Updates on HER2 positive breast cancer

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July 16, 2020
Please note that some of the studies reported in this presentation were published as abstracts only and/or presented at a conference. These data and conclusions are included because expert faculty found them to be important scientific contributions but should be considered to be preliminary until published in a peer-reviewed journal.
I have no disclosures
Outline

- HER2-CLIMB
- TRAIN-2
HER2-CLIMB

Abstract 1005: Tucatinib versus placebo added to trastuzumab and capecitabine for patients with previously treated HER2+ metastatic breast cancer with brain metastases (HER2CLIMB).
Background

- Breast cancer has 2nd highest incidence of brain metastases among all cancers
- Risk and incidence of brain metastases varies depending on subtype
- Brain is frequently the first site of relapse in HER2 breast cancer patients treated with trastuzumab, whether given in adjuvant or metastatic setting
- Outcomes for patients with brain metastases remain poor
  - More treatment options needed
- Tucatinib is an oral TKI (recently FDA approved) that is highly selective for kinase domain of HER2 with minimal inhibition of EGFR
  - Diarrhea, PPE, n/v, fatigue, stomatitis, elevated LFTs
- HER2CLIMB first randomized trial to include patients with:
  - Untreated brain mets
  - Progressive brain mets post-local treatment
Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

HER2CLIMB Trial design

**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

**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/m² PO BID (Days 1-14)

**Placebo + Trastuzumab + Capecitabine**
(21-day cycle)
- Placebo
- Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
- Capecitabine 1000 mg/m² PO BID (Days 1-14)
HER2CLIMB Primary Analysis Results

- 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>PFS by BICR</th>
<th>Overall Survival</th>
<th>PFS by BICR in patients with brain metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=480*</td>
<td>N=612</td>
<td>N=291</td>
</tr>
<tr>
<td>Risk of progression or death was reduced by 46%</td>
<td>Risk of death was reduced by 34%</td>
<td></td>
</tr>
<tr>
<td>95% CI: 0.42 to 0.71, P&lt;0.001</td>
<td>95% CI, 0.50 to 0.88, P=0.005</td>
<td></td>
</tr>
<tr>
<td>Risk of progression or death was reduced by 52%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI, 0.34 to 0.69, P&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Tucatinib vs Placebo Added to Trastuzumab and Capecitabine for Patients with Previously Treated HER2+ Metastatic Breast Cancer with Brain Metastases (HER2CLIMB)

Progression-Free Survival* in Patients with Brain Metastases

Alpha-controlled secondary endpoint in the HER2CLIMB trial

<table>
<thead>
<tr>
<th></th>
<th>Events N=291</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUC+Tras+Cape</td>
<td>106/198</td>
<td>0.48 (0.34, 0.69)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Pbo+Tras+Cape</td>
<td>51/93</td>
<td></td>
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</tr>
</tbody>
</table>

Risk of progression or death in patients with brain metastases was reduced by 52% in the total population

One-year PFS (95% CI):
- TUC+Tras+Cape: 25% (17, 34)
- Pbo+Tras+Cape: 0%

Median PFS (95% CI):
- TUC+Tras+Cape: 7.6 months (6.2, 9.5)
- Pbo+Tras+Cape: 5.4 months (4.1, 5.7)

Prespecified efficacy boundary for PFS-brain metastases (P=0.0080) was met at the first interim analysis.
Data cut off: Sep 4, 2019


*PFS, defined as time from randomization to documented disease progression (assessed by blinded independent central review) or death from any cause. Analysis does not include patients with dural lesions only.
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*

![Diagram]

All Patients with Brain Metastases
N=291

Active Brain Metastases
N=174

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

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

Untreated
N=66

*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.
# Baseline Characteristics of HER2CLIMB Patients with Brain Metastases

<table>
<thead>
<tr>
<th></th>
<th>TUC+Tras+Cape (N=198)</th>
<th>Pbo+Tras+Cape (N=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>53 (22, 75)</td>
<td>52 (25, 75)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>197 (99.5)</td>
<td>92 (98.9)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td>92 (46.5)</td>
<td>38 (40.9)</td>
</tr>
<tr>
<td></td>
<td>106 (53.5)</td>
<td>55 (59.1)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td>107 (54.0)</td>
<td>59 (63.4)</td>
</tr>
<tr>
<td></td>
<td>88 (44.4)</td>
<td>34 (36.6)</td>
</tr>
<tr>
<td>Metastatic (any location) at initial diagnosis, n (%)</td>
<td>77 (38.9)</td>
<td>39 (41.9)</td>
</tr>
<tr>
<td>Non-CNS metastatic disease</td>
<td>192 (97.0)</td>
<td>90 (96.8)</td>
</tr>
<tr>
<td>Prior local therapy for brain metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>140 (70.7)</td>
<td>64 (68.8)</td>
</tr>
<tr>
<td>Whole brain radiation</td>
<td>77 (38.9)</td>
<td>45 (48.4)</td>
</tr>
<tr>
<td>Targeted radiation</td>
<td>92 (46.5)</td>
<td>32 (34.4)</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>33 (16.7)</td>
<td>13 (14.0)</td>
</tr>
</tbody>
</table>
CNS-PFS Benefit in Patients with Brain Metastases

