PERTUZUMAB PLUS TRASTUZUMAB IN PATIENTS WITH UTERINE CANCER WITH ERBB2 OR ERBB3 AMPLIFICATION, OVEREXPRESSION OR MUTATION: RESULTS FROM THE TARGETED AGENT PROFILING AND UTILIZATION REGISTRY (TAPUR™) STUDY

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ERBB2/ERBB3 Amplification/Overexpression in Uterine Cancer

- Clinical significance of ERBB2 protein expression or gene amplification in endometrial cancer as a biomarker to identify patients likely to respond to anti-HER2 therapies is controversial.

- High grade endometrial cancer has a 17-30% rate of ERBB2 gene amplification with up to 80% exhibiting ERBB2 protein overexpression.

- The most likely subtype to be ERBB2+ is uterine serous carcinoma, but only 9/20 ERBB2+ primary tumors had ERBB2+ metastatic lesions (45%) assessed by IHC or CISH.

- Single agent trastuzumab has little activity in ERBB2+ endometrial cancer.

- We evaluated the combination of pertuzumab plus trastuzumab in this population.

1 Konecny et al Br J Cancer 2009
2 Halle et al Br J Cancer 2017
TAPUR Study

- Non-randomized, phase II, basket trial
- 18 treatments
- 85+ genomic targets
- All solid tumors
- Pre-specified genomic matching rules and eligibility criteria
- Virtual Molecular Tumor Board
Primary Objective and Study Endpoints

- **Objective**: Evaluate the anti-tumor activity of commercially available targeted agents in patients with advanced cancers with specific genomic alterations

- **Primary Endpoint**: Disease control (DC) defined as objective response (OR) or stable disease (SD) at 16+ weeks per RECIST v1.1

- **Other Endpoints**:
  - Progression free survival (PFS)
  - Overall survival (OS)
  - Grade 3-5 adverse events (AEs) or serious adverse events (SAEs) at least possibly related to Pertuzumab + Trastuzumab are reported
Study Design

• Simon’s optimal two-stage design
• Null Hypothesis: Disease control rate (DCR) < 15%
• Alternative Hypothesis: DCR ≥ 35%
• Sample size (N=28) achieves 85% power and one-sided Type 1 error rate of 0.10
Key Eligibility Criteria and Treatment Administration

- Advanced uterine cancer
- ECOG Performance Status 0-2
- Adequate organ function
- Measurable disease
- Genomic test performed in CLIA-certified, CAP-accredited laboratory
- \textit{ERBB2} or \textit{ERBB3} amplification or overexpression or any of 13 pre-specified \textit{ERBB2} mutations
- Dose administration per package insert (until disease progression)
  - Pertuzumab initial dose of 840 mg IV over 60 min, followed by 420 mg IV over 30-60 min every 3 weeks and Trastuzumab initial dose of 8mg/kg IV over 90 min, then 6mg/kg over 30-60 min every 3 weeks
# Demographics and Clinical Characteristics (N=28)

## Characteristic

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (range)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>69 (44, 90+)</td>
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<tr>
<td>Sex, N (%)</td>
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</tr>
<tr>
<td>Male</td>
<td>0 (0)</td>
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<tr>
<td>Female</td>
<td>28 (100)</td>
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<tr>
<td>Race, N (%)</td>
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<tr>
<td>White</td>
<td>21 (75)</td>
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<tr>
<td>More than one race</td>
<td>1 (4)</td>
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<tr>
<td>Other</td>
<td>2 (7)</td>
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<td>Prefer not to answer</td>
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<td>Ethnicity, N (%)</td>
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<tr>
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<td>25 (89)</td>
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<tr>
<td>ECOG, PS, N (%)</td>
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<tr>
<td>0</td>
<td>9 (32)</td>
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<tr>
<td>1</td>
<td>16 (57)</td>
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<tr>
<td>2</td>
<td>3 (11)</td>
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<tr>
<td>Number of prior systemic treatments, N(%)</td>
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<td>≥3</td>
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</table>

