Progress on the treatment of HER2+ breast cancer

Ian Krop
Dana-Farber Cancer Institute
Harvard Medical School
HER2+ Disease: Major Clinical Advances

**THEMES**

1. Continuation of HER2-directed therapy after progression
2. Use of combined HER2 blockade
3. Next generation HER2-directed agents demonstrate efficacy
Agenda

• Incorporating new anti-HER2 agents in management of HER2+ metastatic disease

• Treatment of HER2+ brain metastases

• Treatment of small HER2+ cancers
What is the preferred 1st line regimen in 2015?
Trastuzumab and Pertuzumab Bind to Different Regions on HER2 and Have Synergistic Activity

- Trastuzumab suppresses HER2 activity
- Flags cells for destruction by the immune system

- Pertuzumab inhibits HER2 heterodimerization
- Suppresses multiple HER signaling pathways
- Flags cells for destruction by the immune system
**CLEOPATRA Study Design**

- Randomization stratified by geographic region and neo/adjuvant chemotherapy
- Study dosing q3w:
  - Pertuzumab/placebo: 840 mg loading → 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading → 6 mg/kg maintenance
  - Docetaxel: 75 mg/m² → 100 mg/m² escalation if tolerated

CLEOPATRA: Final OS Analysis

Median follow-up 50 months (range 0–70 months)

**ORR**
- Ptz + T + D: 80.2%
- Pla + T + D: 69.3%
- p = 0.001

**HR 0.68**
- 95% CI = 0.56, 0.84
- p = 0.0002

**OS (%)**
- 40.8 months
- Δ 15.7 months
- 56.5 months

**n at risk**
<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Ptz + T + D</th>
<th>Pla + T + D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>402</td>
<td>406</td>
</tr>
<tr>
<td>10</td>
<td>371</td>
<td>350</td>
</tr>
<tr>
<td>20</td>
<td>318</td>
<td>289</td>
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<tr>
<td>30</td>
<td>268</td>
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<td>40</td>
<td>226</td>
<td>179</td>
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<tr>
<td>50</td>
<td>104</td>
<td>91</td>
</tr>
<tr>
<td>60</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>70</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain et al, ESMO 2014
Adverse Events (All Grades) with ≥ 25% Incidence or ≥ 5% Difference between Groups Overall

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Placebo + T + D (n = 396), %</th>
<th>Pertuzumab + T + D (n = 408), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>60.6</td>
<td>60.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48.7</td>
<td>68.4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>50.0</td>
<td>53.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>42.4</td>
<td>44.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37.4</td>
<td>38.0</td>
</tr>
<tr>
<td>Rash</td>
<td>24.0</td>
<td>37.5</td>
</tr>
<tr>
<td>Asthenia</td>
<td>30.8</td>
<td>27.7</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26.8</td>
<td>29.7</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>28.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24.5</td>
<td>26.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>25.0</td>
<td>24.3</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19.9</td>
<td>27.2</td>
</tr>
<tr>
<td>Headache</td>
<td>19.2</td>
<td>25.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>25.5</td>
<td>15.9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14.4</td>
<td>20.8</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10.1</td>
<td>17.6</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7.6</td>
<td>13.7</td>
</tr>
<tr>
<td>Dry skin</td>
<td>6.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>5.1</td>
<td>10.3</td>
</tr>
</tbody>
</table>

Swain et al, ESMO 2014
Pertuzumab: Key Clinical Questions

• Is the use of pertuzumab standard in the first-line setting?
Pertuzumab: Key Clinical Questions

• Is the use of pertuzumab standard in the first-line setting?
  – YES
Pertuzumab: Key Clinical Questions

• Is the use of pertuzumab standard in the first-line setting?
  – YES

• What chemotherapy partners are acceptable?
Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel

- 36 evaluable pts with 1st or 2nd line HER2+ MBC
- ORR = 47%
- No cardiac events

Datko F et al, SABCS 2012. Abstract P5-18-20
Vinorelbine with trastuzumab, and pertuzumab: VELVET study

- Single arm, phase 2 study in 1\textsuperscript{st} line HER2+ MBC (n=213)
  - Vinorelbine 25mg/m\textsuperscript{2} on day 1 and 8 cycle 1 then 35mg/m\textsuperscript{2} subsequent cycles

