Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

HER2-Positive and Triple-Negative Breast Cancer

Tuesday, January 30, 2024
5:00 PM – 6:00 PM ET

Faculty

Ian E Krop, MD, PhD
Priyanka Sharma, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Faculty

Ian E Krop, MD, PhD
Associate Cancer Center Director for Clinical Research
Director, Clinical Trials Office
Yale Cancer Center
New Haven, Connecticut

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Priyanka Sharma, MD
Frank B Tyler Professor in Cancer Research
Division of Medical Oncology, Department of Internal Medicine
Co-Program Leader
Drug Discovery, Delivery and Experimental Therapeutics Program
The University of Kansas Cancer Center
Westwood, Kansas

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, and Puma Biotechnology Inc.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI Biopharma, a Sobi company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Legend Biotech, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Krop — Disclosures

Advisory Committees	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Novartis, Seagen Inc
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group
Contracted Research	MacroGenics Inc, Pfizer Inc
Data and Safety MonitoringBoards/Committees	Merck, Novartis, Seagen Inc

Dr Sharma — Disclosures

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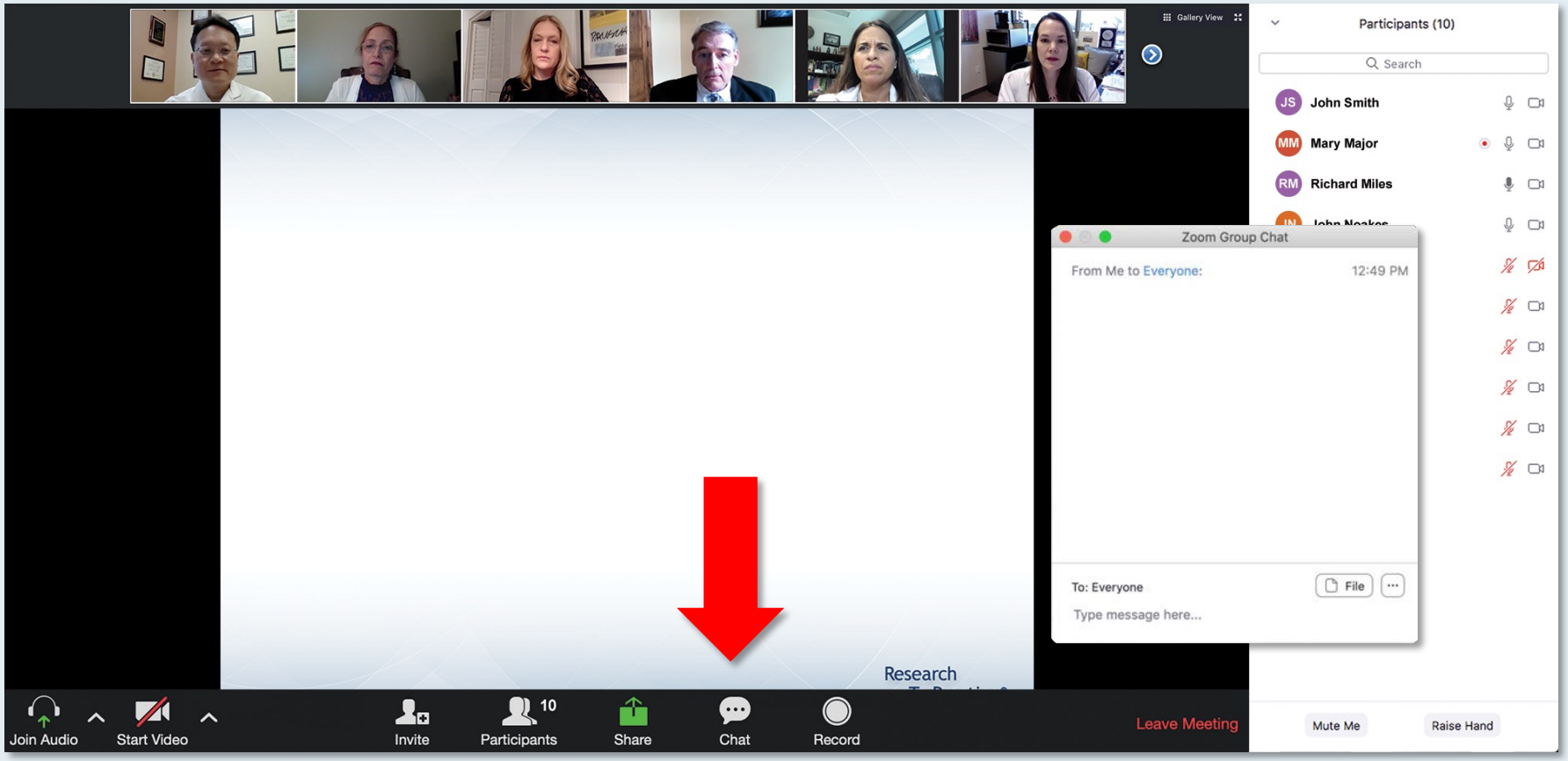
Contracted Research	Gilead Sciences Inc, Merck, Novartis
Stock Options/Stock — Public Company	Amgen Inc, Janssen Biotech Inc, Johnson & Johnson Pharmaceuticals, Sanofi

We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

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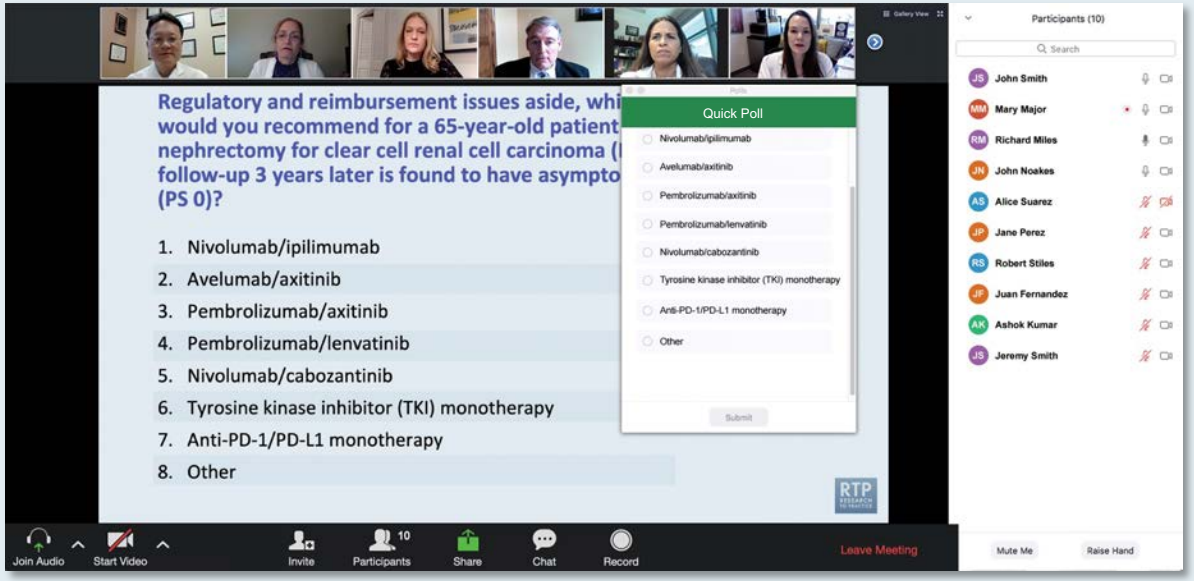
Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



RTP RESEARCH TO PRACTICE

ONCOLOGY TODAY

WITH DR NEIL LOVE

Implications of Recent Data Sets for the Current and Future Management of Breast Cancer

ADITYA BARDIA, MD, MPH
MASSACHUSETTS GENERAL HOSPITAL

SARA M TOLANEY, MD, MPH
DANA-FARBER CANCER INSTITUTE

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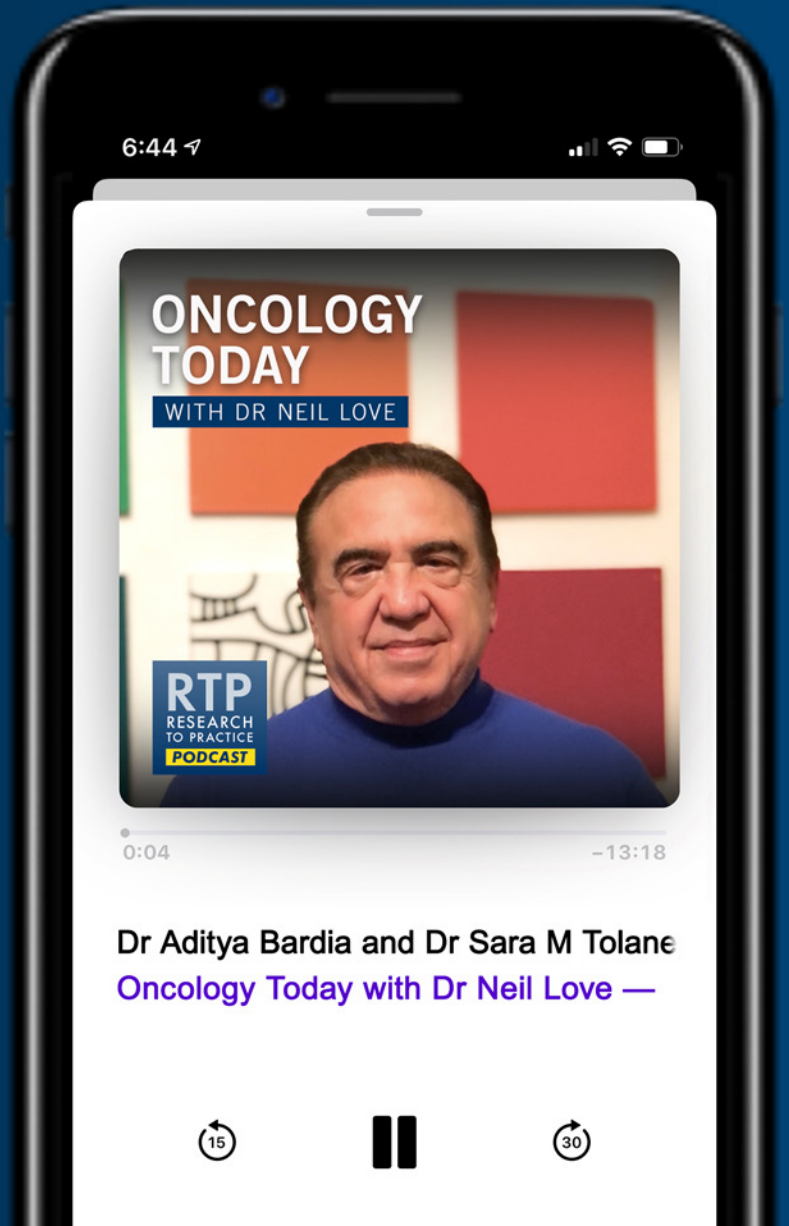

Meet The Professor

Optimizing the Management of Myelofibrosis

Thursday, February 1, 2024
5:00 PM – 6:00 PM ET

Faculty

Stephen T Oh, MD, PhD

Moderator

Neil Love, MD

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Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Chronic Lymphocytic Leukemia

Tuesday, February 6, 2024
5:00 PM – 6:00 PM ET

Faculty

Lindsey Roeker, MD

Jeff Sharman, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

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Gastroesophageal Cancers

Thursday, February 8, 2024
5:00 PM – 6:00 PM ET

Faculty

Yelena Y Janjigian, MD

Zev Wainberg, MD, MSc

Moderator

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RTP Year in Review 2024

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Lymphoma

Tuesday, February 13, 2024
5:00 PM – 6:00 PM ET

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Andrew M Evens, DO, MBA, MSc
Sonali M Smith, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

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Urothelial Bladder Cancer

Thursday, February 22, 2024
5:00 PM – 6:00 PM ET

Faculty

Shilpa Gupta, MD

Thomas Powles, MBBS, MRCP, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

JOIN US IN MARCH FOR THE RETURN OF

The Annual National General Medical Oncology Summit

A Multitumor CME/MOC- and NCPD-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

MARCH 22-24, 2024

JW Marriott Miami Turnberry

To Learn More or to Register, Visit
www.ResearchToPractice.com/Meetings/GMO2024

Agenda

INTRODUCTION: Educating Non-Breast Cancer Specialty Oncologists About HER2-Targeted Therapies – ASCO Genitourinary Cancers Symposium 2024

MODULE 1: HER2-Positive Breast Cancer — Dr Krop

MODULE 2: Triple-Negative Breast Cancer — Dr Sharma

Thank you for joining us!

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

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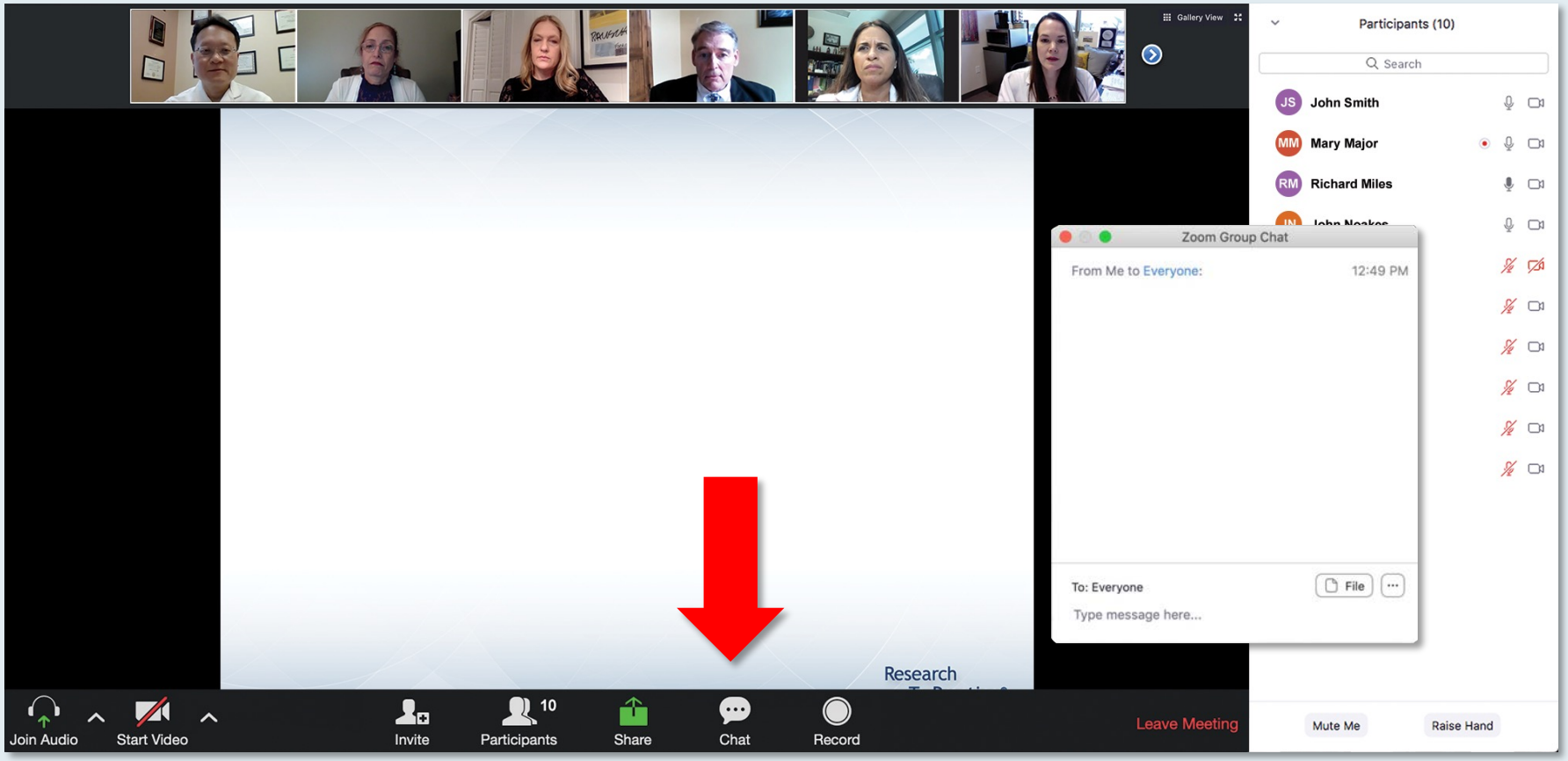

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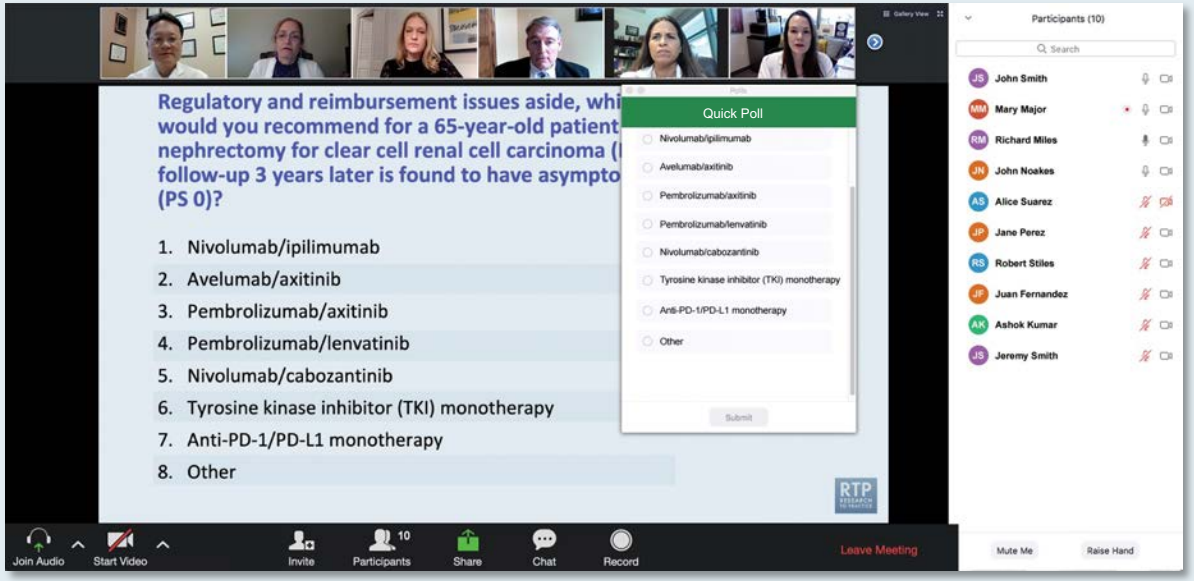

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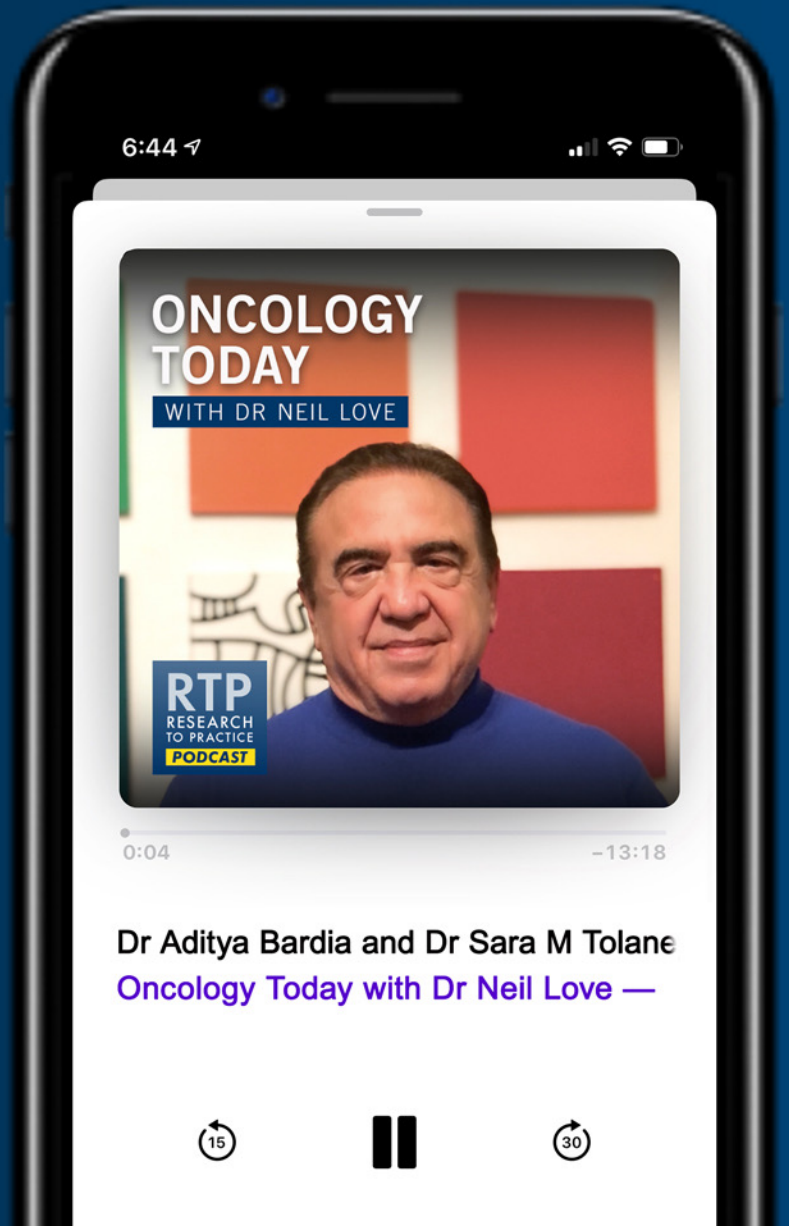

