New Drugs For Metastatic Breast Cancer

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City of Hope Comprehensive Cancer Center
Disclosure

Consulting/Advisory for Genentech, Novartis, AstraZeneca, Abbvie, Pfizer, Nanostring, Celgene, and funds to institution for research support from Celgene, Genentech, Merck

Research collaboration: Agendia

Speaker’s Bureau: Takeda
Metastatic Breast Cancer

- 40,000 deaths per year in the US
- Median survival is 13 months from diagnosis of stage IV disease for triple negative disease, and 36-48 months (60?) for HER2+ and HE+ diseases.

- CDK 4/6 targeting in ER+ disease
- Anti-HER2 therapy
- Immune environment as a target

Combining Pertuzumab and Trastuzumab for More Comprehensive HER2 Blockade

- Pertuzumab targets the extracellular dimerization domain (subdomain II) of HER2
  - Blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4
- Trastuzumab binds to subdomain IV and disrupts ligand-independent HER2 signaling
Figure 2: Kaplan-Meier estimates of overall survival (intention-to-treat population)
Patients are stratified by previous treatment status and region. Tick marks indicate censoring events.
Figure 4: Kaplan-Meier estimates of progression-free survival (intention-to-treat population). Patients are stratified by previous treatment status and region. Tick marks indicate censoring events.
T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC (EMILIA): PFS

T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC (EMILIA): OS (Interim Analysis)

Proportion Surviving

Median, Mos
Capecitabine/lapatinib 23.3
T-DM1 NR

Events, n
129
94

Efficacy stopping boundary $P = .0003$ or HR: 0.617 $P = .0005$)

84.7%
77.0%
65.4%
47.5%

Phase III MARIANNE Study: T-DM1 ± Pertuzumab in HER2+ MBC

- **Patients with HER2+, previously untreated MBC** (N = 1092)
  - **Trastuzumab + Taxane** (n = 364)
  - **T-DM1 + Pertuzumab** (n = 364)
  - **T-DM1 + Placebo** (n = 364)

- Primary endpoints: PFS as assessed by IRF, AEs
- Secondary endpoints: OS, TTF by IRF, ORR, CBR,
- Press release this year: no difference across arms..

ClinicalTrials.gov. NCT01120184.
**MARIANNE** (BO22589) Phase III ado-Trastuzumab Emtansine (T-DM1) + Pertuzumab vs Trastuzumab + Taxane in First-line MBC: **Overall Survival (OS) (First Interim Analysis)**


- **HT** = trastuzumab + taxane; **NR** = not reached; **Pert** = pertuzumab

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Median OS, Months</th>
<th>Stratified HR (97.5% CI) vs HT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HT</strong></td>
<td>123</td>
<td>NR</td>
<td>–</td>
</tr>
<tr>
<td>T-DM1</td>
<td>116</td>
<td>NR</td>
<td>0.86 (0.64-1.16)</td>
</tr>
<tr>
<td>T-DM1 + Pert</td>
<td>115</td>
<td>NR</td>
<td>0.82 (0.61-1.11)</td>
</tr>
</tbody>
</table>

**Number at risk:**

- **HT**: 365, 335, 303, 273, 250, 218, 98, 25, 1
- **T-DM1**: 367, 345, 321, 291, 263, 224, 104, 37, 3
- **T-DM1 + Pert**: 363, 341, 309, 282, 257, 231, 106, 28, 1

Preferred first-line agents for HER2-positive disease:

- Pertuzumab + trastuzumab + docetaxel
  - Pertuzumab 840 mg IV day 1 followed by 420 mg IV
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
  - Docetaxel 75–100 mg/m² IV day 1
  - Cycled every 21 days.

- Pertuzumab + trastuzumab + paclitaxel
  - Pertuzumab 840 mg IV day 1 followed by 420 mg IV cycled every 21 days
  - Trastuzumab
    - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    - 8 mg/kg IV day 1 followed by 6 mg/kg IV cycled every 21 days
  - Paclitaxel 80 mg/m² IV day 1 weekly
  - Paclitaxel 175 mg/m² day 1 cycled every 21 days

Other agents for HER2-positive disease:

- Ado-trastuzumab emtansine (T-DM1)
  - 3.6 mg/kg IV day 1
  - Cycled every 21 days.

