Molecular characterization of metastatic colorectal cancer (mCRC) in patients (pts) treated with cetuximab and pembrolizumab.

Christos Fountzilas, Spencer Rosario, Henry G. Withers, Sarbajit Mukherjee, David L Bajor, Joel N. Saltzman, Chong Wang, Kristopher Attwood, Erik S. Knudsen, Agnieszka K Witkiewicz, Renuka V. Iyer, Patrick M Boland; Division of GI Medicine, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY; Roswell Park Comprehensive Cancer Center, Buffalo, NY; University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH; Cleveland Clinic, Cleveland, OH; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: Anti-EGFR therapy has the potential to increase a localized anti-tumor immune response. We recently published the results of a phase Ib/II trial of the anti-EGFR antibody cetuximab in combination with the anti-PD1 antibody pembrolizumab in pts with advanced, RASwt CRC (PMID: 34645646). Despite its partial local immunologic efficacy, this combination of cetuximab and pembrolizumab was inactive. Here we present the results of comprehensive molecular characterization of pts with tumors amenable to DNA and RNA sequencing. **Methods:** Forty-two pts with RASwt mCRC were treated with cetuximab plus pembrolizumab. Archival or fresh tumor samples were obtained at baseline and, in select patients, on-treatment. Tumor samples underwent targeted DNA sequencing and whole transcriptome sequencing. Gene set enrichment analysis (GSEA), metabolic dysregulation assessment, and immune deconvolution were performed. Genomic data were linked to clinical outcomes. **Results:** Eighteen pts had tissue available for dual DNA/RNA extraction and sequencing. Of these, 10 had available matched on-treatment tumor samples. The most common mutations detected in protein coding regions were *TP53* (14 pts), *ERBB4* (5 pts), *CDKN2A* and *APC* (6 pts each). There were no statistically significant differences in progression-free survival (PFS) in pts with and without resistance-associated mutations (i.e., *RAS, MET, ERBB4*). Further, there was no significant difference associated with the consensus molecular subtype (CMS). However, when we compared patients with stable/increased tumor change percentage to those with decreased tumor change percentage, we found downstream transcriptional differences associated with altered metabolism, and in particular lipid and amino acid metabolism. **Conclusions:** We identified a significant number of patients with mutations predicting resistance to either or both cetuximab and pembrolizumab; however, none were associated with survival. However, we did identify metabolic pathways of interest, which may be associated with response to therapy. It is important to note, our analysis is limited by the small number of specimens (Trial registration NCT02713373). Clinical trial information: NCT02713373. Research Sponsor: Roswell Park Alliance Foundation, Merck Sharp & Dohme LLC.