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Third Annual **National General Medical Oncology Summit**

Friday, March 22, 2024

6:30 PM – 7:00 PM

Welcome Reception

7:00 PM – 9:00 PM

Keynote Session: ER-Positive Metastatic Breast Cancer

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Special Feature: Clinicians with Breast Cancer

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

7:30 AM – 9:10 AM

Hodgkin and Non-Hodgkin Lymphoma

Ann S LaCasce, MD, MMSc
Matthew Lunning, DO
Kami Maddocks, MD
Andrew D Zelenetz, MD, PhD

9:30 AM – 10:20 AM

Gynecologic Cancers

Bradley J Monk, MD
David M O'Malley, MD

10:20 AM – 11:10 AM

Localized Breast Cancer; SABCS 2023 Review

Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD

11:10 AM – 12:00 PM

Metastatic Breast Cancer, Triple-Negative Breast Cancer, HER2-Positive Breast Cancer; SABCS 2023 Review

Erika Hamilton, MD
Virginia Kaklamani, MD, DSc
Hope S Rugo, MD

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

12:30 PM – 1:20 PM

Prostate Cancer

Emmanuel S Antonarakis, MD
Rana R McKay, MD

1:20 PM – 2:10 PM

Urothelial Bladder Cancer

Matthew D Galsky, MD
Jonathan E Rosenberg, MD

2:10 PM – 3:00 PM

Renal Cell Carcinoma

Eric Jonasch, MD
Brian Rini, MD

3:20 PM – 4:10 PM

Targeted Therapy for Non-Small Cell Lung Cancer

Ibiayi Dagogo-Jack, MD
Helena Yu, MD

4:10 PM – 5:00 PM

Nontargeted Treatments for Lung Cancer

Edward B Garon, MD, MS
Corey J Langer, MD

Third Annual **National General Medical Oncology Summit**

Sunday, March 24, 2024

7:30 AM – 8:20 AM

Multiple Myeloma

Natalie S Callander, MD
Paul G Richardson, MD

8:20 AM – 9:10 AM

Gastroesophageal Cancers

Yelena Y Janjigian, MD
Samuel J Klempner, MD

9:30 AM – 10:20 AM

Hepatobiliary Cancers

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD

10:20 AM – 11:10 AM

Colorectal Cancer

Kristen K Ciombor, MD, MSCI
John Strickler, MD

11:10 AM – 12:00 PM

Topic and faculty to be announced

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Research To Practice CME Planning Committee Members, Staff and Reviewers

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Dr Krop — Disclosures

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Dr Sharma — Disclosures

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Contracted Research	Gilead Sciences Inc, Merck, Novartis
Stock Options/Stock — Public Company	Amgen Inc, Janssen Biotech Inc, Johnson & Johnson Pharmaceuticals, Sanofi

2023 Year in Review: HER2-Positive Breast Cancer

Ian Krop MD PhD
Yale Cancer Center
January 2024

Yale University School of Medicine

Yale Cancer Center

Triple Negative Breast Cancer

Priyanka Sharma, MD
Professor of Medicine
University of Kansas Medical Center

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

The University of Kansas Cancer Center

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Key Data Sets

Ian E Krop, MD, PhD

- Tolaney SM et al. **Adjuvant paclitaxel and trastuzumab** for node-negative, HER2-positive breast cancer: Final 10-year analysis of the open-label, single-arm, phase 2 **APT trial**. *Lancet Oncol* 2023;24(3):273-85.
- Cortes J et al. 3-year invasive disease-free survival (iDFS) of the strategy-based, randomized phase II **PHERGain trial** evaluating **chemotherapy (CT) de-escalation** in human epidermal growth factor receptor 2-positive (HER2[+]) early breast cancer (EBC). ASCO 2023;Abstract LBA506.
- Holmes FA et al. Overall survival with **neratinib after trastuzumab-based adjuvant therapy** in HER2-positive breast cancer **(ExteNET)**: A randomised, double-blind, placebo-controlled, phase 3 trial. *Eur J Cancer* 2023;184:48-59.
- Chan A et al. Final findings from the **CONTROL trial**: Strategies to **reduce the incidence and severity of neratinib-associated diarrhea** in patients with HER2-positive early-stage breast cancer. *Breast* 2023:67:94-101.

Key Data Sets

Ian E Krop, MD, PhD (continued)

- Jhaveri K et al. **Neratinib + fulvestrant + trastuzumab** for **HR-positive, HER2-negative, HER2-mutant metastatic breast cancer**: Outcomes and biomarker analysis from the **SUMMIT trial**. *Ann Oncol* 2023;34(10):885-98.
- André F et al. **Trastuzumab deruxtecan versus treatment of physician's choice** in patients with HER2-positive metastatic breast cancer **(DESTINY-Breast02):** A randomised, open-label, multicentre, phase 3 trial. *Lancet* 2023;401(10390):1773-85.
- Hurvitz SA et al. **Trastuzumab deruxtecan versus trastuzumab emtansine** in patients with HER2-positive metastatic breast cancer: Updated results from **DESTINY-Breast03**, a randomised, open-label, phase 3 trial. *Lancet* 2023;401(10371):105-17.
- Krop IE et al. An **age-specific pooled analysis** of **trastuzumab deruxtecan** (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) from **DESTINY-Breast01, -02, and -03**. ASCO 2023;Abstract 1006.

Key Data Sets

Ian E Krop, MD, PhD (continued)

- Hurvitz SA et al. A **pooled analysis of trastuzumab deruxtecan** (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with **brain metastases** (BMs) from **DESTINY-Breast (DB) -01, -02, and -03**. ESMO 2023;Abstract 377O.
- Pérez-García JM et al. **Trastuzumab deruxtecan** in patients with **central nervous system involvement** from HER2-positive breast cancer: The **DEBBRAH trial**. *Neuro Oncol* 2023;25(1):157-66.
- Lin NU et al. **Tucatinib** vs placebo, both **in combination with trastuzumab and capecitabine**, for previously treated ERBB2 (HER2)-positive metastatic breast cancer in patients with **brain metastases**: Updated exploratory analysis of the **HER2CLIMB** randomized clinical trial. *JAMA Oncol* 2023;9(2):197-205.
- Hurvitz S et al. **HER2CLIMB-02**: Randomized, double-blind phase 3 trial of **tucatinib and trastuzumab emtansine** for previously treated HER2-positive metastatic breast cancer. SABCS 2023;Abstract GS01-10.

Key Data Sets

Priyanka Sharma, MD

- Schmid P et al. **Pembrolizumab** or placebo **plus chemotherapy followed by pembrolizumab** or placebo for **early-stage TNBC**: Updated EFS results from the phase III **KEYNOTE-522** study. ESMO 2023;Abstract LBA18.
- Gianni L et al. Event-free survival (EFS) analysis of **neoadjuvant taxane/carboplatin with or without atezolizumab followed by an adjuvant anthracycline regimen** in high-risk triple negative breast cancer (TNBC): **NeoTRIP Michelangelo** randomized study. ESMO 2023;Abstract LBA19.
- Ignatiadis M et al. **Adding atezolizumab to adjuvant chemotherapy** for stage II and III triple-negative breast cancer is unlikely to improve efficacy: Interim analysis of the **ALEXANDRA/IMpassion030** phase 3 trial. SABCS 2023;Abstract GS01-03.
- Rugo HS et al. **KEYNOTE-355**: Outcomes in **patients who discontinued chemotherapy before pembrolizumab**and in **patients with immune-mediated AEs**. ESMO Breast 2023;Abstract 191M0.
- Jiang Z et al. **TORCHLIGHT:** A randomized, double-blind, phase III trial of **toripalimab** versus placebo, **in combination with nab-paclitaxel (nab-P)** for patients with metastatic or recurrent triple-negative breast cancer (TNBC). ASCO 2023;Abstract LBA1013.

Key Data Sets

Priyanka Sharma, MD (continued)

- 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;178:23-33.
- Bar Y et al. **Dynamic HER2-low status** among patients with triple negative breast cancer (TNBC): The impact of **repeat biopsies.** ASCO 2023;Abstract 1005.
- Modi S et al. **Trastuzumab deruxtecan** (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with **HER2-low** unresectable and/or metastatic breast cancer (mBC): Updated survival results of the randomized, phase III **DESTINY-Breast04** study. ESMO 2023;Abstract 376O.
- Robson ME et al. **OlympiAD** extended follow-up for overall survival and safety: **Olaparib** versus chemotherapy treatment of physician's choice in **patients with a germline BRCA mutation** and HER2-negative metastatic breast cancer. *Eur J Cancer* 2023;184:39-47.

Key Data Sets

Priyanka Sharma, MD (continued)

- Khan QJ et al. Randomized trial of **fixed dose capecitabine** compared to standard dose capecitabine in metastatic breast cancer: The **X-7/7 trial**. ASCO 2023;Abstract 1007.
- 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 Ib/II study. ESMO 2023;Abstract 379MO.
- Krop IE et al. **Patritumab deruxtecan** (HER3-DXd), a human epidermal growth factor receptor 3-directed antibody-drug conjugate, in patients with **previously treated human epidermal growth factor receptor 3-expressing metastatic breast cancer**: A multicenter, phase I/II trial. *J Clin Oncol* 2023;41(36):5550-60.
- Zhang J et al. First-in-human/phase I trial of **HS-20089, a B7-H4 ADC,** in patients with advanced solid tumors. ESMO 2023;Abstract 381O.

Agenda

INTRODUCTION: Educating Non-Breast Cancer Specialty Oncologists About HER2-Targeted Therapies – ASCO Genitourinary Cancers Symposium 2024

MODULE 1: HER2-Positive Breast Cancer — Dr Krop

MODULE 2: Triple-Negative Breast Cancer — Dr Sharma

Agenda

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MODULE 2: Triple-Negative Breast Cancer — Dr Sharma

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Urothelial Bladder Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Genitourinary Cancers Symposium

Friday, January 26, 2024

7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Matthew Milowsky, MD, FASCO

Peter H O'Donnell, MD

Jonathan E Rosenberg, MD

Arlene Siefker-Radtke, MD

Moderator

Evan Y Yu, MD

RTP RESEARCH TO PRACTICE

Consulting Faculty Questions

Perspectives from the breast cancer experience: Identification and management of T-DXd-associated side effects

Neil Love, MD

Priyanka Sharma, MD

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Agenda

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De-escalation of Perioperative Treatment

HER2-Positive Breast Cancer

- Tolaney SM et al. **Adjuvant paclitaxel and trastuzumab** for node-negative, HER2-positive breast cancer: Final 10-year analysis of the open-label, single-arm, phase 2 **APT trial**. *Lancet Oncol* 2023;24(3):273-85.
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Third Annual **National General Medical Oncology Summit**

Friday, March 22, 2024 — 7:00 PM – 9:00 PM

Keynote Session Special Feature: Clinicians with Cancer

What adjuvant treatment do you think a medical oncologist would prefer to receive for a subcentimeter, node-negative, HER2-positive breast cancer?

The era of personalized medicine in HER2+ EBC

- The favorable outcomes of HER2+ breast cancers provide opportunity to:
  - De-escalate therapy for lower risk patients to reduce the toxicities of treatment
  - Escalate therapy for minority of patients who are risk for recurrence despite maximal current management

Courtesy of Ian E Krop, MD, PhD

APT: Conclusions

- Paclitaxel and trastuzumab (TH) is associated with excellent outcomes and is a standard of care for patients with stage I HER2+ breast cancer
  - Favorable outcomes for both ER+ and ER- HER2+ cancers and for T1C cancers
  - Not all patients require adjuvant trastuzumab-based chemotherapy (particularly T1aN0)

- Is there a role for T-DM1 in stage I pts?

Courtesy of Ian E Krop, MD, PhD

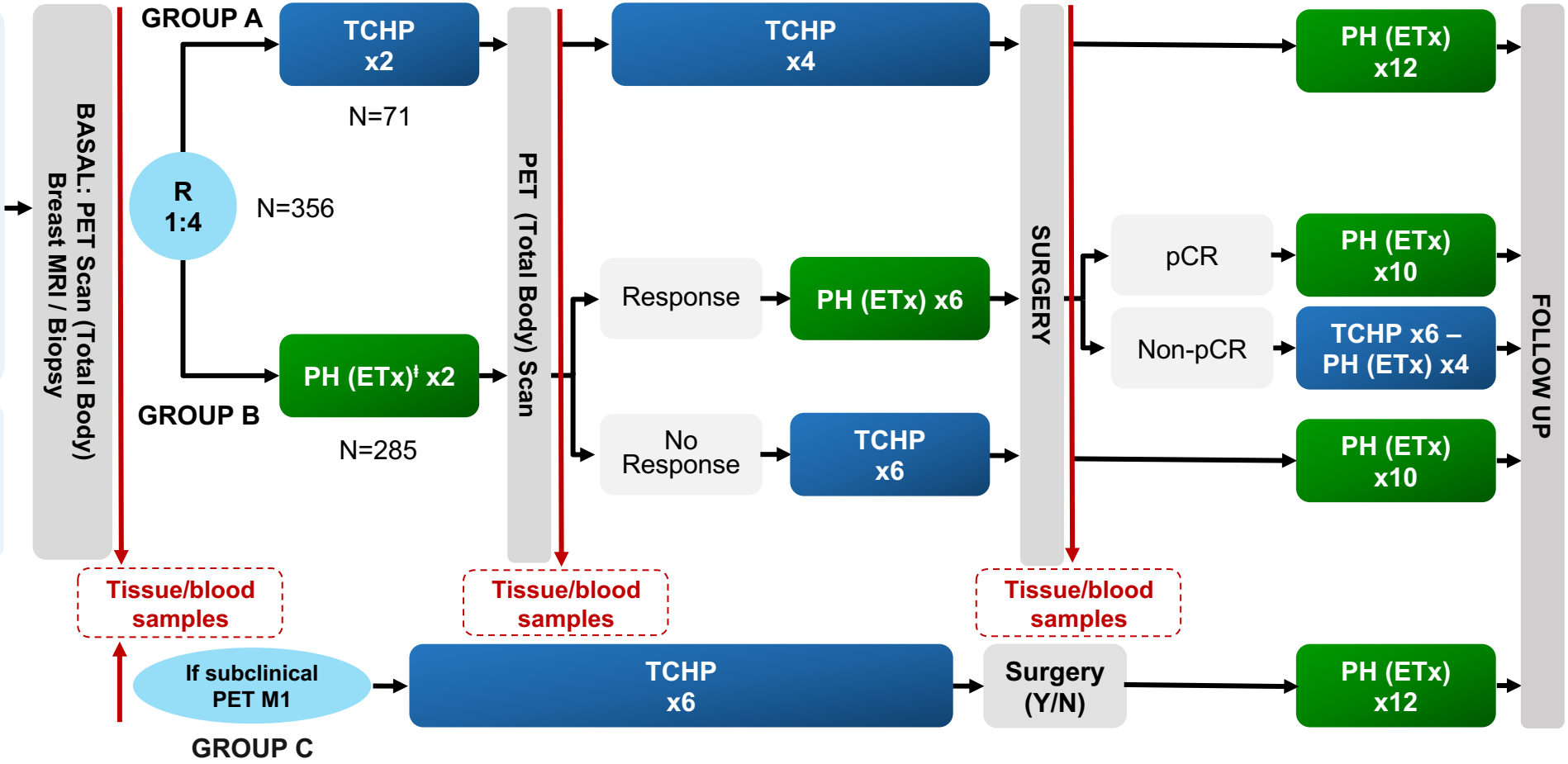
PHERGain: Can PET response be used to guide therapy de-escalation in HER2+ EBC?

Key Eligibility Criteria

1. Centrally confirmed HER2[+] stage I-IIIA EBC.
2. Tumor diameter ≥ 1.5 cm by MRI or ultrasound.
3. Presence of a breast PET-evaluable lesion.

Stratification factors

- Hormonal receptor status (+/-)



First Primary Endpoint

- pCR in PET Responders (Arm B)

Second Primary Endpoint

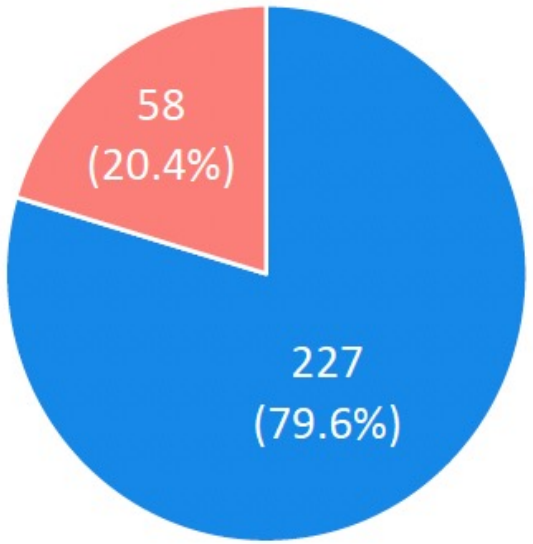
- 3-year iDFS rate in Arm B

C: Carboplatin; D: Docetaxel; EBC: Early breast cancer; ETx: Endocrine therapy (letrozole post-menopausal/tamoxifen pre-menopausal), Adjuvant ETx up to 3 years from surgery; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; H: Trastuzumab SC; HER2: Human Epidermal Growth Factor Receptor 2; iDFS: Invasive disease-free survival; MRI: Magnetic resonance Imaging; P: Pertuzumab IV; R: Randomization; TCHP: Trastuzumab, pertuzumab, docetaxel, and carboplatin. ‡ All hormonal receptor-positive patients received ETx concomitantly with PH (except on chemotherapy).

- PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction ≥40%.
- pCR, Pathological complete response (ypT0/isN0)

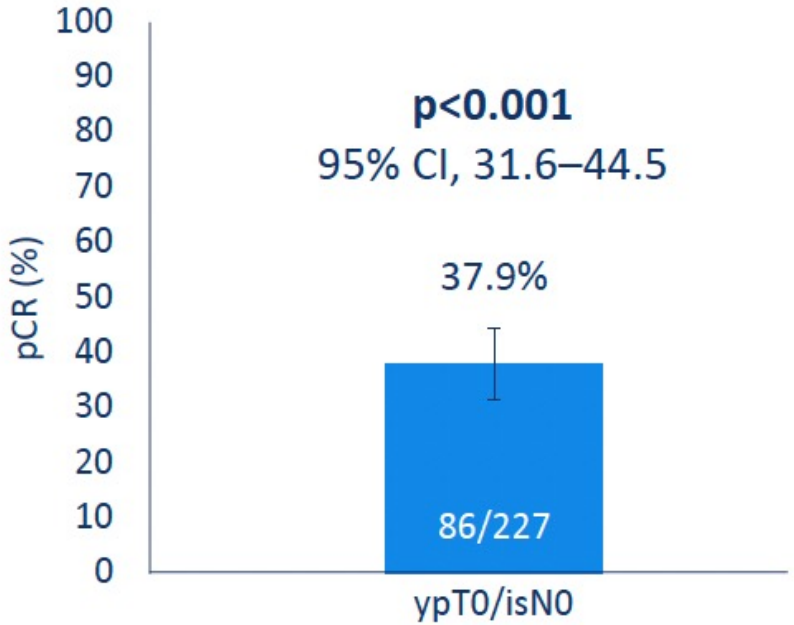
PHERGain Primary Endpoint: pCR in ^{18}F-FDG-PET responders in group B

PET Responders and Non-Responders



PET Responder PET Non-Responder

pCR rate



Null hypothesis: pCR ≤20%

pCR was observed in patients with both HER2++ and HER2+++, pts with stage II and stage III, and pts ER+ and ER-.

Pérez-García, JM, et al. (2021). *Lancet Oncol*, 22(6), 858-871.

CI: Confidence interval; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response (ypT0/isN0).

PHERGain Conclusions

- PET-guided de-escalation approach yields generally favorable overall outcome: 3-year iDFS of 95.4%
  - Allows 30% of pts to omit chemotherapy
  - Note relatively short-term follow-up
- How does this compare to short course of neoadj chemo (eg THP) with pCR rate of ≈55% and presumably no need for additional chemotherapy (eg COMPASS pCR trial)?
- Can we use upfront biomarker selection to enrich these types of approaches with patients most likely to do well with de-escalation approach?

Courtesy of Ian E Krop, MD, PhD

Neratinib in the Post-Adjuvant and Metastatic Settings

HER2-Positive Breast Cancer

- Holmes FA et al. Overall survival with **neratinib after trastuzumab-based adjuvant therapy** in HER2-positive breast cancer **(ExteNET)**: A randomised, double-blind, placebo-controlled, phase 3 trial. *Eur J Cancer* 2023;184:48-59.
- Chan A et al. Final findings from the **CONTROL trial**: Strategies to **reduce the incidence and severity of neratinib-associated diarrhea** in patients with HER2-positive early-stage breast cancer. *Breast* 2023:67:94-101.
- Jhaveri K et al. **Neratinib + fulvestrant + trastuzumab** for **HR-positive, HER2-negative, HER2-mutant metastatic breast cancer**: Outcomes and biomarker analysis from the **SUMMIT trial**. *Ann Oncol* 2023;34(10):885-98.

Third Annual **National General Medical Oncology Summit**

Friday, March 22, 2024 — 7:00 PM – 9:00 PM

Keynote Session Special Feature: Clinicians with Cancer

How do you think a medical oncologist who had recently completed adjuvant therapy for HER2-positive breast cancer would think through the decision to receive postadjuvant neratinib?

