Breast Cancer Update: HR+ and HER2+ disease

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OHSU Breast Medical Oncology
Annual Hematology and Breast Cancer Update
April 16, 2022
Outline

**HR+**

- Adjuvant abemaciclib (monarchE)
- 1L Ribociclib overall survival (Monaleesa-2)
- Elacestrant novel SERD (EMERALD)

**HER2+**

- 2L T-DXd vs TDM1 (DB-03)
- Tucatinib Overall survival & brain metastases update (HER2CLIMB)
CDK4/6 inhibitors mechanism of action

1. RB-dependent proliferation arrest
   - Cytostasis, apoptosis

2. RB non-canonical
   - Recruitment of histone modifiers
   - Activation of transcription factors

3. CDK4/6 non-RB substrates
   - Apoptosis, senescence

4. Differential effects on immune cell function

Goel Nat Rev Cacer 2022
Lallemand BJMO 2017
CDK4/6 inhibitors and immune modulation

CDK4/6i synergy with aPDL1 (CRC xenograft)

Abema
aPDL1
Abema+PDL1

Goel Nat Rev Cancer 2022; Schaer Cell Reports 2018
CDK4/6 inhibitors approved

<table>
<thead>
<tr>
<th>Agent</th>
<th>Selectivity (IC₅₀)</th>
<th>Clinical development</th>
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</thead>
<tbody>
<tr>
<td><strong>Approved</strong></td>
<td></td>
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</tr>
<tr>
<td>Palbociclib</td>
<td>CDK4: 11 nM</td>
<td>Approved for HR⁺, HER2⁻ advanced breast cancer in combination with hormonal therapy</td>
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<tr>
<td></td>
<td>CDK6: 16 nM</td>
<td></td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>CDK4: 2 nM</td>
<td>Approved for HR⁺, HER2⁻ advanced breast cancer in combination with hormonal therapy</td>
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<tr>
<td></td>
<td>CDK6: 10 nM</td>
<td>Approved as monotherapy for advanced HR⁺, HER2⁻ breast cancer</td>
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<tr>
<td></td>
<td></td>
<td>Approved as adjuvant therapy for high-risk, early-stage HR⁺, HER2⁻ breast cancer in</td>
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<tr>
<td></td>
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<td>combination with hormonal therapy</td>
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<tr>
<td>Ribociclib</td>
<td>CDK4: 10 nM</td>
<td>Approved for HR⁺, HER2⁻ advanced breast cancer in combination with hormonal therapy</td>
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<tr>
<td></td>
<td>CDK6: 39 nM</td>
<td></td>
</tr>
<tr>
<td>Trilaciclib</td>
<td>CDK4: 1 nM</td>
<td>Approved to reduce chemotherapy-induced bone marrow suppression in patients with</td>
</tr>
<tr>
<td></td>
<td>CDK6: 4 nM</td>
<td>extensive-stage SCLC</td>
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</tbody>
</table>
CDK4/6 inhibitors in the 1L metastatic setting

**Progression free survival**

**Palbociclib**

*PALOMA-2*

Finn NEJM 2016

Hazard ratio, 0.58
(95% CI, 0.46–0.72)
Two-sided P<0.001

**Ribociclib**

*MONALEESA-2*

Hazard ratio, 0.56 (95% CI, 0.43–0.72)
P=3.29×10⁻⁶ for superiority

**Abemaciclib**

*MONARCH-3*

Censored observations

Abemaciclib arm: median, not reached
Placebo arm: median, 14.7 months

Hazard Ratio = 0.54-0.58
CDK4/6 inhibitors in the adjuvant setting

- **Palbociclib**
  - Penelope-B (x1y)
  - PALLAS (x2y)
  - Negative studies

- **Abemaciclib**
  - monarchE (x2y)
  - FDA approval Oct 2021
  - LN+ Ki67 > 20%

- **Ribociclib**
  - EarLEE (x2y)
  - NATALEE (x3y)
  - Pending

Negative studies Pending FDA approval Oct 2021 LN+ Ki67 > 20%
MonarchE: Adjuvant abemaciclib in HR+ high clinical risk

