Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium®

Session 1: Triple-Negative Breast Cancer

Monday, January 11, 2021
5:00 PM – 6:00 PM ET

Faculty
P Kelly Marcom, MD

Moderator
Neil Love, MD
Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eisai Inc, Genentech, a member of the Roche Group, and Merck.
Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.
## Dr Marcom — Disclosures

<table>
<thead>
<tr>
<th>Role</th>
<th>Companies and Organizations</th>
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<tbody>
<tr>
<td>Advisory Committee</td>
<td>Immunomedics Inc</td>
</tr>
<tr>
<td>Contracted Research</td>
<td>AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, GlycoMimetics Inc, Novartis, Takeda Oncology, Verily</td>
</tr>
<tr>
<td>Data and Safety Monitoring Board/Committee</td>
<td>Genentech, a member of the Roche Group</td>
</tr>
</tbody>
</table>
We Encourage Clinicians in Practice to Submit Questions

Feel free to submit questions now before the program begins and throughout the program.
Familiarizing Yourself with the Zoom Interface

How to answer poll questions

When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.
Year in Review: Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology

Gynecologic Cancers

Tuesday, January 12, 2021
5:00 PM – 6:00 PM ET

Faculty
Robert L Coleman, MD
Richard T Penson, MD, MRCP

Moderator
Neil Love, MD
Year in Review: Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology

Lymphomas

Thursday, January 14, 2021
5:00 PM – 6:00 PM ET

Faculty
Christopher R Flowers, MD, MS
Sonali M Smith, MD

Moderator
Neil Love, MD
Year in Review: Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology

Nontargeted Therapy for Lung Cancer

Tuesday, January 19, 2021
5:00 PM – 6:00 PM ET

Faculty
Matthew Gubens, MD, MS
Suresh S Ramalingam, MD

Moderator
Neil Love, MD
Recent Advances in Hematologic Oncology: A 4-Part Live Webinar Series Reviewing Key Data and Presentations from the 62\textsuperscript{nd} ASH Annual Meeting

Part 1 — Acute Myeloid Leukemia

Wednesday, January 20, 2021
5:00 PM – 6:00 PM ET

Faculty
Daniel A Pollyea, MD, MS
Eytan M Stein, MD
Andrew H Wei, MBBS, PhD

Moderator
Neil Love, MD
Year in Review: Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology

Chronic Lymphocytic Leukemia

Thursday, January 21, 2021
5:00 PM – 6:00 PM ET

Faculty
Matthew S Davids, MD, MMSc
Jennifer Woyach, MD

Moderator
Neil Love, MD
Meet The Professor
Management of Ovarian Cancer

Friday, January 22, 2021
1:15 PM – 2:15 PM ET

Faculty
Professor Jonathan A Ledermann, MD

Moderator
Neil Love, MD
Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium®

Session 1: Triple-Negative Breast Cancer  
Monday, January 11, 2021  
5:00 – 6:00 PM ET  
Faculty  
P Kelly Marcom, MD

Session 2: Triple-Negative Breast Cancer  
Monday, February 22, 2021  
5:00 – 6:00 PM ET  
Faculty  
Joyce O’Shaughnessy, MD

Session 1: HER2-Positive Breast Cancer  
Monday, January 25, 2021  
5:00 – 6:00 PM ET  
Faculty  
Erika Hamilton, MD

Session 2: HER2-Positive Breast Cancer  
Monday, March 8, 2021  
5:00 – 6:00 PM ET  
Faculty  
Mark D Pegram, MD
Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.
Adjuvant and Extended-Adjuvant Therapy for Patients with Localized HER2-Positive Breast Cancer

Martine J Piccart-Gebhart, MD, PhD
Scientific Director
Jules Bordet Institute
 Libre de Bruxelles
Gene Expression Assays in Breast Cancer

- Unsupervised analysis
  - Breast cancer is heterogeneous
  - Distinct subtypes
  - Prognosis varies by subtype (IAM5)h

- Supervised analysis
  - Several other prognostic assays (23-gene, 70-gene, others)
  - Lack of concordance in prognostic classification

Source: et al. (Proc. 2003), 100% (BMJ 2002)
Source: et al. (J Natl Cancer Inst. 2010, 102(1))
Cancer Conference Update: What Happened at the 2020 San Antonio Breast Cancer Symposium®
Session 1: Triple-Negative Breast Cancer

Monday, January 11, 2021
5:00 PM – 6:00 PM ET

Faculty
P Kelly Marcom, MD

Moderator
Neil Love, MD
Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Triple-Negative Breast Cancer

Friday, December 11, 2020
8:30 PM – 10:00 PM ET

Faculty
P Kelly Marcom, MD
Joyce O’Shaughnessy, MD
Hope S Rugo, MD
Professor Peter Schmid, MD, PhD

Moderator
Neil Love, MD
Optimal Integration of Immune Checkpoint Inhibitors into the Management of Metastatic Triple-Negative Breast Cancer (mTNBC)
Professor Peter Schmid, MD, PhD

Novel Applications of Immune Checkpoint Inhibitors for Patients with Early TNBC
Hope S Rugo, MD

Current and Future Role of PARP Inhibitors for Patients with TNBC and a BRCA Mutation
P Kelly Marcom, MD

Current and Future Management of PD-L1-Negative mTNBC
Joyce O’Shaughnessy, MD
Faculty

P Kelly Marcom, MD
Director, Breast Oncology Program
Professor of Medicine
Duke Cancer Institute
Durham, North Carolina

Moderator
Neil Love, MD
Research To Practice
Miami, Florida
We Encourage Clinicians in Practice to Submit Questions

You may submit questions using the Zoom Chat option below.

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ONCOLOGY TODAY
WITH DR NEIL LOVE

IMMUNE CHECKPOINT INHIBITION IN BREAST CANCER

DR SYLVIA ADAMS
PERLMUTTER CANCER CENTER

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Session 1: Triple-Negative Breast Cancer

Monday, January 11, 2021
5:00 PM – 6:00 PM ET

Faculty
P Kelly Marcom, MD

Moderator
Neil Love, MD
Triple-Negative Breast Cancer Survey Participants

1. Sylvia Adams, MD
2. Carey K Anders, MD
3. Aditya Bardia, MD, MPH
4. Joanne L Blum, MD, PhD
5. Adam M Brufsky, MD, PhD
6. Howard A Burris III, MD
7. Harold J Burstein, MD, PhD
8. Lisa A Carey, MD
9. Matthew Goetz, MD
10. Erika Hamilton, MD
11. Sara Hurvitz, MD
12. Virginia Kaklamani, MD, DSc
13. Hannah M Linden, MD
14. P Kelly Marcom, MD
15. Jennifer M Matro, MD
16. Kathy D Miller, MD
17. Rita Nanda, MD
18. Ruth O’Regan, MD
19. Joyce O’Shaughnessy, MD
20. Mark D Pegram, MD
21. Lajos Pusztai, MD, DPhil
22. Hope S Rugo, MD
23. Professor Peter Schmid, MD, PhD
24. Joseph A Sparano, MD
25. Sara M Tolaney, MD, MPH
Atif Hussein, MD, MMM
Program Director, Hematology/Oncology Fellowship
Medical Director, Oncology Clinical Research
Chairman, Cancer Committee
Memorial Healthcare System
Clinical Associate Professor
Florida International University Herbert Wertheim College of Medicine
Hollywood, Florida
Agenda

