Treatment of HER2-Positive Breast Cancer Brain Metastases

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Outline

• Incidence of HER2+ Breast Cancer Brain Metastases
• Management of patients with progression limited to the CNS
• Overview of CNS-permeable approved and investigational agents
  • Overview of data with neratinib, tucatinib and trastuzumab deruxtecan
  • Appropriate sequencing of agents
Brain metastases are a common consequence of advanced cancer

<table>
<thead>
<tr>
<th>Primary site</th>
<th>Incidence Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung (overall)</td>
<td>16.3–19.9%</td>
</tr>
<tr>
<td>SCLC*</td>
<td>29.7% (at 5 years)</td>
</tr>
<tr>
<td>NSCLC*</td>
<td>12.6% (at 5 years)</td>
</tr>
<tr>
<td>Breast</td>
<td>10–15%</td>
</tr>
<tr>
<td>HER2 positive</td>
<td>25–50%</td>
</tr>
<tr>
<td>Triple negative</td>
<td>20%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>6.9–7.4%</td>
</tr>
<tr>
<td>Renal</td>
<td>6.5–9.8%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

*can be up to 50–60% depending on study and disease duration

40 – 50%


Courtesy of Carey K Anders, MD
The brain is a common site of HER2+ breast cancer metastases

Smid et al. CCR 2008

Courtesy of Carey K Anders, MD
Radiographic Images of Brain Metastases

- Solitary lesion
- Limited lesions
- Multiple lesions

Courtesy of Carey K Anders, MD
Local Therapy for Brain Metastases: General Approach

Solitary Lesion

Consideration of Resection
- Yes: Post-surgical radiosurgery
- No: Radiosurgery

Limited number of lesions (2–10+)

Radiosurgery

Multiple lesions

Whole Brain Radiation (consideration of hippocampal-sparing and memantine)

Courtesy of Carey K Anders, MD
Recommendations on Disease Management for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: ASCO Clinical Practice Guideline Update

Naren Ramakrishna, Sarah Tenlin, Sarat Choudhary, Jennie R. Creos, Nancy E. Davidson, Francisco J. Esteva, Sharon H. Giordano, Jeffrey J. Krischer, Ian E. Kroop, Jennifer Levinson, Shari Moli, Debra A. Put, Jane Perlmutter, Eric F. Winer, and Nancy U. Lin

For patients with progressive intracranial metastases despite initial radiation therapy, options include SRS, surgery, WBRT, a trial of systemic therapy, or enrollment in a clinical trial, depending on initial treatment. For patients in this group who also have diffuse recurrence, best supportive care is an additional option.

For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, systemic therapy should not be switched.

For patients whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer.
NCCN: Systemic Therapy Options Expanded in 2020

*NCCN Guidelines Version 2.2020
Central Nervous System Cancers

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY
BRAIN METASTASES

- Tumor agnostic
  - NTRK gene-fusion tumors
    - Larotrectinib\(^{113,114}\)
    - Entrectinib\(^{115,116}\)
    - Temozolomide 5/28 schedule

- Breast Cancer\(^{4}\)
  - HER2-positive
    - Capecitabine + lapatinib\(^{117,118}\)
    - Capecitabine + neratinib\(^{119,120}\)
    - Paclitaxel + neratinib (category 2B)\(^{121}\)
    - Capecitabine (category 2B)\(^{122-126}\)
    - Tucatinib + trastuzumab + capecitabine (if previously treated with 1 or more anti-HER2-based regimens)\(^{127}\)
  - HER2 non-specific
    - Cisplatin (category 2B)\(^{128,129}\)
    - Etoposide (category 2B)\(^{128,129}\)
    - Cisplatin + etoposide (category 2B)\(^{129,130}\)
    - High-dose methotrexate (category 2B)\(^{m,131}\)

- Melanoma\(^{5}\)
  - BRAF V600E positive
    - Dabrafenib\(^{132-134}\)/trametinib\(^{135}\)
    - Vemurafenib\(^{136,137}\)/cobimetinib\(^{1}\) (category 2B)
  - BRAF non-specific
    - Ipilimumab + nivolumab (preferred)\(^{138-140}\)
    - Ipilimumab\(^{141}\)
    - Nivolumab\(^{139}\)
    - Pembrolizumab\(^{142}\)

