Best of ASCO 2019:
Update on GI Cancers

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LINEBERGER COMPREHENSIVE CANCER CENTER
The role of PARP inhibitor maintenance in gBRCA mutated mPDAC

RESULTS OF THE PHASE III POLO TRIAL

Synthetic Lethality and DNA Repair in Pancreatic Cancer

Iglehart JD and Silver DP, NEJM 2009; 361: 189-191
Kaufman B et al, JCO 2015; 33: 244-250

| Phase II trial of olaparib in BRCA mutated cancers (PDAC, N = 23) |
|---------------------------------|--------------|
| Median PFS                     | 4.6 months   |
| ORR                             | 21.7%        |

Phase II trial of olaparib in BRCA mutated cancers (PDAC, N = 23)

Median PFS 4.6 months
ORR 21.7%
Phase III POLO trial: olaparib as maintenance therapy following platinum-based chemo in gBRCA mutated mPDAC

METHODS

- 3315 patients screened with a 7% detection rate of gBRCA1/2 mutation (247 patients identified) -> 154 randomized
- Received at least 16 weeks of first line platinum based chemo for metastatic disease without progression
- 154 patients randomized 3:2 to maintenance olaparib (300mg BID) or placebo
- Primary endpoint: PFS (starting from time of randomization)

PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Olaparib (N = 92)</th>
<th>Placebo (N = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from diagnosis to randomization</td>
<td>Median, months (range)</td>
<td>6.9 (3.6 – 38.4)</td>
</tr>
<tr>
<td>Duration of first-line chemotherapy</td>
<td>Median, months (range)</td>
<td>5.0 (2.5 – 35.2)</td>
</tr>
<tr>
<td>First-line chemo</td>
<td>FOLFIRINOX</td>
<td>79 (85.9)</td>
</tr>
<tr>
<td>Best response on chemo</td>
<td>CR or PR</td>
<td>46 (50)</td>
</tr>
</tbody>
</table>

Kindler HL et al, JCO suppl; abstract LBA4

Improved PFS with olaparib maintainance

Primary endpoint: PFS by blinded independent central review*

- Median PFS, months
  - Olaparib (N=92): 7.4
  - Placebo (N=62): 3.8
  - HR 0.53
  - 95% CI 0.35, 0.82;
  - P=0.0038

Progression-free at data cut-off:
- 30 olaparib patients (32.6%)
- 12 placebo patients (19.4%)

*Data analysis complete as of January 23, 2018, 9:30am, EST
Other Conclusions

- Interim OS data showed no difference between arms at 46% maturity (18.9 vs 18.1 months, HR 0.91, p = 0.68)
- No difference between the two arms in terms of quality of life assessments
- There was no unexpected toxicity from olaparib compared to AE data from other trials
  - Most common AEs: fatigue, nausea, diarrhea, abdominal pain, anemia, decreased appetite, constipation, vomiting, back pain and arthralgia

Is there a role for 1st line therapy with FOLFOXIRI in mCRC

VISNU-1: FOLFOXIRI + bevacizumab vs FOLFOX + bevacizumab in mCRC deemed high risk by presence of ≥ 3 CTC

TRIBE-2: FOLFOXIRI plus bevacizumab vs sequential FOLFOX + bevacizumab -> FOLFIRI plus bevacizumab
General Principles of Treating Metastatic Colorectal Cancer Patients

**CLINICAL PARAMETERS**
- Burden of metastatic disease
- Potential for curative resection
- Age, performance status, comorbidities

**TUMOR/MOLECULAR PARAMETERS**
- Extended RAS/RAF testing
- MSI status
- Sidedness of the tumor (right vs left)
- Next generation sequencing data

**CALGB 80405: Establishing a paradigm for RAS/RAF wild-type mCRC**

- First line randomized study of mFOLFOX6 vs FOLFIRI combined with either cetuximab or bevacizumab in 1137 patients with untreated RAS wt mCRC
- Global provider preference for FOLFOX over FOLFIRI (73 vs 27%)
- Response rates were 55% in the bevacizumab group and 59% in the cetuximab group (p = 0.13)
- 140 patients underwent curative resection following chemotherapy (mOS for bevacizumab group 62 months, cetuximab 65 months).