Module 1: Optimal Integration of Immune Checkpoint Inhibitors into the Management of Metastatic Triple-Negative Breast Cancer (TNBC)

Module 2: Novel Applications of Immune Checkpoint Inhibitors for Patients with Early TNBC

Module 3: Current and Future Role of PARP Inhibitors for Patients with TNBC and a BRCA Mutation

Module 4: Current and Future Management of PD-L1-Negative Metastatic TNBC
SABCS 2020 Educational Session (ES4)
Triple-Negative Breast Cancer – Tuesday, December 8, 2020

Deconstructing Triple Negative Breast Cancer
Rebecca A Dent, MD, MSc

State of the Art Treatment for Neoadjuvant/Adjuvant Triple Negative Breast Cancer
Lisa A Carey, MD

Metastatic TNBC – What’s New on the Horizon?
Jennifer K Litton, MD

How and When to Use Immunotherapy and Related Toxicities
Javier Cortes, MD, PhD
Deconstructing Triple Negative Breast Cancer

Rebecca A Dent, MD FRCP (Canada)
Head Dept of Medical Oncology
Senior Consultant
National Cancer Center Singapore
Associate Professor, Duke – NUS Medical School

HCC38
ER PR ERBB2

HCC1937
ER PR ERBB2
BRCA1 null

PD3664a
ER PR ERBB2

Dent R et al. SABCS 2020;Education Session ES4.
Not All Breast Cancers Are Equally Suitable for Immunotherapy

Somatic mutations in breast cancer subtypes

Quality as well as quantity
Of aberrations determine immune checkpoint sensitivity

Mutation rate higher in TNBC compared to other subtypes

Banerji
Nature. 2012

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State of the art treatment for early triple negative breast cancer

SABCS 2020

Lisa A. Carey
University of North Carolina
Lineberger Comprehensive Cancer Center
The Drugs Work! Early TNBC Relapse Rates over Time

Early relapse is the vast majority of all relapses
Decreased by 25-45% from years 0-6
However de novo is 20% of mTNBC in modern era

Cossetti R J et al. JCO 2015; File D et al, ASCO 2020

Carey LA et al. SABCS 2020; Education Session ES4.
Study Schema: SWOG 1416

Metastatic and/or loco-regionally recurrent TNBC or BRCA1 or BRCA2 germline mutation-associated HER2-negative MBC

0/1 prior cytotoxic chemotherapy for metastatic disease

Cisplatin 75 mg/m² Day 1 every 21 days
Veliparib 300 mg PO BID (D1-14) every 21 days

Cisplatin 75 mg/m² Day 1 every 21 days
Placebo PO BID (D1-14) every 21 days

Primary end point:
Progression-free survival in three pre-specified groups:
- gBRCA
- BRCA-like
- non-BRCA-like

Secondary end points:
- Overall survival
- Objective response rate
- Clinical benefit rate

Post-randomization germline and BRCA-like biomarker testing assigned patients into pre-specified groups

Deleterious germline BRCA1/2 mutation detected

Deleterious germline BRCA1/2 mutation not detected

BRCA-like Biomarker Analysis
1. HRD genomic instability score ≥42
2. Somatic BRCA1/2 mutation
3. BRCA1 promoter methylation (PM)
4. Germline HR repair genes mutation (excluding BRCA1/2)

Positivity on any one of the above four markers placed patient in BRCA-like group

Primary tumor

BRCA-like group

gBRCA group

Non-BRCA-like group

*TNBC defined as estrogen receptor (ER) and progesterone receptor (PgR) immunohistochemical (IHC) nuclear staining of ≤1% and HER2-negative per ASCO/CAP guidelines

Randomization stratified by number of prior cytotoxic regimens for metastatic disease (0 vs. 1)

Litton JK et al. SABCS 2020;Education Session ES4.
BRCA-like group

**Progression-free survival**
- Cisplatin + Veliparib (n=54)
  - Median PFS: 5.9 (4.3-7.8) months
  - HR (95% CI): 0.53 (0.34-0.83)
  - P-value: 2-sided p=0.005
- Cisplatin + Placebo (n=45)
  - Median PFS: 4.2 (2.3-5.0) months

**Overall survival**
- Cisplatin + Veliparib (n=54)
  - Median OS: 14.0 (10.3-not est) months
  - HR (95% CI): 0.60 (0.35-1.04)
  - P-value: 2-sided p=0.067
- Cisplatin + Placebo (n=45)
  - Median OS: 12.1 (9.0-15.2) months

ORR (n=83): 45% vs 33%
PARP Inhibitors

- PARP inhibition activates the cGAS/STING (stimulator of interferon genes) pathway
  - ↑ proinflammatory cytokines
  - ↑ Ag presentation
  - ↑ PD-L1 expression


Litton JK et al. SABCS 2020;Education Session ES4.
TRIPLE NEGATIVE BREAST CANCER

How and when to use immunotherapy and related toxicities in mTNBC

Javier Cortés
International Breast Cancer Center (IBCC), Madrid & Barcelona, Spain
Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain
Medica Scientia Innovation Research (MedSIR), Valencia, Spain & New Jersey, US

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The "breast cancer immunogram" beyond PD

- "Soil" (e.g., liver metastases)
- PDL1 status
- Tumor metabolism (LDH)
- TMB
- TILs
- General immune status (inflammation, microbiota, drugs)

Cortés J et al. SABCS 2020; Education Session ES4.
## When to rechallenge with ICI

<table>
<thead>
<tr>
<th>Organ</th>
<th>Rechallenge</th>
<th>Do NOT Rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Grade ≤ 1 rash, pruritus</td>
<td>Grade 3/4 severe, life-threatening bullous disease</td>
</tr>
<tr>
<td>GI</td>
<td>Grade 2/3 PD-1/PD-L1–associated colitis*</td>
<td>Grade 3 CTLA-4–associated colitis; grade 4 colitis</td>
</tr>
<tr>
<td>Liver</td>
<td>Grade 2 transaminitis without elevated bilirubin*</td>
<td>Grade 3/4 hepatitis</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Symptomatic grade 2</td>
<td>Grade 3/4 pancreatitis</td>
</tr>
<tr>
<td>Endocrine</td>
<td>After hormone repletion</td>
<td>Symptomatic pituitary inflammation</td>
</tr>
<tr>
<td>Lung</td>
<td>Grade 1/2, off steroids</td>
<td>Grade 3/4 pneumonitis</td>
</tr>
<tr>
<td>Renal</td>
<td>Grade 1/2*</td>
<td>Grade 3/4 proteinuria</td>
</tr>
<tr>
<td>Ocular</td>
<td>Grade 2</td>
<td>Grade 3/4 uveitis, episcleritis</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Grade 1/2 peripheral neuropathy</td>
<td>GBS, encephalitis, transverse myelitis, grade 2-4 myasthenia gravis</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Grade 1 myocarditis</td>
<td>Grade 2-4 myocarditis</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Resume after stabilization, adequate management</td>
<td>Severe inflammatory arthritis that impairs ADLs</td>
</tr>
</tbody>
</table>

