CLN-619 Investor Event at ASCO

JUNE 4, 2023
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<table>
<thead>
<tr>
<th>SECTION</th>
<th>PRESENTER</th>
</tr>
</thead>
</table>
| Opening Remarks                              | Nadim Ahmed  
CEO, Cullinan Oncology                                                |
| Recap of CLN-619 poster                      | Jeff Jones, MD  
CMO, Cullinan Oncology                                                   |
| Unmet need and treatment landscape in endometrial cancer | Vicky Makker, MD  
Section Head, Endometrial Cancer Program,  
Memorial Sloan Kettering Cancer Center |
Our Mission

• Unique modality-agnostic targeted oncology approach:
  • First, identify high-impact oncology targets
  • Then select the best approach to address each target
  • Rigorously and rapidly advancing only highly differentiated molecules

Creating new standards of care for patients with cancer
CULLINAN ONCOLOGY

Our Approach

We seek to achieve our mission through our rigorous and differentiated approach to drug development.

- **Innovate without borders**: Remain open to finding the best solutions in-house or through licensing.
- **Run early “thriller or killer” experiments**: Rapidly advance only potential first-in-class and/or best-in-class molecules.
- **Seek clear evidence of monotherapy activity**: Avoid uncertainty of early-stage clinical combination studies.

Our Vision:

To become a fully integrated, commercial stage oncology company creating new standards of care for patients with cancer.
Diversified pipeline leveraging novel technologies and differentiated mechanisms

<table>
<thead>
<tr>
<th>Program (Subsidiary/Project) Modality/MOA</th>
<th>IND-Enabling</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Status</th>
<th>Geographic Rights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zipalertinib (CLN-081/TAS6417) EGFRex20ins inhibitor</td>
<td>NSCLC with exon 20 insertion mutations</td>
<td></td>
<td></td>
<td></td>
<td>BTD received; actively enrolling pivotal Phase 2b</td>
<td>Co-commercialization and Co-development in US</td>
</tr>
<tr>
<td>CLN-619 Anti-MICA/B IgG1</td>
<td>Pan-cancer</td>
<td></td>
<td></td>
<td></td>
<td>Actively enrolling</td>
<td>Owns U.S. rights</td>
</tr>
<tr>
<td>CLN-049 FLT3 x CD3 bispecific antibody</td>
<td>R/R AML, MDS</td>
<td></td>
<td></td>
<td></td>
<td>Actively enrolling</td>
<td>Owns U.S. rights</td>
</tr>
<tr>
<td>CLN-418 B7H4 x 41BB bispecific immune activator</td>
<td>Multiple solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>Actively enrolling</td>
<td>Owns U.S. rights</td>
</tr>
<tr>
<td>CLN-978 CD19 x CD3 bispecific antibody construct with HSA binding domain</td>
<td>B-cell NHL</td>
<td></td>
<td></td>
<td></td>
<td>FDA IND clearance received</td>
<td>Owns U.S. rights</td>
</tr>
<tr>
<td>CLN-617 Collagen-binding IL-12 x IL-2 fusion protein</td>
<td>Pan-cancer</td>
<td></td>
<td></td>
<td></td>
<td>FDA IND clearance received</td>
<td>Owns U.S. rights</td>
</tr>
</tbody>
</table>

**Early Programs**

Multiple discovery stage programs

- IND cleared, trial start pending
A Phase 1 Dose-Escalation Study to Investigate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamic Activity of CLN-619 (Anti-MICA/MICB Antibody) Alone and in Combination with Pembrolizumab in Patients with Advanced Solid Tumors

Judy Wang¹, Martin Gutierrez², Drew Rasco³, Ignacio Melero Bermejo⁴, John Powderly⁵, Erika Hamilton⁶, Michael Millward⁷, Ana Arance⁸, Rafal Stec⁹, Victor Moreno¹⁰, Manish Sharma¹¹, Iwona Lugowska¹², Mark Shackleton¹³, Sophia Frentzas⁸, John Janik¹⁴, Tracy Liu¹⁴, Irina Shapiro¹⁴, Kerry Whalen¹⁴, Jeffrey Jones¹⁴, Alexander Spira¹⁵

¹Florida Cancer Specialists, ²Hackensack Meridian Health, ³START San Antonio ⁴University of Navarra, Spain, ⁵Carolina BioOncology Institute, ⁶Sarah Cannon Research Institute, ⁷Linear Clinical Research, Australia, ⁸Monash Health, Australia, ⁹Biokinetica, Poland, ¹⁰START Madrid FJD, Spain, ¹¹START Midwest, ¹²Maria Sklodowska-Curie Institute of Oncology, Poland, ¹³Alfred Health, Australia, ¹⁴Cullinan Oncology, ¹⁵Virginia Cancer Center
CLN-619: Engages Both Innate and Adaptive Immune Cells

<table>
<thead>
<tr>
<th>IMMUNE EVASION</th>
<th>RESTORATION OF IMMUNOSURVEILLANCE</th>
<th>ENHANCEMENT BY CHECKPOINT INHIBITION (CPI)</th>
</tr>
</thead>
</table>

- **CLN-619 Single Agent MoA**
  - Prevention of MICA/MICB shedding
  - Antibody-dependent cellular cytotoxicity (ADCC)
  - Antibody-dependent cellular phagocytosis (ADCP)
  - Enhanced binding of MICA to NKG2D

- **CLN-619 Plus CPI MoA**
  - Combination of Single Agent MoA with Checkpoint Inhibition (CPI)
CLN-619-001 Phase 1 Study

**Design:** Global open label, first-in-human, multicenter, dose escalation and dose expansion study of CLN-619 administered alone (Module A) or in combination with pembrolizumab (Module B) in patients with advanced solid tumors.

