With Immunotherapy first line - What are the future opportunities?

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Co-director of the High Therapeutic Definition Program
Princess Margaret Cancer Centre
Associate Professor – University of Toronto (UFT)
# Immunotherapy Combination first line

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Dostarlimab RUBY Part 1</th>
<th>Pembrolizumab NRG-GY018³⁴</th>
<th>Atezolizumab AtTEnd</th>
<th>Placebo + carboplatin/paclitaxel</th>
<th>Pembrolizumab + carboplatin/paclitaxel then pembrolizumab ± cisplatin</th>
<th>Pembrolizumab + carboplatin/paclitaxel then atezolizumab ± cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>494</td>
<td>816</td>
<td>990</td>
<td>550</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study chair</td>
<td>Mirza</td>
<td>Eskander</td>
<td>Van Gorp</td>
<td>Colombo</td>
<td></td>
<td></td>
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<tr>
<td>Treatment arms</td>
<td>Dostarlimab + carboplatin/paclitaxel then dostarlimab vs Placebo + carboplatin/paclitaxel then placebo</td>
<td>Pembrolizumab + carboplatin/paclitaxel then pembrolizumab vs Placebo + carboplatin/paclitaxel then placebo</td>
<td>Pembrolizumab + carboplatin/paclitaxel then pembrolizumab ± RT ± cisplatin vs Placebo + carboplatin/paclitaxel then placebo</td>
<td>Atezolizumab + carboplatin/paclitaxel then atezolizumab vs Placebo + carboplatin/paclitaxel then placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratification</td>
<td>MMR-MSI status, previous external pelvic radiotherapy, and disease status²</td>
<td>MMR status, ECOG PS, and previous chemotherapy⁴</td>
<td>MMR status, RT, histology, and FIGO surgical stage⁶</td>
<td>Histology, disease stage, MSI status, and country of experimental site⁸</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome(s)</td>
<td>PFS (IA), OS</td>
<td>PFS</td>
<td>DFS (IA), OS</td>
<td>PFS, OS</td>
<td></td>
<td></td>
</tr>
</tbody>
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Subgroup of MMRd

Mechanism of MMRd

Somatic or germline mutation in an MMR gene is estimated to account for 10-20% of MMR deficiency in EC.

MLH1 promoter methylation accounts for approximately 75%–80% of cases with MMR deficiency in EC.
Benefit of IO combination

<table>
<thead>
<tr>
<th></th>
<th>No with events%</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>GY018</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrol + CT</td>
<td>23.2</td>
<td>NR (30.6-NR)</td>
</tr>
<tr>
<td>Placebo + CT</td>
<td>52.2</td>
<td>7.6 (6.4-9.9)</td>
</tr>
<tr>
<td>RUBY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsta + CT</td>
<td>35.8</td>
<td>NR (11.8-NR)</td>
</tr>
<tr>
<td>Placebo + CT</td>
<td>72.3</td>
<td>7.7 (5.6-9.7)</td>
</tr>
<tr>
<td>AtTEnd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezo + CT</td>
<td>45.7</td>
<td>NR (12.3-NR)</td>
</tr>
<tr>
<td>Placebo + CT</td>
<td>84.1</td>
<td>6.9 (6.2-9.0)</td>
</tr>
</tbody>
</table>

Eisai has sponsored this initiative with IGCS and had no input into or influence over the content.
NRG-GY018 – PFS and OS by mechanism of MMR loss

No difference in PFS was identified in dMMR EC patients based on mechanism of MMR loss

<table>
<thead>
<tr>
<th>Mechanism of MMR loss, %</th>
<th>dMMR population</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1 promoter hypermethylation</td>
<td>72</td>
</tr>
<tr>
<td>MMR protein loss secondary to gene mutation</td>
<td>13</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median PFS by mechanism of MMR loss</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1 promoter hypermethylation</td>
<td>Not reached</td>
</tr>
<tr>
<td>MMR protein loss secondary to gene mutation</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12-month PFS by mechanism of MMR loss, %</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1 promoter hypermethylation</td>
<td>75</td>
</tr>
<tr>
<td>MMR protein loss secondary to gene mutation</td>
<td>85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median OS by mechanism of MMR loss</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1 promoter hypermethylation</td>
<td>Not reached</td>
</tr>
<tr>
<td>MMR protein loss secondary to gene mutation</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

dMMR = mismatch repair deficient; MLH1 = mutL homolog 1; MMR = mismatch repair; PFS = progression-free survival; OS = overall survival.
Do you need chemo in this group?