Venook AP et al. JAMA 317(23): 2392-2401, 2017
Phase III trials with improved outcomes with FOLFOXIRI compared to FOLFIRI

**Phase III GONO (N = 244)**


**TRIBE (N = 508)**


**Phase III HORG (N = 285)**


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**VISNU-1 Design**

VISNU PROGRAM

- Screened n=1208

**VISNU-1**

- N=349
- Metastatic CRC
- ≥3 CTC
- <70 years
- ECOG PS 0-1

**Randomize**

- FOLFOX-Bevacizumab N=177
- FOLFOXIRI-bevacizumab N=172

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Sastre J et al, JCO 37 (Abstract 3507); ASCO 2019
VISNU-1: Key Results

- Survival shorter in pts with high CTCs compared to other 1st line studies
- Incremental benefit from FOLFOXIRI consistent with prior studies

<table>
<thead>
<tr>
<th></th>
<th>FOLFOXIRI-bev N=172</th>
<th>FOLFOX-bev N=177</th>
<th>HR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>12.4m</td>
<td>9.3m</td>
<td>0.64 (0.49-0.82)</td>
</tr>
<tr>
<td>OS</td>
<td>22.3m</td>
<td>17.6m</td>
<td>0.862 (0.66-1.06)</td>
</tr>
<tr>
<td>RR</td>
<td>59%</td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>

**Primary endpoint PFS**

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TRIBE-2 Design

Unresectable mCRC ≤75 years  
ECOG PS 0-1 (0 if 70-75)  
No adjuvant oxaliplatin  

Randomize

- FOLFOXIRI-bev x 8 N=340  
  SFU-bev as maintenance  
  Progression

- FOLFOXIRI-bev x 8 N=339  
  SFU-bev as maintenance  
  Progression

- FOLFIRI-bev x 8  
  SFU-bev as maintenance

- FOLFOXIRI-bev x8  
  SFU-bev as maintenance

Cremolini C et al. JCO 37, 2019 (Abstract 3508) ASCO 2019
TRIBE2: Key Results

<table>
<thead>
<tr>
<th></th>
<th>FOLFOXIRI-bev</th>
<th>Sequential doublet-bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=339</td>
<td>N=340</td>
<td></td>
</tr>
<tr>
<td>PFS2</td>
<td>19.1m</td>
<td>17.5 m</td>
</tr>
<tr>
<td>HR</td>
<td>0.74 (0.62-0.88)</td>
<td></td>
</tr>
<tr>
<td>PFS1</td>
<td>12.0m</td>
<td>9.8 m</td>
</tr>
<tr>
<td>HR</td>
<td>0.75 (0.63-0.88)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>27.6m</td>
<td>22.6 m</td>
</tr>
<tr>
<td>HR</td>
<td>0.81 (0.67-0.98)</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>62%</td>
<td>50% (FOLFOX-bev)</td>
</tr>
<tr>
<td>2nd line RR</td>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td>2nd line PFS</td>
<td>6.2 m</td>
<td>5.6 m</td>
</tr>
<tr>
<td>HR</td>
<td>0.87 (0.73-1.04)</td>
<td></td>
</tr>
</tbody>
</table>

Time on Treatment during TRIBE-2

- FOLFOXIRI
  - Triplet time: 8 months
  - Maintenance time: 10.2 months

- FOLFIRI
  - Doublet time: 8 months
  - Maintenance time: 7.4 months

Slide courtesy of Dr. Hanna Sanoff, ASCO 2019
Are we burning a bridge by using all our cytotoxics up front?

