Christian Marth

Replacing chemotherapy in first line
Replacing chemotherapy in the first line

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DISCLOSURE INFORMATION

Funded Research: EU, FWF, Astra Zeneca, Roche

Honoraria/Expenses: Roche, Novartis, Amgen, MSD, Pharmamar, Astra Zeneca, Tesaro, GSK

Consulting/Advisory Board: Roche, Novartis, Amgen, MSD, Astra Zeneca, Pfizer, Pharmamar, Cerulean, Vertex, Tesaro, GSK
## Immune Checkpoint Inhibitor Efficacy in Endometrial Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>MMR-d</th>
<th>ORR(%)</th>
<th>N</th>
<th>MMR-p</th>
<th>ORR(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE 158: Marabelle (2019)</td>
<td>Pembrolizumab</td>
<td>79</td>
<td>48%</td>
<td>107</td>
<td>11%</td>
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<tr>
<td>GARNET: Oaknin (2022)</td>
<td>Dostarlimab</td>
<td>143</td>
<td>46%</td>
<td>156</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>PHAEDRA: Antill (2019)</td>
<td>Durvalumab</td>
<td>35</td>
<td>43%</td>
<td>36</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Konstantinopoulos (2019)</td>
<td>Avelumab</td>
<td>15</td>
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O'Malley et al. ESMO 2019. JCO2022; Oaknin, ASCO 2022; Antill ASCO 2019; Konstantinopoulos ASCO 2019, Makker NEJM 2022
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<tr>
<td><strong>KEYNOTE 775 Makker (2022)</strong></td>
<td>Pembrolizumab + Lenvatinib</td>
<td>65</td>
<td>42%</td>
<td>346</td>
<td>32%</td>
</tr>
</tbody>
</table>

O'Malley et al. ESMO 2019. JCO2022; Oaknin, ASCO 2022; Antill ASCO 2019; Konstantinopoulos ASCO 2019, Makker NEJM 2022
Microenvironment, Immunotherapy and Combination
Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors

## Inducers of immunogenic cell death

<table>
<thead>
<tr>
<th>Agent</th>
<th>Main cytokines</th>
<th>Immune infiltrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>↑IL-17, type I IFNs, IFNγ, TGFβ</td>
<td>↑DCs, CD8+ CTLs</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>↑IL-1β, IL-6, IL-12, IL-17, CXCL10, type I IFNs, IFNγ</td>
<td>↑DCs, CD8+ CTLs, γδ TH17 cells; ↓Treg cells, MDSCs</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>↑Type I IFNs, IFNγ, IL-17</td>
<td>↑DCs, CD8+ CTLs, NK cells, NKT cells; ↓MDSCs, Treg cells</td>
</tr>
<tr>
<td>Lurbinectedidin</td>
<td>↑Type I IFNs</td>
<td>ND</td>
</tr>
<tr>
<td>Cis/carboplatin</td>
<td>↑Type I IFNs, IFNγ</td>
<td>↑DCs, CD8+ CTLs, CD4+ T cells; ↓Treg cells, MDSCs</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>↑IL-17</td>
<td>↑DCs, CD8+ CTLs, NKb, and NKT cells; ↓MDSCs, Treg cell</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>↑IL-1β, IL-12, TNF</td>
<td>↑DCs, M1 macrophages; ↓Treg cells</td>
</tr>
<tr>
<td>Tumor treating fields</td>
<td>↑Type I IFNs</td>
<td>↑DCs, CD8+ CTLs</td>
</tr>
</tbody>
</table>

Metronomic Chemotherapy

- Metronomic chemotherapy relies on frequent administration of a low dose of chemotherapy
- Initially considered as an antiangiogenic therapy, metronomic chemotherapy is now regarded as a multi-target therapy with immunological properties, and direct effect on cancer stem cells
- Many clinical studies have demonstrated activity in relapsed and/or refractory disease and several randomized studies are ongoing
- Combined with tumour molecular analysis, metronomic chemotherapy is poised to move towards personalized chemotherapy
- Metronomic therapy is a non-toxic, inexpensive strategy well-suited for global oncology
Chemotherapy and IO: Antagonistic activity

• Impair the proliferative and/or effector functions of peripheral T cells
• Immunosuppression by massive tumor-antigen release. The sudden and systemic release of numerous dying tumour cells resulting from chemotherapy might have deleterious consequences on subsequent tumour-specific immune responses
• Glucocorticoids suppress the production of proinflammatory Cytokines and impair the differentiation of and antigen presentation by dendritic cells
Crossing survival curves of KEYNOTE-177 in MSI-high or MMR-deficient metastatic colorectal cancer illustrate the rationale behind combining immune checkpoint inhibition with chemotherapy.