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

One-year CNS-PFS (95% CI):
- TUC+Tras+Cape: 40.2% (29.5, 50.6)
- Pbo+Tras+Cape: 0%

Median CNS-PFS (95% CI):
- TUC+Tras+Cape: 9.9 months (8.0, 13.9)
- Pbo+Tras+Cape: 4.2 months (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.
OS Benefit in Patients with Brain Metastases

### Risk of death was reduced by 42% 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>68/198</td>
<td>0.58 (0.40, 0.85)</td>
<td>0.005</td>
</tr>
<tr>
<td>Pbo+Tras+Cape</td>
<td>46/93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### One-year OS (95% CI):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUC+Tras+Cape</td>
<td>70.1% (62.1, 76.7)</td>
</tr>
<tr>
<td>Pbo+Tras+Cape</td>
<td>46.7% (33.9, 58.4)</td>
</tr>
</tbody>
</table>

#### Median OS (95% CI):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUC+Tras+Cape</td>
<td>18.1 months (15.5, NE)</td>
</tr>
<tr>
<td>Pbo+Tras+Cape</td>
<td>12.0 months (11.2, 15.2)</td>
</tr>
</tbody>
</table>

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.

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>TUC+Tras+Cape</th>
<th>Pbo+Tras+Cape</th>
</tr>
</thead>
<tbody>
<tr>
<td>198</td>
<td>184 146 108 79 49 26 17 14 7 6 2 0</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>87 67 49 23 12 9 5 0 0 0 0 0 0 0</td>
<td></td>
</tr>
</tbody>
</table>

NE: not estimable
CNS-PFS Benefit in Patients with Active Brain Metastases

Risk of CNS progression or death was reduced by 64% in patients with active brain metastases

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

- TUC+Tras+Cape 35.0% (23.2, 47.0)
- Pbo+Tras+Cape 0%

Median CNS-PFS (95% CI):

- 9.5 months (7.5, 11.1)
- 4.1 months (2.9, 5.6)

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.
OS Benefit in Patients with Active Brain Metastases

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUC+Tras+Cape</td>
<td>39/118</td>
<td>0.49</td>
<td>0.004</td>
</tr>
<tr>
<td>Pbo+Tras+Cape</td>
<td>30/56</td>
<td>(0.30, 0.80)</td>
<td></td>
</tr>
</tbody>
</table>

Risk of death was reduced by 51% in patients with active brain metastases

One-year OS (95% CI):
- TUC+Tras+Cape: 71.7% (61.4, 79.7)
- Pbo+Tras+Cape: 41.1% (25.5, 56.1)

Median OS (95% CI):
- 20.7 months (15.1, NE)
- 11.6 months (10.5, 13.8)

NE: not estimable

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.
CNS-PFS Benefit in Patients with Stable Brain Metastases

Risk of CNS progression or death was reduced by 69% in patients with stable brain metastases

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUC+Tras+Cape</td>
<td>17/80</td>
<td>0.31</td>
<td>0.002</td>
</tr>
<tr>
<td>Pbo+Tras+Cape</td>
<td>13/37</td>
<td>(0.14, 0.67)</td>
<td></td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=117</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUC+Tras+Cape</td>
<td>80</td>
</tr>
<tr>
<td>Pbo+Tras+Cape</td>
<td>37</td>
</tr>
</tbody>
</table>

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.
OS in Patients with Stable Brain Metastases

Risk of death was reduced by 12% in patients with stable brain metastases

One-year OS (95% CI):
- TUC+Tras+Cape: 67.6% (53.8, 78.0)
- Pbo+Tras+Cape: 55.6% (34.1, 72.6)

Median OS (95% CI):
- TUC+Tras+Cape: 15.7 months (13.8, NE)
- Pbo+Tras+Cape: 13.6 months (10.2, 22.0)

No. at Risk
- TUC+Tras+Cape: 80
- Pbo+Tras+Cape: 37

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.
Intracranial Response Rate (ORR-IC) in Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

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**Confirmed Objective Response Rate (RECIST 1.1)**

<table>
<thead>
<tr>
<th>Response Type</th>
<th>TUC+Tras+Cape (N=55)</th>
<th>Pbo+Tras+Cape (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Overall Intracranial Response(^a), n (%)</td>
<td>3 (5.5)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>23 (41.8)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>24 (43.6)</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>2 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive Disease (PD)</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)(^c) (95% CI)(^d), months</td>
<td>6.8 (5.5, 16.4)</td>
<td>3.0 (3.0, 10.3)</td>
</tr>
</tbody>
</table>

\(^a\) 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).