- Paclitaxel/carboplatin + trastuzumab
  - Carboplatin AUC 6 IV day 1
  - Paclitaxel 175 mg/m² IV day 1
  - Cycled every 21 days.
  - Trastuzumab
    - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Weekly paclitaxel/carboplatin + trastuzumab

- Paclitaxel 80 mg/m² IV days 1, 8, & 15
- Carboplatin AUC 2 IV days 1, 8, & 15
- Cycled every 28 days.
  - Trastuzumab
    - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Trastuzumab + paclitaxel

- Paclitaxel
  - 175 mg/m² IV day 1 cycled every 21 days
  - 80–90 mg/m² IV day 1 weekly
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Trastuzumab + docetaxel

- Docetaxel
  - 80–100 mg/m² IV day 1 cycled every 21 days
  - 35 mg/m² IV days 1, 8, and 15 weekly
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER-2 POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Trastuzumab + vinorelbine
- Vinorelbine
  - 25 mg/m² IV day 1 weekly or
  - 30–35 mg/m² IV days 1 and 8
  - Cycled every 21 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Trastuzumab + capecitabine
- Capecitabine 1000–1250 mg/m² PO twice daily days 1–14 cycled every 21 days
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Agents for trastuzumab-exposed HER2-positive disease:

- Lapatinib + capecitabine
  - Lapatinib 1250 mg PO daily days 1–21
  - Capecitabine 1000 mg/m² PO twice daily days 1–14 cycled every 21 days.

- Trastuzumab + capecitabine
  - Capecitabine 1000–1250 mg/m² PO twice daily days 1–14 cycled every 21 days.
  - Trastuzumab
    - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly or
    - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

- Trastuzumab + lapatinib
  - Lapatinib 1000 mg PO daily
  - Trastuzumab
    - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly or
    - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## Emerging Therapies for HER-2 Positive Breast Cancer

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Efficacy</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral, Anti-HER2, Small Molecules</td>
<td>Neratinib</td>
<td>Tyrosine kinase inhibitor (HER2 and HER1)</td>
<td>NEFERTT Phase II Randomized NCT00915018 Neratinib + paclitaxel vs. trastuzumab paclitaxel PFS same, benefit in CNS met? NALA capecitabine + lapatinib vs neratinib NCT01808573 ?HER2 mutated, lapatinib resistant, CNS?</td>
<td>30% grade 3 diarrhea vs. 4% with trastuzumab and paclitaxel</td>
</tr>
<tr>
<td></td>
<td>ONT-380</td>
<td>Tyrosine kinase inhibitor (HER2)</td>
<td>Activity in CNS with TDM-1, trastuzumab, or capecitabine</td>
<td>Minimal skin and no Grade 3 diarrhea</td>
</tr>
</tbody>
</table>

The table above summarizes emerging therapies for HER-2 positive breast cancer. It includes details about the class of drugs, mechanism of action, efficacy, and toxicity.
## Emerging Therapies for HER-2 Positive Breast Cancer

