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MEETING SUMMARY
ASCO GI 2019, San Francisco, USA

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CANCERS OF THE UPPER GI TRACT

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ABSTRACT OVERVIEW

- **KEYNOTE-181**
  - Exploring the role of immunotherapy in 2nd line oesophageal adenocarcinoma and squamous cell carcinoma
- **Janjigian et al. (MSKCC)**
  - Adding pembrolizumab to standard of care 1st 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

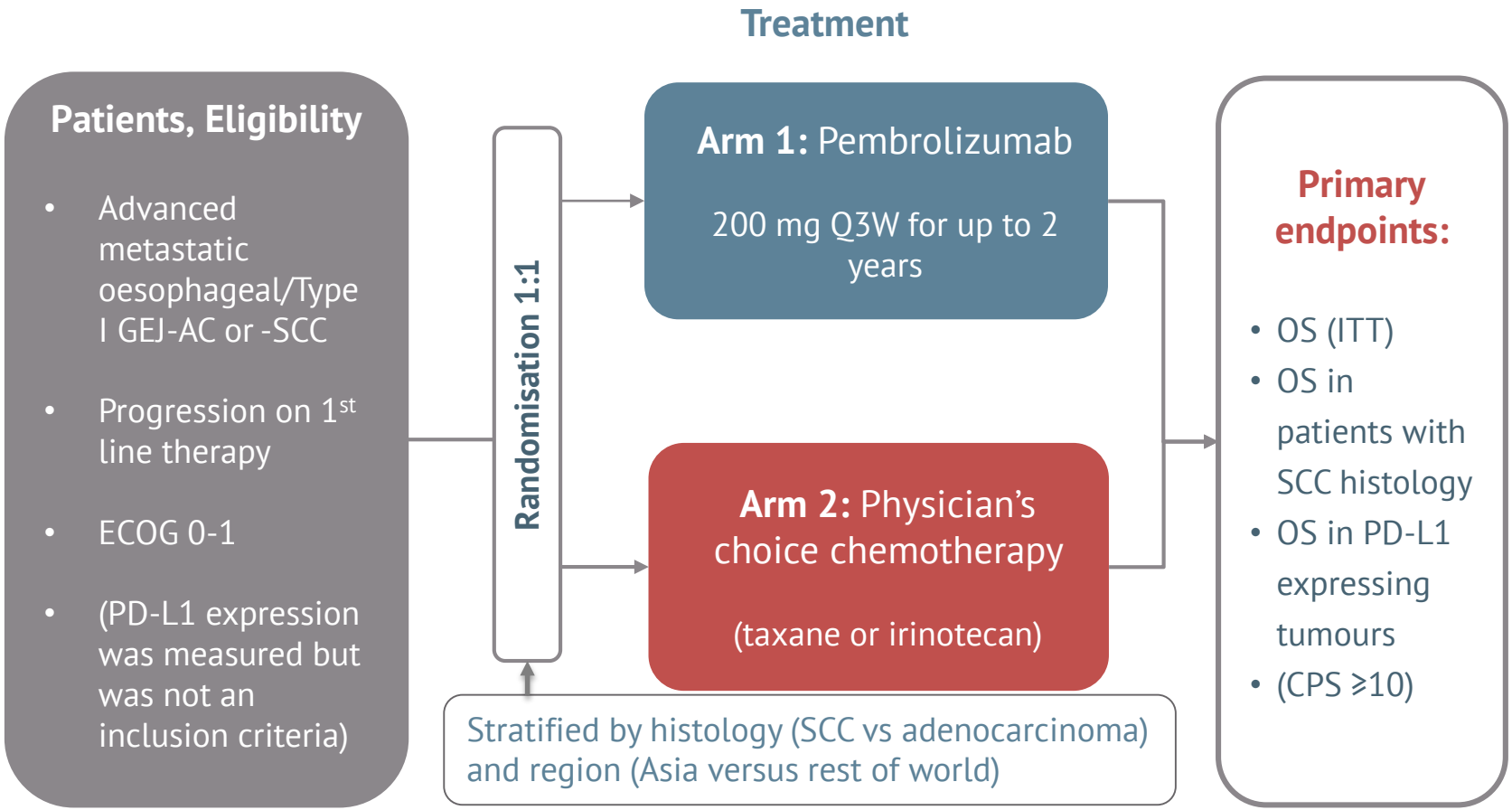
Kojima T, et al. ASCO GI 2019, Abst #2; Janjigian YY, et al. ASCO GI 2019, Abst #62; Mamdani H, et al. ASCO GI 2019, Abst #5
HER2, Human Epidermal Growth Factor Receptor 2; MSKCC, Memorial Sloan Kettering Cancer Center; R0, residual tumour stage 0

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



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

KEYNOTE-181
RESULTS

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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

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- The results of this study support pembrolizumab as a 2nd-line standard of care for oesophageal cancer with PD-L1 CPS ⩾10
- We await the results of the phase III KEYNOTE-590 study of pembrolizumab plus chemotherapy as 1st-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 1st 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**

Janjigian YY, et al. ASCO GI 2019, Abst #62

5-FU, fluorouracil; C, capecitabine; FISH, fluorescence in situ hybridization; HER2, Human Epidermal Growth Factor Receptor 2; IHC, immunohistochemistry; O, oxaliplatin; mEGA, metastatic oesophagogastric adenocarcinoma; P, pembrolizumab; PD-L1, programmed cell death ligand 1; PFS, progression free survival; T, trastuzumab; T-cell, thymocyte-derived lymphocyte

HER2+ mEGA
RESULTS - EFFICACY

- **Results (37 patients enrolled, 24 evaluable for efficacy)[1]**

Endpoint	Results (N=24)
PFS (median, months)	11.4†
ORR (% patients)	83%
Tumor regression (% patients)	100%
Tumor regression (%, range)	-22% to -100%

† For reference PFS in the TOGA[2] 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)

1. Janjigian YY, et al. ASCO GI 2019, Abst #62; 2. Bang Y-J et al, Lancet 2010; 376: 687-697

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)**

Endpoint	Results: AEs (>10%) (N=31)
Grade 2 fatigue	35%
Grade 2/3 nausea	35%
Grade 2 diarrhoea	26%
Grade 2 AST/ALT elevation	16%
Grade 2 neutropenia	16%

- 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%)

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

AEs, Adverse events; EAC, oesophageal adenocarcinoma; GEJ-AC; gastroesophageal junction adenocarcinoma; RFS, relapse-free survival

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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