Oncology Grand Rounds

New Agents and Strategies in Breast Cancer

Tuesday, May 26, 2020
5:00 PM – 6:30 PM ET

Faculty
Virginia Kaklamani, MD, DSc
Marissa Marti, APRN, AGNP-C, AOCNP
Joyce O’Shaughnessy, MD
Daniel G Pizana, MSN-FNP, OCN

Moderator
Neil Love, MD
Familiarizing yourself with the Zoom interface
How to participate in the chat

Join the chat to send in questions or troubleshoot
<table>
<thead>
<tr>
<th>Date</th>
<th>Topic</th>
<th>Time</th>
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</thead>
<tbody>
<tr>
<td>May 26th</td>
<td>Breast Cancer</td>
<td>5:00 PM – 6:30 PM</td>
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<tr>
<td>May 28th</td>
<td>Gastrointestinal Cancers</td>
<td>5:00 PM – 6:30 PM</td>
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<tr>
<td>June 2nd</td>
<td>Hodgkin and Non-Hodgkin Lymphomas</td>
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<td>June 4th</td>
<td>Chronic Lymphocytic Leukemia</td>
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<td>June 9th</td>
<td>Gynecologic Cancers</td>
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<td>June 11th</td>
<td>Metastatic Lung Cancer</td>
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<td>June 16th</td>
<td>Locally Advanced Non-Small Cell Lung Cancer</td>
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<td>June 18th</td>
<td>Urothelial Bladder Carcinoma</td>
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<td>June 23rd</td>
<td>Chimeric Antigen Receptor T-Cell Therapy</td>
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<td>June 25th</td>
<td>PARP Inhibition in the Management of Common Cancers</td>
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<td>June 30th</td>
<td>Prostate Cancer</td>
<td>5:00 PM – 6:30 PM</td>
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</table>
Oncology Grand Rounds
Gastrointestinal Cancers

Nurse and Physician Investigators Discuss New Agents, Novel Therapies and Actual Cases from Practice

Thursday, May 28, 2020

Faculty
Melony Avella-Howell, NP
Wells A Messersmith, MD
Philip A Philip, MD, PhD, FRCP
Tammy Trigianios, RN, MS, ANP-BC, AOCNP

Moderator
Neil Love, MD
Virginia Kaklamani, MD, DSc
The University of Texas
MD Anderson Cancer Center
San Antonio, Texas
Joyce O’Shaughnessy, MD
Baylor University Medical Center
Dallas, Texas
Marissa Marti, APRN, AGNP-C, AOCNP
Texas Oncology-Baylor Charles A Sammons Cancer Center
Dallas, Texas
Daniel G Pizana, MSN-FNP, OCN
UT Health San Antonio Mays Cancer Center
Breast Oncology Clinic
San Antonio, Texas
Oncology Grand Rounds

Nurse and Physician Investigators Discuss New Agents, Novel Therapies and Actual Cases from Practice

Part 5: Breast Cancer

Faculty
Jamie Carroll, APRN, MSN, CNP
Erika Hamilton, MD
Elizabeth O’Reilly, RN, NP, MSN, MPH
Hope S Rugo, MD

Thursday, April 11, 2019
6:00 PM – 8:00 PM
Anaheim Marriott
Anaheim, California
Research To Practice's 2019 San Antonio Breast Cancer Symposia

DATA + PERSPECTIVES
Clinical Investigators Explore the Current and Future Management of ER-Positive Breast Cancer
Wednesday, December 11, 2019
7:30 PM – 9:00 PM
San Antonio, Texas

Moderator
Neil Love, MD

Faculty
Harold J Burstein, MD, PhD
Matthew Goetz, MD
Stephen RD Johnston, MA, PhD
Joseph A Sparano, MD

DATA + PERSPECTIVES
Clinical Investigators Explore the Current and Future Management of HER2-Positive Breast Cancer
Friday, December 13, 2019
7:30 PM – 9:00 PM
San Antonio, Texas

Moderator
Neil Love, MD

Faculty
Adam M Bruckman, MD, PhD
Lisa A Carey, MD
Sara Hurvitz, MD
Martine J Piccart-Gebhart, MD, PhD

DATA + PERSPECTIVES
Clinical Investigators Explore the Current and Future Management of Triple-Negative Breast Cancer
Thursday, December 12, 2019
7:30 PM – 9:00 PM
San Antonio, Texas

Moderator
Neil Love, MD

Faculty
Erika Hamilton, MD
Professor Sherene Loi, MBBS, PhD
Mark E Robson, MD
Hope S Rugo, MD

Research To Practice®
Agenda

Module 1: Management of HER2-Positive Breast Cancer
• Neoadjuvant, adjuvant treatment of localized disease
• New agents, regimens in metastatic disease

Module 2: Anti-PD-1/PD-L1 Antibodies, Novel Agents in Triple-Negative Breast Cancer (TNBC)
• Metastatic TNBC: Atezolizumab/nab paclitaxel, pembrolizumab/chemotherapy
• Neoadjuvant pembrolizumab/chemotherapy in localized TNBC
• Recent FDA approval of sacituzumab govitecan

