MEETING SUMMARY
ASCO 2020, VIRTUAL MEETING

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HIGHLIGHTS FROM GI CONNECT
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DISCLAIMER

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Disclosures: Assoc. Prof. Shubham Pant has the following financial relationships to disclose: Xencor, 4D, Tyme
PEMBROLIZUMAB VERSUS CHEMOTHERAPY FOR MICROSATELLITE INSTABILITY-HIGH/MISMATCH REPAIR DEFICIENT METASTATIC COLORECTAL CANCER: THE PHASE 3 KEYNOTE-177 STUDY

Andre T, et al.
**BACKGROUND**

**Introduction**

A subset of CRC are characterised by dMMR → resulting in MSI

CRCs with MSI-H → high levels of lymphocyte infiltrates
→ high expression of PD-1 and PD-L1

**KEYNOTE-016 study (Phase 2)**

Pembrolizumab (anti–PD-1 antibody) showed ORR of 40% in patients with progressive dMMR mCRC vs 0% in patients with MMR-proficient mCRC

**KEYNOTE-177 (Phase 3)**

Designed to evaluate the efficacy and safety of pembrolizumab vs standard-of-care chemotherapy as first-line therapy for dMMR or MSI-H mCRC

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CRC, colorectal cancer; dMMR, mismatch repair deficiency; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; MSI-H, microsatellite instability-high; ORR, overall response rate; PD-1, programmed death-1; PD-L1, programmed death ligand-1

TRIAL DESIGN

KEYNOTE-177 (NCT02563002): 2-arm, randomised, open-label, phase 3 study

Some eligibility criteria
• Treatment naive mCRC
• dMMR or MSI-H
• ECOG PS 0-1
• No active brain metastases

307 patients

Pembrolizumab 200 mg IV Q3W n=153

Investigator’s choice*
mFOLFOX6 +/- Bev or cetuximab
FOLFIRI +/- Bev or cetuximab n=154

Randomisation 1:1

Primary endpoints: PFS (RECIST v1.1, central review) and OS
Secondary endpoints: ORR (RECIST v1.1, central review) and safety

Treatment Duration: until PD, unacceptable toxicity, patient/investigator decision to withdraw, or completion of 35 cycles (pembrolizumab only)

* Patients with progressive disease have the option of receiving pembrolizumab 200 mg IV q3wk
Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; dMMR, mismatch repair deficiency; FOLFIRI, leucovorin + irinotecan + 5-fluorouracil; IV, intravenously; mFOLFOX6, modified oxaliplatin + leucovorin + 5-fluorouracil; MSI-H, microsatellite instability-high; ORR, overall response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response evaluation criteria in solid tumours
## RESULTS

**Data cut-off date:** Feb 19, 2020

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Pembro</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>16.5</td>
<td>8.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.60 (0.45-0.80)</td>
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<tr>
<td>P-value</td>
<td>0.0002</td>
<td></td>
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<tr>
<td>12-months PFS rates</td>
<td>55.3%</td>
<td>37.3%</td>
</tr>
<tr>
<td>24-months PFS rates</td>
<td>48.3%</td>
<td>18.6%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Pembro</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>43.8%</td>
<td>33.1%</td>
</tr>
<tr>
<td>Median DoR (months)</td>
<td>NR</td>
<td>10.6</td>
</tr>
<tr>
<td>Grade 3-5 TRAE rates</td>
<td>22%</td>
<td>66%*</td>
</tr>
</tbody>
</table>

* One patient in the chemo arm died due to a treatment-related AE.

CI, confidence interval; chemo, chemotherapy; DoR, duration of response; HR, hazard ratio; ORR, overall response rate; pembro, pembrolizumab; PFS, progression-free survival; TRAE, treatment-related adverse event.
CONCLUSIONS

PEMBROLIZUMAB = THE NEW STANDARD OF CARE IN 1-L FOR mCRC PATIENTS WITH dMMR OR MSI-H?