Inclusion:
- LN+ microscopic or macroscopic
- Pre & postmenopausal
- Bilateral disease allowed

Exclusion:
- History of VTE (including line thrombosis)

Early stage HR+, HER2-, LN+  
N = 5,637

Cohort 1 (Any Ki67)
- ≥ 4 axillary LN + OR
- ≥ 1 LN+ (1-3) AND Grade 3 or T ≥ 5cm

Cohort 2 (Ki67 ≥ 20%)
- ≥ axillary LN+ (1-3) AND Grade < 3 or T <5cm

Abemaciclib + ET x2 years

ET alone x2 years

ET: Tamoxifen, anastrozole, letrozole, exemestane

Ki67 ≥ 20% on primary untreated specimen (MIB-1)
LN on pathologic staging
Cohort 2 started enrolling 1y after
MonarchE: patient population

**Postmenopausal** 60%

**Aromatase inhibitor** 70%
- OFS 15%
- Tamoxifen 30%

**Chemotherapy** 95%
- Anthracycline + taxane 80%

**Axillary LN > 4** 60%

**Grade 3** 40%
- G1 10%
- G2 50%

**Tumor > 5cm** 20%
- T < 2cm 30%
- T 2-5cm 50%

**Ki67 > 20%** 45%
MonarchE: invasive disease free survival at 2 years

2y iDFS 92.2% versus 88.7%
HR 0.75, p = 0.01
Distant recurrence: 70%

P = .01
HR (95% CI): 0.75 (0.60 to 0.93)

No. Patients  No. Events
Abemaciclib + ET  2,808  136
ET alone  2,829  187

△ +3.5%
monarchE: iDFS ITT population at 3 years
Cohort 1 & 2 (included low ki67)

Graph showing invasive disease-free survival (in %) over time (months).
Nominal $P < 0.0001$
$HR = 0.70$ (95% CI 0.59-0.82)

- 2-year rate: 92.7%
- 3-year rate: 88.8%

2-year rate: 90.0%
3-year rate: 83.4%

$\Delta +5.3\%$
monarchE: iDFS cohort 1 by Ki67 (3 year follow-up)

Ki67 low: ∆ +4.5%

Ki67 high: ∆ +7.1
20-year risks of breast cancer recurrence after stopping endocrine therapy at 5 years

N = 62,923 patients

MonarchE Cohort 1: 50% will have late recurrences

*Ki-67 independent prognostic factor during the first 5 years but only moderate relevance thereafter.
monarchE: iDFS cohort 2 (3 year follow-up)

Cohort 2 (Ki67 ≥ 20%)
> axillary LN+ (1-3)
AND
Grade < 3 or T <5cm

Nominal $P = 0.0005$
HR = 0.66 (95% CI 0.52-0.84)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abemaciclib + ET</td>
<td>1262</td>
</tr>
<tr>
<td>ET alone</td>
<td>1236</td>
</tr>
</tbody>
</table>

2-year rate: 91.9%
3-year rate: 86.8%
2-year rate: 87.9%
3-year rate: 80.8%

△ +6%
Penelope-B: adjuvant Palbociclib

Palbociclib x1y
No pCR after NACT CPS-EG >3 or >2 ypN+
Discontinuation rate 20%
Median follow-up 42.8m
No difference Ki67 (post chemo <15 or >15%)
- Ki67 <15% roughly 75% both arms

PALLAS: adjuvant palbociclib

Palbociclib x2y
Stage II/III
Discontinuation rate 42%
Median follow-up 23.7m
No difference by grade
Ki67 not assessed

MonarchE
Slightly higher risk population
Lower discontinuation rate?
Continuous dosing, CDK4>CDK6
Adjuvant abemaciclib toxicity considerations

- 6.5% versus 1.1% of patients discontinued for AEs
- Patient time: lab monitoring, time, additional visits
- Rare serious side effects

Diarrhea – Monarch3: abemaciclib + AI

70-75% of patients required loperamide
Supplementary Table S4. Safety data in safety population at AFU1