Module 3: Genomic Testing and PARP Inhibitors
• Germline and somatic mutation testing
• Indications for and selection of available PARP inhibitors (olaparib, talazoparib)

Module 4: CDK4/6 and PI3 Kinase Inhibitors in ER-Positive Disease
• Current role of CDK4/6 inhibitors for pre- and postmenopausal women
• Alpelisib/fulvestrant (PIK3CA mutation)

Module 5: Management of Breast Cancer in the Era of COVID-19
Module 1: Management of HER2-Positive Breast Cancer

- **Neoadjuvant, Adjuvant Treatment of Localized Disease**
  - Pertuzumab and neratinib for patients with higher-risk disease
  - T-DM1 as adjuvant and postneoadjuvant therapy

- **New Agents, Regimens in Metastatic Disease**
  - Neratinib/capecitabine, tucatinib, trastuzumab deruxtecan
A 60-year-old woman presents with a palpable 2.5-cm breast mass that on biopsy is diagnosed as an ER-negative, HER2-positive infiltrating ductal carcinoma (IDC). Biopsy of a small axillary lymph node is positive. In general, the most common next step in this situation is…

a. Surgery to remove the primary tumor and axillary dissection followed by systemic therapy
b. Neoadjuvant systemic therapy followed by surgery
c. Either a or b
d. Neither a nor b
e. I don’t know
A patient with a HER2-positive IDC responds to neoadjuvant chemotherapy and trastuzumab/pertuzumab, but at surgery residual disease is detected. In general, the most common next treatment is…

a. Trastuzumab
b. Trastuzumab/pertuzumab
c. T-DM1
d. Any of the above
e. I don’t know
The toxicity associated with pertuzumab most likely to affect patient quality of life is...

a. Hand-foot syndrome
b. Peripheral neuropathy
c. Diarrhea
d. I don’t know
Patients who receive postadjuvant neratinib after chemotherapy/anti-HER2 therapy for HER2-positive localized breast cancer have a significant reduction in the risk of recurrence if the tumor is...

a. ER-positive
b. ER-negative
c. Both a and b
d. Neither a nor b
e. I don’t know
The most common side effect/toxicity of neratinib is…

a. Hand-foot syndrome
b. Diarrhea
c. Cytopenias
d. I don’t know
APHINITY: A Phase III adjuvant study investigating the benefit of pertuzumab when added to trastuzumab + chemotherapy

Central confirmation of HER2 status (N = 4805) → Randomization and treatment within 8 weeks of surgery → Anti-HER2 therapy for a total of 1 year (52 weeks) (concurrent with start of taxane) Radiotherapy and/or endocrine therapy may be started at the end of adjuvant chemotherapy

Chemotherapy* + trastuzumab + placebo (N = 2405)

Chemotherapy* + trastuzumab + pertuzumab (N = 2400)

* Standard anthracycline or non-anthracycline (TCH) regimens were allowed: 3–4 x FEC (or FAC) → 3–4 x TH; 4 x AC (or EC) → 4 x TH; 6 x TCH

• Primary endpoint: IDFS (APHINITY definition differs from STEEP definition)
• Secondary endpoint: IDFS with 2nd primary non-breast primary cancers included, DFS, OS, RFI, DRFI, safety, and HRQoL
• Stratification factors: nodal status, HR status, chemotherapy regimen, geographic region, Protocol version (A vs. B)
• Clinical cut off date (CCOD) at the time of primary analysis was 19 Dec 2016, median follow up of 45.4 months

DFS, disease-free survival; DRFI, distant relapse-free interval; HR, hormone receptor; HRQoL, health-related quality of life; IDFS, invasive disease-free survival; OS, overall survival; RFI, relapse-free interval

Adapted from von Minckwitz et al. N Engl J Med 2017
www.clinicaltrials.gov/ct2/show/NCT01358877

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KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Geyer CE et al. SABCS 2018;Abstract GS1-10.
Invasive Disease-Free Survival

Trastuzumab vs T-DM1

IDFS Events, no. (%) 165 (22.2) 91 (12.2)
Unstratified HR=0.50 (95% CI, 0.39–0.64)

3-year IDFS 77.0% 88.3%

Geyer CE et al. SABCS 2018;Abstract GS1-10.
## Safety Overview

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab n=720</th>
<th>T-DM1 n=740</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with at least one, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade ≥3 AEs</td>
<td>111 (15.4)</td>
<td>190 (25.7)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>58 (8.1)</td>
<td>94 (12.7)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>15 (2.1)</td>
<td>133 (18.0)</td>
</tr>
<tr>
<td>AE with fatal outcome^</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

^Fatal AE was intracranial hemorrhage diagnosed after a fall with platelet count of 55,000.
Study Design: ATEMTPT Trial

Key Eligibility Criteria
- Stage 1 HER2+ breast cancer
  - HER2 centrally tested (ASCO CAP 2013 guidelines)
- N0 or N1mic
- Left Ventricular EF ≥ 50%
- No prior invasive breast cancer
- ≤90 days from last surgery

Stratification factors:
- Age (<55, ≥55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

Radiation and endocrine therapy could be initiated after 12 weeks on study therapy

Tolaney SM et al. SABCS 2019;Abstract GS1-05.