ExteNET: Cumulative incidence of CNS disease as 1st site of recurrence

Population or Subgroup	CNS Events (No. Patients)		Cumulative Incidence of CNS Recurrences at 5 Years, % (95% CI)	
	Neratinib	Placebo	Neratinib	Placebo
HR+/≤ 1-year population	4 (670)	12 (664)	0.7 (0.2–1.7)	2.1 (1.1–3.5)
Nodal status				
Positive	4 (540)	10 (539)	0.8 (0.3-2.0)	2.2 (1.1-3.8)
Negative	0 (130)	2 (125)	0 (NE)	1.9 (0.4-6.0)
Prior trastuzumab regimen				
Concurrent	2 (411)	8 (415)	0.6 (0.1-1.9)	2.3 (1.1-4.3)
Sequential	2 (259)	4 (249)	0.9 (0.2-3.0)	1.8 (0.6-4.3)
Adjuvant or neoadjuvant therapy				
Adjuvant	3 (508)	6 (472)	0.7 (0.2-2.0)	1.5 (0.6-3.0)
Neoadjuvant	1 (162)	6 (192)	0.7 (0.1-3.3)	3.7 (1.5-7.4)
pCR status[a]				
No	1 (131)	5 (164)	0.8 (0.1-4.0)	3.6 (1.3-7.8)
Yes	0 (17)	1 (21)	0 (NE)	5.0 (0.3-21.2)

Courtesy of Ian E Krop, MD, PhD

Chan et al Clin Breast Cancer 2021 Feb;21(1):80-91.e7.

Who Should Receive Neratinib?

- Neratinib benefit (relative and absolute) in ER+HER2+ high risk patients
  - Must be balanced against toxicity risk
- No data giving neratinib after pertuzumab or T-DM1
  - All patients at sufficiently high risk to receive neratinib will have received pertuzumab and T-DM1
- So who should receive it?
  - Unclear, but my opinion is that it is reasonable option to consider in ER+ patients with positive nodes after neoadjuvant therapy

Courtesy of Ian E Krop, MD, PhD

How to mitigate neratinib induced diarrhea?

- Neratinib dose escalation, along with loperamide, is associated with relatively low rates of gr3 diarrhea

- Most pts who get through 1st cycle have low rate of drug discontinuation due to diarrhea
  - Patient education is key

Courtesy of Ian E Krop, MD, PhD

SUMMIT: Does neratinib have activity in breast cancers with somatic HER2 mutations?

- Somatic HER2 mutations seen in 3-5% of HR+ HER2 non-amplified cancers
  - More common in lobular cancers (5-8%)
  - May be acquired with endocrine resistance
- SUMMIT trial is basket study evaluating neratinib alone and in combination in patients with HER2 mutant breast cancer
  - Initial results showed single agent activity: 17% ORR in HR+ HER2mutant MBC
  - Combination of neratinib and fulvestrant: 30% ORR
  - ctDNA data suggested secondary HER2 mutations or HER2 amplification as mechanism of resistance
- Data led to cohort of neratinib + fulvestrant + trastuzumab (NFT) performed (n=71) in pts previously treated with CDK4/6 inhibitor
  - Randomized subset: F vs FT vs NFT (n=21)

Courtesy of Ian E Krop, MD, PhD

Jhaveri et al, Annals of Oncology 34:885 2023

SUMMIT: Does neratinib have activity in breast cancers with somatic HER2 mutations?

Parameter	Non-randomized + randomized HR+, prior CDK4/6i (N+F+T, *N*=57)	Randomized HR+, prior CDK4/6i (F+T, *n*=7)	After crossover from F+T to N+F+T (*n*=4)	Randomized HR+, prior CDK4/6i (F, *n*=7)	After crossover from F to N+F+T (*n*=6)
Objective response (confirmed CR or PR)[b], *n* (%)	22 (39)	0	1 (25)	0	2 (33)
CR	1 (2)	0	0	0	0
PR	21 (39)	0	1 (25)	0	2 (33)
Best overall response (confirmed or unconfirmed PR or CR), *n* (%)	29 (51)	0	1 (25)	0	3 (50)
Median DOR[c], months (95% CI)	14.4 (6.4–21.7)	No response	6.2 (NE–NE)	No response	6.3 (6.2–6.4)
Clinical benefit[d], *n* (%)	31 (54)	0	1 (25)	0	5 (83)
Median PFS[c], months (95% CI)	8.3 (6.0–15.1)	3.9 (1.9–4.1)	5.8 (3.3–8.3)	4.1 (1.6–4.1)	9.5 (3.9–NE)

- ORR: 63% V777L
  24% L755S
  80% dual mutation
- HER2 expression level or FISH amplification were not assoc with ORR
- Grade 3 diarrhea was 53% with triplet despite loperamide prophylaxis

Courtesy of Ian E Krop, MD, PhD

Jhaveri et al, Annals of Oncology 34:885 2023

SUMMIT: Conclusion

- Neratinib + fulvestrant has clinically meaningful activity in patients with ER+HER2mutant MBC
  - Addition of trastuzumab may further increase benefit
  - Substantial Gr3 diarrhea – consider neratinib dose escalation
- Neratinib based therapy can be considered an effective treatment option for ER+HER2mutant MBC
  - Included in NCCN guidelines
- These data provide additional support for obtaining somatic tumor sequencing (tissue or ctDNA) in the MBC setting

Courtesy of Ian E Krop, MD, PhD

Sequencing of Therapy for HER2-Positive mBC

HER2-Positive Breast Cancer

- Hurvitz SA et al. **Trastuzumab deruxtecan versus trastuzumab emtansine** in patients with HER2-positive metastatic breast cancer: Updated results from **DESTINY-Breast03**, a randomised, open-label, phase 3 trial. *Lancet* 2023;401(10371):105-17.
- André F et al. **Trastuzumab deruxtecan versus treatment of physician's choice** in patients with HER2-positive metastatic breast cancer **(DESTINY-Breast02):** A randomised, open-label, multicentre, phase 3 trial. *Lancet* 2023;401(10390):1773-85.
- Krop IE et al. An **age-specific pooled analysis** of **trastuzumab deruxtecan** (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) from **DESTINY-Breast01, -02, and -03**. ASCO 2023;Abstract 1006.

DESTINY-Breast03: Adjudicated Drug-Related Interstitial Lung Disease/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- Adjudicated drug-related ILD/pneumonitis rates were similar to other mBC trials with T-DXd[1,2]
- With longer treatment exposure and follow-up, the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis[3] to 15.2%
  - There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- The overall incidence of grade 3 events (0.8%) was the same as in the PFS interim analysis[3]
- There were no adjudicated drug-related grade 4 or 5 events

ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Modi S et al. *N Engl J Med* 2020; 382(7): 610-21. 2. Powell CA et al. *ESMO Open* 2022; 7(4): 100554. 3. Cortes J et al. *N Engl J Med.* 2022;386:1143-1154.

Courtesy of Ian E Krop, MD, PhD

Hurvitz SA et al. Lancet 2023;401:105

DB-03 Conclusions

- Establishes T-DXd role as preferred 2nd line SOC for most patients
  - Unprecedented levels of activity and reassuring ILD data

- Should there be a different SOC for pts with active CNS metastases?

Courtesy of Ian E Krop, MD, PhD

Adverse Events of Special Interest: ILD and LV Dysfunction

Adjudicated as Drug-related ILD[a]						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 404)	11 (2.7)	26 (6.4)	3 (0.7)	0	2 (0.5)	42 (10.4)
TPC (n = 195)	0	0	1 (0.5)	0	0	1 (0.5)

- Median time to onset of adjudicated drug-related ILD was 209.5 days (range, 41-638 days) with T-DXd

LV dysfunction[b]

- In the T-DXd arm, 18 (4.5%) patients experienced an LV dysfunction event[c]
  - 2 (0.5%) patients had a grade ≥3 event
- In the TPC arm, 3 (1.5%) patients experienced an LV dysfunction[d]
  - 1 (0.5%) patient had a grade ≥3 event

ILD, interstitial lung disease; LV, left ventricular; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The safety analysis set includes all randomly assigned patients who received at least 1 dose of study treatment. [b]Left ventricular dysfunction included preferred terms of acute left ventricular failure, acute right ventricular failure, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, chronic left ventricular failure, chronic right ventricular failure, ejection fraction decreased, left ventricular failure, right ventricular failure, ventricular failure, and left ventricular dysfunction. [c]17 ejection fraction decreased (2 grade ≥3), 1 LV dysfunction (grade 1). [d]1 ejection fraction decreased (grade 1), 2 cardiac failure (1 grade ≥3).

Courtesy of Ian E Krop, MD, PhD

André F et al. Lancet 2023;401:1773

DB-02 Conclusions

- Provides first randomized data demonstrating benefit of one ADC after cancer has progressed on a different ADC
  - Provides support for paradigm of treating pts with HER2+ breast cancer with sequential ADCs with different payloads

Courtesy of Ian E Krop, MD, PhD

Does age impact efficacy or tolerability of T-DXd?

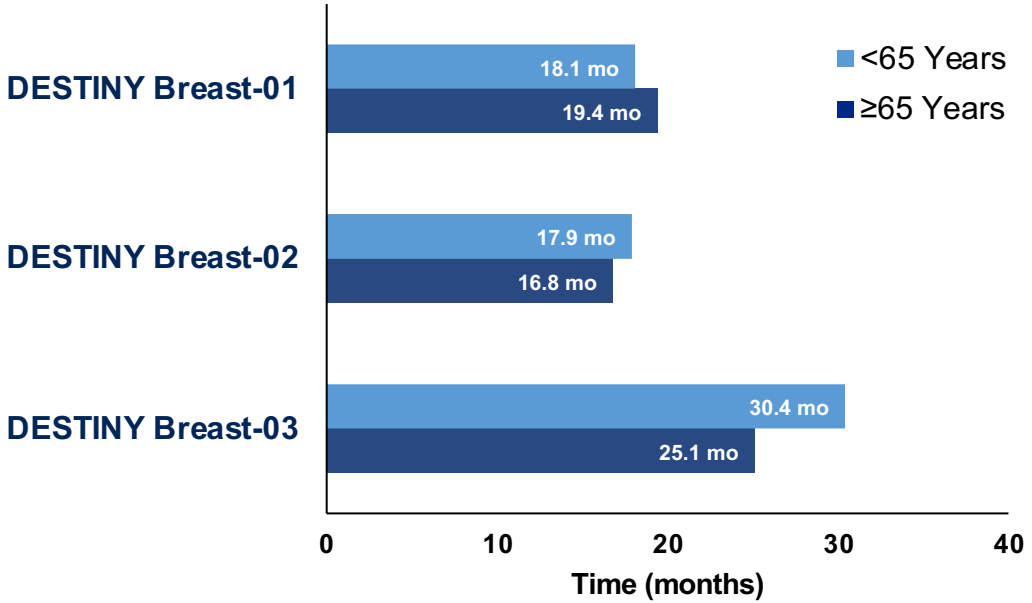
- Older patients experience higher rates of toxicity from chemotherapy

- To determine if this effect is observed with T-DXd, an analysis of pts <65yo vs ≥65 was conducted in pooled data from DB-01, -02, 03

Courtesy of Ian E Krop, MD, PhD

Descriptive Efficacy According to Age for T-DXd[a]

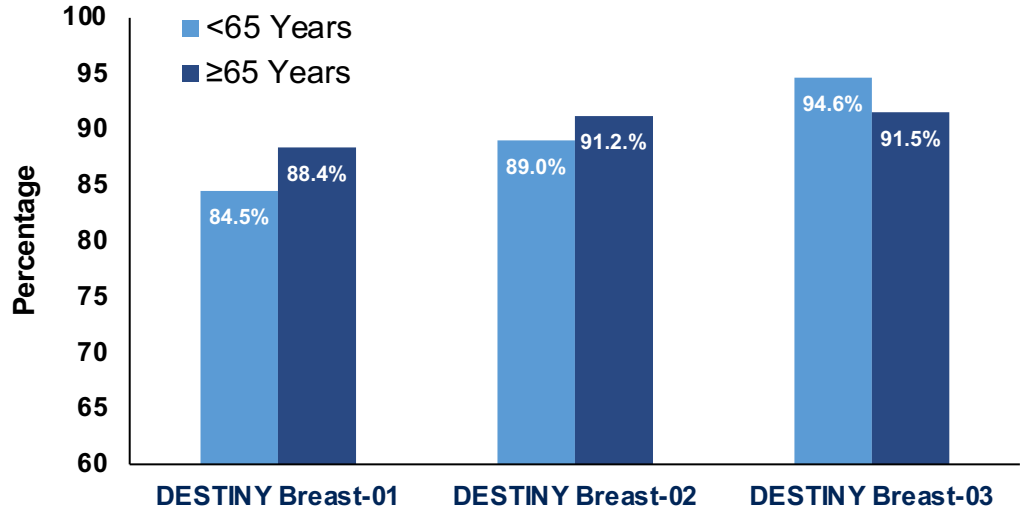
Median Progression Free Survival



Median Overall Survival

	DESTINY-Breast01		DESTINY-Breast02		DESTINY-Breast03	
	<65 (n = 140)	≥65 (n = 44)	<65 (n = 321)	≥65 (n = 85)	<65 (n = 212)	≥65 (n = 49)
mOS, months (95% CI)	28.1 (23.3-36.1)	30.9 (21.9-NE)	NR (35.5-NE)	30.2 (22.3-39.2)	NR (40.5-NE)	NR (26.3-NE)

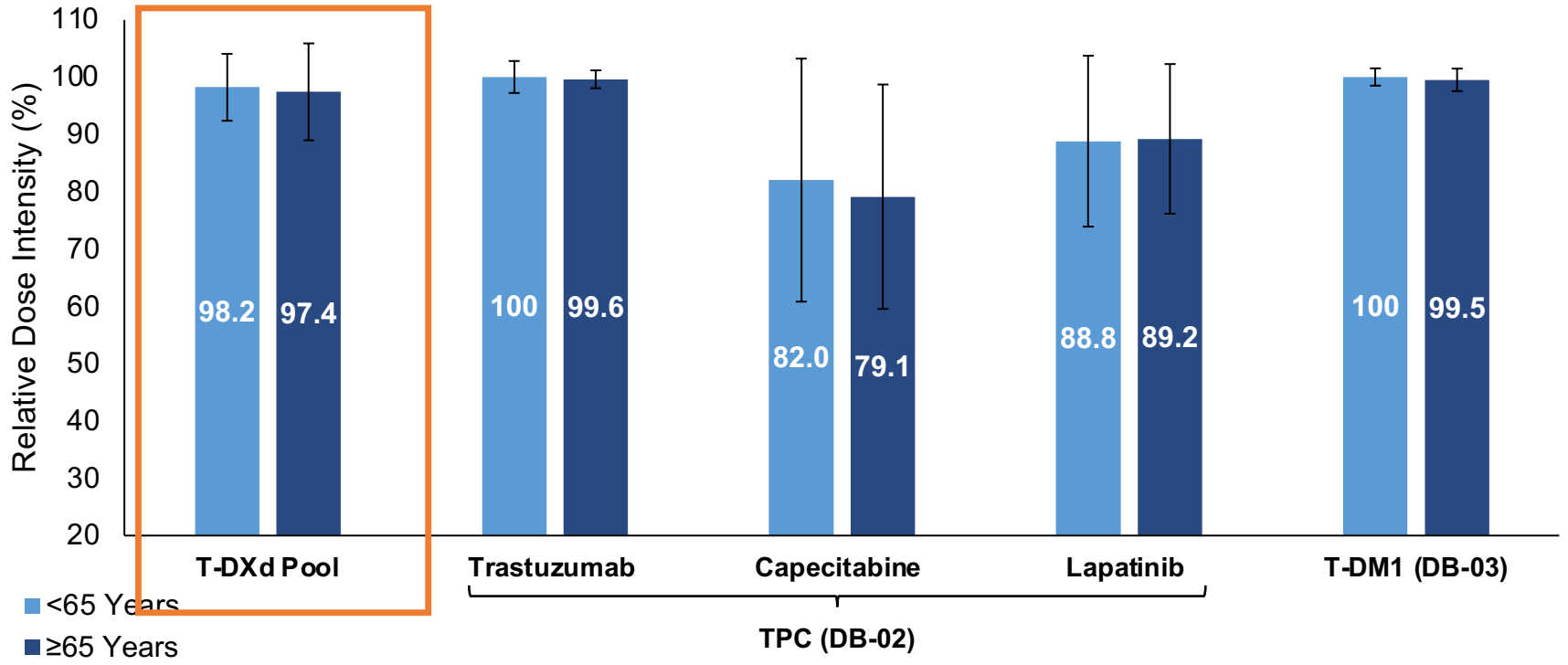
12-month Landmark Overall Survival



- Efficacy in patients aged <65 and ≥65 years treated with T-DXd was generally similar; however no formal comparison was made

[a]Efficacy data was not pooled due to bias induced by the heterogeneity of the study population. Trial data cutoffs; DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022.
mOS, median overall survival; NE, not estimable; NR, not reached; T-DXd, trastuzumab deruxtecan.

Relative Dose Intensity



- Relative dose intensity was similar between <65 and ≥65 age groups, regardless of treatment received

[a]Relative dose intensity (%) = (dose intensity/planned dose intensity) ×100.
DB, DESTINY-Breast; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Courtesy of Ian E Krop, MD, PhD

Most Common Grade ≥3 Drug-related TEAEs in ≥5% of Patients

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)	<65 (n = 157)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 204)	≥65 (n = 57)	≥75 (n = 8)
Grade ≥3[a] drug-related TEAEs, n (%)	**291 (43.6)**	**96 (54.2)**	**13 (39.4)**	**48 (30.6)**	**12 (31.6)**	**5 (62.5)**	**82 (40.2)**	**28 (49.1)**	**3 (37.5)**
Neutropenia[b]	117 (17.5)	41 (23.2)	4 (12.1)	5 (3.2)	1 (2.6)	1 (12.5)	6 (2.9)	3 (5.3)	0
Fatigue[c]	52 (7.8)	20 (11.3)	5 (15.2)	1 (0.6)	1 (2.6)	1 (12.5)	2 (1.0)	0	0
Nausea	43 (6.4)	15 (8.5)	4 (12.1)	3 (1.9)	0	0	0	1 (1.8)	0
Anemia[d]	42 (6.3)	20 (11.3)	3 (9.1)	1 (0.6)	0	0	6 (2.9)	6 (10.5)	1 (12.5)
Leukopenia[e]	42 (6.3)	15 (8.5)	2 (6.1)	0	0	0	3 (1.5)	0	0
Lymphopenia[f]	28 (4.2)	11 (6.2)	1 (3.0)	2 (1.3)	0	0	2 (1.0)	1 (1.8)	0
Thrombocytopenia[g]	28 (4.2)	9 (5.1)	0	2 (1.3)	0	0	47 (23.0)	19 (33.3)	2 (25.0)
Transaminases increased[h]	18 (2.7)	1 (0.6)	0	1 (0.6)	1 (2.6)	0	16 (7.8)	4 (7.0)	0
Diarrhea	9 (1.3)	4 (2.3)	0	10 (6.4)	2 (5.3)	1 (12.5)	2 (1.0)	0	0

- Patients ≥65 years of age experienced more grade ≥3 TEAEs across all trials

[a]Grade ≥3 drug-related TEAEs present in ≥5% of patients, sorted in descending order of frequency in the T-DXd pooled arm for the <65 years age group. Grade ≥3 drug-related TEAEs calculated in all patients in the analysis set. [b]Neutropenia includes the preferred terms neutrophil count decreased and neutropenia. [c]Fatigue includes the preferred terms fatigue, asthenia, malaise, and lethargy. [d]Anemia includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [e]Leukopenia includes the preferred terms white blood cell count decrease and leukopenia. [f]Lymphopenia includes the preferred terms lymphocute count decreased and lymphopenia. [g]Thrombocytopenia includes the preferred terms platelet count decreased and thrombocytopenia. [h]Transaminases increased includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increased.
T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent adverse event; TPC, treatment of physician's choice.

Courtesy of Ian E Krop, MD, PhD

Adjudicated Drug-related ILD/Pneumonitis[a]

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)	<65 (n = 157)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 204)	≥65 (n = 57)	≥75 (n = 8)
Any grade, n (%)	**79 (11.8)**	**31 (17.5)**	**5 (15.2)**	**0**	**1 (2.6)**	**0**	**6 (2.9)**	**2 (3.5)**	**1 (12.5)**
1	21 (3.1)	7 (4.0)	0	0	0	0	3 (1.5)	1 (1.8)	0
2	48 (7.2)	20 (11.3)	5 (15.2)	0	0	0	2 (1.0)	1 (1.8)	1 (12.5)
3	4 (0.6)	3 (1.7)	0	0	1 (2.6)	0	1 (0.5)	0	0
4	0	0	0	0	0	0	0	0	0
5	6 (0.9)	1 (0.6)	0	0	0	0	0	0	0

- Rates of adjudicated ILD/pneumonitis were generally higher in patients ≥65 years of age across all trials compared to patients <65 years of age
- Most drug-related ILD/pneumonitis cases were of low grade

[a]No ILD/pneumonitis cases were pending adjudication at the respective data cutoff dates (DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022).
ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Courtesy of Ian E Krop, MD, PhD

Conclusion

- Results of this pooled analysis indicate that T-DXd remains an effective treatment option for patients ≥65 years of age
  - mPFS and confirmed ORR by BICR were similar with T-DXd in patients <65 and ≥65 years of age within each trial
- The safety profile of T-DXd was acceptable across all age subgroups
  - Patients ≥65 years of age experienced more grade ≥3 TEAEs across all trials
- Further research/real-world evidence studies for older patients, also addressing aspects of comorbidities and frailty, would be informative

T-DXd may be considered as an effective option for patients across all age subgroups with an acceptable safety profile

BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mPFS, median progression free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent adverse event.

