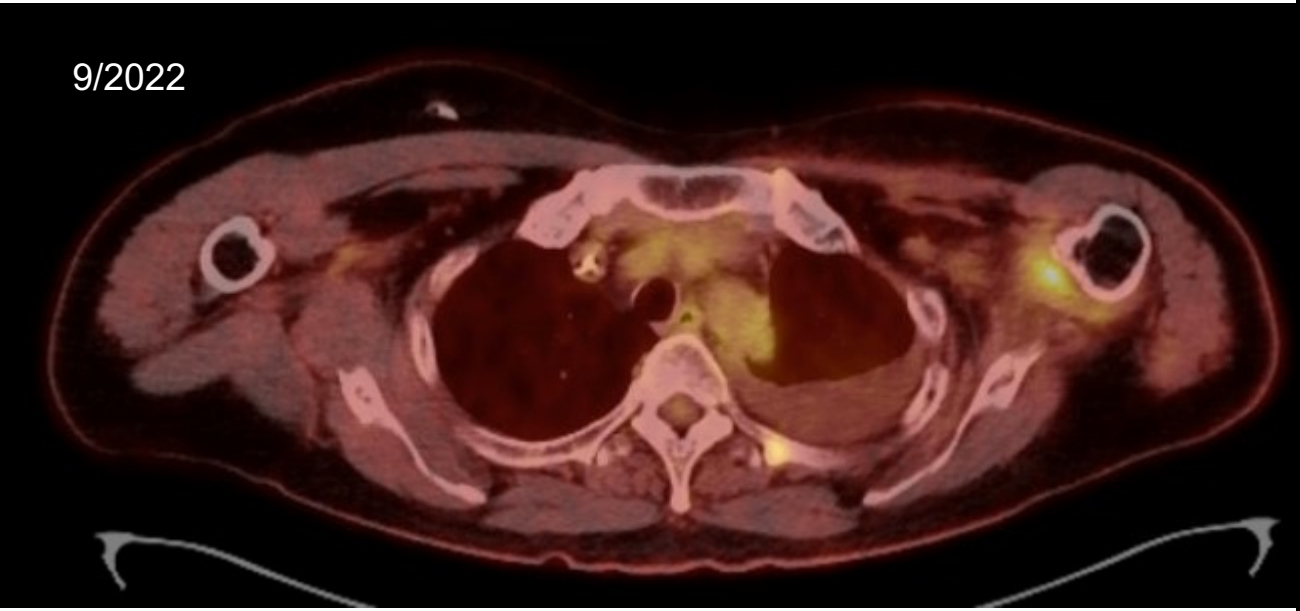
Clinical benefit rate (CR+PR+SD≥6 mo) = 45.4% (49/108)

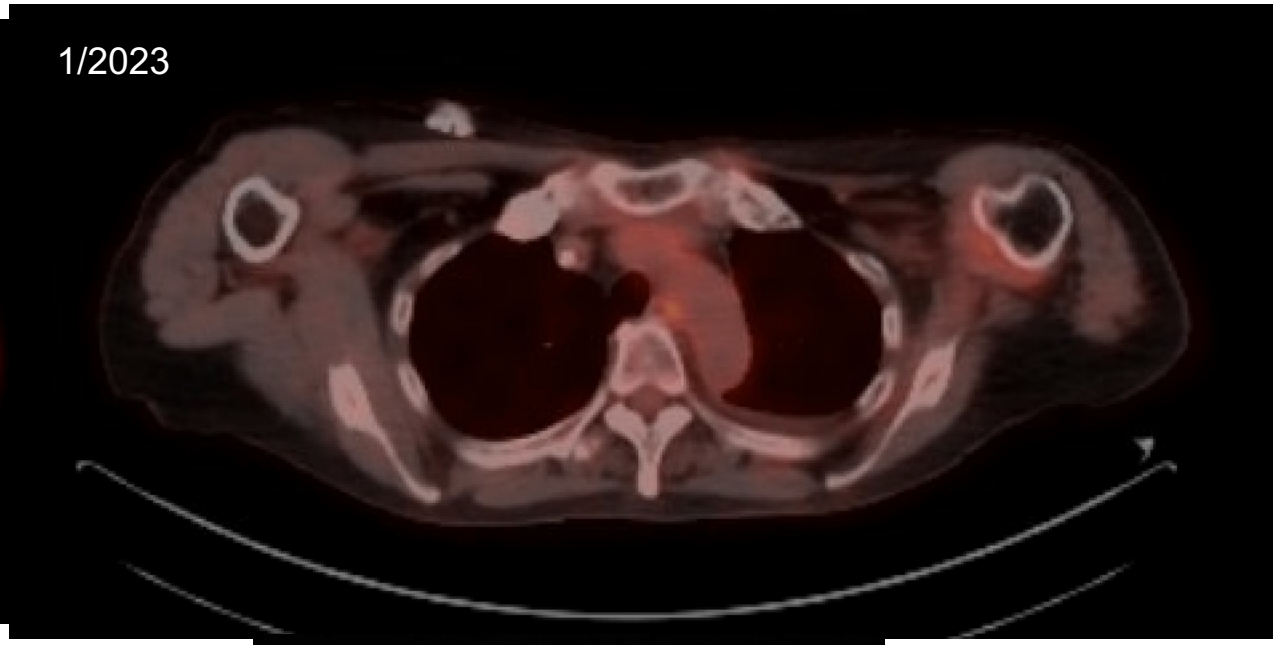
Courtesy of Hope S Rugo, MD

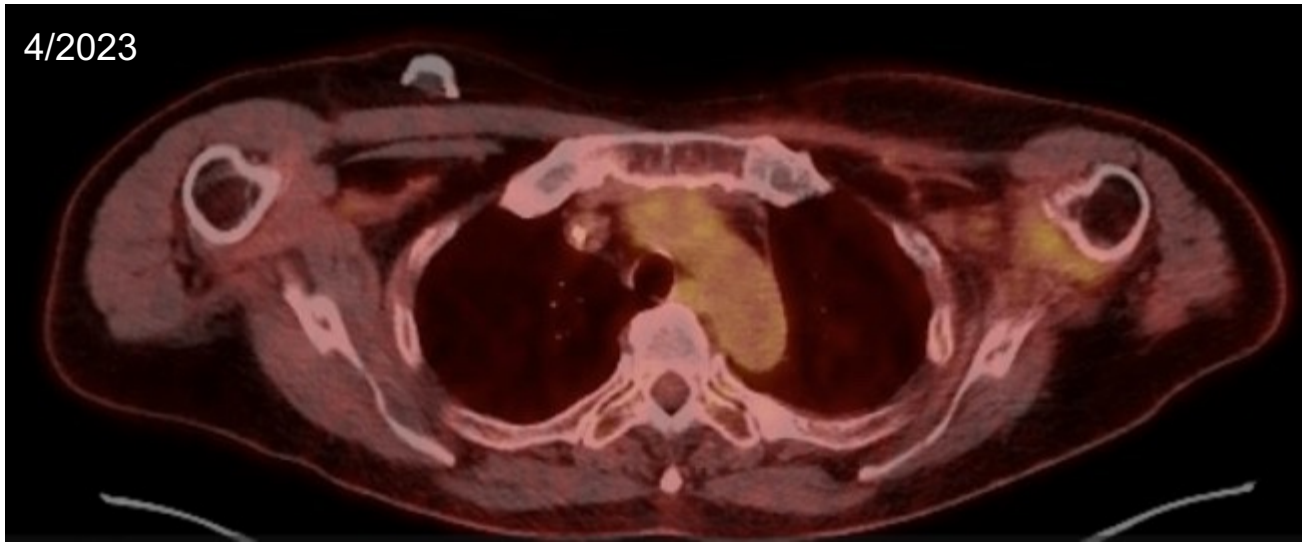
Bardia et al. *NEJM*. 2019.

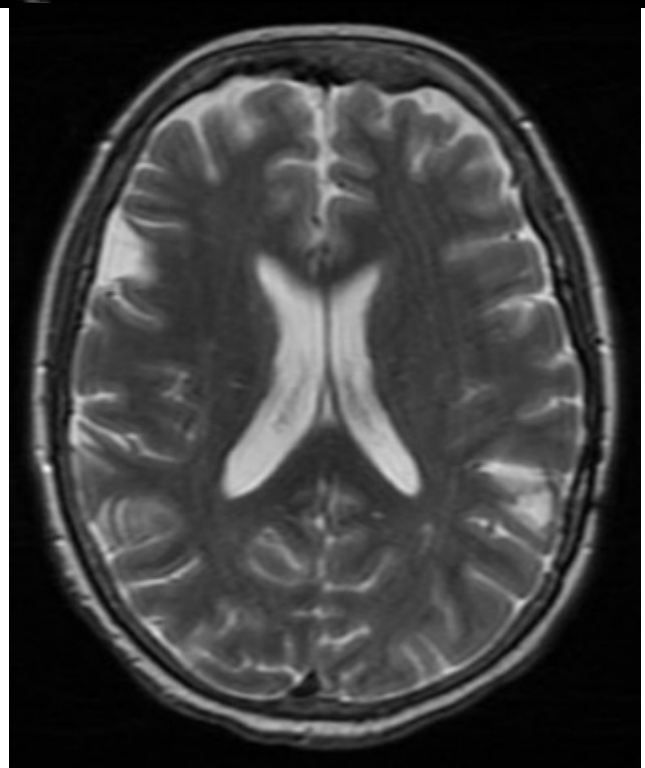
Case – Dr Rugo: Sacituzumab Govitecan – Treatment Efficacy

- 57 yo woman with metastatic TNBC
  - 2004 (age 38): stage IIa ER+/PR+/HER2 negative breast cancer
    - Rx: AC/docetaxel, tamoxifen x 2 years, then anastrozole x 3 years post BSO
  - 2017 recurrence in multiple neck/axillary nodes and rib, 8mm brain metastases
    - Rare cells without clear pathology, Rx with radiation to nodes and bone
    - Capecitabine x 6 months
  - 2020: left brachial plexus infiltration, left SC node
    - Biopsy +carcinoma c/w breast primary, ER/PR/HER2 negative, PD-L1 by CPS=10
    - 1/21 – 11/21 paclitaxel/pembrolizumab with PD in brachial plexus
    - 12/21 – 9/22 capecitabine with PD in nodes, ribs, brachial plexus with disease in spinal canal at C6
  - 10/22 Sacituzumab govitecan: excellent response.
    - 5/23 found to have extensive LMD, treated with WBRT followed by cisplatin plus etoposide
    - Required just two doses of filgrastim





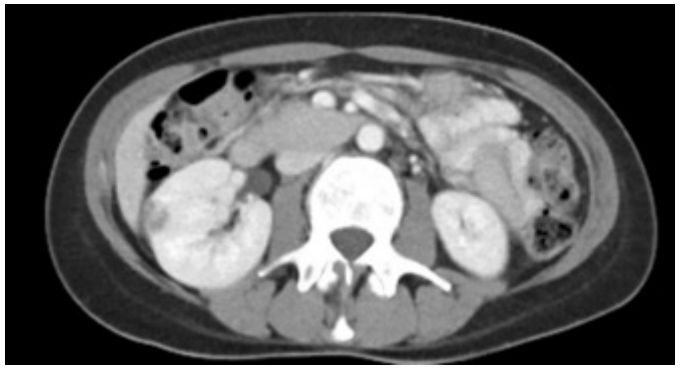


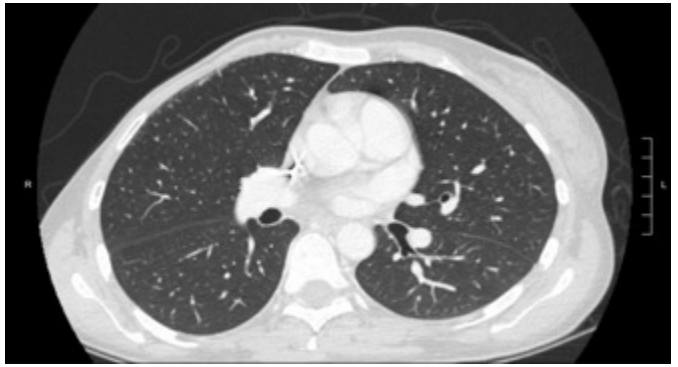


Courtesy of Hope S Rugo, MD

Case – Dr Rugo: Sacituzumab Govitecan – Toxicity Management

- 40 yo woman with metastatic TNBC
  - 12/2020 right breast TNBC; Ki-67 90%; abnormal nodes
  - RX: paclitaxel, carboplatin, pembrolizumab followed by DD AC x 3 with continued pembro; stopped due to primary disease growth
  - 6/21 Bilateral mastectomy: 4.9 cm residual disease, node negative; cellularity 90%
    - Radiation therapy, 11/21 – 3/22 capecitabine with ongoing pembrolizumab
    - 1/22 solitary lung nodule, resected with path + 1.2 cm TNBC
  - 3/22 witnessed seizure; brain MRI + multiple mets
    - 3-4/22 WBRT
    - NGS: PIK3CA mutation; PD-L1 by CPS=40
  - 4/22 – 8/23 Sacituzumab with PD in lung
    - 10/22 SBRT to left acetabulum; 1/23 GK to 5 brain lesions
    - 2/23 new renal lesions, biopsy + TNBC
    - 4/23 IMRT renal lesions
    - 8/23 IMRT to dominant lung lesion, change to gem/carbo





Case – Dr Rugo: Sacituzumab Govitecan – Toxicity Management (cont)

- Nausea
  - The patient had fatigue after each infusion, without nausea compounded by significant insomnia
    - Dose reduction and eventual discontinuation of dexamethasone premedication
    - Added olanzapine for the first 3 nights at bedtime with resolution of symptoms
- Neutropenia
  - Significant neutropenia with cycle 1 required used of filgrastim x 2-3 doses after each infusion
    - Filgrastim caused generalized aching, fatigue
    - Changed to peg-filgrastim on day 9 after each cycle day 8 with complete resolution of her symptoms
- Diarrhea
  - Rare episodes occurring only with travel
    - Solution: prophylactic loperamide with change in diet/long travel
- Alopecia

A 54-year-old woman with localized BRCA wild-type, HRP TNBC receives adjuvant dose-dense AC → paclitaxel. 18 months later she presents with multiple bone lesions consistent with the primary and receives gemcitabine/carboplatin x 4 with response but now has disease progression. PD-L1 testing is negative, HER2 IHC = 0. Regulatory and reimbursement issues aside, which treatment would you most likely recommend next if the patient …

	Remained asymptomatic?	Developed symptomatic visceral metastases?	Had CNS involvement?
 Dr Rugo	Capecitabine	Sacituzumab govitecan	Sacituzumab govitecan
 Dr Traina	Sacituzumab govitecan	Sacituzumab govitecan	Sacituzumab govitecan
 Dr Bardia	Sacituzumab govitecan	Sacituzumab govitecan	Sacituzumab govitecan
 Dr Brufsky	Sacituzumab govitecan	Sacituzumab govitecan	Sacituzumab govitecan
 Dr Telli	Sacituzumab govitecan	Sacituzumab govitecan	Capecitabine
 Dr Tolaney	Sacituzumab govitecan	Sacituzumab govitecan	Sacituzumab govitecan

In general, for which patients with metastatic TNBC are you using sacituzumab govitecan?