**Treatment Plan:**

- CLN-619 monotherapy was administered intravenously every three weeks.
- Standard pre-medications were administered 30-60 minutes prior to each dose.
- Corticosteroid pre-medication was mandated prior to the first dose starting at the 3 mg/kg dose level.
Monotherapy Module Enrollment and Disposition (Data cut-off 31 March 2023)

- Standard 3+3 escalation began at the first dose level tested 0.1 mg/kg*; dose levels cleared for DLT could be expanded up to total n = 10

<table>
<thead>
<tr>
<th>DOSE ESCALATION*</th>
<th>DOSE-LEVEL COHORT EXTENSIONS</th>
<th>TOTAL BY DOSE LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg</td>
<td>10 mg/kg* n = 1</td>
<td>10 mg/kg n = 7</td>
</tr>
<tr>
<td>n = 6</td>
<td></td>
<td>6 mg/kg n = 10</td>
</tr>
<tr>
<td>6 mg/kg</td>
<td></td>
<td>6 mg/kg n = 10</td>
</tr>
<tr>
<td>n = 3</td>
<td></td>
<td>3 mg/kg n = 10</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td></td>
<td>3 mg/kg n = 10</td>
</tr>
<tr>
<td>n = 7</td>
<td></td>
<td>3 mg/kg n = 10</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td></td>
<td>1 mg/kg n = 10</td>
</tr>
<tr>
<td>n = 4</td>
<td></td>
<td>1 mg/kg n = 10</td>
</tr>
<tr>
<td>0.3 mg/kg</td>
<td></td>
<td>0.3 mg/kg n = 10</td>
</tr>
<tr>
<td>n = 3</td>
<td></td>
<td>0.3 mg/kg n = 10</td>
</tr>
<tr>
<td>0.1 mg/kg*</td>
<td></td>
<td>0.1 mg/kg n = 10</td>
</tr>
<tr>
<td>n = 3</td>
<td></td>
<td>0.1 mg/kg n = 10</td>
</tr>
</tbody>
</table>

*Protocol permitted accelerated titration until Gr ≥2 TRAE, which occurred at the 0.1 mg/kg dose level
**Enrollment ongoing

- 37 patients treated across all dose-levels
- Median age 63, 62% female
- Median 3 prior therapies, 54% prior checkpoint inhibitors
- Median number (range) of cycles initiated was 2 (0–13)
Monotherapy Efficacy Observed Across Multiple Dose Levels

Time on Treatment and Clinical Activity

All Patients (n=37) by Dose Level

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>All Patients (n=37)</th>
<th>Response Evaluable(^1) at ≥1 mg/kg (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete Response (CR)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partial Response (PR)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stable Disease (SD)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>CR + PR + SD</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Progressive Disease (PD)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Not Evaluable (NE)</td>
<td>9</td>
</tr>
</tbody>
</table>

\(^1\) Patients who underwent at least one RECIST response assessment or who had clinically assessed PD prior to first planned response assessment
Notable Monotherapy Activity in Patients with Gynecological Cancers

Time on Treatment and Clinical Activity

Study Duration (weeks)

All Patients (n = 37) by GYN vs Other Indication

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>All Patients (n=37)</th>
<th>Response Evaluable¹ (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>CR + PR + SD</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Not Evaluable (NE)</td>
<td>9</td>
<td>NA</td>
</tr>
</tbody>
</table>

¹Patients who underwent at least one RECIST response assessment or who had clinically assessed PD prior to first planned response assessment
²Endometrial, cervical, and ovarian
Monotherapy Activity Achieved in Heavily Pre-Treated Patients, Including after Progression on anti-PD1 Therapy

### Objective Response Detail (Data cutoff March 31, 2023*)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Tumor Type</th>
<th>Prior Therapy</th>
<th>Response Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/kg</td>
<td><strong>Parotid</strong> (mucoepidermoid)</td>
<td>2 prior therapies Prior anti-PD1 (PR x 30 months)</td>
<td>CR at C4D1 (confirmed) ongoing</td>
</tr>
<tr>
<td></td>
<td><strong>Endometrial</strong> (serous)</td>
<td>5 prior therapies Prior anti-PD1 + lenvatinib (SD x 9 months)</td>
<td>PR at C4D1 (confirmed) ongoing</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td><strong>Endometrial</strong> (endometrioid)</td>
<td>3 prior therapies No prior anti-PD1</td>
<td>PR at C7D1 (confirmed) ongoing</td>
</tr>
</tbody>
</table>