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Disease-Free Survival: T-DM1

Tolaney SM et al. SABCS 2019;Abstract GS1-05.

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## Clinically Relevant Toxicity

<table>
<thead>
<tr>
<th>Clinically Relevant Toxicity</th>
<th>T-DM1 (n = 383) N (%)</th>
<th>TH (n = 114) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 non-hematologic toxicity</td>
<td>37 (10%)</td>
<td>13 (11%)</td>
</tr>
<tr>
<td>Grade ≥2 neurotoxicity</td>
<td>42 (11%)</td>
<td>26 (23%)</td>
</tr>
<tr>
<td>Grade ≥4 hematologic toxicity</td>
<td>4 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Any toxicity requiring dose delay</td>
<td>106 (28%)</td>
<td>30 (26%)</td>
</tr>
<tr>
<td>Any toxicity requiring early discontinuation</td>
<td>67 (17%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Total</td>
<td>176 (46%)</td>
<td>53 (46%)</td>
</tr>
</tbody>
</table>

\( p=0.91 \)

Tolaney SM et al. SABCS 2019;Abstract GS1-05.
ExteNET: Study Design

**Primary endpoint:** invasive disease-free survival (iDFS)

**Secondary endpoints:** DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, OS, safety

**Other analyses:** biomarkers, health outcome assessment (FACT-B, EQ-5D)

**Stratified by:** nodes 0, 1–3 vs. 4+, ER/PR status, concurrent vs. sequential trastuzumab

Follow-up for overall survival is ongoing (estimated: Q3 2019)

CNS=central nervous system; DCIS=ductal carcinoma in situ; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=in situ hybridization; PR=progesterone receptor; OS=overall survival.

ExteNET: Five-Year Invasive Disease-Free Survival by Patient Population

ITT (n = 2,840)

HR = 0.73

90.2% - Neratinib
87.7% - Placebo

HR-positive (n = 1,631)

91.2% - Neratinib
86.8% - Placebo

HR = 0.60

HR-negative (n = 1,209)

88.8% - Neratinib
88.9% - Placebo

HR = 0.95*

* Not statistically significant

Martin M et al. Lancet Oncol 2017;18(12):1688-700; Martin M et al. ESMO 2017;Abstract 149O.
CONTROL Study Schema

- Prophylactic study to prevent and manage neratinib-associated diarrhea
  - Stage I-IIIc HER2+ disease; prior therapy allowed: endocrine therapy, pertuzumab, and T-DM1

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Neratinib</th>
<th>Loperamide</th>
<th>Budesonide</th>
<th>Colestipol</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Neratinib 240 mg/day for 1 year (13 cycles*)</td>
<td>Loperamide 4 mg initial dose, then 4 mg TID on days 1–14 (i.e., 12 mg/day), then 4 mg BID on days 15–56 (i.e., 8 mg/day)†</td>
<td>Budesonide 9 mg/day for 1 cycle</td>
<td>Colestipol 2 gm BID for 1 cycle</td>
</tr>
<tr>
<td>2</td>
<td>Neratinib dose escalation #1</td>
<td>Loperamide as needed (16 mg/day max)</td>
<td>Loperamide as needed (16 mg/day max)</td>
<td>Colestipol 2 gm BID for 1 cycle</td>
</tr>
<tr>
<td>3</td>
<td>Neratinib 240 mg/day for 1 year (13 cycles*)</td>
<td>Loperamide 4 mg initial dose, then 4 mg TID on days 1–14 (i.e., 12 mg/day), then 4 mg BID on days 15–56 (i.e., 8 mg/day)†</td>
<td>Budesonide 9 mg/day for 1 cycle</td>
<td>Colestipol 2 gm BID for 1 cycle</td>
</tr>
<tr>
<td>4</td>
<td>Neratinib dose escalation #2</td>
<td>Loperamide as needed (16 mg/day max)</td>
<td>Loperamide as needed (16 mg/day max)</td>
<td>Colestipol 2 gm BID for 1 cycle</td>
</tr>
</tbody>
</table>

*One cycle=28 days. †Under the original protocol, subjects received loperamide 4 mg initial dose, 2 mg every 4 hours days 1–3, and 2 mg every 6 to 8 hours days 4–56 (n=28) before the “standard” loperamide regimen of 4 mg initial dose, 4 mg TID for 14 days and 4 mg BID days 14–56 was introduced (n=109). All subjects received loperamide as needed (16 mg/day max) after completion of mandated loperamide prophylaxis.