<table>
<thead>
<tr>
<th></th>
<th>Abemaciclib + ETN=2791, n (%)</th>
<th>ET alone N=2800, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Additional adverse events of interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolic event&lt;sup&gt;d&lt;/sup&gt;</td>
<td>71 (2.5%)</td>
<td>32 (1.1%)</td>
</tr>
<tr>
<td>PE</td>
<td>28 (1.0%)</td>
<td>24 (0.9%)</td>
</tr>
<tr>
<td>Interstitial lung disease&lt;sup&gt;a&lt;/sup&gt;</td>
<td>89 (3.2%)</td>
<td>10 (0.4%)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any SAEs</td>
<td>424 (15.2%)</td>
<td></td>
</tr>
</tbody>
</table>
Abemaciclib approved LN+ & Ki67 ≥ 20%, not anatomically high-risk
  • Benefit not restricted to high Ki67 (similar hazard rates)
  • FDA weighed in immature OS data into decision (no difference in OS in the ITT)
  • Reliability of Ki67

Waiting for long term follow-up

Will the benefit be sustained?

Can cytostatic therapy can do any more than delay an inevitable relapse?

Added toxicity

Patient selection?
DARE Trial
Phase II trial of ctDNA guided adjuvant therapy for high risk stage II-III ER+, HER2- breast cancer

Surveillance phase

Adjuvant ET x6m → Serial ctDNA → If ctDNA+ NED by imaging

Treatment phase

R 1:1

- Palbociclib + Fulvestrant
- Continue same ET or switch between AI or TAM
Intolerance to adjuvant endocrine therapy and outcomes

In real world 20% stop within 1 year and 30-60% stop before 5 years

Early cessation (within 6m) versus completion
Ribociclib overall survival benefit

Monaleesa-2: Postmenopausal
1L Ribociclib + letrozole

Maintained across bone-only, visceral mets, number of metastatic sites, prior chemo, prior endocrine therapy
Ribociclib overall survival benefit

Monaleesa-3

Monaleesa-3: Postmenopausal
Ribociclib + fulvestrant

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>No. of Deaths</th>
<th>Median Overall Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribociclib + Fulvestrant</td>
<td>484</td>
<td>167</td>
<td>Not reached</td>
</tr>
<tr>
<td>Placebo + Fulvestrant</td>
<td>242</td>
<td>108</td>
<td>40.0</td>
</tr>
</tbody>
</table>

Hazard ratio for death, 0.72 (95% CI, 0.57–0.92)
P = 0.00455
Ribociclib Overall Survival Benefit
Monaleesa-7

Monaleesa-7: Premenopausal
Ribociclib + TAM or AI/OFS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>No. of Deaths</th>
<th>Median Overall Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribociclib + Endocrine Therapy</td>
<td>335</td>
<td>83</td>
<td>NE</td>
</tr>
<tr>
<td>Placebo + Endocrine Therapy</td>
<td>337</td>
<td>109</td>
<td>40.9</td>
</tr>
</tbody>
</table>

Hazard ratio for death, 0.71 (95% CI, 0.54–0.95)
P=0.00973

Im NEJM 2019
Ribociclib OS benefit by intrinsic subtype
Pooled analysis Monaleesa -2, -3, 7

<table>
<thead>
<tr>
<th>Intrinsic Subtype</th>
<th>Placebo + ET</th>
<th>Ribociclib + ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>222 (54) 122 54.6 48.3-66.2</td>
<td>320 (55) 135 68.0 61.5-NR</td>
</tr>
<tr>
<td>Luminal B</td>
<td>124 (30) 79 44.9 35.5-52.6</td>
<td>154 (26) 75 58.8 48.3-79.2</td>
</tr>
<tr>
<td>HER2E</td>
<td>52 (13) 39 29.4 23.9-42.0</td>
<td>95 (16) 59 40.3 33.4-49.0</td>
</tr>
<tr>
<td>Basal-like</td>
<td>14 (3) 11 21.2 12.8-NR</td>
<td>16 (3) 14 19.4 10.7-33.2</td>
</tr>
</tbody>
</table>

Survival Probability

- Luminal-A
- Luminal-B
- HER2E
- Basal-like
Oral selective estrogen receptor degraders