Bomze D, et al. Lancet Oncol. 2022
Primary Endpoint: PFS in dMMR/MSI-H Population

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

<table>
<thead>
<tr>
<th></th>
<th>No. with event, %</th>
<th>Median (95%CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dostarlimab + carboplatin/paclitaxel</td>
<td>35.8</td>
<td>NE (11.8–NE)</td>
</tr>
<tr>
<td>Placebo + carboplatin/paclitaxel</td>
<td>72.3</td>
<td>7.7 (5.6–9.7)</td>
</tr>
</tbody>
</table>

PFS maturity 55.9 Censored + Probability of PFS

0.0 0.2 0.4 0.6 0.8 1.0

Dostarlimab + carboplatin/paclitaxel

Placebo + carboplatin/paclitaxel

Chemotherapy Period

Median duration of follow-up 24.79 months.

Mansoor Mirza, et al NEJM 2023
Primary Endpoint: PFS in Overall Population

HR 0.64
(95% CI, 0.507–0.800)

P<0.0001

No. at Risk
(No. of Events)

dose

Dostarlimab +
carboplatin/paclitaxel

245 (0)
220 (12)
197 (25)
157 (55)
130 (80)
105 (103)
94 (110)
84 (118)
78 (122)
72
52
47
24
24
15
12
8
6
4
2
0

Placebo +
carboplatin/paclitaxel

249 (0)
219 (14)
200 (29)
144 (77)
103 (115)
74 (141)
59 (155)
57 (157)
48 (170)
39 (170)
32 (172)
20 (175)
14 (175)
12
5
2
0

No. with event, %

Median
(95%CI), mo

Dostarlimab +
carboplatin/paclitaxel

55.1
11.8
(9.6–17.1)

Placebo +
carboplatin/paclitaxel

71.1
7.9
(7.6–9.5)

PFS maturity

63.2

38

Chemotherapy Period

Dostarlimab +
carboplatin/paclitaxel

Placebo +
carboplatin/paclitaxel

Median duration of follow-up 25.3 months.

Mansoor Mirza, et al NEJM 2023

Dieses Slide enthält off Label Informationen
PFS in the 462 Patients

HR 0.76
(95% CI: 0.592–0.981)

- Carbo = carboplatin; HR, hazard ratio; MMRp = mismatch repair proficient; MSS = microsatellite stable; PFS = progression-free survival.

Mansoor Mirza, et al NEJM 2023
TEAEs in ≥20% of Either Arm

Toxicity is mainly driven by chemotherapy

- Any grade TEAE Dostarlimab + CP
- Any grade TEAE Placebo + CP
- Grade ≥3 TEAE Dostarlimab + CP
- Grade ≥3 TEAE Placebo + CP

CP = carboplatin/paclitaxel; TEAE = treatment emergent adverse event.

Mansoor Mirza, et al NEJM 2023
Treatment-Related irAEs in ≥5% of Either Arm

- Hypothyroidism: 11.2%
- Rash: 2.8% (2.0% Grade ≥3)
- Arthralgia: 5.8% (6.5% Grade ≥3)
- Alanine aminotransferase increased: 5.8% (0.8% Grade ≥3)

\*All other irAEs that occurred did so at a frequency below 5% in either arm. Immune-related AEs are defined as grade 2 and above from a predefined list. AE = adverse event; ir = immune-related.
Moving Efforts to the Frontline: Immunotherapy vs. Chemotherapy

ENGOT-en15 KN-C93
- Pembrolizumab
- Chemo
- Primary endpoints: PFS, OS
- Key secondary endpoints: ORR, DCR, DOR
- Recruitment ongoing
- dMMR patient population

ENGOT-en13 DOMENICA
- Dostarlimab
- Chemo
- Primary endpoint: PFS
- Key secondary endpoints: OS, PROs, ORR, DOR
- Recruitment ongoing
- dMMR patient population

ENGOT-en9 LEAP-001
- Lenvatinib + pembrolizumab
- Chemo
- Primary endpoints: PFS, OS
- Key secondary endpoints: ORR, HRQOL, safety
- Completed enrollment
dMMR and pMMR patient populations
MK-3475-C93/KEYNOTE-C93/GOG-3064/ENGOT-en15
1L dMMR platinum doublet chemotherapy vs pembro with cross over