- Common AE’s: Diarrhea, neutropenia, nausea
  - Gr 3 AE’s: Neutropenia (28%), diarrhea (5.7%)

- Efficacy (interim)
  - ORR 62.9%
  - PFS 14.3 mo

Andersson et al, ESMO 2014
Pertuzumab: Key Clinical Questions

• Is the use of pertuzumab standard in the first-line setting?
  – YES

• What chemotherapy partners are acceptable?
  • Docetaxel is standard. Paclitaxel and potentially vinorelbine may also be appropriate options
Pertuzumab: Key Clinical Questions

• Is the use of pertuzumab standard in the first-line setting?
  – YES

• What chemotherapy partners are acceptable?
  • Docetaxel is standard. Paclitaxel and potentially vinorelbine may also be appropriate options

• Should pertuzumab be given beyond progression on pertuzumab?
Pertuzumab: Key Clinical Questions

• Is the use of pertuzumab standard in the first-line setting?
  – YES

• What chemotherapy partners are acceptable?
  • For now, docetaxel (or paclitaxel)

• Should pertuzumab be given beyond progression on progression?
  • NO, but an important question to test in clinical trial(s)
What is the preferred 2nd line regimen in 2015?
Trastuzumab Emtansine (T-DM1)

- T-DM1 is a novel antibody drug-conjugate.
- Trastuzumab linked to DM1, a microtubule inhibitor up to 400-fold more potent than paclitaxel.
- Average of 3.5 DM1 per antibody.
- T-DM1 binds to HER2 with affinity similar to trastuzumab.
T-DM1 selectively delivers DM1 to HER2-positive tumor cells

T-DM1 binds to the HER2 protein on cancer cells

Receptor-T-DM1 complex is internalized into HER2-positive cancer cell

Potent antimicrotubule agent is released once inside the HER2-positive tumor cell
**EMILIA Study Design**

**HER2+ (central)**

- LABC or MBC (N=980)
  - Prior taxane and trastuzumab
  - Progression on metastatic tx or within 6 mos of adjuvant tx

**T-DM1**

- 3.6 mg/kg q3w IV

**Capecitabine**

- 1000 mg/m² orally bid, days 1–14, q3w

**Lapatinib**

- 1250 mg/day orally qd

- **1:1**

- **PD**

- **PD**

**Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease

**Primary end points:** PFS by independent review, OS, and safety

**Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

Blackwell et al, ASCO 2012
Overall Survival: Confirmatory Analysis

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</td>
<td>25.1</td>
<td>182</td>
</tr>
<tr>
<td>T-DM1</td>
<td>30.9</td>
<td>149</td>
</tr>
</tbody>
</table>

Stratified HR = 0.682 (95% CI, 0.55, 0.85); \( P = 0.0006 \)

Efficacy stopping boundary \( P = 0.0037 \) or HR = 0.727

Data cut-off July 31, 2012; Unstratified HR = 0.70 (\( P = 0.0012 \)).
Objective Response Rate (ORR) and Duration of Response (DOR) in Patients with Measurable Disease

**ORR**

Difference: 12.7% (95% CI, 6.0, 19.4)  
\( P = 0.0002 \)

- **Cap + Lap**: 30.8% (120/389)
- **T-DM1**: 43.6% (173/397)

**DOR**

- **Cap + Lap**: Median, mos (95% CI) 6.5 (5.5, 7.2)  
  \( P = 0.0002 \)
- **T-DM1**: 12.6 (8.4, 20.8)

Verma et al, ESMO 2012
Questions regarding T-DM1

- What are the clinically relevant toxicities seen with T-DM1
T-DM1 is NOT associated with typical chemotherapy toxicity

- No alopecia

- Significant nausea, diarrhea, fatigue, neutropenia, neuropathy are rare (<3% of patients)

Diéras et al and Krop, JCO 2014. 32:2750  
Verma et al, ESMO 2012
Cardiac toxicity is rarely seen with T-DM1