Courtesy of Ian E Krop, MD, PhD

HER2-Positive Brain Metastases

HER2-Positive Breast Cancer

- Hurvitz S et al. **HER2CLIMB-02**: Randomized, double-blind phase 3 trial of **tucatinib and trastuzumab emtansine** for previously treated HER2-positive metastatic breast cancer. SABCS 2023;Abstract GS01-10.
- Hurvitz SA et al. A **pooled analysis of trastuzumab deruxtecan** (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with **brain metastases** (BMs) from **DESTINY-Breast (DB) -01, -02, and -03**. ESMO 2023;Abstract 377O.
- Pérez-García JM et al. **Trastuzumab deruxtecan** in patients with **central nervous system involvement** from HER2-positive breast cancer: The **DEBBRAH trial**. *Neuro Oncol* 2023;25(1):157-66.

HER2CLIMB-02 Study Design

- HER2+ LA/MBC with progression after trastuzumab and taxane in any setting[a]
- ECOG PS ≤1
- Previously treated stable, progressing, or untreated brain metastases not requiring immediate local therapy

N≈460

R 1:1

Stratification factors:
- Line of treatment for metastatic disease (1L vs other)
- Hormone receptor status (positive vs negative)
- Presence or history of brain metastases (yes vs no)
- ECOG PS (0 vs 1)

T-DM1 + Tucatinib

T-DM1 3.6 mg/kg IV and Tucatinib 300 mg PO BID

T-DM1 + Placebo

T-DM1 3.6 mg/kg IV and Placebo PO BID

Outcomes

Primary
- PFS by investigator assessment per RECIST v1.1

Key Secondary (hierarchical)
- OS
- PFS in patients with brain metastases
- cORR per RECIST v1.1
- OS in patients with brain metastases

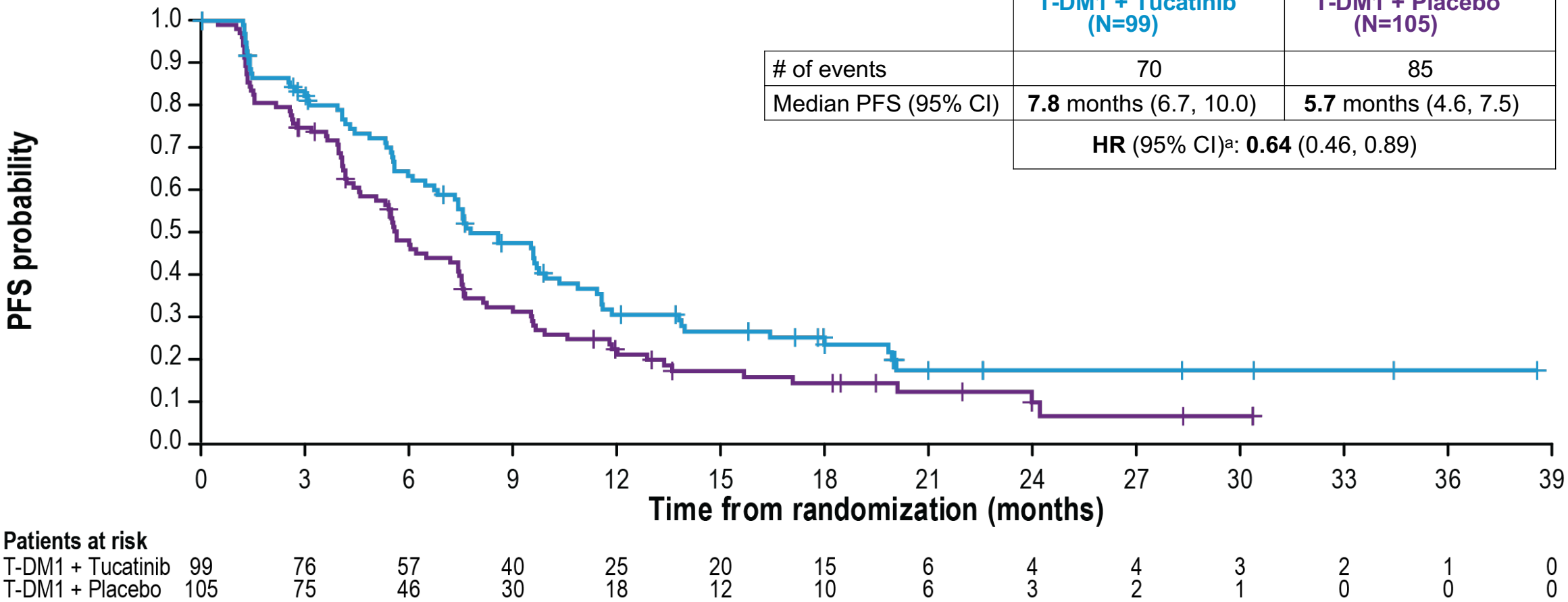
The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7 at two-sided alpha level of 0.05. The first of two interim analyses for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive[b].

No prior HER2 TKI or T-DXd

NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Accessed Oct 5, 2023.
a Patients who received prior tucatinib, afatinib, T-DXd, or any investigational anti-HER2, anti-EGFR, or HER2 TKIs were not eligible. Patients who received lapatinib and neratinib were not eligible if the drugs were received within 12 months of starting study treatment, and patients who received pyrotinib for recurrent or metastatic breast cancer were not eligible. These patients were eligible if the drugs were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity.
b Subsequent OS analyses are planned upon 80% and 100% of required events for the final OS analysis.
1L, first-line; BID, twice daily; cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; LA/MBC, locally advanced or metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PO, orally; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors.
Date of data cutoff: Jun 29, 2023. Patients were enrolled from Oct 8, 2019, to Jun 16, 2022.

HER2CLIMB-02: PFS in Patients with Brain Metastases

	T-DM1 + Tucatinib (N=99)	T-DM1 + Placebo (N=105)
# of events	70	85
Median PFS (95% CI)	**7.8** months (6.7, 10.0)	**5.7** months (4.6, 7.5)
	HR (95% CI)[a]: **0.64** (0.46, 0.89)	



a The outcome was not formally tested.
HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Courtesy of Ian E Krop, MD, PhD

HER2CLIMB-02: Conclusion

- Addition of tucatinib to T-DM1 modestly improves PFS
  - Relative benefit larger in patients with CNS disease
  - No OS benefit, but data immature
  - Increased toxicity appears manageable, but ≈20% drug discontinuation
  - Caveat: data are in T-DXd naïve patients

- Unclear whether tucatinib should be used with T-DM1 or trastuzumab/capecitabine
  - Is there a role for using it in both combinations sequentially?

Courtesy of Ian E Krop, MD, PhD

Are there other options for active brain mets besides TKIs?

- Does trastuzumab deruxtecan have activity in HER2+ brain metastases?

- Dogma had been that large biologics like ADCs cannot cross the blood brain barrier

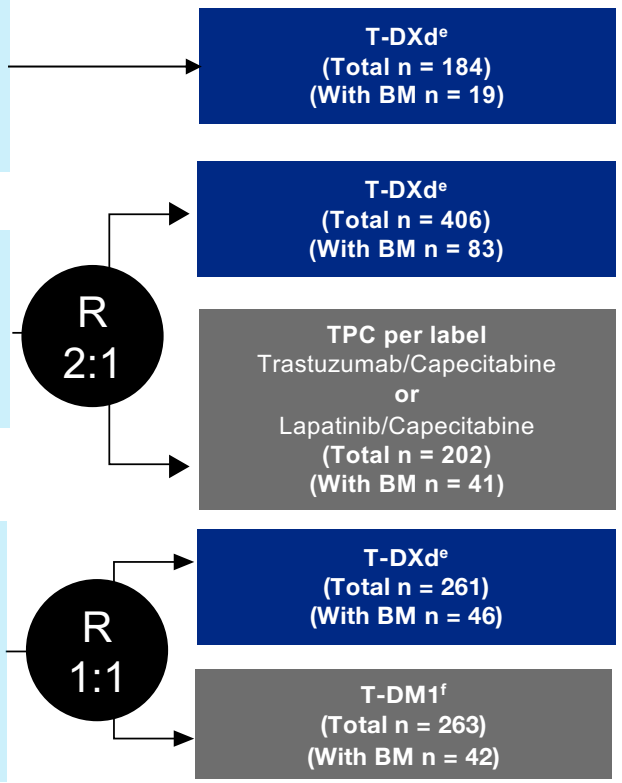
Courtesy of Ian E Krop, MD, PhD

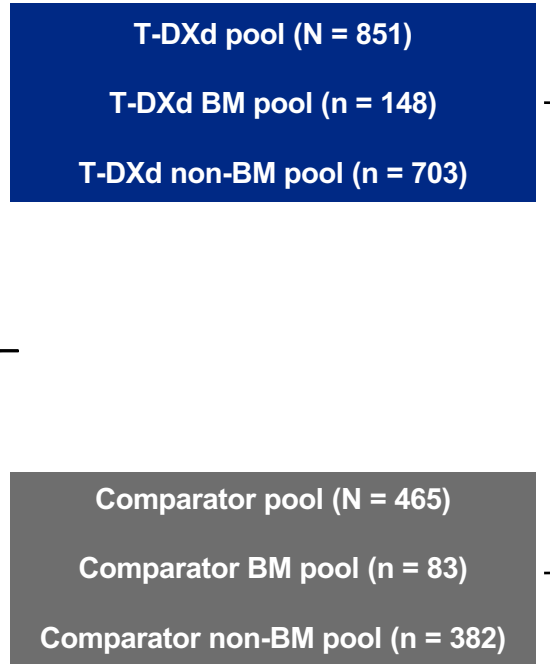
Retrospective Exploratory Pooled Analysis Plan[1-3]

DESTINY-Breast01 (N = 253)[a,b]
- Phase II study
- Patients previously treated with T-DM1
- Patients with asymptomatic and previously locally treated BM eligible
- Prior BM therapy within 60 days prohibited

DESTINY-Breast02 (N = 608)[a,c]
- Phase III study
- Patients previously treated with T-DM1
- Patients with asymptomatic and previously treated/untreated BM eligible
- Prior BM therapy within 14 days of randomization prohibited

DESTINY-Breast03 (N = 524)[a,d]
- Phase III study
- Patients previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy
- Patients with asymptomatic and previously treated/untreated BM eligible
- Prior BM therapy within 14 days of randomization prohibited





Endpoints:
- IC-ORR (CR+PR in brain) per BICR per RECIST v1.1
- IC-DoR per BICR
- CNS-PFS per BICR
- Safety and tolerability

- **The BM and non-BM pools were determined by BICR at baseline among all patients based on mandatory brain CT/MRI screening**

BICR, blinded independent central response; BM, brain metastasis; CNS, central nervous system; CR, complete response; CT, computed tomography; DB, DESTINY-Breast; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IC, intracranial; mBC, metastatic breast cancer; MRI, magnetic resonance imaging; ORR, objective response rate; PFS, progression-free survival; PR, partial response; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice (trastuzumab/capecitabine or lapatinib/capecitabine).

Data for patients in the 5.4 mg/kg T-DXd arms were pooled from the DB-01, DB-02, and DB-03 trials. Comparator data were pooled from the DB-02 and DB-03 trials. All three studies were conducted in unresectable/mBC; HER2 status was confirmed centrally; and a documented radiographic progression after most recent treatment was required.

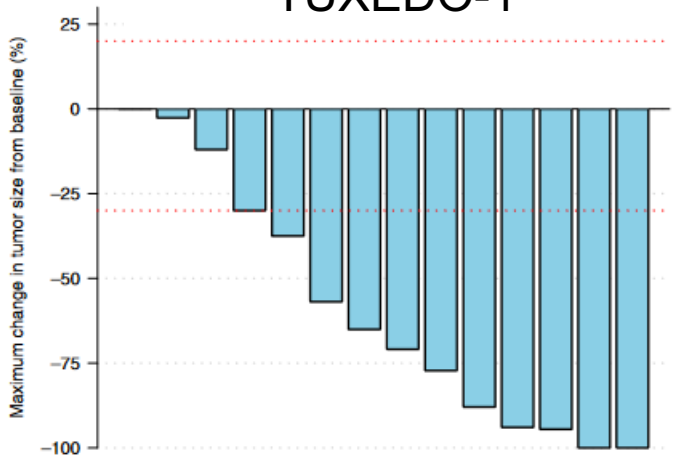
[a]The presence of BMs was not a stratification factor. [b]Data Cutoff: March 26, 2021. [c]Data Cutoff: June 30, 2022. [d]Data Cutoff: May 21, 2021. [e]5.4 mg/kg Q3W. [f]3.6 mg/kg Q3W.

1. Modi S et al. *N Engl J Med.* 2020; 382:610-621 [article and supplementary appendix]. 2. André F et al. *The Lancet.* 2023. https://doi.org/10.1016/S0140-6736(23)00725-0 [article and supplementary appendix]. 3. Cortes J et al. *N Engl J Med.* 2022; 368(12):1143-1154 [article and supplementary appendix].

Courtesy of Ian E Krop, MD, PhD

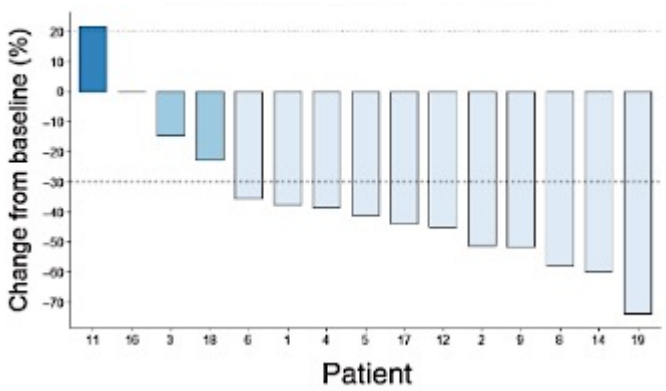
Small studies of T-DXd in patients with HER2+ progressive brain metastases

TUXEDO-1



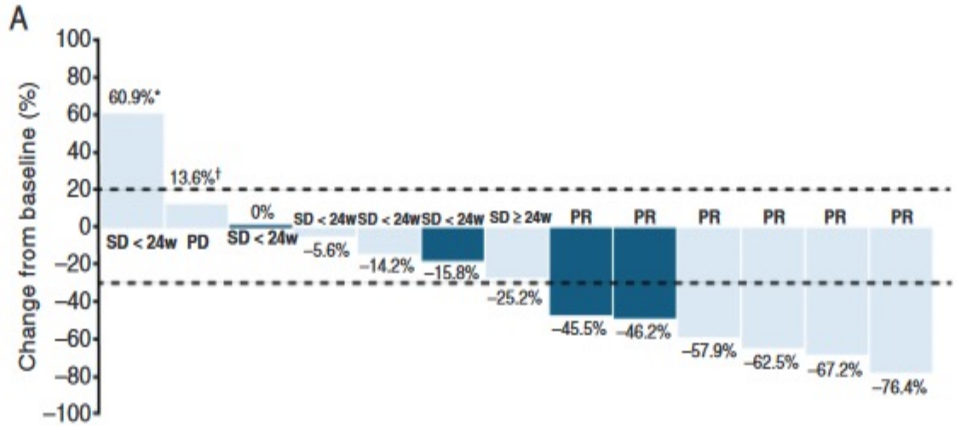
Intracranial RR: 73%
n=15

DFCI/MDACC/Duke case series



Intracranial RR: 73%
n=15

DEBBRAH trial



Intracranial RR: 50% (untreated/asymptomatic)
Intracranial RR: 44% (progressing)
n=4/9

Courtesy of Ian E Krop, MD, PhD

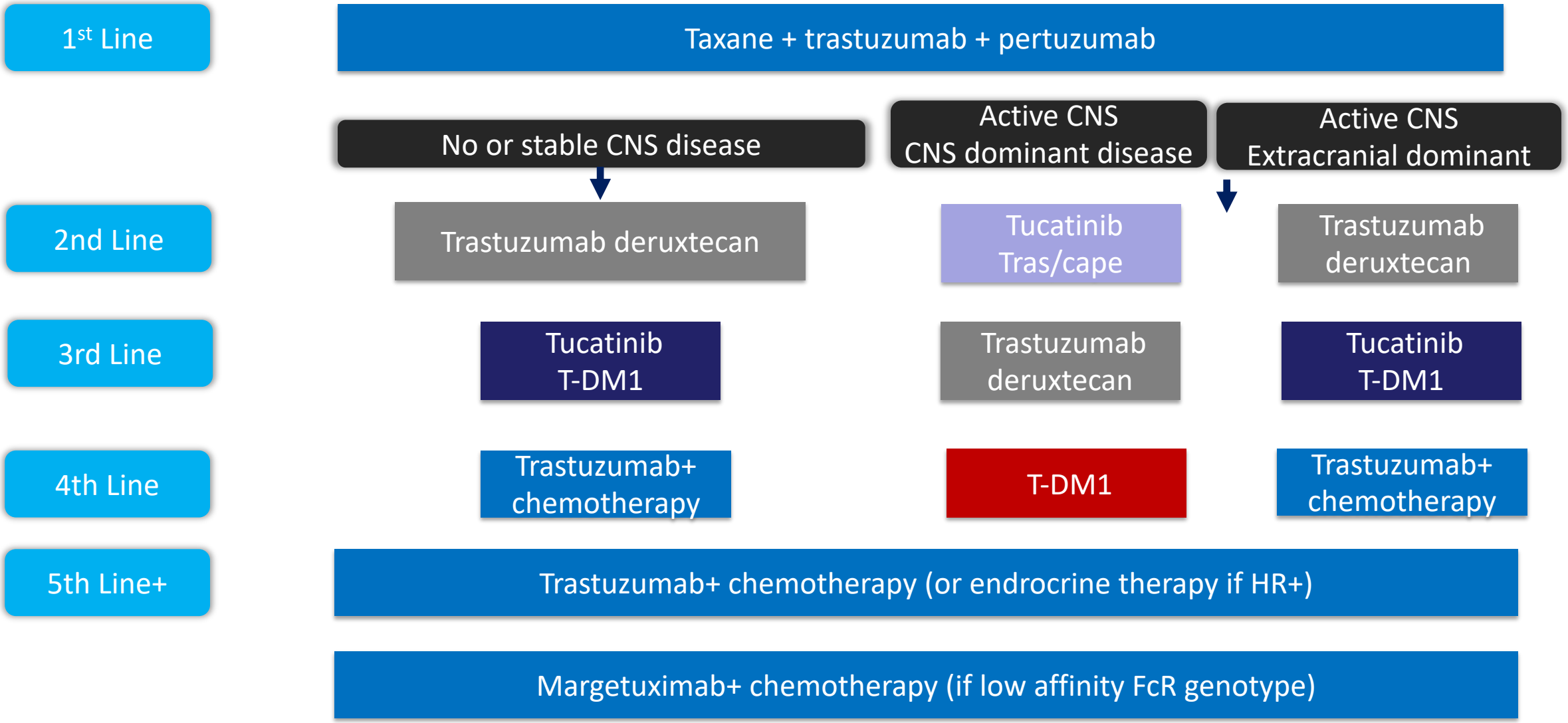
Bartsch R, et al. Nat Med. 28:1840. 2022
Kabraji S, et al. Clin Cancer Res. 29:174. 2023
Pérez-García et al. Neuro-Oncology 25:157. 2023

T-DXd CNS Studies Conclusions

- Pooled analysis of DB-01,-02,-03 show strong evidence of activity of T-DXd in patients with both stable and active brain mets
  - Most pts had previously untreated and asymptomatic brain mets
- Several additional studies (all small) of T-DXd also demonstrate intracranial activity of T-DXd in patients with progressive brain mets
- Together, these studies provide compelling evidence of intracranial activity of T-DXd

Courtesy of Ian E Krop, MD, PhD

Approach to Therapy for Metastatic HER2+ Disease



Courtesy of Ian E Krop, MD, PhD

Agenda

INTRODUCTION: Educating Non-Breast Cancer Specialty Oncologists About HER2-Targeted Therapies – ASCO Genitourinary Cancers Symposium 2024

MODULE 1: HER2-Positive Breast Cancer — Dr Krop

MODULE 2: Triple-Negative Breast Cancer — Dr Sharma

Neoadjuvant Chemoimmunotherapy

Triple-Negative Breast Cancer

- Schmid P et al. **Pembrolizumab** or placebo **plus chemotherapy followed by pembrolizumab** or placebo for **early-stage TNBC**: Updated EFS results from the phase III **KEYNOTE-522** study. ESMO 2023;Abstract LBA18.
- Gianni L et al. Event-free survival (EFS) analysis of **neoadjuvant taxane/carboplatin with or without atezolizumab followed by an adjuvant anthracycline regimen** in high-risk triple negative breast cancer (TNBC): **NeoTRIP Michelangelo** randomized study. ESMO 2023;Abstract LBA19.
- Ignatiadis M et al. **Adding atezolizumab to adjuvant chemotherapy** for stage II and III triple-negative breast cancer is unlikely to improve efficacy: Interim analysis of the **ALEXANDRA/IMpassion030** phase 3 trial. SABCS 2023;Abstract GS01-03.