**KEYNOTE-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

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## Why this is important?

### Sparing Chemo related toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Chemotherapy period</th>
<th>Monotherapy period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>Frequency (%)</td>
<td>Median duration</td>
</tr>
<tr>
<td></td>
<td>51.9%</td>
<td>25.6 (10.1-81.3)</td>
</tr>
<tr>
<td></td>
<td>48.4%</td>
<td>24.1 (1.0-99.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Frequency (%)</td>
<td>Median duration</td>
</tr>
<tr>
<td></td>
<td>47.7%</td>
<td>14.2 (&lt;1.0-116.0)</td>
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<tr>
<td></td>
<td>48.0%</td>
<td>23.4 (&lt;1.0-93.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>Frequency (%)</td>
<td>Median duration</td>
</tr>
<tr>
<td></td>
<td>45.5%</td>
<td>10.4 (&lt;1.0-100.9)</td>
</tr>
<tr>
<td></td>
<td>40.7%</td>
<td>22.1 (&lt;1.0-125.3)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Frequency (%)</td>
<td>Median duration</td>
</tr>
<tr>
<td></td>
<td>42.3%</td>
<td>7.0 (&lt;1.0-64.3)</td>
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<tr>
<td></td>
<td>39.8%</td>
<td>8.7 (&lt;1.0-75.9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>Frequency (%)</td>
<td>Median duration</td>
</tr>
<tr>
<td></td>
<td>32.0%</td>
<td>6.7 (&lt;1.0-64.3)</td>
</tr>
<tr>
<td></td>
<td>38.6%</td>
<td>9.1 (&lt;1.0-75.9)</td>
</tr>
</tbody>
</table>

*TRAEs occurring in >30% in either arm. n/N represents the number of patients with duration data over the number of patients with onset data.

The duration is defined as time from onset of any AE considered in this analysis to the first time the subject is free of any such event. It requires at least one day gap between the resolution of all events from first course to the onset of second course. AE = adverse event; C/P = carboplatin-paclitaxel; TRAE = treatment-related adverse event.

Beyond MMRd- Molecular Subgroup

PFS according biomarkers – RUBY trial

Based on 400/494 patients with known molecular classification per whole exome sequencing

HR, 0.31* (95% CI, 0.17–0.56)

HR, 0.55 (95% CI, 0.30–0.99)

HR, 0.77 (95% CI, 0.55–1.07)

Mirza M et al. ESMO 2023
IO – Pattern of disease response

Primary Resistance

Primary resistance is common even in “hot” tumors
Gap in MMRd

Subsequent immunotherapy

Atezolizumab arm 6.2%
Placebo arm 40.9%

Redzone dMMR patients: IO + chemo
⇒ IO is not sufficient
Factors - Response and Resistance to IO

- **IPRES signature**
- **Oncogene activation** (WNT/β-catenin)
- **Alteration of antigen presentation pathway**
- **Loss of oncosuppressor genes** (PTEN)
- **Genetic alteration of IFN-γ pathway**
- **High PD-L1 expression on tumor cells**

**CONSTITUTIVE RESISTANCE**

- **Copy number loss in tumor suppressive genes**
- **Loss of mutation-associate neoantigens**
- **Mutations (JAK1/2)**
- **New mutations (B2-microglobulin)**
- **Chronic IFN-γ exposure**
- **High MDSC infiltrate**
- **Upregulation of inhibitory molecules on adaptive and innate immune cells (TIM-3 and VISTA)**

**ACQUIRED RESISTANCE**

**EXTRINSIC FACTORS**

**INTRINSIC FACTORS**

- **Downregulation of IFNAR1 on CTLs**
- **Poor infiltration by CD8+ T cells**
- **Poor expression of IFN-induced gene**

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Eisai has sponsored this initiative with IGCS and had no input into or influence over the content.