<table>
<thead>
<tr>
<th>Cardiac dysfunction AEs, a n (%)</th>
<th>Cap + Lap</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All grades</strong></td>
<td>(n=488)</td>
<td>(n=490)</td>
</tr>
<tr>
<td>15 (3.1%)</td>
<td>9 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>2 (0.4%)</td>
<td>1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>2 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lowest post-baseline LVEF value, n (%)</th>
<th>Cap + Lap</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥45%</td>
<td>(n=461)</td>
<td>(n=482)</td>
</tr>
<tr>
<td>454 (98.5%)</td>
<td>476 (98.8%)</td>
<td></td>
</tr>
<tr>
<td>≥40 to &lt;45%</td>
<td>4 (0.9%)</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>&lt;40%</td>
<td>3 (0.7%)</td>
<td>3 (0.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LVEF &lt;50% and ≥15-point decrease from baseline, n (%)</th>
<th>Cap + Lap</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=445)</td>
<td>(n=481)</td>
<td></td>
</tr>
<tr>
<td>7 (1.6%)</td>
<td>8 (1.7%)</td>
<td></td>
</tr>
</tbody>
</table>

aIncludes preferred terms ‘decreased ejection fraction’ and ‘left ventricular dysfunction’; Does not include cardiac AEs (e.g. myocardial infarction, atrial fibrillation).

Verma et al, ESMO 2012
Common toxicities of T-DM1

- Thrombocytopenia
  - Grade ≥3 in approximately 10% of patients
  - Nadir on day 8
  - Nadir is typically lowest in cycle 1
  - Not typically cumulative
  - Usually manageable with dose reduction

Diéras et al and Krop, JCO 2014. 32:2750
T-DM1 induced thrombocytopenia is transient and not cumulative.

T-DM1 administered on Day 21 of each cycle.

Diéras et al and Krop, JCO 2014. 32:2750
Uncommon toxicities of T-DM1

• Severe hemorrhage
  – 9 fatal cases reported in 4200 pts
  – 1 case reported by investigator to be TDM1 related
  – 4 of the pts on concurrent anti-coagulation
Common toxicities of T-DM1

• Transaminase elevation
  – Grade $\geq 3$ in approximately 5% of patients
  – Not typically cumulative
  – Usually manageable with dose reduction
  – Severe hepatic dysfunction very rare

Diéras et al and Krop, JCO 2014. 32:2750
Uncommon toxicities of T-DM1

• Pneumonitis (≈1% of pts)
  – Typically grade 1/2
  – T-DM1 should be discontinued

• Nodular regenerative hyperplasia (<0.5%)
  – Can lead to noncirrhotic portal hypertension
  – Requires bx to diagnose
  – T-DM1 should be discontinued

Diéras et al and Krop, JCO 2014. 32:2750
Questions regarding T-DM1

• What are the clinically relevant toxicities seen with T-DM1

• Should T-DM1 only be used in the second line setting?
Th3RESA: Study Schema

HER2 positive (Centrally confirmed)

Unresectable locally advanced/recurrent or Metastatic breast cancer

Prior trastuzumab, lapatinib and taxane,

N = 600
2:1 randomization

T-DM1 q3w

Study treatment continues until disease progression or unmanageable toxicity

Treatment of physician’s choice

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PFS by Investigator Assessment

<table>
<thead>
<tr>
<th></th>
<th>TPC (n=198)</th>
<th>T-DM1 (n=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>3.3</td>
<td>6.2</td>
</tr>
<tr>
<td>No. of events</td>
<td>129</td>
<td>219</td>
</tr>
<tr>
<td>Stratified HR</td>
<td>0.528 (95% CI, 0.422, 0.661)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk:

- **TPC**
  - 198
  - 120
  - 62
  - 28
  - 13
  - 6
  - 1
  - 0

- **T-DM1**
  - 404
  - 334
  - 241
  - 114
  - 66
  - 27
  - 12
  - 0

Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR=0.521 (P<0.0001).