 Dr Rugo	All my patients receive SG, which improves survival; first line in patients relapsing on adjuvant therapy, and in the second line otherwise (when not enrolled on a trial)
 Dr Traina	Second- or third-line TNBC
 Dr Bardia	After 1 line of chemotherapy
 Dr Brufsky	Almost all, except for elderly and poor morbidity
 Dr Telli	I am using it in the second-line setting consistently
 Dr Tolaney	Second line or with very early relapse <6 mo from adjuvant therapy in first line

RTP RESEARCH TO PRACTICE

What is your global view on the antitumor efficacy of sacituzumab govitecan in patients with metastatic TNBC? (Eg, approximate proportion of patients who experience a clinical response; general duration of response)

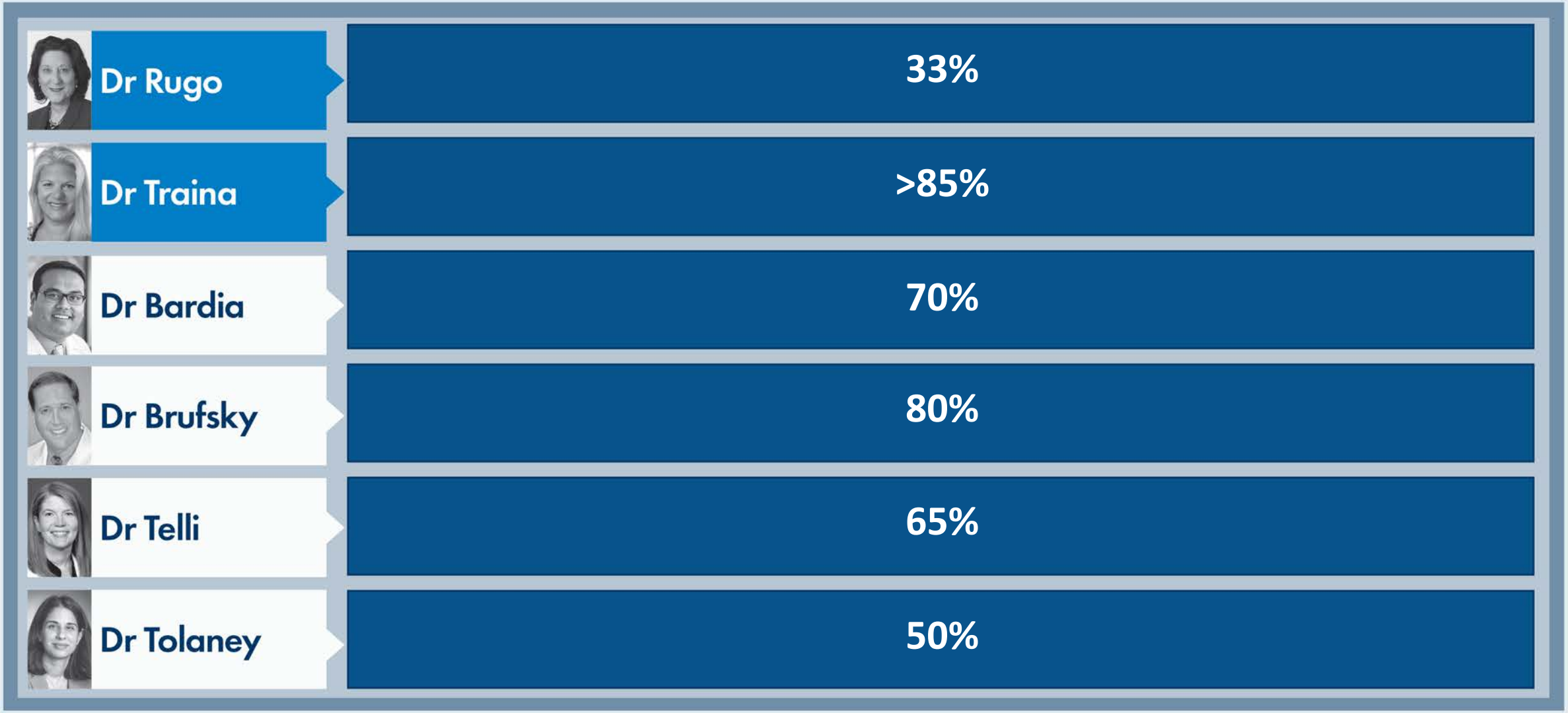
 Dr Rugo	Majority of patients respond; occasionally a patient has disease resistance to all therapies including SG (in particular bone only inexorable progression). Responses, particularly in earlier lines, last from 4 or 5 to 11 months
 Dr Traina	Sense that the majority of patients have good response and more durable benefit from response
 Dr Bardia	70%-80% patients have clinical response; duration: 6-9 months
 Dr Brufsky	Response rate 40%, PFS 6-7 months, OS 8-12 months
 Dr Telli	>50% experience clinical response, and it is typical for those who respond to have a duration of response >6 months
 Dr Tolaney	Generally patients are on therapy for 4-6 months

PFS = progression-free survival; OS = overall survival

In general, for patients eligible for both treatments, how do you sequence trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan? How, if at all, does this order vary based on the level of HER2 expression (IHC 1+ versus 2+)?

	Sequence	Impact of HER2 expression
 Dr Rugo	Sacituzumab → T-DXd	Does not influence decision
 Dr Traina	Sacituzumab → T-DXd	Does not influence decision
 Dr Bardia	Sacituzumab → T-DXd	Does not influence decision
 Dr Brufsky	Sacituzumab → T-DXd	Does not influence decision
 Dr Telli	Sacituzumab → T-DXd	Does not influence decision
 Dr Tolaney	Sacituzumab → T-DXd	Does not influence decision

In your experience, what proportion of patients with metastatic TNBC tolerate sacituzumab without significant issues?



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What would you estimate is the likelihood that a patient receiving sacituzumab govitecan will need to have therapy held or discontinued because of tolerability issues?

 Dr Rugo	Held due to neutropenia: 35% Discontinued: very rarely
 Dr Traina	<10%
 Dr Bardia	15%
 Dr Brufsky	20%
 Dr Telli	15%
 Dr Tolaney	50%

RTP RESEARCH TO PRACTICE

Do you routinely employ G-CSF prophylaxis for all patients receiving sacituzumab govitecan, or only for select patients?

 Dr Rugo	Anyone with prior neutropenia requiring growth factors, now very common
 Dr Traina	Heavily pretreated, issues with neutropenia in the past, older patients
 Dr Bardia	As secondary prophylaxis
 Dr Brufsky	Patients with comorbidity or prior severe neutropenia will get it first dose
 Dr Telli	All patients
 Dr Tolaney	In pts who have required prior growth factor support with chemotherapy or pts with blood counts that are borderline at start of therapy

RTP RESEARCH TO PRACTICE

Approximately what proportion of your patients who receive sacituzumab govitecan generally experience gastrointestinal (GI) side effects (eg, diarrhea, nausea, vomiting)? Do you generally recommend any form of prophylaxis to prevent GI toxicities in patients about to initiate sacituzumab govitecan?

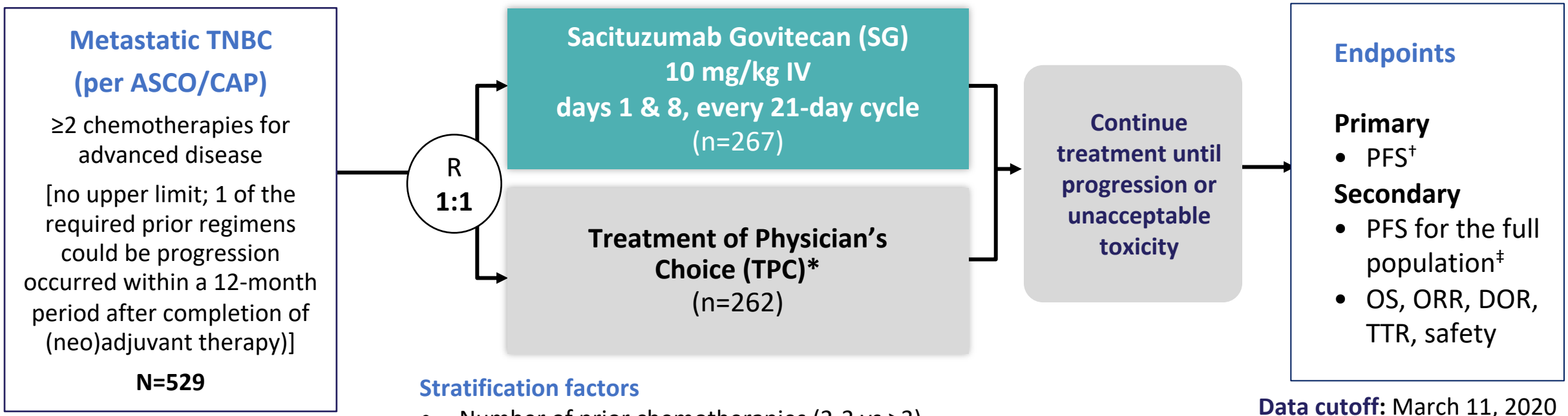
	Patients with GI side effects	GI prophylaxis?
 Dr Rugo	Nausea: 60% Diarrhea: 10%	No
 Dr Traina	20%	Yes, prophylaxis with antiemetics and loperamide prn
 Dr Bardia	80%	No
 Dr Brufsky	70%	No
 Dr Telli	50%	Yes, day of treatment take home anti-emetics and prescription for loperamide
 Dr Tolaney	10%-20%	Antiemetic prophylaxis

How would you rate your enthusiasm for enrolling a patient on the randomized, open-label Phase III ASCENT-05/OptimICE-RD (AFT-65) study evaluating adjuvant sacituzumab govitecan with pembrolizumab versus pembrolizumab with or without capecitabine for patients with TNBC and residual disease after neoadjuvant therapy and surgery?

	Enthusiasm*	Comments
 Dr Rugo	4	Important question asking if this ADC can improve outcomes combined with pembro
 Dr Traina	4	–
 Dr Bardia	3	Important study evaluating role of SG in the adjuvant setting
 Dr Brufsky	4	Good design, will answer the questions one way or the other
 Dr Telli	2	Control arm problematic, not all patients getting cape, pembro; SG toxicity issue in the setting
 Dr Tolaney	4	Capecitabine doesn't add much in this space so sacituzumab is likely to do better

* 1 = not at all enthusiastic, 4 = very enthusiastic

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



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

NCT02574455

Demographics:

TPC: 53% eribulin, 20% vinorelbine, 15% gemcitabine, 13% capecitabine; 70% TN at initial diagnosis

Median prior regimens 4 (2-17); ~88% with visceral disease; 15% cap on pts with brain mets

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation.

*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.

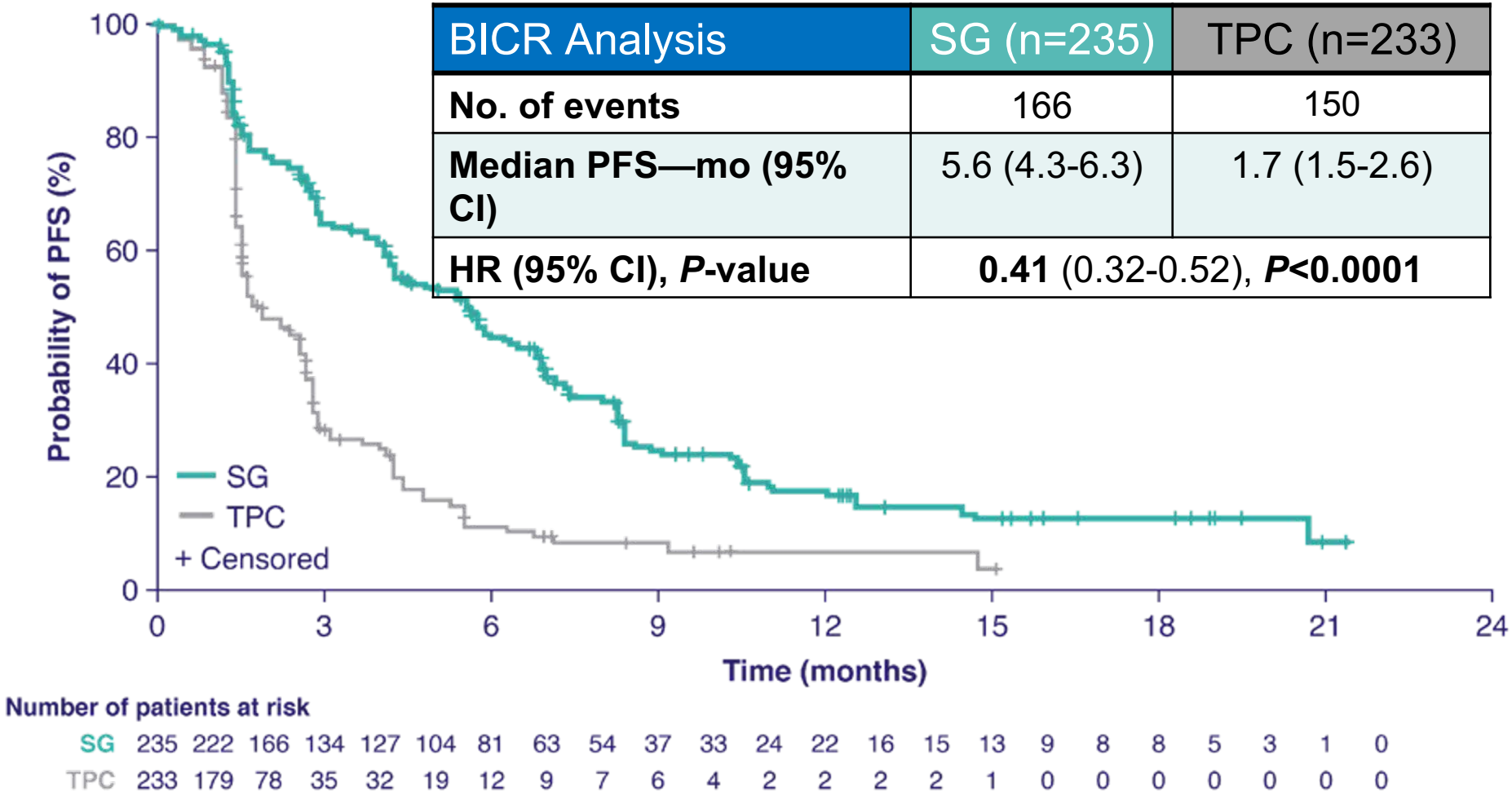
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Courtesy of Hope S Rugo, MD

Bardia et al, NEJM 2021

Progression-Free Survival (BICR Analysis)

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

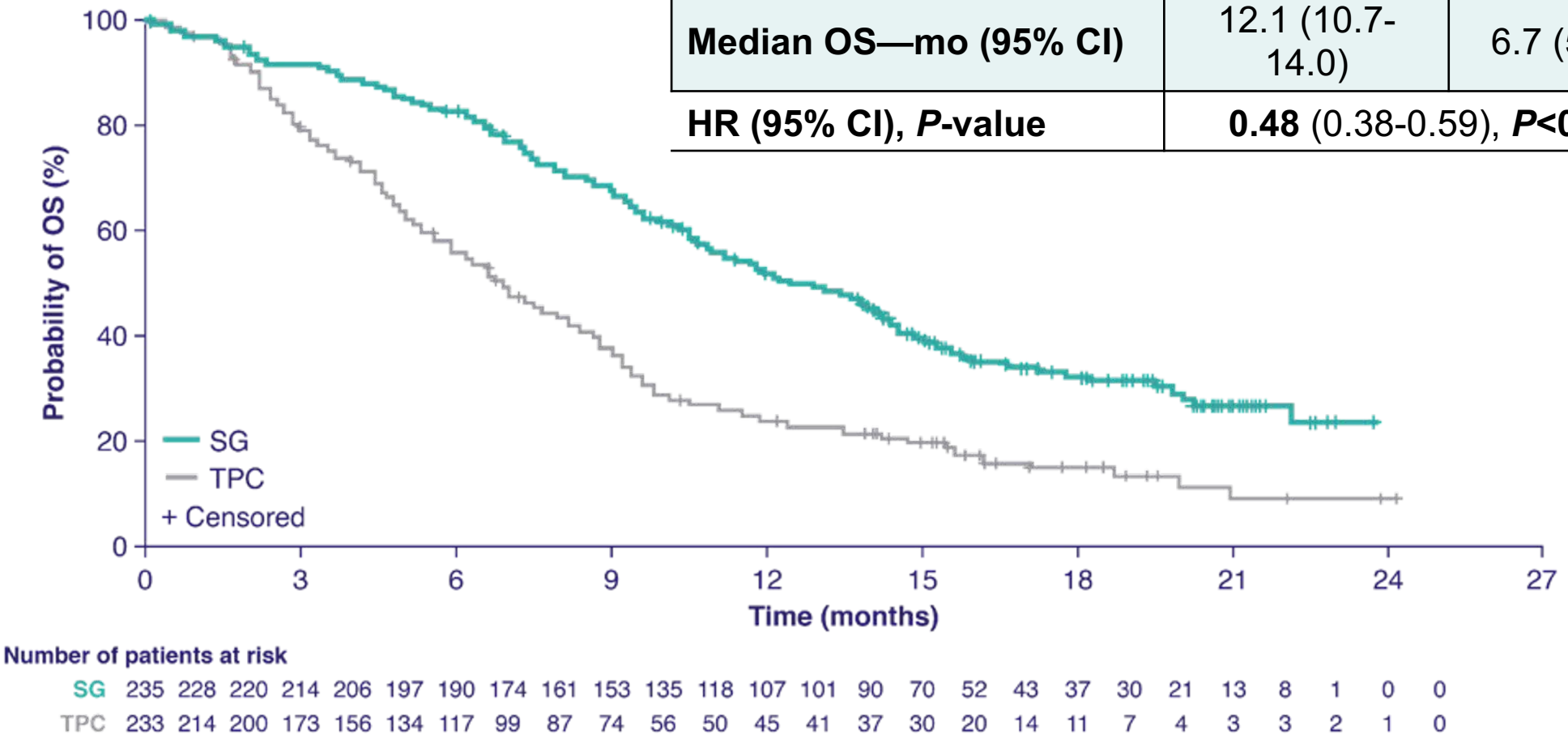


Primary endpoint (PFS) assessed by independent central review in the brain metastases-negative population, as pre-defined in the study protocol.
Secondary endpoint (PFS) assessed in the full population (brain metastases-positive and -negative) and PFS benefit was consistent (HR=0.43 [0.35-0.54], *P*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

