NEW HORIZONS IN BREAST CANCER IMMUNOTHERAPY

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CONFLICTS OF INTEREST

• Nothing to disclose
BREAST CANCER: WHERE ARE WE NOW?

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Female Breast Cancer

- Localized (62%)
- Confined to Primary Site
- Regional (36%)
- Spread to Regional Lymph Nodes
- Distant (9%)
- Cancer Has Metastasized
- Unknown (2%)
- Unstaged

5-Year Relative Survival

SEER 18 2010-2016, All Races, Females by SEER Summary Stage 2000

Worse Prognosis

Intrinsic subtypes

- Basal
- HER2 over-expression
- BRCA1 mutation

Better Prognosis

- Luminal B
- Luminal A
- ER/PR positivity

Molecular subtypes

ER-PR-HER2-
ER-PR-HER2+
[ER+|PR+]HER2-
[ER+|PR+]HER2+
SURVIVAL BY SUBTYPE

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Localized</th>
<th>Regional</th>
<th>Distant</th>
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<tbody>
<tr>
<td>HR+/HER2-</td>
<td>100.0%</td>
<td>89.7%</td>
<td>35.4%</td>
</tr>
<tr>
<td>HR+/HER2+</td>
<td>51.2%</td>
<td>65.0%</td>
<td>11.5%</td>
</tr>
<tr>
<td>HR-/HER2-</td>
<td>50.7%</td>
<td>89.5%</td>
<td>43.5%</td>
</tr>
<tr>
<td>HR-/HER2+</td>
<td>96.1%</td>
<td>81.7%</td>
<td>36.8%</td>
</tr>
<tr>
<td>Unknown</td>
<td>65.7%</td>
<td>77.1%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Total</td>
<td>58.9%</td>
<td>85.7%</td>
<td>28.1%</td>
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</tbody>
</table>

SEER 18 2010–2016, All Races, Females by SEER Summary Stage 2000
Cancer Epidemiol Biomarkers Prev; 27(6), 1-8. 2018; AACR.

CANCER AND THE IMMUNE SYSTEM

- Role of the immune system in cancer control first proposed in 1909 by Ehrlich
- Studies in mice with deficient innate and adaptive immune systems have increased tumor incidence
- Higher incidence of malignancy in immunosuppressed organ transplant patients
- Lymphocyte infiltration in solid tumors correlates with improved survival
- Increased presence of T-regs in tumor microenvironment associated with poor prognosis
- Mutations in CASP8 identified in TNBC promotes evasion of cytotoxic CD8+ T-cells

**MECHANISM OF IMMUNE EVASION**

- Immunomodulation/suppression
  - Deletion of effector cells via expression of death-inducing ligands
  - Suppression of tumor-reactive T-cells by regulatory T-cells
  - Tolerance - central or peripheral
- Immune recognition
  - Ignorance

**PRINCIPLES OF IMMUNOTHERAPY**

- What is immunotherapy?
  - “a therapeutic approach that targets or manipulates the immune system”
- Utilize host adaptive and innate immune responses to effectuate life-long disease elimination/control
- Restore the capacity of the immune system to recognize and reject cancer
- Types of Immunotherapy:
  - Passive - administration of ex vivo generated elements (antibodies) to patients and does not stimulate the host immune response
  - Active - induces an immune response resulting in production of specific immune response (antibodies, T cells)

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MONOCLONAL ANTIBODIES

- Concept initially introduced in 19th Century with “serotherapy”
- 1980s development of mAb for follicular lymphoma
- Mechanisms:
  - Induction of death signal or blocking growth signals
  - Antibody-dependent cellular cytotoxicity
  - Complement mediated cytotoxicity
- Used in Breast Ca Treatment
  - Trastuzumab
  - Pertuzumab

TRASTUZUMAB

- Humanized monoclonal antibody to HER2 homodimers
- 1986- Role of HER2 gene in breast cancer first noted
- 1992- First trial of Trastuzumab in metastatic breast cancer
- 1998- Breakthrough FDA approval for use in metastatic disease
- 2006- FDA approval for use in adjuvant setting

