Preliminary efficacy and safety of pembrolizumab (MK-3475) in patients with PD-L1-positive, estrogen receptor-positive (ER+)/HER2-negative advanced breast cancer enrolled in KEYNOTE-028

Hope S. Rugo: Research funding to the institution from Merck & Co., Inc., and Genentech

Study supported by Merck & Co., Inc., Kenilworth, NJ, USA

Editorial assistance by the ApotheCom Merck oncology team (Yardley, PA, USA) and supported by Merck & Co., Inc.

Preliminary Efficacy and Safety of Pembrolizumab in Patients With PD-L1–Positive, Estrogen Receptor-Positive/HER2-Negative Advanced Breast Cancer Enrolled in KEYNOTE-028

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PD-1 Pathway and Pembrolizumab

- The PD-1 pathway has been implicated in tumor immune evasion.
- PD-1 inhibitors target the interaction between PD-1 and its ligands PD-L1 and PD-L2.
- The anti-PD-1 antibody pembrolizumab has demonstrated clinical activity in multiple tumor types:
  - Approved for metastatic melanoma and NSCLC.


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Pembrolizumab has Single Agent Activity in PD-L1+ Triple Negative Breast Cancer

<table>
<thead>
<tr>
<th>Evaluable for Response</th>
<th>N=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall RR</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Progression</td>
<td>12 (44.4%)</td>
</tr>
<tr>
<td>No data</td>
<td>3 (11.1%)</td>
</tr>
</tbody>
</table>

Median duration of response not reached: 15 - 40+ weeks
(3 of 5 responders still on drug for >11 months)
Median time to response: 18 weeks

Nanda et al, SABCS 2014

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ER*/HER2- Advanced Breast Cancer and PD-L1 Expression

- ER*/HER2- disease (luminal A and luminal B subtypes) is the most common subtype of breast cancer
  - Accounts for >50% of all breast cancers
- PD-L1 is expressed in breast cancer cells and stroma
  - 4-20% of ER*/HER2- tumors previously reported as PD-L1 positive
    - May be more frequent in luminal B vs luminal A phenotype
  - PD-L1 expression inversely correlated with ER expression
  - PD-L1 expression may be a prognostic factor in breast cancer
  - Reported association with worse (IHC) or better (mRNA) outcome


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KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1* Advanced Solid Tumors

- Colon or rectal adenocarcinoma
- Anal canal squamous cell* (20.0%)
- Pancreatic adenocarcinoma
- Esophageal squamous cell carcinoma or adenocarcinoma* (30.4%)
- Biliary tract adenocarcinoma
- Carcinoid tumors
- Neuroendocrine tumors
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- Prostate Adenocarcinoma
- Endometrial Carcinoma
- Cervical Squamous Cell Cancer
- Vulvar Squamous Cell Carcinoma
- Small Cell Lung Cancer* (29.2%)
- Mesothelioma (MPM)* (28.0%)
- Thyroid Cancer
- Sallivary Gland Carcinoma
- Nasopharyngeal Carcinoma* (22.2%)
- Glioblastoma Multiforme
- Leiomyosarcoma

*Data has been reported, percentages indicate response.

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**KEYNOTE-028: ER+/HER2- Breast Cancer Cohort**

- **Patients**
  - ER+/HER2- tumors
  - Locally advanced or metastatic disease
  - Failure of or inability to receive standard therapy
  - ECOG PS 0 or 1
  - CAE measurable lesion
  - PD-L1 positivity

- **Pembrolizumab**
  - 10 mg/kg IV Q2W

- **Response Assessment**
  - Every 8 weeks for the first 6 months; every 12 weeks thereafter

- **Primary end points:** ORR per RECIST v1.1 by investigator and safety
- **Secondary end points:** PFS, OS, duration of response

*Defined by institutional standards. If disease stable, patients were to remain on pembrolizumab until progressive disease was confirmed or a second scan performed 24 weeks later. Only patients who discontinued pembrolizumab for complete response or after 24 months of continuous treatment without evidence of disease progression were eligible for up to 5 years of additional pembrolizumab.*