Stable Disease for >3 cycles has been observed in 7 other patients

- 1 mg/kg: 1 cervical (PD after 9 cycles)
- 3 mg/kg: 1 ovarian (clinical PD after 6 cycles), 1 breast (ongoing after 6 cycles), 1 cervical (ongoing after 6 cycles), 1 adenoid cystic carcinoma salivary gland (ongoing after 3 cycles)
- 10 mg/kg: 1 ovarian (ongoing after 3 cycles), 1 cervical (ongoing after 6 cycles)

* Confirmation of 2 endometrial PRs occurred after data cutoff date
83-year-old male patient with mucoepidermoid parotid cancer. Prior systemic therapy before relapse included anti-PD1 antibody therapy with 30 month sustained PR before PD (last dose 4 months before study entry)
Monotherapy Efficacy: Confirmed Partial Response in a Patient with Pulmonary Metastases

76 year-old patient with endometrial cancer, relapsed after platinum chemotherapy + trastuzumab, doxorubicin, and anastrazole. Progressed at 9-months during immediate prior therapy with pembrolizumab + lenvatinib.

BASELINE

CYCLE 7 CLN-619
### Treatment Emergent Adverse Events (TEAE) in ≥10% of Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any n (%)</th>
<th>Grade 1/2 N (%)</th>
<th>Grade 3+ n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion Related Reaction</td>
<td>8 (21.6)</td>
<td>8 (21.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (21.6)</td>
<td>8 (21.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>8 (21.6)</td>
<td>6 (16.2)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>6 (16.2)</td>
<td>6 (16.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (13.5)</td>
<td>5 (13.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (13.5)</td>
<td>5 (13.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (13.5)</td>
<td>5 (13.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (10.8)</td>
<td>4 (10.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>4 (10.8)</td>
<td>4 (10.8)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

- CLN-619 was well-tolerated and most TEAEs were Grade 1/2
- No AEs met protocol-defined DLT criteria, and no Grade ≥ 4 TEAE
- The most common TRAEs in ≥5% of pts were IRR (21.6%), pyrexia (8.1%), and fatigue (8.1%)
  - Only 1 Gr3 TRAE of laryngeal edema occurred at the 10 mg/kg DL in the absence of mandated steroid premedication
  - IRRs (n=8 patients) occurred only in Cycle 1 and were all Grade 1/2 in patients who received protocol-mandated steroid pre-medication

*Patients experiencing at least one TEAE = 34 (91.9%)
*Patients experiencing at least one Grade 3 TEAE 11 (29.7%); no Grade ≥ 4 TEAE
*TEAE leading to discontinuation [2, 5.4%; Grade 3 Laryngeal Edema (related), Grade 3 Dehydration (unrelated)]
## Contextual Phase One Monotherapy Response Data

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Large 20 Year Retrospective Analysis</th>
<th>Immunotherapy Agents with Later Stage Combination Data at ASCO 2023</th>
<th>Cullinan’s CLN-619 Phase 1 Monotherapy Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCI-Sponsored Monotherapy Phase 1 Studies(^1) (n=4108)</td>
<td>LAG-3 (fianlimab, Regeneron) Phase 1 Monotherapy(^2) (n=27)</td>
<td>Response Evaluable(^4) at (\geq 1) mg/kg (n=22)</td>
</tr>
<tr>
<td>ORR</td>
<td>3.5%</td>
<td>0</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>SD</td>
<td>N/A</td>
<td>11 (41%)</td>
<td>7 (32%)</td>
</tr>
<tr>
<td>DCR</td>
<td>N/A</td>
<td>11 (41%)</td>
<td>10 (45%)</td>
</tr>
</tbody>
</table>

### Comparative data is provided for contextual purposes only and should not be used to draw conclusions about CLN-619.

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ORR = confirmed overall response rate, SD = stable disease, DCR = disease control rate; CR+PR+SD
Monotherapy Dose Escalation Conclusions

• CLN-619 monotherapy was well tolerated
  ✓ No dose-limiting toxicities observed at doses up to 10 mg/kg

• Objective responses have been observed across multiple tumor types, including after progression on checkpoint inhibitor therapy

• Notable monotherapy activity observed in gynecological malignancies
CLN-619 Next Steps

• Based on activity in gynecological tumors, expansion cohorts in endometrial and cervical cancers are planned

<table>
<thead>
<tr>
<th></th>
<th>Endometrial Cancer</th>
<th>Cervical Cancer</th>
<th>Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Annual Incidence¹</td>
<td>66,000</td>
<td>14,000</td>
<td>20,000</td>
</tr>
<tr>
<td>Estimated U.S. Annual Number of Patients Receiving Systemic Therapy²</td>
<td>25,000</td>
<td>11,000</td>
<td>17,000</td>
</tr>
</tbody>
</table>

• Additional monotherapy expansion cohorts may be opened based upon clinical activity observed in the current trial