*May resume once prednisone < 10 mg/day*

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Agenda

Module 1: Optimal Integration of Immune Checkpoint Inhibitors into the Management of Metastatic (TNBC)

Module 2: Novel Applications of Immune Checkpoint Inhibitors for Patients with Early TNBC

Module 3: Current and Future Role of PARP Inhibitors for Patients with TNBC and a BRCA Mutation

Module 4: Current and Future Management of PD-L1-Negative Metastatic TNBC
Additional Efficacy Endpoints from the Phase 3 KEYNOTE-355 Study of Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy as First-Line Therapy for Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer

Rugo HS et al.
SABCS 2020;Abstract GS3-01.
Pembrolizumab (anti-PD-1) plus chemotherapy in TNBC

KEYNOTE-355 study design

N = 847; no crossover permitted

- Pembrolizumab + Chemotherapy
- Placebo + Chemotherapy

Stratification factors:
- PD-L1 expression (CPS ≥1 vs CPS <1)
- Chemo on study (Taxane vs G/C)
- Prior treatment with same class chemo

Study Population:
- CPS≥10, 75%; CPS≥1, 38%; CPS <1, 25%
- Taxane, 45%; Gem/carboplatin, 55%
- Prior treatment with same class chemo, 22%
- De novo MBC, 30%; DFI 6-12, 21%; DFI >12, 49%

Co-primary endpoints were PFS and OS in the CPS ≥10, CPS ≥1, and ITT populations

Statistical design: Overall alpha controlled at one-sided 0.025, split among PFS (0.005), OS (0.018), and ORR (0.002); hierarchical testing PFS (CSP10>CP1>ITT)

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## KEYNOTE-355: Progression-Free Survival in Subgroups by On-Study Chemotherapy

### PD-L1 CPS ≥10

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Median PFS (mo)</th>
<th>Hazard Ratio for Progression or Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pembrolizumab + Chemo</td>
<td>Placebo + Chemo</td>
</tr>
<tr>
<td>Overall</td>
<td>323</td>
<td>9.7</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.65 (0.49 to 0.86)</td>
<td></td>
</tr>
<tr>
<td>On-study chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nab-Paclitaxel</td>
<td>99</td>
<td>9.9</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.57 (0.34 to 0.95)</td>
<td></td>
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<tr>
<td>Paclitaxel</td>
<td>44</td>
<td>9.6</td>
<td>3.6</td>
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<tr>
<td></td>
<td></td>
<td>0.33 (0.14 to 0.76)</td>
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<tr>
<td>Gemcitabine-Carboplatin</td>
<td>180</td>
<td>8.0</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.77 (0.53 to 1.11)</td>
<td></td>
</tr>
</tbody>
</table>

Rugo H et al. SABCS 2020;Abstract GS3-01.

This presentation is the intellectual property of Hope Rugo. Contact her at Hope.Rugo@ucsf.edu for permission to reprint and/or distribute.
KEYNOTE-355: Progression-Free Survival in Subgroups by On-Study Chemotherapy

PD-L1 CPS ≥1

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Median PFS (mo)</th>
<th>Hazard Ratio for Progression or Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>636</td>
<td>7.6</td>
<td>5.6</td>
</tr>
<tr>
<td>On-study chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nab-Paclitaxel</td>
<td>204</td>
<td>6.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>84</td>
<td>9.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Gemcitabine-Carboplatin</td>
<td>348</td>
<td>7.5</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Rugo H et al. SABCS 2020; Abstract GS3-01.

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KEYNOTE-355: Response Rate in Subgroups by On-Study Chemotherapy

PD-L1 CPS ≥10

- Nab-Paclitaxel: ORR 54.0%
- Paclitaxel: ORR 36.1%
- Gem-Carbo: ORR 27.3%

PD-L1 CPS ≥1

- Nab-Paclitaxel: ORR 43.1%
- Paclitaxel: ORR 29.7%
- Gem-Carbo: ORR 36.4%

ITT

- Nab-Paclitaxel: ORR 40.5%
- Paclitaxel: ORR 28.4%
- Gem-Carbo: ORR 28.1%

Data cutoff December 11, 2019.

Rugo H et al. SABCS 2020;Abstract GS3-01.
Genomic Profiling and Clinical Outcomes with First-Line Atezolizumab and Nab-Paclitaxel in Triple-Negative Breast Cancer: An Exploratory Analysis from the Phase 3 IMpassion130 Trial

Emens L et al.
SABCS 2020;Abstract PD14-05.
Atezolizumab (anti-PD-L1) plus chemotherapy in TNBC

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

IMpassion130 study design

- Metastatic or inoperable locally advanced TNBC
- No prior therapy for advanced TNBC
  - Prior (neo)adjuvant chemo allowed if TFI ≥ 12 months
- 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%])

Atezolizumab + nab-paclitaxel

Placebo + nab-paclitaxel

RECIST v1.1
PD or toxicity

Double blind; no crossover permitted

1:1

R

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Courtesy of Professor Peter Schmid, MD, PhD
Progression-free survival: PD-L1 predicts benefit with atezolizumab

<table>
<thead>
<tr>
<th>Population</th>
<th>PFS HR (95% CI)</th>
<th>Interaction Test (treatment × PD-L1 IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 IC+</td>
<td>0.62 (0.49, 0.78)</td>
<td>P &lt; 0.0001 0.0055</td>
</tr>
<tr>
<td>PD-L1 IC−</td>
<td>0.94 (0.78, 1.13)</td>
<td>0.5152</td>
</tr>
<tr>
<td>ITT</td>
<td>0.80 (0.69-0.92)</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

**Atezo + nab-P (PD-L1 IC+ n = 185)**
**Plac + nab-P (PD-L1 IC+ n = 184)**
**Atezo + nab-P (PD-L1 IC− n = 266)**
**Plac + nab-P (PD-L1 IC− n = 267)**

Courtesy of Professor Peter Schmid, MD, PhD
Overall survival: PD-L1 status predicts benefit with atezolizumab

Median OS (95% CI):
- A + nP (PD-L1+ population): 17.9 mo (13.6, 20.3)
- P + nP (PD-L1+ population): 25.4 mo (19.6, 30.7)

3-year OS:
- A + nP: 36%
- P + nP: 22%

### Table: PD-L1 IC+ population

<table>
<thead>
<tr>
<th></th>
<th>A + nP (n = 185)</th>
<th>P + nP (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS events, n (%)</td>
<td>120 (65)</td>
<td>139 (76)</td>
</tr>
<tr>
<td>Stratified HR (95% CI)</td>
<td>0.67 (0.53, 0.86)</td>
<td></td>
</tr>
</tbody>
</table>