<table>
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<th>Toxicity</th>
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<tbody>
<tr>
<td>Anti HER2 Anti Body-Drug Conjugates</td>
<td>T-DM1</td>
<td>Trastuzumab-like effect</td>
<td>Efficacy</td>
<td>Toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intracellular release of emtansine-cytotoxic toxicity in HER2-overexpressing cells</td>
<td>FDA-approved for trastuzumab-treated stage IV disease</td>
<td>Less neurotoxicity, thrombocytopenia, elevated LFTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emilia : TDM-1 vs. capecitabine + lapatinib</td>
<td>Monitor LVEF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MARIANNE Trial: T-DM1 + pertuzumab is not superior to paclitaxel and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>trastuzumab</td>
<td></td>
</tr>
<tr>
<td>MM-302</td>
<td></td>
<td>Intracellular release of pegylated liposomal doxorubicin in HER2-overexpressing cells</td>
<td>Response seen in heavily pretreated patients (trastuzumab, TDM-1, pertuzumab)</td>
<td>Phase I: &gt; 20% constipation, cough, GI side effects, stomatitis, neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MM-302 plus trastuzumab vs MM-302 or trastuzumab and single agent</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02213744</td>
<td></td>
</tr>
</tbody>
</table>
After Di Cosimo and Baselga Nature Rev Clin Oncol 2010; 7 139-147
The alpha isoform is the dominant PI3K in breast cancer.
Pan PI3K Inhibitors

- Buparlisib
- Pictilisib
- Pilaralisib

Catalytic subunit (p110)

Regulatory subunit (p85)
## Non-Selective Inhibitors: Current Data

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Design</th>
<th>Backbone therapy</th>
<th>n</th>
<th>Results</th>
<th>Predictive value PIK3CA mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FERGI (Krop, SABCS)</td>
<td>GDC-0941 Pictilisib</td>
<td>Phase II randomized</td>
<td>fulvestrant</td>
<td>168</td>
<td>0.73 (0.51-1.05) (PFS) 6.6 vs 5.5months 7.4 vs 3.7 (ER/PR+)</td>
<td>no</td>
</tr>
<tr>
<td>OPPORTUNE (Schmid, SABCS)</td>
<td>GDC-0941 Pictilisib</td>
<td>Phase II randomized Neoadjuvant</td>
<td>Anastrozole</td>
<td>75</td>
<td>Ki67 decrease (A+P/A Ratio 0.48 (0.29 – 0.78) , P = 0.004) 83.8 vs 66% mean ki-67 suppression</td>
<td>No</td>
</tr>
<tr>
<td>BELLE2 (Baselga, SABCS 2015 S6-01)</td>
<td>BKM 120 Buparlisib</td>
<td>Phase III registration trial</td>
<td>fulvestrant</td>
<td>1149</td>
<td>HR:0.78 (0.67-0.89) 6.9 vs 5 months (PFS)</td>
<td>Yes, ctDNA (in 200 patients) PFS : 7 vs 3.2months</td>
</tr>
</tbody>
</table>
Isoform specific PI3K Inhibitors

- **p110α inhibitors**
  - Alpelisib
  - Taselisib
  - INK1117

- **p110β inhibitors**
  - GSK2636771
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<th>Mechanism of Action</th>
<th>Efficacy</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTOR/PI3K/Akt Inhibitors</td>
<td>Everolimus</td>
<td>mTOR inhibition</td>
<td>Bolero 1 (paclitaxel/trastuzumab) and Bolero 3 (navelbine, trastuzumab) :no meaningful benefit, hint of benefit for PTEN loss and PIK3-mutated set Andre et al, JCO 2016</td>
<td>Stomatitis, pulmonary, metabolic problems</td>
</tr>
<tr>
<td></td>
<td>Buparlisib</td>
<td>Pan-class I PI3K inhibitor</td>
<td>Hint of activity with trastuzumab Saura et al Clin Cancer Res 2014</td>
<td></td>
</tr>
<tr>
<td>CDK4/6 Inhibitors</td>
<td>Palbociclib</td>
<td></td>
<td>Patricia NCT02448420 Phase II randomized trial of trastuzumab, letrozole +/- palbo</td>
<td>neutropenia</td>
</tr>
<tr>
<td></td>
<td>Abemaciclib</td>
<td></td>
<td></td>
<td>diarrhea</td>
</tr>
<tr>
<td>Checkpoint Inhibitors</td>
<td>Pembrolizumab</td>
<td>Anti-PD-1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Outcome of Patients With Stage IV Breast Cancer

~ 40,000 deaths per year

Median Overall survival

- Triple negative breast cancer: 13 months
- HER+ and HR+ breast cancer: 36 – 48 months

