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P-142 Early gastric cancer: Identification of molecular markers able to distinguish penetrating lesions with different prognosis

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Background: Early Gastric Cancer (EGC) represents 25% of the gastric cancers surgically treated and is usually characterized by a good prognosis (5-year survival >90%). However, some patients show a significantly worse prognosis. In particular, among penetrating EGCs classified according to Kodama's criteria, Pen A tumors are characterized by extensive submucosal invasion, lymph node metastases, and worse prognosis, whereas Pen B tumors seem to be associated with a better prognosis.

The aim of the study was to characterize the differences between Pen A, Pen B and locally advanced gastric cancers (T3N0) in order to identify biomarkers involved in aggressiveness and clinical outcome of such tumors.

Methods: Formalin-fixed paraffin-embedded (FFPE) tissues were obtained from 87 patients (33 Pen A, 34 Pen B, and 20 T3N0 tumors), matched for age, gender and lymph nodes status. Mucins analysis (MUC2, MUC6, MUC5AC) was performed by immunohistochemistry; copy number variation (CNV) analysis by multiplex ligation-dependent probe amplification (MLPA); TP53 mutational status by Sanger sequencing; TP53 loss of heterozygosity (LOH) and microsatellite instability (MSI) evaluations by fragment analysis.

Results: MUC6 expression significantly distinguished Pen A and Pen B tumors, being overexpressed in 33.3% and 2.9% of the two subgroups, respectively (p=0.014). CNV evaluation of PIK3CA, EGFR, CDK6, MET, GATA4, FGFR1, MYC, PTP4A3, FGFR2, CCND1, KRAS, KLF5, ERBB2, TOP2A, GATA6, and CCNE1 genes showed that amplification was the most frequently observed alteration, but the only gene that was significantly different between tumor groups was the GATA6 gene (p=0.02), amplified in 33.3% and 66.7% of Pen A and Pen B, respectively. The evaluation of MSI showed no significant differences between Pen A and Pen B. Finally, TP53 gene analysis showed that 34.0% of Pen tumors have a mutation in TP53 exons 5-8 and 38.5% has LOH, suggesting the early onset of alterations of this gene in gastric carcinogenesis. No differences between Pen A and Pen B tumors were observed in terms of TP53 mutation frequency and site of mutation, even if a different frequency of TP53 missense variants was detected (78% of Pen A and 67% of Pen B tumors). Preliminary data showed that TP53 mutation and LOH co-occur mainly in Pen A tumors with respect to Pen B (p=0.001).

Conclusion: Overall, our analyses revealed that clinicopathological parameters, microsatellite status and frequency of TP53 mutations do not seem to distinguish Pen A and Pen B tumors. Alternatively, the overexpression of gastric mucin MUC6 significantly characterized Pen A tumors, as well as the amplification of the GATA6 gene was associated with Pen B tumors. The co-occurrence of TP53 mutations and LOH in EGC needs further investigations.

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P-143 Lack of expression of CDX2: Prognostic biomarker in stage IV colorectal cancer

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Background: Lack of expression of caudal homeobox 2 transcription factor (CDX2) is associated with a high risk of relapse in patients with stage II / III colon cancer after complete surgical resection, but its role in metastatic colorectal cancer (CRC) remains uncertain.

Methods: Patients with metastatic CRC at diagnosis treated at our institution and with available histological material from the primary tumor were selected. Patient tissue microarrays were performed and the samples analyzed by immunohistochemistry. We defined CDX2 negativity as an absence of expression of CDX2 in IHC in archived tumor tissue. Retrospective analysis of all patients diagnosed with RCC between January 2011 and December 2017 was performed. Demographic, clinical and survival data were analyzed using SPSS v24. A multivariate analysis was performed using the Cox proportional hazard regression model.

Results: We included 125 patients, with male predominance (n=73). The median age at metastatic diagnosis was 65 years and 105 patients had colon cancer. In total, 52.8% (n=66) of the patients had liver metastasis. Median overall survival was 17,66 months (95%CI 11,98-23.34) for a median follow up time of 17,66 months (0.03-91.81 months). 38 patients had a loss of CDX2 expression, and 87 patients had CDX2 positive. We have found that the CDX2 positive correlates with a lower risk of death (HR 0.44 (95%CI 0.26-0.73) p=0.002) as well as a decreasing trend in the likelihood of progression with first-line chemotherapy (HR 0.86 (95%CI 0.44-1.66) p=0.942). In total, 19% of patients CDX2 negative versus 12.1% CDX2 positive were grade 3 (p = 0.540). 53% of CDX2 negative were women versus 47.4% men (p = 0.073). Focusing on the metastasization sites, 22.75% of CDX2-negative had hepatic metastasis and 50% had peritoneal metastasis. 77.3% of patients with CDX2 positive tumours had liver metastasis. Partial responses were more frequent in CDX2 positive patients. We detected a negative predictive value (NPV), about 75-80%, for death/progression in the first 6 months after metastatic diagnosis.