- Non-Small Cell Lung Cancer\(^{4d}\)
  - EGFR-sensitizing mutation positive
    - Osimertinib (EGFR T790M positive)\(^{143-145}\)
    - Pulsatile erlotinib\(^{146-148}\)
    - Afatinib (category 2B)\(^{149}\)
    - Gefitinib (category 2B)\(^{150,151}\)
  - ALK rearrangement positive
    - Brigatinib\(^{152,153}\)
    - Alectinib\(^{154,155}\)
    - Ceritinib\(^{156}\)
  - ALK rearrangement positive or ROS1 positive
    - Crizotinib (category 2B)\(^{157}\)
  - PD-L1 positive
    - Pembrolizumab\(^{142,158}\)
    - Nivolumab\(^{159-161}\)
  - Small Cell Lung Cancer\(^{4d}\)
    - Topotecan (category 2B)
  - Lymphoma\(^{1}\)
    - High-dose methotrexate\(^{162}\)

*Tucatinib added to list in 2020

Courtesy of Carey K Anders, MD

www.NCCN.org
Systemic therapy for HER2+ breast cancer brain metastases

Commercially available:
• Lapatinib-capecitabine
• T-DM1
• Neratinib-capecitabine*
• Tucatinib/trastuzumab/capecitabine (HER2Climb)
• Trastuzumab deruxtecan
• Anthracyclines (e.g. trastuzumab-doxorubicin)
• Platinum salts (e.g. trastuzumab-carboplatin)

Selected completed and ongoing clinical trials:
• Neratinib + T-DM1
• T-DM1 +/- Tucatinib
• T-DM1-temozolomide s/p SRS
• Trastuzumab/pertuzumab/atezolizumab
• “High dose” trastuzumab (closed to accrual, awaiting mature data)

*2020 NCCN Guidelines on Neuro-Oncology include neratinib-capecitabine as an option for patients with HER2+ breast cancer brain metastases.
## HER2+ Breast Cancer Brain Metastases: Lapatinib

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>CNS ORR</th>
<th>Minor response 20-50% vol</th>
<th>TTP/PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al JCO 2008</td>
<td>39</td>
<td>2.6% (RECIST) 5.2% (50% volumetric reduction)</td>
<td>10%</td>
<td>3.0 mo</td>
</tr>
<tr>
<td>Lin et al CCR 2008</td>
<td>237*</td>
<td>6% (composite criteria) 20% (optional extension)</td>
<td>15% 18%</td>
<td>2.4 mo 3.6 mo</td>
</tr>
</tbody>
</table>

(Courtesy of Carey K Anders, MD)
LANDSCAPE: Lapatinib/Capecitabine in XRT-Naïve HER2+ BCBM

Primary Endpoint: CNS volumetric response rate (>50% reduction)

CNS-OR : 29/43 = 67.4% (95% CI: 52-81)

<table>
<thead>
<tr>
<th>CNS Volumetric change</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80% Reduction</td>
<td>9</td>
<td>(20.9)</td>
</tr>
<tr>
<td>50- &lt;80% Reduction</td>
<td>20</td>
<td>(46.5)</td>
</tr>
<tr>
<td>20- &lt;50% Reduction</td>
<td>6</td>
<td>(14)</td>
</tr>
<tr>
<td>&gt; 0- &lt;20% Reduction</td>
<td>2</td>
<td>(4.7)</td>
</tr>
<tr>
<td>Progression*</td>
<td>6</td>
<td>(14)</td>
</tr>
</tbody>
</table>

NSS improvement : 14/24 = 58.3% (95% CI: 36.6-77.9)

TTP: 5.5 months (95% CI = 4.3 – 6mos); OS: 6mos survival = 91%

Bachelot et al. ASCO 2011, Abstr # 509; Lancet Oncology 2013.
**TBCRC 022 (Ph II neratinib/capecitabine): Study Design**