• A parallel dose-escalation arm in combination with pembrolizumab is ongoing, and data will be presented at a future medical congress

¹ American Cancer Society
² Global Data epidemiology estimates for 2028, including patients receiving chemo or other systemic therapies
Therapeutic Landscape of Advanced/Recurrent Endometrial Cancer

Vicky Makker, MD
Associate Attending Physician
Section Head Endometrial Cancer
Gynecologic Medical Oncology Service
Memorial Sloan Kettering Cancer Center
Director Hematology-Oncology Fellowship
Associate Professor of Medicine
Weill Cornell Medical Center
DECLARATION OF INTERESTS

Vicky Makker, MD

Unpaid Consulting or Advisory Role: ArQule, AstraZeneca, Clovis Oncology, Cullinan Oncology, Duality, Eisai, Faeth Therapeutics, GlaxoSmithKline, Immunocore, ITeos Therapeutics, Prelude, Kartos Therapeutics, Karyopharm Therapeutics, Lilly, Merck, Moreo, Morphosys, Novartis, Takeda, Zymeworks.

Research Funding: AstraZeneca (Inst), Bayer (Inst), Bristol-Myers Squibb (Inst), Clovis Oncology (Inst), Duality (Inst), Eisai (Inst), Faeth Therapeutics (Inst), Karyopharm Therapeutics (Inst), Lilly (Inst), Merck (Inst), Takeda (Inst), Zymeworks (Inst).

Travel, Accommodations: Eisai, Merck.

Dr Makker is supported in part by the NIH/NCI Cancer Center Support Grant P30 CA008748
Rising Incidence and Mortality of Endometrial Cancer

65,950
New Cases Uterine Cancer Projected in U.S. for 2022

122,000
New Cases Uterine Cancer Projected in U.S. for 2030

1.8%
ANNUAL Increase in Uterine Cancer Mortality Rates in U.S. 2010-2017

Worldwide in 2020:
417,000 New Cases
97,000 Deaths

References:
2 Clarke et al. JAMA Oncol. Published online May 5, 2022. doi:10.1001/jamaoncol.2022.0009
4 Courtesy: Stephanie Gaillard, ASCO 2022
**Endometrial Cancer: US**

- 65,950 estimated cases in 2022
- 12,550 deaths
- Fourth most common cancer in US
- Cumulative Lifetime risk in the general population is 3.1%
- Median Age 63
- Usually confined to the uterus at diagnosis
- 5-year cancer specific survival 81%
- Increasing 1.7% (2010-2019)
  - Increasing 2% in Blacks annually!
  - The uterine cancer mortality rate ratio for Black compared with White patients increased from 1.83 (95% CI 1.77–1.89) in 1990–1994 to 1.98 (95% CI 1.93–2.02) in 2015–2019

- Early Stage (low-risk) EC has 5-year survival of ~ 80%
- Most recurrences occur within 2 yrs of diagnosis
- > 60% of pts recur with distant mets
- Late Stage EC has 5-year survival of ~ 17%
• Two Endometrial Carcinoma Classifications

**Histology-driven**

Endometrial Carcinoma Classification

- H&E
- IHC upon indication

**Type I**
- Endometrioid Carcinoma (EEC) Grade 1-3
- Uterine Serous Carcinoma (USC)
- Clear Cell Carcinoma (CCC)

**Type II**
- Uterine Carinosarcoma (UCS)
- Mixed Endometrial Carcinoma
- Un-/De-differentiated Carcinoma

**Molecular-driven**

Endometrial Carcinoma Classification

- POLE sequencing + MMR and p53 IHC

**POLEmut Endometrial Carcinoma (POLEmut EC)**

**MMRd Endometrial Carcinoma (MMRd EC)**

**p53-abnormal Endometrial Carcinoma (p53abn EC)**

**No Specific Molecular Profile Endometrial Carcinoma (NSMP EC)**
Prognostic Relevance of Molecular EC Classification

Multiple independent studies convincingly show the molecular EC classification carries relevant, significant and reproducible prognostic information.
Molecular Groups in Endometrial Cancer TCGA & Surrogate Markers

GOG 209

- Established carboplatin and paclitaxel as the chemotherapy backbone for patients with advanced stage or recurrent disease
GOG 209: Survival Outcomes