Data cutoff, 14 April 2020. NE, not estimable. *P value not formally tested per hierarchical study design.*

This presentation is the intellectual property of the presenter. Contact p.Schmid@qmul.ac.uk for permission to reprint and/or distribute.
Atezolizumab (anti-PD-L1) plus Paclitaxel in TNBC

IMpassion131 study design

- Metastatic or inoperable locally advanced TNBC with measurable disease
- No prior therapy for advanced TNBC
  - Prior (neo)adjuvant chemo allowed if TFI ≥ 12 months
- ECOG PS 0-1

Study Population:
- SP142≥1%, 45%
- Taxane, 49%
- De novo MBC, 30%

Stratification factors:
- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (≥ 1% vs < 1%)
- Geographical region

Co-primary endpoints were PFS (investigator assessed) in the PD-L1+ and ITT populations

Double blind; no crossover permitted

8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

Miles D, et al. ESMO 2020

Courtesy of Professor Peter Schmid, MD, PhD

Prof. P. Schmid, Barts Cancer Institute
Atezolizumab plus Paclitaxel: Progression-free Survival in PD-L1+

Events in 61% of patients (data cut-off: 15 Nov 2019)

Stratified HR = 0.82 (95% CI 0.60–1.12)
Log-rank p=0.20

Median duration of follow-up: 8.6 months (placebo + PAC) vs 9.0 months (atezolizumab + PAC). CI = confidence interval

Courtesy of Professor Peter Schmid, MD, PhD

Miles D, et al. ESMO 2020
Atezolizumab plus Paclitaxel: Interim Survival Analysis

Updated interim OS analysis (data cut-off: 19 Aug 2020), events in 47% of the ITT population

Deaths in PD-L1+ 38 (38%) vs 82 (43%)

OS probability (%)

Stratified HR = 1.12 (95% CI 0.76–1.65)

PD-L1+

Atezolizumab + PAC

Placebo + PAC

100
90
80
70
60
50
40
30
20
10
0

0 3 6 9 12 15 18 21 24 27 30 33 36

Number at risk

Placebo + PAC 101 99 89 86 75 53 34 25 12 6 2 1 0
Atezolizumab + PAC 191 184 171 160 129 95 60 43 30 19 6 1 0

OS probability (%)

Stratified HR = 1.11 (95% CI 0.87–1.42)

ITT

Atezolizumab + PAC

Placebo + PAC

100
90
80
70
60
50
40
30
20
10
0

0 3 6 9 12 15 18 21 24 27 30 33 36

Number at risk

Placebo + PAC 220 213 191 174 141 102 71 50 27 15 9 1 0
Atezolizumab + PAC 431 406 366 331 267 194 126 76 56 35 16 3 0

Median duration of follow-up: 14.5 months (placebo + PAC) vs 14.1 months (atezolizumab + PAC) in the ITT population

Prof. P. Schmid, Barts Cancer Institute

Courtesy of Professor Peter Schmid, MD, PhD
PD-L1 assessment: key variables to take into account

**Type of cell to be considered**
- Only tumor cells (TC)
- Only immune cells (IC)
- Both (e.g. CPS)

**Modality of the scoring calculation**
- Enumeration of positive cells (CPS)
- Area occupied by positive ICs (SP142)

**Cut-off value**
- ≥1, ≥10, ≥20, >50 ..... 

**Primary antibody clones**
- SP142, SP263 and 22C3
Lenvatinib plus Pembrolizumab for Previously Treated, Advanced Triple-Negative Breast Cancer: Early Results from the Multicohort Phase 2 LEAP-005 Study

Chung HC et al.
SABCS 2020;Abstract PS12-07.
LEAP-005 Study Design

**Study Population**
- Women aged ≥18 years
- Histologically/cytologically confirmed, advanced TNBC
- 1 or 2 prior lines of therapy
- Measurable disease per RECIST version 1.1
- ECOG PS 0-1
- Tissue for PD-L1 assessment

N = 30

**Pembrolizumab 200 mg IV Q3W + lenvatinib 20 mg orally QD**

Evaluation

- PD
- SD, PR, CR

**30-day safety FU + survival status**

**Pembrolizumab 200 mg IV Q3W + lenvatinib 20 mg orally QD**

Up to 35 cycles or meeting DC

Chung HC et al. SABCS 2020;Abstract PS12-07.
LEAP-005: Best Percentage Change from Baseline in Target Lesion Size

Includes patients with one or more evaluable post-baseline imaging assessment (n = 27).

Chung HC et al. SABCS 2020;Abstract PS12-07.
LEAP-005: Treatment Duration and Response Evaluation

Chung HC et al. SABCS 2020;Abstract PS12-07.
A 32-year-old woman who completed neoadjuvant FEC/T and postoperative radiation therapy 21 months ago for localized TNBC now presents with small-volume liver and nodal metastases: BRCA wild type, PD-L1 positive. What therapy would you recommend?

1. Chemotherapy
2. Atezolizumab/nab paclitaxel
3. Atezolizumab/paclitaxel
4. Pembrolizumab/nab paclitaxel
5. Pembrolizumab/paclitaxel
6. Pembrolizumab/gemcitabine/carboplatin
7. Other
A 32-year-old woman who completed neoadjuvant FEC/T and radiation therapy 21 months ago for localized TNBC now presents with liver and nodal metastases. Biomarker assessment reveals BRCA WT, PD-L1-positive disease. What therapy would you recommend?

Survey of 25 breast cancer clinical investigators

- Atezolizumab/nab paclitaxel: 20 votes
- Pembrolizumab/gemcitabine/carboplatin: 5 votes
Case Presentation: A very anxious 50-year-old woman with metastatic triple-negative breast cancer – PD-L1 of 1%

- 2/2019: Diagnosed with ER/PR/HER2-negative, node-negative IDC
- Patient declines neoadjuvant therapy
- 3/2019: Genetic counseling unremarkable
- 5/2019: Left breast nipple sparing mastectomy + SLNB
  - 6/2019: Adjuvant paclitaxel/carboplatin weekly x 12 → dose-dense AC x 4
  - 7/2019 – 9/2019: Left chest wall RT
- 10/2020: Chest pain → Biopsy of right lung nodule: ER/PR/HER2-negative tumor compatible with mBC
  - 12/2020: NGS: PD-L1: 1%, CT abdomen/pelvis: No evidence of metastatic disease
- 12/15/2020: Atezolizumab/nab-paclitaxel (Cycle 1, Day 1)
  - 12/14/2020: Total bilirubin 0.7, ALP 141, AST 39, ALT 47
  - 12/22/2020: Total bilirubin 0.6, ALP 332, AST 235, ALT 398 (Cycle 1, Day 8)
  - 12/29/2020: Total bilirubin 1.0, ALP 471, AST 288, ALT 492
  - 1/05/2021: Total bilirubin 0.5, ALP 479, AST 88, ALT 254

Question
- What would you do next? Do I stop this regimen completely? Do I add some other chemotherapy to atezolizumab?
Module 1: Optimal Integration of Immune Checkpoint Inhibitors into the Management of Metastatic Triple-Negative Breast Cancer (TNBC)

Module 2: Novel Applications of Immune Checkpoint Inhibitors for Patients with Early TNBC

Module 3: Current and Future Role of PARP Inhibitors for Patients with TNBC and a BRCA Mutation

Module 4: Current and Future Management of PD-L1-Negative Metastatic TNBC
Immunologic Differences Between Primary and Metastatic Tumor Samples

Percent TIL counts in full sections and TMAs.

