3589 General Poster Session (Board #7H), Sun, 2:00 PM - 6:00 PM

Analysis of EGFR pathway mediators in KRAS wild-type primary tumors is not representative of their status in related metastases. *P. Cejas, M. Lopez-Gomez, C. Aguayo, R. Madero, J. De Castro, C. Belda-Iniesta, J. Barriuso, E. Burgos, M. Gonzalez-Baron, J. Feliu; Translational Oncology Unit IIB/CSIC/HULa Paz, Madrid, Spain; Hospital Infanta Sofia, San Sebastian de los Reyes, Spain; Department of Medical Oncology, La Paz University Hospital, Madrid, Spain; Biostatistics Unit, La Paz University Hospital, Madrid, Spain; Department of Pathology, La Paz University Hospital, Madrid, Spain*

Background: KRAS mutated CRC patients are nonresponsive to anti-EGFR. In contrast, the clinical benefit of KRAS wild type is uncertain and needs further studies. Our retrospective study compared the status of the most relevant EGFR pathway downstream regulators between primary tumors and related metastases of KRAS wild type patients. **Methods:** One hundred and seventeen pairs of primaries and metastases from patients diagnosed with CRC were tested for KRAS mutated status. Wild type KRAS pairs were further analyzed downstream for EGFR mediators and for EGFR itself. Pair concordance and impact of clinicopathological variables was analyzed. Patients were anti-EGFR therapy naive. **Results:** The level of concordance in the presence of KRAS mutations was 92% between the primary tumor and the related metastases. KRAS wild type pairs were analyzed for BRAF and PI3KCA mutational status and for EGFR and pAKT expression and PTEN lost in patients pairs and levels of concordances were 100%, 94%, 61%, 53% and 73% respectively. Of the 61% KRAS wild type patients, only 18% showed complete concordance between the primary tumor and the related metastases for the rest of the five markers analyzed. Thus, 82% of KRAS wild type pairs showed a different EGFR pathway status between the primary tumor and the related metastasis. **Conclusions:** In this most extensive study to date of tumoral pairs, results show that for 82% of the KRAS wild type patients, the analysis of the primary tumor is not representative of the related metastases, suggesting the need for rebiopsy of the metastases to adjust the anti-EGFR therapy predictive value of some EGFR mediators.

3590 General Poster Session (Board #8A), Sun, 2:00 PM - 6:00 PM

Association of GRP78 polymorphisms with response and TTP in patients with mCRC treated with FOLFOX/BV or XELOX/BV. *H. Lenz, W. Zhang, D. Yang, A. B. El-Khoueiry, Y. Ning, A. Pohl, P. O. Bohanes, K. D. Danenberg, T. Winder; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Response Genetics, Los Angeles, CA*

Background: GRP78, a major endoplasmatic chaperone, is suggested to be critical for tumor angiogenesis. Recent data suggested GRP78 protein overexpression as a major player in tumor recurrence and poor survival by protecting cancer cells from apoptosis, promoting metastasis and chemoresistance to doxorubucin hydrochloride in breast tumors. We tested whether germ-line polymorphisms within the GRP78 gene were associated with clinical outcome in mCRC patients treated with FOLFOX/BV or XELOX/BV and investigated if there is a correlation with gene expression levels of VEGF and its receptors. **Methods:** gDNA was isolated from peripheral blood of 91 patients with mCRC and three potentially functional genotypes (rs391957, rs12009, rs17840761) within the GRP78 gene were determined using PCR-RFLP. mRNA was extracted from laser-capture-microdissected tumor tissue. Intratumoral gene expression levels of VEGF and VEGFR-1,-2 and -3 from 79 patients with mCRC were analyzed by RT-PCR. **Results:** In univariate analysis two GRP78 SNPs (rs391957 and rs12009) were significantly associated with TTP (Table). In multivariate analysis GRP78rs391957 remained significantly associated with TTP (adjusted p value=0.012). Moreover, two GRP78 polymorphisms (rs391957 and rs12009) were in linkage disequilibrium (D'=0.93 and r^2=0.73). Patients harbouring the C-A-T haplotype were at lowest risk to develop tumor progression [HR 0.49 (CI 95 %; 0.29-0.82)] and showed the highest response rate [OR 2.56(CI 95%;1.07- 6.22)]. The three tested GRP78 polymorphisms were not associated with gene expression levels of VEGF or its receptors (p values > 0.05). **Conclusions:** Our data suggest that polymorphisms in GRP78 gene may be potential predictive markers to FOLFOX/BV or XELOX/BV therapy in mCRC patients. Moreover, GRP78 polymorphisms may play a major role in VEGF-independent tumor angiogenesis.

Univariate analysis	N	Time to progression Median, months (95% CI)	P* value
GRP78rs391957			0.004
CC	33	7.9 (6.9, 12.4)	
CT	35	15.8 (10.8, 22.9)	
TT	5	19.9 (1.9, 38.6)	
GRP78rs12009			0.021
TT	31	8.1 (7.0, 11.7)	
TC	36	13.9 (10.8, 22.2)	
CC	7	19.9 (7.8, 38.6)	
GRP78rs17840761			0.074
AA	22	8.3 (6.9, 15.0)	
AG	41	12.4 (8.1, 17.0)	
GG	13	13.9 (12.4, 38.6)	

* Log-rank test.