Courtesy of Hope S Rugo, MD

Overall Survival

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



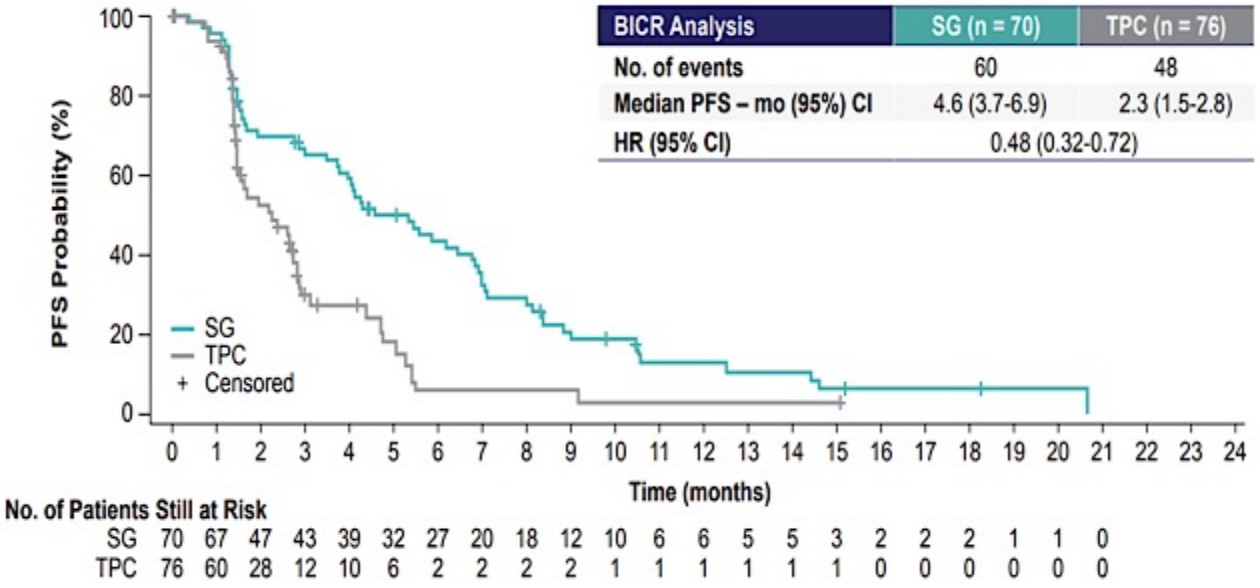
Assessed by independent central review in the brain metastases-negative population.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Courtesy of Hope S Rugo, MD

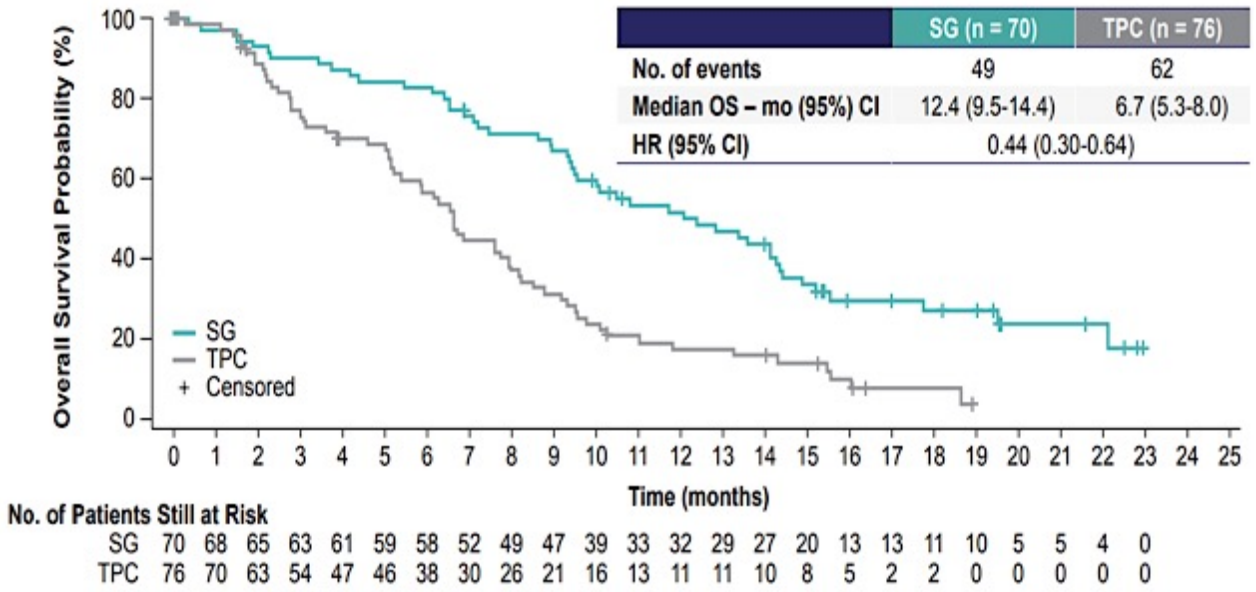
Bardia A, et al. N Engl J Med. 2021 and ASCO 2022

Patients Without TNBC at Initial Diagnosis

In the ASCENT trial, approximately one-third of patients did not have TNBC at initial breast cancer diagnosis



BICR Analysis	SG (n = 70)	TPC (n = 76)
No. of events	60	48
Median PFS – mo (95% CI	4.6 (3.7-6.9)	2.3 (1.5-2.8)
HR (95% CI)	0.48 (0.32-0.72)	



	SG (n = 70)	TPC (n = 76)
No. of events	49	62
Median OS – mo (95% CI)	12.4 (9.5-14.4)	6.7 (5.3-8.0)
HR (95% CI)	0.44 (0.30-0.64)	

Treatment with SG demonstrated superior efficacy over TPC in this subgroup of patients, similar to that of SG in the overall BM Neg population

O'Shaughnessy et al, BCRT 2022

Courtesy of Hope S Rugo, MD

ASCENT-03 (NCT05382299): PD-L1 negative
N=540

First-line therapy
- PD-L1 neg TNBC
- TNBC Rxd with IO in early stage

→ Sacituzumab govitecan

→ TPC: paclitaxel, *nab* paclitaxel, gem/carbo

ASCENT-04 (NCT05382286): PD-L1 positive
N=570

1L mTNBC PD-L1+
- Previously untreated, inoperable, locally advanced, OR metastatic TNBC
- PD-L1+ (CPS ≥10, IHC 22C3 assay)
- PD-L1 and TNBC status centrally confirmed
- Prior anti-PD-(L)1 allowed in the curative setting
- ≥6 months since treatment in curative setting

1:1

N=570
(≤25% *de novo*)

→ SG + pembrolizumab
(SG: 10 mg/kg IV on days 1 and 8 of 21-day cycles; Pembro: 200 mg IV on day 1 of 21-day cycles)

→ TPC chemotherapy + pembrolizumab
(Pembro dosed as above. TPC: gem 1000 mg/m² with carbo AUC 2 IV on days 1 and 8 of 21-day cycles OR paclitaxel 90 mg/m² IV on days 1, 8, and 15 of 28-day cycles OR *nab* paclitaxel: 100 mg/m² IV on days 1, 8, and 15 of 28-day cycles)

SACI-IO TNBC and HR+: Sacituzumab govitecan +/− pembrolizumab in 1L PD-L1− mTNBC and HR+

Garrido-Castro/Tolaney

mTNBC
- No prior chemo
  No prior PD-1/L1
- PD-L1 <1% by SP-142
  ER ≤5%
  PR ≤5%
  HER2-
- Stable brain mets
- Exclude prior: PD-1/L1, SG, Irinotecan

mHR+/HER2-
- ≥ 1 Hormonal
- 0-1 Prior Chemo
- Exclude prior: PD-1/L1, SG, Irinotecan

N=110

1:1

N=110

→ Sacituzumab govitecan 10 mg/kg IV d1, 8 q21 days + pembrolizumab 200 mg/kg d1 q21 days

→ Sacituzumab govitecan 10 mg/kg d1,8 q21 days

Endpoints
Primary
- PFS

Secondary
- OS, ORR
- Duration and time to objective response, time to progression, CBR
- Safety and tolerability

80% power to detect PFS improvement from 5.5 months (Arm B) to 8.5 months (Arm A)

Courtesy of Hope S Rugo, MD

ASCENT-07:
First-line Chemotherapy in HR+

Key eligibility criteria:
- HR+/HER2* negative, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced mBC
- Progressed after 1 or more ET for mBC, or relapsed within 12 months of completing adjuvant ET or while receiving adjuvant ET
- No prior treatment with a topoisomerase I inhibitor
- Measurable disease per RECIST v1.1
- Prior CDK 4/6i not required (no prior CDK 4/6i capped at 30%)

N = 654

2:1 randomization

→ Sacituzumab govitecan 10 mg/kg IV Days 1 and 8, every 21 days

→ Treatment of physician's choice (capecitabine, paclitaxel, *nab* paclitaxel)

Stratification:
- Duration of prior CDK 4/6i in metastatic setting (none/≤12 mos vs >12 mos)
- HER2 IHC (HER2 IHC 0 vs HER2 IHC-low ([IHC 1+; 2+/ISH-])
- Geographic region (US/CAN/EU vs. ROW)

Primary Endpoint
- PFS by BICR

Key Secondary Endpoints
- OS
- ORR by BICR
- TTDD to Physical functioning

Secondary Endpoints
- PFS by investigator
- ORR by investigator
- DOR
- Safety

GBG: SASCIA Post-Neoadjuvant Trial
NCT04595565

N=1200
HER2-negative early breast cancer

- At least 16 weeks of taxane-based NACT
- No pCR:
  - TNBC
  - HR-positive and CPS-EG score ≥3 or 2 and ypN+

R 1:1

→ Sacituzumab govitecan (8 cycles d1, 8 q3w)

→ Treatment of physician´s choice*

Follow-up

Stratification factors:
- HR-positive vs HR-negative
- ypN+ vs ypN-0

Phase III Trial: OptimICE-RD/ASCWENT-05
Residual disease in TNBC

Residual invasive TNBC disease in breast or positive node(s) after anthracycline, taxane, and checkpoint inhibitor-based neoadjuvant therapy
N = 1514

R 1:1

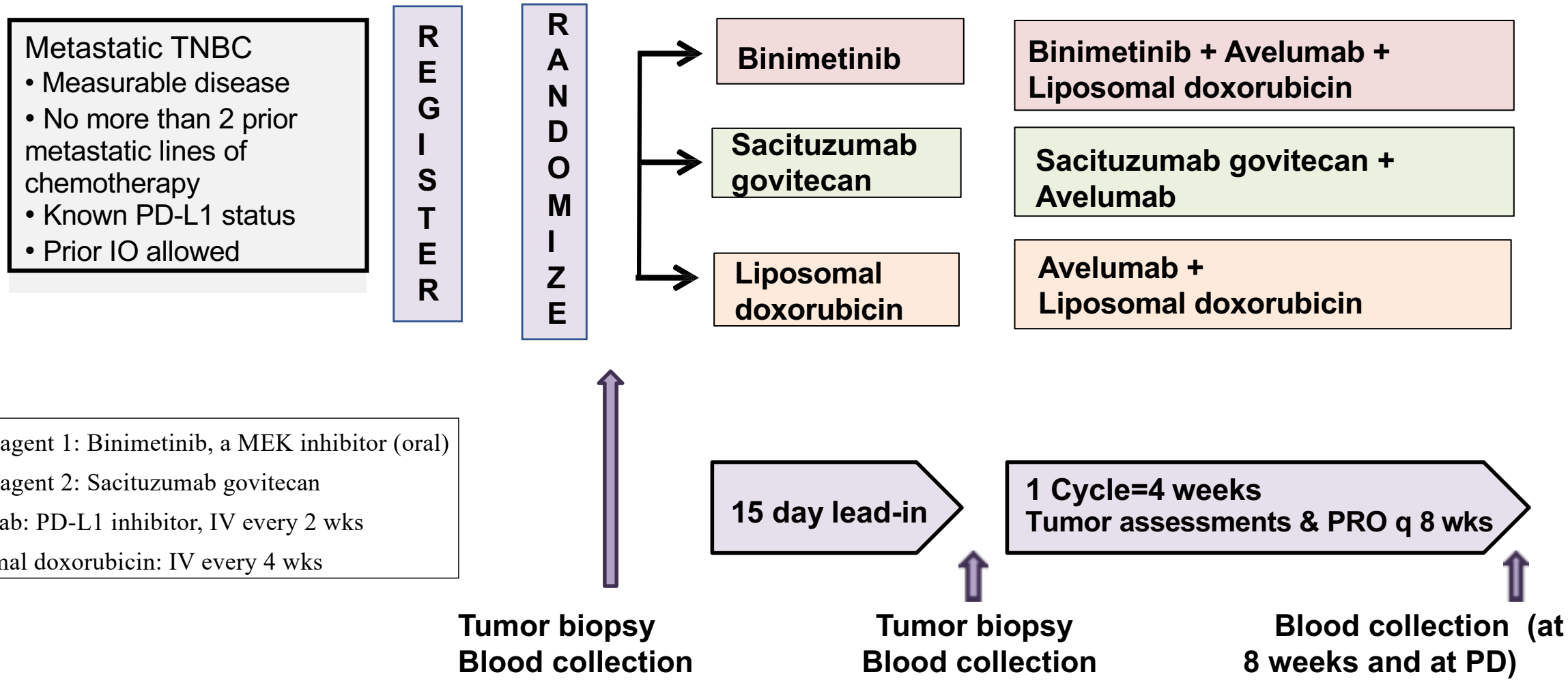
→ A: Sacituzumab Govitecan x 8 cycles + Pembrolizumab x 8 cycles

→ B: Pembrolizumab x 8 cycles (add-on capecitabine per physician's choice)

Follow-up

PI: Sara Tolaney; Alliance Foundation Trial

TBCRC 047: InCITe Trial Design



*Safety combination data from MiLO trial
#Safety combination data from several ongoing trials

PI: Hope S. Rugo

Courtesy of Hope S Rugo, MD

Agenda

INTRODUCTION: “Isn’t oncology depressing?”

MODULE 1: Checkpoint inhibitors

MODULE 2: Antibody-drug conjugates

MODULE 3: HER2-low disease

MODULE 4: Other agents under development

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Key Data Sets

Tiffany A Traina, MD, FASCO (continued)

- Modi S et al. **Trastuzumab deruxtecan** in previously treated **HER2-low** advanced breast cancer. *N Engl J Med* 2022 July 7;387(1):9-20.
- Mosele F et al. **Trastuzumab deruxtecan** in metastatic breast cancer with **variable HER2 expression**: The **phase 2 DAISY trial**. *Nat Med* 2023 August;29(8):2110-20.
- Schmid P et al. **Trastuzumab deruxtecan (T-DXd) + durvalumab (D)** as first-line (1L) treatment for unresectable locally advanced/metastatic hormone receptor-negative (HR-), **HER2-low** breast cancer: Updated results from **BEGONIA**, a phase 1b/2 study. SABCS 2022;Abstract PD11-08.