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**Analysis of PD-L1 Expression**

- Tumor samples: archival or newly obtained core or excisional biopsy of a nonirradiated lesion
- Immunohistochemistry: assessed at a central laboratory using a prototype assay and 22C3 antibody clone (Merck)
- Positivity: membranous PD-L1 expression in ≥1% of tumor cells or any staining in stroma

**Examples of PD-L1 Staining in Breast Cancer Specimens**

- PD-L1 Negative
- PD-L1 Positive

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Preliminary Efficacy and Safety of Pembrolizumab (MK-3475) in Patients with PD-L1-Positive, Estrogen Receptor-Positive (ER+)/HER2-Negative Advanced Breast Cancer Enrolled in Keynote-028

Speaker: Hope S Rugo

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Patients Screened for Tumor PD-L1 Expression in the ER+/HER2- Breast Cancer Cohort

- Patients Screened for PD-L1: n = 261
- Samples Evaluable for PD-L1: n = 248
- PD-L1-Positive Tumors: n = 48
- 19.4% PD-L1+

Patients Treated as of July 1, 2015: N = 25

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Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>N = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>53.0 (36–79)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>16 (64)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13 (52)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (44)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>10 (40)</td>
<td></td>
</tr>
<tr>
<td>Prior (neo)adjuvant therapy</td>
<td>17 (68)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>N = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lines of prior therapy for metastatic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5 (20)</td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>11 (44)</td>
<td></td>
</tr>
<tr>
<td>Type of prior therapy&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>25 (100)</td>
<td></td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>22 (88)</td>
<td></td>
</tr>
<tr>
<td>Other investigational therapy</td>
<td>6 (24)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Patients could have received ≥1 type of prior therapy. Not all prior therapies are listed.

Dataset as of July 1, 2015.

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**Treatment-Related Adverse Events**<sup>a</sup> (N=25)

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>15 (60.0)</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (20.0)</td>
<td>Autoimmune hepatitis (grade 3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (12.0)</td>
<td>γ-glutamyltransferase increased (grade 3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (8.0)</td>
<td>Muscular weakness (grade 3)*</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (8.0)</td>
<td>Nausea (grade 3)*</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>2 (8.0)</td>
<td>Septic shock (grade 4)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td>2 (8.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Reported during treatment or within 30 days thereafter.

*Occurred in the same patient.

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**AEs of Interest Based on Immune Etiology** (N=25)

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
<th>Resulted in Treatment Interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hepatitis (grade 3)</td>
<td>1 (4.0)</td>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hyperthyroidism (grade 2)</td>
<td>1 (4.0)</td>
<td>No&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypothyroidism (grade 2)</td>
<td>3 (12.0)</td>
<td>No&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pneumonitis (grade 1)</td>
<td>1 (4.0)</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Event resolved at data cutoff.

*Managed with oral steroids, discontinued. *No medical intervention indicated.

Data cutoff date: July 1, 2015.

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Antitumor Activity (N =25)
(RECIST v1.1, Investigator Review)

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>3 (12.0)</td>
<td>2.5-31.2</td>
</tr>
<tr>
<td>Complete response</td>
<td>0 (0.0)</td>
<td>0.0-13.7</td>
</tr>
<tr>
<td>Partial response*</td>
<td>3 (12.0)</td>
<td>2.5-31.2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (16.0)</td>
<td>4.5-36.1</td>
</tr>
<tr>
<td>Clinical benefit rate*</td>
<td>5 (20.0)</td>
<td>6.8-40.7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>15 (60.0)</td>
<td>38.7-78.9</td>
</tr>
<tr>
<td>No assessment*</td>
<td>3 (12.0)</td>
<td>2.5-31.2</td>
</tr>
</tbody>
</table>

In the 22 patients with at least one scan after baseline, ORR was 14% and CBR was 23%

*Includes confirmed response only.