Progression Free Survival

Overall Survival

**Hormonal Therapy in Endometrial Cancer**

### Hormonal treatment of advanced/recurrent endometrial cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 153 [2]</td>
<td>56</td>
<td>MA 80 mg b.i.d. X 3 weeks alternating with T 20 mg b.i.d. p.o. X 3 weeks</td>
<td>27% (21.4 CR, 5.4 PR) [CI 17–38%]</td>
<td>2.7 mos</td>
<td>14.0 mos</td>
<td>28 mos</td>
</tr>
<tr>
<td>GOG 121 [8]</td>
<td>58</td>
<td>Phase II—High dose MA 800 mg/day</td>
<td>24%</td>
<td>2.5 mos</td>
<td>7.6 mos</td>
<td>8.9 mos</td>
</tr>
<tr>
<td>GOG 81 [9]</td>
<td>145</td>
<td>MPA high dose: 1000 mg/day p.o. vs High: 15%</td>
<td>2.5 mos</td>
<td>7.0 mos</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>154</td>
<td>MPA low dose: 200 mg/day p.o. Low: 25%</td>
<td>3.2 mos</td>
<td>11.1 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 119 [3]</td>
<td>35</td>
<td>Daily T (20 mg b.i.d.) with MPA</td>
<td>33% [CI 21–46%]</td>
<td>3.0 mos</td>
<td>12.8 mos</td>
<td>NR</td>
</tr>
<tr>
<td>GOG B1F [10]</td>
<td>68</td>
<td>T 20 mg b.i.d.</td>
<td>10% [CI 5.7–17.9%]</td>
<td>1.9 mos [1.7–3.2]</td>
<td>8.8 mos [7.0–10.1]</td>
<td>NR</td>
</tr>
</tbody>
</table>

MA, Megestrol acetate; MPA, medroxy progesterone acetate; T, Tamoxifen; CI, confidence interval (95%); RR, response rate; PFS, progression free survival (median); OS, overall survival (median); DOR, duration of response (median); NR, not reported.

### Progestins and endometrial cancer: hormone response by tumor grade

<table>
<thead>
<tr>
<th>Study</th>
<th>Response—Grade 1</th>
<th>Response—Grade 2</th>
<th>Response—Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 153 [2]</td>
<td>33%</td>
<td>24%</td>
<td>22%</td>
</tr>
<tr>
<td>GOG 119 [3]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>GOG 81 [9]</td>
<td>37%</td>
<td>23%</td>
<td>9%</td>
</tr>
<tr>
<td>GOG 121 [8]</td>
<td>37% combined</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>GOG 81F [10]</td>
<td>23%</td>
<td>14%</td>
<td>3%</td>
</tr>
</tbody>
</table>
### Single agent chemotherapy (1 prior chemotherapy)

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>N</th>
<th>RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>129-C</td>
<td>Paclitaxel</td>
<td>44</td>
<td>27.3a</td>
</tr>
<tr>
<td>129-H</td>
<td>Liposomal doxorubicin</td>
<td>42</td>
<td>9.5</td>
</tr>
<tr>
<td>129-J</td>
<td>Topotecan</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>129-K</td>
<td>Oxaliplatin</td>
<td>52</td>
<td>13.5</td>
</tr>
<tr>
<td>129-N</td>
<td>Docetaxel (weekly)</td>
<td>26</td>
<td>7.7b</td>
</tr>
<tr>
<td>129-P</td>
<td>Ixabepilone</td>
<td>50</td>
<td>12c</td>
</tr>
<tr>
<td>129-O</td>
<td>Pemetrexed</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>129-Q</td>
<td>Gemcitabine</td>
<td>23</td>
<td>4</td>
</tr>
</tbody>
</table>

# Endometrial Cancer: Molecular Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Characteristics</th>
<th>Prognosis</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POLE ultramutated</strong></td>
<td>- Ultra-high somatic mutation frequency, MSS; frequent mutations in the exonuclease domain of POLE; high ASNS and CCNB1 expression&lt;br&gt;- Represents ~4% of endometrioid tumors*&lt;br&gt;- Best prognosis</td>
<td></td>
<td>Clear IO efficacy</td>
</tr>
<tr>
<td><strong>MSI hypermutated</strong></td>
<td>- High mutation rate and few copy number alterations; high rate of MLH1 promoter methylation; high phospho-AKT; low PTEN expression; frequent PIK3CA and PIK3R1 mutations co-occurring with PTEN mutations&lt;br&gt;- Represents ~39% of endometrioid tumors†</td>
<td></td>
<td>Clear IO efficacy</td>
</tr>
<tr>
<td><strong>Copy number low</strong></td>
<td>- High frequency of mutations in CTNNB1, KRAS, SOX17; frequent PIK3CA and PIK3R1 mutations co-occurring with PTEN mutations; elevated levels of progesterone receptor and RAD50 expression&lt;br&gt;- Represents ~49% of endometrioid tumors*</td>
<td></td>
<td>Unclear IO efficacy?</td>
</tr>
<tr>
<td><strong>Copy number high</strong></td>
<td>- Greatest transcriptional activity; frequent TP53 mutations; decreased levels of phospho-AKT; mutually exclusive PIK3CA, PIK3R1, and PTEN mutations&lt;br&gt;- Represents ~9% of endometrioid tumors*&lt;br&gt;- Worst prognosis</td>
<td></td>
<td>Unclear IO efficacy?</td>
</tr>
</tbody>
</table>

*The frequency of each molecular subgroup among endometrioid tumors was calculated in a follow-up study using a clinically applicable molecular classification system derived from the TCGA study. †Tumors were classified as dMMR based on MSI and/or IHC defects. ‡Tumors were clustered into low or high copy number groups based on the extent of somatic copy number alterations.