Fulvestrant
ESR1-mutations: resistance to aromatase inhibitors

ESR1-mt, incidence 20-40% advanced disease

Combined analysis SoFEA/EFECT by ESR1
Exemestane vs fulvestrant

- Median PFS (95% CI)
  - Wild-type + E 106/121 4.8 mth (3.7–6.2)
  - Wild-type + F 120/147 4.1 mth (3.6–5.5)
  - Mutant + F 69/73 3.9 mth (3.0–6.0)
  - Mutant + E 40/42 2.4 mth (2.0–2.6)
Elacestrant: oral selective estrogen receptor degrader

In vivo efficacy

**ESR1-wt**

- Vehicle
- Fulvestrant 3 mg/dose
- Fulvestrant + palbociclib
- Elacestrant 30 mg/kg
- Elacestrant 60 mg/kg

**ESR1-mt**

- Vehicle
- Fulvestrant 1 mg/dose
- Elacestrant 30 mg/kg
- Elacestrant 60 mg/kg

Phase 1

- Maximum % Change in the Sum of Dimensions of Target Lesions
- PD
- SD
- PR

Bihani CCR 2017
Bardia JCO 2021
EMERALD: P3 Elacestrant vs SOC for ER+/HER2- advanced breast cancer

N = 477

**Inclusion**
- 1-2 L of endocrine therapy
- Prior tx with CDK4/6i
- ≤ 1L of chemo

**Elacestrant**
- 400mg PO daily

**SOC**: fulvestrant or AI

(70% received fulvestrant)

Co-Primary: PFS ESR1-mt
- PFS in all patients
- (ESR1-mt by ctDNA Guardant360)
### EMERALD: Demographics and characteristics

**Majority of patients had visceral disease**
50% received 1L ET
20% received 1L chemotherapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Elacestrant</th>
<th>SOC</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All (N=239)</td>
<td>mESR1 (N=115)</td>
</tr>
<tr>
<td>Visceral metastasis*, n (%)</td>
<td>163 (68.2)</td>
<td>81 (70.4)</td>
</tr>
<tr>
<td>Bone-only disease, n (%)</td>
<td>38 (15.9)</td>
<td>14 (12.2)</td>
</tr>
<tr>
<td>Prior adjuvant therapy, n (%)</td>
<td>158 (66.1)</td>
<td>62 (53.9)</td>
</tr>
<tr>
<td>Number of prior lines of endocrine therapy,** n (%)</td>
<td>129 (54.0)</td>
<td>73 (63.5)</td>
</tr>
<tr>
<td></td>
<td>110 (46.0)</td>
<td>42 (36.5)</td>
</tr>
<tr>
<td>Number of prior lines of chemotherapy,** n (%)</td>
<td>191 (79.9)</td>
<td>89 (77.4)</td>
</tr>
<tr>
<td></td>
<td>48 (20.1)</td>
<td>26 (22.6)</td>
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</tbody>
</table>
EMERALD: PFS ITT population (ESR-wt + ESR-mt)

mPFS 2.8 versus 1.9 months
EMERALD: PFS all patients and mESR1 by PFS 6/12m

6m: 34% vs 20% \(\Delta +14\%\)
12m: 22% vs 9% \(\Delta +13\%\)

6m: 41% vs 19% \(\Delta +22\%\)
12m: 27% vs 8% \(\Delta +19\%\)
EMERALD: Overall survival interim analysis (mature late 2022/early 2023)

Trend towards OS benefit
### EMERALD: Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Elacestrant</th>
<th>Fulvestrant/AI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>G3/4</td>
</tr>
<tr>
<td>Nausea</td>
<td>35%</td>
<td>19%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Dec appetite</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Constipation</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Back pain</td>
<td>14%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>

Roughly same:
- Fatigue, arthralgias, diarrhea, AST/ALT elevations,
- hot flushes, headache
EMERALD: Conclusions

• 40-50% of patients will progress within 2 months
• Activity in ESR1-mutants
• Oral SERD >> versus fulvestrant
• Will elacestrant replace AI in early stage or 1L setting?
Novel estrogen degraders, modulators in development

Open at OHSU:

**Neoadjuvant (ISPY2)**
- Amcenestrant

**Metastatic**
- Camizestrant (SERENA4)
- OP-1250 (Olema)
# Landscape of treatment for advanced HER2+ disease

<table>
<thead>
<tr>
<th>First line</th>
<th>Second line</th>
<th>Third line</th>
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<tbody>
<tr>
<td>Docetaxel + HP</td>
<td>T-DM1</td>
<td>Trastuzumab deruxtecan</td>
</tr>
<tr>
<td>Paclitaxel + HP</td>
<td>Trastuzumab deruxtecan</td>
<td>Tucatinib + trastuzumab + capecitabine</td>
</tr>
<tr>
<td>Doce + Carbo+ HP</td>
<td>Tucatinib + trastuzumab + capecitabine</td>
<td>Neratinib + capecitabine</td>
</tr>
</tbody>
</table>

Trastuzumab/Margetuximab chemo partners
- Capecitabine
- Docetaxel
- Paclitaxel +/- carboplatin
- Eribulin
- Gemcitabine
- Vinorelbine
Dual blockade improved mOS by 16 months
Median OS = 4.7 years
Alive at 8y 37%
EMILIA\textsuperscript{[1]}: Randomized phase III study of lapatinib + capecitabine vs T-DM1 for HER2+ MBC with progression on trastuzumab + taxane (N = 991)

<table>
<thead>
<tr>
<th></th>
<th>Lapatinib + Cape</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, Mos</td>
<td>25.1</td>
<td>30.9</td>
</tr>
</tbody>
</table>

HR: 0.68 (95% CI: 0.55-0.85; P < .001)*

Patients at Risk, n
Lapatinib + Cape T-DM1
496 471 453 435 403 368 297 240 201 159 133 110 86 63 45 27 17 7 4
495 485 474 457 439 418 349 293 242 197 164 136 111 86 62 38 28 13 5

TH3RESA\textsuperscript{[2]}: Randomized phase III study of physician’s choice vs T-DM1 for HER2+ MBC with progression on a taxane, lapatinib, and ≥ 2 HER2-targeted regimens including trastuzumab (N = 602)

<table>
<thead>
<tr>
<th></th>
<th>Physician’s choice</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, Mos</td>
<td>15.8</td>
<td>22.7</td>
</tr>
</tbody>
</table>

HR: 0.68 (95% CI: 0.54-0.85; P = .0007)

Patients at Risk, n (censored)
Physician’s choice T-DM1
198(0) 150(28) 122(31) 107(33) 80(34) 66(36) 59(37) 39(45) 16(68) 1(80) 0
404(0) 368(17) 321(29) 280(35) 225(43) 192(44) 167(45) 132(36) 54(138) 12(172) 0

Verma NEJM 2012, Krop Lancet Oncol 2017
Trastuzumab deruxtecan (T-Dxd)

Stable linker in circulation (released in plasma 2% vs 18% TDM1)
Wider therapeutic index with lower toxicity

Fluorescence labeled- Datopotomab-DXd
3L Trastuzumab deruxtecan (T-Dxd): DESTINY-Breast01 P2 single arm

Median follow-up 20.5 months
ORR 61.4%

Median PFS 19.4 mo (14.1 – NE)

Median OS 24.6 mo (23.1 - NE)
Only 35% of events

Modi NEJM 2020
2L DESTINY-Breast03: Trastuzumab deruxtecan vs TDM1

N = 524

Advanced HER2+
Prior taxane + trastuzumab
Stable brain mets
No HER2 ADC <12m (TDM1)

R 1:1

T-Dxd
5.4 mg/kg q3w

T-DM1
3.6mg/kg q3w

Primary: PFS
Secondary: OS

Prior trastuzumab = 100%
Prior pertuzumab = 62%
Prior lines of therapy for metastatic dz
 1 = 50%, >1 = 50%
History of brain mets 23%
Baseline brain mets: 16%
At data cutoff, 84 (32.2%) patients treated with T-DXd versus 155 (58.9%) with T-DM1 had progressive disease.