Szekely, et al (Pusztai), Ann Oncol 2018
Key Eligibility Criteria
- Age ≥ 18 years
- Newly diagnosed TNBC of either T1c N1-2 or T2-4 N0-2
- ECOG PS 0-1
- Tissue sample for PD-L1 assessment

Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

PD-L1 + defined by CPS ≥ 1

Courtesy of Hope S Rugo, MD
Schmid et al, NEJM 2020
Event-Free Survival at IA2: 1st Interim Analysis

P value boundary for significance 0.000051 (HR<0.4)

Prespecified P value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS).

IA2: If pCR hypothesis successful at IA1, pCR will not be formally tested at IA2.

HR (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by randomization stratification factors.

Data cutoff April 24, 2019; 24 mo after last pt enrolled

Immune related AEs:
• 14.1 vs 2.1% grade 3-5

Discontinuation of any drug:
• 9.5 vs 2.6%

9% events with median FU 15.5 months

Events

No. at Risk

Months

Pembro + Chemo/Pembro
7.4%
0.63a
(0.43-0.93)

Placebo + Chemo/Placebo
11.8%

91.3% 85.3%

EFS, %

Events (95% CI)

Courtesy of Hope S Rugo, MD

*Prespecified P value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS). IA2: If pCR hypothesis successful at IA1, pCR will not be formally tested at IA2. HR (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by randomization stratification factors. Data cutoff April 24, 2019; 24 mo after last pt enrolled.
Patient-Reported Outcomes (PROs) from the Ph 3 IMpassion031 Trial of Neoadjuvant (NA) Atezolizumab + Chemo in Early Triple-Negative Breast Cancer (eTNBC)

Mittendorf EA et al.
SABCS 2020;Abstract GS3-02.
IMpassion031: Randomized Phase III Trial

- 333 patients with TNBC, T>2cm
- Co-primary endpoints: pCR in ITT and PD-L1+ (SP142)

**Randomization 1:1**

**Placebo + nab-paclitaxel 125 mg/m² IV qw**

**Atezolizumab 840 mg IV q2w + nab-paclitaxel 125 mg/m² IV qw**

- **12 weeks**
- **8 weeks pCR**
- **SURGERY**
- **Atezolizumab 1200 mg IV q3w x 11 doses**
- **Observation**
- **Survival follow-up**

**Placebo + Doxorubicin 60 mg/m² IV q2w**

**Doxorubicin 60 mg/m² IV q2w**

**Cyclophosphamide 600 mg/m² IV q2w**

- **12 weeks**
- **8 weeks**

45-47% PD-L1+
76% stage II; 23% stage III
Median FU ~20 months

Courtesy of Hope S Rugo, MD
Harbeck et al, ESMO 2020 and Mittendorf et al, Lancet 2020
Primary Endpoint: pCR

Δ 16.5% (5.9, 27.1)

P = 0.0044

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Atezolizumab-Chemo</th>
<th>Placebo-Chemo</th>
<th>Difference in pCR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>57.6% 95/165</td>
<td>41.1% 69/168</td>
<td>16.5% (5.9, 27.1)</td>
</tr>
<tr>
<td>AJCC BC Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>61.9% 78/126</td>
<td>46.5% 60/129</td>
<td>15.4% (3.3, 27.5)</td>
</tr>
<tr>
<td>III</td>
<td>44.7% 17/38</td>
<td>23.1% 9/39</td>
<td>21.7% (1.1, 42.3)</td>
</tr>
<tr>
<td>PD-L1 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1-positive</td>
<td>68.8% 53/77</td>
<td>49.3% 37/75</td>
<td>19.5% (4.2, 34.8)</td>
</tr>
<tr>
<td>PD-L1-negative</td>
<td>47.7% 42/88</td>
<td>34.4% 32/93</td>
<td>13.3% (−0.9, 27.5)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>58.8% 20/34</td>
<td>35.7% 15/42</td>
<td>23.1% (11.1, 45.1)</td>
</tr>
<tr>
<td>≥ 40 years</td>
<td>57.3% 75/131</td>
<td>42.9% 54/126</td>
<td>14.4% (2.3, 26.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>57.8% 69/102</td>
<td>44.4% 48/108</td>
<td>13.4% (0, 26.8)</td>
</tr>
<tr>
<td>Black</td>
<td>44.4% 4/9</td>
<td>26.7% 4/15</td>
<td>17.8% (−21.7, 57.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>57.4% 24/47</td>
<td>34.1% 14/41</td>
<td>23.3% (3.0, 43.6)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>57.7% 90/156</td>
<td>43.1% 66/153</td>
<td>14.6% (3.5, 25.6)</td>
</tr>
<tr>
<td>1</td>
<td>62.5% 5/8</td>
<td>21.4% 3/14</td>
<td>41.2% (1.2, 80.9)</td>
</tr>
<tr>
<td>Regional lymph node</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LN-negative</td>
<td>57.8% 63/109</td>
<td>49% 47/96</td>
<td>8.8% (−4.8, 22.5)</td>
</tr>
<tr>
<td>LN-positive</td>
<td>57.1% 32/56</td>
<td>30.6% 22/72</td>
<td>26.6% (9.8, 43.4)</td>
</tr>
</tbody>
</table>

DFS and OS too early

AEs leading to discontinuation of any drug: 22.6 v 19.8%

AEs requiring corticosteroids: 12.8 v 9.6%

Harbeck et al, ESMO 2020 and Mittendorf et al, Lancet 2020

Courtesy of Hope S Rugo, MD
# Ongoing Phase III Trials with IO in TNBC

## Neoadjuvant/adjuvant
- **Atezolizumab**
  - NSABP B59/GeparDouze (n=1520)
  - Pac/carbo → AC/EC
  - EFS NeoTRIPaPDL1 (n=272)
  - EFS IMpassion031 (n=333)
- **Pembrolizumab**
  - EFS KEYNOTE-522 (n=1174)
  - NeoPACT (n=100)
    - Docetaxel/carbo/pembro x 6

## Adjuvant
- **Atezolizumab**
  - IMpassion030 (n=2300)
    - Pac → AC/EC
- **Avelumab**
  - A-Brave (n=335)
    - Adjuvant and post NAC high risk: avelumab alone
- **Pembrolizumab**
  - SWOG S1418/NRG-BR006 (n=1000)
    - Post NAC: Pembro vs Obs x 1 yr

Courtesy of Hope S Rugo, MD
Regulatory and reimbursement issues aside, have you or would you attempt to access an anti-PD-1/PD-L1 antibody as part of neoadjuvant therapy for a 60-year-old patient with a 6-cm TNBC with 3 positive axillary nodes on biopsy (PD-L1 60%)?