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

Randomization

First CNS Progression*

Local Therapy

Second Progression (CNS, body or both) or Death

Study treatment

Continue study treatment

Randomization to second progression or death †

First CNS progression to second progression or death ‡

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Median time from randomization to second progression or death</th>
<th>HR (95% CI)</th>
<th>Median time from first CNS progression to second progression or death</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUC+Tras+Cap 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>Pbo+Tras+Cap 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.
Duration on Treatment for Patients with Isolated Progression in the Brain Who Continued with Assigned Study Treatment

PD: progressive disease; EOT: end of treatment

Presented by Nancy Lin, njlin@partners.org
Conclusions

• The addition of tucatinib to trastuzumab and capecitabine doubled the intracranial response rate, reduced the risk of CNS progression or death by two-thirds, and reduced the risk of death by nearly half.

• The CNS-PFS results represent a delay in progression in the brain.

• Tucatinib is the first TKI to demonstrate prolongation of overall survival in patients HER2+ MBC with brain metastases in a randomized, controlled trial.

• These results together with the HER2CLIMB primary analysis demonstrate that this is an active regimen for intracranial and extracranial disease in patients with HER2+ MBC.

TKI: tyrosine kinase inhibitor
Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial

Nancy U. Lin, MD; Virginia Borges, MMSc, MD; Carey Anders, MD; Rashmi K. Murthy, MD, MBE; Elisavet Paplomata, MD; Erika Hamilton, MD; Sara Hurvitz, MD; Sherene Loi, MD, PhD; Alicia Okines, MBChB, MD; Vandana Abramson, MD; Philippe L. Bedard, MD; Mafalda Oliveira, MD, PhD; Volkmar Mueller, MD; Amelia Zeinak, MD; Michael P. DiGiovanna, MD, PhD; Thomas Bachelot, MD; A. Jo Chien, MD; Ruth O’Regan, MD; Andrew Wardley, MBChB, MSc, MD; Alison Conlin, MD, MPH; David Cameron, MD, MA; Lisa Carey, MD; Giuseppe Curigliano, MD, PhD; Karen Gelmon, MD; Sibylle Loibl, MD, PhD; JoAl Mayor, PharmD; Suzanne McGoldrick, MD, MPH; Xuebei An, PhD; and Eric P. Winer, MD
Thoughts/Future directions

- Timing of drugs with CNS activity
  - Use earlier to prevent development of mets?
- More study of tucatinib after first CNS progression
- Future trials should have broader eligibility criteria to ensure real-world population derive benefit
  - Patients with brain metastases is unmet need
- Leptomeningeal disease
TRAIN-2

Background

- Optimal chemotherapy backbone for dual HER2-blockade in neoadjuvant setting for early stage breast cancer is unknown
- Overlap of cardiotoxicity with trastuzumab and anthracyclines
  - Anthracycline-free regimens have been assessed
  - HOWEVER - Trials directly comparing anthracycline-containing regimens & anthracycline-free regimens are rare
- Role of anthracyclines in era of dual HER2 blockade is unknown
- TRAIN study – single arm, neoadjuvant
  - Weekly paclitaxel, trastuzumab, carboplatin
  - 43% of 108 patients achieved pathCR
  - <5% febrile neutropenia, and no LV dysfunction
- TRAIN-2:
  - Multicenter (Netherlands), phase III
  - Designed to directly compare efficacy & safety of anthracycline-containing chemo regimen (FEC x 3 → paclitaxel, carboplatin, trastuzumab x 6) with anthracycline-free chemo regimen of same duration (paclitaxel, carboplatin, trastuzumab x 9 cycles) in combination with HP in both groups

Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial

Primary endpoint - pCR

67\% (95\% CI 60-73)  
68\% (95\% CI 61-74)

TRAIN-2 – 3 year follow up

- 438 patients (219/arm) were randomized and evaluable for long-term efficacy.
- Median follow up of 48.8 months.
- 23 EFS (event-free survival) events in FECT-PTC-PTz-arm (anthracycline-containing) vs. 21 in PTC-Ptz-arm (HR 0.90; 95% CI 0.5 – 1.63).
- 3 year EFS estimates were 92.7% (anthracyline-containing arm) vs. 93.6%.
- 3 year OS estimates were 97.7% (anthracyline-containing arm) vs. 98.2%.
  - Results irrespective of hormone receptor & nodal status.
- LVEF decline >10% and <50% more common in anthracyline-containing arm (8.6 vs. 3.2%).
- Two patients in anthracyline-containing arm developed acute leukemia.
- No other new safety concerns seen.
Conclusions:

3 year follow up confirms results of primary outcome that anthracyclines do not improve efficacy and are associated with clinically relevant toxicity

A neoadjuvant carboplatin-taxane-based regimen with dual HER2-blockade can be considered in all stage II-III patients with breast cancer, regardless of hormone receptor & nodal status.