**Consent and Screening**

1. Baseline brain MRI (≥ 1 measurable lesion)
   - CT Chest/Abdomen/Pelvis, CTCs, cfDNA

2. Neratinib (240 mg orally once daily) and capecitabine 750 mg/m² BID for 14 days followed by 7 days rest

3. Follow-up every 3 weeks
   - Brain MRI & body CT re-imaging at week 6

**Diagnosis**

- CR, PR, SD – Continue therapy
- PD (CTCs, cfDNA)
  - If CNS PD – Off study
  - If non CNS PD– extension with trastuzumab offered

**Diarrhea prophylaxis**

- Loperamide 16 mg daily for C1; RN phone call C1 at 24, 48, 72 hours

**References**


**Courtesy of Carey K Anders, MD**
Primary Endpoint – Neratinib/Capecitabine: CNS Volumetric Response

CNS ORR = 49% (95% CI 32-66%)

* 6 patients did not reach first re-staging evaluation and are categorized as ‘0’
+ No patient had clear increase in steroid use, non-target lesions, non-CNS lesions, or worsening neurological symptoms at time of radiographic response

Neratinib vs. lapatinib both plus capecitabine in HER2+ MBC

NALA study design

Inclusion criteria
- Metastatic breast cancer (MBC)
- Centrally confirmed HER2+ disease
- ≥2 lines of HER2-directed therapy for MBC
- Asymptomatic and stable brain metastases permitted

Stratification variables
- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints
- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

Neratinib 240 mg/d + Capecitabine 1500 mg/m² 14/21 d
Loperamide (cycle 1)*

Follow-up (survival)

No endocrine therapy permitted

Lopatinib 1250 mg/d + Capecitabine 2000 mg/m² 14/21 d

R (1:1)
n=621

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed
Centrally confirmed PFS (co-primary endpoint)

30% of patients had received prior trastuzumab, pertuzumab and T-DM1
70% had 2 prior lines of therapy
30% had 3 prior lines of therapy

8.8 vs. 6.6 mos; p = 0.0003

Time to intervention for CNS Mets:
- Neratinib/cape = 22%
- Lapatinib/cape = 29%
  p = 0.043

Presented By Cristina Saura at 2019 ASCO Annual Meeting and Saura et al. JCO 2020.
Tucatinib (ONT-380) in metastatic HER2+ breast cancer

*Highly selective to HER2*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cellular Selectivity Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HER2 IC_{50} (nM)</td>
</tr>
<tr>
<td>tucatinib (ONT-380)</td>
<td>8</td>
</tr>
<tr>
<td>Neratinib</td>
<td>7</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>49</td>
</tr>
</tbody>
</table>

Preclinical data in intracranial HER2+ BCBM models (BT-474)

Courtesy of Carey K Anders, MD
**HER2CLIMB: Background**

- Up to half of patients with HER2+ metastatic breast cancer may develop brain metastases and effective and tolerable treatment options are needed.\(^1-4\)
- Tucatinib is an oral TKI, recently approved by the FDA, that is highly selective for the kinase domain of HER2 with minimal inhibition of EGFR.\(^5-6\)

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**HER2CLIMB Randomized, Double-blind, Pivotal Trial**

**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

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

![HER2CLIMB Trial Diagram](https://clinicaltrials.gov/ct2/show/NCT02614794)

**Tucatinib vs Placebo**

- **Tucatinib**
  - 300 mg PO BID
  - 21-day cycle
- **Trastuzumab**
  - 6 mg/kg Q3W, loading dose 8 mg/kg C1D1
  - 21-day cycle
- **Capecitabine**
  - 1000 mg/m\(^2\) PO BID Days 1-14

- **Placebo**
  - 21-day cycle

**Locality**


**TKI: tyrosine kinase inhibitor**

Courtesy of Carey K Anders, MD
HER2CLIMB Primary Analysis Results – SABCS 2019

• The HER2CLIMB trial met all primary and alpha-controlled secondary endpoints at the first interim analysis.

• Importantly, the secondary endpoint of PFS in patients with brain metastases was met.

<table>
<thead>
<tr>
<th>Study Type</th>
<th>N</th>
<th>Risk Reduction</th>
<th>CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS by BICR</td>
<td>480*</td>
<td>46%</td>
<td>0.42 to 0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>612</td>
<td>34%</td>
<td>0.50 to 0.88</td>
<td>0.005</td>
</tr>
<tr>
<td>PFS by BICR in patients with brain metastases</td>
<td>291</td>
<td>52%</td>
<td>0.34 to 0.69</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PFS: progression-free survival; BICR: blinded independent central review
*NThe primary endpoint of PFS was assessed in the first 480 patients enrolled.