Bellone M, Elia AR. Constitutive and Factor Rev. 2017
Strategies to Prevent and Revert Resistance

Zhang T et al. J Immunother Cancer. 2023
Potential Strategies after IO

- Alternative Proangiogenicic Pathways
- Immunotherapies / Enhancing IO
- Metabolic Pathways
- PARP Inhibitors
The TKI lenvatinib: 
- Increases CD8+ T-cell function 
- Increases cytotoxicity of NK cells 
- Decreases expression of PD-1, CTLA-4, and TIM3 in T cells 
- Inhibits T-cell exhaustion

Rationale for combining TKI and anti-PD-(L)1


CD8 = cluster of differentiation 8; CTLA-4 = cytotoxic T-lymphocyte associated protein 4; IL-10 = interleukin 10; NK = natural killer; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand-1; TGF-β = transforming growth factor beta; TIM3 = T-cell immunoglobulin and mucin domain 3; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

Approved Combination IO Approaches in Advanced/Recurrent EC: Phase 3 KEYNOTE-775

**KEYNOTE-775**

Key Eligibility Criteria
- Advanced, metastatic, or recurrent EC
- Measurable disease by BICR
- 1 prior platinum-based chemotherapy regimen\(^a\)
  - ECOG PS 0-1
- Tissue available for MMR testing

**IO naive**

- **Lenvatinib**
  - 20 mg po qd
- **Pembrolizumab**
  - 200 mg IV q3w

**Treatment until progression or unacceptable toxicity**

**Stratification Factors**
- MMR status (dMMR vs MMRp)
- MMRp by ECOG PS, geographic region, prior pelvic radiation

**Primary Endpoints**
- PFS by BICR and OS

**Secondary Endpoints**
- ORR, HRQoL, PK, safety

**Key Exploratory Endpoint**
- DOR

\(^a\) Patients may have received up to 2 prior platinum-based CT regimens if 1 was given in the neoadjuvant or adjuvant treatment setting.

\(^b\) Maximum of 35 doses.

\(^c\) Maximum cumulative dose of 500 mg/m\(^2\).

These data were full FDA approval based on mPFS of 6.6 vs 3.8 (HR 0.60) and mOS of 17.4 vs 12.0 (HR 0.68). Makker V, et al. J Clin Oncol. 2023;JCO2202152. doi:10.1200/JCO.22.02152.

**mPFS in KEYNOTE-775: MMRp**

- **Len + Pem (n=346)**
  - 6.7 (5.6-7.4)
  - 0.60 (0.50-0.72)
- **CT (n=351)**
  - 3.8 (3.6-5.0)
  - P<0.001

How much does Lenvatinib add to pembrolizumab in dMMR EC? Do all patients with dMMR EC need combination (Lenvatinib+pembrolizumab)?
IO after IO in Endometrial Cancer ➔ Need for Clinical Trial
Combination in Renal Cell Carcinoma

Pembrolizumab-lenvatinib

Pts with either treatment-naive or previously treated (Study 111/KEYNOTE-146): a phase 1b/2 study

Chung-Han Lee et al, Lancet Oncology 2011
IO after IO in Renal Cell Carcinoma

CONTACT-03 trial

Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial

Key eligibility criteria
- Advanced/metastatic clear cell or non-clear cell\(^a\)
- RCC with or without a sarcomatoid component
- Radiographic progression on or after prior ICI treatment
  - ICI as adjuvant, 1L or 2L (single agent or in combination with another permitted agent)
  - ICI in the immediately preceding line of therapy

Stratification factors
- IMDC risk group
  - 0 vs 1-2 vs \(\geq 3\)
- Histology
  - Dominant clear cell without sarcomatoid vs dominant non-clear cell without sarcomatoid vs any sarcomatoid\(^b\)
- Most recent line of ICI
  - Adjuvant vs 1L vs 2L

