25th Multidisciplinary Management of Cancers: A Case-based Approach

Breast Cancer Tumor Board Cases

Friday, March 7, 2025
8:30-10:30 AM

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24th Multidisciplinary Management of Cancers: A Case-based Approach

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Panelists

Session Chair: Laura Huppert, MD
Assistant Professor | University of California, San Francisco

Fellow, Case Presenter: Kelsey Natsuhara, MD
Senior Oncology Fellow | University of California, San Francisco

Medical Oncology
- Dr. Mili Arora, UC Davis
- Dr. Helen Chew, UC Davis
- Dr. Allison Kurian, Stanford
- Dr. Amy McMullen, Central Coast Oncology & Hematology
- Dr. Melinda Telli, Stanford

Surgical Oncology
- Dr. Michael Alvarado, UCSF
- Dr. Candice Sauder, UC Davis
- Dr. Kimberly Stone, Stanford

Radiation Oncology
- Dr. Cathy Park, UCSF

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Disclosures

Full Name	Role	Type of Financial Relationship	Company
Laura Huppert	**Chair**	Advisory Board or Panel Grants/Research Support2	AstraZeneca and Pfizer Greenwich LifeSciences
Kelsey Natsuhara	**Fellow**	Disclosed no relevant financial relationships.	
Michael Alvarado	Panelist	Disclosed no relevant financial relationships.	
Mili Arora	Panelist	Disclosed no relevant financial relationships.	
Helen Chew	Panelist	Disclosed no relevant financial relationships.	

ANCO and i3 Health have mitigated all relevant financial relationships.

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Disclosures

Allison Kurian	Panelist	Grants/Research Support2	Research support for an investigator-initiated study to my institution from Myriad Genetics, 2017-2019.
Amy McMullen	Panelist	Disclosed no relevant financial relationships.	
Catherine Park	Panelist	Disclosed no relevant financial relationships.	
Candice Sauder	Panelist	Disclosed no relevant financial relationships.	
Kimberly Stone	Panelist	Advisory Board or Panel (no finacanical realtionship)	Petal Surgical and Always Health
Melinda Telli	Panelist	Advisory Board or Panel Consultant Grants/Research Support2	Astra Zeneca, Arivinas, Blueprint Medicines, Daiichi Sankyo, Foresight Diagnostics, Genentech, GSK, Merck, Natera, Novartis, Pfizer DSMC: G1 Therapeutics, Gilead Astra Zeneca, Arivinas, Blueprint Medicines, Genentech, GSK, Hummingbird Bioscience, Merck, OncoSec Medical, Pfizer.

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Outline

Case 1: Early-stage triple negative breast cancer

Case 2: Early-stage node negative HR+/HER2- BC

Case 3: Early-stage node positive HR+/HER2- BC → HR+ MBC

Case 4: De novo HER2+ MBC

Case 5: Metastatic triple negative breast cancer

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Case 1 – Early-stage TNBC

- 45 yo pre-menopausal female palpates a right breast mass.
- Ultrasound and mammogram demonstrate a 2.5cm mass with one enlarged axillary LN
- MRI breast: 3cm right breast mass, level 1 lymphadenopathy
- Ultrasound-guided core needle biopsy:
  - Grade 3 IDC, ER neg, PR neg, HER2 neg (IHC 1+, FISH non-amplified), Ki67 80%.
  - Axillary LN: Metastatic carcinoma to the LN
- PET/CT no evidence of metastatic disease
- Genetic testing: No pathogenic mutations or VUS

Case 1 – Early-stage TNBC

- Patient presents to medical oncology clinic to discuss systemic therapy.
- You recommend neoadjuvant treatment with the KEYNOTE-522 regimen including:
  - Neoadjuvant weekly carboplatin + paclitaxel x 12 weeks, followed by Q2 week dose dense doxorubicin + cyclophosphamide
  - Neoadjuvant and adjuvant Q3 week pembrolizumab to complete 1 year total.
- After this discussion, the patient is hesitant about the intensity of this regimen and asks you, **how will this benefit me?**

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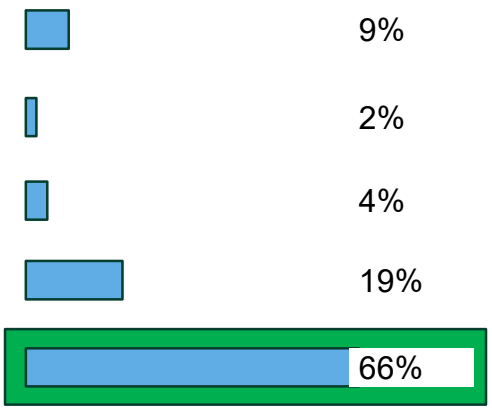
How do you respond?

The KEYNOTE-522 regimen will:

A. Increase your chance of achieving a pathologic complete response — 9%
B. Decrease the chance the cancer comes back in the future — 2%
C. Help you live longer — 4%
D. A + B — 19%
E. All of the above — 66%



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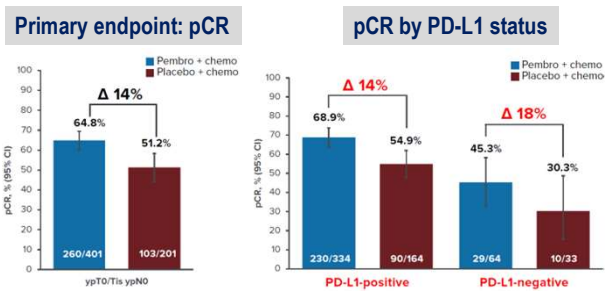
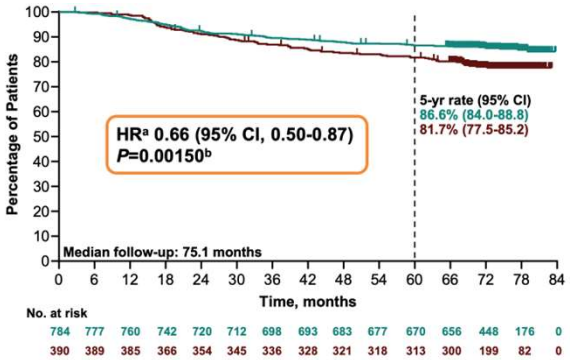
KEYNOTE-522: Overall survival benefit

pCR



Overall survival



Addition of pembrolizumab improved:

- pCR rate (**51.2%** vs. **64.8%)**
- 5-yr OS rate (**86.6%** vs. **81.7%**, HR **0.66**)

Schmid et. al. *NEJM* 2020; Schmid et. al. *NEJM* 2024.

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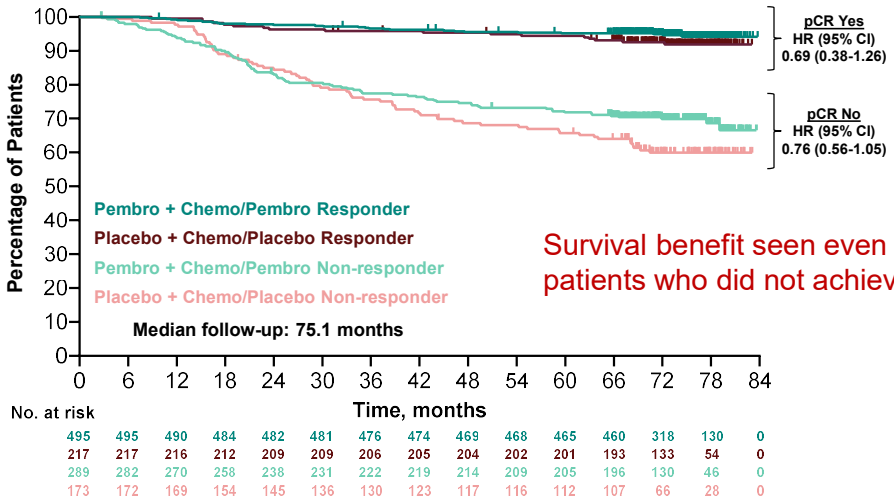
KEYNOTE-522: Overall survival benefit



Survival benefit seen even for patients who did not achieve pCR

Schmid et. al. *NEJM* 2020; Schmid et. al. *NEJM* 2024.

Case 1 – Panel Discussion

- How do you approach this discussion with patients?
- Is there any patient with stage II-III TNBC to whom you do not give KEYNOTE-522?
- What if this were a T1c TNBC?

Case 1 – Early-stage TNBC

- She is treated in the neoadjuvant setting with the KEYNOTE-522 regimen.
- She undergoes lumpectomy SLNB and pathology shows **pathologic compete response** in the breast and lymph nodes!
- She is referred to radiation oncology to discuss radiation.

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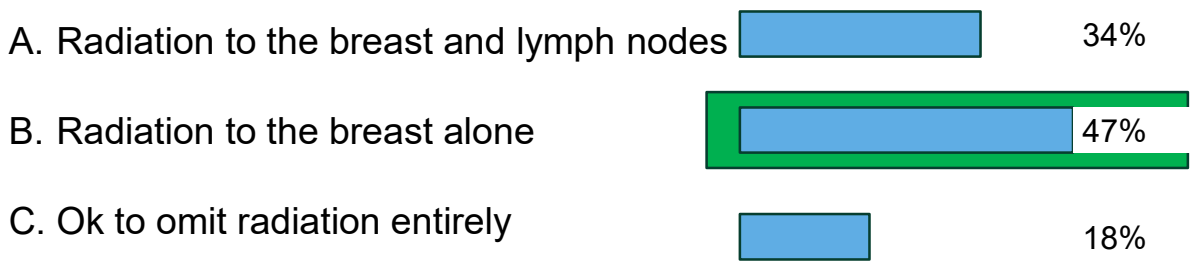
What would you recommend regarding radiation therapy for this patient?



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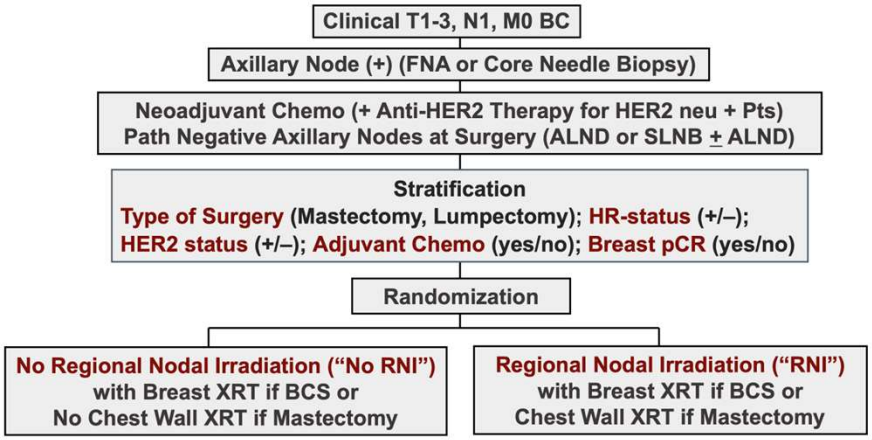
NSABP B-51 Study



FNA: Fine Needle Aspiration; ALND: Axillary Lymph Node Dissection; SLNB: Sentinel Lymph Node Biopsy; XRT: Radiation

Mamounas et. al., SABCS 2023.

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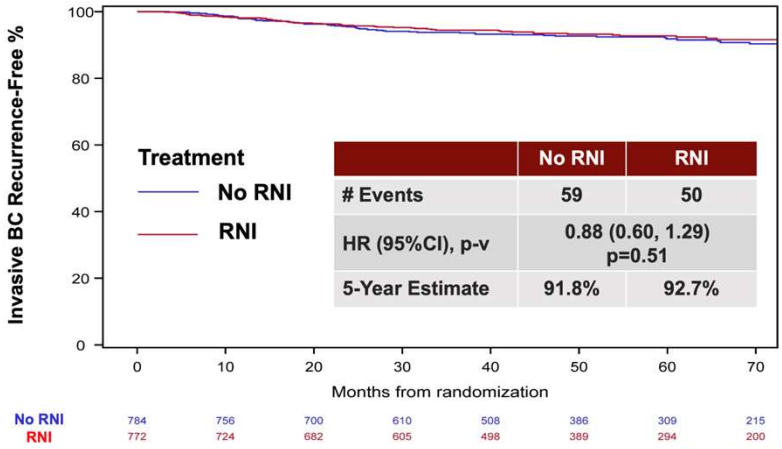
NSABP B-51 Study

Invasive Breast Cancer Recurrence-free Interval

- 1,641 patients randomized
- Median follow-up 59.5 mos
- No difference in isolated locoregional recurrence, disease free survival, or OS.



	No RNI	RNI
# Events	59	50
HR (95%CI), p-v	0.88 (0.60, 1.29) p=0.51	
5-Year Estimate	91.8%	92.7%

Mamounas et. al., SABCS 2023.

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Case 1 – Panel Discussion

- Have you adopted omission of nodal irradiation in your practice for patients who are pN0 after neoadjuvant therapy?
- What is your practice on additional axillary surgery for patients with pN+ disease after SLNB?

Case 1 – Early-stage TNBC

- The patient decides to omit regional nodal irradiation and proceed with whole breast radiation alone.
- She has continued on adjuvant pembrolizumab since finishing chemo, but asks you…

"Do I really need to continue pembrolizumab for a year even after I had a pCR?"