- Previously untreated mCRC
- WHO PS 0-2

1st line therapy provides majority of benefit with lower 2nd line PFS

<table>
<thead>
<tr>
<th></th>
<th>1st line RR</th>
<th>1st PFS</th>
<th>2nd line RR</th>
<th>2nd line PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX/FOLFIRI</td>
<td>54%</td>
<td>8.0 months</td>
<td>4%</td>
<td>2.5 months</td>
</tr>
<tr>
<td>FOLFIRI/FOLFOX</td>
<td>56%</td>
<td>8.5 months</td>
<td>15%</td>
<td>4.2 months</td>
</tr>
</tbody>
</table>

Overview of treating mCRC

• While FOLFOXIRI has been shown to improve outcomes compared to both FOLFIRI and FOLFOX, this approach is not appropriate for all patients
  • Both trials excluded patients based on age (no one greater than 75). For frailer patients or those with lower burden of disease, may be more reasonable to start with a doublet

• Importantly, patients having received adjuvant oxaliplatin were excluded from TRIBE2 (only 4% in VISNU1)
• TRIBE2 shows minimal benefit for re-introducing FOLFOXIRI vs restarting a doublet at time of progression
Outline

Neoadjuvant and Adjuvant Therapies
- HER2+ breast cancer (Abstract 500)
- HR+ breast cancer (Abstract 514)

Metastatic Breast Cancer Therapies
- HER2+ breast cancer (Abstract 1000)
- HR+ breast cancer (Late-breaking abstract 1008)
- Triple negative breast cancer (Abstract 1003)

Supportive Therapies (Abstract 6527)

Neoadjuvant and Adjuvant Therapies

HER2+ breast cancer

  ◦ Established the role of trastuzumab emtansine (T-DM1), an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1) in the adjuvant setting for patients with residual invasive breast cancer following neoadjuvant therapy
  ◦ Invasive disease–free survival was significantly higher in the T-DM1 group than in the trastuzumab group (HR 0.50)
**KRISTINE Study Design**

**Primary Results**

- Neoadjuvant TCH+P resulted in a superior pCR rate compared with T-DM1+P
  - 56% vs 44%, \( P = 0.0155 \)\(^1\)
  - pCR rates were higher with TCH+P in tumors with IHC2+ HER2 staining (21% vs 7%), or IHC3+ HER2 staining (61% vs 50%)\(^2\)

- During neoadjuvant treatment, T-DM1+P had a more favorable safety profile than TCH+P\(^1\)
  - Lower incidence of grade ≥3 adverse events (13% vs 64%)
  - Lower incidence of serious adverse events (5% vs 29%)
  - Lower incidence of adverse events leading to treatment discontinuation (3% vs 8%)

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EFS Events

<table>
<thead>
<tr>
<th>Event</th>
<th>T-DM1+P (n=223)</th>
<th>TCH+P (n=221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of EFS events</td>
<td>31 (13.9)</td>
<td>13 (5.9)</td>
</tr>
<tr>
<td>Locoregional progression before surgery</td>
<td>15 (6.7)</td>
<td>0</td>
</tr>
<tr>
<td>Invasive disease recurrence after surgery</td>
<td>11 (4.9)</td>
<td>11 (5.0)</td>
</tr>
<tr>
<td>Non-invasive recurrence (DCIS) after surgery</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Death without prior EFS event</td>
<td>2 (0.9)</td>
<td>2 (0.9)</td>
</tr>
</tbody>
</table>

*No surgery date was recorded for these patients; therefore they were not included in the EFS analysis. All of these patients, however, were included in the OS analysis.*

Event-Free Survival

- **TCH + P**
- **TDM1 + P**

Event-Free Survival (%)

- **TCH + P**: 84.2% (95.0–97.4)
- **TDM1 + P**: 85.9% (80.9–90.1)

Survival at 18 months: 61% (95% CI: 59%–64%)

No. of Patients at Risk

- **TCH + P**: 221
- **TDM1 + P**: 223

Time (months)