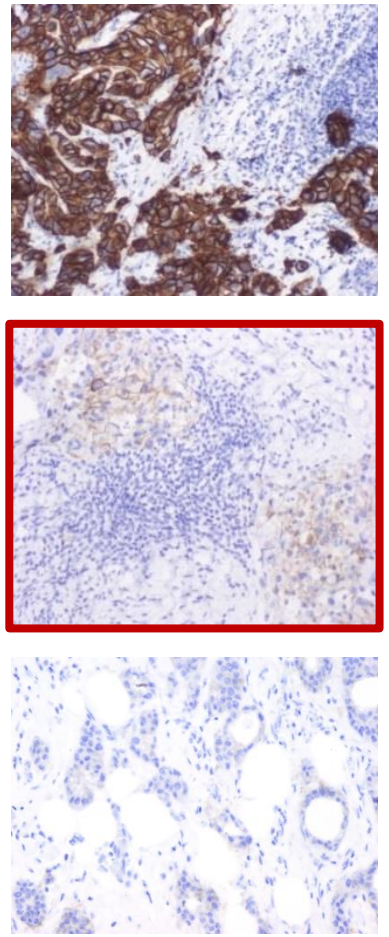
Prevalence of HER2-low Breast Cancer (IHC 1+/2+, FISH negative)

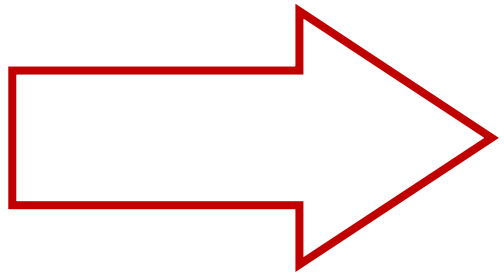
HER2 IHC examples

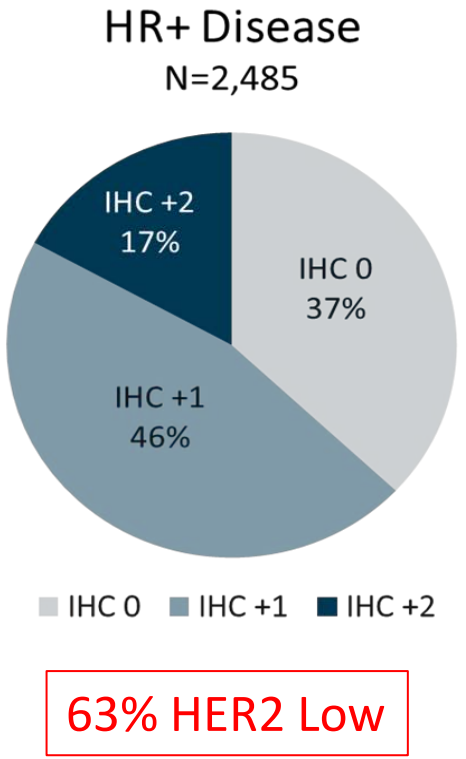
HER2+

HER2-low

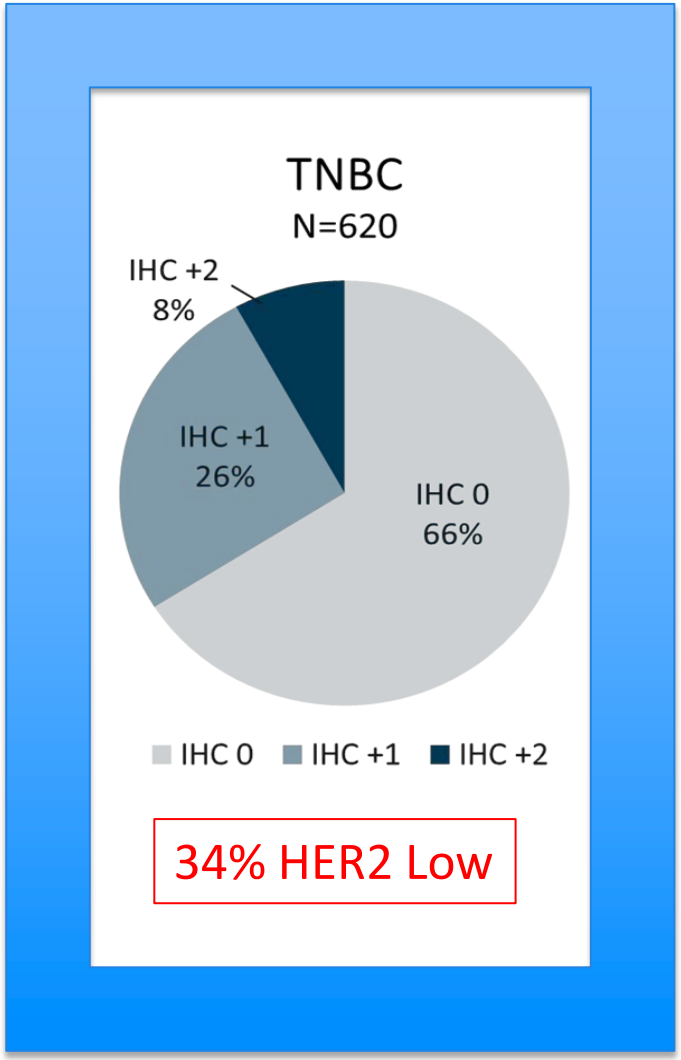
HER2-







63% HER2 Low



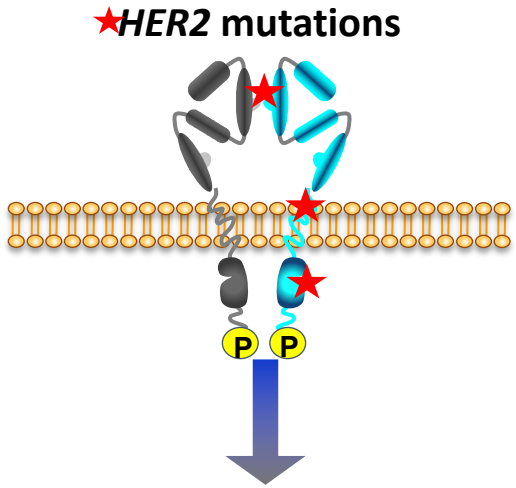
34% HER2 Low

Schettini. ESMO Breast Cancer Virtual Meeting 2020. Abstr 23P. Slide courtesy of Aleix Prat.

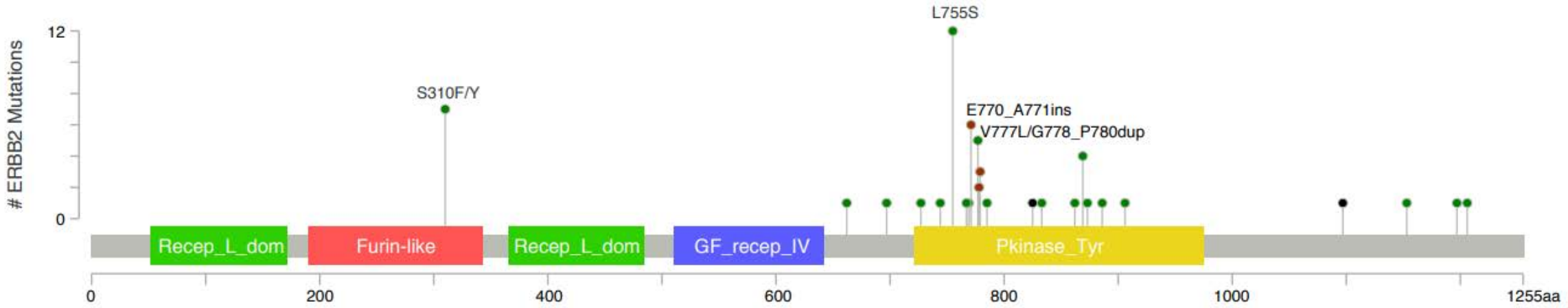
Courtesy of Tiffany A Traina, MD, FASCO

HER2 (*ERBB2*) Mutations and Breast Cancer

- Somatic *ERBB2* mutations
- Majority of missense mutations are seen involving kinase domain
- In 5% up to 26% of lobular breast cancers



Activation of downstream signal transduction pathways and tumor growth survival

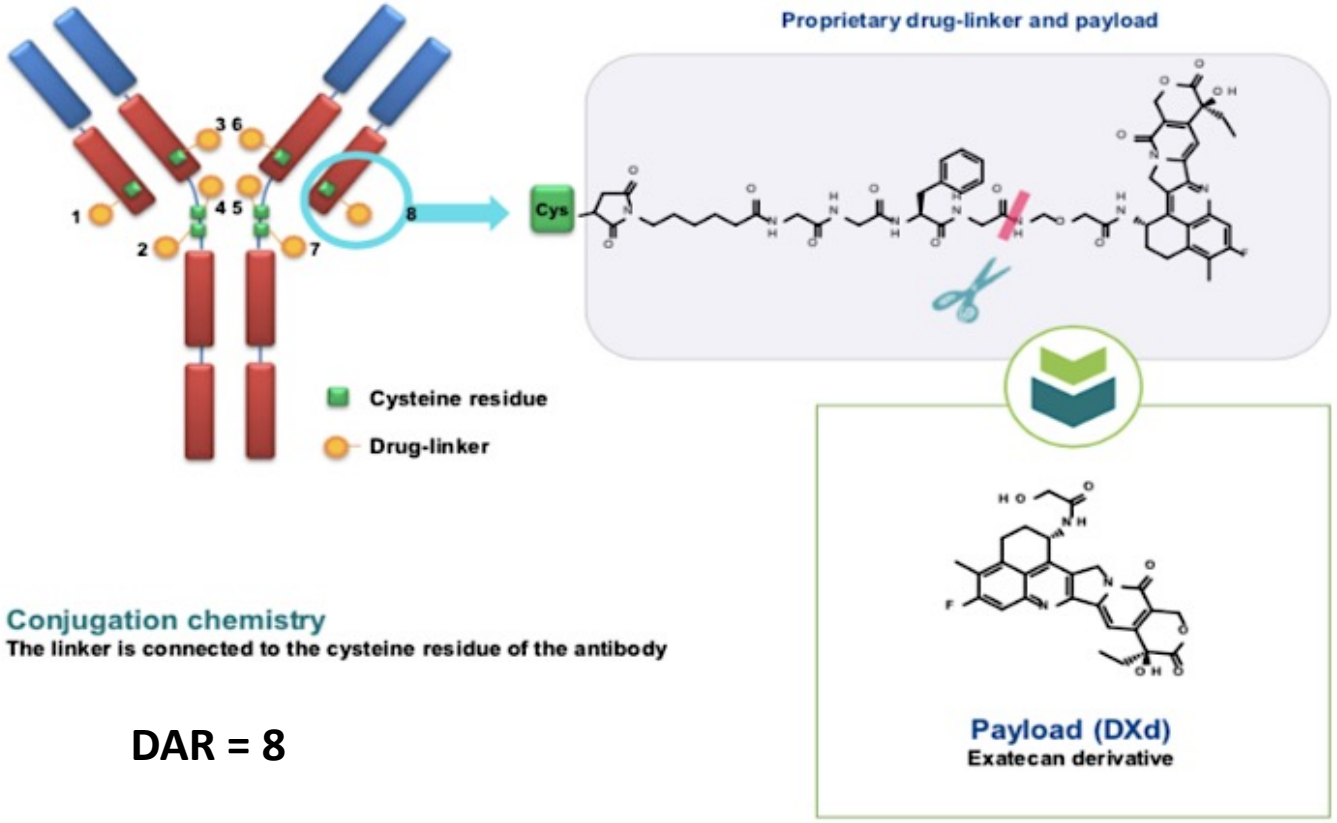


Razavi et al Cancer Cell 2018; Bose R, et al. Cancer Discov. 2013; Hyman D et al. Nature 2018; Rosa-Rosa J et al. Cancers 2019

Courtesy of Tiffany A Traina, MD, FASCO

Memorial Sloan Kettering Cancer Center
@jhaveri_komal

Trastuzumab Deruxtecan (T-DXd)



- High drug-to-antibody ratio: ~8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Modi S, et al. NEJM 2021

Courtesy of Tiffany A Traina, MD, FASCO

Memorial Sloan Kettering Cancer Center

Case – Dr Traina: HR-negative HER2-low MBC on T-DXd

- 68yo practicing physician presented with palpable left breast mass 2019 → imaging with multifocal left breast masses and left axillary mass
- Biopsy showing ER 50%, PR 0, HER2 2+ and ER 10% PR 0 HER2+ in the 2 biopsied lesions (FISH neg)
- PET/CT negative for distant metastases
- s/p neoadjuvant ddAC-T
- Left total mastectomy with axillary lymph node dissection = 2 foci identified (1) ER 1-5%, PR 0, HER2 1+ and ER 20-30%, PR 0, HER2 1+ with >10 lymph nodes involved (ypT1N3)
- Anastrozole
- PMRT
- Adjuvant Capecitabine x6 mo (last 2020)

Case – Dr Traina: HR-negative HER2-low MBC on T-DXd (cont)

- Summer 2022 Bone pains → PET/CT with suspicious bone lesions --> bx confirmed
  ER 0% HER2 1-2+ FISH not amplified
- PDL1 negative CPS <10
- Guardant with ERBB2 mutation; Tumor sequencing unremarkable

- Began 1L carboplatin and denosumab
- 3 months later, PET/CT w overall increased extent of FDG uptake in multiple osseous lesions. Decreased in size and FDG uptake of two right axillary lymph nodes.
- 10/2022 Began C1 T-Dxd
- 01/2023 PET/CT w response
- Continued benefit from ongoing therapy w T-Dxd

What is your global view on the antitumor efficacy of trastuzumab deruxtecan in patients with ER/PR-negative, HER2-low breast cancer? (Eg, approximate proportion of patients who experience a clinical response; general duration of response)

 Dr Rugo	Reasonably high initial response rates ~50%, PFS 4-6 months – shorter than the DB-04 data. Better in pts with previously HR+ who are losing ER over time
 Dr Traina	Active drug with clinical response
 Dr Bardia	70% response; duration 6-9 months
 Dr Brufsky	PFS 8-10 months; RR about 50%
 Dr Telli	Clinical response in 50% of patients with duration of response of at least 6 months
 Dr Tolaney	In our clinical experience, probably about 30%-40% have a response, but PFS is around 5 months

RTP RESEARCH TO PRACTICE

What is your global view on the toxicity of trastuzumab deruxtecan in patients with ER/PR-negative, HER2-low breast cancer? (Eg, approximate proportion of patients who experience tolerability issues that lead to holding or discontinuing the agent; GI issues, hair loss)

 Dr Rugo	There is no difference compared to HR+; hold or discontinuation is primarily due to pneumonitis, rarely GI
 Dr Traina	Nausea, anorexia are common; alopecia as well. ILD is rare but I have seen it
 Dr Bardia	Generally well tolerated; 30%-40% need dose reduction; 10% discontinue due to AEs, including pneumonitis
 Dr Brufsky	Hair loss 25%, nausea 75%, ILD 15%
 Dr Telli	<10% Nausea and fatigue can be problems, but generally can be managed without discontinuation; infrequently dose reduce. Hair loss rare
 Dr Tolaney	~25% need a dose hold/modification, often for Grade 1 ILD or fatigue; ~20% hair loss; nausea is well controlled with proper management

ILD = interstitial lung disease; AE = adverse event

Approximately what proportion of patients receiving trastuzumab deruxtecan for ER/PR-negative, HER2-low breast cancer experience ILD?

 Dr Rugo	12%-15%
 Dr Traina	10%
 Dr Bardia	10%
 Dr Brufsky	15%
 Dr Telli	15%
 Dr Tolaney	20% (a little higher in our clinic than the literature)

For a patient who is receiving trastuzumab deruxtecan for metastatic ER/PR-negative, HER2-low breast cancer and whose disease is currently outside the thoracic cavity and does not require chest imaging, do you routinely order chest imaging to assess for ILD?