Third Annual **National General Medical Oncology Summit**

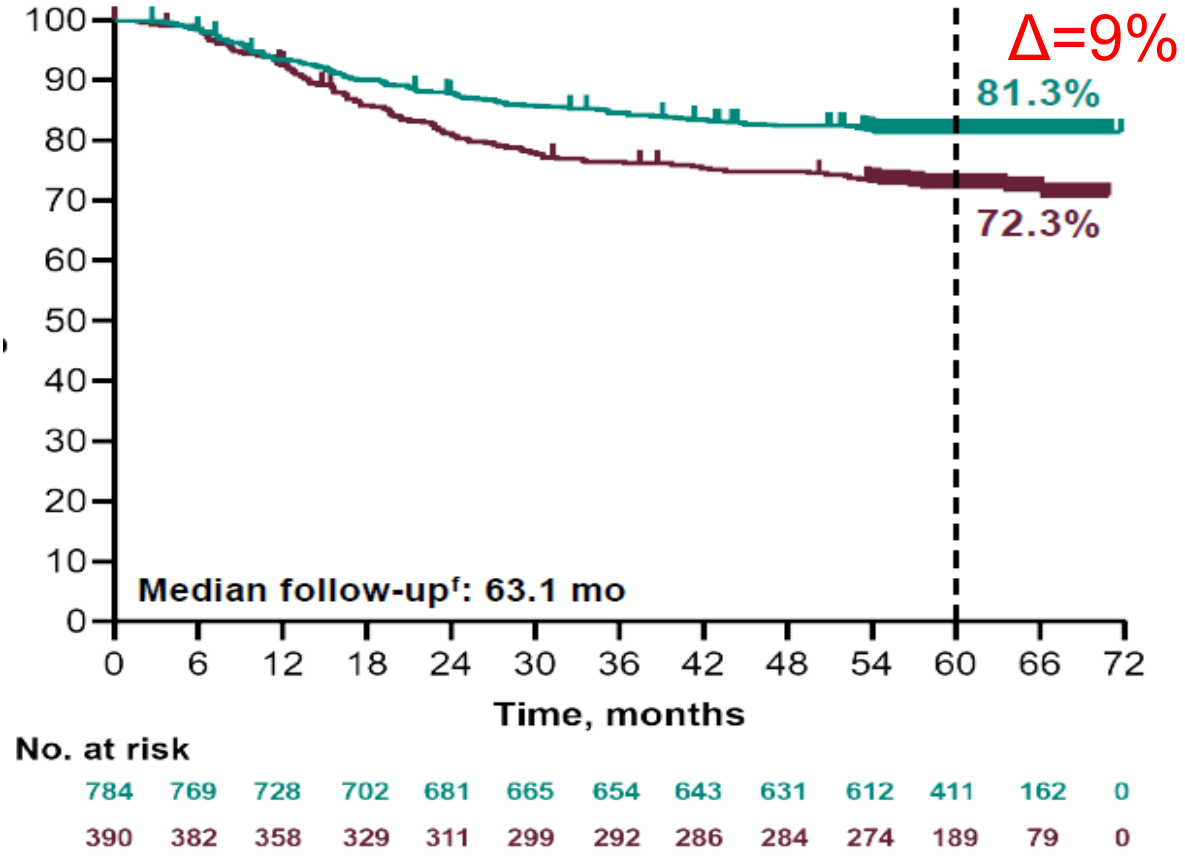
Friday, March 22, 2024 — 7:00 PM – 9:00 PM

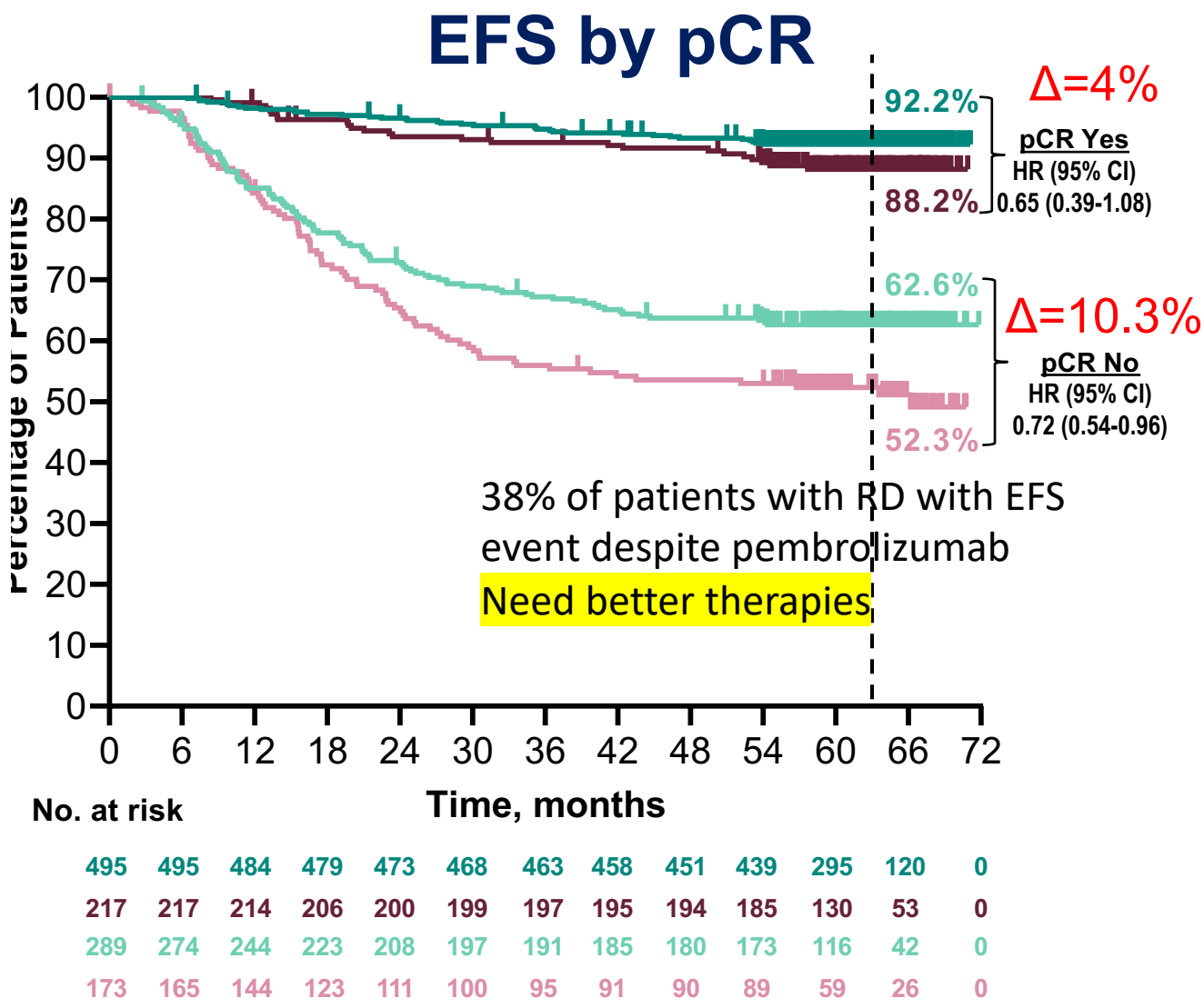
Keynote Session Special Feature: Clinicians with Cancer

How do you think a medical oncologist with localized TNBC would think through the choice and duration of chemotherapy to receive in combination with neoadjuvant pembrolizumab? How would they approach adjuvant therapy?

KEYNOTE-522: IA6

IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	





Data cutoff date: March 23, 2023.

Schmid et al ESMO 2023

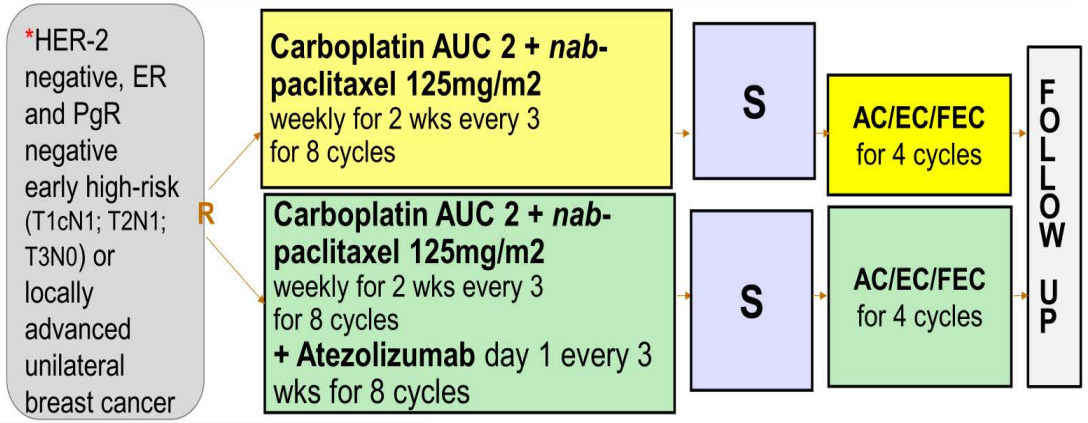
Courtesy of Priyanka Sharma, MD

KN-522: IA6 summary

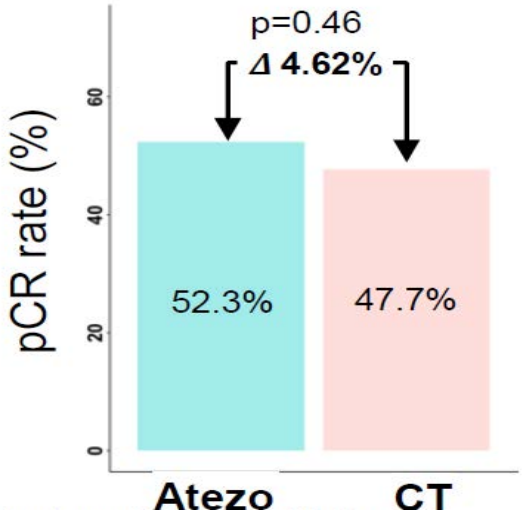
- After a median follow-up of >5 years, neoadjuvant pembro + chemo followed by adjuvant pembrolizumab continues to show a clinically meaningful improvement in EFS compared with neoadjuvant chemo alone
- The EFS benefit was generally consistent in subgroups based on TNM stage (II/III) and nodal status (+/-)
- Follow-up for OS is ongoing
- EFS improvement in pembrolizumab group was observed regardless of pCR outcome
  - ? Driven primarily by neoadjuvant pembrolizumab. ? What is the relative contribution of adjuvant pembrolizumab
- pCR/RD: locally assessed. ? Reliability of local assessment of pCR in an international trial

Courtesy of Priyanka Sharma, MD

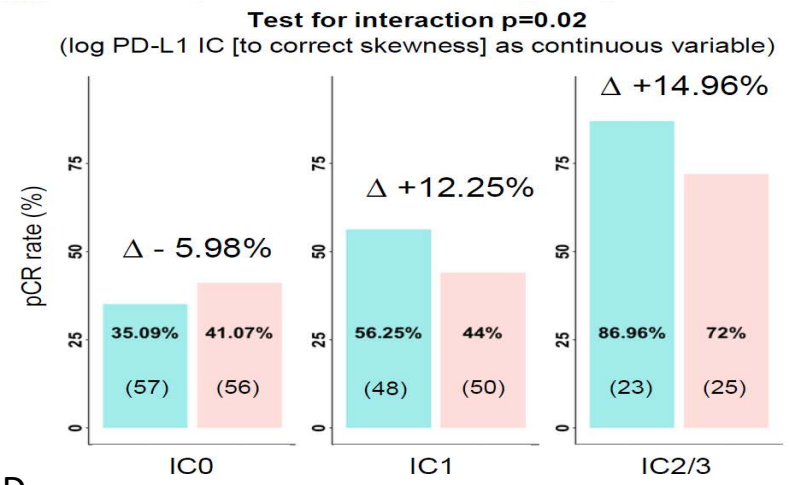
NeoTRIPaPDL1: Atezolizumab plus weekly Carboplatin + Nab-paclitaxel



No adjuvant ICB

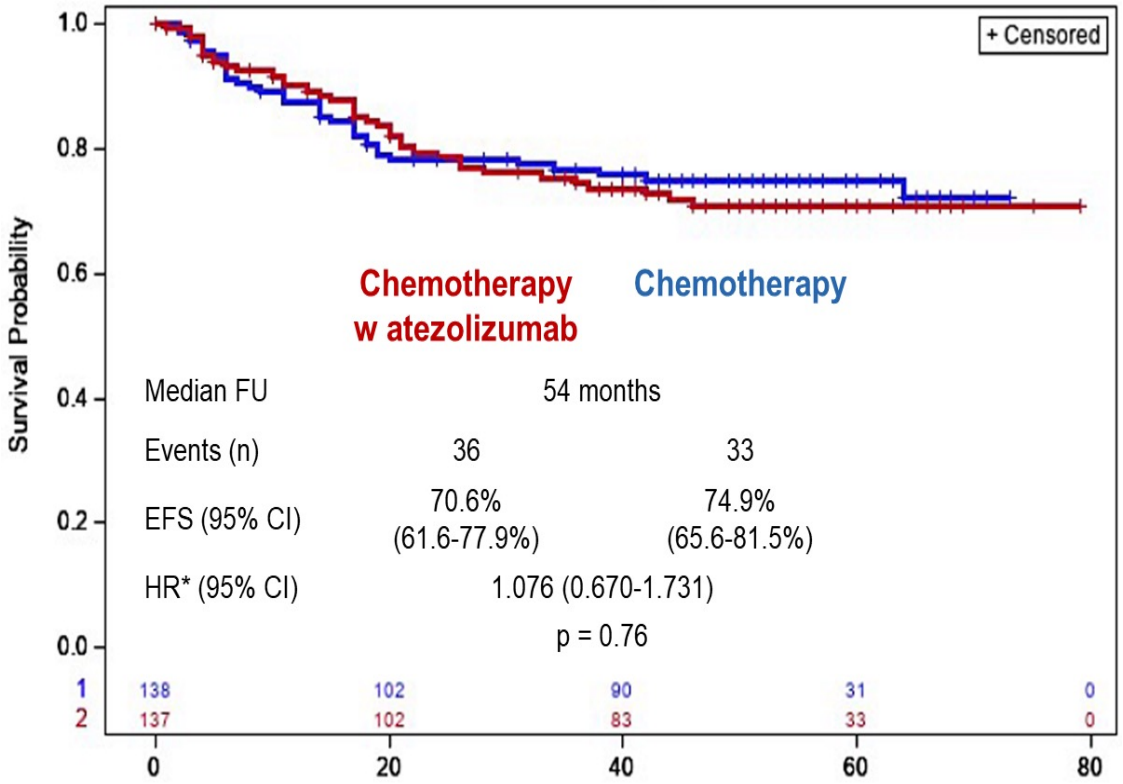


PD-L1 status and pCR



Courtesy of Priyanka Sharma, MD

EFS



pCR, positive PD-L1, earlier stage as well as higher sTILs were all prognostic and linked to better EFS, but they were not predictive of atezolizumab benefit

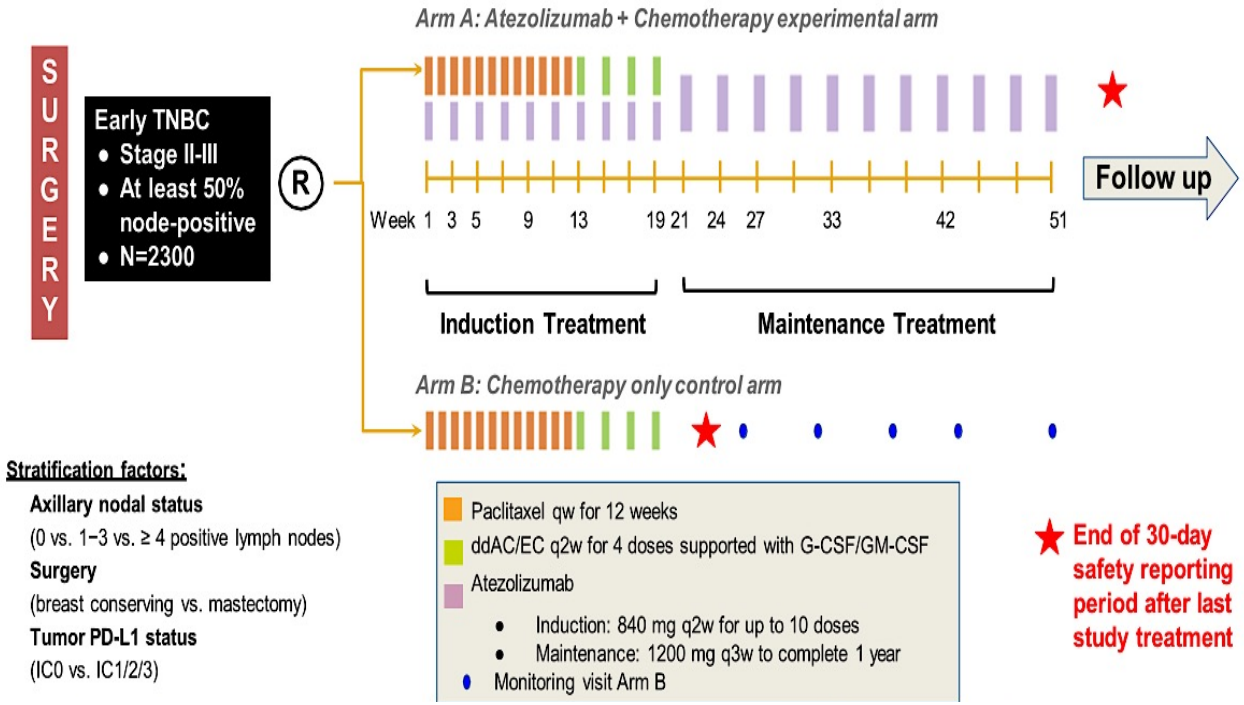
Gianni et al Annal Oncol 2022, Gianni et al ESMO 2023

Why no pCR or EFS Benefit in NeoTRIPaPDL1?

