Optimizing anti-HER-2 therapies for ABC
Potential role of immunotherapy

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Cancer and Immunity

Active Immune system (Host Immunity)  
Immune Targets (Neoantigens)  

TILs  
Activation Status  
Mutations  

Activators  
Inhibitors (Checkpoints)  

ABC4 Conference
Is breast cancer immunogenic?

- Not traditionally thought to be immunogenic
  - Spontaneous remissions are rare
  - No increased risk in organ transplantation or HIV patients
- However HER2 has long been considered a tumor-associated antigen
- Lymphocytic infiltrates are prominent in early-stage HER2+ disease
Somatic mutations in cancers

Breast Cancer and mutations: Lower median rate detected compared to the most immune-sensitive cancers but wide range of mutations detected

Alexandrov L.B. Nature 2013
Mutational rates in breast cancer

Tumor Mutational Burden & TIL correlation

A
Number of single nucleotide variants per exome by PAM50 subtype in TCGA breast cancers

B
% stromal TILs by PAM50 subtype in TCGA breast cancers

Luen, The Breast, 2016
Tumor Mutational Burden & TIL correlation

No correlation with mutational burden (neoantigens)

Luen, The Breast, 2016
TILS ARE PROGNOSTIC IN PRIMARY HER2+ DISEASE TREATED WITH ANTI-HER2 THERAPIES
FinHER: benefit from addition of adjuvant trastuzumab to chemo

LPBC, Lymphocyte-predominant breast cancer

TILs and a TILs immune signature in NSABP-31 adjuvant herceptin (n=731)

High (HR=0.06, CI 0.01-0.47, p=0.007) vs. Low TILs (HR=0.57, CI 0.43-0.76, p<0.001)
Interaction p=0.03

12% (86/731) pts with high expression of TILs genes may benefit more from trastuzumab

Kim et al, AACR 2015
Lymphocyte-predominant (≥60%) HER2+ breast cancer and trastuzumab survival benefit in the adjuvant setting

Retrospective Analysis from N9831 trial (n=945/2,027)

ARM A = NO TRASTUZUMAB
ARM C = TRASTUZUMAB

Interaction P=0.04

\[ \text{HR, 2.43 (95\% CI, 0.58-10.22), } P=0.22 \]
Log rank P=0.21

\[ \text{HR, 0.49 (95\% CI, 0.25-0.69), } P<0.001 \]
Log rank P<0.001

Total 8 events

Perez et al. JAMA Oncology 2016
N9831 Relapse Free Survival by Rx Arm and Immune Signature

14-gene algorithm

Not immune signature enriched

Immune signature enriched

Interaction term $P < .001$

Perez EA, et al. JCO 2015
N9831 Relapse Free Survival by Rx Arm and Immune Signature

Gavin PG, et al. JCO 2015
TILS ARE PREDICTIVE IN PRIMARY HER2+ DISEASE TREATED WITH ANTI-HER2 THERAPIES
High pCR rate with high TILs/immune GS in primary HER2+ with dual anti-HER2 agents

Four studies now that support this

• NeoALTTO (T+Lap)
• Cher-Lob (T+Lap)
• CALGB (T+Lap)
• NeoSphere T+ Pertuzumab

Gianni et al, AoO2015; Denkert et al JCO 2015; Salgado et al JAMA onc 2015; Guanerri et al SABCS 2014; Carey et al, JCO 2015
Tumor-infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy + HER2 Blockade in HER2+ Breast Cancer

NeoALTTO (n=387)  
Salgado et al. JAMA Oncol 2015

NeoSphere (n=243)  
Bianchini et al. Annals Oncol 2015

- Low TILs (<5%) are associated with low pCR rates following either single anti-HER2 + chemotherapy or dual HER2 blockade without chemotherapy

→ dual HER2 blockade and chemotherapy seems to improve pCR rates in this group.
Tumor-infiltrating Lymphocytes and Survival Outcome Following Chemotherapy + HER2 Blockade in HER2+ Breast Cancer: NeoALTTO

Salgado et al. JAMA Oncol 2015
TILS ARE PREDICTIVE IN HER2+ MBC TREATED WITH ANTI-HER2 THERAPIES
Tumor-infiltrating lymphocytes in advanced HER2+ breast cancer treated with trastuzumab and docetaxel +/- pertuzumab

Retrospective Analysis from CLEOPATRA trial (n=678/808)

93% Primary Tissue vs 7% Metastatic Tissue

- No significant association between TILs and PFS
- TILs was significantly associated with longer OS (adjusted HR 0.89, 95% CI 0.83–0.96, p=0.0014).
- The treatment effect of pertuzumab did not differ by stromal TILs

Luen et al. Lancet Oncol 2017
IMMUNOTHERAPY IN HER+ BC
Immune effects of trastuzumab