3591 General Poster Session (Board #8B), Sun, 2:00 PM - 6:00 PM

Lessons from PETACC 2: No prognostic impact of KRAS-/BRAF-status in stage III colon cancer treated with adjuvant 5-FU monotherapy. *D. E. Aust, M. P. Lutz, M. Mauer, I. Popov, G. B. Baretton, L. Bedenne, A. Carrato, C. Kohne; University Hospital Carl Gustav Carus, Dresden, Germany; Caritasklinik St. Theresia, Saarbruecken, Germany; EORTC Headquarters, Brussels, Belgium; Institute for Oncology and Radiology of Serbia, Belgrade, Serbia and Montenegro; University Hospital, Dijon, France; Servicio de Oncologia, Hospital Ramón y Cajal, Madrid, Spain; Onkologie Klinikum Oldenburg, Oldenburg, Germany*

Background: KRAS and possibly BRAF mutations are negative predictors for anti-EGFR therapy in colorectal cancer. The prognostic impact of these mutations is less clear. This study aimed to assess the correlation of KRAS/BRAF status with morphological characteristics and its prognostic impact for long-term outcome in UICC stage III colon cancer (CC). **Methods:** FFPE material from 493 patients treated with adjuvant 5-FU/FA in the PETACC2 trial (ClinicalTrials.gov NCT00004150) was collected retrospectively. KRAS mutations were detected by direct sequencing (ABI Prism 310), BRAF mutations by pyrosequencing (Pyromark Q24). Statistical analysis was done using Fisher exact test and Kaplan Meier survival analyses (level of significance:0.05). **Results:** Neither KRAS nor BRAF mutations were associated with patient age or patient sex. KRAS mutations did also not correlate with any pathological parameters. BRAF mutations, however, were significantly more frequent in mucinous (n = 12/45; 26.7%) than in nonmucinous carcinomas (n = 36/408; 8.8%, p = 0.001). BRAF mutations were also associated with higher pT stage (p = 0.016): while pT1 and pT2 tumors showed BRAF mutations in 0 (n = 0/13) and 5.1% (n = 2/39), pT3 and pT4 tumors showed them in 9.2% (n = 32/347) and 20.2% (n = 17/84). BRAF-mutation frequency increased with decreasing histologic differentiation (p = 0.002): only 1.9% of grade 1 (n = 1/35) and 8.2% of grade 2 (n = 26/316) whereas 18.8% of the grade 3 tumors (n = 24/128) had a BRAF mutation. Location in the right-sided colon was correlated with BRAF mutation (p = 0.034): 15.4% of the right-sided tumors (n = 23/149) showed a mutation as opposed to 8.4% of the left sided tumors (n = 25/298). Neither KRAS nor BRAF status showed any impact on disease-free and overall survival in univariate analyses. After 3 years, 63% of the patients with KRAS mutation, 68% with KRAS/BRAF wildtype (HR 0.89) and 65% with BRAF mutation (HR 1.08) were still alive. **Conclusions:** KRAS/BRAF status has no prognostic impact in stage III CC treated with adjuvant 5-FU/FA therapy. While BRAF mutations are associated with tumor location, histological type, differentiation and pT stage, KRAS mutations are not.

3592 General Poster Session (Board #8C), Sun, 2:00 PM - 6:00 PM

Differences in sites of metastatic disease and outcomes observed in patients with BRAF mutant colorectal cancers. *B. Tran, S. Kopetz, J. Tie, P. Gibbs, Z. Jiang, C. H. Lieu, A. Agarwal, D. Maru, O. Sieber, J. Desai; Royal Melbourne Hospital, Melbourne, Australia; University of Texas M. D. Anderson Cancer Center, Houston, TX; Ludwig Colon Cancer Initiative Laboratory, Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Australia; Royal Melbourne Hospital, Parkville, Australia; Ludwig Institute for Cancer Research, Parkville, Australia; Royal Melbourne Hospital and Cancer Trials Australia, Melbourne, Australia*

Background: It has been hypothesized that BRAF mutant cancers represent a distinct subset of colorectal cancer (CRC), with $BRAF^{V600E}$ mutant metastatic CRC patients appearing to have a significantly poorer survival than the BRAF wild-type population. Resistance to antibodies targeting EGFR may be one contributing factor but this alone does not explain all observed survival differences. This study investigates whether there are differences in sites of metastatic disease between $BRAF^{V600E}$ and wild-type patients, a possible contributor to poorer outcomes. **Methods:** Data was collected from two major centers using prospective databases supplemented by review of medical records. All patients with known BRAF mutation status were analyzed for sites of metastatic disease and clinical characteristics. Differences in sites of metastases between $BRAF^{V600E}$ and wild-type populations were analyzed using Fisher's exact test. **Results:** We identified 524 metastatic CRC patients with known BRAF mutation status. $BRAF^{V600E}$ was identified in 57 patients (11%) with the remaining 467 patients all wild-type. $BRAF^{V600E}$ patients trended to older ages (median age 66 v 63, p = 0.175), were more likely to have a right sided primary (67% v 34%, p < 0.0001) and had poorer overall survival (median 10.4 v 34.7 months, p < 0.0001). There was no difference in proportion of liver metastases between the $BRAF^{V600E}$ and wild-type groups (63% v 72%, p = 0.163). However there was a significantly lower incidence of lung metastases (35% v 49%, p = 0.049) and higher incidence of peritoneal metastases (46% v 24%, p = 0.001). Data regarding the rate of CNS metastases suggests a clinically significant but not statistically significant difference (8.8% v 4.7%, p = 0.199). **Conclusions:** Patients with BRAF mutant CRC appear to have a distinct pattern of metastatic spread. Our data provides further evidence that this population represents a distinct subset of CRC. Further confirmatory data should explore whether BRAF mutant CRC is associated with an increased rate of peritoneal and brain metastases, known adverse prognostic factors in CRC, as this may be one factor contributing to the inferior outcome in this patient subgroup.