12m PFS △ +41.7m

Patients Still at Risk:

T-DXd (261) 261 256 250 244 240 224 214 202 200 183 168 164 150 132 112 105 79 64 53 45 36 29 25 19 10 6 5 3 2 0
T-DM1 (263) 263 252 200 163 155 132 108 96 93 78 65 60 51 43 37 34 29 23 21 16 12 8 6 4 1 1 1 1 1 1 1 0

BICR: blinded independent central review; CI: confidence interval; DCO: data cutoff; HR: hazard ratio; mPFS: median progression-free survival; NE: not evaluable; NR: not reached; PFS: progression-free survival;
T-DXd: ado-trastuzumab emtansine; T-DM1: fam-trastuzumab deruxtecetab

Median PFS follow-up for T-DXd was 15.5 months (95% CI, 15.1-16.8) and for T-DM1 was 13.9 months (95% CI, 11.8-15.1).

DESTINY-Breast03: Overall survival

12m OS

$\Delta +8m$

<table>
<thead>
<tr>
<th></th>
<th>T-DXd (261)</th>
<th>T-DM1 (263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mo (95% CI)</td>
<td>NE (NE-NE)</td>
<td>NE (NE-NE)</td>
</tr>
<tr>
<td>12-mo OS rate, % (95% CI)</td>
<td>94.1, 90.3-96.4</td>
<td>85.9, 80.9-89.7</td>
</tr>
</tbody>
</table>
| HR (95% CI) | 0.56 (0.36-0.86) | **P = .007172**

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm) 

$^a$P = .007172, but does not cross pre-specified boundary of $P < .000265$

**DCO**, data cutoff; **HR**, hazard ratio; **mOS**, median overall survival; **NE**, not evaluable; **OS**, overall survival; **T-DM1**, ado-trastuzumab emtansine; **T-DXd**, fam-trastuzumab deruxtecan-nokri.

DESTINY-Breast03: Confirmed best ORR

**T-DXd (n = 245)**

**T-DM1 (n = 228)**

<table>
<thead>
<tr>
<th>Confirmed ORR</th>
<th>T-DXd (n = 261)</th>
<th>T-DM1 (n = 263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>208 (79.7)</td>
<td>90 (34.2)</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[74.3-84.4]</td>
<td>[28.5-40.3]</td>
</tr>
<tr>
<td>P</td>
<td>&lt; .0001</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>42 (16.1)</td>
<td>23 (8.7)</td>
</tr>
<tr>
<td>PR</td>
<td>166 (63.6)</td>
<td>67 (25.5)</td>
</tr>
<tr>
<td>SD</td>
<td>44 (16.9)</td>
<td>112 (42.6)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (1.1)</td>
<td>46 (17.5)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>6 (2.3)</td>
<td>15 (5.7)</td>
</tr>
<tr>
<td>CR + PR + SD</td>
<td>252 (96.6)</td>
<td>202 (76.8)</td>
</tr>
</tbody>
</table>

CR, complete response; DCO, data cutoff; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.

*a Only subjects with measurable disease at baseline and at least one postbaseline target lesion assessment are included. 
*b Based on BICR.


DESTINY-Breast03: Intracranial brain mets ORR

**T-DXd (n = 21)**

**T-DM1 (n = 23)**

### Best Overall Response, n (%)*

<table>
<thead>
<tr>
<th>Response</th>
<th>T-DXd</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>10 (27.8)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>PR</td>
<td>13 (36.1)</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>Non-CR/Non-PD</td>
<td>6 (16.7)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>SD</td>
<td>4 (11.1)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (2.8)</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>0</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (5.6)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Patients with Objective Response of CR or PR, n</td>
<td>23</td>
<td>12</td>
</tr>
</tbody>
</table>

*See full list of abbreviations in the speaker notes.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
*Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment.
DESTINY Breast 04: T-DXd in HER2-low

Press Release February 21 2021

Endpoints met: PFS and OS (regardless of HR-status)
HER2CLIMB: Tucatinib + capecitabine + trastuzumab
Prior TH, T-DM1 (2-3L)

Stratified by brain mets (yes vs no), ECOG PS (0 vs 1),
and region (US or Canada vs rest of world)

Patients with HER2+ MBC;
prior trastuzumab, pertuzumab,
and T-DM1; ECOG PS 0/1;
brain mets allowed* (N = 612)

*Including previously treated stable mets, untreated mets not needing immediate local therapy, and previously treated progressing mets not needing immediate local therapy.

Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m² PO BID on Days 1-14
(n = 410)

Placebo PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m² PO BID on Days 1-14
(n = 202)

50% presence or history of brain metastases
Treated/stable: 60%
Untreated 22%
Treated progressing 18%
HER2CLIMB: tucatinib + capecitabine + trastuzumab: final analysis

Prior TH, T-DM1 (2-3L)

**PFS**

- Tucatinib combination: 57% at 6 months, 29% at 1 year
- Placebo combination: 14% at 1 year

**OS**

- Tucatinib combination: 75% at 1 year, 51% at 2 years
- Placebo combination: 65% at 1 year, 40% at 2 years

**Median PFS**

- Tucatinib combination: 7.6 months (95% CI: 6.9-8.3)
- Placebo combination: 4.9 months (95% CI: 4.1-5.8)

**Median OS**

- Tucatinib combination: 24.7 months (95% CI: 21.6-26.9)
- Placebo combination: 19.2 months (95% CI: 16.4-21.4)

**PFS**

- Δ +3 months

**OS**

- Δ +5.5 months

(Curigliano Annals of Oncol 2022)
HER2CLIMB: tucatinib + capecitabine + trastuzumab: intracranial efficacy
Prior TH, T-DM1 (2-3L)

### Table: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tucatinib, Trastuzumab, and Capecitabine (n = 198)</th>
<th>Placebo, Trastuzumab, and Capecitabine (n = 93)</th>
<th>Total (N = 291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM treatment status at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated and stable</td>
<td>80 (40.4)</td>
<td>37 (39.8)</td>
<td>117 (40.2)</td>
</tr>
<tr>
<td>Treated and progressing</td>
<td>74 (37.4)</td>
<td>34 (36.6)</td>
<td>108 (37.1)</td>
</tr>
<tr>
<td>Untreated</td>
<td>44 (22.2)</td>
<td>22 (23.7)</td>
<td>66 (22.7)</td>
</tr>
<tr>
<td>Prior therapy for BMs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>140 (70.7)</td>
<td>64 (68.8)</td>
<td>204 (70.1)</td>
</tr>
<tr>
<td>WBRT</td>
<td>77 (38.9)</td>
<td>45 (48.4)</td>
<td>122 (41.9)</td>
</tr>
<tr>
<td>Targeted radiation therapy</td>
<td>92 (46.5)</td>
<td>32 (34.4)</td>
<td>124 (42.6)</td>
</tr>
<tr>
<td>Surgery</td>
<td>33 (16.7)</td>
<td>13 (14.0)</td>
<td>46 (15.8)</td>
</tr>
</tbody>
</table>

### Graphs:
- **Stable brain mets**: 
  - Tucatinib, trastuzumab, and capecitabine: 17 of 80 (19.2%) with median PFS of 32 months.
  - Placebo, trastuzumab, and capecitabine: 15 of 37 (40.5%) with median PFS of 32 months.

- **Active brain mets**: 
  - Tucatinib, trastuzumab, and capecitabine: 54 of 118 (45.9%) with median PFS of 9.5 months.
  - Placebo, trastuzumab, and capecitabine: 33 of 50 (66.0%) with median PFS of 4.1 months.

- **Isolated CNS progression (continued on therapy)**: 
  - Tucatinib, trastuzumab, and capecitabine: 12 of 21 (57.1%) with median PFS of 15.0 months.
  - Placebo, trastuzumab, and capecitabine: 8 of 10 (80.0%) with median PFS of 9.7 months.
Outline

HR+

- Adjuvant abemaciclib (monarchE)
- 1L Ribociclib overall survival (Monaleesa-2)
- Elacestrant novel SERD (EMERALD)

HER2+

- 2L T-DXd vs TDM1 (DB-03)
- Tucatinib Overall survival & brain metastases update (HER2CLIMB)
Questions?

hobbev@ohsu.edu