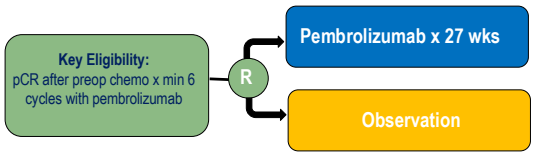
Case 1 – Panel Discussion

- How do you discuss the need for adjuvant pembrolizumab with your patients?
- If a patient has an IRAE while on adjuvant pembro, do you have a lower threshold to stop pembro in these cases?
- What if she hadn't achieved a pCR? What treatment would you offer her in this case?

Select Trials in Progress

Do we need both neoadjuvant ***and*** adjuvant immunotherapy for patients with early-stage TNBC, particularly for those who achieve pCR after NACT + IO?

OptimICE-pCR
(NCT05812807)



Stratification Factors:
- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

Among patients with early-stage TNBC who do NOT achieve a pCR after neoadjuvant chemo + IO, can we improve outcomes with better adjuvant treatments?

Ongoing post-neoadjuvant clinical trials with ADCs:

- **SASCIA**: (ER+/HER2- and TNBC): Sacituzumab govitecan x 8 vs. TPC (NCT04595565)
- **Optimize RD/ASCENT-05**: Sacituzumab govitecan + pembrolizumab x 8 vs. pembrolizumab +/- capecitabine (NCT05633654)
- **Tropion Breast03**: Dato-DXd +/- durvalumab vs. capecitabine and/or pembrolizumab (NCT05629585)

Case 1 – Early-stage TNBC

- After the patient completes 1 year of pembrolizumab, you discuss that there will be no further systemic therapy.
- You plan to monitor with imaging and clinical exams.
- The patient asks about ctDNA and whether this should be used to monitor her cancer.

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Case 1 – Panel Discussion

- Do you use ctDNA in your clinical practice for early-stage patients? For metastatic?
- How do you discuss the utility of ctDNA with patients in clinic?

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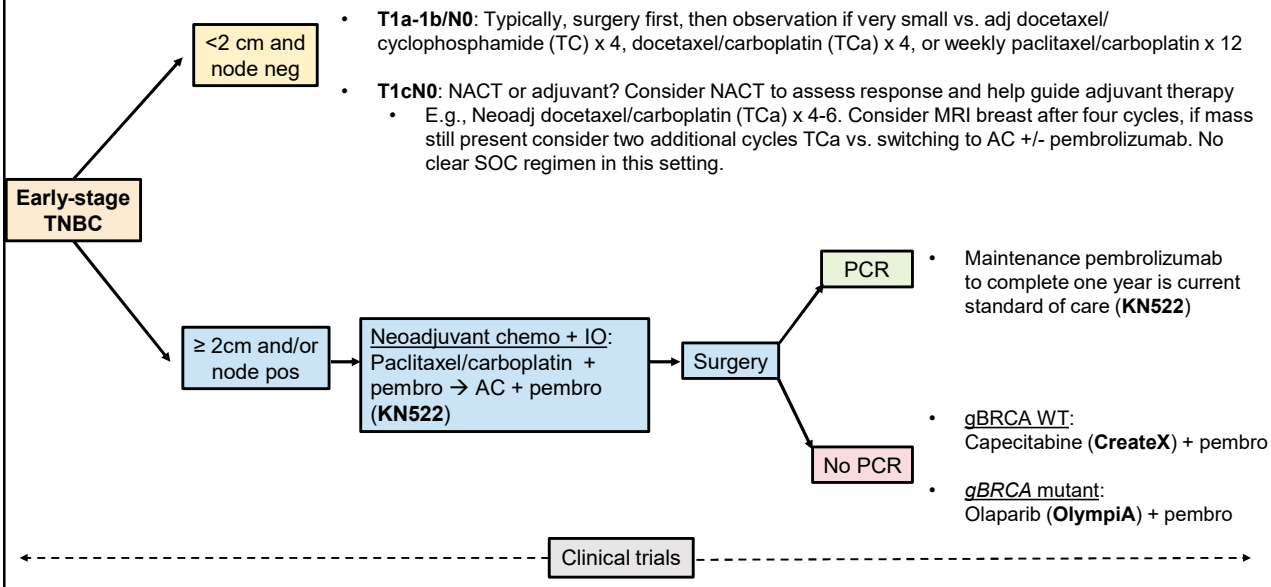
Roadmap: Early-stage TNBC



- **T1a-1b/N0**: Typically, surgery first, then observation if very small vs. adj docetaxel/ cyclophosphamide (TC) x 4, docetaxel/carboplatin (TCa) x 4, or weekly paclitaxel/carboplatin x 12
- **T1cN0**: NACT or adjuvant? Consider NACT to assess response and help guide adjuvant therapy
  - E.g., Neoadj docetaxel/carboplatin (TCa) x 4-6. Consider MRI breast after four cycles, if mass still present consider two additional cycles TCa vs. switching to AC +/- pembrolizumab. No clear SOC regimen in this setting.

- Maintenance pembrolizumab to complete one year is current standard of care (**KN522**)
- gBRCA WT: Capecitabine (**CreateX**) + pembro
- *gBRCA* mutant: Olaparib (**OlympiA**) + pembro

Huppert 2025

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Case 1 – Take Home Points

- For clinical stage II-III TNBC, standard of care neoadjuvant chemo-immunotherapy has shown improved rates of PCR, event-free survival, and overall survival(**KEYNOTE-522**)
- For cN+ patients who achieve pCR in the node after neoadjuvant therapy, the **NSABP-51** trial showed no difference in invasive breast cancer recurrence free interval at 5 yrs with the **omission of nodal irradiation.**
- Currently, we **do not have data to omit adjuvant pembrolizumab**, but can consider enrolling patients to the ongoing OptimICE-pCR trial.
- There is **insufficient data to utilize ctDNA** to guide adjuvant decision-making, so we do not recommend sending it outside the context of a clinical trial at this time.

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Case 2 – Early stage HR+/HER2- Breast Cancer

- A 60 yo post-menopausal woman is diagnosed with a screen-detected cT1bN0 HR+/HER2- left breast cancer.
- MMG/US show a 1.1 cm mass in the left breast and no axillary adenopathy
  - Core biopsy of the mass confirms grade 1 invasive ductal carcinoma, ER 90%, PR 60%, HER2 neg (IHC 0), Ki67 10%
- Patient now presents for her initial surgical oncology appointment to discuss management.

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Case 2 – Early stage HR+/HER2- Breast Cancer

- Left lumpectomy is recommended, to which she is amenable.
- However, she has questions about the **need for axillary surgery** given her small tumor.

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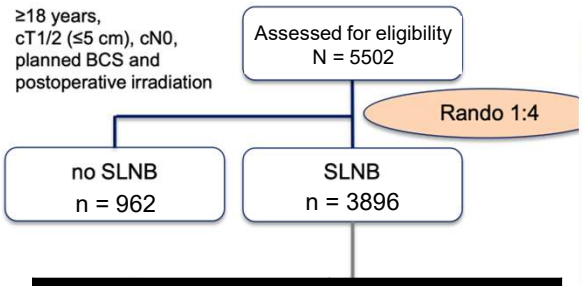
INSEMA Trial



Nodal Result	N (%)
No SLN detected	38 (1.0%)
SLN negative	3275 (84.1%)
SLN micromet	133 (3.4%)
SLN positive (1-3 LN)	438 (11.3%)
SLN positive (≥4 LN)	8 (0.2%)

Baseline Patient Characteristics

Parameter	Category	No SLNB N=962 N (%)	SLNB N=3896 N (%)
Age	median (IQR)	62 (53-68)	62 (53-68)
	<65 years	583 (60.6)	2387 (61.3)
	≥65 years	379 (39.4)	1509 (38.7)
Preop. tumor size	≤2 cm	871 (90.5)	3521 (90.4)
	>2 cm	91 (9.5)	375 (9.6)
Grading	G1	372 (38.7)	1463 (37.6)
	G2	552 (57.4)	2294 (58.8)
	G3	38 (3.9)	139 (3.6)
Tumor type	NST	726 (75.5)	2828 (72.6)
	Invasive/mixed lobular carcinoma	125 (13.0)	491 (12.6)
	other	111 (11.5)	576 (14.8)
ER/PgR	both negative	15 (1.6)	58 (1.5)
	ER and/or PgR positive	946 (98.4)	3835 (98.5)
HER2 status	negative	914 (95.4)	3755 (96.7)
	positive	44 (4.6)	130 (3.3)

Reimer et al., *NEJM* 2024; Reimer et al., SABCS 2024.

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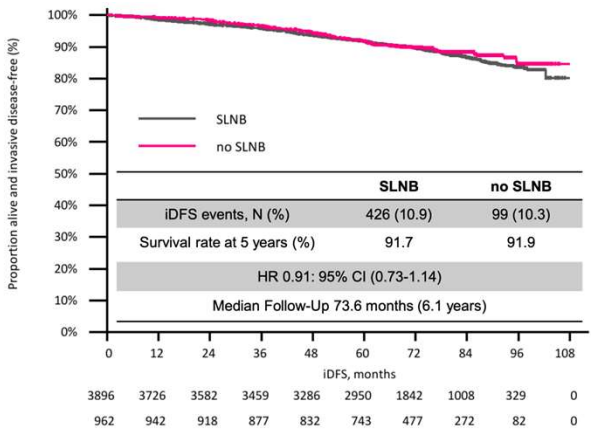
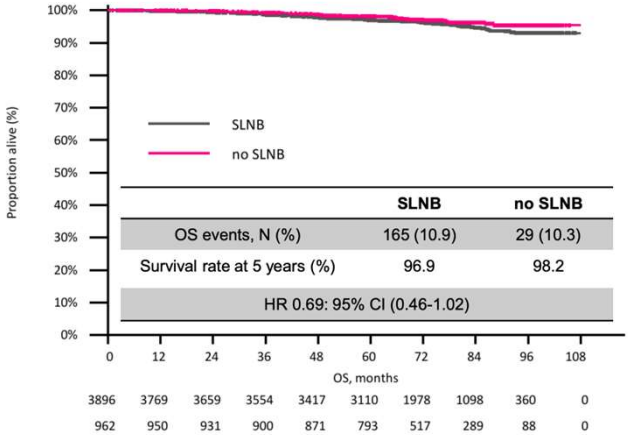
INSEMA Trial

Non-inferior iDFS and OS at 5-years for patients with omission of SLNB





Reimer et al., *NEJM* 2024; Reimer et al., SABCS 2024.

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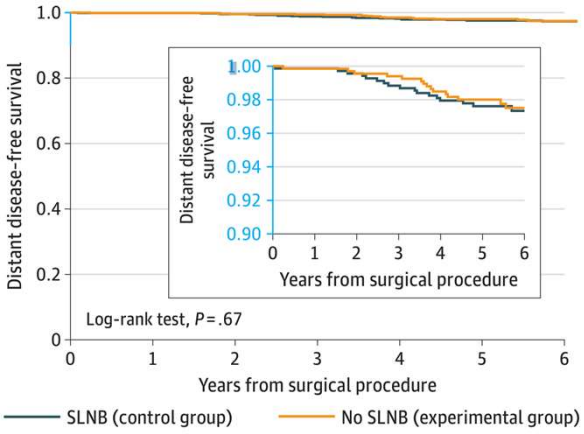
SOUND Trial

- Phase 3 randomized trial evaluating SLNB vs omission of axillary surgery
- Eligible patients with T≤2 cm and cN0 by axillary US +/- FNA, planning to undergo lumpectomy

Key patient characteristics
- 78% peri/post-menopausal
- 78% ductal carcinoma
- 95% patients with pT1 disease
- 93% ER+ ; 88% Luminal subtype

13.7% of patients in SLNB arm had pN+ disease!
8.6% macromets, 5.1% micromets,
0.6% 4+ nodes



Non-inferior distant disease-free survival at 5-years for omission of axillary surgery vs SLNB (97.7% vs 98.0%)

Gentillini et al., *JAMA Oncol* 2023

Case 2 – Panel Discussion

- For what patients with HR+/HER2- breast cancer do you consider omission of axillary surgery?
- The INSEMA and SOUND trials included mostly patients with HR+/HER2- BC. Do you extrapolate these data to small HER2+ and TNBC?

Case 2 – Early stage HR+/HER2- Breast Cancer

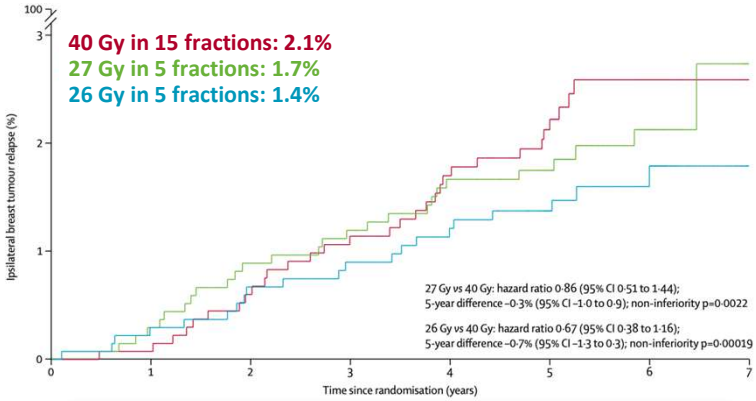
- Patient proceeds with lumpectomy without SLNB
- At surgery, she has 1.0 cm of grade 1 IDC, ER 95%, PR 60%, HER2 neg (IHC 0), Ki67 10%, negative margins.
- She meets with medical oncology. Oncotype 10, no chemotherapy recommended, she is started on an aromatase inhibitor x 5 yrs.
- She is referred to radiation oncology to discuss post-lumpectomy radiation therapy and has **questions about an abbreviated course of radiation.**

FAST Forward Trial

- Phase 3 randomized trial comparing hypofractionated breast RT: 1 week vs 3 weeks
- Patients with pT1-3, pN0-1 disease after BCS were eligible and randomized to an RT course.

