7LB Late Breaking

Analysis of KRAS mutations in patients with metastatic colorectal cancer receiving panitumumab monotherapy

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Background: Panitumumab (Pmab), a fully human antibody against the epidermal growth factor receptor (EGFr), is approved for treating metastatic colorectal cancer (mCRC) in the USA. The molecular alterations that predict for responsiveness to anti-EGFr antibodies are unknown. Though mutations in KRAS (a small G protein that acts downstream of EGFr) have been correlated with lack of response to anti-EGFr antibodies in CRC, the importance of KRAS mutations in identifying patients who could benefit from therapy has not been assessed in randomized, controlled trials (RCT).

Materials and Methods: KRAS status was assessed in tumor samples from a phase 3, RCT of Pmab (6 mg/kg every two weeks) plus best supportive care (BSC) vs BSC alone in chemorefractory mCRC. BSC patients (pts) with disease progression (PD) could cross over to receive Pmab, and tumor status was assessed by blinded central review per RECIST criteria. Activating KRAS mutations were detected using real-time PCR on DNA from fixed tumor sections. The primary objective was to examine if Pmab efficacy on progression-free survival (PFS) was significantly greater in pts with wild-type (WT) KRAS vs mutant KRAS.

Results: KRAS status was determined in 427 of 462 randomized pts (208 Pmab; 219 BSC alone); 43% of pts had tumors bearing mutant KRAS. The hazard ratios (HRs) for PFS (comparing Pmab:BSC) were 0.45 (95%CI, 0.34–0.59) in the WT KRAS group and 0.99 (95%CI, 0.73–1.36) in the mutant KRAS group ($p < 0.0001$ using a quantitative-interaction test to compare HRs). Median time to PFS in Pmab pts was 12.3 weeks (wks) and 7.4 wks in the WT and mutant KRAS groups, respectively. Median time to PFS in pts who had BSC alone was 7.3 wks in both KRAS groups. For Pmab pts, 17% responded and 34% had stable disease in the WT KRAS group compared with a 0% response rate and 12% with stable disease in the mutant KRAS group. Of 168 BSC pts who crossed over to receive Pmab (77% of all BSC pts; median time of 7 wks), 20/91 (22%) in the WT KRAS subset and 0/77 (0%) in the mutant KRAS subset responded. When treatment (tx) arms were combined, WT KRAS status identified a group with longer OS compared with mutant KRAS (HR = 0.67, 95% CI, 0.55–0.82). Consistent with longer panitumumab exposure, more tx-related grade 3 toxicities occurred in pts with WT KRAS (25%) vs pts with mutant KRAS (12%). No grade 4 tx-related events were reported.

Conclusions: Efficacy of Pmab monotherapy in CRC is confined to pts with tumors lacking KRAS mutations. Thus, KRAS status should be considered as a selection marker in CRC pts who are candidates for Pmab monotherapy.

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