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Original Research

Final results and outcomes by prior bevacizumab exposure, skin toxicity, and hypomagnesaemia from ASPECCT: randomized phase 3 non-inferiority study of panitumumab versus cetuximab in chemorefractory wild-type *KRAS* exon 2 metastatic colorectal cancer

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Abstract ***Purpose:*** The primary analysis of the ASPECCT study demonstrated that panitumumab was non-inferior to cetuximab for overall survival (OS) in patients with chemotherapy-refractory wild-type *KRAS* exon 2 metastatic colorectal cancer (mCRC). Here, we report the final analysis results of ASPECCT.
Patients and methods: Patients with wild-type *KRAS* exon 2 mCRC who progressed on or were intolerant to irinotecan- or oxaliplatin-based chemotherapy were randomised to receive panitumumab 6 mg/kg once every 2 weeks or cetuximab (400 mg/m^2) followed by 250 mg/m^2 weekly. The primary end-point was OS assessed for non-inferiority. Patients were followed for

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survival for 24 months after the last patient was randomised and a final analysis was conducted. No formal hypothesis testing was done. Post hoc analyses of outcomes by prior bevacizumab exposure, worst-grade skin toxicity (0–1 versus 2–4) and worst-grade hypomagnesaemia (0 versus 1–4) were conducted.

Results: Nine hundred ninety-nine patients were randomised and received ≥1 treatment dose (panitumumab, n = 499; cetuximab, n = 500). Median OS was 10.2 months with panitumumab versus 9.9 months with cetuximab (hazard ratio = 0.94; 95% confidence interval = 0.82–1.07). Median progression-free survival was 4.2 months with panitumumab and 4.4 months with cetuximab (hazard ratio = 0.98; 95% confidence interval = 0.87–1.12). Longer OS was observed for patients with increased skin toxicity and with hypomagnesaemia in both arms. Furthermore, OS was longer for patients with prior bevacizumab exposure treated with panitumumab than with cetuximab. The observed safety profiles were consistent with previous studies.

Conclusion: Consistent with the primary analysis, the final analysis of ASPECCT showed panitumumab was non-inferior to cetuximab for OS for patients with chemotherapy-refractory, wild-type *KRAS* exon 2 mCRC.

Trial registration: ClinicalTrials.gov, NCT01001377.

1. Introduction

For patients with metastatic colorectal cancer (mCRC), improvements in survival after irinotecan- or oxaliplatin-based chemotherapy in combination with targeted therapies [1–5] likely lead to an increase in patients eligible for third-line treatment. Panitumumab, a fully human monoclonal antibody targeting the epidermal growth factor receptor (EGFR), and cetuximab, a chimeric anti-EGFR antibody, have demonstrated clinical efficacy in patients with chemotherapy-refractory wild-type *KRAS* exon 2 mCRC [6–9]. In the phase 3 CO.17 study, cetuximab monotherapy improved overall survival (OS) and progression-free survival (PFS) versus best supportive care (BSC) in patients with wild-type *KRAS* exon 2 tumours [10,11]. Similarly, in the phase 3 20020408 study, panitumumab in combination with BSC improved PFS in patients with wild-type *KRAS* exon 2 mCRC, versus BSC alone [12–14]. A statistically significant OS benefit was not seen with panitumumab monotherapy in the 20020408 study, potentially because of patient crossover from the BSC arm (i.e. from BSC to panitumumab plus BSC after disease progression) [12].

ASPECCT was the first head-to-head, randomised, phase 3 study to evaluate efficacy and safety of panitumumab versus cetuximab for treatment of chemotherapy-refractory wild-type *KRAS* exon 2 mCRC. The primary analysis demonstrated that panitumumab was non-inferior to cetuximab, and the antibodies provided a similar OS benefit to this patient population (median, 10.4 months versus 10.0 months; Z-score = −3.19; $P = 0.0007$; hazard ratio [HR] = 0.97; 95% confidence interval [CI] = 0.84–1.11) [15]. Safety profiles were similar between groups [15]. We report results of the prespecified final descriptive analysis of outcomes in the ASPECCT study, which was planned for 24 months after the final patient was randomised, and results from ad hoc subgroup analyses by prior bevacizumab, skin toxicity, and hypomagnesaemia.

2. Patients and methods

2.1. Study design and patients

Detailed information regarding patient inclusion criteria, study design, and treatment schedules has been previously reported and is described in the Appendix [15]. The protocol received institutional/ethical approval at each site. Patients provided written informed consent.

2.2. Treatment

Patients received either panitumumab (6 mg/kg) intravenously on day 1 of each 14-day cycle or cetuximab at an initial dose of 400 mg/m^2 intravenously followed by 250 mg/m^2 intravenously on day 1 of each 7-day cycle. Patients in the cetuximab arm received treatment consistent with product labelling in their respective countries, including premedication with an H1 antagonist before infusion; premedication for infusion reaction was not required for panitumumab. Treatment continued until disease progression, intolerability or withdrawal of consent.

2.3. Study end-points

The primary end-point was OS (defined as time from randomisation to death) assessed for non-inferiority.