Barcenas et al. ASCO 2019 #548.
CONTROL Trial

Diarrhea grade on neratinib

Discontinuation rate: 3.3%

Barcenas CH et al. ASCO 2019
56-year-old woman (from the practice of Mr Pizana)

- 11/2018: Presents with left breast pain and nipple inversion → Mammography
- Pathology (lymph node): Grade 3, triple-positive (ER: >95%, PR: 75%, HER2: 2+) IDC, with lobular features, positive lymph node
- 3/28/2019: Completed neoadjuvant TCHP x 6
  - Gr 1 fatigue, diarrhea, nausea/vomiting
  - Lost to follow-up, noncompliance
- 8/02/2019: Left mastectomy, ALND, tissue expander
  - 1.2-cm, pT2c pN3a, Nodes 15+ with residual disease
- 9/26/2019: Switched to T-DM1, initiated anastrozole
- 11/2019: RT
- Currently, on cycle 11 of T-DM1
- Plan to initiate neratinib after completion of T-DM1
43-year-old woman (from the practice of Mr Pizana)

- 5/2018: Right, Grade 3, ER-positive (90%), PR-positive (2%), HER2-positive IDC
  - Lumpectomy (pT2pN0)
  - AC x 4 → weekly paclitaxel and trastuzumab → RT → tamoxifen
- 11/2019: Neratinib
  - Initial diarrhea controlled with loperamide and budesonide
- Currently, remains on neratinib and doing well
Module 1: Management of HER2-Positive Breast Cancer

• Neoadjuvant, Adjuvant Treatment of Localized Disease
  – Pertuzumab and neratinib for patients with higher-risk disease
  – T-DM1 as adjuvant and postneoadjuvant therapy

• New Agents, Regimens in Metastatic Disease
  – Neratinib/capecitabine, tucatinib, trastuzumab deruxtecan
The recently approved agent tucatinib is classified as which type of anti-HER2 agent?

a. Monoclonal antibody
b. Antibody-drug conjugate
c. Small molecule tyrosine kinase inhibitor
d. I don’t know
Trastuzumab deruxtecan carries a black box warning for...

a. QT interval prolongation
b. Interstitial lung disease
c. Cardiovascular events
d. I don’t know
Trastuzumab Deruxtecan in HER2-Positive mBC Previously Treated with T-DM1: Best Tumor Size Response

Patients who received T-DXd 5.4 mg/kg (N=184)

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Any Grade/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial lung disease</td>
<td>5 (2.7)</td>
<td>15 (8.2)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>4 (2.2)</td>
<td>25 (13.6)</td>
</tr>
</tbody>
</table>

Confirmed ORR: 60.9% (95% CI, 53.4%–68.0%)

11/168 CRs

Median time from the first infusion of T-DXd to onset of ILD was 27.6 weeks (range, 6–76 weeks)

Krop IE et al. SABCS 2019;Abstract GS1-03.
**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

*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

**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)

N=410
N=202

Murthy R et al. SABCS 2019;Abstract GS1-01.

https://clinicaltrials.gov/ct2/show/NCT02614794

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Most Common Adverse Events (≥20% in the Tucatinib Arm)

PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

Murthy R et al. SABCS 2019;Abstract GS1-01.
75-year-old woman (from the practice of Dr Kaklamani)

- Presents with ER-negative, HER2-positive mBC, with a breast mass and liver metastases
- Paclitaxel, trastuzumab and pertuzumab x 2 years → PD
- T-DM1
  - Not tolerated due to low blood counts
- Capecitabine/lapatinib
  - Capecitabine discontinued due to tolerability issues
  - Lapatinib continued x 8 cycles → PD
- Tucatinib/trastuzumab
- Currently on treatment and doing well
40-year-old woman (from the practice of Dr O’Shaughnessy)

- Stage III ER/PR-negative, HER2-positive breast cancer
- Neoadjuvant TCHP (pCR in breast and axilla)
- Currently, S/P SRS for brain met, but still with multiple, small untreated brain mets
- Tucatinib + trastuzumab (tolerating well)
- Initiating lower-dose capecitabine and will increase dose as tolerated
34-year-old woman (from the practice of Dr Kaklamani)

- Presents with a 3.5-cm, ER-negative, HER2-positive mass in left breast
- Neoadjuvant TCHP and atezolizumab on a clinical trial
  - 2-cm residual disease after completion of neoadjuvant therapy
- T-DM1 x 14 cycles
  - Remained disease free x 6 months → liver metastases
- Trastuzumab deruxtecan
  - Currently receiving her third cycle
55-year-old woman (from the practice of Dr O’Shaughnessy)

• ER/PR-negative, HER2-positive breast cancer
• Neoadjuvant TCHP \( \rightarrow \) mastectomy (residual disease) \( \rightarrow \) T-DM1 + RT
• Recurrence in left axilla, with multiple 1-2 cm nodules (ER-neg, HER2+)
• Capecitabine/trastuzumab (no response)
• Ibrutinib/trastuzumab on trial (no response)
• Axillary disease grew into a confluent flat mass across anterior axilla and ventral surface of her upper arm
• Trastuzumab deruxtecan
  – After 1 cycle: Major response
  – After 2 cycles: Axillary mass no longer palpable
  – Tolerating therapy well, mild nausea for 2-3 days after each infusion
Module 2: Anti-PD-1/PD-L1 Antibodies, Novel Agents in Triple-Negative Breast Cancer (TNBC)