Concluded that both 26 and 27 Gy* in 5 fractions was non-inferior to standard 40 Gy in 15 fraction treatment

Risk of ipsilateral tumor relapse at 71.5 month median follow-up



***However, increased cosmetic complications at 5 years for the 27 Gy in 5 fractions group**

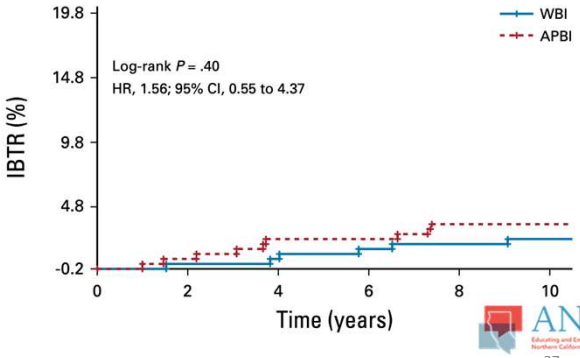
Brunt et al., *Lancet* 2020

FLORENCE APBI Trial

- Phase 3 randomized trial comparing accelerated partial breast irradiation (APBI) vs whole-breast irradiation (WBI)
- 520 patients > 40 yrs, with max tumor 2.5 cm who underwent BCS were randomized 1:1 to WBI or APBI
  - WBI: 50 Gy in 25 fractions + boost to surgical bed 10 Gy in 5 fractions
  - APBI: 30 Gy in 5 non-consecutive daily fractions
- *Ineligible*: multifocal disease, close surgical margins (<5mm)

No difference in ipsilateral breast tumor relapse or overall survival between WBI and APBI!

- 10-year incidence of **ipsilateral breast tumor relapse 2.5% WBI vs 3.7% APBI** (HR 1.56, p=0.40)
- **10-year OS 91.9% in both arms** (HR 0.95, p=0.86)
- APBI arm showed less acute toxicity, late toxicity, and improved cosmetic outcome



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Meattini et al., *J Clin Oncol* 2020

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Case 2 – Panel Discussion

- For what patients do you use hypofractionated radiation therapy?
- What patients do you consider omission of post-lumpectomy radiation altogether?

Stanford Cancer Institute | UC DAVIS HEALTH | UCSF COMPREHENSIVE CANCER CENTER | Helen Diller Family Comprehensive Cancer Center

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Case 2 – Summary

- The **INSEMA** and **SOUND** trials demonstrated omission of SLNB for select patients with cT1-2 cN0 disease may be safe, although longer follow-up is needed.
- The **FAST FORWARD** trial demonstrated the safety of hypofractionated radiation in 1 week for select patients.

Case 3 – Early-stage HR+ BC

- 52 yo post-menopausal woman with a new diagnosis of right-sided HR+ breast cancer who undergoes up-front lumpectomy + SLNB.
- Surgical pathology shows:
  - 2.8 cm grade 3 IDC, ER 90%, PR 80%, HER2 IHC 1+, Ki67 40%. No LVI. Negative margins.
  - 1/3+ LNs with a macrometastasis (4mm deposit) and no extranodal extension
  - Oncotype DX Recurrence Score 24
- Genetic testing negative

Case 3 – Early-stage HR+ BC

- She meets with medical oncology, who does not recommend chemotherapy given Oncotype 24 in post-menopausal patient per RxPonder trial.
- She is started on adjuvant letrozole with plans to discuss adding a CDK4/6i after radiation
- She undergoes radiation to the breast and axilla
- She now presents to medical oncology to finalize her decision about whether to add a CDK4/6 inhibitor.

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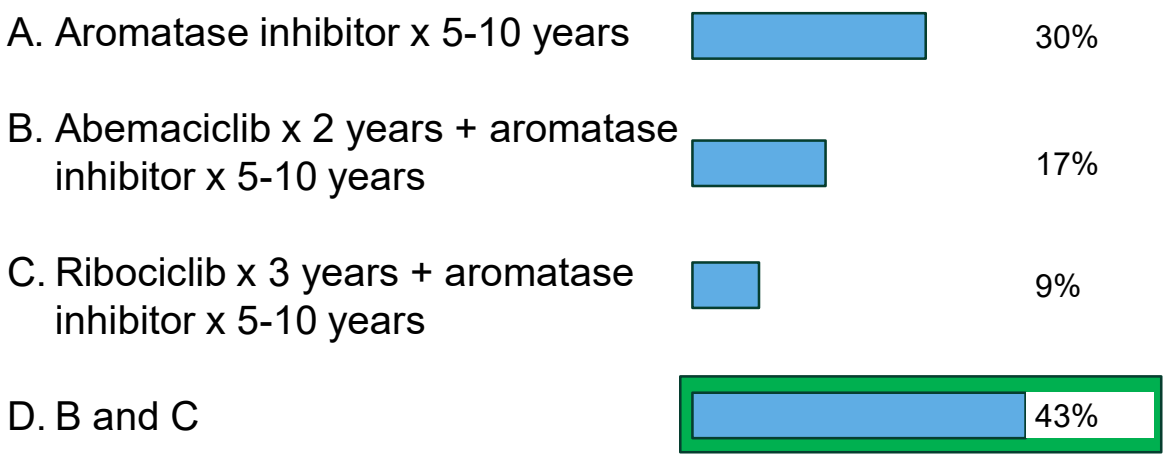
What would you recommend for her adjuvant systemic therapy?



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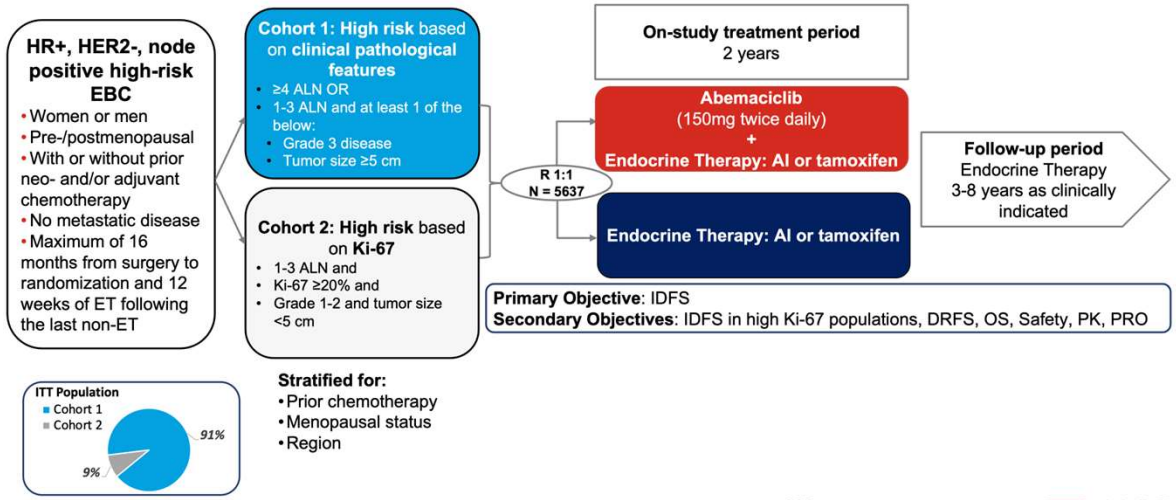
MonarchE: Adjuvant abemaciclib for high-risk HR+/HER2- EBC



Harbeck et al, ESMO 2023

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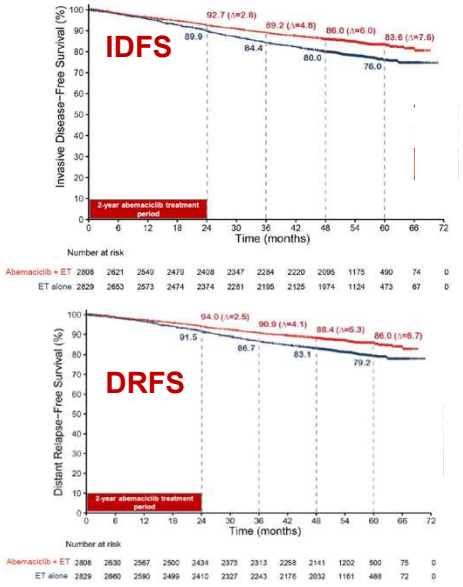
MonarchE: Efficacy Analysis at 5 years



- The abemaciclinb benefit in monarchE was sustained at **5-yr** follow-up:
  - The absolute IDFS (Δ=**7.6%**) and DRFS (Δ=**6.7%**) benefit at 5 years was increased compared with 2-, 3-, and 4-year rates
- Overall survival data is immature; there were fewer deaths in the abema + ET arm vs. ET only arm
- No changes in previously reported safety profile
  - Diarrhea, Fatigue, neutropenia, elevated LFTs, rare risk lung inflammation/pneumonitis, VTE

Harbeck et al, ESMO 2023

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NATALEE: Adjuvant ribociclib for high-risk HR+/HER2- EBC

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 ***or***
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N=5101[b]

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

R 1:1[c]

Ribociclib 400 mg/d
3 wk on/1 wk off
for 3 y

NSAI
Letrozole or anastrozole[d] for ≥5 y
+ goserelin in men and premenopausal women

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Fasching et al., ESMO 2024; Slamon et al., *NEJM* 2024

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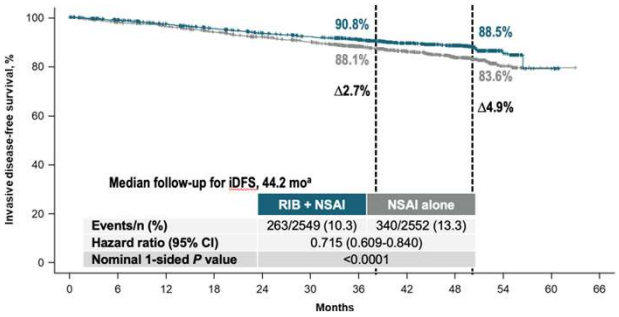
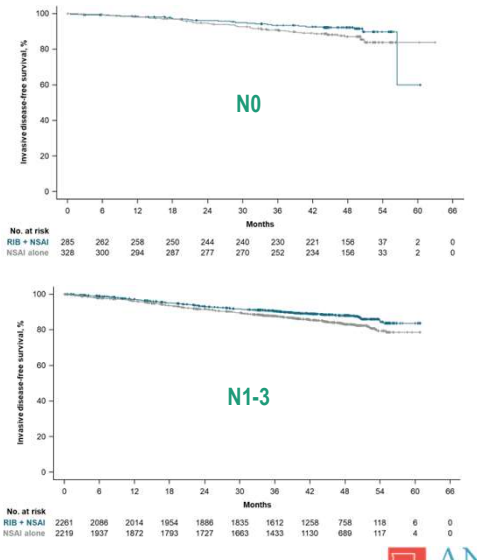
NATALEE: IDFS at 4 years





- Absolute benefit with ribociclib + NSAI at **4 yrs**
  - IDFS: **Δ 4.9%**
- Node negative pts – similar benefit
- OS data immature
- No changes in previously reported safety profile
  - Fatigue, prolonged QTc, neutropenia, elevated LFTs, rare risk lung inflammation/pneumonitis, VTE

Fasching et al., ESMO 2024; Slamon et al., *NEJM* 2024

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Comparing MonarchE to NATALEE

	monarchE	NATALEE
Study drug	abemaciclib	ribociclib
Dosing	150 mg twice daily	400 mg 3 wk on, 1 wk off
Duration of therapy	2 y	3 y
ET	anastrozole, letrozole, exemestane, tamoxifen, +/– OFS	anastrozole, letrozole, +/– OFS
Eligible patients	4+ LN or 1 to 3+ LN and • tumor size ≥ 5 cm or ☆ • histologic grade 3 or • Ki-67 ≥ 20%	Any LN+ or tumor > 2 cm and ☆ • G3 or • G2 and Ki-67 > 20% or • G2 and high genomic risk (oncotype RS > 26, MammaPrint high)
2-y invasive disease-free survival	Δ 3.5%, 92.2% abemaciclib vs 88.7% ET, HR 0.75, $P = .01$[2]	Δ 3.3%, 90.4% ribociclib vs 87.1% ET, HR 0.748, $P = .0014$[1]
Proportion who had completed treatment period	707 (12.5%) 2-y treatment period	515 (20%) 3-y treatment period
invasive disease-free survival	IDFS Δ 7.6% at 5 years	IDFS Δ 4.9% at 4 years
Proportion who had completed treatment period	100% (2,794 treated, including 510 early discontinuation)	62.8% (1,601 treated, 509 early discontinuation)
Any grade neutropenia (≥ G3)	44.6% (18.0%)[2]	62.1% (43.8%)[1]
Liver-related AE (≥ G3)	ALT: 9.5% (2.1%)[2]	25.4% (8.3%)[1]
Diarrhea (≥ G3)	82.2% (7.6%)[2]	14.2% (0.6%)[1]
QT prolongation (≥ G3)	0.0% (0.0%)[2]	5.3% (1.0%)[1]
ILD pneumonitis (≥ G3)	2.7% (0.3%)[2]	1.5% (0.0%)[1]