1. I have
2. I haven’t but would for the right patient
3. I haven’t and would not
Have you or would you attempt to access an anti-PD-1/PD-L1 antibody as part of neoadjuvant therapy off protocol for a 60-year-old patient with TNBC with the following characteristics?

Tumor size: 6 cm, Nodal status: 3 positive nodes, PD-L1: 60%

Survey of 25 breast cancer clinical investigators
Regulatory and reimbursement issues aside, have you or would you attempt to access an anti-PD-1/PD-L1 antibody as part of neoadjuvant therapy off protocol for a 60-year-old patient with TNBC with the following characteristics?

Tumor size: 6 cm, Nodal status: node-negative, PD-L1: 10%

Survey of 25 breast cancer clinical investigators
Case Presentation: A 44-year-old woman with triple-negative, node-positive breast cancer – PD-L1 CPS 8

- Right breast and axillary biopsies: 4.5-cm ER/PR/HER2-negative adenocarcinoma
- Imaging studies: No disease outside right breast and axilla
- PD-L1 CPS: 8

Questions
- What would you recommend as neoadjuvant treatment for this patient?
- After neoadjuvant pembrolizumab/carboplatin/paclitaxel, what type of adjuvant treatment would you give?
- How do you incorporate treatment with capecitabine, based on the adjuvant data?
- How do you incorporate immune checkpoint inhibitor therapy after surgery?
Agenda

Module 1: Optimal Integration of Immune Checkpoint Inhibitors into the Management of Metastatic Triple-Negative Breast Cancer (TNBC)

Module 2: Novel Applications of Immune Checkpoint Inhibitors for Patients with Early TNBC

Module 3: Current and Future Role of PARP Inhibitors for Patients with TNBC and a BRCA Mutation

Module 4: Current and Future Management of PD-L1-Negative Metastatic TNBC
TBCRC 048 Study: A Phase II study of olaparib monotherapy in metastatic breast cancer patients with germline or somatic mutations in homologous recombination (HR) pathway genes (Olaparib Expanded) (Nadine Tung, PI)

Hypothesis: Olaparib will have an overall response rate ≥ 20% in breast cancer patients with a germline or somatic mutation in DNA damage response (DDR) pathway genes associated with HR other than BRCA1/2 or with a somatic BRCA1/2 mutation.

- Primary Aim: ORR (CR + PR by RECIST 1.1)
- Secondary Aim: CBR (CR + PR + SD ≥ 18 weeks), Duration of Response, Progression-Free Survival, Toxicity.

Eligibility: Measurable metastatic disease; no prior PARPi; No more than 2 prior chemotherapy regimens; Not platinum refractory.

Courtesy of P Kelly Marcom, MD

TBCRC 048 Trial Schema: Olaparib Expanded

Single arm, Phase 2 study

- Olaparib 300 mg bid Q 3 wks
- Tumor Assessment Q 6wks x 24 wks then q 12 wks
- CR, PR, SD → Continue
- PD, Toxicity Requiring discontinuation → Off study
  - Optional research biopsy at progression

Cohort 1: Germline Mutation
Cohort 2: Somatic Mutation
sBRCA1/2 allowed if gBRCA negative

ATM, ATR, BAP1, BARD1, BLM, BRIP1 (FANCJ), CHK1 (CHEK1), CHEK2, CDK12, FANCA, FANCC, FANCD2, FANCF, MRE11A, NBN (NBS1), PALB2, RAD50, RAD51C, RAD51D, WRN

Tung NM et al. ASCO 2020;Abstract 1002.

Courtesy of P Kelly Marcom, MD
TBCRC 048 Trial Germline Cohort: Best Response and DOR

Tung NM et al. ASCO 2020;Abstract 1002.
TBCRC 048 Trial Somatic Cohort: Best Response and DOR

Tung NM et al. ASCO 2020;Abstract 1002.

Courtesy of P Kelly Marcom, MD
Talazoparib Beyond BRCA (TBB)

- 2 separate cohorts: A: HRD >42; B: Germline or somatic mutation in DDR pathway
- N=20 (13 germline, 7 somatic mutations)

Dent R et al. SABCS 2020; Education Session ES4.
PARPi (Neo) Adjuvant Trials

Preoperative Talazoparib Study:
Single Agent for 6 months gBRCA+

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>20</td>
</tr>
<tr>
<td>Median (range)</td>
<td>38 (23-58)</td>
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<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7</td>
</tr>
<tr>
<td>Black</td>
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</tr>
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<td>Hispanic</td>
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<td>Asian</td>
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<td>BRCA</td>
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<td>1</td>
<td>16</td>
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<td>I</td>
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<td>II</td>
<td>12</td>
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<td>III</td>
<td>3</td>
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<td>Histology</td>
<td></td>
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<tr>
<td>Ductal</td>
<td>18</td>
</tr>
<tr>
<td>Lobular</td>
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<tr>
<td>Metaplastic chondrosarcomatus</td>
<td>1</td>
</tr>
<tr>
<td>Tissue receptor subtype</td>
<td></td>
</tr>
<tr>
<td>TNBC (ER and PR &lt; 10%)</td>
<td>15</td>
</tr>
<tr>
<td>Hormone receptor positive (≥ 10%)</td>
<td>5</td>
</tr>
</tbody>
</table>

pCR 53%

OlympiA: Adjuvant Olaparib gBRCA+/HER2-
(NSABP B55/BIG 6-13)

Estimated primary completion date: November 18, 2020

Courtesy of P Kelly Marcom, MD
KEYLYNK-009: A Phase 2/3, Open-Label, Randomized Study of Pembrolizumab plus Olaparib vs Pembrolizumab plus Chemotherapy After Induction with First-Line Pembrolizumab plus Chemotherapy in Patients with Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer (TNBC)

Rugo H et al.
SABCS 2020;Abstract OT-30-01.
New Approaches: Durvalumab/Olaparib in I-SPY 2

- Rationale for combining PARPi/checkpoint inhibitor
  - Impaired nucleotide and base excision repair increase mutation and neoantigen load\(^1\)
    - DNA fragments activate intracellular STING (Stimulator of Interferon Genes) pathway
    - PARP inhibition upregulates PD-L1 expression in breast cell lines

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\(^1\)Pusztai et al, AACR 2020

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Lancet Oncology. 2019 Mar 1;20(3):e175-86

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Pusztai et al, AACR 2020

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\(^1\)Lancet Oncology. 2019 Mar 1;20(3):e175-86