Primary endpoints
- Independent centrally-assessed PFS\(^c\)
- OS

Key secondary endpoints
- Investigator-assessed PFS\(^c\)
- ORR (per central review and per investigator)\(^d\)
- Duration of response (per central review and per investigator)\(^d\)
- Safety

Atezolizumab 1200 mg IV q3w + Cabozantinib 60 mg daily PO

Cabozantinib 60 mg daily PO
IO after IO in Renal Cell Carcinoma

Primary analysis of centrally reviewed PFS (primary endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Atezo + Cabo (n=263)</th>
<th>Cabo (n=259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n (%)</td>
<td>177 (65)</td>
<td>166 (64)</td>
</tr>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>10.6 (9.8, 12.3)</td>
<td>10.8 (10.0, 12.5)</td>
</tr>
<tr>
<td>12-month PFS (95% CI), %</td>
<td>44 (38, 50)</td>
<td>48 (42, 54)</td>
</tr>
<tr>
<td>Stratified HR (95% CI)^2</td>
<td>1.03 (0.83, 1.28); P=0.784^2</td>
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</tbody>
</table>

Interim analysis of OS (primary endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Atezo + Cabo (n=263)</th>
<th>Cabo (n=259)</th>
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</thead>
<tbody>
<tr>
<td>PFS events, n (%)</td>
<td>89 (34)</td>
<td>87 (34)</td>
</tr>
<tr>
<td>Median OS (95% CI), mo</td>
<td>25.7 (25.1, NE)</td>
<td>NE (21.1, NE)</td>
</tr>
<tr>
<td>12-month OS (95% CI), %</td>
<td>76 (73, 84)</td>
<td>76 (71, 81)</td>
</tr>
<tr>
<td>Stratified HR (95% CI)^4</td>
<td>0.94 (0.70, 1.27); P=0.690</td>
<td></td>
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</tbody>
</table>

^2 Stratified for age, sex, race, ECOG performance status, renal function, and prior IO treatment.
IO after IO in Endometrial Cancer

Advanced Recurrent Endometrial Cancer
At least one line of previous platinum
ECOG 0-2

MSS/MSI Stratification

2:1

ARM A
Cabozantinib 40mg PO daily
Nivolumab 240mg IV q2w
From cycle 5: 480mg IV q4w

ARM B
Nivolumab 240mg IV q2w
From cycle 5: 480mg IV q4w

ARM C
Cabozantinib 40mg PO daily
Nivolumab 240mg IV q2w
From cycle 5: 480mg IV q4w

Cross Over from Arm B -
Post progression on immune therapy
OR
Recurrent Carcinosarcoma

Biopsy

Crossover

PFS Endpoint

Eisai has sponsored this initiative with IGCS and had no input into or influence over the content.
Exploratory Cohort: Post IO

Lheureux S et al, JITC 2022

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Baseline Biopsy - CyTOF

- Mass cytometry (CyTOF): High dimensional examination of the immune system to identify potential predictive markers of response
- Baseline biopsies analyzed by CyTOF using a 37-marker immune profiling panel.
- UMAP clustering of pooled CD45+ cells resulted in 35 unique immune populations defined by their lineage and phenotypic markers.

Cohort C (n=12)
Potential Biomarkers

Non-progressors had higher proportions of activated tissue-resident (CD103+CD69+) \( \gamma \delta \) T cells than progressors (adjusted p=0.009)

Cohort C – Prior IO
Approach based on Molecular Subgroup

p53 as predictive biomarker: GOG 86P

Patients based on TP53 status and Bev

Potential Strategies post IO

- Alternative Proangiogenic Pathways
- Immunotherapies / Enhancing IO
- Metabolic Pathways
- PARP Inhibitors
Therapies to Target the Cancer – Immunity Cycle

Eisai has sponsored this initiative with IGCS and had no input into or influence over the content.