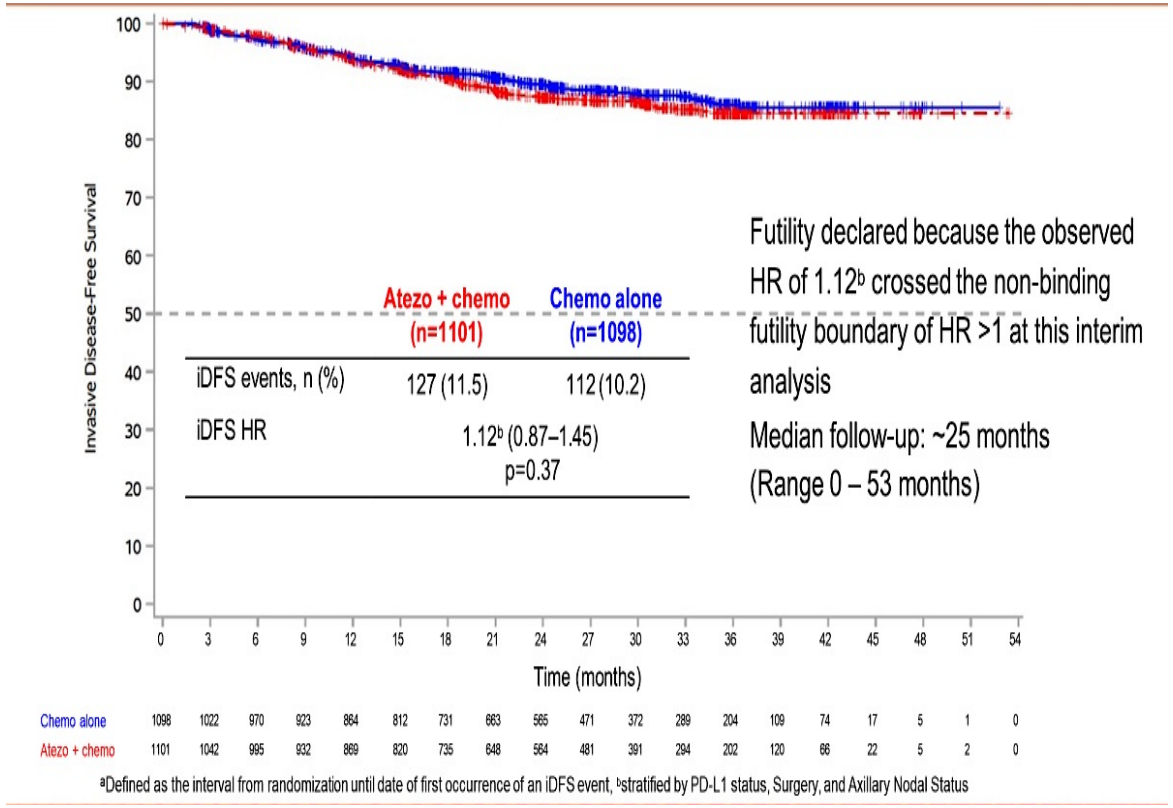
- PDL-1 vs PD-1 inhibitor
  - IMpassion031: pCR better, EFS numerically better with atezolizumab
  - mTNBC: Atezo plus taxane not statistically superior to taxane (IMpassion130, 131)
- Chemotherapy backbone: no anthracycline
- Anatomic risk of enrolled population:
  - 90% with node positive disease (compared to 30% in IMpassion031)
  - With high anatomical risk would efficacy be more in line with what is observed in mTNBC?
- Differences in tumour biology: Higher TILs in chemo alone arm giving the control arm inherent better prognosis compared to IO arm
- Chance

Courtesy of Priyanka Sharma, MD

ALEXANDRA/IMpassion030 phase 3 trial : Adjuvant IO (without neoadjuvant component)



iDFS: Primary End Point

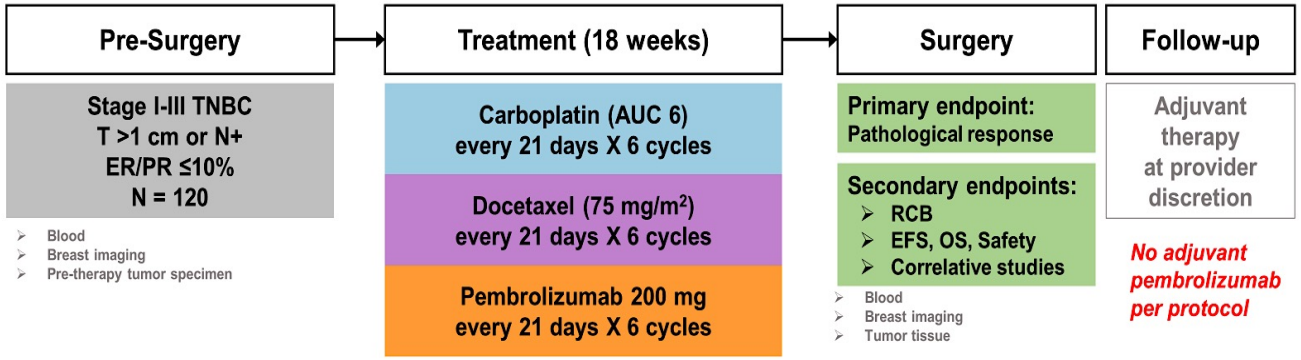


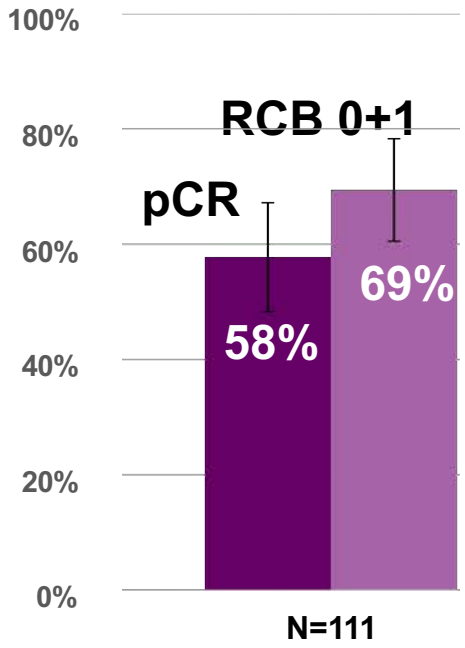
Timing of IO matters: Neoadjuvant more effective than adjuvant IO
Previous Animal data consistent with clinical findings (Liu et al Cancer Discover 2015)
Similar observations in other cancer like Melanoma

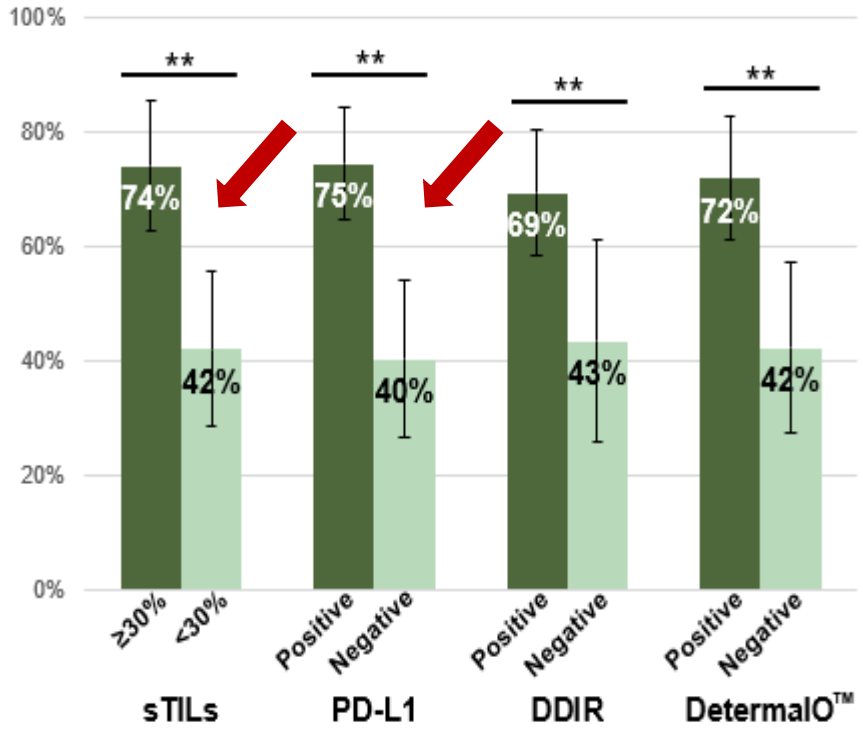
Courtesy of Priyanka Sharma, MD

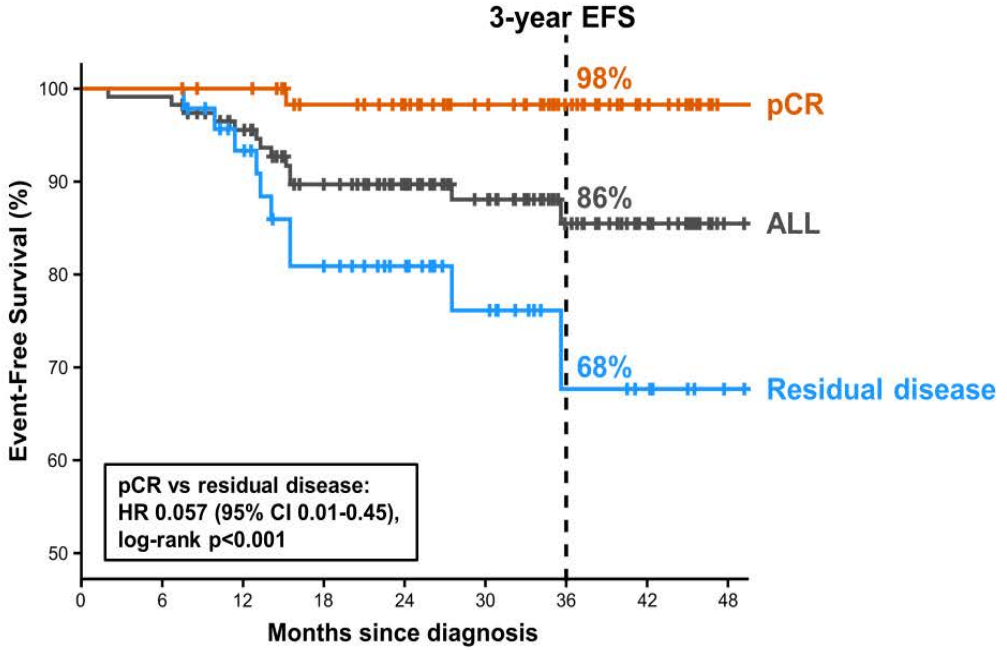
Ignatiadis SABCS 2023

NeoPACT: Carboplatin + Docetaxel+ Pembrolizumab









Provide data on an alternative anthracycline-free chemoimmunotherapy regimen for patients who are not eligible/wish to avoid anthracycline-based regimens and support further evaluation of this regimen as a chemotherapy de-escalation strategy in randomized studies (On going SWOG 2212 trial)

Immune enrichment assessed by sTILs, PD-L1 or IO response signature was noted in almost 50% of patients and was associated with high pCR rates exceeding 70%.

Sharma et al JAMA Oncology 2023

Courtesy of Priyanka Sharma, MD

irAE: KN-522 real world toxicity

Real World data

N=577 (17 sites), 18.2% Blacks

Adverse drug events(ADE) causing dose reduction	37.6%
ADE leading to early discontinuation	39.5%
irAE, all grades	71%
irAE ≥ 3	**33.5%**

	Blacks	Whites	p
pCR	52.3%	55.9%	0.6
≥ 3 irAE	20.9%	33.8%	0.01
Hospitalization rate	39%	36%	0.5

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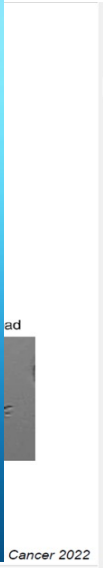


Hofherr et al SABCS 2023, Jacob et al SABCS 2023

Courtesy of Priyanka Sharma, MD

Chemoimmunotherapy for mTNBC

Triple-Negative Breast Cancer

- Rugo HS et al. **KEYNOTE-355**: Outcomes in **patients who discontinued chemotherapy before pembrolizumab**and in **patients with immune-mediated AEs**. ESMO Breast 2023;Abstract 191M0.
- Jiang Z et al. **TORCHLIGHT:** A randomized, double-blind, phase III trial of **toripalimab** versus placebo, **in combination with nab-paclitaxel (nab-P)** for patients with metastatic or recurrent triple-negative breast cancer (TNBC). ASCO 2023;Abstract LBA1013.

KEYNOTE-355: Outcomes in Patients Who Discontinued Chemotherapy Before Pembrolizumab and in Patients With Immune Mediated AEs

- KEYNOTE-355 (NCT02819518): phase 3, randomized, double-blind study of pembrolizumab 200 mg Q3W plus chemotherapy[a] vs placebo plus chemotherapy[a] for previously untreated, locally recurrent inoperable or metastatic TNBC

	PD-L1 CPS ≥10		PD-L1 CPS ≥1[b]		ITT[c]	
	Pembro + Chemo	Placebo + Chemo	Pembro + Chemo	Placebo + Chemo	Pembro + Chemo	Placebo + Chemo
Median OS, mo[1]	23.0	16.1	17.6	16.0	17.2	15.5
HR (95% CI)	0.73 (0.55–0.95) One-sided $P = 0.0093$[d,2]		0.86 (0.72–1.04)		0.89 (0.76–1.05)	
Median PFS, mo[3]	9.7	5.6	7.6	5.6	7.5	5.6
HR (95% CI)	0.65 (0.49–0.86) One-sided $P = 0.0012$		0.74 (0.61–0.90)		0.82 (0.69–0.97)	

PFS and OS in Patients treated with pembro+ chemo with or without irAE

Analysis Population	N	Median Pembro Treatment Duration (range), mo	Median Chemo Treatment Duration (range), mo	Median (95% CI) PFS[b], mo	Median (95% CI) OS[b], mo
All patients as treated					
Patients who had immune-mediated AEs	149	8.8 (0.0–29.0)	7.2 (0.3–41.7)	9.7 (8.0–11.6)	23.9 (20.6–28.6)
All	562	5.6 (0.0–32.2)	5.1 (0.0–48.8)	7.5 (6.3-7.7)	17.2 (15.3–19.0)
PD-L1 CPS ≥1					
Patients who had immune-mediated AEs	109	8.8 (0.7–29.0)	7.3 (1.0–34.8)	9.8 (8.0–16.5)	26.3 (21.2–32.7)
All	421	5.9 (0.0-32.2)	5.1 (0.0-48.8)	7.6 (6.6-8.0)	17.6 (15.5–19.5)
PD-L1 CPS ≥10					
Patients who had immune-mediated AEs	64	10.4 (0.8–29.0)	8.4 (2.3–34.8)	11.8 (9.5–NR)	35.6 (26.3–NR)
All	219	7.6 (0.0-32.2)	5.8 (0.0-45.8)	9.7 (7.6-11.3)	22.8 (18.8–26.2)

30% of patients with irAE

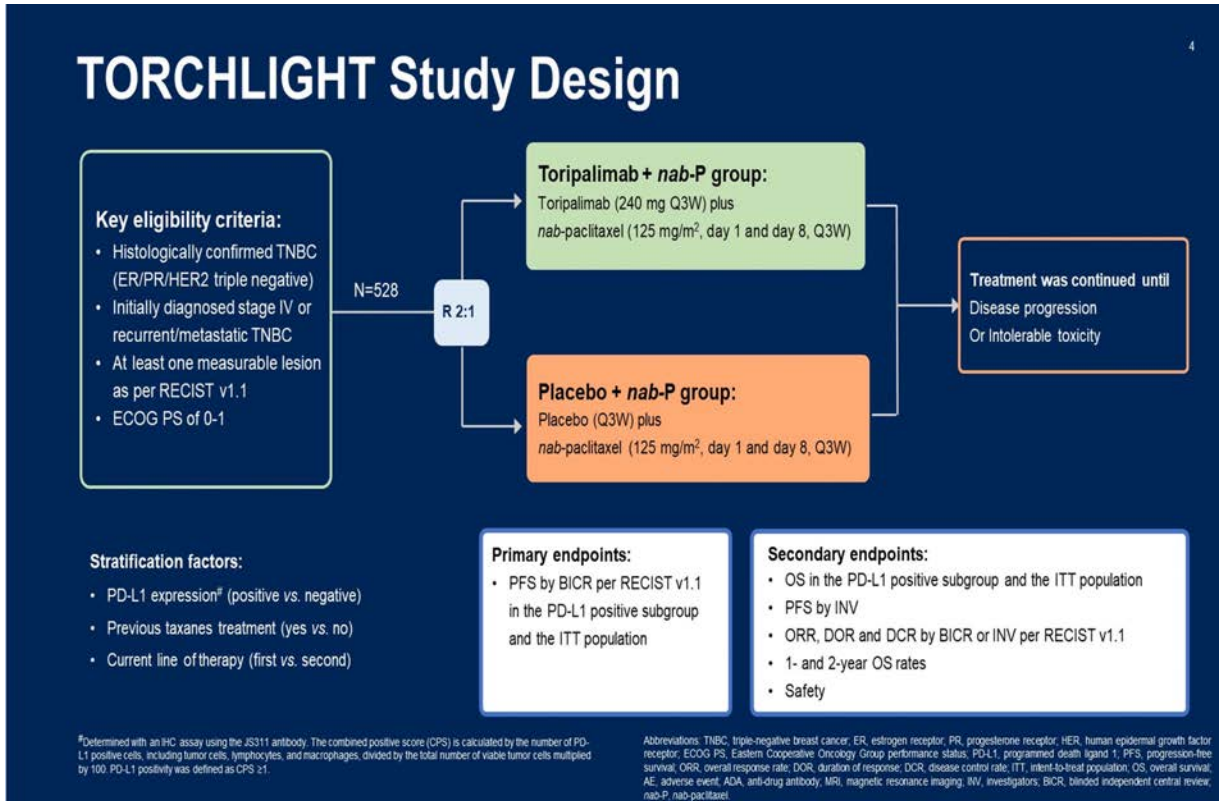
[a]Only treated patients in the part 2 pembrolizumab plus chemotherapy group were analyzed. [b]Per Kaplan-Meier method.
Data cutoff date: June 15, 2021.

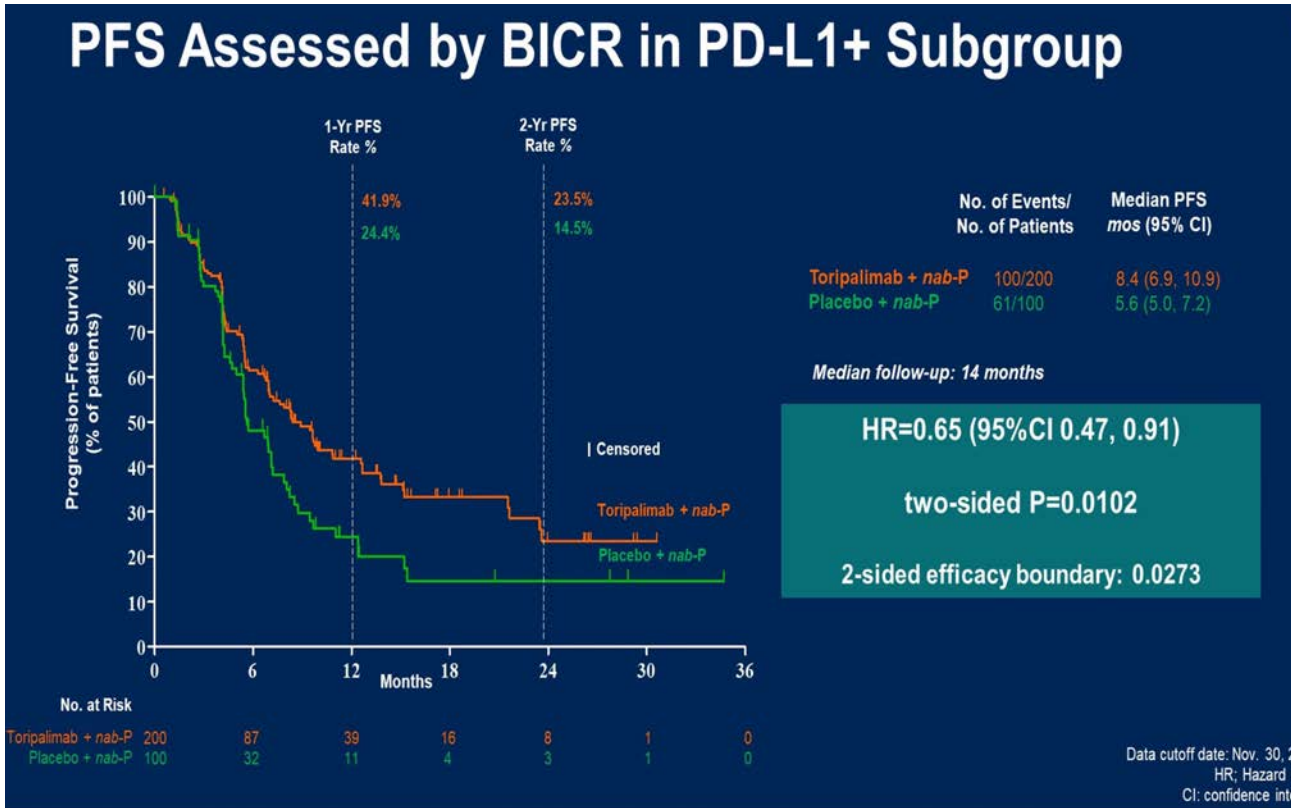
Exploratory analyses to evaluate efficacy in patients who:
–Had disease control and discontinued chemotherapy before pembrolizumab
–Experienced immune-mediated AEs

Rugo et al ESMO 2023

Courtesy of Priyanka Sharma, MD

TORCHLIGHT: A randomized, double-blind, phase III trial of toripalimab versus placebo, in combination with nab-paclitaxel (nab-P) for patients with metastatic or recurrent triple-negative breast cancer (TNBC). ASCO 2023;Abstract LBA1013





N=531, Toripalimab:PD1 antibody

-PDL1 assay (CPS, JS311 antibody): CPS > 1 considered PDL1+ve, **56% PDL1+ve**

-Data presented: prespecified IA of PFS in PDL1+ population and ITT

-93% first line, 28-31% de-novo metastatic, Prior taxane in only 15%

Median PFS 8.4 vs 5.6 months, HR 0.65

Liu et al ASCO 2023

Courtesy of Priyanka Sharma, MD

TORCHLIGHT: Summary

- At IA 1 PFS prolonged with addition of toripalimab to nab-paclitaxel in PDL1+ population
  - HR and Median PFS very similar to KN355
- PFS in ITT did not meet the prespecified hierarchal testing boundary at IA 1
- OS data is immature, Follow up ongoing
- PDL1 testing by yet another assay and threshold
- Enrollment only in China: ? approval path for other countries/regions
- Limited toxicity data provided

Courtesy of Priyanka Sharma, MD

PARP Inhibitors

Triple-Negative Breast Cancer

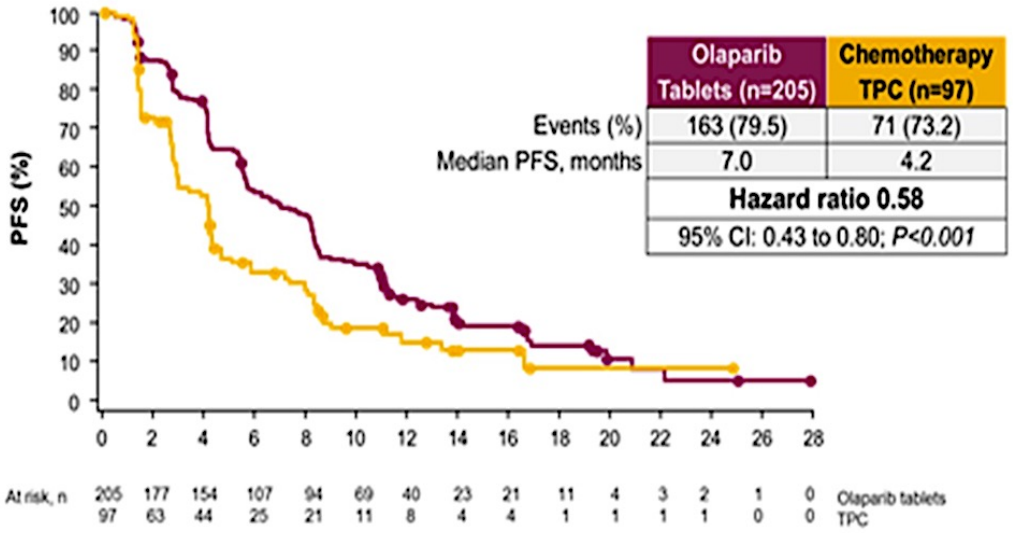
- Robson ME et al. **OlympiAD** extended follow-up for overall survival and safety: **Olaparib** versus chemotherapy treatment of physician's choice in **patients with a germline BRCA mutation** and HER2-negative metastatic breast cancer. *Eur J Cancer* 2023;184:39-47.

