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Adjuvant FOLFOX4 with or without cetuximab (CTX) in patients (pts) with resected stage III colon cancer (CC): DFS and OS results and subgroup analyses of the PETACC8 Intergroup Phase III Trial

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Body

Background: The potential benefit of adding CTX to the current standard treatment for stage III CC, was assessed. Subgroup analyses of demographic, oncologic and molecular data may improve our understanding of this patient population. Methods: CC pts were randomized 28-56 days following resection. They received 12 biweekly cycles of oxaliplatin 85 mg/m2 day (d) 1, with leucovorin 200 mg/m2, 5-FU 400 mg/m2 bolus IV, followed by 5-FU 600 mg/m2 22-hr IV on d1-2 (FOLFOX4), without (arm A) or with weekly CTX (arm B) 250 mg/m2 (initial dose 400 mg/m2, cycle 1). Primary endpoint was disease free survival time (DFS). Secondary endpoints included overall survival (OS), treatment compliance and safety. Planned accrual of 1,407 KRAS wild-type (wt) pts provided 90% power to detect a hazard ratio (HR) of 0.75 with 2-sided α=0.05, with interim analyses after 65% of planned events. Preplanned subgroup analyses were performed. Results: 1,602 KRAS wt pts (811 arm A, 791 arm B), were randomized. BRAF status was determined in 1134 (71%) KRAS wt pts; median follow-up ~40 months. This interim analysis showed no difference between arms for DFS (HR 1.047, 95% CI 0.85, 1.29; p=0.66) or OS (HR 1.09, 95% CI 0.81, 1.46; p=0.55) in KRAS wt pts or for DFS (HR 0.985, 95% CI 0.75, 1.28; p=0.91) or OS (HR 0.98, 95% CI 0.67, 1.44; p=0.92) in KRAS/BRAF wt pts (n=984). Worse outcomes were seen with CTX in pts >70 years (n=149, DFS: HR 1.97, 95% CI 0.99, 3.93; p=0.051), in females (n=666, HR 1.45, 95% CI 1.03, 2.02; p=0.03) and pts with right-sided CC (n=570, HR 1.40, 95% CI 1.01, 1.94; p=0.04). Conversely, a trend towards a better outcome was seen in pts with poor prognosis tumors (high grade, T4, N2, perforation/obstruction, VELI+) and was significant in pts with pT4N2 at diagnosis (n=146, HR 0.55, 95% CI 0.35-0.88; p=0.01). Conclusions: In this trial adding CTX to FOLFOX4 offered no benefit to pts with resected stage III KRAS wt and KRAS/BRAF wt CC. Subgroup analyses in this large population suggest that pts with pT4N2 tumors may receive some benefit from CTX in this setting. MSI status determination is ongoing to explore its interaction with poor outcome in female pts and those with right-sided tumors. Supported by Merck-Serono, Sanofi-Aventis.

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