Stagg et al, Cancer Cell 2011; Park et al, Cancer Cell 2011
Trastuzumab monotherapy can induce inflammation (NeoPHOEBE Trial)

- Change in TILs baseline to D15 as well as D15 levels were strongly associated with pCR (per 10% increment)
- Turn non-immunogenic into immunogenic tumors

EGF104900 study: lapatinib ± trastuzumab in progressing mBC

HER2-positive mBC (FISH+)
(n=296)

Lapatinib 1,000mg daily + trastuzumab 2mg/kg weekly (n=148)

Lapatinib 1,500mg daily (n=148)

Crossover if PD

Blackwell K, et al. JCO 2012
**EGF104900: Significant Overall Survival (OS) Benefit With Trastuzumab + Lapatinib Following Disease Progression**

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<tr>
<td></td>
<td>N = 148</td>
<td>N = 148</td>
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<tr>
<td>Died, N (%)</td>
<td>113 (78)</td>
<td>105 (72)</td>
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<tr>
<td>Median, months</td>
<td>9.5</td>
<td>14.0</td>
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<td>Hazard ratio (95% CI)</td>
<td>.74 (.57-.97)</td>
<td>.026</td>
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*Survival, %*

- **6 Month OS**: 80%
- **12 Month OS**: 70%

*Time from Randomization, months*

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Blackwell K, et al. JCO 2012
Combination strategy: “old” molecules with new mechanisms of action

Trastuzumab + lapatinib

- Treatment with lapatinib plus trastuzumab resulted in complete tumor remission
  - Effect was durable: no tumor relapse observed after 8 mo post treatment
- Lapatinib induced accumulation of inactive HER2 at plasma membrane
  - Trastuzumab-mediated cytotoxicity was higher with the addition of lapatinib in MCF7/HER2 cells
- In vivo activity was consistent with in vitro data demonstrating the combination as synergistic

Scaltriti, et al, Oncogene 2009
Enhanced immune effects of trastuzumab & pertuzumab

• Increases immunogenicity:
  – Clear synergism with greater suppression of oncogenic signaling
  – ADCC also induced
  – Likely enhances pre-existing TILs

Scheuer et al, Can Res 2009
Combination of Anti-HER2 antibody and PD-1 inhibition is synergistic

Stagg et al. PNAS 2011
Combination of T-DM1 and CTLA-4/PD-1 inhibition is synergistic

Muller et al. SciTransMed 2015
PANACEA trial: NCT02129556

Phase Ib/II trial of anti-PD-1 monoclonal ANtibody in AdvanCED, Trastuzumab-resistant, HER2-positive breast cancer

**Advanced HER2+ BC**
- Trastuzumab resistant
- Up to 3 lines previous anti-HER2 therapy

**Confirmed PD-L1 expression on metastatic lesion**

**Tratuzumab+MK3 475 until progression**

**Biopsy on PD**

Primary Endpoint is efficacy of the combination (ORR)

Study Chairs: S Loi, F Andre
Margetuximab

To evaluate the safety of margetuximab using two dosing regimens
Enhanced Antitumor Activity through Effector Cell Engagement

Margetuximab: same signaling properties as trastuzumab plus enhanced ADCC
FIH phase 1 Study with Margetuximab

All evaluable pts

Evaluate MBC

39/60 prior antiHER2 therapy

22/23 prior antiHER2 therapy

Burris HA, et al. ASCO 2015
MCLA-128, a new IgG1 bispecific antibody targeting HER2 and HER3 receptors

Docking of the HER2 arm on HER2 expressed by tumor cells optimally positions the HER3 arm to block heregulin-driven tumor cell growth

<table>
<thead>
<tr>
<th>Dock on HER2</th>
<th>Block HER3</th>
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<tr>
<td><img src="HER2.png" alt="Image" /></td>
<td><img src="HER3.png" alt="Image" /></td>
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<td><img src="Tumor_Cell.png" alt="Image" /></td>
<td><img src="Tumor_Cell.png" alt="Image" /></td>
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<tr>
<td>+ Tumor growth</td>
<td>X Growth inhibition</td>
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Merus
MCLA-128, a new IgG1 bispecific antibody targeting HER2 and HER3 receptors

In a preclinical study more effective than trastuzumab and pertuzumab in inhibiting the growth of cell lines resistant to HER2-targeted therapies

Merus
Conclusions: relevance of immunity in HER2+ BC

- Immunotherapy in BC is still in early days
- In HER2+ disease, TILs are clinically relevant and represent pre-existing anti-tumor immunity
  - Associated with better outcomes to therapy
  - Induction of TILs is associated with higher pCR rates
- The presence of TILs provides rationale for evaluation of checkpoint blockade
Dushyanthen et al, BMC Medicine 2015
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