Modified from Graff et al., *ASCO Daily News* 2023

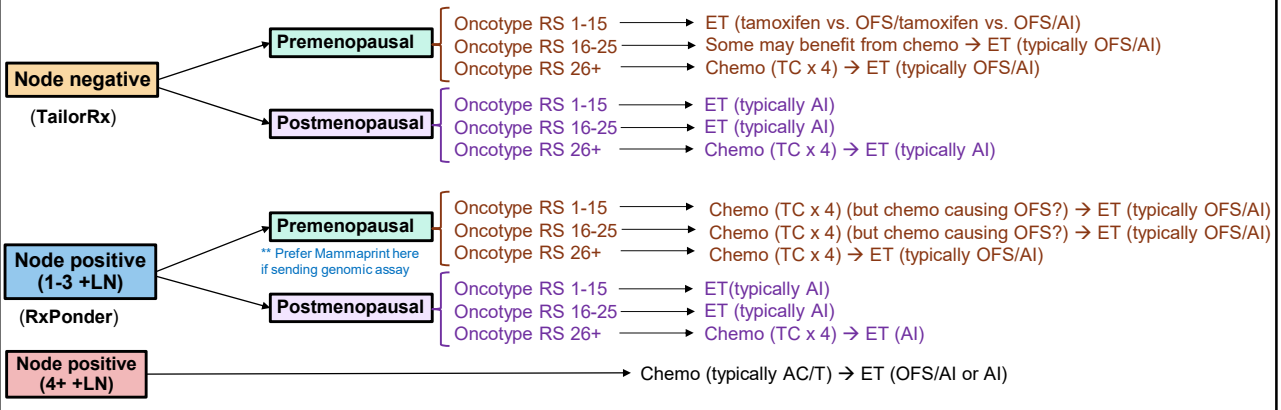
Case 3 – Panel Discussion

- What has been your experience discussing adjuvant CDK4/6 inhibitors with patients?
- In a patient that meets criteria for both MonarchE and NATALEE, what do you generally prefer?

Case 3 – Early-stage HR+ BC

- After this discussion, she starts on adjuvant abemaciclib given longer follow-up.
- However, she has persistent diarrhea despite loperamide and dose reduction. After two months, she is switched to adjuvant ribociclib with plan to complete three total years CDK4/6i therapy.
- She also continues on adjuvant letrozole.

Roadmap: Early-stage HR+/HER2- Breast Cancer



***Adjuvant targeted therapy options:**

- Pathogenic germline *BRCA1 or 2* mutation:
  - Consider **one year of adjuvant olaparib** for patients with high-risk HR+/HER2- BC who meet criteria (**OlympiA**)
  - In highest risk, can consider one year of olaparib first followed by CDK4/6i (no data for this, but can be considered)
- No pathogenic germline *BRCA1* or *2* mutation:
  - Consider **two years of adjuvant abemaciclib** (**MonarchE**) or **three years of adjuvant ribociclib (NATALEE)** for patients with high-risk HR+/HER2- BC who meet criteria

- Also consider clinical trials at any step above if patient eligible
- **Future options** – Neoadj immunotherapy for high-risk patients? (KN756, Checkmate-7FL) ADCs? Novel endocrine therapies?

Huppert 2025

24th Multidisciplinary Management of Cancers: A Case-Based Approach

Case 3 – Metastatic HR+ BC

- Unfortunately, after completing 2 years of adjuvant ribociclib and letrozole, she is found to have a concerning rib lesion on CXR ordered by her PCP for rib pain.
- PET-CT shows 2 FDG-avid lesions at T12 and in one left posterior rib, as well as a 3.2 cm hypermetabolic liver lesion.
- CT-guided liver biopsy confirms metastatic breast adenocarcinoma, ER+ (80%), PR+ (70%), HER2 neg (IHC 1+)
- NGS from the liver biopsy is sent and returns with a PIK3CA mutation.

She is seeing you in med onc clinic to discuss next steps.

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What do you recommend to this patient for 1st line treatment in the metastatic setting?

A. Fulvestrant + abemaciclib — 38%

B. Fulvestrant + inavolisib + palbociclib — 45%

C. Everolimus + exemestane — 2%

D. Chemotherapy — 14%

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24th Multidisciplinary Management of Cancers: A Case-Based Approach

INAVO120: 1L Therapy for Early Relapse and PIK3CA-Mutated HR+ HER2- advanced breast cancer

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Enrolment period: December 2019-September 2023

N=325

R 1:1

- **Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)****
- **Placebo (PO QD) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)****

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

~1% prior CDK4/6i use in adjuvant setting

Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

Jhaveri et al., SABCS 2023; Turner et al., *NEJM* 2024

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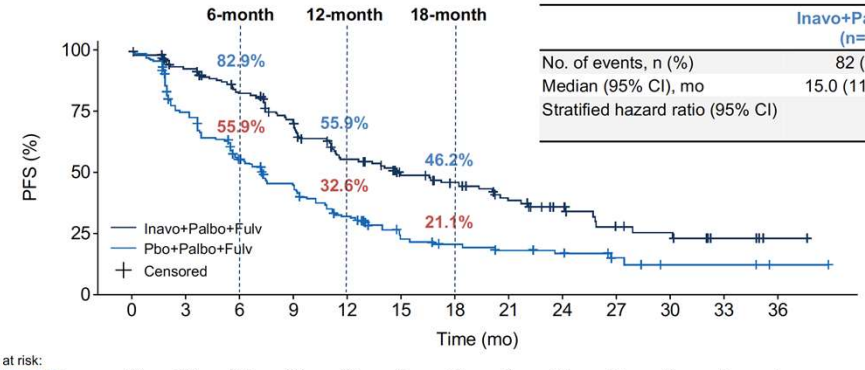
INAVO120: Primary Endpoint PFS



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59) p<0.0001**	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up: **21.3 months**

- Median PFS 15.0 vs. 7.3 months with addition of inavo
- OS data not yet mature. Does earlier use of PIK3Ca inhibitors improve overall survival?
- Approved Oct 2024!

Jhaveri et al., SABCS 2023; Turner et al., *NEJM* 2024

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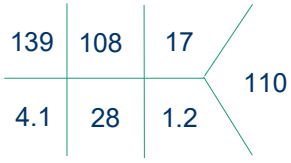
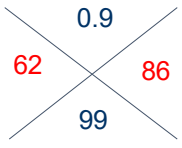
Case 3 – Panel Discussion

- What has been your experience with toxicity management on the INAVO 120 regimen? How do you monitor blood sugar? Do you start any medications to prevent side effects?
- If instead this patient had asymptomatic bone lesions, would you start the INAVO-120 triplet that case? What other options would you consider?
- What is your approach to NGS testing for HR+/HER2- MBC? When do you test and tissue, blood, or both?

Case 3 – Metastatic HR+ BC

- The patient is started on fulvestrant/palbociclib/inavolisib.
- She has stable disease on her first scan. Unfortunately, PET/CT at 6 months shows progression in the liver with 3 new lesions (largest 5cm)
- She has had mild abdominal discomfort and labs show:





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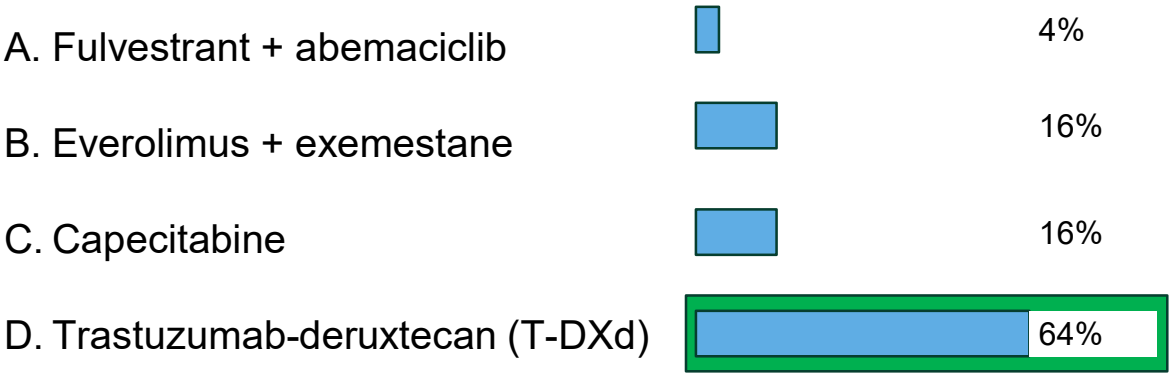
What would you recommend for next line of therapy?



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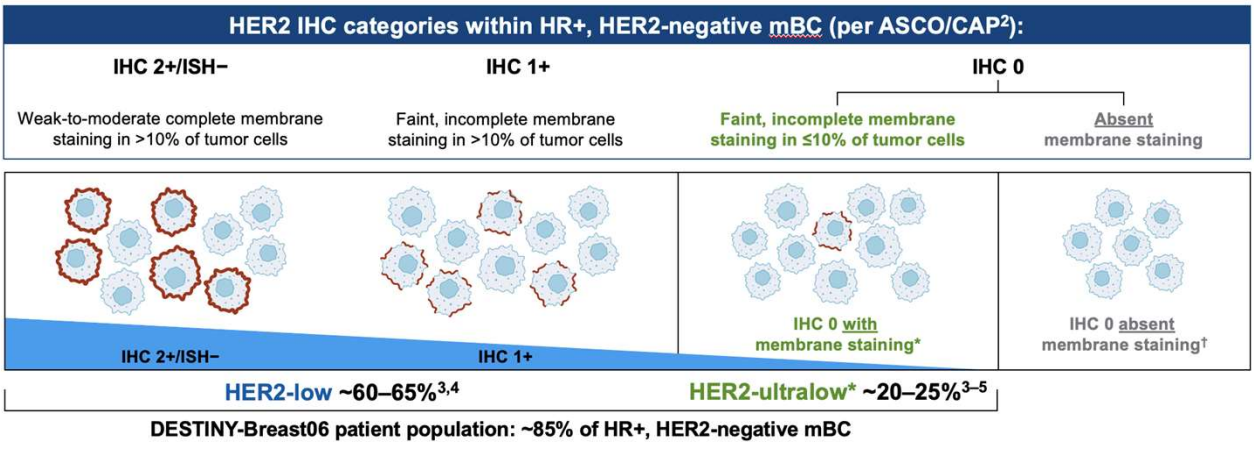
24th Multidisciplinary Management of Cancers: A Case-Based Approach

DESTINY-Breast06: T-DXd vs. TPC for 1L chemo in patients with HER2-low and ultralow HR+/HER2- MBC



Viale et al., ASCO 2024

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24th Multidisciplinary Management of Cancers: A Case-Based Approach

DESTINY-Breast06: T-DXd vs. TPC for 1L chemo in pts with HER2-low and ultralow HR+/HER2- MBC

Patient population
- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) **OR** HER2-ultralow (IHC 0 with membrane staining) status
- Chemotherapy naïve in the mBC setting

Prior lines of therapy
- ≥2 lines ET ± targeted therapy for mBC
  OR
- 1 line for mBC AND
  - Progression ≤6 mo of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 mo of starting adjuvant ET

R 1:1

T-DXd 5.4 mg/kg Q3W (n=436)

TPC (n=430)

HER2-low = 713
HER2-ultralow = 153

Capecitabine, 59.8%; nab-paclitaxel, 24.4%; paclitaxel, 15.8%

Baseline characteristics*
- Median age **58 years**; ECOG PS ≥1 **~42%**
- **De-novo mBC ~31%; liver metastases ~67%; visceral disease ~85%; primary endocrine resistance ~31%**

Primary endpoint
- PFS (BICR) in HER2-low
  - Median **13.2 mo T-DXd** vs **8.1 mo TPC** (hazard ratio 0.62; P<0.0001)†

Secondary endpoints
- PFS (BICR) in ITT (HER2-low + HER2-ultralow)
  - Median **13.2 mo T-DXd** vs **8.1 mo TPC** (hazard ratio 0.64; P<0.0001)‡
- OS
  - Data maturity ~40% at first IA; early trend favoring T-DXd in ITT
- **PFS2 (INV)**
- Safety and tolerability

Bardia et al., SABCS 2024

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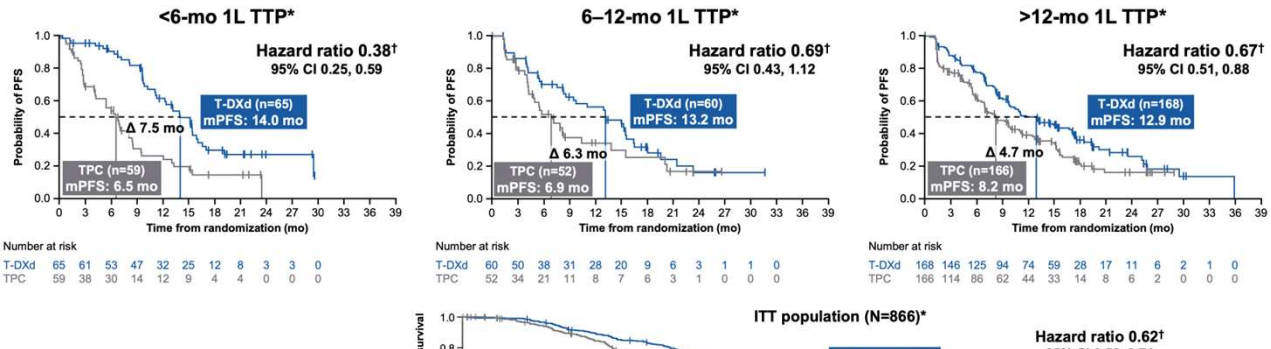
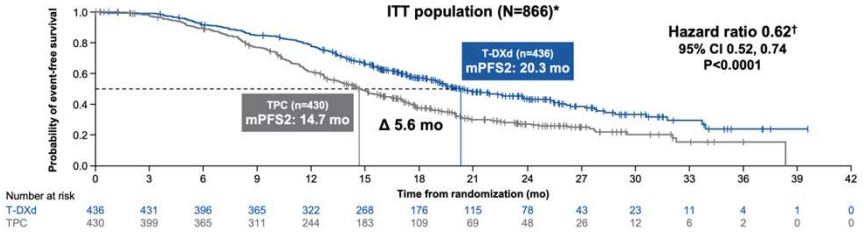
24th Multidisciplinary Management of Cancers: A Case-Based Approach