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Courtesy of Hope S Rugo, MD
Novel Combinations: PARPi and Immune Checkpoints

• RATIONALE: PARPi activates intratumoral STING/c-GAS pathway causing CD8+ T-cell recruitment. IC might act synergistically with this activation. (Pantelidou, Cancer Discovery, 9: 722, 2019)

<table>
<thead>
<tr>
<th>Trial</th>
<th>BRCA1/2 Status</th>
<th>Drugs</th>
<th>Eligibility</th>
<th>Cohort Size</th>
<th>Overall Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPACIO</td>
<td>Any BRCA or PD-L1 status</td>
<td>Niraparib Pembrolizumab</td>
<td>≤ 2 chemo</td>
<td>55</td>
<td>21%</td>
</tr>
<tr>
<td>MEDIOLA</td>
<td>gBRCA</td>
<td>Olaparib Durvalumab</td>
<td>≤ 2 chemo</td>
<td>30</td>
<td>63%</td>
</tr>
</tbody>
</table>

Courtesy of P Kelly Marcom, MD
TOPACIO: Best Overall Response

Vinayak, JAMA Oncol. 2019;5(8):1132-1140

Courtesy of P Kelly Marcom, MD
MEDIOLA Trial


Courtesy of P Kelly Marcom, MD
Efficacy of Combined CDK4/6 Inhibitor and PARP Inhibitor in the Treatment of BRCA1 Mutant Triple Negative Breast Cancer

Zhu X et al.
SABCS 2020;Abstract PS4-39.
A 41-year-old woman with a gBRCA mutation who completed neoadjuvant AC/docetaxel and postoperative radiation therapy 21 months ago for localized TNBC now presents with liver, lung and nodal metastases. What therapy would you recommend if the tumor is PD-L1-positive?

1. Olaparib
2. Talazoparib
3. Olaparib or talazoparib — coin flip
4. Atezolizumab/nab paclitaxel
5. Pembrolizumab/chemotherapy
6. Chemotherapy
7. Chemotherapy followed by maintenance PARP inhibitor
8. Other
A 41-year-old woman with a gBRCA mutation who completed neoadjuvant AC/docetaxel and postoperative radiation therapy 21 months ago for localized TNBC now presents with liver, lung and nodal metastases. What therapy would you recommend if the tumor is PD-L1-positive?

**Survey of 25 breast cancer clinical investigators**

- Atezolizumab/nab paclitaxel: 16 votes
- Pembrolizumab/gemcitabine/carboplatin: 6 votes
- Platinum-containing chemotherapy regimen: 1 vote
- Talazoparib: 1 vote
- Olaparib or talazoparib — coin flip: 1 vote
The patient in the previous scenario receives first-line atezolizumab/nab paclitaxel but experiences disease progression after 29 months. What would you recommend next?

1. Olaparib
2. Talazoparib
3. Olaparib or talazoparib — coin flip
4. Nonplatinum chemotherapy
5. Platinum-containing chemotherapy
6. Chemotherapy followed by maintenance PARP inhibitor
7. Chemotherapy combined with a PARP inhibitor
8. Other
The patient in the previous scenario receives first-line atezolizumab/nab paclitaxel but experiences disease progression after 29 months. What would you recommend next?

- Olaparib or talazoparib — coin flip: 13
- Olaparib: 7
- Talazoparib: 4
- Platinum-containing chemotherapy regimen: 1

Survey of 25 breast cancer clinical investigators
What would be your preferred treatment approach for a 60-year-old patient with a BRCA germline mutation and de novo metastatic TNBC that is PD-L1-negative?

1. Olaparib
2. Talazoparib
3. Olaparib or talazoparib — coin flip
4. Nonplatinum chemotherapy
5. Platinum-containing chemotherapy
6. Chemotherapy followed by maintenance PARP inhibitor
7. Chemotherapy combined with a PARP inhibitor
8. Other
What would be your preferred treatment approach for a 60-year-old patient with a BRCA germline mutation and de novo metastatic TNBC that is PD-L1-negative?

Survey of 25 breast cancer clinical investigators

- Olaparib or talazoparib — coin flip: 11
- Chemotherapy followed by maintenance with a PARP inhibitor:
  - Olaparib: 4
  - Talazoparib: 3
- Platinum-containing chemotherapy regimen: 1
- Nonplatinum chemotherapy regimen: 1
Regulatory and reimbursement issues aside, have you or would you attempt to access a PARP inhibitor for a patient with metastatic TNBC and a **germline** PALB2 mutation?

1. I have
2. I haven’t but would for the right patient
3. I haven’t and would not
Regulatory and reimbursement issues aside, have you attempted or would you attempt to access a PARP inhibitor for a patient with metastatic TNBC and a germline PALB2 mutation?

Survey of 25 breast cancer clinical investigators
Regulatory and reimbursement issues aside, have you or would you attempt to access a PARP inhibitor for a patient with metastatic TNBC and a germline ATM mutation?

1. I have
2. I haven’t but would for the right patient
3. I haven’t and would not
Regulatory and reimbursement issues aside, have you attempted or would you attempt to access a PARP inhibitor for a patient with metastatic TNBC and a germline ATM mutation?

Survey of 25 breast cancer clinical investigators

- I have: 4
- I haven’t but would for the right patient: 2
- I haven’t and would not: 19
Regulatory and reimbursement issues aside, have you attempted or would you attempt to access a PARP inhibitor for a patient with metastatic TNBC and a somatic BRCA mutation?

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I have

I haven’t but would for the right patient
Case Presentation: A 54-year-old woman with metastatic triple-negative breast cancer – gBRCA1m, PD-L1 of 2%

- Diagnosed with 3-cm ER/PR/HER2-negative IDC of left breast
- CT/PET/CT guided biopsy: Hepatic metastatic triple-negative adenocarcinoma
- PD-L1: 2%
- Deleterious germline BRCA1 mutation
- Olaparib 300 mg BID, with mild nausea treated with ondansetron
  - After 3 months: 40% reduction in breast mass and hepatic lesions
  - Baseline Hgb: 11.9 → 9.8 → 10.8 g/dL and currently stable

Questions
- How do you incorporate PARP inhibitors in the treatment of triple-negative breast cancer? What line would you use a PARP inhibitor?
- What do we know about chemotherapy after a PARP inhibitor?
Agenda

Module 1: Optimal Integration of Immune Checkpoint Inhibitors into the Management of Metastatic Triple-Negative Breast Cancer (TNBC)

Module 2: Novel Applications of Immune Checkpoint Inhibitors for Patients with Early TNBC

Module 3: Current and Future Role of PARP Inhibitors for Patients with TNBC and a BRCA Mutation

Module 4: Current and Future Management of PD-L1-Negative Metastatic TNBC
**Study 301: eribulin vs capecitabine 2L MBC**