• Pembrolizumab provided a clinically meaningful and statistically significant improvement in PFS versus chemotherapy as first-line therapy for patients with MSI-H/dMMR mCRC, with fewer treatment-related AEs observed

• The study is ongoing in order to evaluate the OS

1-L, first line; AEs, adverse events; dMMR, mismatch repair deficiency; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; OS, overall survival; PFS, progression-free survival
PEMBROLIZUMAB VERSUS PACLITAXEL FOR PREVIOUSLY TREATED PATIENTS WITH PD-L1–POSITIVE ADVANCED GASTRIC OR GASTROESOPHAGEAL JUNCTION CANCER (GC): UPDATE FROM THE PHASE III KEYNOTE-061 TRIAL

Fuchs CS, et al.
ASCO 2020. Abstract #4503. Oral presentation
Standard second-line therapy for gastric/GEJ cancer:

- **Combination therapy:** ramucirumab + paclitaxel
- **Monotherapy:** docetaxel, paclitaxel or irinotecan

**KEYNOTE-061** (NCT02370498) is a global phase 3 study of pembrolizumab vs paclitaxel as second-line therapy for gastric/GEJ cancer

**Results** (primary analysis: Oct 26, 2017)¹:

- In patients with CPS ≥1:
  - **pembrolizumab did not significantly prolong OS** vs paclitaxel (9.1 vs 8.3 months)
  - **DoR: substantially longer with pembrolizumab** vs paclitaxel (18.0 vs 5.2 months)

→ Longer-term results after additional 2 years of follow up are presented; CPS ≥1, CPS ≥5 and CPS ≥10 patient data are also assessed

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CPS, combined positive score; DoR; duration of response; GC, gastric cancer; GEJ, gastroesophageal junction; OS, overall survival
### RESULTS: EFFICACY BY CPS

**Data cut-off date:** Oct 7, 2019

<table>
<thead>
<tr>
<th></th>
<th>Pembro CPS ≥1 (n=196)</th>
<th>Paclitaxel CPS ≥1 (n=199)</th>
<th>Pembro CPS ≥5 (n=95)</th>
<th>Paclitaxel CPS ≥5 (n=91)</th>
<th>Pembro CPS ≥10 (n=53)</th>
<th>Paclitaxel CPS ≥10 (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS, deaths, n (%)</strong></td>
<td>176 (89.8)</td>
<td>190 (95.5)</td>
<td>84 (88.4)</td>
<td>86 (94.5)</td>
<td>44 (83.0)</td>
<td>51 (92.7)</td>
</tr>
<tr>
<td><strong>OS, months, median (95% CI)</strong></td>
<td>9.1 (6.2-10.7)</td>
<td>8.3 (7.6-9.0)</td>
<td>10.4 (6.7-15.5)</td>
<td>8.3 (6.8-9.4)</td>
<td>10.4 (5.9-18.3)</td>
<td>8.0 (5.1-9.9)</td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>0.81 (0.66-1.00)</td>
<td>0.72 (0.53-0.99)</td>
<td>0.69 (0.46-1.05)</td>
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<tr>
<td><strong>P value</strong></td>
<td>0.03</td>
<td>0.02</td>
<td>0.04</td>
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<tr>
<td><strong>PFS, months, median (95% CI)</strong></td>
<td>1.5 (1.4-2.0)</td>
<td>4.1 (3.2-4.3)</td>
<td>1.6 (1.4-2.8)</td>
<td>4.0 (2.8-4.4)</td>
<td>2.7 (1.4-4.3)</td>
<td>4.0 (2.7-4.4)</td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>1.25 (1.02-1.54)</td>
<td>0.98 (0.71-1.34)</td>
<td>0.79 (0.51-1.21)</td>
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<tr>
<td><strong>ORR, % (n)</strong></td>
<td>16.3 (32)</td>
<td>13.6 (27)</td>
<td>20.0 (19)</td>
<td>14.3 (13)</td>
<td>24.5 (13)</td>
<td>9.1 (5)</td>
</tr>
<tr>
<td><strong>DoR, months, (range)</strong></td>
<td>19.1 (1.4+ to 47.1+)</td>
<td>5.2 (1.3+ to 16.8)</td>
<td>32.7 (4.1+ to 47.1+)</td>
<td>4.8 (1.3+ to 15.3)</td>
<td>NR (4.1 to 47.1+)</td>
<td>6.9 (2.6 to 6.9)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CPS, combined positive score; DoR, duration of response; HR, hazard ratio; ORR, overall response rate; OS, overall survival; NR, not reached; Pembro, pembrolizumab; PFS, progression-free survival
CONCLUSIONS

AS 2-L THERAPY, PEMBROLIZUMAB CAN BE BENEFICIAL FOR PD-L1-POSITIVE GC PATIENTS

• After 2 additional years of follow up: pembrolizumab did not significantly improve OS and PFS over paclitaxel (consistent with primary analysis)
• Response rates were numerically higher and more durable with pembrolizumab
• Treatment with pembrolizumab resulted in fewer treatment-related AEs