Mellman I et al, Cell 2023
Combination Therapy

- Role of CTLA4 and T-regs in dMMR and POLE EC and dMMR CRC

- **Rationale**
  - Dual immune checkpoint

  - Immune evasion mechanism of dMMR tumors
    - Up-regulation of PD1, CTLA4 and other exhaustion markers like LAG3
    - CTLA4 up-regulated in dMMR and POLE EC

  - Targeting T-regs
    - Immunosuppressive cells
    - In EC, high T-regs counts, T-regs/CD8 ration → worse outcome and prognosis

Recurrent MMRd – NRG GY025

Stratification:
- Prior Radiation
- Prior anti-PD1/PD-L1 therapy
- Measurable disease (yes/no)

Randomization:
- Arm 1: Nivolumab Q3W and Low-Dose Ipilimumab Q6W (every other cycle x 4) and then nivolumab alone Q4W until disease progression, unacceptable toxicities or CR
- Arm 2: Nivolumab Q3W x 8 cycles then Q4W until disease progression, unacceptable toxicities or CR

New agent combining dual checkpoint inhibitor
Ex: PD1/CTLA4 – PD1/TIGIT

Safety lead-in
Open to NRG Oncology Phase I Sites ONLY

Study Chairs: Haider Mahdi, MD, MPH; K. Moore, MD; Matthew Powell, MD; Stephanie Gaillard, MD, PhD.

Eisai has sponsored this initiative with IGCS and had no input into or influence over the content.

Combination ICI (PD1-LAG3)

- LAG-3 and PD-1 are distinct inhibitory immune checkpoints that contribute to T-cell exhaustion.
- Simultaneous blockade of LAG-3 and PD-1 may synergistically restore T-cell activation and enhance antitumor immunity.

Melanoma pre-treated

<table>
<thead>
<tr>
<th>Table: LBA18 Response by LAG-3(^a) and PD-L1(^b) expression</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>PD-L1 expression</td>
</tr>
<tr>
<td>≥ 1%</td>
</tr>
<tr>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

\(^a\)Immunohistochemistry (IHC) with percentage of positive cells among all nucleated cells within the tumor and invasive margin using mouse antibody clone 17B4. Expression ≥ 1% was identified in 33/53 (62%) of evaluable samples.

\(^b\)Tumor cell expression determined using Dako PD-L1 IHC 28-8 kit. Expression ≥ 1% was identified in 20/44 (45%) of evaluable samples.
Combination ICI (PD1-LAG3)

Untreated Melanoma

Tawbi HA et al, NEJM 2023
Potential Strategies post IO

- Alternative Proangiogenic Pathways
- Immunotherapies / Enhancing IO
- Metabolic Pathways
- PARP Inhibitors - ADC
Importance of the molecular profiling

Benefit of IO combo and DDR agents

DUO-E: PFS by Subgroup

PFS: ITT population
Primary endpoint

Prespecified exploratory analysis

dMMR (20% of population)

No. at risk

Control

Durva

Durva+Ola

Control

Events, n (%)

Control

Durva

Durva+Ola

Control

Median PFS (95% CI),* months

HR (95% CI) vs Control

HR (95% CI) vs Durva

PFS %

No. at risk

Months since randomisation

Control

Durva

Durva+Ola

No. at risk

Events, n (%)

Median PFS (95% CI),* months

HR (95% CI) vs Control

HR (95% CI) vs Durva

Westin et al ESMO 2023
Importance of the molecular profiling
Benefit of AO combo and DDR agents

UTOLA: PFS by TP53 Status

Phase II study of ceralasertib (AZD6738) in combination with durvalumab in patients with advanced/metastatic melanoma who have failed prior anti-PD-1 therapy

Response rate 31%
Median duration of response 8.8 months
Tumours with an immune-enriched microenvironment or alterations in the DDR pathway were more likely to respond

Joly F et al, ESMO 2023

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Conclusion / Discussion

Considerations In the post IO setting

- Time of Progression: PD during IO versus post IO likely different
- Combination Strategies
- Type of Molecular Subgroup - Biomarkers
- New drug design: Improving drug delivery (ADC)
  Improve inhibition by dual targeting (bifunctional Mabpair)
- Need for Clinical trials & Biomarkers assessment
Thank you to patients, clinical & research teams & research funds.