OlympiAD: Extended follow-up for overall survival and safety

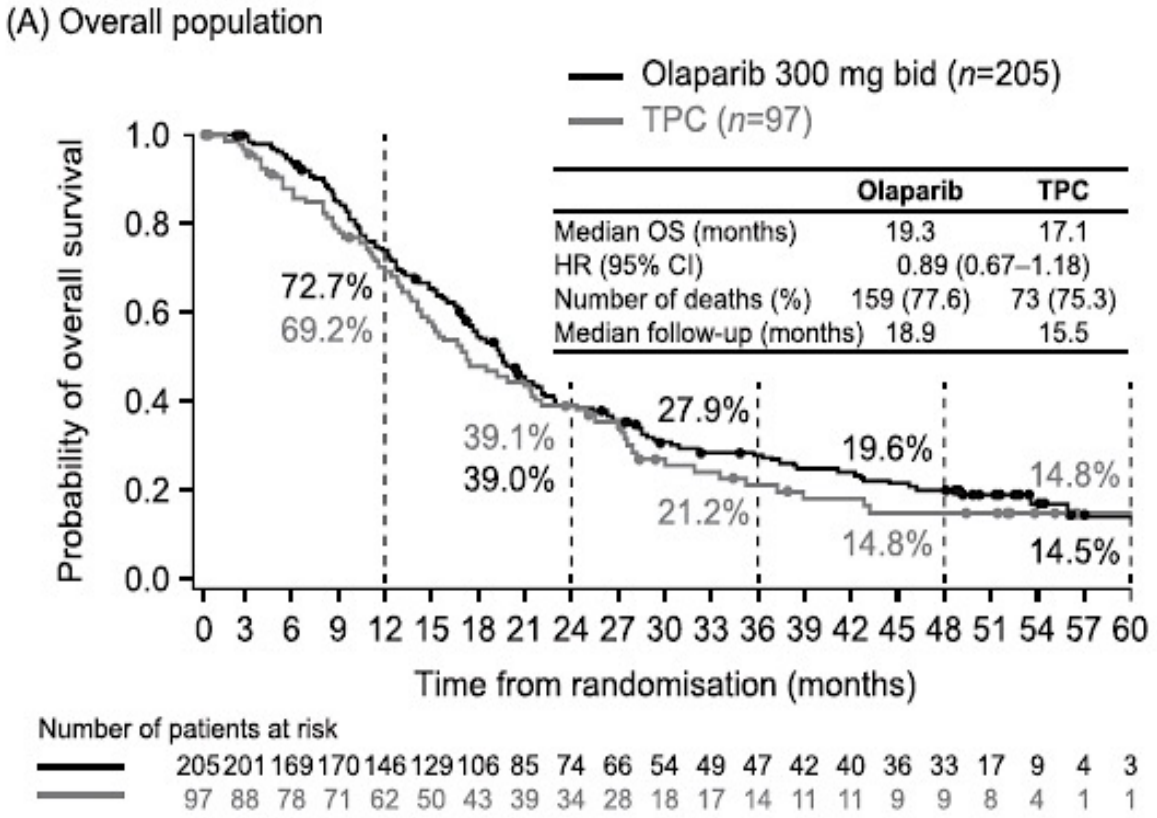
- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious g*BRCA*m
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

Olaparib
300 mg tablets bd

Chemotherapy treatment of physician's choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine



	Olaparib Tablets (n=205)	Chemotherapy TPC (n=97)
Events (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
Hazard ratio 0.58		
95% CI: 0.43 to 0.80; *P*<0.001		



	Olaparib	TPC
Median OS (months)	19.3	17.1
HR (95% CI)	0.89 (0.67–1.18)	
Number of deaths (%)	159 (77.6)	73 (75.3)
Median follow-up (months)	18.9	15.5

Median follow-up: 25.7 months longer than that previously reported for OS and safety

Median OS: Olaparib (19.3 months) vs TPC (17.1 months)
HR 0.90 (0.66 1.23)

Courtesy of Priyanka Sharma, MD

Robson et al European Journal of Cancer 184 (2023) 39e47

PARPi for MBC

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

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)

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	PD-L1 CPS ≥10[g] regardless of germline *BRCA* mutation status[b]	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[h] (Category 1, preferred)
	PD-L1 CPS <10[g] and no germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	PD-L1 CPS <10[g] and germline *BRCA1/2* mutation[b]	• PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan[i] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
	No germline *BRCA1/2* mutation[b] and HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)
	Any	Systemic chemotherapy see BINV-Q (5)

Courtesy of Priyanka Sharma, MD

Antibody-Drug Conjugates – Part 1

Triple-Negative Breast Cancer

- Bar Y et al. **Dynamic HER2-low status** among patients with triple negative breast cancer (TNBC): The impact of **repeat biopsies.** ASCO 2023;Abstract 1005.
- Modi S et al. **Trastuzumab deruxtecan** (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with **HER2-low** unresectable and/or metastatic breast cancer (mBC): Updated survival results of the randomized, phase III **DESTINY-Breast04** study. ESMO 2023;Abstract 376O.
- 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;178:23-33.

Third Annual **National General Medical Oncology Summit**

Friday, March 22, 2024 — 7:00 PM – 9:00 PM

Keynote Session Special Feature: Clinicians with Cancer

How do you think a medical oncologist with metastatic breast cancer would feel about enrolling on a clinical trial of a novel agent or strategy, such as an antibody-drug conjugate, after exhausting all available treatment options?

DB-04: Updated OS and safety

DESTINY-Breast04 Study Design:

An open-label, multicenter study (NCT03734029)[1-3]

Patients[a]
- HER2-low (IHC 1+ or IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

- **T-DXd** 5.4 mg/kg Q3W (n = 373)
- **TPC** Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c] (n = 184)

Stratification factors
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

Primary endpoint
- PFS by BICR (HR+)

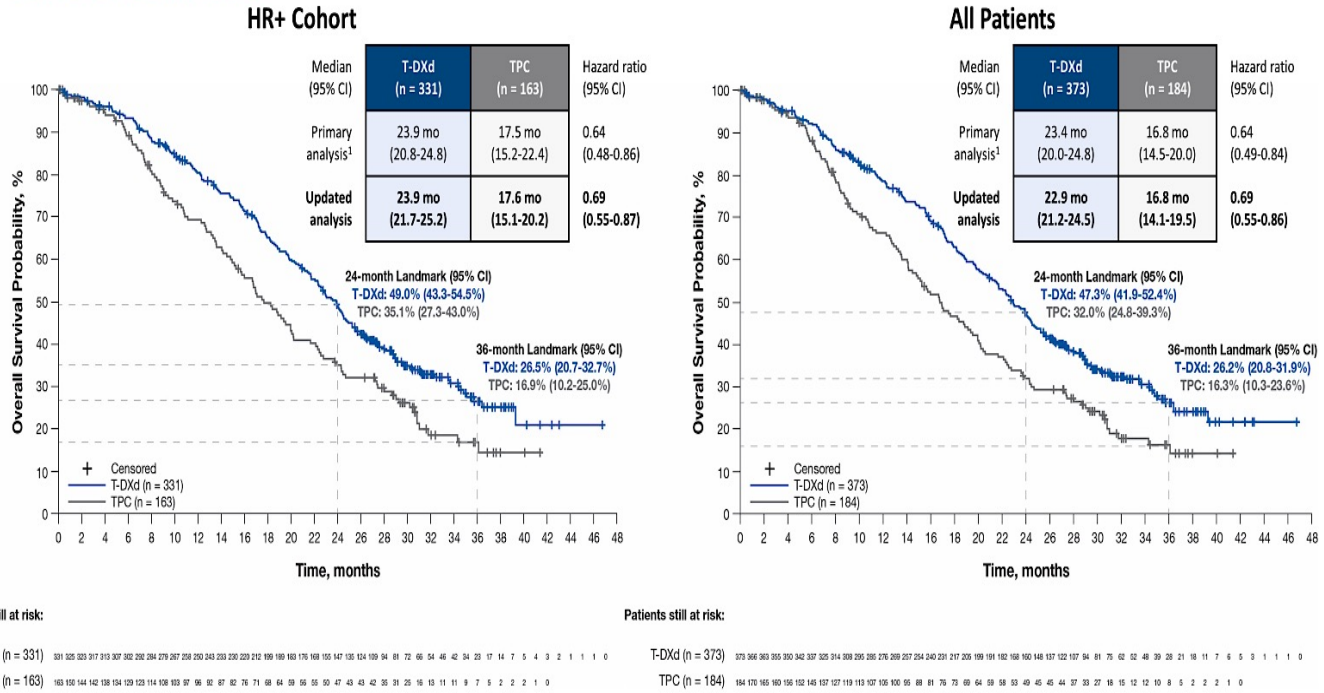
Key secondary endpoints[d]
- PFS by BICR (all patients)
- **OS (HR+ and all patients)**

Secondary endpoints[d]
- **PFS by investigator**
- ORR by BICR and investigator
- DOR by BICR
- **Safety**
- Patient-reported outcomes (HR+)[e]

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

The median follow-up was 18.4 months at initial reporting

Overall Survival



There were no new cases of ILD/pneumonitis since the primary analysis (data cutoff, January 11, 2022)

In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis, showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

Modi et ESMO 2023

Courtesy of Priyanka Sharma, MD

Impact of repeat biopsies on HER2-low status among patients with TNBC

789 pts in the institutional TN database (2000-2022)

Overall study population:
512 pts with TNBC at diagnosis and at least one Bx with known HER2 status

Characteristics, no. (%)	TNBC cohort N=512
Age, median (range)	52 (25-97)
Age groups	
≤ 50	238 (46%)
> 50	274 (54%)
Self reported race	
White	423 (83%)
Black/African American	34 (7%)
Asian	25 (5%)
Hispanic	14 (3%)
Other	8 (2%)
Not reported	8 (2%)
Stage at Dx	
1	145 (28%)
2	247 (48%)
3	74 (14%)
4	43 (8%)
Unknown	3 (1%)

Characteristics, no. (%)	TNBC cohort N=512
ER status	
Negative (<1%)	447 (87%)
Low (1-10%)	65 (13%)
NA therapy, no.	
Yes	278 (54%)
No	238 (45%)
Unknown	4 (1%)
Total no. of Bxs per pt	
1	194 (38%)
2	233 (45%)
3	48 (9%)
4	29 (6%)
≥ 5	8 (2%)

Retrospective study

Bar Y et al ASCO 2023, Abstract # 1005

Courtesy of Priyanka Sharma, MD

Health-related quality of life in the phase III ASCENT trial of sacituzumab govitecan versus TPC in metastatic TNBC

- HRQoL was assessed on day 1 of each treatment cycle using the EORTC QLQ-C30. Score changes from baseline were analysed using linear mixed-effect models for repeated measures. Stratified Cox regressions evaluated time to first clinically meaningful change of HRQoL.
  - Data collected up to C6D1
  - The analysis population comprised 236 patients randomized to SG and 183 to TPC.
- SG > TPS: global health status (GHS)/QoL, physical functioning, fatigue, and pain
- TPC> SG : nausea/vomiting and diarrhea
- SG arm had a significantly better QLQ-C30 summary score Least-Square (LS) mean change from baseline than TPC arm.
- Median TTW of GHS/QoL was similar in both treatment arms (14.1 weeks for SG and 15.1 weeks for TPC; HR Z 0.87, 95% CI 0.70 to 1.07; P Z 0.18)
- Median time to first clinically meaningful worsening was longer for SG than for TPC for physical functioning (22.1 versus 12.1 weeks, $P < 0.001$), role functioning (11.4 versus 7.1 weeks, $P < 0.001$), fatigue (7.7 versus 6.0 weeks, $P < 0.05$), and pain (21.6 versus 9.9 weeks, $P < 0.001$).
- SG prolongs progression-free survival and overall survival in patients with refractory/relapsed metastatic TNBC.
  - SG generally associated with greater improvements and delayed worsening of HRQoL scores compared with TPC supporting its use for patients with mTNBC over TPC

Loibl et al Eur J of Cancer 2023

Courtesy of Priyanka Sharma, MD

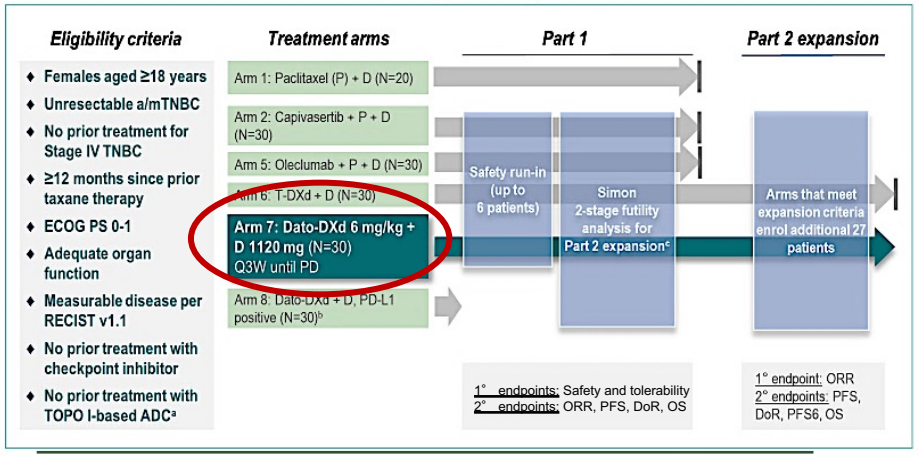
Antibody-Drug Conjugates – Part 2

Triple-Negative Breast Cancer

- 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 Ib/II study. ESMO 2023;Abstract 379MO.
- Krop IE et al. **Patritumab deruxtecan** (HER3-DXd), a human epidermal growth factor receptor 3-directed antibody-drug conjugate, in patients with **previously treated human epidermal growth factor receptor 3-expressing metastatic breast cancer**: A multicenter, phase I/II trial. *J Clin Oncol* 2023;41(36):5550-60.
- Zhang J et al. First-in-human/phase I trial of **HS-20089, a B7-H4 ADC,** in patients with advanced solid tumors. ESMO 2023;Abstract 381O.

Datopotamab deruxtecan (Dato-DXd) + durvalumab as first-line treatment for unresectable locally advanced/metastatic TNBC: Updated Arm 7 results from phase Ib/II BEGONIA study

Study Design



Characteristic	Dato-DXd + D N=62
Age, median (range), years	53 (31–74)
No prior treatment, n (%)	26 (42)
Prior treatments for early-stage disease, n (%)	
Radiotherapy	30 (48)
Cytotoxic chemotherapy	33 (53)
Taxane	26 (42)
Anthracycline	29 (47)
Platinum compound	9 (15)
Hormonal therapy	10 (16)
Targeted therapy	1 (2)
Visceral metastases,[c] n (%)	37 (60)
Lymph node metastases, n (%)	42 (68)
PD-L1 expression,[d] n (%)	
High (TAP ≥10%)	7 (11)
Low (TAP <10%)	54 (87)
Unknown/Missing	1 (2)

Schmid P et al ESMO 2023, Abstract # 379MO

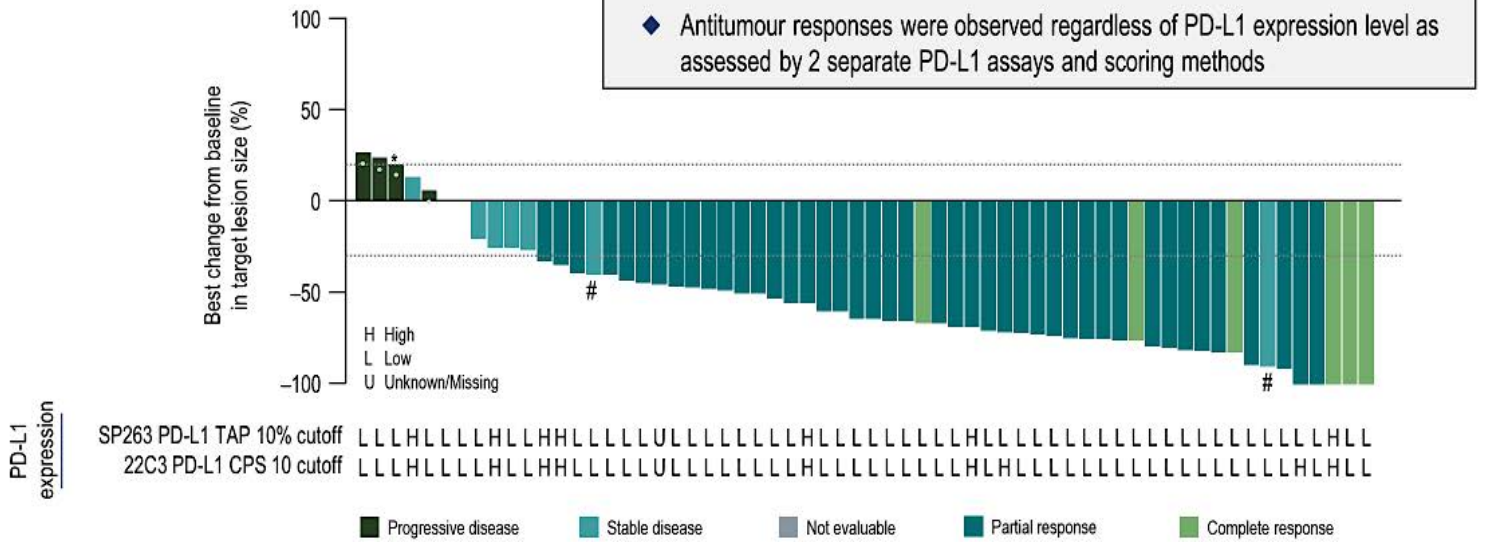
MADRID 2023 ESMO congress

BEGONIA Arm 7: Dato-DXd + Durvalumab

Antitumour Responses in 1L a/mTNBC

Confirmed ORR was 79% (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods



Dotted lines indicate thresholds for partial response (–30%) and progressive disease (20%). PD-L1 expression was assessed by 1) immunohistochemistry using the VENTANA PD-L1 (SP263) Assay with expression defined as the percentage of the tumour area populated by tumour or immune cells with membranous staining (TAP), or 2) immunohistochemistry using the 22C3 antibody with expression defined as the number of PD-L1–staining tumour cells, lymphocytes, and macrophages, divided by the total number of viable tumour cells, multiplied by 100 (CPS). *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 PD as best overall response. #Unconfirmed response.

1L, first line; a/m TNBC, advanced/metastatic triple–negative breast cancer; CI, confidence interval; CPS, combined positive score; CR, complete response; Dato-DXd, datopotamab deruxtecan; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PR, partial response; TAP, tumour area positivity.

