MEETING SUMMARY
ASCO GI 2019, San Francisco, USA

Autumn J. McRee, MD
Associate Professor,
University of North Carolina at Chapel Hill, USA

CANCERS OF THE UPPER GI TRACT
DISCLAIMER

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ABSTRACT OVERVIEW

• **KEYNOTE-181**
  – Exploring the role of immunotherapy in 2\textsuperscript{nd} line oesophageal adenocarcinoma and squamous cell carcinoma

• **Janjigian et al. (MSKCC)**
  – Adding pembrolizumab to standard of care 1\textsuperscript{st} line therapy in advanced HER2 amplified gastro-oesophageal adenocarcinoma

• **Mamdani et al.**
  – Adjuvant immunotherapy for patients with locally advanced oesophageal adenocarcinoma having received neoadjuvant chemoradiotherapy with residual disease at the time of R0 resection

HER2, Human Epidermal Growth Factor Receptor 2; MSKCC, Memorial Sloan Kettering Cancer Center; R0, residual tumour stage 0
PEMBROLIZUMAB VS CHEMOTHERAPY AS 2ND-LINE THERAPY FOR ADVANCED ESOPHAGEAL CANCER: PHASE III KEYNOTE-181 STUDY

Kojima T, et al. ASCO GI 2019, Abst #2
KEYNOTE-181

DESIGN

Phase III, randomised, 2nd line treatment setting

Patients, Eligibility

- Advanced metastatic oesophageal/Type I GEJ-AC or -SCC
- Progression on 1st line therapy
- ECOG 0-1
- (PD-L1 expression was measured but was not an inclusion criteria)

Treatment

Arm 1: Pembrolizumab
200 mg Q3W for up to 2 years

Arm 2: Physician’s choice chemotherapy
(taxane or irinotecan)

Primary endpoints:

- OS (ITT)
- OS in patients with SCC histology
- OS in PD-L1 expressing tumours
- (CPS ≥10)

Randomisation 1:1

Stratified by histology (SCC vs adenocarcinoma) and region (Asia versus rest of world)

Kojima T, et al. ASCO GI 2019, Abst #2

CPS, combined positive score; ECOG, Eastern cooperative oncology group; GEJ-AC, gastroesophageal junction adenocarcinoma; ITT, intention to treat population; OS, overall survival; PD-L1, antibody to programmed cell death ligand-1; Q, every; SCC, squamous cell carcinoma; W, weeks
Results in 628 patients (pembrolizumab vs. chemotherapy)

Primary endpoints:

- OS not statistically significant in ITT population (7.1 vs 7.1 months, p=0.056)
- OS was significantly improved in those with PD-L1 expressing tumors (9.3 vs 6.7 months, p=0.0074)
- 12 months OS rate in patients with CPS ≥10 was 43% vs 20%

Safety:

- Fewer patients had adverse events of with pembrolizumab than with chemotherapy

Kojima T, et al. ASCO GI 2019, Abst #2
CPS, combined positive score; ITT, intention to treat population; OS, overall survival; p, probability; PD-L1, programmed cell death ligand-1; SCC, squamous cell carcinoma; vs, versus
KEYNOTE-181
CONCLUSIONS

• The results of this study support pembrolizumab as a 2\textsuperscript{nd}-line standard of care for oesophageal cancer with PD-L1 CPS $\geq 10$

• We await the results of the phase III KEYNOTE-590 study of pembrolizumab plus chemotherapy as 1\textsuperscript{st}-line therapy for advanced oesophageal cancer to gain further insights into the role of immunotherapy in treatment of this tumor

Kojima T, et al. ASCO GI 2019, Abst #2
CPS, combined positive score; PD-L1, programmed cell death ligand-1
1ST-LINE PEMBROLIZUMAB, TRASTUZUMAB, CAPECITABINE AND OXALIPLATIN IN HER2-POSITIVE METASTATIC ESOPHAGOGASTRIC ADENOCARCINOMA

Janjigian YY, et al. ASCO GI 2019, Abst #62
HER2+ mEGA
INTRODUCTION

• Trastuzumab increases tumor PD-L1 expression and stimulates HER2-specific T-cell responses
• Anti-PD-1 antibody enhances the T-cell-specific immunity of trastuzumab
• Oxaliplatin can also enhance T-cells by activating dendritic cells
• This study investigated all 3 treatments in a phase II trial

Janjigian YY, et al. ASCO GI 2019, Abst #62
Anti-PD-1, antibody to programmed cell death 1 receptor; HER2, Human Epidermal Growth Factor Receptor 2; mEGA, metastatic esophagogastric adenocarcinoma; PD-L1, programmed cell death ligand-1; T-cell, thymocyte-derived lymphocyte
**HER2+ mEGA**

**DESIGN**

- **Schema**
  - Single arm phase II study of 1\(^{st}\) line CAPOX + T + P
  - P 200 mg flat dose
  - T 6 mg/kg (after 8 mg/kg load),
  - O 130 mg/m\(^2\) every 3 weeks and
  - C 850 mg/m\(^2\) (oral) 2 weeks on/1 week off (or 5-FU continuous infusion).