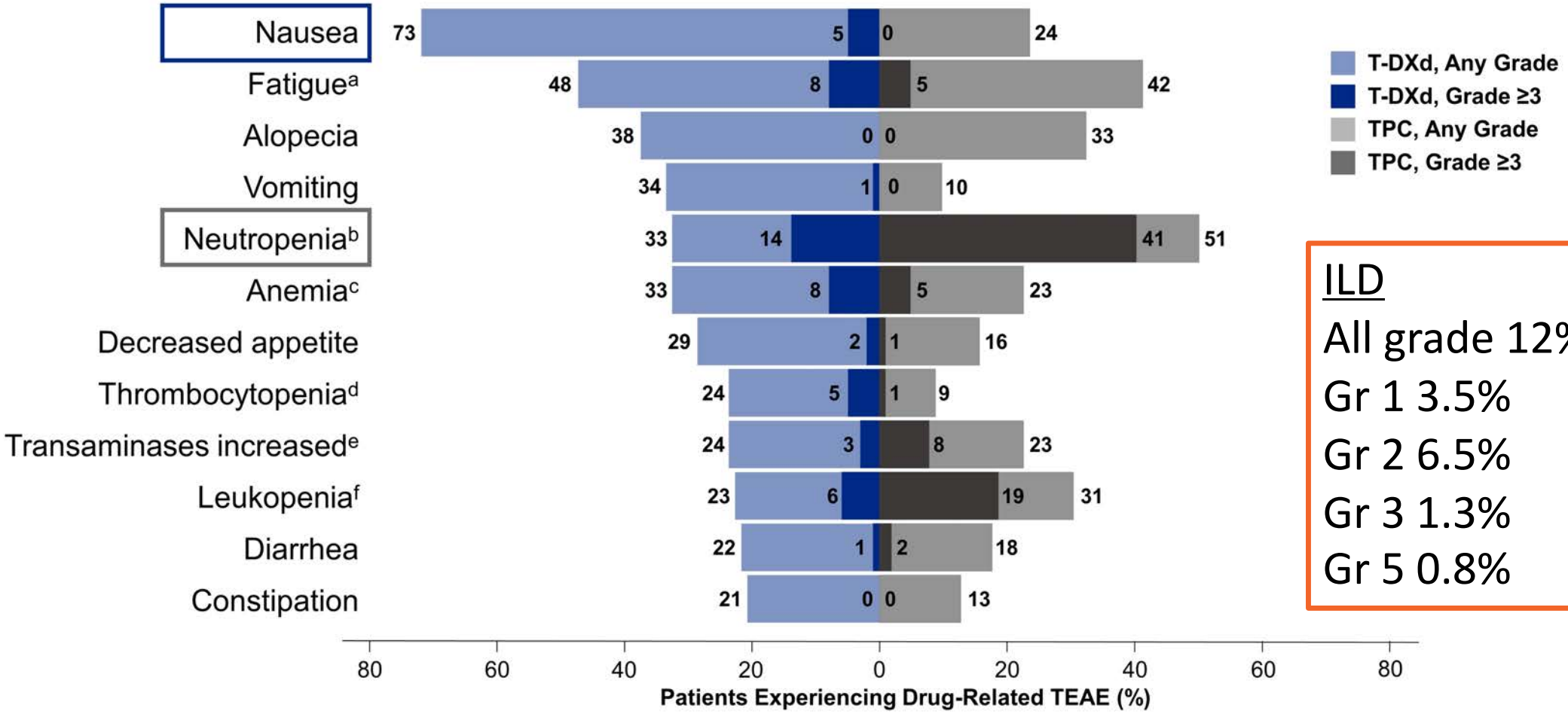
 Dr Rugo	Yes, I usually get the first scan at 6 weeks then every 9 weeks for the first year
 Dr Traina	Yes, will be sure chest is imaged at least every 3 months
 Dr Bardia	Yes, every 6-9 weeks
 Dr Brufsky	Yes, every 3 months
 Dr Telli	Yes, every 3 cycles initially, then every 4 cycles
 Dr Tolaney	Yes, I generally restage every 6-9 weeks

RTP RESEARCH TO PRACTICE

Have you readministered or would you readminister trastuzumab deruxtecan to a patient who developed Grade 2 ILD?

 Dr Rugo	No
 Dr Traina	No
 Dr Bardia	No
 Dr Brufsky	No
 Dr Telli	No
 Dr Tolaney	No

Drug-Related TEAEs in ≥20% of Patients



ILD
All grade 12%
Gr 1 3.5%
Gr 2 6.5%
Gr 3 1.3%
Gr 5 0.8%

T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

Courtesy of Tiffany A Traina, MD, FASCO

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a]

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

Left ventricular dysfunction[b]

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

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

Courtesy of Tiffany A Traina, MD, FASCO

DESTINY-Breast06: T-DXd in Chemotherapy Naive and HER2-Ultralow Advanced/Metastatic Breast Cancer

Randomized, open-label phase III study

Stratified by: prior CDK4/6 inhibitor; HER2 IHC 2+ vs 1+ vs 0; prior taxane in non-metastatic setting.

Patients with advanced/metastatic breast cancer with progression on 2 previous endocrine therapy; restricted to HR+ Disease; HER2 IHC* 0+, 1+, or 2+ based on central IHC assessment at diagnosis of first metastatic disease or later
(N = 850)

T-DXd
(n = 425)

Chemotherapy
(n = 425)

Until PD or toxicity

*Investigator's choice chemotherapy may consist of capecitabine, paclitaxel, or nab-paclitaxel.

- Primary endpoint: PFS (per BICR) in HER2 IHC 1+/2+
- Key secondary endpoints: OS in HER2 IHC 1+/2+ population, PFS and OS in ITT
- Secondary endpoints: PFS (per INV) in HER2 1+/2+, ORR and DoR in HER2 1+/2+and ITT, safety and tolerability, symptoms, functioning and QoL
- Exploratory: OS in HER2 IHC 1+/2+ population

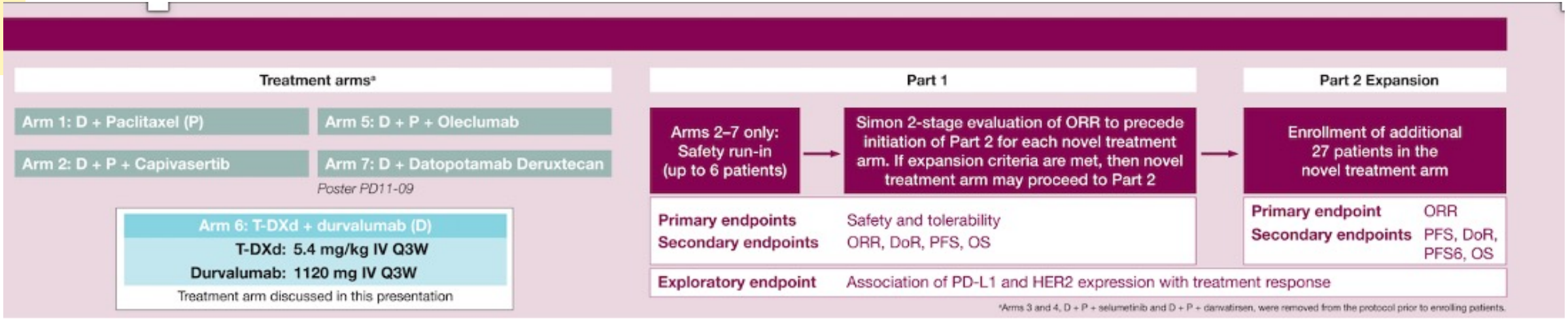
HER2 IHC 0+ defined by any IHC staining up to 10% of tumor cells. Futility analysis in HER2 IHC 0+ cohort will be done.

NCT04494425.

Courtesy of Tiffany A Traina, MD, FASCO

Memorial Sloan Kettering Cancer Center

BEGONIA Study Design



Eligibility criteria:

- Metastatic TNBC
- No prior treatment for MBC
- > 12m DFI
- Measurable disease
- Normal organ function and no contraindication to IO
- For TDxd cohort:
  - HER2 low
  - No pulmonary disorders

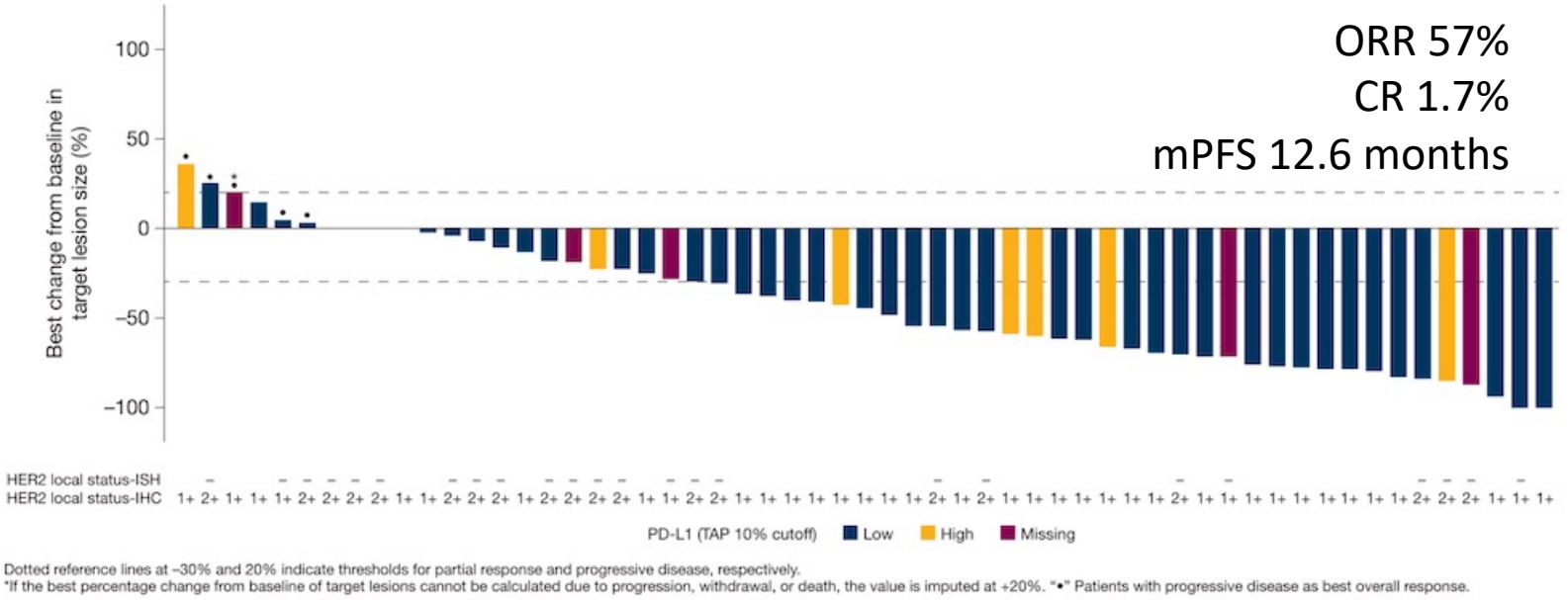
Courtesy of Tiffany A Traina, MD, FASCO

Memorial Sloan Kettering Cancer Center

Schmidt et al SABCS Poster 2022

BEGONIA Cohort 6 – T-DXd + Durvalumab

Figure 1. Best change from baseline of target lesion size



Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively.
*If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with progressive disease as best overall response.

ORR 57%
CR 1.7%
mPFS 12.6 months

Table 2. Safety summary

	N=58
Any Grade AE, n (%)	57 (98.3)
Common AEs (≥20% patients, any grade)	
Nausea	45 (77.6)
Fatigue	30 (51.7)
Neutropenia	18 (31.0)
Vomiting	17 (29.3)
Alopecia	16 (27.6)
Decreased appetite	15 (25.9)
Anemia, constipation	14 (24.1) each
Asthenia, diarrhea	12 (20.7) each
Any Grade 3/4 AE	25 (43.1)
Any serious AE	12 (20.7)
Any treatment-related AE[a]	55 (94.8)
Grade 3/4	20 (34.5)
Any durvalumab AESI	43 (74.1)
Any T-DXd AESI	13 (22.4)
AE leading to T-DXd + D discontinuation	10 (17.2)
AE leading to dose interruption	32 (55.2)
AE leading to death[b]	2 (3.4)
Durvalumab dose delay	26 (44.8)
T-DXd dose delay	24 (41.4)
T-DXd dose reduction	6 (10.3)

AESI, adverse event of special interest.

N=56
TDXd 5.4mg/kg q3 weeks +
Durva 1120mg IV q3 weeks

Discontinuation rate 17%
TDxD delay or reduction in 51%

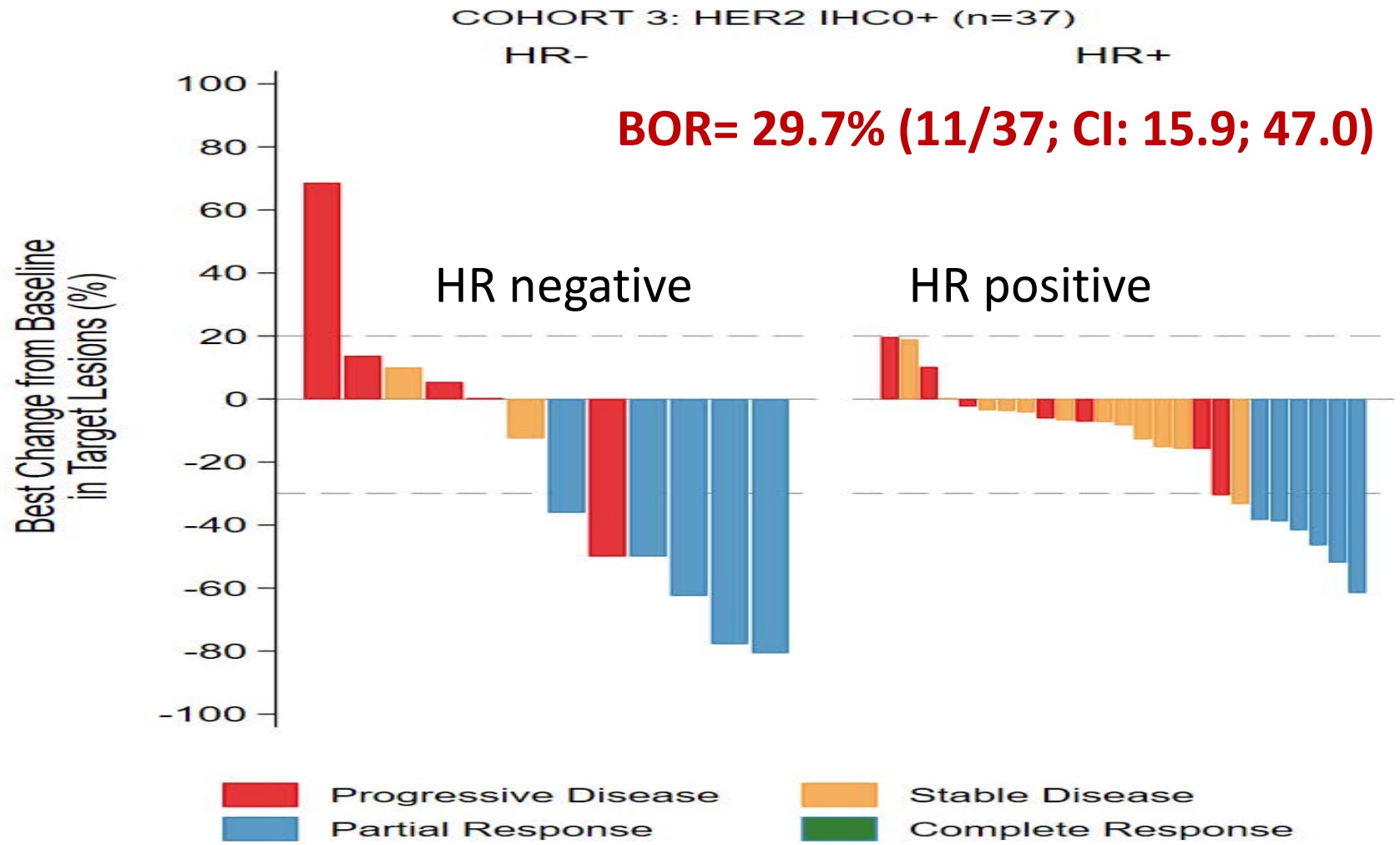
* 8 cases of ILD (1 Gr 5)

Schmidt et al SABCS Poster 2022

Courtesy of Tiffany A Traina, MD, FASCO

Memorial Sloan Kettering Cancer Center

DAISY Trial: Waterfall Plot of Best Overall Response to T-DXd in HER2 IHC 0+ (HER2 non-detected) MBC, N=37



Dieras, V et a; SABC 2021

med DoR: 6.8mo (CI: 2.8; NR) ; med PFS: 4.2mo (CI: 2.0; 5.7)

Courtesy of Tiffany A Traina, MD, FASCO

Mosele F et al. *Nat Med*. 2023;29(8):2110-2120.

Agenda

INTRODUCTION: “Isn’t oncology depressing?”

MODULE 1: Checkpoint inhibitors

MODULE 2: Antibody-drug conjugates

MODULE 3: HER2-low disease

MODULE 4: Other agents under development

RTP
RESEARCH
TO PRACTICE

Key Data Sets

Hope S Rugo, MD

- Meric-Bernstam F et al. Phase 1 **TROPION-PanTumor01** study evaluating **datopotamab deruxtecan (Dato-DXd)** in unresectable or metastatic hormone receptor-positive/HER2-negative breast cancer (BC). SABCS 2022;Abstract PD13-08.

Tiffany A Traina, MD, FASCO

- Bardia A. **Datopotamab deruxtecan (Dato-DXd),** a TROP2-directed antibody-drug conjugate (ADC), for triple-negative breast cancer (TNBC): Preliminary results from an ongoing phase 1 trial. *Ann Oncol* 2021;32(Suppl 2):60-78;Abstract LBA4.
- Schmid P et al. **Datopotamab deruxtecan (Dato-DXd) + durvalumab (D)** as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): Updated results from **BEGONIA**, a phase 1b/2 study. SABCS 2022;Abstract PD11-09.