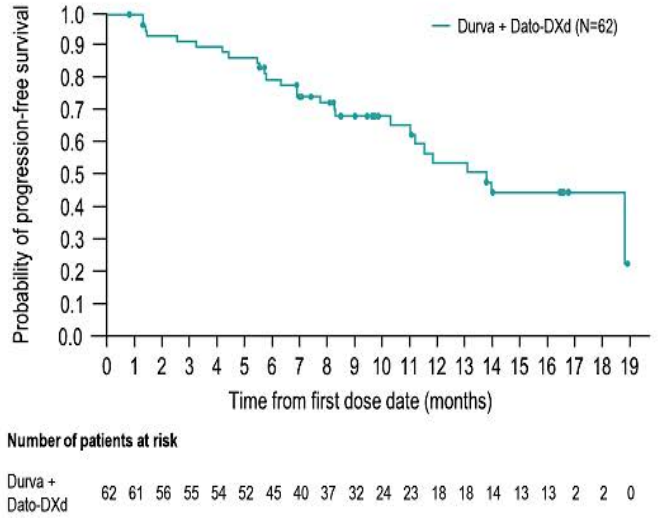
Data cutoff: 02 Feb 2023

Courtesy of Priyanka Sharma, MD

BEGONIA: Durvalumab plus Dato-DXd

Progression-Free Survival and Duration of Response

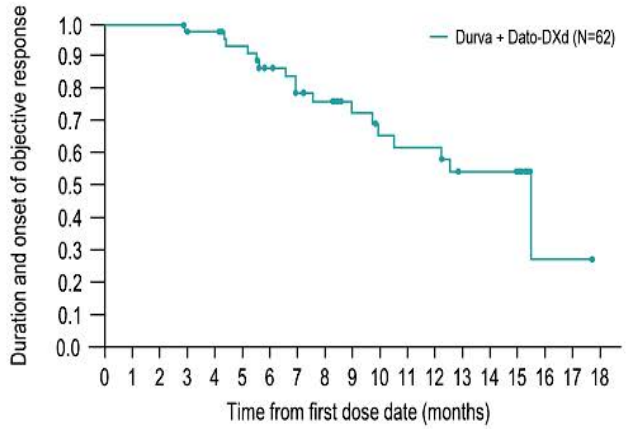
Median PFS was 13.8 months (95% CI, 11.0–NC)



Number of patients at risk

Durva + Dato-DXd	62	61	56	55	54	52	45	40	37	32	24	23	18	18	14	13	13	2	2	0

Median DoR was 15.5 months (95% CI, 9.92–NC)



Number of patients at risk

Durva + Dato-DXd	49	49	49	47	46	42	35	30	28	21	18	17	17	13	13	12	1	1	0

- The most common AEs were gastrointestinal
- Stomatitis was the most common AE leading to Dato-DXd dose reduction (11 patients)
- There were 3 (5%) adjudicated treatment-related ILD/pneumonitis events (2 grade=2, 1 grade=1)
- The most frequent AESIs were for stomatitis (65%), rash (32%), dry eye (21%), hypothyroidism (14.5%), and keratitis (14.5%)

Courtesy of Priyanka Sharma, MD

Safety

Patients, n (%)	Dato-DXd + D N=62
Any AEs	62 (100)
Grade 3/4	35 (57)
Any treatment-related AEs[a]	62 (100)
Grade 3/4	27 (44)
Any serious AEs	14 (23)
Treatment-related	6 (10)
AEs leading to discontinuation of any treatments	10 (16)
AEs leading to death[b]	1 (2)
Dose adjustments	
Dato-DXd dose reduction	**18 (29)**
Dato-DXd dose delay	**28 (45)**
Durvalumab dose delay	**31 (50)**

Most frequently reported adverse events (≥15%) (N=62)

AE preferred term	Any grade, n (%)	Grade 3/4, n (%)
Nausea	40 (65)	0
Stomatitis	40 (65)	7 (11)
Alopecia	31 (50)	0
Constipation	29 (47)	1 (2)
Fatigue	28 (45)	1 (2)
Rash	20 (32)	0
Vomiting	16 (26)	1 (2)
Amylase increased	13 (21)	11 (18)
COVID-19	13 (21)	0
Dry eye	13 (21)	0
Decreased appetite	12 (19)	1 (2)
Pruritus	10 (16)	0
Cough	10 (16)	0

ADC plus IO combination in TNBC

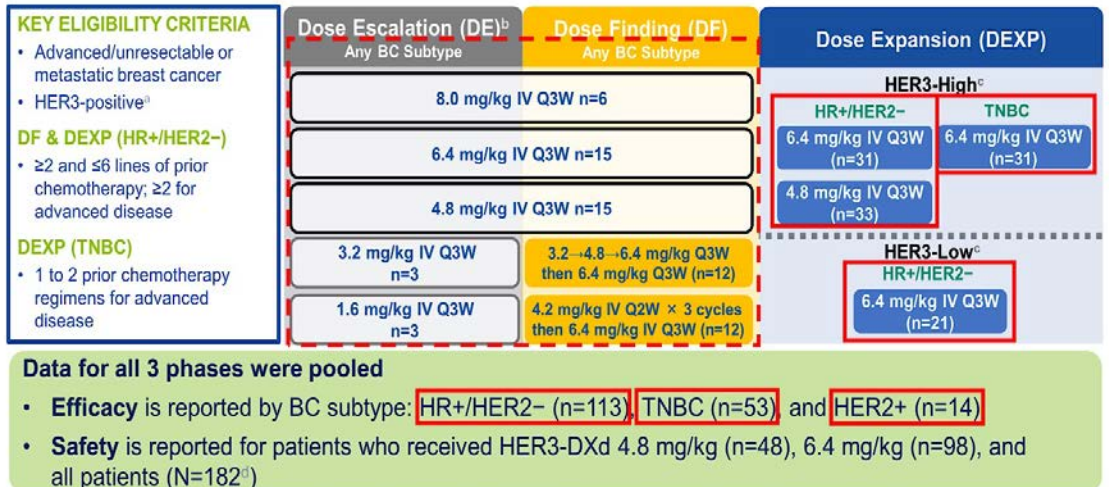
- Combination of Dato-DXd plus Durva yielded robust activity in first line setting
  - Only 50% had prior chemotherapy for early-stage disease
  - Single arm design prohibits assessment of combination vs Dato-DXd monotherapy efficacy
    - Data-DXd monotherapy ORR in much heavily pre-treated patient population (TROPION-PanTumor01, Median of 3 prior lines of therapy): 33%
- Ocular toxicity: pretreatment ophthalmology evaluation required
- Stomatitis: Prophylactic management with steroid mouth wash

On-going Phase III trials of ADC plus IO in TNBC

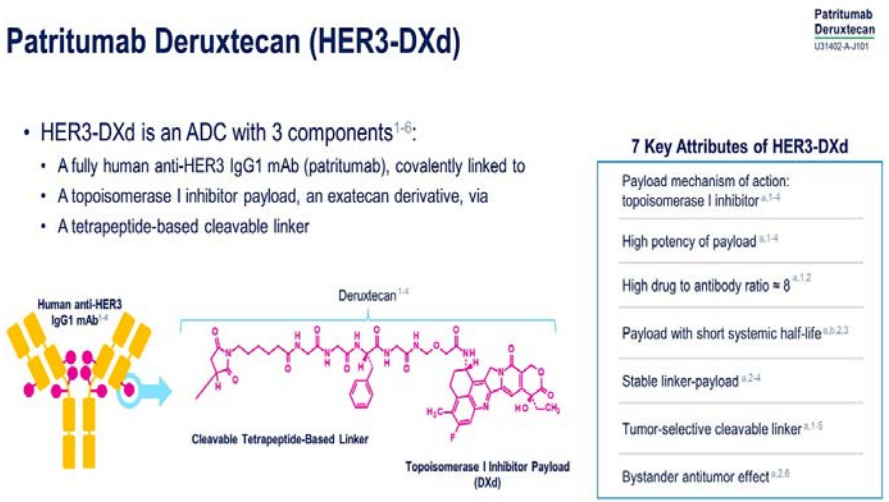
- TROPION-Breast02 (recruiting): 1st line trial comparing Dato-DXd to investigator's choice chemotherapy in patients with mTNBC who are not candidates for PD-1/PD-L1 Inhibitor therapy (NCT05374512)
- TROPION-Breast03 (recruiting): Dato-DXd with or without Durvalumab Versus Investigator's Choice of Therapy in Patients With Stage I-III TNBC with residual disease Following Neoadjuvant Therapy (NCT05629585)
- TROPION-Breast04 (recruiting): Randomized Study of Neoadjuvant Dato-DXd Plus durvalumab followed by adjuvant durvalumab Versus neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab for Triple-Negative or Hormone Receptor-low/HER2-negative Breast Cancer (NCT06112379)
- ASCENT-04 (recruiting): Sacituzumab Govitecan and Pembrolizumab Versus TPC and Pembrolizumab in Previously Untreated, Locally Advanced Inoperable or Metastatic TNBC (PD-L1+) (NCT05382286)
- ASCENT-05 (recruiting): Sacituzumab Govitecan and Pembrolizumab Versus Treatment of Physician's Choice TNBC with Residual Invasive Disease after neoadjuvant Therapy and Surgery (NCT05633654)

Courtesy of Priyanka Sharma, MD

Patritumab deruxtecan (HER3-DXd) in previously treated HER3-expressing metastatic breast cancer: Phase I/II trial



HER3 was determined by IHC in archival tumor tissue (pre-treatment samples [<6 months prior to HER3-DXd treatment])
-HER3-positive was defined as IHC 2+ and IHC 3+ for DE/DF cohorts and as ≥25% membrane positivity at 10x for DEXP cohorts.
-HER3-high was defined as ≥75% membrane positivity at 10x
-HER3-low was defined as ≥25% and <75% membrane positivity at 10x



Patients, n (%) Median treatment duration: 5.9 mo (range 0.7-30.6 mo)	4.8 mg/kg n=48	6.4 mg/kg n=98	All Doses N=182
Any TEAE	47 (97.9)	98 (100)	181 (99.5)
Associated with discontinuation	5 (10.4)	8 (8.2)	18 (9.9)
Associated with dose reduction	6 (12.5)	22 (22.4)	35 (19.2)
Associated with drug interruption	23 (47.9)	57 (58.2)	100 (54.9)
Associated with death	1 (2.1)[b]	6 (6.1)[b]	7 (3.8)[b]
Grade ≥3 TEAE	31 (64.6)	80 (81.6)	130 (71.4)
Treatment-related TEAE	47 (97.9)	97 (99.0)	180 (98.9)
Associated with death	0	1 (1.0)[c]	1 (0.5)[c]
Grade ≥3	27 (56.3)	76 (77.6)	120 (65.9)
Serious TEAE	7 (14.6)	23 (23.5)	38 (20.9)
Adjudicated treatment-related ILD[d]			
Grade 1	0	2 (2.0)	3 (1.6)
Grade 2	1 (2.1)	2 (2.0)	5 (2.7)
Grade 3	0	2 (2.0)	3 (1.6)
Grade 4	0	0	0
Grade 5	0	1 (1.0)	1 (0.5)
Total	**1 (2.1)**	**7 (7.1)**	**12 (6.6)**

- GI and hematologic toxicity were the most common TEAEs
- The rate of adjudicated treatment-related ILD was 7%; most cases were grade 1 and 2

Krop IE et al JCO 2023;41(36):5550-60.

Courtesy of Priyanka Sharma, MD

Clinical Activity of HER3-DXd Across BC Subtypes

Outcomes (BICR per RECIST 1.1)	HR+/HER2− (n=113) HER3-High and -Low	TNBC (n=53) HER3-High	HER2+ (n=14) HER3-High
Confirmed ORR, % (95% CI[a])	30.1 (21.8-39.4)	22.6 (12.3-36.2)	42.9 (17.7-71.1)
Best overall response, %[b]			
PR	30.1	22.6	42.9
SD	50.4	56.6	50.0
PD	11.5	17.0	7.1
NE	8.0	3.8	0.0
DOR, median (95% CI), mo	7.2 (5.3-NE)	5.9 (3.0-8.4)	8.3 (2.8-26.4)
PFS, median (95% CI), mo	7.4 (4.7-8.4)	5.5 (3.9-6.8)	11.0 (4.4-16.4)
6-month PFS rate, % (95% CI)	53.5 (43.4-62.6)	38.2 (24.2-52.0)	51.6 (22.1-74.8)
OS, median (95% CI), mo	14.6 (11.3-19.5)	14.6 (11.2-17.2)	19.5 (12.2-NE)

HER3-DXd demonstrated antitumor activity across BC subtypes
Antitumor activity was also demonstrated across the range of HER3 expression

As a similar safety profile was seen with 4.8 mg/kg and 6.4 mg/kg

5.6 mg/kg dose is being evaluated in BC in many ongoing trials

Courtesy of Priyanka Sharma, MD

Krop IE et al Clin Oncol 2023;41(36):5550-60.

First-in-human/phase I trial of HS-20089, a B7-H4 ADC, in patients with advanced solid tumors.

Figure 1. Expression of B7-H4 in Multiple Tumors*

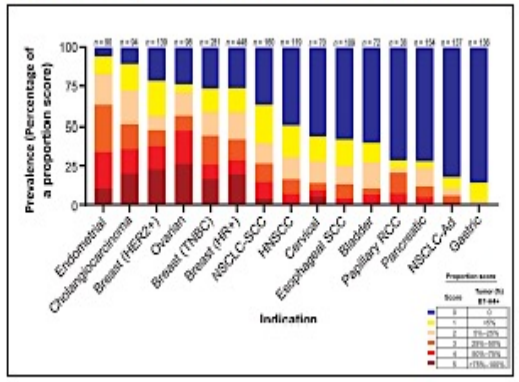
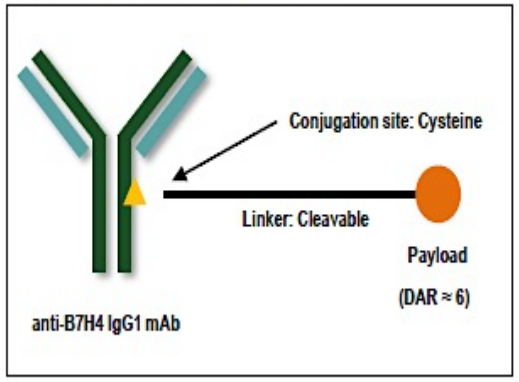
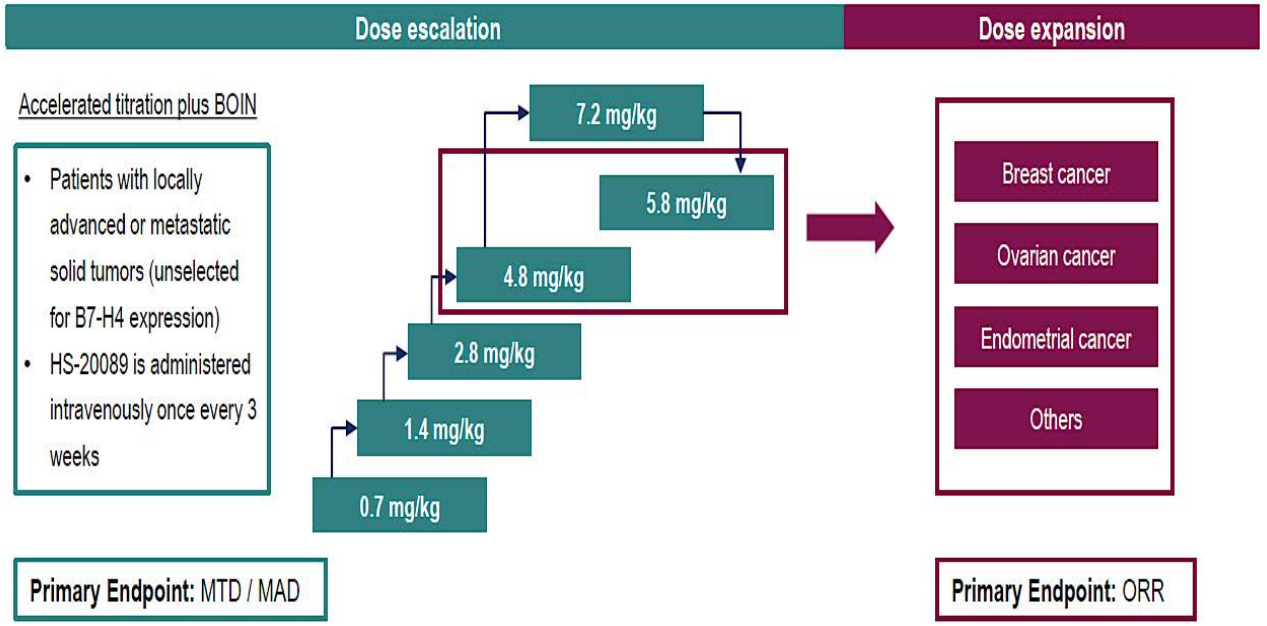


Figure 2. Structure of HS-20089



- B7 homolog 4 protein (B7-H4), a transmembrane glycoprotein in the B7 superfamily, is highly expressed in various types of solid tumors with low expression in normal tissues
- HS-20089 is a novel B7-H4 targeted ADC
  - Target; B7-H4, Toxin: topoisomerase I inhibitor (DAR:6)
  - protease-cleavable linker



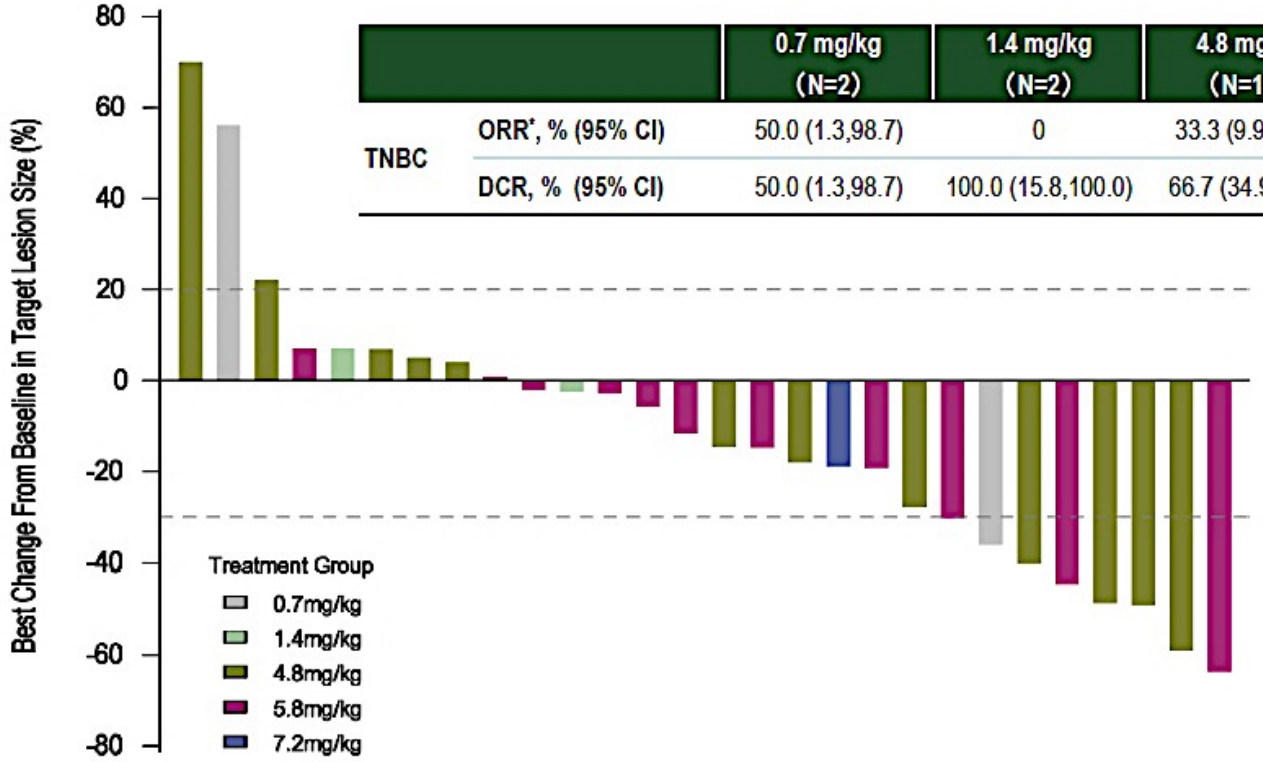
- N=52 patients treated at 6 dose levels
- Mean of 3.7 prior therapy lines:
- N=48 with breast cancer (n=32 TNBC)
- MTD: 5.8 mg/kg.
- Most common Gr 3 TRAEs were hematological toxicity. Grade 1-2 N/V and LFT increase noted in >20% of patients
- There was no adverse event leading to death. No interstitial pneumonia or infusion reactions reported.

Zhang J et al. ESMO 2023;Abstract 381O.

Courtesy of Priyanka Sharma, MD

B7-H4 ADC, in patients with advanced solid tumors: Efficacy in TNBC

Figure 5. Best Percent Change of Target Lesions in TNBC



		0.7 mg/kg (N=2)	1.4 mg/kg (N=2)	4.8 mg/kg (N=12)	5.8 mg/kg (N=11)	7.2 mg/kg (N=1)	Total (N=28)
TNBC	ORR*, % (95% CI)	50.0 (1.3,98.7)	0	33.3 (9.9,65.1)	27.3# (6.0,61.0)	0	28.6 (13.2,48.7)
	DCR, % (95% CI)	50.0 (1.3,98.7)	100.0 (15.8,100.0)	66.7 (34.9,90.1)	81.8 (48.2,97.7)	100.0 (2.5,100.0)	75.0 (55.1,89.3)

*Assessed according to RECIST 1.1 by investigators.
#Including 1 confirmed PR and 2 PRs awaiting confirmation. Others were confirmed PRs.
ORR: Objective response rate.
DCR: Disease control rate.
PR: Partial response.

- At potential target therapeutic doses of 4.8 and 5.8 mg/kg, the ORRs were 33.3% and 27.3%, respectively.
- ORR in patients treated with prior IO (n=7): 42%
- ? ORR in patients treated with prior ADC
- PFS and median duration of response not reported
- Expansion is ongoing

Zhang J et al. ESMO 2023;Abstract 381O.

Courtesy of Priyanka Sharma, MD

ADCs in TNBC: present and future

- TROP-2 ADCs with Topo-1 payload: SG approved regardless of HER2 low/zero (≥1 Line)
  - Dato-DXd, SKB264 (MK-2870)
- HER2 ADC: T-DXd (Topo-1 payload) Approved for HER2 low mTNBC (≥ 1L)
- HER3 ADC: HER3-DXd (Topo 1 payload): In trials
- B7-H4 ADC: HS-20089 (Topo 1 payload): In trials
- Bispecific antibodies: In trials

- ? ADC with non-Topo 1 payload
- Very little is known about mechanisms of resistance:
  - ? Target, ? Payload, ? Both ? others
- ? ADC after ADC efficacy:
  - Optimal sequence for mTNBC?: Should level of target expression guide decisions? current methods of target level expression (IHC based) are not optimal to guide selection of therapy
    - Need quantitative assays

Will be an important question to answer if ADCs move in curative setting (Residual disease and Neoadjuvant trials are ongoing)

Courtesy of Priyanka Sharma, MD

Meet The Professor

Optimizing the Management of Myelofibrosis

Thursday, February 1, 2024
5:00 PM – 6:00 PM ET

Faculty

Stephen T Oh, MD, PhD

Moderator

Neil Love, MD

RTP
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TO PRACTICE

Thank you for joining us!

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

RTP Year in Review 2024