References:
TRASTUZUMAB

- Humanized monoclonal antibody to HER2 preventing HER2/HER3 heterodimers
- For use in combination with trastuzumab
- 2012 - FDA approval in HER2 positive metastatic breast cancer (CLEOPATRA)
- 2013 - FDA accelerated approval in neoadjuvant breast cancer treatment (NeoSPHERE)
- 2017 - FDA approved for use in combination with trastuzumab for adjuvant treatment (APHINITY)

https://www.perjeta.com/hcp/how-perjeta-works.html
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pertruzumab-adjuvant-treatment-her2-positive-breast-cancer
IMMUNE CHECKPOINT INHIBITORS

- Anti-CTLA-4
  - Not currently FDA approved for use in BC treatment
  - Clinical trials ongoing (SWOG 1609, ICON, NIMBUS)
- PD-1 inhibitors
  - Pembrolizumab
  - Nivolumab
- PD-L1 inhibitors
  - Atezolizumab

PDL-1 AND BREAST CANCER

- PD-L1 expression present in 20-30% of BC, mostly TNBC
- Current agents approved in breast ca treatment:
  - Atezolizumab
  - Pembrolizumab
Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

Peter Schmid, M.D., Ph.D., Sylvia Adams, M.D., Hope S. Rugo, M.D., Andreas Schneeweiss, M.D., Carlos H. Barrios, M.D., Hiroji Iwata, M.D., Ph.D., Véronique Diéras, M.D., Roberto Hegg, M.D., Seock-Ah Im, M.D., Ph.D., Gail Shaw Wright, M.D., Volkmar Henschel, Ph.D., Luciana Molinero, Ph.D., for the IMpassion130 Trial Investigators.

NEOADJUVANT ATEZOLIZUMAB IN COMBINATION WITH SEQUENTIAL NAB-PACLITAXEL AND ANTHRACYCLINE-BASED CHEMOTHERAPY VERSUS PLACEBO AND CHEMOTHERAPY IN PATIENTS WITH EARLY-STAGE TRIPLE-NEGATIVE BREAST CANCER (IMPASSION031): A RANDOMISED, DOUBLE-BLIND, PHASE 3 TRIAL

PROF ELIZABETH A MITTENDORF, MD, PROF HONG ZHANG, MD, CARLOS H BARRIOS, MD
PROF SHIGEHIRA SAJI, MD, KYUNG HAE JUNG, MD, ROBERTO HEGG, MD, ET AL.

Pemolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer (KEYNOTE-355): A Randomised, Placebo-Controlled, Double-Blind, Phase 3 Clinical Trial

Javier Cortés, MD, David Cescon, MD, Hoff S. Ruggo, MD, Tiziana Nowell, MD, Stockham, MD, Mastura Md Yusof, MD, et al.

- ~60% received prior chemo
- ~20% received prior chemo of same class
- CPS ≥10, mPFS 9.7 vs 5.6 months
- CPS ≥1, mPFS 7.6 vs 5.6 months


Pembrolizumab for Early Triple-Negative Breast Cancer
Peter Schmid, M.D., Javier Cortés, M.D., Lajos Pusztai, M.D., Heather McArthur, M.D., xbox Kümmel, M.D., Jonas Bergh, M.D., •Carsten Denkert, M.D., Yeon Hee Park, M.D., Rina Hui, Ph.D., Nadia Harbeck, M.D., Masato Takahashi, M.D., Theodoros Fouakas, M.D., for the KEYNOTE-522 Investigators.


DOI: 10.1056/NEJMoa1910549


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IMMUNE RELATED ADVERSE EVENTS

- Diarrhea/colitis
- Endocrinopathies
- Skin rash/pruritis
- Hepatitis

ANTIBODY-DRUG CONJUGATES

- Ado-trastuzumab emtansine
  - First approval for MBC 2013
  - May 2019 expanded approval to adjuvant treatment
- Trastuzumab Deruxtecan
  - FDA approved in Dec 2019
- Sacituzumab-govitecan
  - Approved April 2020
PRINCIPLES OF ADC