- **Eligibility**
  - Previously untreated metastatic HER2+ oesophagogastric adenocarcinoma defined as IHC 3+ or FISH+
  - No biomarker selection for PD-L1

- **Primary endpoint: 6 month PFS**
HER2+ mEGA

RESULTS - EFFICACY

• Results (37 patients enrolled, 24 evaluable for efficacy)¹

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Results (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (median, months)</td>
<td>11.4†</td>
</tr>
<tr>
<td>ORR (% patients)</td>
<td>83%</td>
</tr>
<tr>
<td>Tumor regression (% patients)</td>
<td>100%</td>
</tr>
<tr>
<td>Tumor regression (% range)</td>
<td>-22% to -100%</td>
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</tbody>
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† For reference PFS in the TOGA² trial was 6.7 months

• Of the 6 patients with PD-L1 expressing tumors, 1 had a CR and 5 had a PR

• In 6 paired pre- and at progression biopsies, 2 patients had loss of ERBB2 amplification (mechanism of resistance)

CR, complete response; ERBB2, Erb-b2 Receptor Tyrosine Kinase 2 Gene; HER2, Human Epidermal Growth Factor Receptor 2; IHC, immunohistochemistry; mEGA, metastatic oesophagogastric adenocarcinoma; ORR, objective response rate; PFS, progression free survival; PR, partial response
HER2+ mEGA
RESULTS - SAFETY
• Results (37 patients enrolled, 31 evaluable for safety)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Results: AEs (&gt;10%) (N=31)</th>
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</thead>
<tbody>
<tr>
<td>Grade 2 fatigue</td>
<td>35%</td>
</tr>
<tr>
<td>Grade 2/3 nausea</td>
<td>35%</td>
</tr>
<tr>
<td>Grade 2 diarrhoea</td>
<td>26%</td>
</tr>
<tr>
<td>Grade 2 AST/ALT elevation</td>
<td>16%</td>
</tr>
<tr>
<td>Grade 2 neutropenia</td>
<td>16%</td>
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</table>

• Immune related toxicities observed in 1 patient each: Grade 2 colitis, Grade 3 interstitial nephritis, Grade 3 AST/ALT elevation; and resolved with steroids

Janjigian YY, et al. ASCO GI 2019, Abst #62
AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate transaminase; HER2, Human Epidermal Growth Factor Receptor 2; mEGA, metastatic oesophagogastric adenocarcinoma; N, number of patients
HER2+ mEGA

CONCLUSIONS

• Future plans
  – KEYNOTE-811: definitive randomised phase III trial

Janjigian YY, et al. ASCO GI 2019, Abst #62
HER2, Human Epidermal Growth Factor Receptor 2; mEGA, metastatic oesophagogastric adenocarcinoma
SAFETY AND EFFICACY OF DURVALUMAB FOLLOWING TRIMODALITY THERAPY FOR LOCALLY ADVANCED ESOPHAGEAL AND GEJ ADENOCARCINOMA: EARLY EFFICACY RESULTS FROM BIG TEN CANCER RESEARCH CONSORTIUM STUDY

Mamdani H, et al. ASCO GI 2019, Abst #5
EAC AND GEJ-AC

OBJECTIVES

• **Primary objective:** 1-year relapse-free survival with the hypothesis of increasing from historical control of 50% to 75%

• **Secondary objectives:** incidence and severity of treatment related adverse events

Mamdani H, et al. ASCO GI 2019, Abst #5
EAC, oesophageal adenocarcinoma; GEJ-AC; gastroesophageal junction adenocarcinoma
EAC AND GEJ-AC

DESIGN

- **Schema**
  - Single arm phase II study of durvalumab for 12 months
  - Durvalumab 1500mg IV every 4 weeks for up to 1 year after surgery

- **Eligibility**
  - Locally advanced oesophageal and GEJ-AC treated with neoadjuvant CRT, followed by R0 resection who had residual disease at the time of surgery (did not achieve pCR)
  - No biomarker selection for PD-L1 expression

Mamdani H, et al. ASCO GI 2019, Abst #5

CRT, chemoradiation therapy; EAC, oesophageal adenocarcinoma; GEJ-AC, gastroesophageal junction adenocarcinoma; IV, intravenous; pCR, pathologic complete response; PD-L1, antibody to programmed cell death ligand-1; R0, residual tumour stage 0
EAC AND GEJ-AC

RESULTS

Results in 24 patients

Primary endpoint: RFS at 1 year was 78.6%

Safety:

• 5 patients (20.8%) developed grade 3 AEs
  – diarrhoea, hepatitis, encephalopathy, hyperglycaemia and hypoglycaemia

• Most common grade 1 and 2 AEs were:
  – fatigue (33.3%)
  – nausea (25.0%)
  – cough (20.8%)
EAC AND GEJ-AC: CONCLUSIONS

- Adjuvant durvalumab is safe with a 1-year RFS of 79.2% in patients with EAC and GEJ-AC who have residual disease following trimodality therapy of neoadjuvant CRT followed by R0 resection

Mamdani H, et al. ASCO GI 2019, Abst #5
CRT, chemoradiation therapy; EAC, oesophageal adenocarcinoma; GEJ-AC, gastroesophageal junction adenocarcinoma; R0, residual tumour stage 0; RFS, relapse-free survival
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Email antoine.lacombe@cor2ed.com
Dr. Antoine Lacombe  
Pharm D, MBA  
Phone: +41 79 529 42 79  
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef  
MD  
Phone: +31 6 2324 3636  
froukje.sosef@cor2ed.com