- Metastatic TNBC: Atezolizumab/nab paclitaxel, pembrolizumab/chemotherapy
- Neoadjuvant pembrolizumab/chemotherapy in localized TNBC
- Recent FDA approval of sacituzumab govitecan
The anti-PD-L1 antibody atezolizumab is currently FDA approved in combination with *nab* paclitaxel as first-line treatment for...

a. All patients with metastatic breast cancer  
b. Metastatic triple-negative breast cancer  
c. Metastatic PD-L1-positive triple-negative breast cancer  
d. I don’t know
Anti-PD-1/PD-L1 Antibodies: Mechanism of Action

• PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function
• 3 approved drugs:
  – Nivolumab/pembrolizumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function
  – Atezolizumab binds PD-L1 receptors

Nivolumab/pembrolizumab: PD-1 receptor blocking Ab
Atezolizumab: PD-L1 receptor blocking Ab
KEYNOTE-522: A Phase III Trial of Neoadjuvant Chemotherapy with Pembrolizumab or Placebo Followed by Adjuvant Pembrolizumab or Placebo for TNBC

N = 1,174

- Locally advanced, nonmetastatic TNBC (T1c N1-2, T2-4, N0-2)
- Previously untreated

Stratification factors: Tumor nodal status (positive or negative), size (T1/T2 vs T3/T4) and carboplatin choice (q3wk vs qwk)

Primary endpoints: pCR rate and event-free survival

Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations.

Key IMpassion130 eligibility criteria:
- Metastatic or inoperable locally advanced TNBC
  - Histologically documented
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:
- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])

Atezo + nab-P arm:
- Atezolizumab 840 mg IV
  - On days 1 and 15 of 28-day cycle
- nab-paclitaxel 100 mg/m² IV
  - On days 1, 8 and 15 of 28-day cycle

Plac + nab-P arm:
- Placebo IV
  - On days 1 and 15 of 28-day cycle
- nab-paclitaxel 100 mg/m² IV
  - On days 1, 8 and 15 of 28-day cycle

Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated.
KEYNOTE-355: A Phase III Study of Chemotherapy +/- Pembrolizumab

N = 882
- Locally recurrent inoperable TNBC not previously treated with chemo and cannot be treated with curative intent, OR
- Metastatic TNBC not treated with chemo

Primary endpoints: Progression-free and overall survival

- In Part 1, individual chemo regimens combined with pembrolizumab were evaluated.
- In Part 2, participants receive 1 of 3 chemo regimens: nab paclitaxel, paclitaxel or gemcitabine/carboplatin.

FDA Grants Accelerated Approval to Sacituzumab Govitecan for Metastatic TNBC
Press Release – April 22, 2020

“The Food and Drug Administration granted accelerated approval to sacituzumab govitecan-hziy for adult patients with metastatic triple-negative breast cancer who received at least two prior therapies for metastatic disease.

Efficacy was demonstrated in IMMU-132-01 (NCT 01631552), a multicenter, single-arm trial enrolling 108 patients with metastatic triple negative breast cancer (mTNBC) who received at least two prior treatments for metastatic disease. Patients received sacituzumab govitecan-hziy 10 mg/kg intravenously on days 1 and 8 every 21 days. Tumor imaging was obtained every 8 weeks, and patients were treated until disease progression or intolerance to therapy.

The primary efficacy outcome measures were investigator assessed overall response rate (ORR) using RECIST 1.1 and response duration. The ORR was 33.3%. The median response duration was 7.7 months.”

67-year-old woman with triple-negative mBC (from the practice of Ms Marti)

- 6/2018: 5-cm, ER-positive, PR-negative, HER2-positive mixed metaplastic and IDC, with LVI
- Neoadjuvant TCHP (no response, PD) → surgery
- Pathology: Grade 3, ER (1-4%), PR-negative, HER2 IHC1+ metaplastic carcinoma, N-negative
- Postmastectomy RT → adjuvant dose-dense AC → capecitabine x 6 mos → adj anastrozole
- 7/2019 New lung nodules, brain mets
- Repeat testing (mastectomy tissue): TNBC, PD-L1 1%
- 10/2019: Nab paclitaxel/atezolizumab → atezolizumab alone after 6 mos
  - Minimal side effects; fatigue and hypothyroidism resolved with low-dose levothyroxine
- 2/2020 Brain MRI: Response to SRS
- 4/2020 Chest CT: Negative
Module 3: Genomic Testing and PARP Inhibitors

- Germline and somatic mutation testing
- Indications for and selection of available PARP inhibitors (olaparib, talazoparib)
A germline mutation is found in every cell in the body and a somatic mutation is found in the tumor.

a. Agree
b. Disagree
c. I don’t know
The PARP inhibitors olaparib and talazoparib are FDA approved for patients with metastatic breast cancer and a germline BRCA mutation:

a. As maintenance therapy after platinum chemotherapy
b. As monotherapy
c. Both a and b
d. I don’t know
A higher proportion of TNBC patients have BRCA mutations than HR+ patients... \cite{1,2}

The majority of TNBC are BRCA1m and HR+ tumours are BRCA2m \cite{1,2}

\begin{itemize}
  \item TNBC patients: \sim 17\% have BRCA mutations
  \item HR+ patients: \sim 6\% have BRCA mutations
\end{itemize}

Hormone receptor status in BC patients by BRCA status:

- \textbf{BRCA1m}:
  - ER+: 17\%
  - TNBC: 7.4\%

- \textbf{BRCA2m}:
  - ER+: 85.2\%
  - TNBC: 67.4\%

Note that these calculations are based on very small patient populations.