Conclusion: CDX2 negativity was associated with a higher risk of death and a trend for increased risk of progression after first-line ChT. Due to the high NPV, patients are less likely to die or progress at 6 months when they have CDX2 positive mCRC.

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P-144 Infigratinib versus gemcitabine plus cisplatin as first-line therapy in patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations: phase 3 PROOF trial

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Background: Treatment options for metastatic or unresectable cholangiocarcinoma are limited with a need to provide increased disease control, improved outcomes, and targeted therapy that is less toxic than standard chemotherapy. As the understanding of the molecular landscape of cholangiocarcinoma has increased, the fibroblast growth factor receptor (FGFR) family has been found to play an important role in cholangiocarcinoma. FGFR translocations (i.e. fusion events) represent driver mutations in cholangiocarcinoma. They are present in 13−17% of intrahepatic cholangiocarcinomas (IHC) and may predict tumor sensitivity to FGFR inhibitors. Infigratinib (BGJ398) is an ATP-competitive, FGFR1−3 selective oral tyrosine kinase inhibitor that demonstrated excellent preliminary anti-tumor activity in patients with relapsed/refractory cholangiocarcinoma with FGFR2 fusions/translocations in a phase 2 study (CBJG398X2204) [Javle et al. J Clin Oncol 2018]. The PROOF trial is evaluating infigratinib versus current standard-of-care gemcitabine + cisplatin in front-line patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations (ClinicalTrials.gov identifier: NCT03773302).

Trial design: PROOF is a multicenter, open-label, randomized, controlled, phase 3 trial. Patients with previously untreated advanced/metastatic or inoperable cholangiocarcinoma with FGFR2 gene fusions (determined by local CLIA-certified or central laboratory) are randomized 2:1 to oral infigratinib 125 mg once daily for 21 days of a 28-day treatment cycle versus intravenous standard gemcitabine (1000 mg/m^2) + cisplatin (25 mg/m^2) on days 1 and 8 of a 21-day cycle. Treatment will continue until confirmed progressive disease by central review, intolerance, withdrawal of informed consent, or death. Patients assigned to the gemcitabine + cisplatin arm who progress can cross-over to infigratinib. The primary endpoint is progression-free survival (PFS, RECIST v1.1 by blinded central review). Secondary endpoints include overall survival, PFS (investigator determined), overall response rate, disease control rate, duration of response, and safety. Quality of life, pharmacokinetics and exploratory genetic alterations/biomarkers will also be assessed. The trial will have sites in the US, EU, and APAC, including Australia. The target population size is 384 patients. Recruitment started in December 2019, and the study has an estimated primary completion date of September 2023.

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P-145 CT-based texture analysis using radiomics for hepatic sinusoidal obstruction syndrome (HSOS) in colorectal cancer patients treated with oxaliplatin containing chemotherapy

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Background: Oxaliplatin containing chemotherapy is known to induce HSOS, which is also expressed by its appearance as blue liver syndrome. HSOS has been reported to increase morbidity and mortality in surgical patients (pts), and thus, its extent could affect treatment outcomes. However, the assessment of its severity solely depends on laboratory findings of hepatic indices, and the quantitative evaluation of HSOS is not sufficient in clinical use. The purpose of this study is to construct a non-invasive prediction model for HSOS by applying radiomics which provides a comprehensive quantification of CT image textures.

Methods: We retrospectively analyzed 32 colorectal cancer patients treated in our hospital from November 2011 to May 2017. There were 16 males and 16 females with a mean age of 64.3 (38-81). These 32 pts consisted of two sub-groups; 16 HSOS-positive pts with abnormal hepatic indices who underwent oxaliplatin containing chemotherapy, and 16 HSOS-negative pts with normal hepatic laboratory findings who did not have any oxaliplatin chemotherapy. The whole liver was semi-automatically delineated. 38 radiomic features were extracted by LIFEx software (www.lifexsoft.org). Feature extractions were performed, first by a univariate analysis by Wilcoxon rank-sum test, followed by multivariate logistic regression analysis with a step-wise feature-reduction. ROC (receiver operating characteristic) analysis was performed to generate the radiomic signature for the assessment of HSOS.