Day 1 6 12 18 24 30 36 42 48

- 221
- 214
- 211
- 209
- 197
- 190
- 140
- 10

- 223
- 199
- 192
- 185
- 177
- 173
- 126
- 16
Invasive Disease-Free Survival

No. of Patients at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TCH + P (n=214)</th>
<th>TDM1 + P (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCH + P</td>
<td>214</td>
<td>193</td>
</tr>
<tr>
<td>TDM1 + P</td>
<td>193</td>
<td>187</td>
</tr>
</tbody>
</table>

Time (months)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>80</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Presented By Sara Hurvitz at 2019 ASCO Annual Meeting
Take-Home Points

Higher risk of EFS event in T-DM1+P arm (HR 2.61, 95% CI 1.36-4.98)
  • Driven by presurgical locoregional progression which was associated with lower HER2 expression and greater HER2 heterogeneity

Similar risk of IDFS event between arms (HR 1.11, 95% CI 0.52-2.40)
  • Is systemic chemotherapy unnecessary for some patients?
  • Area of needed investigation before can be implemented in practice

Patients attaining pCR had ~97% 3-year IDFS

AEs and PROs favor T-DM1

Clinical Application

Would not routinely use T-DM1+P in the neoadjuvant setting

Could consider using for patients unable to tolerate chemotherapy or unwilling to take chemotherapy

Unclear if we can use chemotherapy-sparing neoadjuvant regimens in some patients – further investigation required
Neoadjuvant and Adjuvant Therapies

HR+ breast cancer – Duration of Endocrine Tx

The Clinical Treatment Score at 5 years (CTS5) is a prognostic tool using clinicopathological data to estimate distant recurrence (DR) risk after 5 years of endocrine therapy for postmenopausal women with estrogen receptor positive (ER+) breast cancer.

It was developed and validated in the ATAC and BIG 1-98 trials.

https://www.cts5-calculator.com/
HR+ breast cancer – Duration of ET

Methods: The validity of CTSS was tested in a retrospective cohort of unselected, non-trial patients diagnosed with early ER+ breast cancer at the Royal Marsden Hospital from 2000-2007 who were alive and distant recurrence-free at 5 years.

Primary endpoint: Time to late distance recurrence (5-10 years).

<table>
<thead>
<tr>
<th></th>
<th>HR for late distant recurrence (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal (N=1662, DR=107)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTSS (continuous)</td>
<td>1.95 (1.59-2.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CTSS low</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>CTSS intermediate</td>
<td>2.28 (1.32-3.93)</td>
<td>0.003</td>
</tr>
<tr>
<td>CTSS high</td>
<td>3.81 (2.27-6.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Premenopausal (N=776, DR=51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTSS (continuous)</td>
<td>1.72 (1.23-2.40)</td>
<td>0.001</td>
</tr>
<tr>
<td>CTSS low</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>CTSS intermediate</td>
<td>1.69 (0.84-3.51)</td>
<td>0.16</td>
</tr>
<tr>
<td>CTSS high</td>
<td>2.63 (1.29-5.34)</td>
<td>0.008</td>
</tr>
</tbody>
</table>
HR+ breast cancer – Duration of ET

**Figure 2:** Observed versus expected events for the postmenopausal cohort.
Take-Home Points

CT55 is validated in an unselected, non-trial cohort, including pre-menopausal patients.
Calibration was less accurate in pre-menopausal patients compared to post-menopausal.

Clinical Application

These findings highlight the **prognostic value** of the CTS5 calculator, not the **predictive value** (i.e. likelihood of benefit of further endocrine therapy).

- Therefore, this tool should be used to identify patients whose risk of distant recurrence after 5 years of ET is so low that extended ET could not possibly be beneficial.
Clinical Application

Proposed extended endocrine therapy algorithm, adapted from Richman and Dowsett, NCRO, 2018.