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Change From Baseline in Target Lesion Size
(RECIST v1.1, Investigator Review)

Only patients with ≥1 evaluable post-baseline tumor assessment are included (n = 25). Data are presented for 20 patients; 2 patients were excluded due to non-evaluable post-baseline lesions. Data cut-off date: July 3, 2023.

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### Slide 15/20

**Longitudinal Change From Baseline in Target Lesion Size (RECIST v1.1, Investigator Review)**

- **Responder**
- **Nonresponder**

Data cut-off date: July 1, 2015

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**Treatment Exposure and Response Duration (RECIST v1.1, Investigator Review)**

- All 3 responders remain on study treatment for ≥26 weeks at time of data cutoff
- Median time to response: 8.0 weeks (range, 7.6-8.7)
- Median duration of response: not reached (range, 8.7+ to 44.3+ weeks)
- Median duration of SD: 16.0 weeks (range, 13.1+ to 24.0)

Time of data cut-off date: July 1, 2015

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Why are These Results Different?

<table>
<thead>
<tr>
<th>ER+/HER2 neg</th>
<th>Target</th>
<th>PD-L1 Expression ≥ 1%</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>19.4% (48/248)</td>
<td>12% (3/25)</td>
</tr>
<tr>
<td>Avelumab¹</td>
<td>PD-L1</td>
<td>55.4% (31/56)</td>
<td>2.8% (2/72)</td>
</tr>
</tbody>
</table>

- Different IHC assays led to marked differences in PD-L1 positivity
- Standardization of assays is critical
- Avelumab trial included all comers, and 22% were not evaluable for PD-L1 expression
- Not all immune checkpoint inhibitors are the same?
- PD-1 vs PD-L1 inhibitors

¹. Dirix et al. SABCS 2015

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KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1¹ Advanced Solid Tumors

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- Thyroid Cancer
- Salivary Gland Carcinoma
- Nasopharyngeal Carcinoma¹ (22.2%)
- Glioblastoma Multiforme
- Leiomyosarcoma

¹. ER Positive/HER2 Negative Breast Cancer¹ (12.0%)

*Data has been reported, percentages indicate response.

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Summary and Conclusions

- In patients with heavily pretreated, PD-L1–positive, advanced ER⁺/HER2⁻ breast cancer
  - Pembrolizumab showed a manageable safety profile
  - Pembrolizumab was associated with an ORR of 12% and a CBR of 20%
    - In the 22 evaluable patients, ORR was 14% and CBR was 23%
    - Responses were durable (range, 8.7+ to 44.3+ weeks)
- Further investigation of immune therapies in ER⁺/HER2⁻ breast cancer, particularly combination therapies, is warranted

Acknowledgements

- PATIENTS AND THEIR FAMILIES
  - Investigators and site personnel from the following centers that enrolled patients:
    - Dana-Farber Cancer Institute, Boston, MA
    - Gustave-Roussy, Paris, France
    - Institut Claudius Regaud, Toulouse, France
    - Institut Curie, Paris, France
    - Netherlands Cancer Institute, Amsterdam, Netherlands
    - Princess Margaret Cancer Centre, Toronto, ON
    - Rutgers Cancer Institute of New Jersey, New Brunswick, NJ
    - Scottsdale Healthcare Shea Medical Center, Scottsdale, AZ
    - Seoul National University Hospital, Seoul, Korea
    - University of California, San Francisco, San Francisco, CA
    - University of Texas MD Anderson Cancer Center, Houston, TX
  - AgilentCom Merck oncology team: Tracie Brown and Melanie Leiby
  - QualTek Molecular Laboratories: Tiffany Murphy
  - Merck & Co., Inc.: Roger Dansey, Gurserk Aktan, Hieu Mai Dang, Marlena Gould, Ann Lovell, Pradeep Thanigaimani, Shari Thomas, Anne Morosky, Christine Gause

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