Krop et al, Lancet Oncology In press
Wildiers et al, ECC-ESMO 2013

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MARIANNE Study Design

- HER2-positive (central) LABC\(^a\) or MBC
- No prior chemotherapy for LABC/MBC
- >6 months from prior (neo)adjuvant vinca alkaloid or taxane chemotherapy

N = 1095

Trastuzumab + docetaxel
(8 mg/kg LD then 6 mg/kg + 100 or 75 mg/m\(^2\) q3w) OR
Trastuzumab + paclitaxel
(4 mg/kg LD then 2 mg/kg + 80 mg/m\(^2\) qw)

T-DM1 + placebo\(^b\)
(3.6mg/kg + 840 mg LD then 420 mg q3w)

T-DM1 + pertuzumab
(3.6mg/kg + 840 mg LD then 420 mg q3w)

- **Stratification factors**: World region, Prior neo-/adjuvant therapy (if Yes: prior trastuzumab/lapatinib), Visceral disease
- **Primary end point**: PFS by independent review facility (IRF), non-inferiority and superiority assessed
- **Key secondary end points**: OS, PFS by investigator, ORR, Safety, Patient-reported outcomes

LD, Loading dose. \(^a\)Locally progressive or recurrent and not amenable to resection with curative intent; \(^b\)Pertuzumab placebo.
Progression-Free Survival by IRF

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (mo.)</td>
<td>13.7</td>
<td>14.1</td>
<td>15.2</td>
</tr>
<tr>
<td>Events (no.)</td>
<td>231</td>
<td>236</td>
<td>217</td>
</tr>
<tr>
<td>Stratified HR vs HT</td>
<td>—</td>
<td>0.91 (0.73–1.13)</td>
<td>0.87 (0.69–1.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratified HR vs T-DM1</td>
<td>—</td>
<td>0.91 (0.73–1.13)</td>
<td></td>
</tr>
</tbody>
</table>

Non-inferiority: Established if the upper limit of the 97.5% CI for the HR is below 1.1765 (non-inferiority margin).
What is the preferred 3rd line regimen in 2015?
Therapy for HER2+ MBC: Lessons Learned

- Trastuzumab + chemotherapy $\gg$ chemo alone

- Multiple acceptable chemotherapy partners with trastuzumab

- Chemo doublet + trastuzumab = chemo + trastuzumab
Treatment Approach For Patient Presenting With HER2+ MBC in 2014

First Line: Taxane + Trastuzumab + Pertuzumab

Second Line: TDM-1

Third, Fourth, Fifth, Sixth Line:
- Capecitabine + Lapatinib
- Capecitabine + Trastuzumab
- Vinorelbine + Trastuzumab
- Lapatinib + Trastuzumab
- Pertuzumab + Trastuzumab (?? if no prior Pertuzumab)
- Other chemotherapy + Trastuzumab
- Endocrine Therapy + Trastuzumab
Management of HER2+ brain metastases
CNS Disease is Frequent in HER2+ MBC

• 30-50% incidence—risk continues over time

Risk of CNS Metastases Continues Over Time

- Of N=64 patients alive >/= 3 yrs from HER2+ MBC diagnosis, the number of patients who developed new brain metastases in each time interval

Olson et al, Ann Oncol. 2013, 24(6):1526
CNS Disease is Frequent in HER2+ MBC

- 30-50% incidence—risk continues over time

- Radiation typically first line therapy

- Lapatinib monotherapy
  - CNS ORR 2-6% in pretreated pts

- Lapatinib + capecitabine
  - CNS ORR 18-36%, PFS 3.6-5.1 months in pre-treated pts
  - CNS ORR 67%, PFS 5.5 months in up-front setting

Current DFCI trials for HER2+ CNS disease

- Neratinib + capecitabine
- ARRY-380 + trastuzumab
- KD019 and trastuzumab
- Cabozatinib + trastuzumab
- Abemaciclib + trastuzumab
- IT trastuzumab
Case report of CNS response after treatment with T-DM1

Pre-T-DM1

Post-T-DM1

Rate of CNS progression was low in both arms of EMILIA

<table>
<thead>
<tr>
<th></th>
<th>Capecitabine/lapatinib N=446</th>
<th>T-DM1 N=450</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of CNS progression*</td>
<td>0.6%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

*In patients without CNS mets at baseline (N=896)

Krop et al, SABCS 2013
In patients with treated CNS mets, T-DM1 was associated with improved survival.

Krop et al, SABCS 2013
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.