Detailed analysis of BRCAm prevalence, age of onset and survival outcomes are currently lacking for breast cancer subtypes.

\emph{BRCA}m=BRCA mutation; TNBC=triple negative breast cancer; HR+=hormone receptor positive; ER+=oestrogen receptor positive

Mechanism of Cell Death from Synthetic Lethality Induced by PARP Inhibition

Homologous recombination (HR) repair
Base excision DNA repair

No HR repair

Specific tumor cell killing

PARP inhibitor inhibits base excision DNA repair

DNA repair

 Courtesy of Jenny C Chang, MD
Common Side Effects of PARP Inhibitors Olaparib and Talazoparib

**Hematologic**
- Anemia
- Neutropenia
- Thrombocytopenia (more with talazoparib)

  Grade ≥3 in 10% to 40% of patients

**Nonhematologic**
- Nausea
- Vomiting
- Fatigue

  Mostly Grade 1 or 2

Phase III trials of PARP inhibitors in gBRCA HER2-negative metastatic breast cancer patients

**OlympiAD**

- **Patient Selection**
  - gBRCAm HER2- mBC
  - $\leq 2$ prior chemotherapy lines for mBC
  - Previous treatment with anthracycline and taxane in either the (neo)adjuvant or metastatic setting

- **Randomisation** 2:1

- **Treatment**
  - Olaparib 300mg po bid
  - Treatment of Physician’s Choice (TPC)

- **Primary Endpoint**
  - PFS (BICR)

**EMBRACA**

- **Patient Selection**
  - gBRCAm HER2- LABC or ABC
  - $\leq 3$ prior lines of chemotherapy
  - Previous treatment with a taxane, an anthracycline, or both, unless this treatment was contraindicated

- **Randomisation** 2:1

- **Treatment**
  - Talazoparib 1mg po qd
  - Treatment of Physician’s Choice (TPC)

- **Primary Endpoint**
  - PFS (BICR)

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## Phase III trials of PARP inhibitors in gBRCA HER2-negative metastatic breast cancer patients

Olaparib and talazoparib both improve PFS in gBRCA mBC patients vs chemotherapy of physician’s choice

### OlympiAD: Olaparib PFS\(^1,2\)

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Olaparib (N=205)</th>
<th>TPC (N=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>7.0</td>
<td>4.2</td>
</tr>
</tbody>
</table>

HR: 0.58  
95% CI (0.43-0.80)  
\(P<0.001\)

- Olaparib 300 mg bid (N=205)  
- TPC (N=97)

### EMBRACA: Talazoparib PFS\(^3\)

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Talazoparib (N=287)</th>
<th>Overall PCT (N=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo (95% CI)</td>
<td>8.6 (7.2, 9.3)</td>
<td>5.6 (4.2, 6.7)</td>
</tr>
</tbody>
</table>

HR: 0.54,  
95% CI (0.41-0.71)  
\(P<0.001\)

36-year-old woman with triple-negative mBC and a gBRCA mutation (from the practice of Ms Marti)

- 2013: cT3N3M0 TNBC while pregnant (Germline testing: gBRCA1 mutation)
- Preop cisplatin → bilateral mastectomy (MRD, 10+ LNs) → adjuvant TC → PMRT → BSO
- 2015: Nodal recurrence
- Gemcitabine/carboplatin (response) → PD in nodes → RT → capecitabine
- 4/2017: Recurrence (PD-L1: Negative in tumor and IC)
  - Brain MRI: 11-mm cerebellum mass with edema → SRS
- Clinical trial: PI3K/TORC1/2 inhibitor → PD (multiple, small lung mets) → nab paclitaxel/cisplatin
  - 12/2017 Restaging CT: CR of pulmonary mets and LNs
- 4/2018: Pembrolizumab → new rib lesion
- 12/2018: Discontinued pembrolizumab, initiated olaparib — rising TSH (thyroid replacement)
- Currently, on olaparib x 15 mos (+ zoledronic acid), with no PD or serious AEs, excellent PS
Module 4: CDK4/6 and PI3 Kinase Inhibitors in ER-Positive Disease

- Current role of CDK4/6 inhibitors for pre- and postmenopausal women
- Alpelisib/fulvestrant (PIK3CA mutation)
The mechanism of action of fulvestrant is essentially the same as that of tamoxifen, but fulvestrant is administered via intramuscular injection, whereas tamoxifen is administered orally.