- Stage III or IV, persistent/recurrent, or metastatic EC
- Measurable/non-measurable disease
- dMMR
- No previous chemo for adjuvant or first line except as part of radiosensitizing
- ECOG 0-1

**ClinicalTrials.gov Identifier: NCT05173987**
Domenica– Trial design and endpoints

Phase III Trial

- Endometrial cancer
- MMR deficient (local IHC)
- Metastatic/ advanced
- Stage IV, Relapse or stage IIIC2 (with residual disease)

Stratification factors:
- CT adj/ yes – no
- Previous pelvic irradiation

Primary endpoint
- PFS by RECIST V1.1 *
  - Investigator–assessed

Secondary endpoints
- OS and PROs (key secondary endpoints)
- ORR, DoR,
- PFS2,
- TFST, TSST
- Safety and tolerability
- Central MMR

Exploratory endpoints
- Translational (MSI, PD1/L1 status, immune signature); PFS according iRECIST

* Radiologic scans ~6 weeks up to 1 year or progression and then ~12 weeks thereafter until progression

ENGOT-en13

ENGOT – European Network of Gynaecological Oncological Trial groups
New amendment under approval

Phase III Trial: initial design; new amendment:

- Endometrial cancer
- MMR deficient (local IHC, confirmed by centralized analysis)
- Metastatic/advanced
- Stage IV, Relapse or stage IIC2 (with residual disease)

Stratification factors:
- CT adj/yes-no
- Previous pelvic irradiation

Stage III A to III C2, evaluable disease

Initial-relapse

R 1:1

n = 142

n = 71

Dostarlimab 500 mg
Every 3W, 4 cycles

Dostarlimab 1000 mg
every 6W

Up to 2 years or to progression

Carbo AUC5-Paclitaxel
175mg/m², 6 cycles

Mirrored cross-over

 amendment to allow cross over to Dosta arm at progression accepted

260

BICR

OS: key 2nd

Primary endpoint

Secondary endpoints

- Quality of life (key secondary endpoint)
- ORR, DoR,
- PFS2,
- TFST, TSST
- Self-reported toxicity PRO-CTC-AE
- OS
- Safety and tolerability

Translational (MSI, PD1/L1 status, immune signature); PFS according iRecist

Exploratory endpoints

* Continued treatment with dostarlimab beyond 2 years may be considered case by case, only after discussion with the sponsor and its agreement.

** Radiologic scans ~6 weeks up to 1 year or progression and then ~12 weeks thereafter until progression
Recruitment

- 12 Patients in screening
- 50 Patients randomized
- 7 Patients Screen Failed
## Global study progress

<table>
<thead>
<tr>
<th>Group/country</th>
<th>Nb sites</th>
<th>Submission status</th>
<th>Nb patients screened</th>
<th>Nb patients randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>GINECO / France</td>
<td>42</td>
<td>Initial approval received in Dec2021 Amdt 1 v2.0 approval received in Aug2022</td>
<td>68</td>
<td>49</td>
</tr>
<tr>
<td>AGO / Germany</td>
<td>8</td>
<td>Submitted in Dec2022</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BGOG / Belgium</td>
<td>3</td>
<td>Migration to CTIS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GEICO / Spain</td>
<td>8</td>
<td>Initial approval received in Jul2022</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MITO / Italy</td>
<td>11</td>
<td>Approval received in Apr2023</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MaNGO / Italy</td>
<td>10</td>
<td>Approval received in Apr2023</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>NCRI / UK</td>
<td>10</td>
<td>In preparation</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PMC / Canada</td>
<td>5</td>
<td>1st EC approval on Jan2023</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ANZGOG / Australia</td>
<td>15</td>
<td>In preparation</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GCGS / Singapore</td>
<td>2</td>
<td>In preparation</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>KGOG / S. Korea</td>
<td>7</td>
<td>In preparation</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SAKK / Switzerland</td>
<td>10</td>
<td>In preparation</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TRSGO / Turkey</td>
<td>6</td>
<td>Feasibility ongoing</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
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- Stage III, IV or recurrent endometrial carcinoma
- No prior chemotherapy (except chemoradiation)
- ECOG 0 or 1
- 888 randomized patients

Stratify:
- MMR status (pMMR vs. dMMR)
  - If pMMR,
    - ECOG (0 versus 1)
    - Measurable disease (yes vs. no)
    - prior chemoradiation (yes vs. no)