Molecular Subtype Distribution

**PAM50 Subtype\(^1\)**
- n = 65

- 65 patients with GE

**Vanderbilt TNBC Subtype\(^2\)**
- n = 51

- 51 passed ER filter

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## TNBC subtype from TCGA

<table>
<thead>
<tr>
<th>TNBC Molecular Subtype</th>
<th>Gene Ontology</th>
<th>Therapeutic Targets/Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL1</td>
<td>DNA Damage Response and Cell Proliferation</td>
<td>Cisplatin, PARP inhibitors</td>
</tr>
<tr>
<td>BL2</td>
<td>TP63, EGFR and MET Signaling</td>
<td>mTOR, Growth Factor inhibitors</td>
</tr>
<tr>
<td>IM</td>
<td>Immune Signaling</td>
<td>Cisplatin, PARP inhibitors</td>
</tr>
<tr>
<td>M</td>
<td>EMT, Wnt, TGFβ, IG1FR, Notch, Cell Proliferation</td>
<td>mTOR, Growth Factor inhibitors, Src inhibitors</td>
</tr>
<tr>
<td>MSL</td>
<td>EMT, Wnt, TGFβ, MAPK, Rac, PI3K, PDGF</td>
<td>mTOR, PI3K, MEK and Growth Factor inhibitors</td>
</tr>
<tr>
<td>LAR</td>
<td>AR signaling, FOXA1 and ERBB4 Signaling</td>
<td>AR antagonists, PI3K inhibitors</td>
</tr>
<tr>
<td>UNC</td>
<td>DNA Damage Response and Cell Proliferation</td>
<td>Cisplatin, PARP inhibitors</td>
</tr>
</tbody>
</table>
Triple Negative Breast Cancer and BRCA-ness

- The majority of BRCA1 mutation-associated breast cancers are triple negative/basal-like subtype

- What is behind the BRCA1-ness?

*Genomic instability*

- Impaired Double strand DNA repair by homologous recombination
- BRCA carriers as well as sporadic BLBCs have reduced BRCA1 expression

Promoter methylation defect in non-BRCA-mutated BLBCs
Loss Of Heterozygosity
High levels of activity of a negative regulator of BRCA1: ID4
BRCA1 functional loss
Other pathway abnormalities
PARP Inhibitors in gBRCA Mutated Cancer

Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial

Andrew Tutt, Mark Robson, Judy E Gøger, Susan M Domchek, M William Audah, Jeffrey N Weitzel, Michael Friedlander, Irau Arun, Nikos Lomans, Rita K Schmutzler, Andrew Wardley, Gillian Mitchell, Helena Earl, Mark Wickens, James Carmichael

Ramanathan et al. Abst 29LBA.ECCO 2013

Michie et al. Abst 2513 ASCO 2013
Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre open-label, non-randomized study.

- Stratification by BRCA status
- Objective response rate
- 91 enrolled (65 ovarian ca vs 26 breast ca)

Objective Response Rate
Overall RR : 29%
- 7/17 (41%) RR in BRCA 1 or BRCA2 carriers
- 11/46 (25%) in non-carriers

- No objective response in non-carrier breast cancer

## DNA repair deficiency in metastatic TNBC

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Line of Rx</th>
<th>ChemoTx</th>
<th>RR (%)</th>
<th>HRD score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBCRC 009</td>
<td>86</td>
<td>1st &amp; 2nd Single phase II</td>
<td>Cis 75/m² OR Carbo AUC6 q3w (Physician’s Choice)</td>
<td>qBRCA1/2 55%</td>
<td>BRCA1/2 carrier vs not 13.8 vs 6.5 P = 0.0089</td>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TNBC non BRCA 26%</td>
<td>TNBC non BRCA responder vs non 12.7 vs 5.1 P = 0.03</td>
</tr>
<tr>
<td>TNT</td>
<td>376</td>
<td>1st Randomized Phase III</td>
<td>Carbo AUC6 vs Docetaxel 100/m²</td>
<td>BRCA1/2 Carbo 68% vs. Docet 33.3%</td>
<td>BRCA1/2 High Myriad HRD Scores and Platinum Response</td>
</tr>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TNBC non BRCA Carbo 28% vs. Docet 36%</td>
<td>TNBC non BRCA No diff in either low or high Myriad HRD score</td>
</tr>
</tbody>
</table>