References:

Courtesy of Carey K Anders, MD
HER2CLIMB Analysis of Patients with Brain Metastases

- Brain MRI at baseline for all patients
- Brain MRI for brain metastases patients every 6 weeks in first 24 weeks, every 9 weeks thereafter
- Eligible brain metastases patients:
  - Not requiring immediate local therapy
  - Requiring local therapy during screening could be eligible after washout*

All Patients with Brain Metastases
N=291

Active Brain Metastases
N=174

Treated Progressing
N=108
Previously treated but progression of existing lesions, new lesions or untreated lesions at baseline

Untreated
N=66

Treated Stable Brain Metastases†
N=117
Previously treated and no evidence of progression at baseline

†Includes patients requiring immediate local therapy before enrollment. These patients were not considered evaluable for intracranial response.

*These patients were included in the Treated Stable group for analysis.

†Includes patients requiring immediate local therapy before enrollment. These patients were not considered evaluable for intracranial response.

Courtesy of Carey K Anders, MD
**HER2CLIMB: CNS-PFS Benefit in Patients with Brain Metastases**

Risk of CNS progression or death was reduced by 68% in patients with brain metastases

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUC+Tras+Cape</td>
<td>71/198</td>
<td>0.32 (0.22, 0.48)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Pbo+Tras+Cape</td>
<td>46/93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One-year CNS-PFS (95% CI):

- TUC+Tras+Cape: 40.2% (29.5, 50.6)
- Pbo+Tras+Cape: 0%

Median CNS-PFS (95% CI):

- Stable BrMets: 13.9 mos (8.0, 13.9)
- Active BrMets: 9.5 mos (3.6, 5.7)

CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment.

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

Courtesy of Carey K Anders, MD
HER2CLIMB: OS Benefit in Patients with Brain Metastases

Risk of death was reduced by 42% in patients with brain metastases

One-year OS (95% CI):
- TUC+Tras+Cape: 70.1% (62.1, 76.7)
- Pbo+Tras+Cape: 46.7% (33.9, 58.4)

Median OS (95% CI):
- Stable BrMets: 15.7 mos (13.6 mos)
- Active BrMets: 20.7 mos (11.6 mos)

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

NE: not estimable

 Courtesy of Carey K Anders, MD
HER2CLIMB: Intracranial Response Rate (ORR-IC) in Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

### Confirmed Objective Response Rate (RECIST 1.1)

<table>
<thead>
<tr>
<th></th>
<th>TUC+Tras+Cape (N=55)</th>
<th>Pbo+Tras+Cape (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best Overall Intracranial Response</strong>&lt;sup&gt;a&lt;/sup&gt;, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>3 (5.5)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>23 (41.8)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>24 (43.6)</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>2 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Not Available&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (5.5)</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with Objective Response of Confirmed CR or PR, n</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Duration of Intracranial Response (DOR-IC)&lt;sup&gt;e&lt;/sup&gt; (95% CI)&lt;sup&gt;f&lt;/sup&gt;, months</td>
<td>6.8 (5.5, 16.4)</td>
<td>3.0 (3.0, 10.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Confirmed Best overall response assessed per RECIST 1.1. (b) Subjects with no post-baseline response assessments. (c) Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934). (d) Cochran-Mantel-Haenszel test controlling for stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. (e) As estimated using Kaplan-Meier methods. (f) Calculated using the complementary log-log transformation method (Collett, 1994).