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

N Ramakrishna et al, JCO, 2014:2100
Recent progress in adjuvant therapy of stage I HER2+ cancers
Risk of recurrence by HER2 Status in untreated cancers ≤1cm

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>n</th>
<th>5 yr RFS</th>
<th>5 yr Distant RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>98</td>
<td>77.1%</td>
<td>84.4%</td>
</tr>
<tr>
<td>HER2-</td>
<td>867</td>
<td>93.7%</td>
<td>97.2%</td>
</tr>
</tbody>
</table>

Gonzalez-Angulo A M et al. JCO 2009;27:5700-5706
Treatment of small Node-Negative HER2+ Tumors

- Risk is significant

- These cancers were generally not included in large randomized trastuzumab studies
  - No clear standard of care

- Given lower risk, and significant benefits of trastuzumab, a less intensive chemotherapy regimen may be most appropriate

- Randomized trial not feasible
DFCI-Led Single Arm, Multicenter, Low Risk Trial

HER2+ ER+ or ER- Node Negative < 3 cm PS 0-1 Adequate organ fx

413 patients enrolled
Accrual closed October, 2010
Results at SABCS 2013

Enroll

12 WEEKS OF PACLITAXEL/TRASTUZUMAB

FOLLOWED BY 13 EVERY 3 WEEK DOSES OF TRASTUZUMAB
Disease-Free Survival

- **3-year DFS**: 98.7%
- **95% Conf. Interval**: 97.6% to 99.8%
- **Poisson p-value**: <0.0001

**Number at risk**

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk</td>
<td>406</td>
<td>390</td>
<td>382</td>
<td>307</td>
<td>126</td>
<td>27</td>
</tr>
</tbody>
</table>

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# Disease-Free Survival Events

<table>
<thead>
<tr>
<th>DFS Event</th>
<th>N (%)</th>
<th>Time to event (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any recurrence or death</td>
<td>10 (2.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Local/Regional Recurrence</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral axilla (HER2+)</td>
<td>3 (0.7)</td>
<td>12, 20, 54</td>
</tr>
<tr>
<td>Ipsilateral breast (HER2+)</td>
<td>1 (0.2)</td>
<td>37</td>
</tr>
<tr>
<td><strong>New Contralateral Primary Breast Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HER2-</td>
<td>3 (0.7)</td>
<td>12, 37, 59</td>
</tr>
<tr>
<td><strong>Distant Recurrence</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (0.5)</td>
<td>27, 46</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-breast cancer related</td>
<td>1 (0.2)</td>
<td>13</td>
</tr>
</tbody>
</table>

* Recurrence-free interval (RFI) event
Disease-Free Survival by Tumor Size

<table>
<thead>
<tr>
<th>Stratum</th>
<th>No. of Events</th>
<th>3-yr DFS</th>
<th>95% Conf. Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1cm</td>
<td>5</td>
<td>98.0%</td>
<td>96.0% to &gt;99.9%</td>
</tr>
<tr>
<td>≤ 1cm</td>
<td>5</td>
<td>99.5%</td>
<td>98.4% to &gt;99.9%</td>
</tr>
</tbody>
</table>

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## Adverse Events

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Maximum Grade</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>81 (20)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47 (12)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>39 (10)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26 (6)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>35 (9)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28 (7)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>28 (7)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>23 (6)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>28 (7)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>
Implications

• Paclitaxel and trastuzumab (TH) can be considered a reasonable and appealing approach for the majority of patients with stage I HER2+ breast cancer
  – Not all patients require adjuvant trastuzumab-based chemotherapy (particularly T1aN0)
  – Standard regimens from the pivotal trials can be considered for patients with particularly high risk features
ATTEMPT Trial
PI Sara Tolaney, MD/Ian Krop MD, PhD

N=500

HER2+ ER/PR + or - Stage I

1

TH x 12 followed by completion of 1 year of H

3

T-DM1 every 3 weeks x 1 year
Summary

• Pertuzumab and T-DM1 lead to improved survival with favorable toxicity in 1\textsuperscript{st} and 2\textsuperscript{nd} line HER2+ MBC

• In 3\textsuperscript{rd} and later lines of therapy, combinations of trastuzumab or lapatinib and chemotherapy are active and should be continued

• CNS disease is common and challenging to treat
  – Studies of newer BBB-penetrating agents underway

• For patients with Stage I HER2+ cancers, paclitaxel + trastuzumab leads to very favorable outcomes