DESTINY-Breast06: PFS by time to progression on 1L ET + CDK 4/6i & PFS2



PFS2
* Type of treatment given in 2L setting is not available



Bardia et al., SABCS 2024

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DESTINY-Breast06: Interpretation

T-DXd >> TPC as first line chemotherapy

- No OS benefit to date, cross-over may impact this endpoint
- More toxicity w/ T-DXd (grade ≥3 AEs, fatal AEs), similar PROs

Exploratory endpoint: Similar efficacy in HER2-low and ultralow → T-DXd is a reasonable and effective option in HER2-ultralow subset

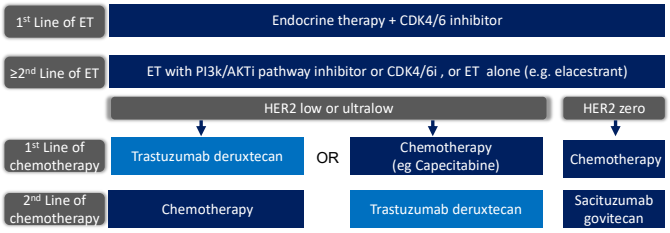
Definition of ultra-low: 0-1+?

- A challenge for our pathologists!
- Multiple new assays in development
- DestinyBreast-15 evaluating clinically HER2 0 cancers

Highly effective option after endocrine therapy, but appropriate sequence (1L or 2L chemo) should be determined for individual patients

- **1L:** Visceral dominant, symptomatic, short DFI
- **2L:** Bone/soft tissue dominant, asymptomatic, long DFI

FDA approved January 2025!



Krop, ASCO 2024

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Case 3 – Panel Discussion

- How would you treat this patient at this juncture?
- When do you think about using T-DXd as first line chemotherapy for HR+ MBC vs. using capecitabine first and then T-DXd second line?
- How often do you get chest CTs to monitor for ILD while patients are on T-DXd?

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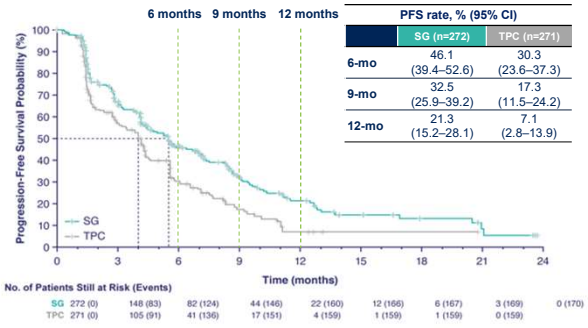
Case 3 – Metastatic HR+ BC

- She is started on T-DXd given symptomatic disease with rapid progression over 6 months.
- She tolerates T-DXd well and remains on treatment for 1 year until she has further PD in the liver.
- She has some abdominal discomfort, but it is mild and she is otherwise asymptomatic, ECOG 1, and her liver function remains normal.
- She is seeing you in clinic to discuss next line of therapy and you are considering another ADC.

TROPICS-02: SG vs. Chemo for 3-5L HR+/HER2- MBC

PFS

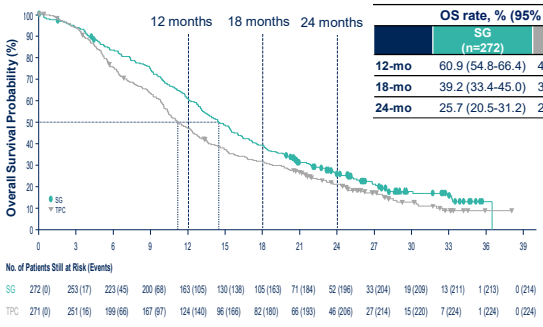
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

OS

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.5 (13.0–16.0)	11.2 (10.2–12.6)
Stratified HR (95% CI)	**0.79** (0.65–0.95)	
Nominal *P* value	*P*=0.0133	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-mo	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-mo	25.7 (20.5-31.2)	21.1 (16.3-26.3)

- SG demonstrated improvement in PFS (5.5 vs. 4.0 mo, HR 0.66) and OS (14.5 vs. 11.2 mo, HR 0.78)
- Major toxicities: Diarrhea, neutropenia, alopecia, fatigue

Bardia et al. *NEJM* 2021
Rugo et. al. *Lancet* 2023

24th Multidisciplinary Management of Cancers: A Case-Based Approach

TROPION-Breast01: Phase III trial of Dato-DXd vs. chemo for 2-3L HR+/HER2- MBC

Key eligibility
- HR+/HER2–[a] breast cancer
- Previously treated with 1–2 lines of chemo (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0/1

R 1:1

- **Dato-DXd 6 mg/kg IV Day 1 Q3W (n=365)**
- **TPC[b] (n=367)**

Continue until PD, unacceptable toxicity / other discontinuation criteria

Dual primary endpoints[c]:
- PFS by BICR
- OS

Key secondary endpoint:
- ORR
- PFS (investigator assessed)
- Safety

Stratification factors
- Lines of chemo in unresectable/ metastatic setting (1 vs 2)
- Geographical location (US/Canada/ Europe vs ROW)
- Previous CDK4/6 inhibitor (yes vs no)

- At data cutoff (July 17, 2023), patients remaining on treatment:
  - Dato-DXd, n=93
  - TPC, n=39
- Median follow-up: 10.8 months
- Median one line of prior therapy

[a]IHC 0/1+/2+; ISH–; [b]Investigator's choice of chemotherapy; [c]By BICR per RECIST v1.1.
Dato-DXd, datopotamab deruxtecan; TPC, treatment of physician's choice.

Bardia et al. SABCS 2023

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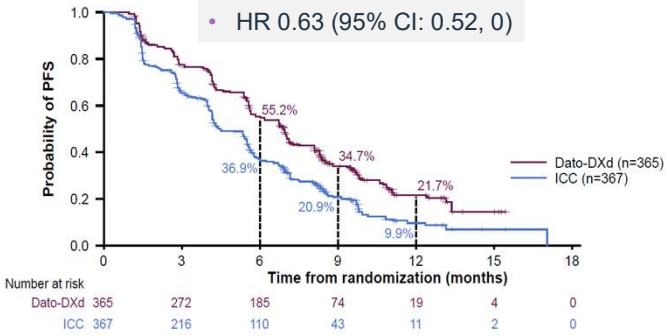
24th Multidisciplinary Management of Cancers: A Case-Based Approach

TROPION-Breast01: Results - PFS and OS (dual primary endpoints)

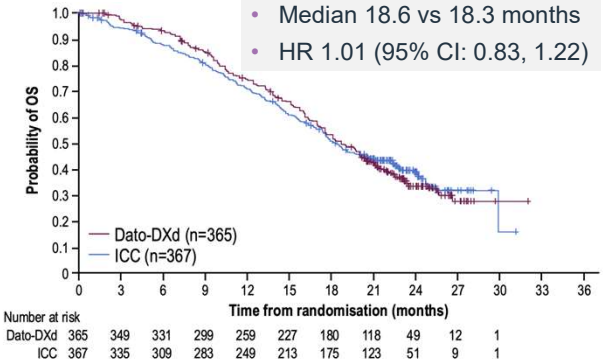
PFS

PFS by BICR
- Median 6.9 vs 4.9 months
- HR 0.63 (95% CI: 0.52, 0)



OS

Overall survival
- Median 18.6 vs 18.3 months
- HR 1.01 (95% CI: 0.83, 1.22)



Dato-DXd FDA approved Jan 17, 2025!

Bardia et al. SABCS 2023
Schmid et al., ESMO Virtual Plenary 2025

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Sequential use of ADCs? Retrospective multi-center study

- Prospective trials ongoing! e.g., TRADE-DXd, SERIES, ENCORE (TBCRC-067)
- Need to identify biomarkers of response and resistance

Huppert et al. ASCO 2024

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Case 3 – Panel Discussion

- After progression on T-DXd, what would you choose next for this patient?
- Now that we have three FDA-approved ADCs for HR+/HER2- MBC (T-DXd, SG, Dato-DXd), how do you think about sequencing ADCs?
- For anyone on the panel who has given Dato-DXd, what has been your experience in terms of tolerance and toxicity management?

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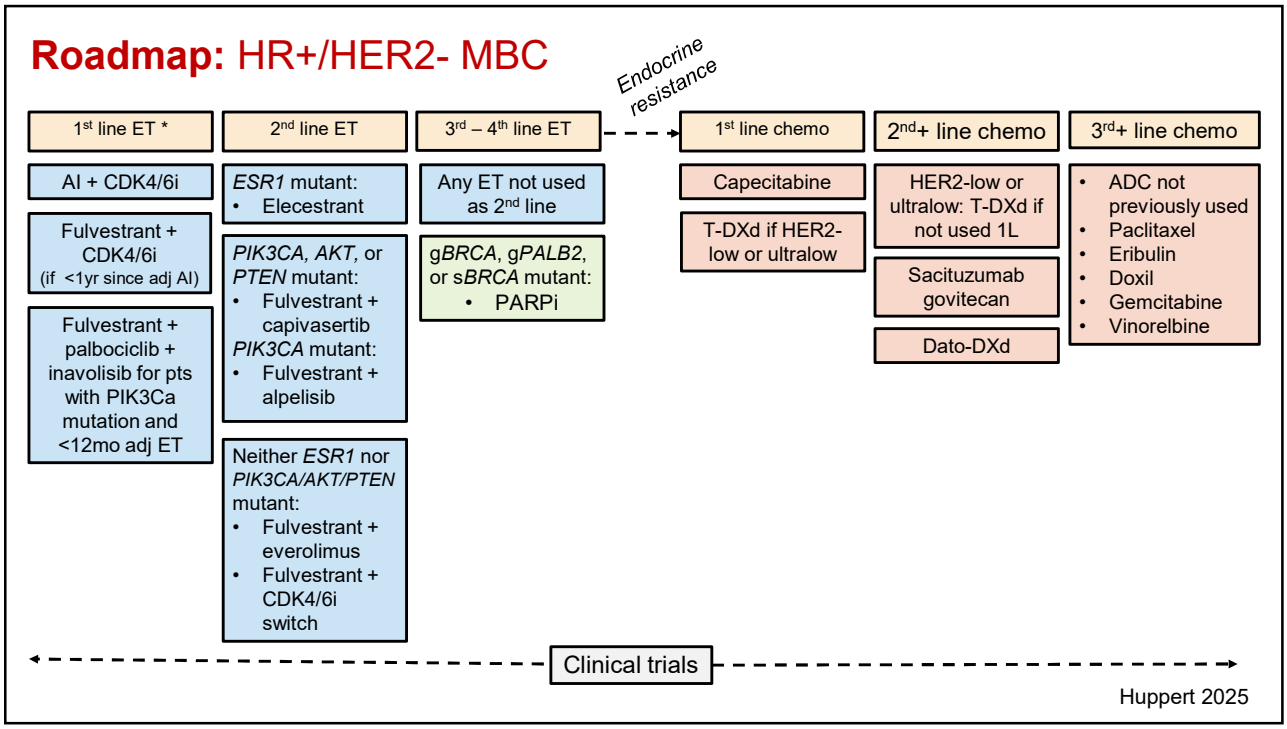

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24th Multidisciplinary Management of Cancers: A Case-Based Approach

Case 3 – Summary

- **Ribociclib and abemaciclib** are approved for adjuvant high-risk node-positive HR+ breast cancer. Longer follow up data available for abemaciclib at this time.
- The **INAVO-120** trial showed efficacy for inavolisib + fulvestrant + palbociclib for 1L therapy for early relapse in PIK3CA-Mutated HR+ HER2- advanced BC.
- T-DXd as 1L chemotherapy for HR+ MBC has shown efficacy in **DESTINY-Breast06**; whether to use it 1L vs. 2L depends on clinical context.
- Three ADCs now approved for HR+/HER2- MBC: **T-DXd**, **SG**, and most recently **Dato-DXd.**

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24th Multidisciplinary Management of Cancers: A Case-Based Approach

Case 4 – De novo HR+ / HER2+ MBC

- A 55 yo post-menopausal woman presents with de novo metastatic HR+ / HER2+ breast cancer to liver and bone.
- She is started on 1st line paclitaxel + trastuzumab + pertuzumab (THP).
- After 4 months, she has a complete response on imaging.
- She is otherwise healthy and wants to optimize her chance of a durable disease-free interval.