Key Data Sets

Tiffany A Traina, MD, FASCO (continued)

- Krop I et al. Results from the phase 1/2 study of **patritumab deruxtecan**, a HER3-directed antibody-drug conjugate (ADC), in patients with **HER3-expressing metastatic breast cancer** (MBC). ASCO 2022;Abstract 1002.
- Schmid P et al. Mature survival update of the double-blind placebo-controlled randomised phase II **PAKT tria**l of first-line **capivasertib plus paclitaxel** for metastatic triple-negative breast cancer. SABCS 2020;Abstract PD1-11.
- Rainey N et al. A phase 2 randomized study of **magrolimab combination therapy** in adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC): ELEVATE-TNBC. Abstract TPS1130.

What other novel agents and strategies are under investigation for patients with metastatic TNBC that you believe are promising?

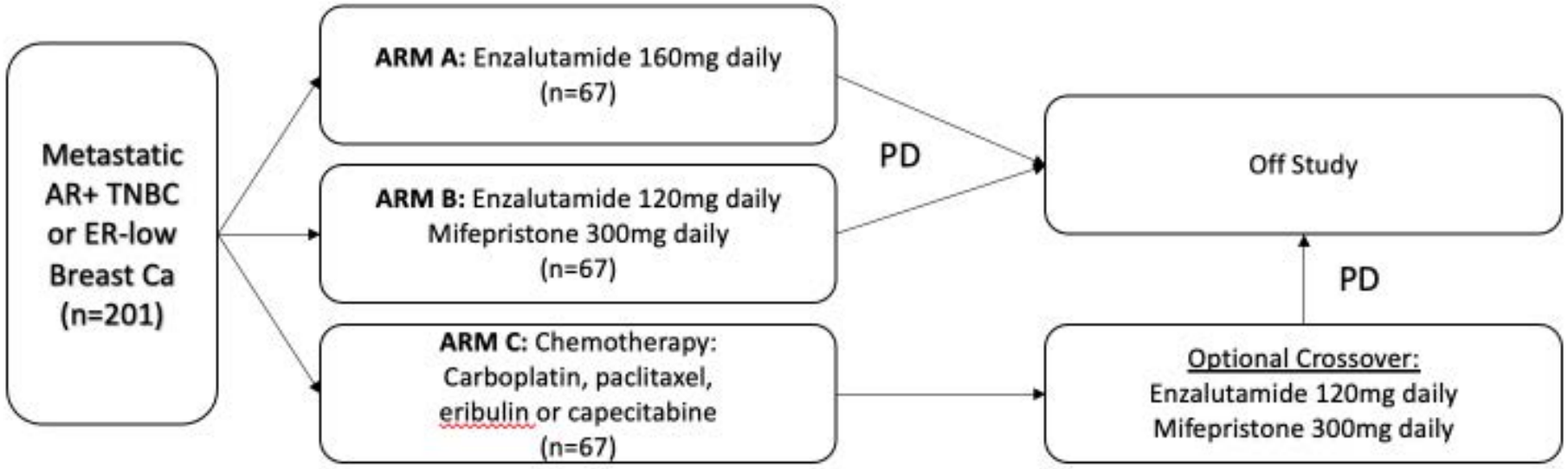
 Dr Rugo	Magrolimab, TROP2 ADCs, engineered viruses, vaccines
 Dr Traina	Dato-DXd, capivasertib, other ADCs (ie, enfortumab vedotin)
 Dr Bardia	Datopotamab deruxtecan
 Dr Brufsky	Other ADCs
 Dr Telli	AZD5305 PARP 1 selective inhibitor
 Dr Tolaney	B7H4-directed ADCs and AKT inhibitors and mutant selective PI3Ki

ADC = antibody-drug conjugate

IRB#: 22-334 (TBCRC 058)

A Randomized, Phase II Study of Enzalutamide, Enzalutamide With Mifepristone, and Treatment of Physician's Choice in Patients with AR+ Metastatic Triple-Negative or ER-Low Breast Cancer

SCHEMA

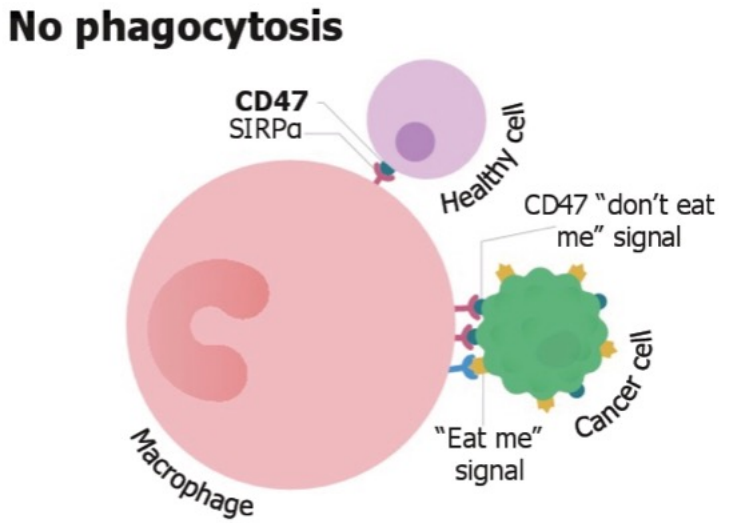


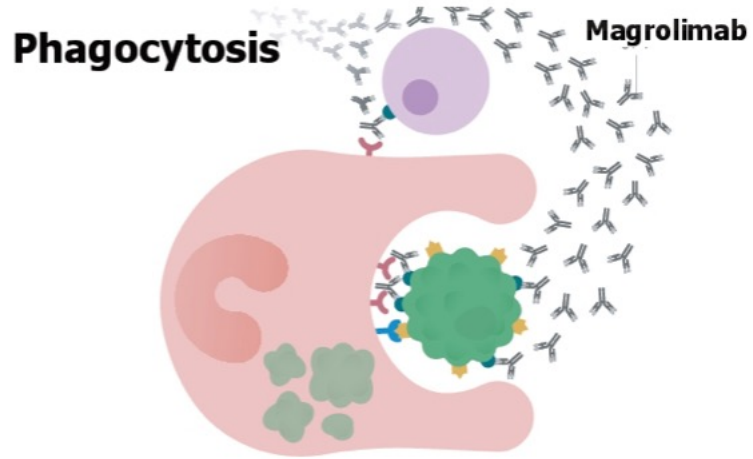
This phase II study will randomize eligible patients (1:1:1) between enzalutamide 160 mg orally daily (Arm A), enzalutamide 120mg daily with mifepristone 300mg daily (Arm B) and TPC (Arm C; standard of care carboplatin, paclitaxel, capecitabine, or eribulin).
A cycle length equals 3 weeks (21 days).

PI: Tiffany A Traina and Rita Nanda

Courtesy of Tiffany A Traina, MD, FASCO

Magrolimab Mechanism of Action



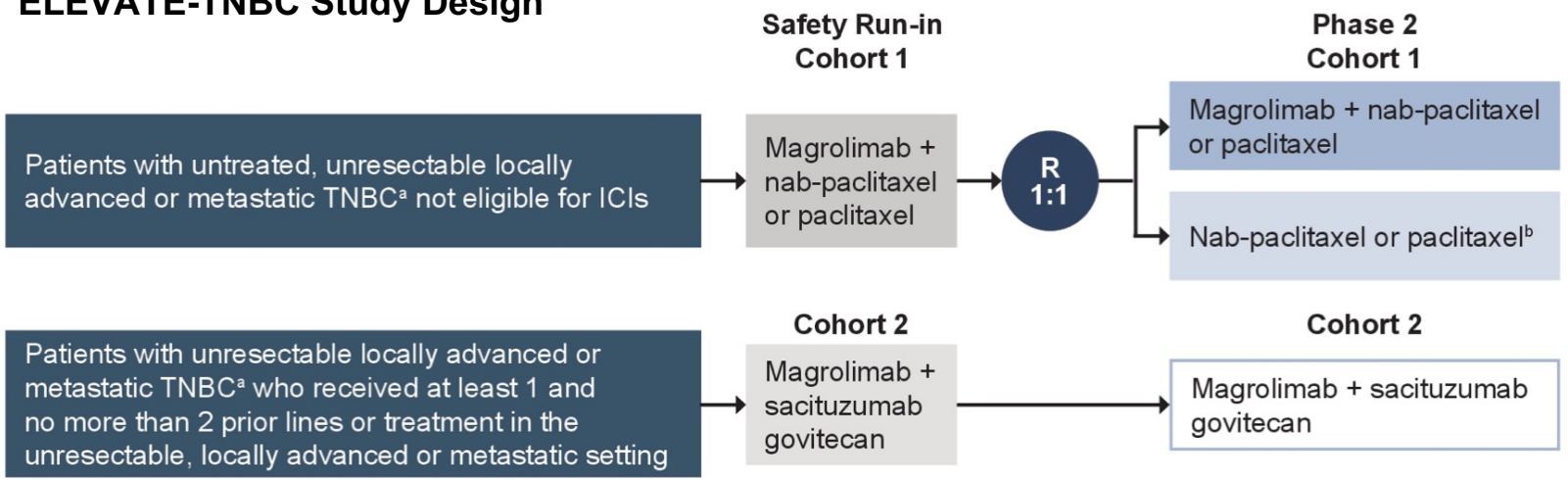


CD47, cluster of differentiation 47; SIRPα, signal-regulatory protein alpha.

ELEVATE-TNBC: Taxane +/- CD47 Inhibitor for mTNBC (NCT04958785)

- CD47: "don't eat me" signal overexpressed in some cancers
  - Magrolimab blocks CD47, facilitates macrophage induced phagocytosis of cancer cells
- Some chemotherapy, including taxanes enhance phagocytic signals on tumor cells
  - Potential for synergistic activity between chemo and magrolimab

ELEVATE-TNBC Study Design



ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; ICI, Immune checkpoint inhibitors; IHC, immunohistochemistry; ISH, in situ hybridization; PR, progesterone receptor; R, randomized; TNBC, triple-negative breast cancer.
[a]TNBC defined by the American Society of Clinical Oncology/College of American Pathologists guidelines as absence of ER and PR (IHC <1% of nuclei stain for each) and HER2 (IHC 0, 1+, 2+/ISH−). [b]Patients enrolled in Cohort 1 Arm B with documented progressive disease can rescreen to enroll in Cohort 2 as long as they meet all other eligibility criteria.

Courtesy of Hope S Rugo, MD

Rainey N et al, ASCO 2023

How would you rate your enthusiasm for enrolling a patient on the MARIA study of an MRD (minimal residual disease) assay to evaluate recurrence and response via a tumor-informed assessment?

	Enthusiasm*	Comments
 Dr Rugo	4	Not ready for clinical use, but important to continue to collect data and develop trials
 Dr Traina	3	–
 Dr Bardia	4	Wave of the future
 Dr Brufsky	2	OS benefit hard to prove
 Dr Telli	4	Appealing but logistically challenging strategy
 Dr Tolaney	3	More sensitive assays are needed and are coming

* 1 = not at all enthusiastic, 4 = very enthusiastic

How would you rate your enthusiasm for enrolling a patient on the open-label Phase II Adaptive Multi-Drug Treatment of Evolving Cancers (AMTEC) study of olaparib in combination with durvalumab, selumetinib or capivasertib, or ceralasertib monotherapy for patients with metastatic TNBC?

	Enthusiasm*	Comments
 Dr Rugo	3	A fishing expedition with some preclinical supportive data, but we need new therapies for this setting desperately
 Dr Traina	3	–
 Dr Bardia	2	Basket study with PARP inhibitor
 Dr Brufsky	3	Interesting design
 Dr Telli	2	Interesting combinations, but role of olaparib in unselected mTNBC is not established
 Dr Tolaney	2	Olaparib +/- atezo RP2 was a negative trial, making IO combo with PARP less attractive

* 1 = not at all enthusiastic, 4 = very enthusiastic

How would you rate your enthusiasm for enrolling a patient on the TILS-001-DC study: Treatment of advanced or metastatic TNBC with adoptive therapy of PD-1-positive tumor-infiltrating lymphocytes?

	Enthusiasm*	Comments
 Dr Rugo	3	Important area to study, hard timing-wise as cells take time and TNBC progresses quickly
 Dr Traina	2	–
 Dr Bardia	3	Exciting concept that could major impact if successful
 Dr Brufsky	2	Tough to grow TILs
 Dr Telli	4	Exciting approach with potential for long-term response
 Dr Tolaney	2	None

* 1 = not at all enthusiastic, 4 = very enthusiastic

TILs = tumor-infiltrating lymphocytes

Based on the published literature and your clinical experience, what are the most common tolerability issues that result in therapy being held or discontinued among patients receiving datopotamab deruxtecan?

 Dr Rugo	Stomatitis
 Dr Traina	Very well tolerated; mucositis needs prophylaxis but otherwise favorable toxicity profile
 Dr Bardia	Mucositis
 Dr Brufsky	Mucositis
 Dr Telli	GI toxicity, including stomatitis
 Dr Tolaney	Stomatitis and nausea

RTP RESEARCH TO PRACTICE

Based on the published literature and your clinical experience, approximately what proportion of patients receiving datopotamab deruxtecan experience interstitial lung disease (ILD)?

 Dr Rugo	Available data are insufficient at this time
 Dr Traina	<5%
 Dr Bardia	1%
 Dr Brufsky	2%-5%
 Dr Telli	<10%
 Dr Tolaney	5%

RTP RESEARCH TO PRACTICE

Based on the published literature and your clinical experience, approximately what proportion of patients receiving datopotamab deruxtecan require treatment modifications due to tolerability issues?

 Dr Rugo	At least 10%
 Dr Traina	<10%
 Dr Bardia	25%
 Dr Brufsky	70%
 Dr Telli	25%
 Dr Tolaney	10%-15%

RTP RESEARCH TO PRACTICE

Based on the published literature and your clinical experience, what are the most common Grade ≥3 adverse events associated with patritumab deruxtecan?

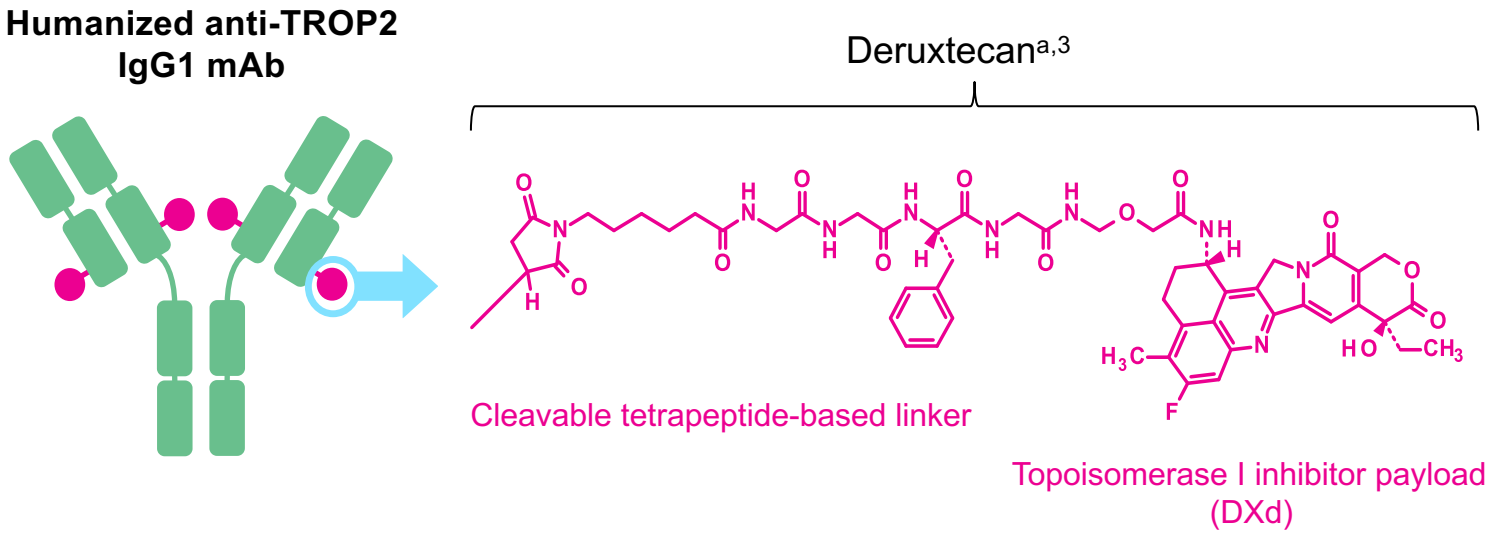
 Dr Rugo	Nausea, diarrhea, ILD
 Dr Traina	Neutropenia, thrombocytopenia; ILD Gr >3 rare
 Dr Bardia	Nausea, diarrhea, myelosuppression
 Dr Brufsky	Mucositis
 Dr Telli	GI toxicity, fatigue
 Dr Tolaney	Neutropenia, thrombocytopenia, fatigue, nausea

RTP RESEARCH TO PRACTICE

Datopotamab Deruxtecan (Dato-DXd)

Dato-DXd is an ADC with 3 components[1,2]:

- A humanized anti-TROP2 IgG1 monoclonal antibody attached to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker



Payload mechanism of action: topoisomerase I inhibitor [b,1]
High potency of payload [b,2]
Optimized drug to antibody ratio ≈4 [b,c,1]
Payload with short systemic half-life [b,c,2]
Stable linker-payload [b,2]
Tumor-selective cleavable linker [b,2]
Bystander antitumor effect [b,2,4]

[a] Image is for illustrative purposes only; actual drug positions may vary. [b] The clinical relevance of these features is under investigation. [c] Based on animal data.