<table>
<thead>
<tr>
<th>Median OS</th>
<th>Eribulin</th>
<th>Cape</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2 status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>14.3 mo</td>
<td>17.1 mo</td>
<td>0.965</td>
</tr>
<tr>
<td>Negative</td>
<td>15.9 mo</td>
<td>13.5 mo</td>
<td>0.838</td>
</tr>
<tr>
<td><strong>ER status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>18.2 mo</td>
<td>16.8 mo</td>
<td>0.897</td>
</tr>
<tr>
<td>Negative</td>
<td>14.4 mo</td>
<td>10.5 mo</td>
<td>0.779</td>
</tr>
<tr>
<td><strong>Triple-negative BC (TNBC)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14.4 mo</td>
<td>9.4 mo</td>
<td>0.702</td>
</tr>
<tr>
<td>No</td>
<td>17.5 mo</td>
<td>16.6 mo</td>
<td>0.927</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>15.9 mo</td>
<td>14.5 mo</td>
<td>0.879</td>
</tr>
</tbody>
</table>

N= 1102  
1:1 Randomization  
MBC or LABC  
1-3 prior lines of Tx  
Prior Anthra. and Taxane

Courtesy of Joyce O'Shaughnessy, MD
EMBRACE: OS (ITT Population)
Eribulin vs Treatment of Physician’s Choice

1-year survival

- Eribulin (n=508) 54.5%
- TPC (n=254) 42.8%

Overall survival (%)
- Eribulin
  Median 13.2 months
- TPC
  Median 10.6 months

HR* 0.81 (95% CI 0.68, 0.96)
Nominal p value=0.014

Courtesy of Joyce O'Shaughnessy, MD

Phase II Trial Sacituzumab Govitecan

Sacituzumab Antibody-Drug Conjugate (ADC)

Humanized RS7 antibody
- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC

SN-38 payload
- Targets 136-fold more SN-38 than the parent compound, irinotecan (topoisomerase I inhibitor)
- ADCs unique chemistry avoids low solubility and selectively delivers SN-38 to the tumor

Linker for SN-38
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid payload release at or inside the tumor

Met TNBC 3/4/5th-line Phase II

Tumor Response to Treatment

Confirmed ORR = 34% (37/110)

Clinical benefit rate (CR+PR+SD≥6 mo) = 45% (50/110)

- 74% (75/102) of patients with at least one CT response assessment had reduction of target lesions (sum of diameters)
- 102 patients had ≥1 scheduled CT response assessment
- 8 patients withdrew prior to assessment (4 PD, 4 MRI brain mets)

Median DoR 7.6 mos
Med PFS 5.5 mos

Bardia A et al. SABCS 2017

Courtesy of Joyce O'Shaughnessy, MD
Biomarker Evaluation in the Phase 3 ASCENT Study of Sacituzumab Govitecan versus Chemotherapy in Patients with Metastatic Triple-Negative Breast Cancer

Hurvitz SA et al.
SABCS 2020;Abstract GS3-06.
ASCENT (Phase III): Sacituzumab Govitecan (SG) vs Treatment of Physician’s Choice (TPC) in pretreated mTNBC (N=529) – Study Design

Metastatic TNBC (per ASCO/CAP)
≥2 chemotherapies for advanced disease
[no upper limit; 1 of the required prior regimens could be progression occurred within a 12-month period after completion of (neo)adjuvant therapy)]
N=529

Sacituzumab Govitecan (SG) 10 mg/kg IV days 1 & 8, every 21-day cycle (n=267)

Treatment of Physician’s Choice (TPC)* (n=262)

Continue treatment until progression or unacceptable toxicity

Endpoints
Primary
• PFS†
Secondary
• PFS for the full population‡
• OS, ORR, DOR, TTR, safety

Data cutoff: March 11, 2020

Stratification factors
• Number of prior chemotherapies (2-3 vs >3)
• Geographic region (North America vs Europe)
• Presence/absence of known brain metastases (yes/no)

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.

*BPC: etirubin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.

NCT02574455

Bardia A, et al. ESMO 2020 (LBA17)

Courtesy of Joyce O'Shaughnessy, MD
Overall Survival by Trop-2 Expression

Assessed in brain metastases-negative population. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring. H-score, histochemical-score; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician’s choice; Trop-2, trophoblast cell surface antigen-2.

<table>
<thead>
<tr>
<th>Trop-2 High</th>
<th>H-score: 200-300</th>
<th>Trop-2 Medium</th>
<th>H-score: 100-200</th>
<th>Trop-2 Low</th>
<th>H-score: &lt;100</th>
</tr>
</thead>
<tbody>
<tr>
<td>SG (n=85)</td>
<td>TPC (n=72)</td>
<td>SG (n=39)</td>
<td>TPC (n=35)</td>
<td>SG (n=27)</td>
<td>TPC (n=32)</td>
</tr>
<tr>
<td>Median OS—mo (95% CI)</td>
<td>14.2 (11.3-17.5)</td>
<td>6.9 (5.3-8.9)</td>
<td>14.9 (6.9-NE)</td>
<td>6.9 (4.6-10.1)</td>
<td>9.3 (7.5-17.8)</td>
</tr>
</tbody>
</table>

Events/Censored

| SG – Trop-2 High | 53/32 |
| SG – Trop-2 Medium | 22/17 |
| SG – Trop-2 Low | 20/7 |
| TPC – Trop-2 High | 64/8 |
| TPC – Trop-2 Medium | 23/12 |
| TPC – Trop-2 Low | 25/7 |

Courtesy of Joyce O'Shaughnessy, MD
Novel Targets in Triple Negative Breast Cancer

Courtesy of Joyce O'Shaughnessy, MD
Double-Blind Placebo (PBO)-Controlled Randomized Phase III Trial Evaluating First-Line Ipatasertib (IPAT) Combined with Paclitaxel (PAC) for PIK3CA/AKT1/PTEN-Altered Locally Advanced Unresectable or Metastatic Triple-Negative Breast Cancer (aNBC): Primary Results from IPATunity130 Cohort A

Dent R et al.
SABCS 2020;Abstract GS3-04.
What treatment would you recommend next for a 60-year-old woman with metastatic TNBC (BRCA wild-type, PD-L1-positive) who experiences disease progression after 7 months of first-line atezolizumab/nab paclitaxel?

1. Gemcitabine
2. Capecitabine
3. Vinorelbine
4. Eribulin
5. Sacituzumab govitecan
6. Platinum-based chemotherapy
7. Other chemotherapy
8. Other
What treatment would you recommend next for a 60-year-old woman with metastatic TNBC (BRCA WT, PD-L1-positive) who experiences disease progression after 7 months of first-line atezolizumab/nab paclitaxel?

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- Sacituzumab govitecan: 9 votes
- Platinum-based chemotherapy: 8 votes
- Capecitabine: 4 votes
- Eribulin: 3 votes
- Gemcitabine: 1 vote
Year in Review: Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology

Gynecologic Cancers

Tuesday, January 12, 2021
5:00 PM – 6:00 PM ET

Faculty
Robert L Coleman, MD
Richard T Penson, MD, MRCP

Moderator
Neil Love, MD
Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.