LBA7_PR Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study

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Background: Nivolumab has a survival benefit for heavily pretreated patients with advanced or recurrent G/GEJ cancer. ATTRACTION-4 is a randomized, multicenter, phase 2/3 study to evaluate the efficacy and safety of nivolumab plus chemotherapy vs. chemotherapy as first-line treatment in patients with HER2-negative, advanced or recurrent G/GEJ cancer. Here we report the results of the double-blind phase III part.

Methods: Patients were randomized 1:1 to receive nivolumab plus chemotherapy (N+C, S-1 plus oxaliplatin or capecitabine plus oxaliplatin) or placebo plus chemotherapy (C). Nivolumab or placebo was intravenously administered every 3 weeks until disease progression or unacceptable toxicity. Tumor assessment was performed every 6 weeks through week 54, then repeated every 12 weeks. The co-primary endpoints were centrally-assessed PFS and OS, and it was prespecified that the primary objective is deemed to be achieved if at least one of the null hypotheses of the primary endpoints is rejected.

Results: A total of 724 Asian patients were randomized to N+C (n=362) or C (n=362) between Mar 7, 2017, and May 10, 2018. At the interim analysis primary for PFS with the median follow-up period of 11.6 mo, PFS was significantly improved in N+C vs. C (HR 0.68; 98.51% CI 0.51-0.90; p=0.0007; median PFS, 10.5 vs. 8.3 mo), meeting the primary endpoint. At the final analysis primary for OS with the median follow-up period of 26.6 mo, there was no statistically significant difference (HR 0.90; 95% CI 0.75-1.08; p=0.257; median OS, 17.5 vs. 17.2 mo), while PFS was continuously longer in N+C than in C. ORR was higher in N+C than in C (57.5 vs. 47.8%; p=0.0088). The incidences of grade 3 to 5 treatment-related adverse events were 57.9% in N+C and 49.2% in C.

Conclusions: PFS was significantly improved in N+C vs. C, achieving the primary objective. The combination of nivolumab and chemotherapy, which demonstrated clinically meaningful efficacy in PFS and ORR with a manageable safety profile but not statistically significant improvement in OS, can be considered a new first-line treatment option in advanced or recurrent G/GEJ cancer.

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LBA8_PR Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-590 study

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Background: KEYNOTE-590 (NCT03189719) is a randomized, international, double-blind study of 1L pembrolizumab (pembro) + chemotherapy (chemo) vs chemo alone in patients (pts) with locally advanced/unresectable or metastatic adenocarcinoma or

esophageal squamous cell carcinoma (ESCC) or Siewert type 1 esophagogastric junction adenocarcinoma (EGJ).

Methods: Eligible pts were randomized 1:1 to pembro 200 mg or placebo Q3W for up to 2 yr + chemo (cisplatin 80 mg/m2 Q3W [d1; 6 doses] + 5-FU 800 mg/m2 on d1-5 Q3W). Randomization was stratified by Asia vs Rest of World, adenocarcinoma vs ESCC, and ECOG PS 0 vs 1. Treatment continued until progression, unacceptable toxicity, or withdrawal, or 2 yr. No crossover was permitted. Primary end points were OS in pts with ESCC PD-L1 combined positive score (CPS) $\geq$10 tumors, and OS and PFS (RECIST v1.1 ; by investigator) in ESCC, PD-L1 CPS $\geq$10, and all pts. The secondary end point was ORR (RECIST v1.1; by investigator) in all pts. Data cutoff for interim OS/final PFS analysis was July 2, 2020.

Results: At data cutoff, 749 pts (83% male, 73% ESCC) were randomized (373 pembro + chemo; 376 chemo). Median follow-up was 10.8 mo. Pembro + chemo vs chemo was superior for OS in pts with ESCC CPS ≥10 (median 13.9 vs 8.8 mo; HR 0.57; 95% CI, 0.43-0.75; $P < 0.0001$), ESCC (median 12.6 vs 9.8 mo; HR 0.72; 95% CI, 0.60-0.88; P = 0.0006), CPS ≥10 (median 13.5 vs 9.4 mo; HR 0.62; 95% CI, 0.49-0.78; $P < 0.0001$), and all pts (median 12.4 vs 9.8 mo; HR, 0.73, 95% CI, 0.62-0.86; $P < 0.0001$). PFS was superior with pembro + chemo vs chemo in ESCC (median 6.3 vs 5.8 mo; HR 0.65; 95% CI, 0.54-0.78; $P < 0.0001$), CPS ≥10 (median 7.5 vs 5.5 mo; HR 0.51; 95% CI, 0.41-0.65; $P < 0.0001$), and all pts (median 6.3 vs 5.8 mo; HR 0.65; 95% CI, 0.55-0.76; $P < 0.0001$). Confirmed ORR was 45.0% vs 29.3% ($P < 0.0001$) in all pts, with median DOR of 8.3 vs 6.0 mo. Grade 3-5 drug-related AE rates were 72% vs 68%. Discontinuation rates from drug-related AEs were 19% vs 12%.

Conclusions: Pembro + chemo provided superior OS, PFS, and ORR vs chemo, with a manageable safety profile in pts with untreated, advanced esophageal and EGJ cancer. These data demonstrate that 1L pembro + chemo is a new standard of care in this pt population.

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LBA9_PR Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study

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Background: The risk of recurrence after neoadjuvant CRT followed by surgery (trimodality therapy) remains high in EC/GEJC and there is no established adjuvant treatment. CheckMate 577 is the first global, randomized, double-blind, phase 3 study to report the efficacy and safety of a checkpoint inhibitor in the adjuvant setting after trimodality therapy for EC/GEJC.

Methods: Adults with resected (R0) stage II/III EC/GEJC who received neoadjuvant CRT and had residual pathologic disease were randomized 2:1 to nivolumab 240 mg or placebo Q2W for 16 weeks, followed by nivolumab 480 mg or placebo Q4W. Maximum treatment duration was 1 year. The primary endpoint was disease-free survival (DFS).

Results: 794 patients were randomized (nivolumab, 532; placebo, 262). Approximately 70% of patients had adenocarcinoma and almost 60% had a pathologic lymph node status ≥ypN1 in both groups. At a pre-specified interim analysis, adjuvant nivolumab showed a statistically significant improvement in DFS vs placebo (HR 0.69 [96.4% CI 0.56 -0.86]; P = 0.0003); median DFS was doubled (22.4 vs 11.0 mo, respectively; Table). The majority of treatment-related adverse events (TRAEs) were grade 1 or 2. The frequency of serious TRAEs and TRAEs leading to discontinuation were ≤ 9% with nivolumab and 3% with placebo (Table). Data including DFS rate and an analysis of DFS across pre-specified subgroups will be presented.

Conclusions: Adjuvant nivolumab is the first therapeutic to provide a statistically significant and clinically meaningful improvement in DFS vs placebo and a well-tolerated safety profile in patients with resected EC/GEJC, who have received neoadjuvant CRT. These results represent the first treatment advance in many years for these patients, potentially establishing adjuvant nivolumab as a new standard of care.