*Stratified Cochran-Mantel-Haenszel P value
# HER2CLIMB: PFS in Patients with Isolated Progression in the Brain Who Continued with Assigned Study Treatment

<table>
<thead>
<tr>
<th>Study treatment</th>
<th>Randomization to second progression or death $\dagger$</th>
<th>First CNS progression to second progression or death $\ddagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TUC+Tras+Cap</strong> N=21</td>
<td>15.9 months (11.7, 28.2)</td>
<td>7.6 months (3.9, 11.3)</td>
</tr>
<tr>
<td><strong>Pbo+Tras+Cap</strong> N=9</td>
<td>9.7 months (4.9, 12.0)</td>
<td>3.1 months (1.2, 4.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median time from randomization to second progression or death</th>
<th>HR</th>
<th>Median time from first CNS progression to second progression or death</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TUC+Tras+Cap</strong> N=21</td>
<td>15.9 months (11.7, 28.2)</td>
<td>0.292 (0.11, 0.77) P=0.009</td>
<td>7.6 months (3.9, 11.3)</td>
<td>0.332 (0.13, 0.85) P=0.02</td>
</tr>
<tr>
<td><strong>Pbo+Tras+Cap</strong> N=9</td>
<td>9.7 months (4.9, 12.0)</td>
<td></td>
<td>3.1 months (1.2, 4.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Note: First CNS progression was captured as a PFS event in the primary analysis.

† Time from randomization to second progression or death among patients who received local therapy and continued study treatment after isolated CNS progression.

‡ Time from first isolated CNS progression to second progression or death among patients who received local therapy and continued study treatment after isolated CNS progression.

**Grant Support:** This work was supported by the National Institutes of Health (NIH) grant P50CA103933 and the National Cancer Institute (NCI) grant R01CA174128.
T-DM1 activity in HER2+ brain metastases: UNC experience and case reports

Ph II study of T-DM1 plus neratinib in HER2+ BCBM activated through TBCRC 022 (PI R. Freedman)

Case report of n = 10 pts illustrated PFS of 5.5 mos; OS 8.5 mos

Four patients treated at UNC with durable responses, one over 16 mos.


Keith, K et al. Cancer Treat Comm 2016.

Courtesy of Carey K Anders, MD
Trastuzumab Deruxtecan (DS-8201) Is a Novel ADC Designed to Deliver an Optimal Antitumor Effect

Trastuzumab deruxtecan is an ADC composed of 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker

Payload MOA:
- Topoisomerase I inhibitor
- High potency of payload
- High drug to antibody ratio ≈ 8
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Membrane-permeable payload

The clinical relevance of these features is under investigation.

ADC, antibody-drug conjugate; MOA, mechanism of action.


Courtesy of Carey K Anders, MD
DESTINY-Breast01 Study Design:
An Open-Label, Multicenter, Phase 2 Study

**Population**
- ≥18 years of age
- Unresectable and/or metastatic BC
- HER2-positive (centrally confirmed on archival tissue)
- Prior T-DM1
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed

**Endpoints**
- **Primary:** confirmed ORR by independent central imaging facility review per RECIST v1.1
- **Secondary:** investigator-assessed ORR, DCR, DOR, CBR, PFS, OS, PK and safety

**PART 1**
<table>
<thead>
<tr>
<th>PK Stage</th>
<th>Dose-Finding Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=65)</td>
<td></td>
</tr>
<tr>
<td>5.4 mg/kg (n=22)</td>
<td>5.4 mg/kg (n=28)</td>
</tr>
<tr>
<td>6.4 mg/kg (n=22)</td>
<td>6.4 mg/kg (n=26)</td>
</tr>
<tr>
<td>7.4 mg/kg (n=21)</td>
<td></td>
</tr>
</tbody>
</table>

**PART 2**
<table>
<thead>
<tr>
<th>Continuation Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=134)</td>
</tr>
<tr>
<td>PART 2a 5.4 mg/kg (n=130)</td>
</tr>
<tr>
<td>PART 2b 5.4 mg/kg (n=4)</td>
</tr>
</tbody>
</table>

184 patients enrolled at 5.4 mg/kg

**Data Cutoff:** August 1, 2019
- 79 patients (42.9%) are ongoing
- 105 patients (57.1%) discontinued, primarily for progressive disease (28.8%)
DESTINY-Breast01: Best Change in Tumor Size

The line at 20% indicates progressive disease; the line at -30% indicates partial response.

Confirmed ORR: 60.9%\(^a\)
(95% CI, 53.4%–68.0%)
11 CRs

By independent central review.

\(^a\) Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).