* LOH; loss of heterozygosity Abkevish BJC 2012; LST; Large Scale Transitions Ca Res Popova 2012
Efficacy of the PARP Inhibitor ABT-888 (veliparib[vel]) either with carboplatin (carb) or as a single agent followed by post-progression therapy in combination with carb in patients (pts) with BRCA1- or BRCA2-(BRCA)-associated metastatic breast cancer (MBC): NCI #8264.

G. Somlo¹, P. Frankel¹, C. Ruel¹, T.H. Luu¹, C. Ma², B. Arun³, A. Garcia⁴, T. Cigler⁵, L. Cream⁶, G.F. Fleming⁷, H.A. Harvey⁸, J.A. Sparano⁹, R. Nanda⁷, H.K. Chew¹⁰, T.J. Moynihan¹⁰, L.T. Vahdat⁵, M.P. Goetz¹¹, A. Hurria¹, J. Mortimer¹, D.R.Gandara¹⁰, A.P. Chen¹¹, J.N. Weitzel¹

City of Hope Cancer Center, Duarte, CA¹; Washington University School of Medicine, St. Louis, MO²; The University of Texas MD Anderson Cancer Center, Houston, TX³; University of Southern California, Los Angeles, CA⁴; Weill Cornell Medical College, New York, NY⁵; Penn State College of Medicine, Hershey, PA⁶; The University of Chicago, Chicago, IL⁷ Hershey Medical Center, Hershey, PA⁸; Montefiore Medical Center, Bronx, NY⁹; University of California, Davis Cancer Center, Sacramento, CA¹⁰; Mayo Clinic, Rochester, MN¹¹; National Cancer Institute, Rockville, MD¹²
Efficacy of the PARP Inhibitor ABT-888 (veliparib [vel]) either with carboplatin (carb) or as a single agent followed by post-progression therapy in combination with carb in patients (pts) with BRCA1- or BRCA2- (BRCA)-associated metastatic breast cancer (MBC): NCI #8264.

**Phase 2:**

- **Carboplatin + Veliparib**
  - MTD
  - Carbo AUC 5 + Veliparib 150mg BID

- **Veliparib Alone**
  - 400mg BID

- **Response Rate**
  - **BRCA1**
    - 6/12 (50%)
    - 4 CRs, 2 PRs
  - **BRCA2**
    - 9/15 (60%)
    - 1 CR, 8 PRs

**Stage IV/LABC, gBRCA1/2 mutant, no prior platinum**
## Phase 2:

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Response Rate (PR+CR)</th>
<th>Clinical benefit (CB)</th>
<th>Response Rate (PR+CR)</th>
<th>Clinical benefit (CB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>3/22 (14%)</td>
<td>5/22 (23%)</td>
<td>1/16 (6%)</td>
<td>1/16 (6%)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>8/22 (36%)</td>
<td>14/22 (64%)</td>
<td>0/13 (0%)</td>
<td>0/13 (0%)</td>
</tr>
</tbody>
</table>

**Stage IV/LABC, BRCA1/2 mutant, no prior platinum**

### Veliparib Alone 400mg BID

### Progressive Disease

### Carbo + Vel at MTD
Survival Outcome

- Further confirmation of proof of concept of PARPi in gBRCA1/2 mutations carriers
- Phase I data on veliparib plus carboplatin yields higher response rates
- Small subset of patients are experiencing durable (multi-year) responses
A Phase III Trial of Carboplatin and Paclitaxel +/- Veliparib (ABT-888) in HER2 Negative Metastatic or Locally Advanced Unresectable BRCA Associated Breast Cancer