Pembrolizumab 200 mg IV infusion Q3W/15 mg/kg q3w
- Up to 35 infusions

Lenvatinib 20mg orally QD
- Up to 7 cycles

Carboplatin AUC 6 (-5) IV infusion Q3W
- Up to 7 cycles

Paclitaxel 175 mg/m² IV infusion Q3W
- Up to 7 cycles

Christian Marth et al. Int J Gynecol Cancer 2021

- Stage III, IV or recurrent endometrial carcinoma
- No prior chemotherapy (except chemoradiation)
- ECOG 0 or 1
- 888 randomized patients

Stratify:
- MMR status (pMMR vs. dMMR)
  - If pMMR,
    - EOG (0 versus 1)
    - Measurable disease (yes vs. no)
    - prior chemoradiation (yes vs. no)
Prevalence and Prognosis of Lynch Syndrome and Sporadic Mismatch Repair Deficiency in Endometrial Cancer

Note: Kaplan-Meier survival curves for recurrence-free survival (A) and overall survival (B) for patients with methylated mismatch repair deficient (MMRd), other MMRd and Lynch syndrome (LS) associated MMRd endometrial cancer (EC). All cases with MMRd phenotype are included in this analysis, including cases with a concurrent POLE variant affecting function (POLEmut-MM Rd-EC). P values reflect 2-sided log-rank test.
MLH1 hypermethylation predicts poor outcomes with pembrolizumab in recurrent endometrial cancer

Lindsay Borden SGO 2022

- MMRd endometrial cancer are a heterogeneous group
- hMLH-1 tumors may not respond as robustly to immune checkpoint inhibitor single agent therapy
A phase 2 evaluation of pembrolizumab for recurrent Lynch-like versus sporadic endometrial cancers with microsatellite instability

- 25 patients (24 evaluable) were treated with pembrolizumab. 6 (25%) harbored Lynch/Lynch-like tumors, whereas 18 (75%) had sporadic EC.
- TMB was higher in Lynch-like (median 2939) versus sporadic tumors (median 604) (P < 0.0076).

S Bellone et al. *Cancer* 2022;128:1206-1218
Post Hoc Analysis of Objective Response Rate by Mismatch Repair Protein Dimer Loss/Mutation Status in Patients with Mismatch Repair Deficient Endometrial Cancer Treated with Dostarlimab

- Most MLH1 loss was not accompanied by mutations, consistent with the estimated rate in the dMMR population\(^1-4\)

<table>
<thead>
<tr>
<th></th>
<th>Patients, N</th>
<th>Responders, n</th>
<th>ORR, % (95% exact CI)</th>
<th>DOR median (95% CI), mo</th>
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<tr>
<td>Cohort A1 (dMMR/MSI-H EC)</td>
<td>143</td>
<td>65</td>
<td>45.5 (37.1–54.0)</td>
<td>NR (38.9–NR)</td>
</tr>
<tr>
<td>Cohort A1 patients with available mutation data</td>
<td>101</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MLH1 loss by IHC (any pattern)(^a)</td>
<td>78</td>
<td>31</td>
<td>39.7 (28.8–51.5)</td>
<td>NR (38.9–NR)</td>
</tr>
<tr>
<td>MLH1 loss by IHC (any pattern) and mutation in \textit{MLH1} or \textit{PMS2} genes</td>
<td>7 (9%)</td>
<td>3</td>
<td>42.9 (9.9–81.6)</td>
<td>NR (NR–NR)</td>
</tr>
<tr>
<td>MLH1 loss by IHC (any pattern) and no mutation in \textit{MLH1} or \textit{PMS2} genes</td>
<td>71 (91%)</td>
<td>28</td>
<td>39.4 (28.0–51.7)</td>
<td>NR (38.9–NR)</td>
</tr>
</tbody>
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\(^a\)Other: any other pattern of loss that is not exclusively MLH1–PMS2 or MSH2–MSH6 dimer loss. This group includes 17 patients with loss of expression of 1 MMR protein, 13 with loss of 3 proteins, 1 with loss of 2 proteins that are not a canonical dimer, and 2 with MMR unknown/MSI-H status. \(^a\)This group includes 65 patients with loss of the MLH1–PMS2 dimer and 12 with another pattern.

dMMR, MMR deficient; EC, endometrial cancer; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, microsatellite instability–high.


Tinker AV et al. Presented at the International Gynecologic Cancer Society (oral poster). September 29 - October 1, 2022; New York, USA
Conclusions

• Concept of chemo-free is appealing
• Avoidance of chemo toxicity: alopecia, neurotoxicity...
• Chemo-free immunotherapy for MMRd?
• POLE?
• Excluding MLH-1 promoter-hypermethylation?
• Combination with Lenvatinib for MMRp?
• Ongoing trials wrong control arm
Thank you