a. Agree
b. Disagree
c. I don’t know
Therapy for premenopausal women with ER-positive metastatic breast cancer who undergo ovarian suppression or ablation is generally approached in the same manner as is therapy for postmenopausal patients.

a. Agree
b. Disagree
c. I don’t know
Which of the following toxicities is more common with palbociclib and ribociclib than with abemaciclib?

a. Gastrointestinal toxicity
b. Neutropenia
c. Anemia
d. Peripheral neuropathy
e. I don’t know
Which of the following toxicities is more common with abemaciclib than with palbociclib and ribociclib?

a. Gastrointestinal toxicity
b. Neutropenia
c. Anemia
d. Peripheral neuropathy
e. I don’t know
Which CDK4/6 inhibitor requires that an electrocardiogram be conducted prior to the initiation of treatment?

a. Palbociclib
b. Ribociclib
c. Abemaciclib
d. I don’t know
The PI3 kinase inhibitor alpelisib is used for patients with metastatic ER-positive, HER2-negative breast cancer with a…

a. PIK3CA germline mutation
b. PIK3CA somatic mutation
c. PIK3CA amplification
d. All of the above
e. I don’t know
HR+ / HER2- Advanced BC: Changing Paradigms

High Endocrine Sensitivity

- ET naive
- Progression > 1 yr after adj ET
- Fulvestrant (bone only, no prior ET)
  - NSAI + CDK4/6i
  - FULV (± EVE)
  - FULV + Alpelisib
  - EXE + EVE

Moderate Endocrine Sensitivity

- Progression between 2-3 yrs from start of or < 1 yr from end of adj ET
- FULV + CDK4/6i
  - PIK3CA wt
  - PIK3CA mut
  - FULV + Alpelisib
  - EXE + EVE

Poor Endocrine Sensitivity

- Progression within 2 yrs from start of adj ET
- Fulvestrant + CDK4/6i
  - PIK3CA wt
  - PIK3CA mut
  - EXE + EVE

CT
- Al + alpelisib

40% ER+ HER2- breast cancers harbor a PIK3CA mutation
CDK4/6 Regulates Cell Cycle Progression

ER+ breast cancer may overexpress Cyclin D with subsequent loss of control of the cell cycle.

M, mitosis; Rb, retinoblastoma.
Adapted from Finn et al, 2016.
# Common Side Effects and Dosing of CDK4/6 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Palbociclib</th>
<th>Abemaciclib</th>
<th>Ribociclib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>125 mg qd 3 wk on, 1 wk off</td>
<td>200 mg BID continuously</td>
<td>600 mg qd 3 wk on, 1 wk off</td>
</tr>
<tr>
<td><strong>Common adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>95% 76%</td>
<td>88% 42%</td>
<td>46% 37%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54% 19%</td>
<td>27% 2%</td>
<td>29% 10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16% 23%</td>
<td>90% 65%</td>
<td>22% 46%</td>
</tr>
<tr>
<td>Nausea</td>
<td>23% 5%</td>
<td>20% 5%</td>
<td>2% 2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5% 0</td>
<td>35% 2%</td>
<td>0 0</td>
</tr>
</tbody>
</table>

MONALEESA-3 Study Design

Men and postmenopausal women with HR+/HER2− ABC
≤ 1 line of prior ET for advanced disease
N = 726

Stratified by:
- Presence/absence of liver/lung metastases
- Prior endocrine therapy

Randomized 2:1

Ribociclib
(600 mg/day; 3 weeks on/1 week off)
+ fulvestrant
(500 mg)a
n = 484

Placebo
+ fulvestrant
(500 mg)a
n = 242

Primary end point
- PFS (locally assessed per RECIST version 1.1)

Secondary end points
- Overall survival
- Overall response rate
- Clinical benefit rate
- Time to response
- Duration of response
- Time to definitive deterioration of ECOG PS
- Patient-reported outcomes
- Safety
- Pharmacokinetics

Patient population definitions

Treatment naive for ABC

TFI > 12 mo

De novo ABC

≤ 1 line ET in ABC

TFI ≤ 12 mo and no treatment for ABC

TFI > 12 mo + PD on 1L ET for ABC

ABC at diagnosis with PD on 1L ET for ABC

1L, first line; 2L, second line; ABC, advanced breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TFI, treatment-free interval.

a Fulvestrant 500 mg intramuscularly every 28 days plus an additional dose on Cycle 1, Day 15.