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24th Multidisciplinary Management of Cancers: A Case-Based Approach

What do you recommend for this patient's treatment (assuming all options available soon):

A. Continue trastuzumab + pertuzumab (HP) alone — 19%

B. Continue HP and add an aromatase inhibitor — 19%

C. Continue HP and add an aromatase inhibitor + palbociclib — 62%

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24th Multidisciplinary Management of Cancers: A Case-Based Approach

PATINA: Addition of CDK 4/6 inhibitors for HR+/HER2+ MBC

Registration
- Histologically confirmed HR+,HER2+ mBC
- No prior treatment in the advanced setting beyond induction treatment
- 6-8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine

Key eligibility criteria
- Completion of induction chemotherapy and no evidence of disease progression (i.e., CR, PR, or SD)

N=518 → R 1:1

- Palbociclib (125 mg PO QD D1-D21) Trastuzumab ± pertuzumab + endocrine therapy*
- Trastuzumab ± pertuzumab + endocrine therapy*

Until PD or toxicity → SURVIVAL FOLLOW-UP

Stratification factors
- Pertuzumab use (yes vs no)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)†
- Response to induction therapy (CR or PR vs SD) by investigator assessment†
- Type of endocrine therapy (fulvestrant vs aromatase inhibitor)

Key Patient Characteristics
- 97% patients received pertuzumab
- 91% of patients were on an AI
- 68.5% of patients achieved CR or PR during induction therapy

*Trastuzumab and pertuzumab were administered per SOC. Endocrine therapy options include an aromatase inhibitor or fulvestrant. †Factors used in stratified analyses. CR=complete response; D=day; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mBC=metastatic breast cancer; PD=progressive disease; PO=orally; PR=partial response; QD=once a day; R=randomization; SD=stable disease; SOC=standard of care.

Metzger et al., SABCS 2024

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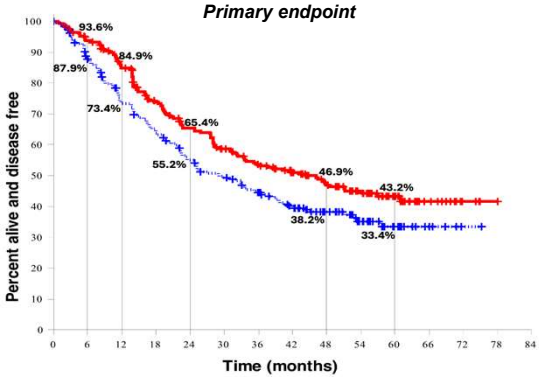
24th Multidisciplinary Management of Cancers: A Case-Based Approach

PATINA: PFS and OS benefit with the addition of palbociclib

mPFS 44.3 vs 29.1 mos

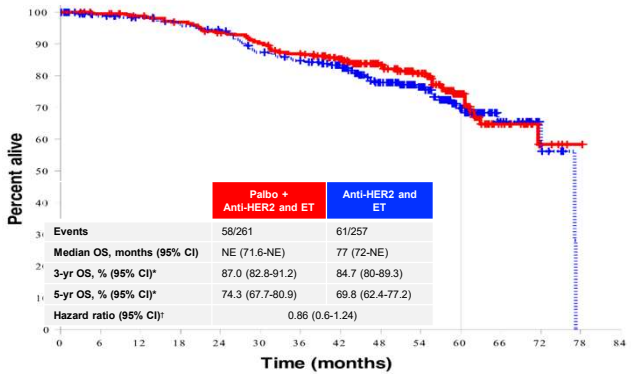
Primary endpoint



	Palbo + anti-HER2 and ET	Anti-HER2 and ET
Events	126/261	136/257
Median PFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P* value	0.0074	

mOS not reached vs 77 mos

Interim analysis



	Palbo + Anti-HER2 and ET	Anti-HER2 and ET
Events	58/261	61/257
Median OS, months (95% CI)	NE (71.6-NE)	77 (72-NE)
3-yr OS, % (95% CI)*	87.0 (82.8-91.2)	84.7 (80-89.3)
5-yr OS, % (95% CI)*	74.3 (67.7-80.9)	69.8 (62.4-77.2)
Hazard ratio (95% CI)†	0.86 (0.6-1.24)	

Toxicity was manageable, with neutropenia, stomatitis, and diarrhea being most common

Metzger et al., SABCS 2024

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Case 4 – Panel Discussion

- How do you think data from PATINA will change your practice if approved? Has anyone applied these data yet?
- For patients with de novo HER2+ disease and a complete response after induction therapy, do you ever consider breast surgery for patients? How do you discuss this?

Case 4 – De novo HR+ / HER2+ MBC

- The patient is treated with HP + letrozole + palbociclib and does well for 2 years.
- On annual screening MRI brain, she is found to have 2 new small left-sided lesions c/f metastatic disease.
- PET-CT also shows small new lesions in her liver.
- She otherwise feels well with normal LFTs
- You refer her to radiation oncology to discuss the utility of stereotactic radio surgery to the 2 CNS lesions.

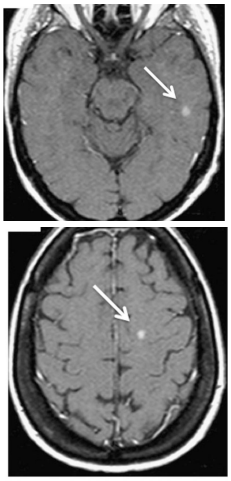
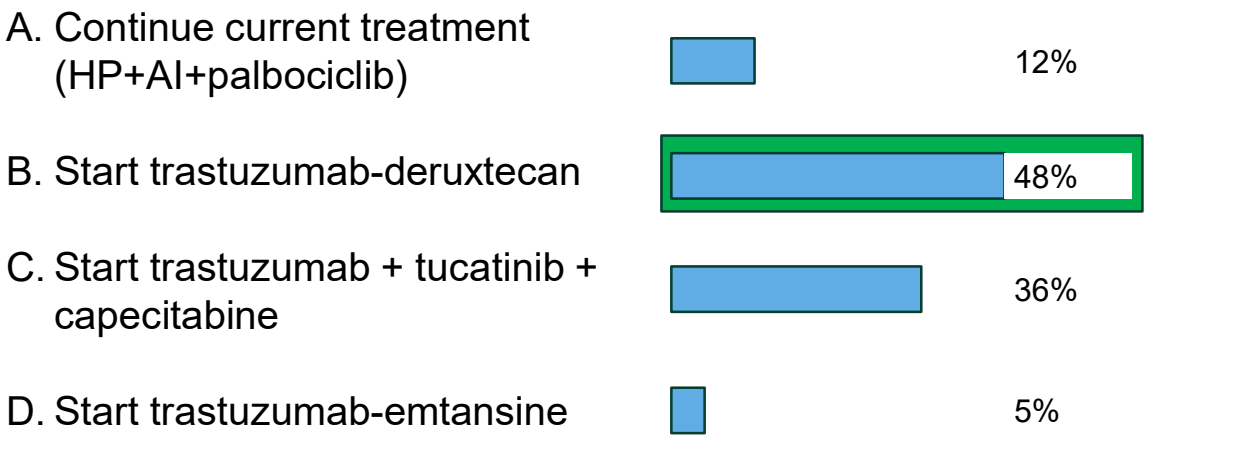


Image credit: Metro et al., *Ann of Oncol* 2011.

Case 4 – Panel Discussion

- Do you typically get screening brain MRIs for patients with HER2+ MBC? What about other subtypes?
- What is your practice around SRS to small asymptomatic CNS lesions like this vs. observation instead when switching to a CNS-penetrant regimen anyway?

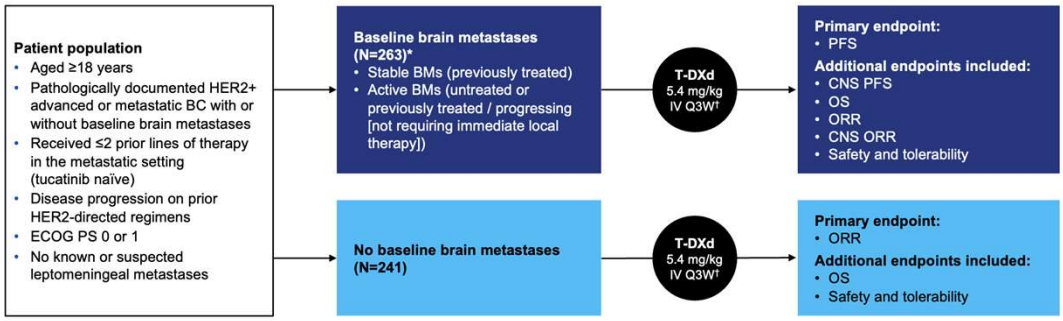
What do you recommend for systemic treatment?



24th Multidisciplinary Management of Cancers: A Case-Based Approach

DESTINY-Breast12: T-DXd in patients with and without brain metastases

Phase 3b/4, multicenter, single-arm, two-cohort, open-label study of T-DXd in previously treated HER2+ mBC with and without brain metastases (BMs); the largest prospective study of T-DXd in patients with stable or active BMs



Baseline brain mets (n=263)
- Stable brain mets (n=157)
- Active brain mets (n=106)
  - Untreated (n=39)
  - Previously treated/progressing (n=67)

Number of lines of prior therapy:
1 (~50%)
2 (~40%)

Prior therapies:
Trastuzumab (~97%)
Pertuzumab (~86%)
TDM1 (~40%)

Lin et al., ESMO 2024; Harbeck et al., *Nature Medicine* 2024

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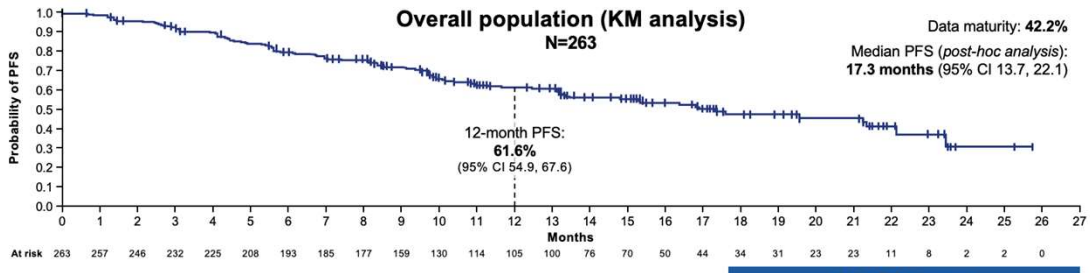
DESTINY-Breast12: Primary Endpoint – PFS in pts with brain mets



	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	Active BM subgroups: Untreated (n=39) Post-hoc analysis	Active BM subgroups: Previously treated / progressing (n=67) Post-hoc analysis
Overall no. events	111	64	47	20	27
12-month PFS, % (95% CI)	61.6 (54.9, 67.6)	62.9 (54.0, 70.5)	59.6 (49.0, 68.7)	47.0 (29.6, 62.7)	66.7 (53.4, 76.9)

- T-DXd showed consistent 12-months PFS in patients with stable and active brain metastases
  - 12-month PFS was **61.6%** overall (stable BMs: **62.9%**; active BMs: **59.6%**)
  - Estimated median PFS was **17.3 months**

Lin et al., ESMO 2024; Harbeck et al., *Nature Medicine* 2024

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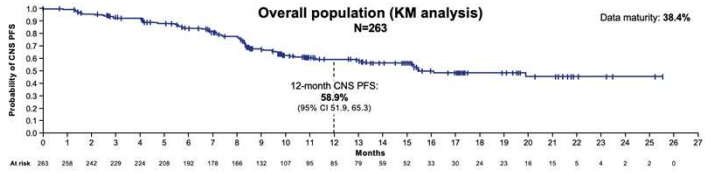
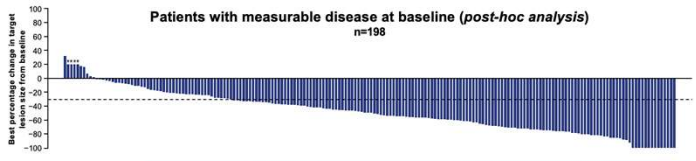
DESTINY-Breast12: Secondary efficacy endpoints and safety

Baseline BMs: CNS PFS



	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)
Overall no. events	101	61	40
12-month CNS PFS, % (95% CI)	58.9 (51.9, 65.3)	57.8 (48.2, 66.1)	60.1 (49.2, 69.4)

Baseline BMs: ORR



	Full analysis set†			Measurable disease at baseline (post-hoc analysis)		
	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	All patients (n=198)	Stable BMs (n=109)	Active BMs (n=89)
Confirmed ORR, % (95% CI)	51.7 (45.7, 57.8)	49.7 (41.9, 57.5)	54.7 (45.2, 64.2)	64.1 (57.5, 70.8)	67.0 (58.1, 75.8)	60.7 (50.5, 70.8)
CR, n (%)	11 (4.2)	–	–	2 (1.0)	–	–
PR, n (%)	125 (47.5)	–	–	125 (63.1)	–	–

- T-DXd showed consistent 12-month CNS PFS and substantial responses in patients with stable and active BMs
- In patients with no BMs, response rates in line with prior DB03 data (ORR **62.7%)**
- Consistent 12mo OS in patients with BMs (**90.3%**) and without BMs (**90.6%**)
- Safety signals overall consistent with prior, except 9 pts with grade 5 ILD (4 with concurrent opportunistic infection)
  - *Remember PJP ppx if pts on steroids!!*

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Lin et al., ESMO 2024; Harbeck et al., *Nature Medicine* 2024

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24th Multidisciplinary Management of Cancers: A Case-Based Approach

HER2 CLIMB: Tucatinib - a potent and selective HER2 TKI

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
  - No evidence of brain metastases

R* (2:1)

N = 410

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (days 1-14)

N = 202

Placebo + Trastuzumab + Capecitabine
(21-day cycle)

Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (days 1-14)

*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world).