Outline

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- HER2+ breast cancer (Abstract 500)
- HR+ breast cancer (Abstract 514)

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- HER2+ breast cancer (Abstracts 1000)
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- Triple negative breast cancer (Abstract 1003)

Supportive Therapies (Abstract 6527)
Metastatic Breast Cancer – HER2+

Persistent Unmet Need in HER2+ MBC After Anti-HER2 Therapy

- Current standard of care for HER2-positive MBC
  - First-line: trastuzumab and pertuzumab with chemotherapy\(^1\)\(^-\)\(^3\)
  - Second-line: T-DM1\(^4\)\(^-\)\(^5\)

- After the above therapies, there is no recognized standard of care
  - Subsequent therapies are poorly defined, including sequential chemotherapy with trastuzumab and/or lapatinib\(^6\)\(^,\)\(^7\)
  - Continued anti-HER2 therapy after progression is generally preferred, in combination with chemotherapy\(^8\)\(^-\)\(^11\)
Margetuximab: Fc-engineered to Activate Immune Responses

Trastuzumab

- Fabs:
  - Binds HER2 with high specificity
  - Disrupts signaling that drives cell proliferation and survival

- Fc:
  - Wild-type immunoglobulin G1 (IgG1) immune effector domains
  - Binds and activates immune cells

Margetuximab

- Fabs:
  - Same specificity and affinity
  - Similarly disrupts signaling

- Fc engineering:
  - \( \uparrow \) Affinity for activating Fc\(\gamma\)RIIA (CD16A)
  - \( \downarrow \) Affinity for inhibitory Fc\(\gamma\)RIIB (CD32B)

Margetuximab Binding to Fc\(\gamma\)RIIa Variants:

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Receptor</th>
<th>Alleric Variant</th>
<th>Relative Fc Binding</th>
<th>Affinity Fold-Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activating</td>
<td>CD16A</td>
<td>158F</td>
<td>Lower</td>
<td>6.1 x ( \uparrow )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>158V</td>
<td>Higher</td>
<td>4.7 x ( \downarrow )</td>
</tr>
<tr>
<td>Inhibitory</td>
<td>CD32A</td>
<td>131R</td>
<td>Lower</td>
<td>6.1 x ( \downarrow )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>131H</td>
<td>Higher</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td></td>
<td>CD32B</td>
<td>232F/232T</td>
<td>Equivalent</td>
<td>8.4 x ( \downarrow )</td>
</tr>
</tbody>
</table>

Study CP-MGAH22-04 (SOPHIA) Design\textsuperscript{1,2}

**HER2+ advanced breast cancer**
- 22 prior anti-HER2 therapies, including pertuzumab
- 1-3 prior treatment lines in metastatic setting
- Prior brain metastases ok if treated and stable

**Investigator’s choice of chemotherapy**
- Trastuzumab + pertuzumab
- Gemcitabine, carboplatin, or vinorelbine

**Randomization (N=536)**
- Arm 1: Margetuximab (15 mg/kg Q3W) + chemotherapy in 3-week cycles
- Arm 2: Trastuzumab (8 mg/kg loading → 6 mg/kg Q3W) + chemotherapy in 3-week cycles

**Stratification:**
- Chemotherapy choice
- Prior therapies (≤2 vs >2)
- Metastatic sites (≤2 vs >2)

**Sequential Primary Endpoints**
- PFS (by CBA; HR=0.67; p=0.05; power=80%)
- OS (n=385; HR=0.75; p=0.05; power=80%)

**Secondary Endpoints**
- PFS (investigator assessed)
- Objective response rate (by CBA)
- Clinical benefit rate (CBR), duration of response (DoR)
- Safety profile, antidrug antibody
- Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

**Tertiary/Exploratory Endpoints**
- HR (stratified Cox model; 0.36
  (95% CI: 0.19–0.69)
- Stratified Log-rank P=0.001

**PFS Analysis in ITT Population**

- **24% Risk Reduction of Disease Progression**
  Central Blinded Analysis (Primary Endpoint)

- **30% Risk Reduction of Disease Progression**
  Investigator Assessed (Secondary Endpoint)

- PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred

**ITT population N=536. O2: Confidence interval.**
### PFS Subgroup Analyses

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median PFS (95% CI), Months</th>
<th>HR by Unstratified Cox Model</th>
<th>Unstratified Log Rank P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, n=236</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>C-reactive protein ≤ 60</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>C-reactive protein ≥ 60</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>Germline BRCA1, n=280</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>Germline BRCA2, n=280</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>Hormone receptor positive, n=290</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>Hormone receptor negative, n=290</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>Age &lt;60 years, n=130</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>Age ≥60 years, n=130</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>Prior (twice) vs none, n=233</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Hormone receptor positive (HR+) and (HR-): hormone receptor negative (HR+) and (HR-): HR=Hormone receptor status.**

### Planned* Exploratory PFS Analyses by FcγR Genotypes (CBA)

**Margrmetuximab benefit appears to be increased in low-affinity CD16A-158F allele carriers**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median PFS (95% CI), Months</th>
<th>HR by Unstratified Cox Model</th>
<th>Unstratified Log Rank P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, n=280</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>CS16A/F carrier (FV or FF), n=487</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>CS16A/FF, n=382</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>CS16A/FF, n=295</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>CS16A/FF, n=280</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>CS16A/FF, n=287</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>CS16A/FF, n=237</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
<tr>
<td>CS16A/FF, n=137</td>
<td>5.4 (3.5-8.03)</td>
<td>0.76</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Non-alpha is locating exploratory analysis.

**CS16A/FF not included on forest plot because n=6 is too small (5 on margrmetuximab, 4 on trastuzumab) to make analysis meaningful.**
Take-Home Points

In combination with chemotherapy in pretreated HER2+ MBC, margetuximab improves PFS over trastuzumab with comparable safety.

Overall survival data in the ITT population showed a non-significant 1.7-month difference favoring the margetuximab arm, which grew to 6.7 months in the CD16A FV/FF allele group (94% of patients)

A second interim analysis for overall survival is expected later this year.
Clinical Application

Margetuximab with chemotherapy could be considered in the 3rd line for patients with HER2+ MBC
- Clear PFS benefit
- OS benefit yet to be established, stay tuned
- Need further investigation regarding patient selection according to genotype

Metastatic Breast Cancer – HR+
**MONALEESA-7 Study Design**

First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients

- **Pre/Postmenopausal women** with HR+/HER2- ABC
- No prior ET for ABC
- 1 prior CT for ABC

N = 672

**Primary endpoint**
- PFS (local)

**Key secondary endpoint**
- OS

**Select secondary endpoints**
- HRQoL
- ORR
- TTD of ECOG PS
- Safety

**Stratification Factors**
- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)

**Ribociclib**
- 600 mg/day
- 3 weeks on/1 week off
- NSAI/TAM® + GOS®
- n = 335

**Placebo**
- 3 weeks on/1 week off
- NSAI/TAM® + GOS®
- n = 337

**Unmet Needs in Premenopausal Patients With Advanced Breast Cancer**

- Young women with breast cancer tend to have poorer prognoses and more aggressive cancer compared with older women, yet premenopausal patients are underrepresented in clinical trials.1-3

- Ribociclib, a CDK4/6 inhibitor, plus ET with ovarian suppression demonstrated a significantly longer PFS vs ET alone as initial ET in premenopausal patients with HR+/HER2- ABC in the MONALEESA-7 trial.4 (23.8 vs 13 mos, HR 0.55)

- To date, there have been no reports of a statistically significant improvement in OS with the addition of a CDK4/6 inhibitor to ET

---


Overall Survival

- Approximately 29% relative reduction in risk of death
- The P value of .00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis

<table>
<thead>
<tr>
<th>Kaplan-Meier Estimate</th>
<th>Ribociclib + ET</th>
<th>Placebo + ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 months</td>
<td>71.9%</td>
<td>64.9%</td>
</tr>
<tr>
<td>42 months</td>
<td>70.2%</td>
<td>46.0%</td>
</tr>
</tbody>
</table>