• Combine the specificity of mAbs with the cytotoxic potential of drugs
• Must have wide distribution of targeted receptor on diseased cells
• Specificity- more specific the target antigen the higher the possible dosing without toxicity to normal tissues
• Internalization- target tumor surface protein must internalize ADC to deliver toxin, should occur frequently and via suitable endosomal compartment
• Stability- toxin must remain inert and attached to antibody until delivery to target cell


Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer
Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Weisblau, M.D., José Baselga, M.D., Ph.D.,
Mark Pegram, M.D., Da-Youn Oh, M.D., Ph.D., Véronique Delrwa, M.D., Elle Guardino, M.D., Ph.D.,
Liang Fang, Ph.D., Michael W. Lu, Pharm.D., for the EMILIA Study Group

• Phase 3 trial of TDM-1 vs lapatinib + capecitabine
• HER2-targeted antibody conjugated with microtubule inhibitor DM1
• 3.2 month improvement in PFS (p<0.001)
• 5.8 month improvement in OS (p<0.001)
Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

Gunter von Minckwitz, M.D., Chiu-Sheng Huang, M.D., Ph.D., Max S. Mano, M.D., Ph.D., Sibylle Lohi, M.D., Eleftherios P. Mamounas, M.D., Michael Untch, M.D., Ph.D., Norman Wolmark, M.D., Priya Rastogi, M.D., Andreas Schneeweiss, M.D., Andres Redondo, M.D., Ph.D., Hans H. Fischer, M.D., Michael Untch, M.D., Ph.D., for the KATHERINE Investigators.

• ADC of anti-HER2 antibody and cytotoxic topoisomerase I inhibitor
• Evaluated in patients previously treated with trastuzumab emtansine
• Cytotoxic effect on neighboring cells
• Median prior therapies = 6 (range 2-27)
• Median PFS 16.4 months
• 11 patient achieved CR
**SACITUZUMAB-GOVITECAN**

- Humanized anti-Trop2 monoclonal antibody with hydrolysable linker to SN-38
- Binds to Trop-2 expressing cancer cells
- FDA approved in Metastatic TNBC
- Phase 3, Sacituzumab vs TPC in mTNBC after ≥2 prior chemos
- mPFS 5.6 vs 1.7 mo (P<0.0001; HR, 0.41)
- Media OS 12.1 vs 6.7 mo (HR, 0.48; p<0.0001)
- ORR 35% vs 5%

**REFERENCES**

**ES4 Educational Session**

**Neoadjuvant ICI Trials in TNBC**

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<th></th>
<th>GeparNuvo</th>
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<td>N</td>
<td>174</td>
<td>333</td>
<td>1174</td>
<td>280</td>
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<td>Primary endpoint</td>
<td>pCR</td>
<td>pCR</td>
<td>pCR + EFS</td>
<td>EFS</td>
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<tr>
<td>ICI</td>
<td>Durvalumab (24-26 w)</td>
<td>Atezolizumab (1y)</td>
<td>Pembrolizumab (1y)</td>
<td>Atezolizumab (24w)</td>
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<td>Chemo</td>
<td>Nab pac – EC</td>
<td>Nab-pac – ddAC</td>
<td>Pac+carbo – AC/EC</td>
<td>Nab pac+carbo</td>
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<td>PDL1 + (multiple Ab)</td>
<td>87%</td>
<td>46%</td>
<td>83%</td>
<td>56%</td>
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<tr>
<td>pCR ITT</td>
<td>58% vs 44%, Δ 9%</td>
<td>58% vs 41%, Δ 17%</td>
<td>65% vs 51%, Δ 14%</td>
<td>44% vs 41%, Δ 3%</td>
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<tr>
<td>PDL1+ (2w durve window 65% vs 41%)</td>
<td>69% vs 49%</td>
<td>69% vs 55%</td>
<td>52% vs 48%</td>
<td></td>
</tr>
<tr>
<td>PDL1-</td>
<td>-</td>
<td>48% vs 34%</td>
<td>45% vs 30%</td>
<td>32% vs 32%</td>
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<tr>
<td>Followup / EFS HR</td>
<td>-</td>
<td>20m / 0.76 (ns)</td>
<td>15m / 0.63 (ns)</td>
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