MONALEESA-7: Overall Survival – Premenopausal 1L mBC

≈ 29% relative reduction in risk of death

The $P$ value of 0.00973 crossed the prespecified boundary to claim superior efficacy

<table>
<thead>
<tr>
<th>Event/N</th>
<th>Median OS, mo</th>
<th>HR (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribociclib + ET</td>
<td>83/335</td>
<td>Not reached</td>
<td>0.712 (0.535-0.948)</td>
</tr>
<tr>
<td>Placebo + ET</td>
<td>109/337</td>
<td>40.9</td>
<td></td>
</tr>
</tbody>
</table>

Kaplan-Meier Estimate

<table>
<thead>
<tr>
<th>Ribociclib + ET</th>
<th>Placebo + ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 months</td>
<td>71.9%</td>
</tr>
<tr>
<td>42 months</td>
<td>70.2%</td>
</tr>
</tbody>
</table>

Landmark Analysis

Im SA, et al. NEJM 2019
**SOLAR-1: Alpelisib Improved PFS in the PIK3CA-mutant Cohort**

Fulvestrant + Alpelisib or Placebo in ER+ HER2- mBC Patients Resistant to AI Therapy

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### Data cut-off: Jun 12, 2018

<table>
<thead>
<tr>
<th></th>
<th>ALP + FUL (n = 169)</th>
<th>PBO + FUL (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PFS events, n (%)</td>
<td>103 (60.9)</td>
<td>129 (75.0)</td>
</tr>
<tr>
<td>Progression</td>
<td>99 (58.6)</td>
<td>120 (69.8)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (2.4)</td>
<td>9 (5.2)</td>
</tr>
<tr>
<td>Censored</td>
<td>66 (39.1)</td>
<td>43 (25.0)</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>11.0 (7.5-14.5)</td>
<td>5.7 (3.7-7.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.65 (0.50-0.85)</td>
<td>0.65 (0.50-0.85)</td>
</tr>
</tbody>
</table>

**One-sided P value**

- **0.00065**

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**Median PFS, months:**

- Alpelisib + fulvestrant (n=169): **11.0** (95% CI: 7.5–14.5)
- Placebo + fulvestrant (n=172): **5.7** (95% CI: 3.7–7.4)

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**Number of subjects still at risk**

- Alpelisib + Fulv: 158, 145, 141, 133, 127, 121, 113, 107, 95, 85, 82, 75, 71, 68, 64, 54, 43, 39, 32, 30, 27, 23, 18, 14, 10, 5, 4, 3, 5, 1, 1, 1, 0
- Placebo + Fulv: 172, 167, 160, 111, 80, 80, 77, 67, 58, 54, 41, 37, 29, 29, 21, 19, 14, 13, 9, 9, 3, 3, 2, 2, 2, 0, 0, 0, 0

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CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

At final PFS analysis, superiority was declared if one-sided, stratified log-rank test P value was ≤ 0.0199 (Haybittle–Peto boundary).

*Mutation status determined from tissue biopsy.

58-year-old woman with ER-positive mBC (from the practice of Ms Marti)

- 10/2005: T1CpN1aM0, ER/PR-positive, HER2-negative IDC
  - BCS
  - Adjuvant AC x 4 → docetaxel/capecitabine x 4 → RT
  - Adjuvant tamoxifen x 4 yrs → anastrozole until metastatic disease
- 9/2014: ER-positive/PR-negative, HER2-negative pleural metastases
- Two lines of chemo, everolimus (x 1 month, not tolerated)
- 3rd-line: Letrozole/palbociclib x 6 mos → PD
- Fulvestrant/abemaciclib x 6 mos → PD
- Plasma testing: 2 PIK3CA mutations
- Fulvestrant/alpelisib x 10 mos
  - No serious AEs, but dose reduced from 300mg to 200mg daily due to 20 lbs weight loss
44-year-old woman with chronic cancer-related pain (from the practice of Mr Pizana)

- 8/2019: 4-cm, right, ER/PR-positive, HER2-negative breast cancer
- 9/2019 Staging scans: Bone and liver metastases
  - Liver biopsy: ER-positive, HER2-negative
- Zoledronic acid, letrozole/palbociclib
  - Myalgias, bone pain, Gr1 fatigue, decreased appetite
- PIK3CA testing: Positive
- 11/2019: Rash of unknown etiology: Palbociclib discontinued
- Nab paclitaxel x 2 cycles
- 2/26/2020: Transition to fulvestrant/alpelisib
  - Myalgias/arthralgias, Gr1 fatigue, oral mucositis, rash, Gr1 diarrhea
- 5/08/2020: Stable disease, plan to re-stage in 3 mos
Module 5: Management of Breast Cancer in the Era of COVID-19
Has the approach to primary surgery for patients with breast cancer changed at your institution during the COVID-19 pandemic?

a. Yes, quite a bit
b. Yes, but not very much
c. No
d. I don’t know
Has the approach to radiation therapy for patients with breast cancer changed at your institution during the COVID-19 pandemic?

a. Yes, quite a bit
b. Yes, but not very much
c. No
d. I don’t know
Do you believe that receiving an anti-PD-1/PD-L1 antibody makes a patient more susceptible to contracting COVID-19?

a. Yes
b. No
c. I don’t know
Do you believe that receiving an anti-PD-1/PD-L1 antibody increases a patient’s risk of developing complications associated with COVID-19?

a. Yes
b. No
c. I don’t know
Thank you for joining us!

CNE (NCPD) credit information will be emailed to each participant tomorrow morning.