Overall Survival in the NSAI Subgroup

- Approximately 30% relative reduction in risk of death

Landmark Analysis

<table>
<thead>
<tr>
<th>Kaplan-Meier Estimate</th>
<th>Ribociclib + ET</th>
<th>Placebo + ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 months</td>
<td>72.2%</td>
<td>64.6%</td>
</tr>
<tr>
<td>42 months</td>
<td>69.7%</td>
<td>43.0%</td>
</tr>
</tbody>
</table>
Take-Home Points

Ribociclib plus ET has favorable PFS and OS compared to ET alone in pre-menopausal patients with HR+ metastatic breast cancer

No other CDK 4/6 inhibitor has a proven OS benefit

Clinical Application

CDK 4/6 inhibitor plus ET is the clear choice for first-line treatment of HR+, HER2-negative advanced breast cancer

- Different agents have been used interchangeably with choice of agent often driven by affordability to patient, dosing, side effect profile

- Ribociclib may become the preferred agent as the only CDK 4/6 inhibitor with proven overall survival benefit
Metastatic Breast Cancer – TNBC

IMpassion130 Study Design

- Patients with metastatic or inoperable, locally advanced TNBC without prior therapy for advanced TNBC

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

Atezolizumab
840 mg IV q2w + nab-paclitaxel 100 mg/m² IV on d1, d8, d15
Double blind; no crossover permitted

Placebo
q2w IV + nab-paclitaxel 100 mg/m² IV on d1, d8, d15

Treatment until PD per RECIST 1.1 or intolerable toxicity

- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

1. Pre chemotherapy in the curative setting allowed if treatment free interval ≥ 12 months. 28 day cycle. 2. Centrally evaluated per transferring IHC assay.

Presented By Peter Schmid at 2019 ASCO Annual Meeting
Take-Home Points

*IMpassion130 is the first and only phase 3 study to show the clinically meaningful benefit of immunotherapy in metastatic TNBC

PD-L1 status predicts clinical benefit of atezolizumab plus nab-paclitaxel

No new safety signals in updated analysis
Clinical Application

Atezolizumab + nab-paclitaxel is FDA approved and recommended for the treatment of patients with PD-L1+ metastatic TNBC

Outline

Neoadjuvant and Adjuvant Therapies
- HER2+ breast cancer (Abstract 500)
- HR+ breast cancer (Abstract 514)

Metastatic Breast Cancer Therapies
- HER2+ breast cancer (Abstracts 1000)
- HR+ breast cancer (Late-breaking abstract 1008)
- Triple negative breast cancer (Abstract 1003)

Supportive Therapies (Abstract 6527)
• Dose-dense paclitaxel
  • Shorter duration of treatment than weekly paclitaxel
    - 8 weeks vs 12 weeks
  • Per NCCN guidelines, requires growth factor support with each cycle

Hypothesis: Growth factor support is not necessary with dd-paclitaxel

Methods: Retrospective chart review of 265 patients receiving dd-paclitaxel for breast cancer (1010 cycles of chemotherapy, 783 without GCSF, 227 cycles with GCSF, dependent on provider standard practice)
Results:

- No episodes of neutropenic fever in all 1010 cycles of dd-paclitaxel
- Similar rates of grade 3/4 neutropenia in both groups (10% without GCSF vs 9% with GCSF)
- Estimated number needed to treat to prevent 1 episode of grade 3/4 neutropenia: 167

Take-Home Points

Dose-dense paclitaxel confers about a 10% risk of grade 3/4 neutropenia but very low risk of febrile neutropenia
Clinical Application

Omission of GCSF following dose-dense paclitaxel seems reasonable in patients who otherwise do not have patient-specific risk factors for myelosuppression:

- Age > 65
- Persistent neutropenia
- Bone marrow involvement by tumor
- Recent surgery / open wounds
- Liver dysfunction (Billirubin > 2)
- Renal dysfunction (Cr clearance < 50)