**Patient Population**
- Women or men ≥18 years
- Locally advanced or metastatic HER2- breast cancer
- gBRCA1 or gBRCA2
- No more than 2 prior lines of DNA-damaging therapy
- No prior PARP-I
- Stable CNS metastases

**Endpoints**
- **Primary Endpoint**
  - Progression Free Survival
- **Additional Endpoints**
  - OS
  - CBR
  - ORR
  - PFS2
- **Duration of Response**
  - Upon confirmation of progression, subjects randomized to placebo will have the option to receive single agent veliparib therapy (crossover)

**Randomization 2:1**
- N = 180
- Pac / Carbo / Veliparib*
- N = 90
- Pac / Carbo / Placebo*

*If carboplatin and paclitaxel are discontinued for toxicity, veliparib/placebo will be continued as a single agent

**Stratification Factors for Randomization:**
- ER and/or PR positive vs. ER and PR negative
- Prior platinum therapy (yes vs. no)
- CNS metastases (yes vs. no)
Tumor Infiltrating Lymphocytes (TILs)
Immunotherapy: Checkpoint Inhibition
Pembrolizumab has Single Agent Activity in PD-L1+ Triple Negative Breast Cancer

| Evaluable for Response |  
|-------------------------|---|
| N=27                    |   |

| Overall RR             | 5 (18.5%) |
| Complete response      | 1 (3.7%)  |
| Partial response       | 4 (14.8%) |
| Stable disease         | 7 (25.9%) |
| Progression            | 12 (44.4%)|
| No data                | 3 (11.1%) |

Median duration of response not reached: 15 - 40+ weeks
(3 of 5 responders still on drug for \(\geq\)11 months)
Median time to response: 18 weeks

JAVELIN: Phase Ib Study Design

Primary endpoint: DLT
Secondary endpoints: clinical activity, immune response, safety
PD-L1 expression assessed by IHC

Pts with refractory or progressive locally advanced or MBC (N = 168)*

Avelumab 10 mg/kg IV Q2W
Dosing until progression

- Primary endpoint: DLT
- Secondary endpoints: clinical activity, immune response, safety
- PD-L1 expression assessed by IHC

*Pts eligible if ≤ 3 previous cytotoxic regimens, previous treatment with taxane + anthracycline, biopsy/tissue sample taken within 90 days of avelumab initial dose, ECOG PS 1 or 2, ≥ 1 quantifiable lesion, life expectancy ≥ 3 mos.
Pts unselected for PD-L1 expression, HER2/ER/PR subtype.

Overall response rate according to molecular subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>n/N1* (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC</td>
<td>5/58 (8.6)</td>
<td>2.9, 19.0</td>
</tr>
<tr>
<td>HER2-/ER+ or PR+</td>
<td>2/72 (2.8)</td>
<td>0.3, 9.7</td>
</tr>
<tr>
<td>HER2+</td>
<td>1/26 (3.8)</td>
<td>0.1, 19.6</td>
</tr>
</tbody>
</table>

- Five of 8 responders had TNBC (62.5%); Among 5 TNBC responders, 4 (80%) had PD-L1+ immune cells
- Responses also achieved by patients in other subtypes
Summary

- Pembrolizumab: manageable safety profile in the 22 evaluable PDL-1 + patients: ORR was 14% and clinical benefit ration was 23%

- Avelumab: manageable safety profile, clinical response in patients with TNBC with PD-L1 expression by immune cells: (44.4% [4/9] vs 2.6% [1/39])

- Both agents need to be tested and their target population and use be optimized in combinations (add a vaccine, targeted therapies-trastuzumab, taxanes, anthracycline, combinatorial phase I-II testing, etc).
**Atezolizumab + Nab-Paclitaxel in Metastatic TNBC: Phase Ib Study Design**

- **GP28328**: a multicenter, multicohort phase Ib study; arm F includes pts with TNBC (metastatic or unresectable, locally advanced)\(^{[1,2]}\)

- **Primary endpoint**: safety and tolerability

- **Secondary endpoints**: response per RECIST v1.1 (ORR, DoR, PFS) and immune-modified response criteria; pharmacokinetics; biomarker analyses

