Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/gastroesophageal junction (G/GEJ) cancer. ATTRACT: 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. ATTRACT-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) or chemotherapy alone (C). The median follow-up was 4 weeks (range: 3 weeks to 1 year). Treatment was given every 2 weeks for the first 2 cycles of C, N+C, or N+C plus nivolumab. Treatment was given every 6 weeks through week 54, then repeated every 12 weeks. The co-primary endpoints were centrally-assessed PFS and OS, and it was presupposed 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, 2016, and May 10, 2018. At the interim analysis primary for PFS with the median follow-up period of 11.6 months, PFS was significantly improved in N+C vs C (HR 0.69; 95% CI 0.51-0.90; p=0.0007; median PFS, 10.5 vs 8.3 months), meeting the primary endpoint. This primary for OS with the median follow-up of 14.9 months, 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 months), 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 combinatorial and clinical benefit of efficacy was demonstrated clearly 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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Nivolumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-950 study

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Background: KEYNOTE-950 (NCT03181979) 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 squamous cell carcinoma (SCC) of the esophagus.
esophageal squamous cell carcinoma (ESCC) or Siewert type I esophageagastic junction adenocarcinoma (EGI).

Methods: Eligible pts were randomized 1:1 to pembro 200 mg or placebo Q2W for up to 2 years (maximum 800 mg/m2 Q2W [d1; 6 dosages of 5-FU 800 mg/m2 on d1 and 6 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 and PFS at best response (CR) <10 tumors, and OS and PFS (RECIST v1.1; by investigator) in ESCC, PD-L1 CPS ≥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 placebo). Median follow-up was 8.0 mo. Pembro + 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 = 0.006), CPS ≥10 (median 13.5 vs 9.4 mo; HR 0.62; 95% CI, 0.49-0.78; P < 0.001), and all pts (median 12.4 vs 9.8 mo; HR; 0.73, 95% CI, 0.62-0.86; P < 0.001). 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 < 0.001). The risk of recurrence after neoadjuvant CRT followed by surgery (trilotherapy therapy) remains high in EG/EIC 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 trilotherapy therapy for EG/EIC.

Methods: Adults with resected (R0) stage II/III EC/EIC who received neoadjuvant CRT and had residual pathologic disease were randomized 2:1 to nivolumab 240 mg or placebo Q4W 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 pathological stage ≥T4N+ in both groups. At a pre-specified interim analysis, adjuvant nivolumab showed a statistically significant improvement in DFS vs placebo (HR 0.69 [95% 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.