Single-Agent IO in “Biomarker”-Selected EC Populations (dMMR/MSI Positive)

- Response to single-agent IO in dMMR or MSI-high EC

<table>
<thead>
<tr>
<th>Study and Drug</th>
<th>Patient Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-158: Pembrolizumab (N = 90)</td>
<td>Advanced-stage or metastatic dMMR EC</td>
<td>ORR: 48%</td>
</tr>
<tr>
<td>PHAEDRA trial: Durvalumab (N = 35 dMMR)</td>
<td>Advanced-stage or metastatic EC</td>
<td>ORR in dMMR: 43%</td>
</tr>
<tr>
<td>GARNET study: Dostarlimab (N = 129)</td>
<td>Previously treated, recurrent advanced-stage EC</td>
<td>ORR in dMMR: 43.5%</td>
</tr>
<tr>
<td>Ph II avelumab study (N = 15 dMMR)</td>
<td>Advanced-stage or metastatic EC</td>
<td>ORR: 26.7%</td>
</tr>
</tbody>
</table>

## Single-Agent IO in pMMR/MSI-Negative Selected EC Populations

<table>
<thead>
<tr>
<th>Study and Drug</th>
<th>Patient Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-28: Pembrolizumab (N = 24)</td>
<td>Advanced-stage or metastatic PD-L1–positive EC</td>
<td>ORR: 13%</td>
</tr>
<tr>
<td>PHAEDRA trial: Durvalumab (N = 36 pMMR)</td>
<td>Advanced-stage or metastatic EC</td>
<td>ORR in pMMR: 3%</td>
</tr>
<tr>
<td>GARNET study: Dostarlimab (N = 94)</td>
<td>Previously treated, recurrent advanced-stage EC</td>
<td>ORR in pMMR: 13.9%</td>
</tr>
<tr>
<td>Ph II avelumab study (N = 16 pMMR)</td>
<td>Advanced-stage or metastatic EC</td>
<td>ORR: 6.25%</td>
</tr>
</tbody>
</table>

Study 309/Keynote 775

- Advanced, recurrent or metastatic endometrial
- Progressive disease 1-2 prior platinum regimens
- Measurable disease per RECIST 1.1
- Available archival tumor tissue
- Performance status of 0 to 1
- Adequate organ function

Stratification:
1. MMR status (pMMR or dMMR)
2. ECOG performance status (0 or 1)
3. Geographic region
4. Prior history of pelvic radiation (yes or no)

Pembrolizumab 200 mg IV q 3 weeks plus lenvatinib 20 mg PO once daily (QD) during each 21-day cycle for up to 35 cycles.

EITHER: Doxorubicin 60 mg/m2 IV q 3 weeks (max cumulative dose of 500 mg/m2) OR Paclitaxel 80 mg/m2 administered by IV on a 28-day cycle: 3 weeks receiving paclitaxel once a week and 1 week not receiving paclitaxel.
Continued OS benefit of lenvatinib plus pembrolizumab vs chemotherapy with extended follow-up

**pMMR Population**

- OS favored lenvatinib plus pembrolizumab despite some pts in the chemotherapy arm receiving subsequent lenvatinib plus pembrolizumab.
- In the chemotherapy arm, 10.0% of pts in the pMMR population and 8.7% of pts in the all-comer population received subsequent lenvatinib plus pembrolizumab.
  - After excluding these pts, the pMMR OS HR was 0.64 (95% CI, 0.54, 0.76); the all-comer OS HR was 0.60 (95% CI, 0.51, 0.71).

**All-Comer Population**

Makker, V ESMO 2022
Keynote 775 Overall Survival dMMR Population

Makker V. et al, SGO 2020 Plenary
Keynote 775-Adverse Events of Any Cause with an Incidence of 25% or More among All the Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Lenvatinib plus Pembrolizumab (N=406)</th>
<th>Chemotherapy (N=388)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>405 (99.8)</td>
<td>361 (88.9)</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>260 (64.0)</td>
<td>154 (37.9)</td>
</tr>
<tr>
<td>Hypothyroidism††</td>
<td>233 (57.4)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>220 (54.2)</td>
<td>31 (7.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>201 (49.5)</td>
<td>14 (3.4)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>182 (44.8)</td>
<td>32 (7.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>149 (36.7)</td>
<td>11 (2.7)</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>138 (34.0)</td>
<td>42 (10.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>134 (33.0)</td>
<td>21 (5.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>124 (30.5)</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Proteinuria†</td>
<td>117 (28.8)</td>
<td>22 (5.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>106 (26.1)</td>
<td>25 (6.2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>105 (25.9)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>104 (25.6)</td>
<td>16 (3.9)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (7.4)</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>22 (5.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

ENGOT-EN6-NSGO/GOG-3031/RUBY

Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC

Eligible patients
• Histologically/cytologically proven advanced or recurrent EC
• Stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
  • Carcinosarcoma, clear cell, serous, or mixed histology permitted
• Naïve to systemic therapy or systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment
• ECOG PS 0-1
• Adequate organ function

Stratification
• MMR/MSI status
• Prior external pelvic radiotherapy
• Disease status

Dostarlimab IV 500 mg
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m²
Q3W for 6 cycles

Dostarlimab IV 1000 mg
Q6W up to 3 years

Placebo IV
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m²
Q3W for 6 cycles

Placebo IV
Q6W up to 3 years

Primary endpoint
• PFS by INV
• OS

Secondary endpoints
• PFS by BICR
• PFS2
• ORR
• DOR
• DCR
• HRQOL/PRO
• Safety
Primary Endpoint: PFS in dMMR/MSI-H Population

HR, 0.28
(95% CI, 0.162–0.495)
P<0.0001

Chemotherapy Period
Median duration of follow-up 24.79 months.