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Murthy et al., *NEJM* 2024

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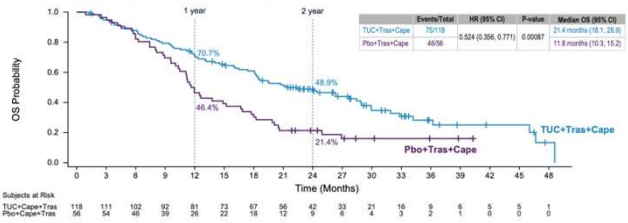
HER2 CLIMB: Updated PFS and OS in patients with brain mets

CNS-PFS for All Patients with Brain Metastases by Subgroup

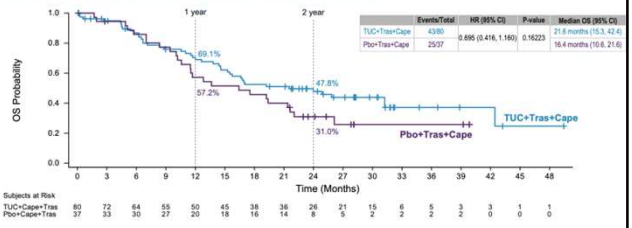
Subgroup	Treatment	Events	HR (95% CI)	P-Value	Median PFS (95% CI)
Patients with active brain metastases	TUC+Tras+Cape	69/118	0.339 (0.215, 0.536)	<0.00001	9.6 months (7.6, 11.1)
	Pbo+Tras+Cape	35/56			4.0 months (2.9, 5.6)
Patients with treated stable brain metastases	TUC+Tras+Cape	25/80	0.406 (0.194, 0.850)	0.01	13.9 months (9.7, 24.9)
	Pbo+Tras+Cape	13/37			5.6 months (3.0, –)

OS for Patients with Active Brain Metastases



- Median OS was 9.6 months longer in the tucatinib arm compared with the control arm in patients with active brain metastases.

OS for Patients with Treated Stable Brain Metastases



- Median OS was 5.2 months longer in the tucatinib arm compared with the control arm in patients with treated stable brain metastases.

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Lin et al, JCO 2020 & SABCS 2021.

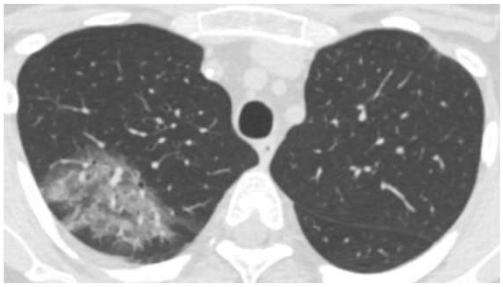
Case 4 – Panel Discussion

- What is your approach to 2L treatment for HER2+ MBC?
  - Without brain mets?
  - Stable brain mets?
  - Active brain mets?

Stanford Cancer Institute cancer.stanford.edu Stanford Medicine | UC DAVIS HEALTH | UCSF COMPREHENSIVE CANCER CENTER | Helen Diller Family Comprehensive Cancer Center | ANCO

Case 4 – De novo HR+ / HER2+ MBC

- She is started on T-DXd and tolerates treatment well, aside from nausea that is controlled with triplet IV therapy + addition of olanzapine.
- However, after 6 months on treatment, she is found to have ground glass opacities on a routine CT chest.
- She is asymptomatic and denies shortness of breath or cough. Normal O2 sat in clinic.
- She is diagnosed with **T-DXd related Grade 1 interstitial lung disease.**



Guidelines for the management of T-DXd related ILD

Monitor for suspected ILD/P

- Interrupt T-DXd if ILD/P is suspected
- Rule out ILD/P if radiographic changes consistent with ILD/P or if acute onset of new or worsening pulmonary symptoms develop

Confirm ILD/P by evaluation

- High-resolution CT, pulmonologist consultation, blood culture and CBC, bronchoscopy or BAL, PFTs and pulse oximetry, arterial blood gases, PK analysis of blood sample (as clinically indicated and feasible)[a]
- **All ILD/P events regardless of severity or seriousness should be followed until resolution including after drug discontinuation**

Manage ILD/P

Grade 1 ILD = asymptomatic
1) Hold T-DXd
2) Consider steroids
3) Consider re-challenge if CT findings resolve

Grade 1	Grade 2 (symptomatic)	Grade 3 or 4
• **Interrupt T-DXd** • T-DXd can be resumed if the ILD/P resolves to grade 0 – If resolved in ≤28 days from onset, maintain dose – If resolved in >28 days from onset, reduce dose by 1 level[b]	**Permanently discontinue T-DXd**	**Permanently discontinue T-DXd**
• **Discontinue T-DXd** if ILD/P occurs beyond day 22 and has not resolved within 49 days from the last infusion		
• Monitor and closely follow-up in 2-7 days for onset of clinical symptoms and pulse oximetry • Consider: – Follow-up imaging in 1-2 weeks, or as clinically indicated – Starting systemic glucocorticoids (e.g. ≥0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over ≥4 weeks *If diagnostic observations worsen despite initiation of corticosteroids, then follow grade 2 guidelines.*	• Promptly start systemic glucocorticoids (e.g. ≥1 mg/kg/day prednisone or equivalent) for ≥14 days until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks • Monitor symptoms closely • Re-image as clinically indicated • If worsening or no improvement in clinical or diagnostic observations in 5 days: – Consider increasing dose of glucocorticoids (e.g. 2 mg/kg/day prednisone or equivalent), and administration may be switched to i.v. (e.g. methylprednisolone) – Reconsider additional workup for alternative etiologies as described above – Escalate care as clinically indicated	• Hospitalization required • Promptly start empirical high-dose methylprednisolone i.v. treatment (e.g. 500-1000 mg/day for 3 days), followed by ≥1.0 mg/kg/day of prednisone (or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks • Re-image as clinically indicated • If still no improvement within 3-5 days: – Reconsider additional workup for alternative etiologies as described above – Consider other immunosuppressants (e.g. infliximab or mycophenolate mofetil) and/or treat per local practice
We suggest considering steroids for selected grade 1 cases that show extensive lung involvement or in patients at increased risk for progression of ILD/P		

Grade 2+ ILD = Symptomatic
1) Permanently discontinue T-DXd
2) Recommend steroids

Rugo et al., *ESMO Open* 2022.

Retrospective data on re-challenge after grade 1 ILD

Pooled data from DESTINY-Breast trials[1] (n=2145)

- 9.0% rate of any grade ILD (n=193)
- 45 patients retreated; 50% received steroids
- **33% rate of recurrent ILD**, all grade 1-2
- Median time to recurrent ILD was 64 days (range 22-391)

	T-DXd retreatment (N = 45)
Dose level of T-DXd retreatment	
Same dose, n (%)	31 (68.9)
Reduced dose, n (%)	14 (31.1)
Median time to retreatment after ILD1 onset (range), days	28 (8-48)
Median retreatment cycles (range)	5.0 (1-37)
Patients with ILD2 (n = 15)	5.0 (2-23)
Patients without ILD2 (n = 30)	4.5 (1-37)
Median retreatment duration (range), days	85.0 (1-848)
Patients with ILD2 (n = 15)	85.0 (22-648)
Patients without ILD2 (n = 30)	82.5 (1-848)

Similar findings seen in real-world studies

French retrospective cohort study[3]

- Median re-treatment duration not reported
- 33% rate of recurrent ILD (grades not reported)

UCSF retrospective cohort study[2]

- Median re-treatment duration 105 days
- 26% rate of recurrent ILD, all grade 1-2

- Re-treatment with T-DXd after grade 1 ILD is safe with low rates of recurrent ILD.
- Patients can have ongoing clinical benefit after re-treatment.

1. Rugo et al., ESMO Breast 2024
2. Canellas et al. ESMO 2024
3. Natsuhara et al., ESMO 2024

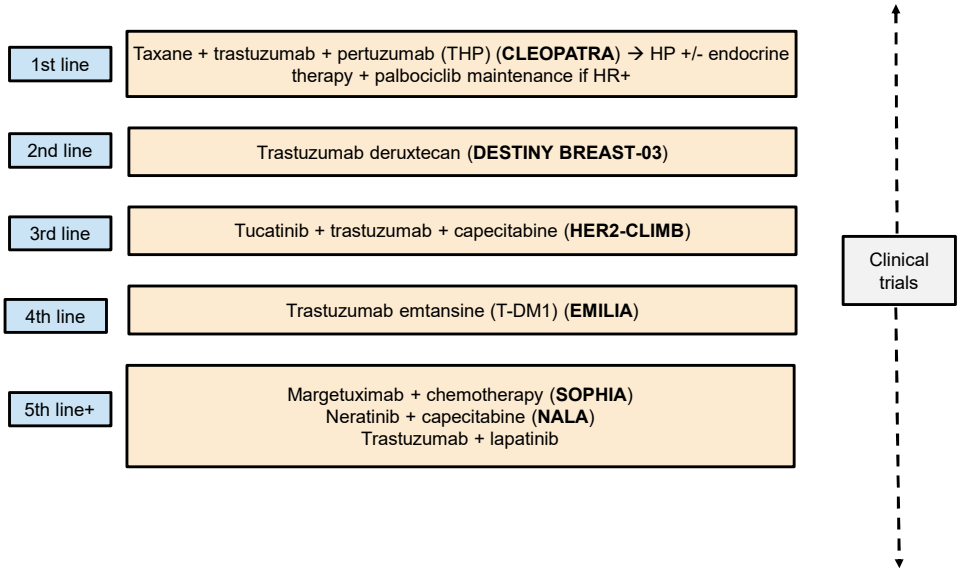
Case 4 – Panel Discussion

- How do you manage T-DXd related ILD in your practice?
- How often do you give steroids? Dose? Duration?
- What is your experience with re-treatment after grade 1 ILD? Do you continue T-DXd at same dose with re-challenge or dose reduce?

Case 4 – De novo HR+ / HER2+ MBC

- The patient has T-DXd held and is started on prednisone 0.5 mg/kg daily + PJP prophylaxis.
- She has a repeat CT in 4 weeks that shows resolution of ground glass opacities.
- She is re-treated with T-DXd at the same dose and steroids are slowly tapered.
- She has not developed recurrent ILD and remains on therapy.

Roadmap: HER2+ MBC



Huppert 2025

Case 4 – Summary

- The **PATINA** trial showed PFS and OS benefit to adding palbociclib to HP + endocrine therapy after induction chemo for HR+/HER2+ MBC; though, not yet FDA-approved.
- **DESTINY-Breast12** demonstrated consistent benefit for patients with both stable and active brain metastases.
- Close monitoring is required for T-DXd related ILD. If patients develop asymptomatic grade 1 ILD, they can be **re-treated with T-DXd** if imaging findings resolve. Rechallenge not recommended for G2+ ILD.

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Case 5 – Metastatic TNBC

- A 58 yo post-menopausal woman presents to her PCP with new back pain that has been present for three months and is worse over the last 2 weeks.
  - X-ray of her lumbar spine demonstrates a suspected lytic bone lesion
  - PET-CT demonstrates diffuse bone lesions and a 1.9 cm lung lesion.
- CT-guided biopsy of lung confirms **breast adenocarcinoma that is ER neg, PR neg, HER2 neg (IHC 1+) with PD-L1 CPS 15**.
- Germline genetic testing shows no pathogenic mutations
- She is referred to radiation oncology for palliative radiation to the spine lesion, and presents to medical oncology to discuss systemic treatment. ECOG 1.

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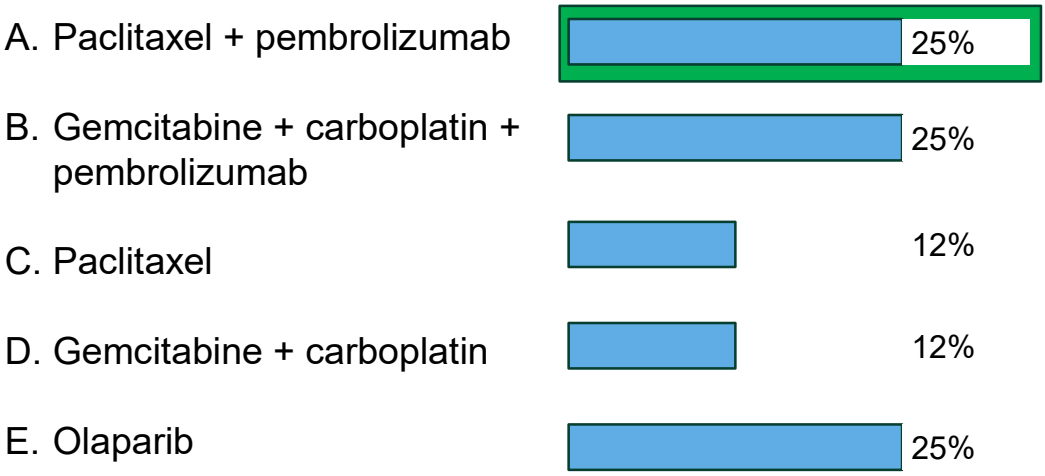
What do you recommend for 1st line systemic treatment?