Courtesy of Carey K Anders, MD
DESTINY-Breast01: Progression-Free and Overall Survival

**Progression-Free Survival**
Median: 16.4 months (95% CI, 12.7-NE)

- Censored: 68.5%
- Events: 31.5%

**Overall Survival**
Median: Not reached (95% CI, NE-NE)

- Censored: 86.4%
- Events: 13.6%

- Median follow-up, 11.1 months (range, 0.7-19.9 months)
- Median PFS in the 24 patients with brain metastases was 18.1 months (95% CI, 6.7-18.1 months)

Patients who received T-DXd 5.4 mg/kg.
CI, confidence interval; NE, not estimable.

Courtesy of Carey K Anders, MD
The median response duration was 14.8 months (95% CI, 13.8 to 16.9) (Figure 3A). The median duration of progression-free survival was 16.4 months (95% CI, 12.7 to not reached) among all patients and 18.1 months (95% CI, 6.7 to 18.1) among the 24 patients who were enrolled with treated and asymptomatic brain metastases. Estimated overall survival was 93.9% (95% CI, 89.3 to 96.6) at 6 months and 86.2% (95% CI, 79.8 to 90.7) at 12 months; the median overall survival was not reached at the time of this report (Fig. S2).
How do we synthesize this data into a practical clinical algorithm?

Many outstanding questions:

1. Would incorporating tucatinib earlier in the treatment for patients with brain metastases be of benefit?

2. Would combining tucatinib with H/P or T-DM1 be of benefit to patients with brain metastases?

3. Would combining tucatinib with trastuzumab deruxtecan be of benefit to patients with brain metastases?

4. Would switching therapy to tucatinib regimen post-CNS XRT be of benefit to patients with brain metastases?

5. Many more.....?

Post-CNS radiation systemic therapy considerations

HER2-targeted therapy algorithms for HER2+ metastatic breast cancer

- 1\textsuperscript{st} line: THP
- 2\textsuperscript{nd} line: T-DM1
- 3\textsuperscript{rd} line: Current options:
  - Trastuzumab-deruxtecan (Stable BrM)
  - Tucatinib/Trastuzumab/Capecitabine
  - Neratinib/Capecitabine
  - Lapatinib/Capecitabine

(Progressive BrM)

Courtesy of Carey K Anders, MD
Question #1:

46 yr old female presents to your clinic for systemic therapy recommendations for metastatic hormone receptor negative, HER2-positive breast cancer metastatic to brain. She was initially diagnosed with *de novo* metastatic breast cancer to the liver 2.5 years prior and initially received paclitaxel/trastuzumab pertuzumab. At her visit, she had been on T-DM1 for 8 months, and had radiosurgery to 3 brain metastases 4 months prior; T-DM1 was continued post-SRS as her liver lesions were stable. She now has intracranial progression with 5 new lesions that are all sub-cm. Her performance status remains excellent and she is hopeful to avoid additional radiation to the brain. Based on the available literature, you advise her that the next best step is:

A. Vinorelbine/trastuzumab
B. Tucatinib/trastuzumab/capecitabine
C. Trastuzumab deruxtecan
D. Abemaciclib/trastuzumab

Answer: The answer is B based on the HER2CLIMB data.

Courtesy of Carey K Anders, MD
Question #2:

47 yr old female with a known ER/PR negative, HER2-positive breast cancer to the liver who has previously progressed on taxane/trastuzumab/pertuzumab, and was on T-DM1 when she developed 3 supratentorial brain metastases that were treated with SRS. She continued on T-DM1 for 6 months following SRS when her LFT’s started to rise and she developed RUQ pain. Her brain lesions remain stable. You recommend which of the following in hopes to achieving highest response in her liver metastases?

A. Vinorelbine/trastuzumab
B. Tucatinib/trastuzumab/capecitabine
C. Trastuzumab deruxtecan
D. Neratinib/capecitabine

Answer: The answer is C based on the DESTINY-Breast01 study with an ORR of 61% which is higher than any other combination therapy.

Courtesy of Carey K Anders, MD
Question #3:

You are meeting with a 62 yr old female who has progressive HER2+ brain metastases and discussing the risks and benefits of tucatinib/trastuzumab/capecitabine (HER2CLIMB regimen). She asks what the expected intracranial response rate is from the phase 3 study. You reply:

A. 10%
B. 30%
C. 45%
D. 80%

Answer: The answer is C based on the HER2CLIMB study.
Thanks and Questions!