1. Okajima D, et al. AACR-NCI-EORTC 2019; [abstract C026]; 2. Nakada T, et al. *Chem Pharm Bull*. 2019;67(3):173-185; 3. Krop I, et al. SABCS 2019; [abstract GS1-03]; 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

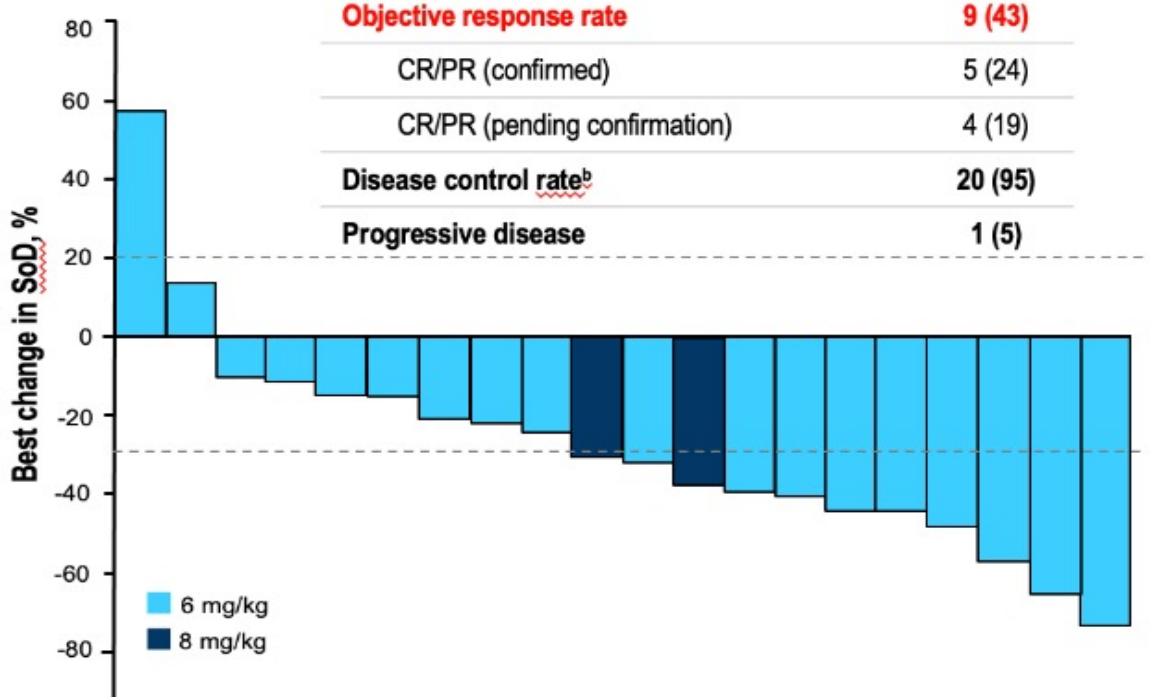
Courtesy of Hope S Rugo, MD

TROPION-PanTumor01 Dato-DXd Efficacy Signal

71% had ≥3 prior lines
8% had prior sacituzumab

Antitumor Activity (by BICR)

Patients, n (%)[a]	N=21
Objective response rate	9 (43)
CR/PR (confirmed)	5 (24)
CR/PR (pending confirmation)	4 (19)
Disease control rate[b]	20 (95)
Progressive disease	1 (5)



Preferred Term, n (%)[a]	N=24	
	Any grade	Grade ≥3
TEAEs	**24 (100)**	**8 (33)**
Stomatitis	15 (63)	3 (13)
Nausea	15 (63)	0
Fatigue	10 (42)	1 (4)
Vomiting	10 (42)	0
Alopecia	6 (25)	–
Cough	5 (21)	0
Pruritus	5 (21)	0
Anemia	4 (17)	1 (4)
Headache	4 (17)	0
Constipation	4 (17)	0

Bardia A, et al. ESMO 2021. *Ann Oncol.* 2021;32 (suppl_2):S60-S78.

Courtesy of Tiffany A Traina, MD, FASCO

Memorial Sloan Kettering Cancer Center

Phase 1 TROPION-PanTumor01: New Trop2 ADC Datopotamab Deruxtecan in HR+ and HR-/HER2- MBC

- Unresectable or metastatic HR+/HER2− (IHC 0/1+ or IHC2+/ISH-) breast cancer
- Progressed on ≥1 endocrine therapy; previously treated with 1-3 prior lines of chemotherapy in the advanced setting
- Unselected for TROP2 expression[a]
- Age ≥18 years (US) or ≥20 years (Japan)
- ECOG PS 0-1
- Measurable disease per RECIST 1.1
- Stable, treated brain metastases allowed

→

NSCLC[b]
(0.27 to 10 mg/kg IV Q3W)

TNBC[c]
8 mg/kg IV Q3W (n=2);
6 mg/kg IV Q3W (n=42)

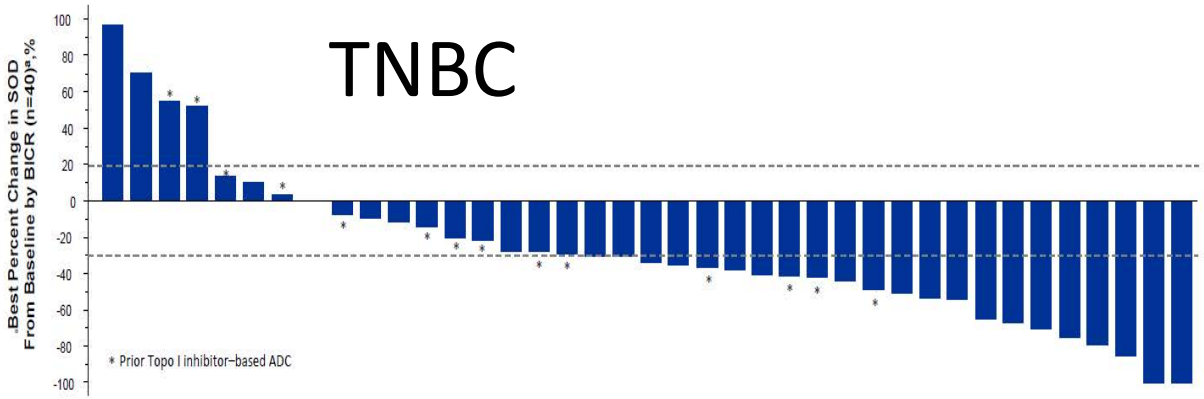
HR+/HER2− breast cancer
6 mg/kg IV Q3W (n=41)

Other tumor types
(SCLC, bladder, gastric, esophageal, CRPC, pancreas)

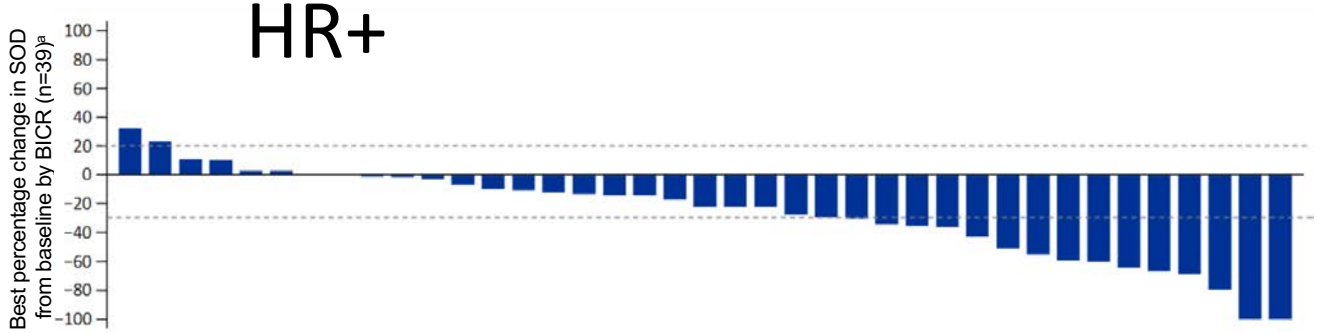
Primary objectives
- Safety
- Tolerability

Secondary objectives[d]
- Efficacy[e]
- Pharmacokinetics
- Antidrug antibodies

TNBC



HR+



ORR by BICR:
- All patients: 32%
- Topo I inhibitor-naive patients: 44%
- Median PFS: 4.4-7.3 mo

Bardia A, et al. SABCS 2022 P6-10-03

AEs:Most common TEAEs:
stomatitis (73 -83%/grade 3 10%),
nausea (66%), vomiting (39%)

Courtesy of Hope S Rugo, MD

- ORR (all PR): 27%;
- CBR: 44%
- Med PFS 8.3 mo
- 59% alive for >1 year

Meric-Bernstam et al, SABCS 2022

TROPION-Breast01

NCT05104866

Key Eligibility Criteria

- HR-positive, HER2-negative inoperable/ metastatic breast cancer with disease progression following 1 or 2 lines of chemotherapy (& progressed on, or not suitable for, endocrine therapy)
- Targeted agents (i.e., inhibitors of mTOR, PD-1/PD-L1, CDK4/6, PARP) and endocrine therapies do not count as prior lines of chemotherapy
- At least 1 measurable lesion
- FFPE tumor sample
- Adequate organ function

Stratification factors:

- 1 vs. 2 previous lines of chemotherapy in the inoperable/metastatic setting
- Geographic location (US/Canada/EU vs rest of world)
- Previous CDK 4/6 inhibitor use

1:1

Dato-DXd
6mg/kg IV Q3W
N=350

Investigator's Choice of Chemotherapy
(Eribulin, Vinorelbine, Capecitabine or Gemcitabine)
N=350

Dual primary endpoints
PFS (BICR), OS

Secondary endpoints
PFS (inv), ORR, DoR, DCR, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints
TROP2 IHC

Statistical Considerations:

To strongly control the familywise type I error rate at the 5.0% level (2-sided), an alpha level of 1.0% will be allocated to the PFS dual primary analysis and the remaining 4.0% alpha level will be allocated to the OS analyses

Response assessment: Scan Q6W for 48 weeks, then Q9W until RECIST1.1 disease progression (as assessed by Investigator), regardless of study intervention discontinuation or start of subsequent anticancer therapy. Following disease progression, 1 additional follow-up scan should be performed as per Imaging schedule.

- 2nd-3rd line therapy for HR+/HER2- mBC
- Completed accrual

TROPION-Breast02

NCT05374512

Key eligibility criteria:

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not a candidate for PD-1 / PD-L1 inhibitor therapy
- Measurable disease as defined by RECIST v1.1
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification factors:

- Geographic location
- DFI (*de novo* vs DFI ≤12 months vs DFI >12 months)

Dual primary endpoints:
PFS (BICR) and OS

Secondary endpoints:
PFS (inv), ORR, DoR, safety

1:1

Dato-DXd

Investigator's choice of chemotherapy

- 1st line therapy for TNBC
- PD-L1 negative

Phase III TROPION-Breast03

NCT05629585

N=1075
Stage I-III TNBC
Residual disease after at least 6 cycles of neoadjuvant chemotherapy

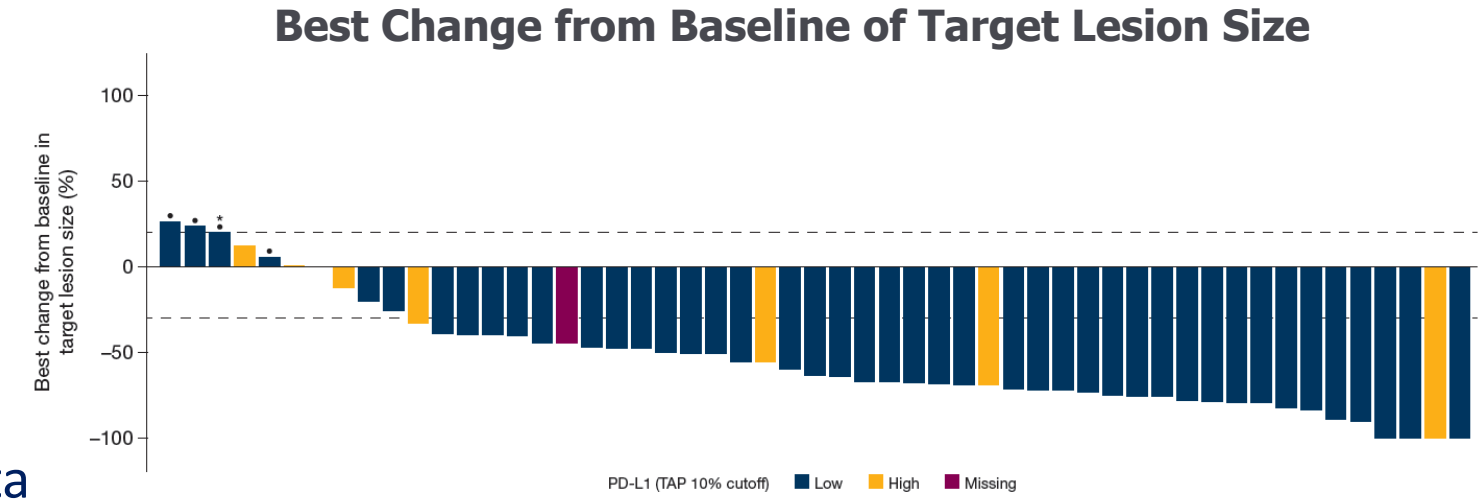
R
1:1:1

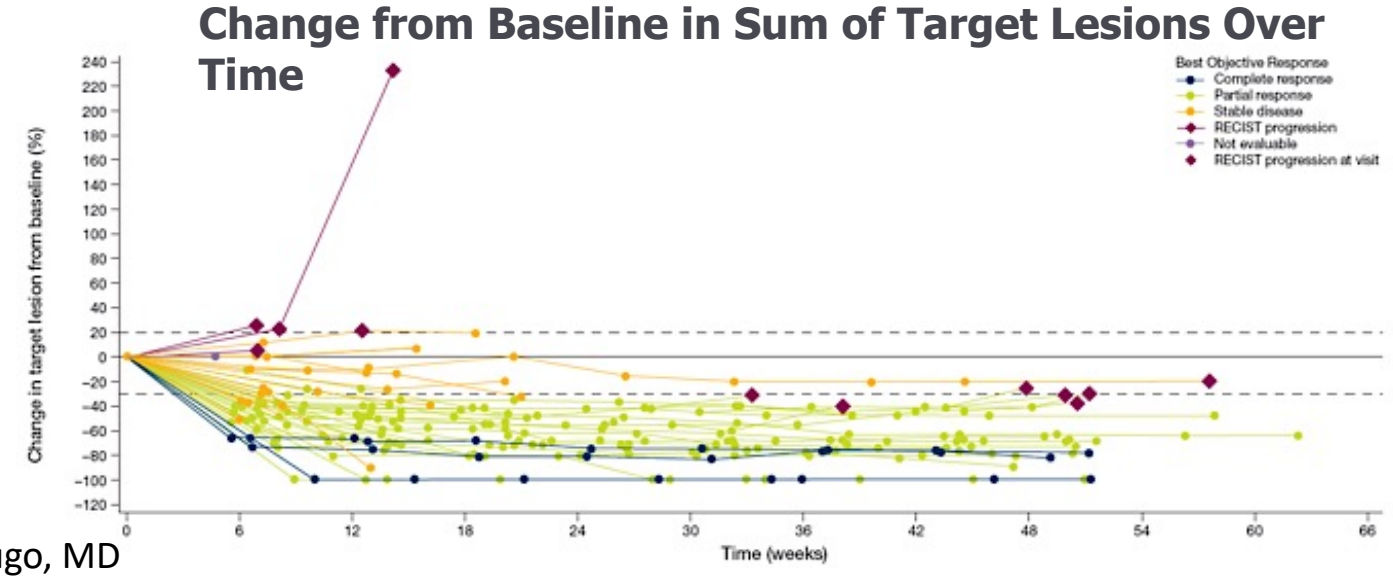
- Datopotamab deruxtecan x 8 cycles Durvalumab x 9 cycles
- Datopotamab deruxtecan x 8 cycles
- Capecitabine x 8 cycles OR Pembrolizumab x 9 cycles OR Cape + Pembro