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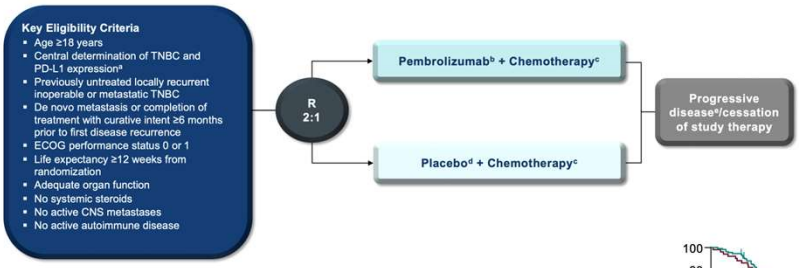
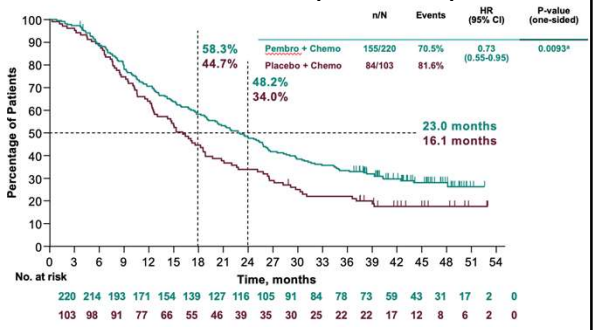
KEYNOTE-355: 1L chemotherapy +/- pembrolizumab for mTNBC



In PDL1+ cohort, addition of pembro resulted in improvement in:

- PFS (**9.7** vs. **5.6** mo, HR 0.65)
- OS (**23.0** vs. **16.1** mo, HR **0.73**)

OS in PDL1+ (CPS ≥ 10)



Cortes et al *Lancet* 2020; Cortes et al *NEJM* 2022

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Case 5 – Metastatic TNBC

- She is treated with paclitaxel + pembrolizumab.
- She is stable for 9 months, until staging PET/CT demonstrates a new 2.1 cm liver lesion.
- She presents to your clinic to discuss next line therapy.
- You recommend sacituzumab-govitecan and discuss the risks/benefits with her.

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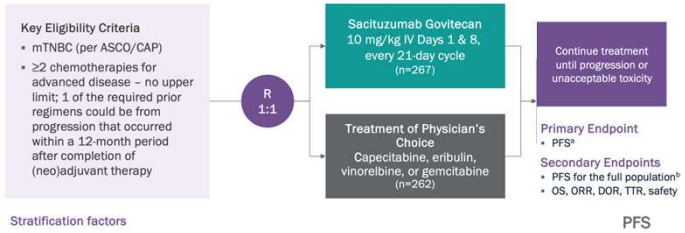
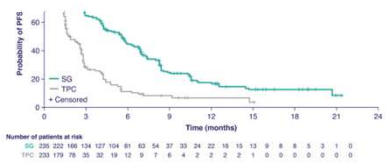
ASCENT: Sacituzumab Govitecan vs. TPC in Refractory/Relapsed mTNBC



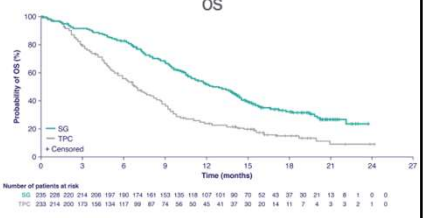
SG resulted in improvement in:
- **PFS** (**5.6** vs. **1.7** mo, HR **0.43**)
- **OS** (**12.1** s. **6.7** mo, HR **0.48**)

PFS



PFS BICR	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<0.001	

OS



OS	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<0.001	

Bardia et. al. *NEJM* 2021

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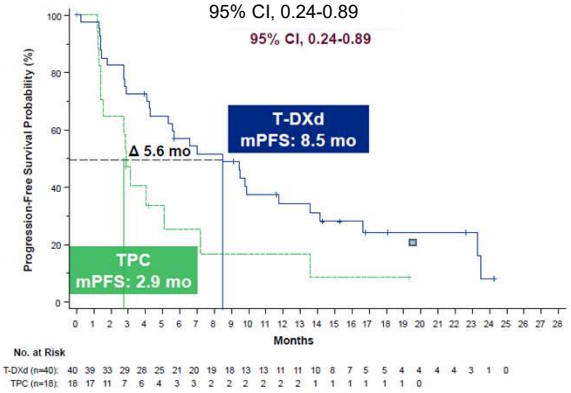
DESTINY-Breast04: T-DXd vs. TPC in HR- Cohort (Exploratory Endpoint, n=58)

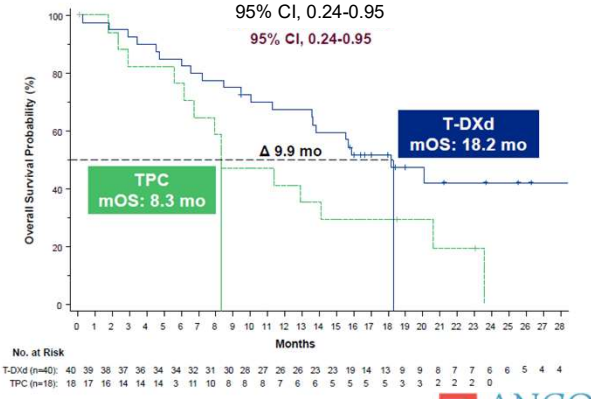
PFS

Hazard ratio: **0.46**
95% CI, 0.24-0.89



OS

Hazard ratio: **0.48**
95% CI, 0.24-0.95



Modi et al., *NEJM* 2022; ESMO 2023 Abstract 376O.

Case 5 – Panel Discussion

- Can you discuss your approach to treatment of 2L mTNBC? What agent do you prefer and why?
- What are the most common toxicities you see with SG? What is your approach to management of neutropenia?
- If a patient has a pathogenic BRCA mutation, when where would you insert a PARPi into your treatment algorithm?

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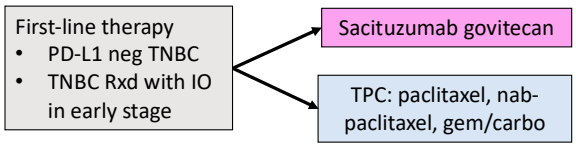
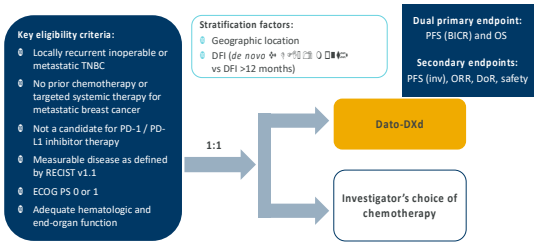
Select 1L mTNBC trials in progress

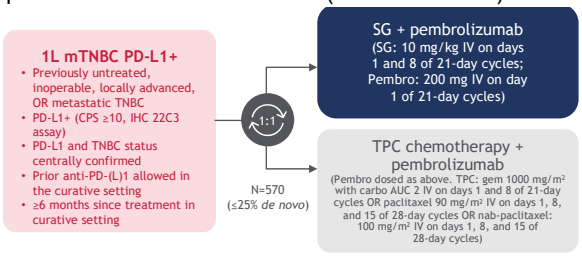
ASCENT-03: **Sacituzumab-govitecan** vs treatment of physician's choice in 1L mTNBC (NCT05382299)



TROPION-Breast02: Datopotamab-deruxtecan vs Investigator's Choice Chemotherapy 1L PDL1- mTNBC (NCT05374512)



ASCENT-04: **Sacituzumab-govitecan + Pembrolizumab** vs treatment of physician's choice + pembro in 1L PDL1+ mTNBC (NCT05382299)



All are anticipated to report in 2025: Look out for new data that may change practice this year!

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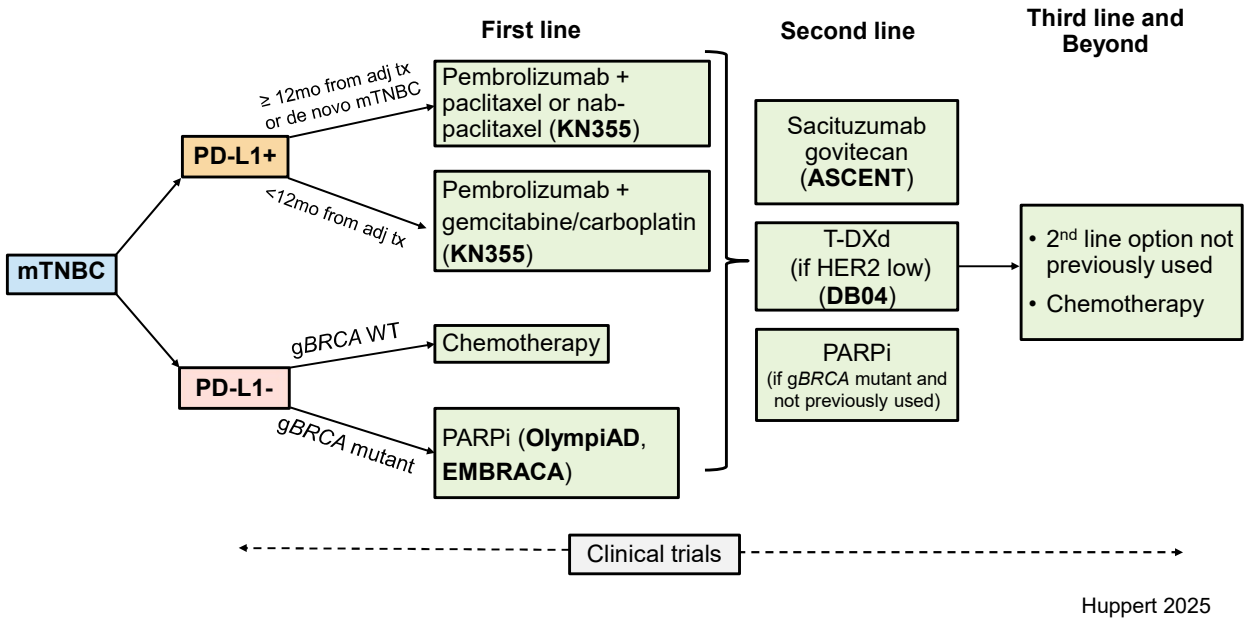
Roadmap: mTNBC



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Case 5 – Summary

- The **KEYNOTE-355** trial demonstrates the benefit of the addition of pembrolizumab to chemotherapy for 1L mTNBC, PD-L1 CPS≥10.
- The **ASCENT** trial showed a PFS and OS benefit of sacituzumab-govitecan for 2L TNBC.
- The **DESTINY-Breast04** trial also included a subset of patients with HR-/HER2-low MBC so T-DXd is also an approved option for mTNBC in 2L+
- Multiple 1L mTNBC trials will be reporting soon that could change practice!

Thank You!

24th Multidisciplinary Management of Cancers: A Case-Based Approach

EXTRA SLIDES:

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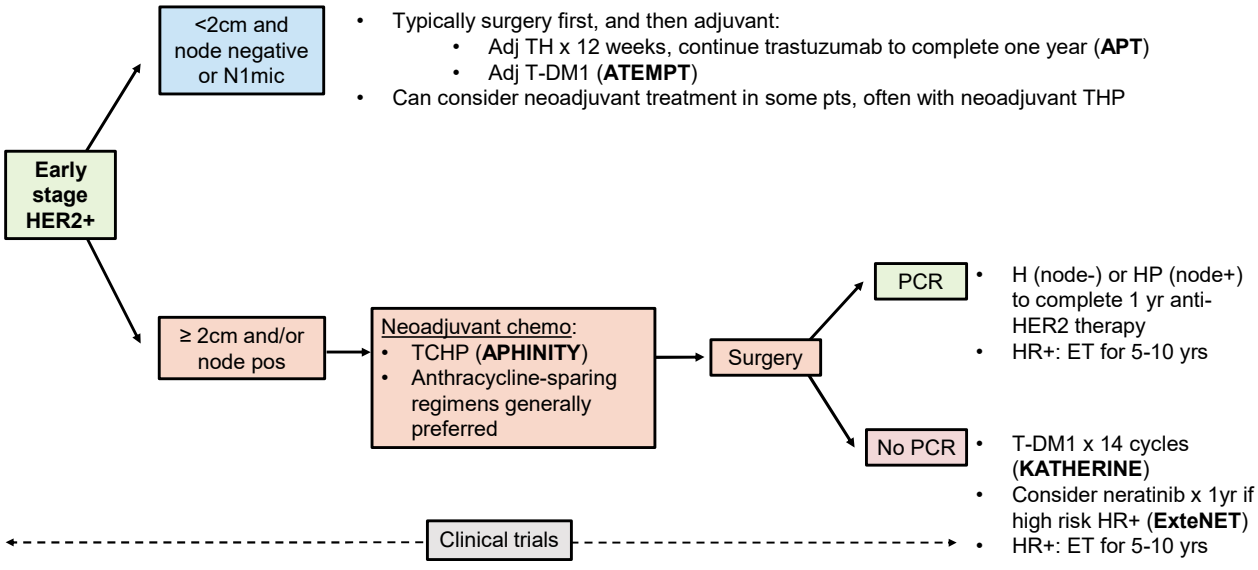
Roadmap: Early-stage HER2+ breast cancer



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