No. with event, %
Median (95%CI), mo

Dostarlimab + CP
Placebo + CP
PFS maturity

At Risk(Events)

Dostarlimab + CP
Placebo + CP

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; PFS, progression-free survival.

Mirza, et al. SGO2023

Chemotherapy Period
Median duration of follow-up 24.79 months.
Primary Endpoint: PFS in Overall Population

HR, 0.64 (95% CI, 0.507–0.800) \( P<0.0001 \)

Probability of Progression-free Survival

<table>
<thead>
<tr>
<th>Months from randomization</th>
<th>Dostarlimab + CP</th>
<th>Placebo + CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>3</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>5</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

No. with event, %

- Dostarlimab + CP: 55.1%
- Placebo + CP: 71.1%

Median (95% CI), mo

- Dostarlimab + CP: 11.8 (9.6–17.1)
- Placebo + CP: 7.9 (7.6–9.5)

PFS maturity

- Dostarlimab + CP: 63.2%
- Placebo + CP: 36.1%

Chemotherapy Period

Median duration of follow-up 25.38 months.

At Risk(Events)

- Dostarlimab + CP: 245(0), 220(12), 197(25), 157(55), 130(80), 105(115), 84(118), 66(127), 52(128), 34(131), 23(132), 12(133), 5(177), 2(177), 0(177)
- Placebo + CP: 249(0), 219(14), 200(29), 144(77), 103(115), 74(141), 48(166), 42(170), 32(172), 20(175), 14(176), 13(176), 5(177), 2(177), 1(177), 0(177)

Mirza, et al. SGO2023
Primary Endpoint: OS in Overall Population (33% maturity)

- **HR, 0.64**
  (95% CI, 0.464–0.870)
- **\(P=0.0021^a\)**

Received subsequent immunotherapy:
- 34.5% of patients on placebo arm
- 15.5% of patients on dostarlimab arm

**Probability of Survival**

- **Dostarlimab + CP**
  - No. with event, %: 26.5
  - Median (95%CI), mo: NE (NE–NE)
- **Placebo + CP**
  - No. with event, %: 40.2
  - Median (95%CI), mo: NE (23.2–NE)

**OS maturity**
- 33.4

**Chemotherapy Period**
- Median duration of follow-up 25.38 months.

---

\(^a\) \(P\leq0.00177\) required to declare statistical significance at first interim analysis.

CP, carboplatin/paclitaxel; HR, hazard ratio; NE, not estimable; OS, overall survival.
OS in dMMR/MSI-H Population

Probability of Survival

Months from randomization

No. with event, %

Median (95%CI), mo

Dostarlimab + CP 13.2 NE (NE–NE)

Placebo + CP 36.9 NE (23.2–NE)

OS maturity 26.3

At Risk(Events)

Dostarlimab + CP

Placebo + CP

Chemotherapy Period

Dostarlimab + CP

Placebo + CP

HR, 0.30
(95% CI, 0.127–0.699)

Received subsequent immunotherapy:
• 38.5% of patients on placebo arm
• 15.1% of patients on dostarlimab arm

Mirza, et al. SGO2023
PFS and OS in MMRp/MSS Population

HR, 0.76 (95% CI, 0.592–0.981)

HR, 0.73 (95% CI, 0.515–1.024)

Received subsequent immunotherapy:
- 33.2% of patients on placebo arm
- 15.6% of patients on dostarlimab arm

PFS

OS

Mirza, et al. SGO2023

Hazard ratio; MMRp, mismatch repair proficient; MSS, microsatellite stable; NE, not estimable; OS, overall survival; PFS, progression-free survival.
NRG-GY018

Key Eligibility Criteria

- Measurable stage III/IVA or measurable/nonmeasurable stage IVB or recurrent endometrial cancer
- Pathology report showing results of institutional MMR IHC testing
- ECOG PS 0, 1, or 2
- No prior chemo except prior adjuvant chemo if completed ≥12 mo before study

Stratification Factors

- dMMR vs pMMR
- ECOG PS (0 or 1 vs 2)
- Prior adjuvant chemo (yes vs no)

Endpoints

- **Primary**: PFS per RECIST v1.1 by investigator in pMMR and dMMR populations
- **Secondary**: Safety, ORR/DOR per RECIST v1.1 by BICR or investigator by treatment arm and MMR IHC status, OS in pMMR and dMMR populations, PRO/QoL in pMMR population, and concordance of institutional vs central MMR IHC testing results