<table>
<thead>
<tr>
<th>Genomic alteration, N (%)</th>
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<tbody>
<tr>
<td><strong>ERBB2 amplification</strong></td>
</tr>
<tr>
<td><strong>ERBB2 overexpression</strong></td>
</tr>
<tr>
<td><strong>ERBB2 mutations</strong></td>
</tr>
<tr>
<td><strong>ERBB3 amplification</strong></td>
</tr>
<tr>
<td><strong>ERBB2 amplification and mutation</strong></td>
</tr>
</tbody>
</table>

1Percentages may not add up to 100% due to rounding.
2Of 5 patients with tumors with ERBB2 mutations, there were 2 tumors with V842I, 2 tumors with S310F, and 1 tumor with R678Q
Efficacy Outcomes

**Efficacy Outcomes (N=28)**

- **DC rate, % (95% CI)**: 37 (21, 50)
- **OR rate, % (95% CI)**: 7 (1, 24)

**Best percent change from baseline target lesion size N=28**

Waterfall plot shows response in 28 evaluable pts.

- 2 pts have a best change percentage of exactly 0.
- * For 2 pts with clinical progression but no post-treatment tumor measurements, a 20% increase was assigned.
- < For 1 pt with most target lesions not measured, but worsening metastatic lesions assessed by treating physician, a 20% increase was assigned.
- + Stable target lesions, but new lesions present.
- ^ Shrinking target lesions, but new lesions present.
Time on Treatment in Pts with SD16+ or OR (n=10)

- ERBB2 amplification
- ERBB2 amplification
- ERBB2 amplification
- ERBB2 amplification
- ERBB2 amplification
- ERBB2 amplification
- ERBB2 mutation: V842I

Start of response in pts with PR
Time of progression or death

Time on Treatment (weeks)
Progression Free Survival and Overall Survival (N=28)

Median PFS = 28.1 weeks
Median OS = 60.9 weeks
Toxicity

- 1 patient experienced grade 3 muscle weakness at least possibly related to Pertuzumab + Trastuzumab
- No other treatment related Grade 3-4 AEs or SAEs reported
HER2-directed Therapies for *ERBB2* Amplified Uterine Cancer: Completed Trials

- **GOG181B phase II trial of trastuzumab for women with stage III/IV endometrial cancer with HER2+ (either by FISH or IHC (2-3+))**
  - 33 women, no objective responses, closed early for low enrollment but had 86.5% power to confirm null hypothesis

- **NCT01367002: Randomized phase II trial of carboplatin/paclitaxel versus carboplatin-paclitaxel-trastuzumab...in uterine serous carcinomas that overexpress ERBB2**
  - 58 women, PFS primary endpoint favoring T-arm 8.0 vs 12.9 months (HR 0.44 (90% CI, 0.26, 0.76), P=0.005)
  - OS analysis (secondary endpoint): 29.6 months vs 24.4 (HR 0.58 (90% CI, 0.34, 0.99), p=0.046)

1 Fleming et al Gynecol Oncol 2010

2 Fader et al Clin Cancer Res 2020
Efficacy Outcomes (N=28)

DC rate, % (95% CI) 50 (36, 60)

OR rate, % (95% CI) 25 (11, 45)

Gupta et al Poster Presentation at ASCO GI Cancers Symposium 2020
Conclusions

• Pertuzumab + Trastuzumab demonstrated anti-tumor activity in heavily pre-treated patients with uterine cancer with ERBB2 amplification and/or certain mutations

• Additional study warranted to confirm the efficacy of Pertuzumab + Trastuzumab in this patient population
Acknowledgments

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• The patients who participated in this TAPUR Study cohort

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  • Cancer Treatment Centers of America, Atlanta, GA
  • Sutter Cancer Research Consortium, San Francisco, CA
  • Inova Schar Cancer Institute, Fairfax, VA
  • The Angeles Clinic and Research Institute, Los Angeles, CA
  • Cancer Research Consortium of West Michigan, Grand Rapids, MI
  • Intermountain Healthcare, St. George, UT
  • Swedish Cancer Institute, Seattle, WA
  • University of Alabama at Birmingham, Birmingham, AL
  • Providence Health and Services, Portland, OR
  • The University of Texas MD Anderson Cancer Center, Houston, TX
  • Coordinating Center: American Society of Clinical Oncology, Alexandria, VA

For a comprehensive list of all participating clinical sites, please see www.TAPUR.org