Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406).

Sub-category: Advanced Disease

Category: Gastrointestinal (Colorectal) Cancer

Meeting: 2017 ASCO Annual Meeting

Abstract No: 3505

Citation: J Clin Oncol 35, 2017 (suppl; abstr 3505)

Author(s): Scott Kopetz, Shannon L McDonough, Heinz-Josef Lenz, Anthony Martin Magliocco, Chloe Evelyn Atreya, Luis A. Diaz, Carmen Joseph Allegra, Kanwal Pratap Singh Raghav, Van Karlyle Morris, Stephen E. Wang, Christopher Hanyoung Lieu, Katherine A Guthrie, Howard S. Hochster; The University of Texas MD Anderson Cancer Center, Houston, TX; Fred Hutchinson Cancer Research Center, Seattle, WA; Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL; University of California, San Francisco, San Francisco, CA; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Florida, Gainesville, FL; GI Medical Oncology Department, The University of Texas MD Anderson Cancer Center, Houston, TX; Kaiser Permanente, Sacramento, CA; University of Colorado, Denver, CO; Yale Cancer Center, New Haven, CT

Abstract Disclosures

Abstract: Background: Metastatic colorectal cancer (mCRC) patients (pts) with BRAFV600 mutations have poor outcomes with standard of care chemotherapy and rarely respond to the BRAF inhibitor vemurafenib. In preclinical models, blockade of BRAFV600 by vemurafenib (V) causes feedback upregulation of EGFR, whose signaling activities can be impeded by cetuximab (C) with anti-tumor activity augmented by irinotecan (I). Methods: Pts with BRAFV600 mutated and extended RAS wild-type mCRC were randomized to irinotecan (180 mg/m^2 IV every 14 days) and cetuximab (500 mg/m^2 IV every 14 days) with or without vemurafenib (960 mg PO twice daily). Eligible pts had ECOG PS ≤1, and had received 1 or 2 prior regimens with no prior anti-EGFR agents. Randomization was stratified for prior irinotecan. Crossover from the control arm (IC) to the experimental arm (VIC) was allowed after documented progression. The primary endpoint was progression-free survival (PFS, investigator assessed), with 90% power to detect a HR of 0.5, with two-sided type 1 error of 5%. Results: 106 pts were enrolled (99 eligible, 49 in the experimental arm) from 12/2014 to 4/2016, with median age 62 years, 59% female, and 39% with prior irinotecan therapy. PFS was improved with the addition of vemurafenib (HR 0.42, 95% confidence interval [CI] 0.26 to 0.66, P < 0.001) with median PFS of 4.4 (95% CI 3.0 – 6.1) mos vs 2.0 (95% CI 1.8 – 2.1) months. Response rate was 16% vs 4% (P = 0.08), with disease control rate of 67% vs 22%. In pts with no prior irinotecan, median PFS was 5.7 (95% CI 3.0-6.1) months in the VIC arm vs 1.9 (95% CI 1.7 – 2.1) months in the IC arm. Grade 3/4 adverse events higher in the VIC arm included neutropenia (28% vs 7%), anemia (13% vs 0%), and nausea (15% vs 0%). There was no increase in skin toxicity or fatigue. 23 pts (46%) in the IC arm crossed over at the time of progression, with median PFS from crossover of 6.0 months (95% CI 3.7 – 7.4). Overall survival (OS) data will be mature for ASCO 2017. Conclusions: These results demonstrate the clinical benefits of the VIC triplet (vemurafenib, cetuximab, and irinotecan) in pts with treatment-refractory BRAFV600 mutated mCRC, and support VIC as a potential new treatment option in this molecular subset. Clinical trial information: NCT02164916