• With increasing PD-L1 enrichment among GC patients:
  – Second-line pembrolizumab prolonged OS
  – Pembrolizumab treatment effect increased for ORR and DoR

2-L, second line; AEs, adverse events; DoR, duration of response; GC, gastric cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD-L1, programmed death ligand-1
REGOMUNE: A PHASE II STUDY OF REGORAFENIB PLUS AVELUMAB IN SOLID TUMOURS—RESULTS OF THE NON-MSI-H METASTATIC COLORECTAL CANCER (mCRC) COHORT

Cousin S, et al.
ASCO 2020. Abstract #4019. Poster presentation
Regorafenib has anti-immunosuppressive property\(^1\)

Synergy between regorafenib and anti–PD-1/PD-L1 antibodies has been shown in pre-clinical models\(^1\)

Combination strategy studies initiated with regorafenib and anti-PD-1/PD-L1:

<table>
<thead>
<tr>
<th>Studies</th>
<th>Phase</th>
<th>Location</th>
<th>Status</th>
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<tbody>
<tr>
<td><strong>REGONIVO</strong>: regorafenib and nivolumab simultaneous combination therapy (NCT03406871)</td>
<td>1b</td>
<td>Japan</td>
<td>36% ORR CRC(^2) 44% ORR GC(^2)</td>
</tr>
<tr>
<td><strong>REGOMUNE</strong>: a phase I/II study of regorafenib plus avelumab in solid tumours (NCT03475953)</td>
<td>1/2</td>
<td>France</td>
<td>Data on mCRC presented here</td>
</tr>
<tr>
<td>Regorafenib and pembrolizumab in treating participants with advanced or metastatic colorectal cancer (NCT03657641)</td>
<td>1/2</td>
<td>USA</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; GC, gastric cancer; ORR, objective response rate; PD-1, programmed death-1; PD-L1, programmed death ligand-1

TRIAL DESIGN

REGOMUNE (NCT03475953): Single arm, open-label, phase 1/2 study

Phase 1: defined the recommended phase II dose of regorafenib with avelumab

Phase 2: assessment of the antitumour activity of regorafenib with avelumab in various cohorts

Cohorts
A: mCRC not MSI-H or dMMR
B: GIST
C: Oesophageal or gastric carcinoma
D: Biliary tract cancer, HCC
E: Soft-tissue sarcoma
F: RR-DTC
G: GEP-NETs

regorafenib (160 mg QD 3 weeks/4) + avelumab (10 mg/kg IV every 2 weeks) Until PD by RECIST v1.1

Primary endpoint: 6-months ORR (RECIST v1.1, central review)
Secondary endpoints: best overall response, 6-month PFS, PFS, OS and safety

dMMR, mismatch repair deficiency; GEP-NETS, Neuroendocrine gastroenteropancreatic tumours; GIST, gastrointestinal stromal tumour; HCC; hepatocellular carcinoma; IV, intravenously; mCRC, metastatic colorectal cancer; MSI-H, microsatellite-instability high; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, every day; RECIST, Response evaluation criteria in solid tumours; RR-DTC, Radioiodine-refractory differentiated thyroid cancer
Results

Period of investigation: Nov. 2018 to Oct. 2019

Cohort assessed: Cohort A: mCRC patients

Number of patients enrolled: 48 patients

- The most common grade 3/4 AEs:
  - palmar-plantar erythrodysesthesia syndrome (30%)
  - hypertension (23%)
  - diarrhoea (13%)

- Overall population:
  - Best response: SD in 23 pts (53.5%) and PD in 17 pts (39.5%)
  - Median PFS: 3.6 months (CI 95%: 1.8–5.4)
  - Median OS: 10.8 months (CI 95%: 5.9–NA)

- Subgroup with low TAMs infiltration and low tumour cells to CD8+ T-cells distance:
  - Median PFS: 5.3 vs 1.9 months (p=0.037)
  - Median OS: NR vs 5.3 months (p=0.02)
CONCLUSIONS

• **Regorafenib + avelumab** achieved PFS and OS that compared favourably with historical data of regorafenib alone in this clinical setting.

• High-resolution analysis of tumour samples identified a composite score based on **TAMs infiltration and tumour cell to CD8+ T-cells distance which could be used as a biomarker** in further studies investigating this approach in mCRC patients.

mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; TAMs, tumour-associated macrophages
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