Courtesy of Hope S Rugo, MD

BEGONIA Trial – Cohort 7: Dato-DXd + Durvalumab

- 1st line TNBC
  - N=61; 53 evaluable
  - ORR 73.6%
  - Durable responses
    - 82% remained in response at data cutoff
    - Responses in PD-L1 low and high tumors (SP263)
  - Previous data
    - 69% stomatitis, 14% grade 3
  - Current:
    - Stomatitis 55.7% no grade given
    - Alopecia 45.9%
    - Nausea 57.4%
    - **ILD/pneumonitis in 3.3% (2)**





Schmid et al, SABCS 2022; PD11-09

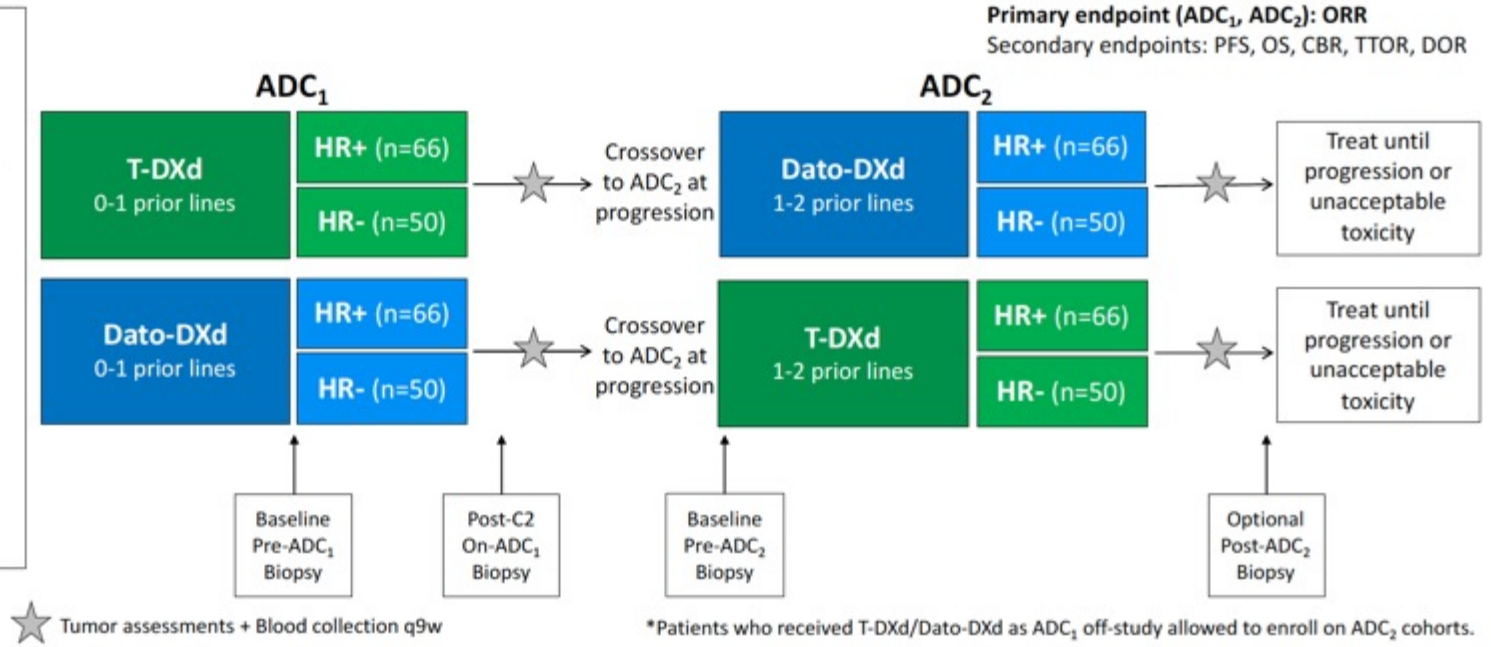
Courtesy of Hope S Rugo, MD

TBCRC 064: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd (TRADE DXd).
PI: Ana Garrido-Castro

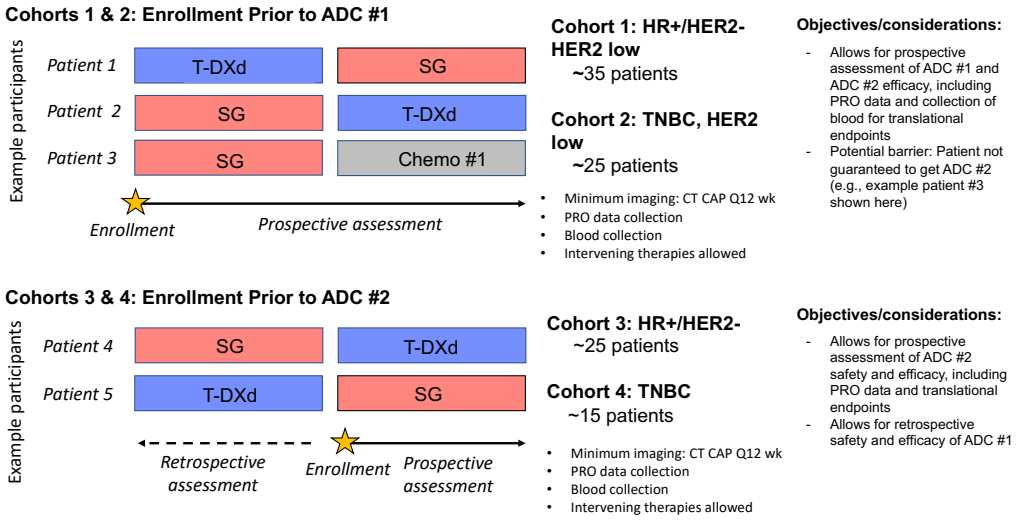
Eligibility:

- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low BC: IHC 1+ or 2+/ISH- (any sample: primary or met)
- Measurable disease
- Prior endocrine therapy and CDK4/6 inhibitor for HR+ MBC
- Prior topo-I inhibitor allowed only in neo-/adjuvant setting(s) and if ≥12m elapsed since last dose to metastatic recurrence

*Randomization 1:1 to T-DXd or Dato-DXd as ADC_1 for allocation purposes.

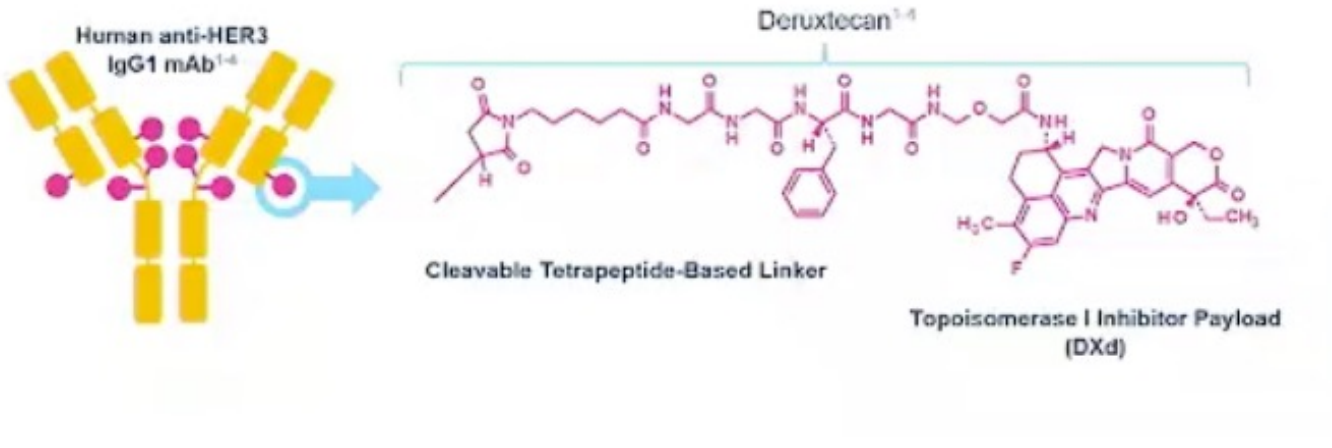


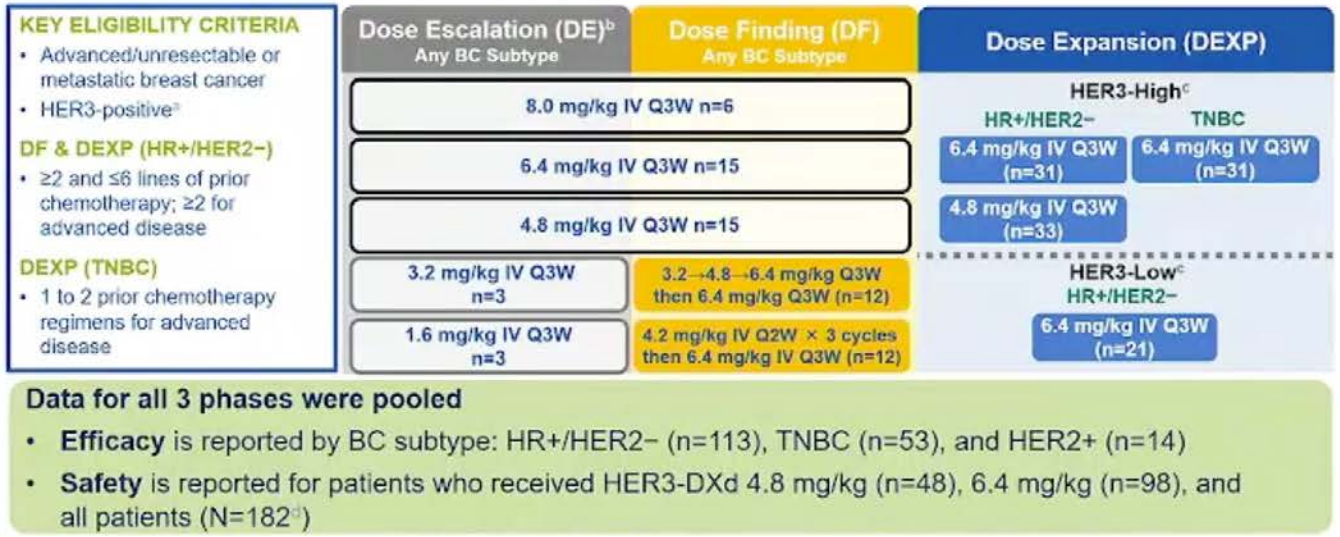
Registry Sequencing Study:
Laura Huppert UCSF



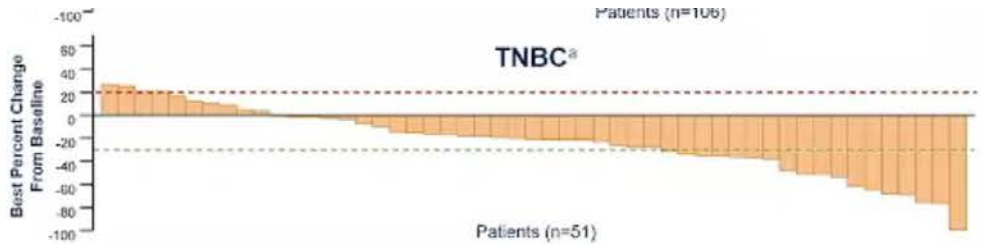
Courtesy of Hope S Rugo, MD

HER3 DXd (Patritumab) in HER3"+" BC





TNBC (n=53)
(HER2 0 36%; HER2 "low" 55%)
Brain metastases 9%
Liver/Lung metastases 64%
Med # prior regimens 2 (1-13)



TNBC	
ORR	22.6%
mDOR	5.9m
mPFS	5.5m
mOS	14.6m

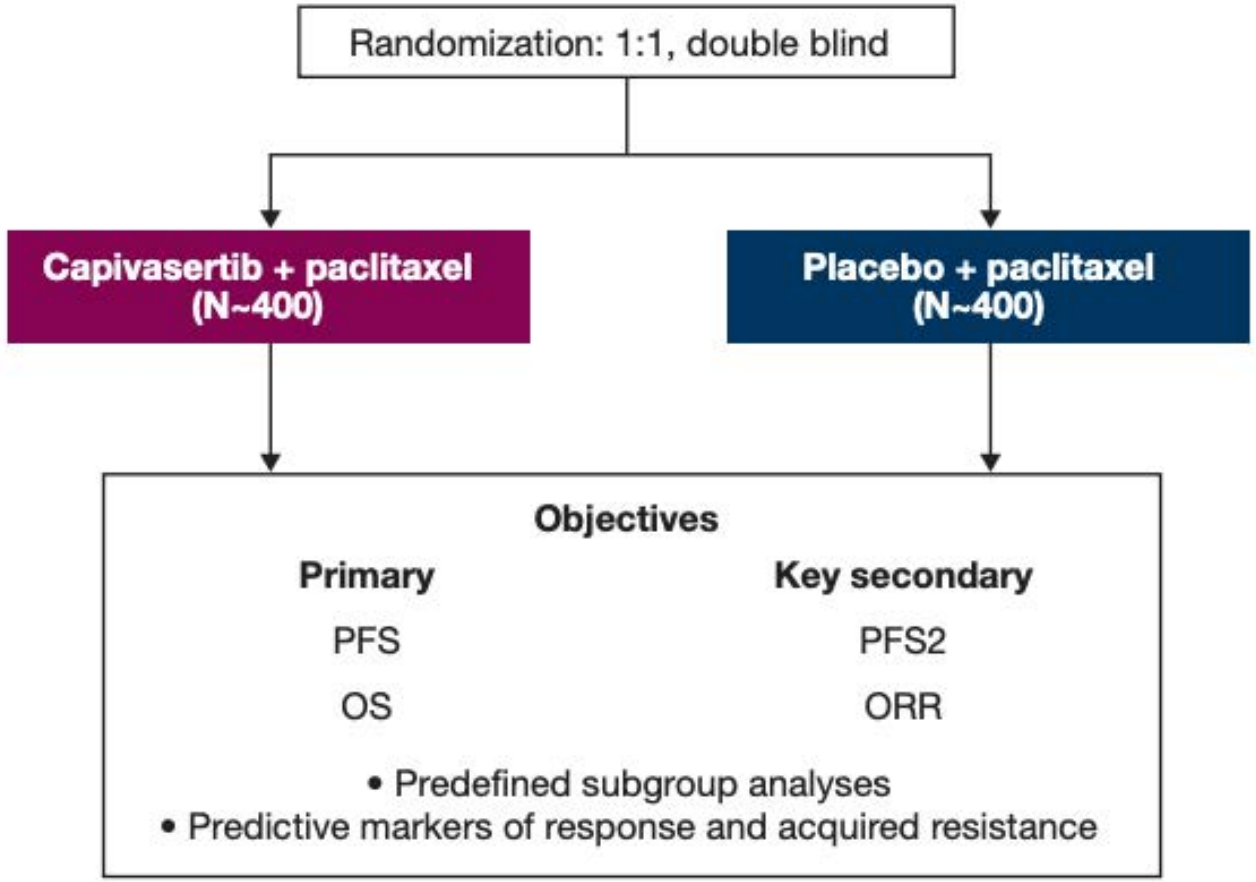
Krop et al, ASCO 2022

Courtesy of Tiffany A Traina, MD, FASCO

Memorial Sloan Kettering Cancer Center

CAPItello: Awaiting randomized phase III

Figure 4. Study design and objectives for CAPItello-290



Crossover from placebo to capivasertib is not permitted. ORR, overall response rate; PFS2, time from randomization to second progression or death

Courtesy of Tiffany A Traina, MD, FASCO

Memorial Sloan Kettering Cancer Center

Meet The Professor

Optimizing the Management of Ovarian Cancer

Thursday, September 14, 2023
5:00 PM – 6:00 PM ET

Faculty

Kathleen N Moore, MD, MS

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open for 5 minutes after the meeting ends.

CME and MOC credit information will be emailed to each participant within 5 business days.

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