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Presentation Abstract

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Presentation Title:	***Ex vivo* kinome profiling of tumors from rectal cancer patients for possible identification of functional biomarkers of EGFR signaling pathway druggability**
Location:	West Hall, Level One, Moscone Center West
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Abstract Body:	In order to optimize and individualize therapeutic efficacy of tyrosine kinase inhibiting agents, it seems rational to exploit the specific pattern of tyrosine kinase activity of the patient's tumor as functional biomarker of druggability. Ample research has focused on identifying biomarkers for the optimum selection of patients with metastatic colorectal cancer to treatment with drugs targeting tyrosine kinase signaling mediated by EGFR. The present study examined to which degree tumor kinase activity might reflect mutations within *KRAS*, *BRAF*, and *PIK3CA* genes, encoding effector proteins downstream of EGFR in the signaling cascade, which have been shown to correlate with intrinsic therapeutic resistance to anti-EGFR monoclonal antibodies. Primary tumors from 63 patients with locally advanced rectal cancer, enrolled onto a prospective study of chemoradiotherapy followed by radical surgery, were biopsied at the time of diagnosis. Mutations in *KRAS* exon 2, *BRAF* exon 15, and *PIK3CA* exons 9 and 20 were determined by denaturant capillary electrophoresis of PCR-amplified gene sequences. Using peptide arrays with tyrosine kinase substrates, phosphopeptide signatures were generated from the tumor biopsies. A model for predicting tumor *KRAS/BRAF* mutation status from the tyrosine kinase activity profile was obtained by partial-least-squares discriminant analysis and evaluated by 20-fold cross validation. Distribution of parameters between different groups was compared using Pearson's Chi-square exact two-sided test, and metastasis-free survival was estimated by the Kaplan-Meier method. Mutation in *KRAS* (p.G12D, p.G12V, p.G13D, p.G12C, p.G12S, or p.G13S), *BRAF* (p.D594G or

p.V600E), and *PIK3CA* was detected in 35%, 6.3%, and 9.5% of cases, respectively, and with the exception of one case, single tumor mutations were found. No differences were observed between patients harboring mutated and non-mutated tumors regarding radiological TNM stage at diagnosis, histological ypTN stage or histomorphologic tumor regression grade of the surgical specimens following the chemoradiotherapy, or development of metastatic disease at median follow-up of 43 months (range 7-65). *Ex vivo* tumor kinase activity profiles were derived from 102 peptide array substrates after substrate signal intensity had been normalized to the mean signal intensity of *KRAS/BRAF* wild-type samples. Using the generated phosphopeptide profiles, correct prediction of tumor *KRAS/BRAF* mutation status was obtained in 67% of cases. No improvement of prediction accuracy was achieved on inclusion of another layer of information, namely *PIK3CA* mutations, to the group of mutated tumor samples. Phosphorylation of 11 peptide array substrates by tumor samples was significantly higher in the *KRAS/BRAF* wild-type cases, with a majority of the phosphosubstrates representing factors involved in the EGFR signaling pathway. In conclusion, tumor tyrosine kinase activity did not strongly reflect *KRAS/BRAF* mutation status in rectal cancer. However, our findings may add to the ongoing debate on the current practice of selecting patients with metastatic colorectal cancer for anti-EGFR antibody treatment solely from the tumor *KRAS/BRAF* mutation status.

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