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2. ClinicalTrials.gov. NCT01633970.
# Atezolizumab + Nab-Paclitaxel in Metastatic TNBC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pts (N = 32*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>56 (32-84)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (19)</td>
</tr>
<tr>
<td>1</td>
<td>26 (81)</td>
</tr>
<tr>
<td>Metastatic sites, n (%)</td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>15 (47)</td>
</tr>
<tr>
<td>Nodal only</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (47)</td>
</tr>
<tr>
<td>Median number of previous systemic therapies, n (range)</td>
<td>5 (1-10)</td>
</tr>
<tr>
<td>Number of previous systemic therapies (including [neo]adjuvant therapy), n (%)</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>2 (6)</td>
</tr>
<tr>
<td>3-4</td>
<td>13 (41)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>17 (53)</td>
</tr>
<tr>
<td>Previous taxane use, n (%)</td>
<td>28 (88)</td>
</tr>
</tbody>
</table>

*Safety evaluable population: ≥ 1 dose atezolizumab.
†Individual agents counted separately.

**Atezolizumab + Nab-Paclitaxel in mTNBC: Safety and Tolerability (Primary Endpoint)**

<table>
<thead>
<tr>
<th>Atezolizumab-Related AE (Any Grade AE in ≥ 10% of Pts), %</th>
<th>Pts (N = 32)</th>
<th>All Grades</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>34</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Neutropenia/decreased neutrophil count</td>
<td>28</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy/peripheral sensory neuropathy</td>
<td>19</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Alopecia</td>
<td>13</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

- Additional atezolizumab-related grade 3/4 AEs: syncope, type 1 diabetes mellitus, anemia, thrombocytopenia/platelet count decreased (n = 3), febrile neutropenia, AST increased, white blood cells decreased, and pneumonia mycoplasmal (n = 1 except where indicated)

Atezolizumab + Nab-Paclitaxel in mTNBC: Efficacy (Secondary Endpoints)

<table>
<thead>
<tr>
<th>Best Overall Response (RECIST v1.1)</th>
<th>First Line (n = 13)</th>
<th>Second Line (n = 9)</th>
<th>Third Line+ (n = 10)</th>
<th>All (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>46 (19-75)</td>
<td>22 (3-60)</td>
<td>40 (12-74)</td>
<td>38 (21-56)</td>
</tr>
<tr>
<td>CR, %</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>PR, %</td>
<td>38</td>
<td>22</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>SD, %</td>
<td>38</td>
<td>67</td>
<td>30</td>
<td>44</td>
</tr>
<tr>
<td>PD, %</td>
<td>15</td>
<td>0</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>Missing or not estimable, %</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Median DoR, mos (range)</td>
<td>NE (2.9 to 11.5+)</td>
<td>NE (9.1 to 13.1+)</td>
<td>NE (1.9+ to 5.6+)</td>
<td></td>
</tr>
</tbody>
</table>

- Among 12 responders, 6 (50%) remain on atezolizumab; 1 for > 17 mos
- Median DoR not reached; PFS and OS data not yet mature
- Responses observed in pts regardless of PD-L1 expression level; trend toward increase in baseline TILs for responding pts

Atezolizumab + Nab-Paclitaxel in Metastatic TNBC: Conclusions

- Atezolizumab + nab-paclitaxel well tolerated and active in metastatic TNBC\(^1\)
  - Safety profile similar to that of single agents
  - Durable responses achieved across all lines of therapy
  - Clinical response seen regardless of PD-L1 expression
- Ongoing phase III randomized trial evaluating this combination in previously untreated metastatic TNBC\(^2\)