N = 816 (591 pMMR, 225 dMMR)

Arm 1
Placebo IV Q3W + Paclitaxel 175 mg/m² IV Q3W + Carboplatin AUC 5 IV Q3W
for 6 cycles

Arm 2
Pembrolizumab 200 mg IV Q3W + Paclitaxel 175 mg/m² IV Q3W + Carboplatin AUC 5 IV Q3W
for 6 cycles

Arm 1
Placebo IV Q6W
for up to 14 additional cycles

Arm 2
Pembrolizumab 400 mg IV Q6W
for up to 14 additional cycles

BICR, blinded independent central review; dMMR, mismatch repair deficient; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; PRO, patient-reported outcomes; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.
PFS per RECIST v1.1: dMMR Population

<table>
<thead>
<tr>
<th></th>
<th>Event s, n/N</th>
<th>Median (95% CI), mo</th>
<th>HR (stratified; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + CT</td>
<td>26/11</td>
<td>NR (30.6–NR)</td>
<td>0.30 (0.19–0.48)</td>
</tr>
<tr>
<td>Placebo + CT</td>
<td>59/11</td>
<td>7.6 (6.4–9.9)</td>
<td>0.00001 (P = &lt;0.00001)</td>
</tr>
</tbody>
</table>

Data cutoff date: December 16, 2022.

Eskander, et al. SGO 2023
Proportion Alive and Progression-Free

Months from Randomization

Number at Risk (Cumulative number censored)

<table>
<thead>
<tr>
<th></th>
<th>Placebo + CT</th>
<th>Pembro + CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n/N</td>
<td>133/29</td>
<td>89/290</td>
</tr>
<tr>
<td>Median (95% CI), mo</td>
<td>8.7 (8.4-10.7)</td>
<td>13.1 (10.5-18.8)</td>
</tr>
<tr>
<td>HR (stratified; 95% CI)</td>
<td>0.54 (0.41-0.71)</td>
<td>P &lt; 0.00001</td>
</tr>
</tbody>
</table>

Eskander, et al. SGO 2023
LEAP-001: NCT03884101

Key eligibility criteria:
- Stage III, Stage IV or recurrent endometrial carcinoma
- Measurable disease or radiographically apparent disease
- May have received prior chemotherapy only if adjuvant/neoadjuvant therapy and/or administered concurrently with radiation
- ECOG PS 0 or 1

Dual Primary Endpoints
- PFS
- OS

Secondary Endpoints
- ORR
- Safety (CTCAE)
- PRO (EORTC QLC-C30)
- PK (lenvatinib)

Stratification factors:
- MMR status (pMMR v dMMR), if pMMR:
  - Measurable disease (yes or no)
  - ECOG (0 vs 1)
  - Prior chemotherapy and/or chemoradiation (yes or no)

Active, Not Recruiting
GOG 3064/ENGOT-en15/MK KN-C93: NCT05173987

Phase 3, multi-center, randomized, open-label

Key Eligibility Criteria:
- Stage III or IV, persistent/ recurrent, or metastatic EC
- Measurable/non-measurable disease (radiological apparent)
- dMMR/MSI-H
- No previous chemo for first line except as part of chemoradiation
- Prior adjuvant/neoadjuvant chemotherapy allowed, as long as completed > 6 mths before recurrence
- ECOG 0-1

Potential Stratification:
- Previous radiation and/or adju chemotherapy
- Histological - endometrioid vs. non-endometrioid

1:1
N=550

Dual Primary Endpoints
- FFS (by BICR)
- OS

Secondary Endpoints
- ORR (by BICR)
- PFS2
- HRQOL

Treatment Phase (up to 2 years of Pembrolizumab)
- Standard of Care
  - Carboplatin + Paclitaxel (Q3W, up to 7 cycles)
- Pembrol Monotherapy
  - Q6W (18 Cycles)

PD (by BICR)

Second line Treatment
- Investigator choice, outside of study

Recruiting

Memorial Sloan Kettering Cancer Center
Endometrial Cancer: Continued Unmet Medical Need

- Endometrial cancer (EC) remains the only gynecologic malignancy with sharply rising incidence and mortality.

- Carboplatin/paclitaxel has been the SOC 1L treatment of primary advanced/recurrent EC; however long-term outcomes are poor, with median OS ~3 years.

- Anti–PD-1 based therapy has transformed the management of EC post-platinum chemotherapy and in the 1L setting for advanced/recurrent disease.

  • Immunotherapy plus carboplatin/paclitaxel represents a new standard of care for patients with primary advanced or recurrent endometrial cancer

- Tremendous unmet needs remains in ≥2L recurrent EC post IO-based therapy.

THANK YOU!

Q&A

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Chief Development Officer, Cullinan Oncology

Vicky Makker, M.D.
Associate Attending Physician, Section Head Endometrial Cancer, Gynecologic Medical Oncology Service, Memorial Sloan Kettering Cancer Center