2. ClinicalTrials.gov. NCT02425891.
# Emerging Agents in Triple Negative Breast Cancer

<table>
<thead>
<tr>
<th>Androgen receptor antagonists</th>
<th>Bicalutamide</th>
<th>CBR 18% Gucalp et al 2013</th>
<th>Weight gain, hot flush, LFTs,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide</td>
<td>CR 42% Traina et al, 2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody Conjugates</td>
<td>Immu-132 Anti-trop-2/SN-38</td>
<td>Phase II: 31% RR, PFS: 7 mos Bardia et al 2015</td>
<td>Cytopenia, diarrhea</td>
</tr>
<tr>
<td>Glembatumumab vedotin</td>
<td>TNBC RR:18% Yardley 2015 Confirmatory trial ongoing</td>
<td></td>
<td>Cytopenia, rash, neuropathy</td>
</tr>
</tbody>
</table>
City of Hope Phase I/II Studies in Metastatic TNBC

• Phase I/IB Study of Eribulin and Everolimus in Patients with Metastatic TNBC (active)

• A Phase I Study of MEDI4736 (Anti-PD-L1 Antibody) in Combination with Tremelimumab (Anti-CTLA-4 Antibody) in Subjects with Advanced Solid Tumors (active)

• Doxorubicin and pembrolizumab (PD-1 antibody) in triple negative stage IV breast cancer (pending)

• Entinostat, nivolumab, and ipilumimab in HER2- (including triple negative) breast cancer (pending-Hopkins and other consortia)

• AR+: Phase II GTX (selective androgen receptor inhibitor) in TNBC
Study Schema

NCI Protocol #: 9844
Version Date: June 16, 2015

Eligible:
- Dose Escalation:
  - Locally advanced or metastatic solid tumor
  - ECOG 0-1
- Dose Expansion:
  - Advanced breast cancer
  - HER2-negative
  - ECOG 0-1

Run-In: Entinostat x 2 weeks
Entinostat + Nivolumab ± Ipilimumab*

Unacceptable Toxicity
- SD/PR/CR or PD (and clinically acceptable to continue therapy)
- PD (not clinically acceptable to continue therapy)

Continue study therapy until additional PD
OFF STUDY

All correlative samples collected at baseline (day -14), day 1 (prior to start of entinostat and nivolumab ± ipilimumab), and 8 weeks (after start of combination treatment).

Tumor biopsy
Blood sampling
Current TNBC programs: Cobimetinib and Atezolizumab

- COLET study is an ongoing Phase II signal seeking study
- Amended to incorporate immunotherapy based on preclinical and clinical data
- GP28328 Phase Ib study provided encouraging safety data
- IMpassion130 study is a filing enabling study poised to be the first targeted therapy for TNBC pts

**Cobimetinib**

- Phase II COLET Cohort I (SRI and Expansion) n = 102

**Atezolizumab**

- Phase Ib GP28328 (nab-paclitaxel + atezolizumab)
- Phase III IMpassion130 n = 900 1L mTNBC nab-paclitaxel + atezolizumab vs nab-paclitaxel + placebo
- Phase II NACT (n=204) nab-Paclitaxel/AC + Atezolizumab
- Phase II ACT (n=1870) Paclitaxel/AC + Atezolizumab
Study WO29479 Dosing, PK & Biomarker Schedule

Biopsy → Optional → Progression

- Atezolizumab*: 840 mg q2w
- Nab-paclitaxel**: 100 mg/m² qw
- Paclitaxel: 80 mg/m² qw
- Cobimetinib/placebo: 60 mg qd x21

Study Day: 1, 8, 15, 22, 28

* Atezolizumab to be used in cohorts II and III only.
** Nab-paclitaxel will be used in cohort III instead of paclitaxel.

PK & ATA samples:
- On PK days cobimetinib should be administered prior to paclitaxel infusion.
- Mandatory biomarker at baseline and progression; optional on tx sample at C1D15.
- PK and ATA samples required predose at C2, C3, 4, 8 and every 8 cycles thereafter and at Tx discontinuation and 120 days after last atezolizumab dose.
- Additional PK sample required at Cycle 3, 30 mins post-atezolizumab.
Acknowledgment

Thanks to all authors for sharing their slides and allowing presentation at this meeting (not for distribution).
Thank you