Results: The radiomic signature demonstrated high discriminatory performance in predicting HSOS with an area under the curve (AUC) of 0.949 with a sensitivity of 93.75% and specificity of 93.75% ($P < 0.001$).

Conclusion: A prediction radiomic model for HSOS was generated successfully. In the next step, we would further refine and generalize its accuracy by adopting the external validation cohort of HSOS by oxaliplatin.

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P-146 A genetic custom-made in vivo drug screening platform for colorectal cancer patients

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Background: Current treatments for colorectal cancer (CRC) patients show disappointing therapeutic outcomes. Therefore, there is a compelling need for better therapy choices. The newest approaches using genomic analysis for precision medicine enable the identification of an actionable cancer driver gene present in the tumor for further targeting (eg, KRAS, BRAF, etc). However, cancer may be promoted by the contribution of several genes rather than the alteration of one or two genes alone. Consequently, current targeted therapeutic strategies are not improving long-term outcomes or progression-free survival. Hence, comprehensive genetic models are required to offer more accurate diagnosing aimed to identify bona personalized therapeutic strategies.

Methods: We employed a method developed at the Icahn School of Medicine at Mount Sinai (NY), which enables simultaneous targeting of multiple mutations driving tumorigenesis. We first identified the whole genomic landscape associated with the patient's tumor. Next, we reconstructed this genetic complexity, including up to 20 cancer-associated altered genes present in the patient's tumor, in the last portion of the intestine of the fruit fly *Drosophila melanogaster*. Thus, this fly developed a CR tumor genetically similar to that of the patient, creating a most complete avatar model. Subsequently, fly avatars were expanded to up to half a million per patient and were then used to screen the full FDA/EMA drug libraries. Finally, effective drug cocktails identified were presented to the patients and oncologists.

Results: We present here a unique methodology to identify personalized CRC drug treatments based on individual patients' entire tumor genomes. This technology has already demonstrated improved progression-free survival in terminal CRC patients. The result is a fully customized treatment program, comprising on- and off-label oncology drugs and non-cancer drugs. Our platform allows the design of N-of-1 clinical studies aimed to identify the specific genetic factors that are necessary for tumor growth in an individual patient, and the best drug combination to tackle it.

Conclusion: This novel platform can make possible a more precise diagnosis, and together with avatar modeling and *in vivo* drug screening, may make it possible to identify fully tailored therapeutics. By addressing the patient tumor genomic complexity, this personalized practice-changing approach may provide an alternative and more efficient treatment option for individual CRC patients.

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P-147 Efficacy and safety data of trifluridine/tipiracil treatment in advanced colorectal cancer based on the experience of Juan Ramón Jiménez Hospital in Huelva

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Background: The clinical efficacy and safety of trifluridine/tipiracil were evaluated in an international phase III, pivotal, randomized, double-blind, placebo-controlled trial (RECOURSE), in patients with previously treated colorectal cancer. We present the results obtained in the Oncology service of Juan Ramón Jiménez Hospital in Huelva to assess our experience with this treatment.

Methods: We conducted an observational and descriptive study of patients with advanced colorectal cancer treated with trifluridine/tipiracil during the years 2017 and 2020. We have used the IBM SPSS Statistics 22 program to analyze the variables: age, start of treatment, end of treatment, progression date, death date, ECOG, Number of prior regimens, progression-free survival (PFS), overall survival (OS), need for admission, delay or dose reduction of treatment, as well as the presence or grade of adverse events related to it.

Results: 24 patients with a median age of 66.5 years were treated. ECOG 0-1 in 91.7%. 75% received treatment in the third palliative regimen and 20.9% in the fourth or subsequent regimen. 41.7% of the patients presented with stable disease as the best response to the treatment and 58.3%, progressive disease. No patient presented partial or complete response. The median OS was 4 months (95% CI, 0.60 to 7.39) and the median PFS was 2 months with (95% CI, 0.74 to 3.2). The most frequently observed and clinically significant adverse event was asthenia, which occurred in 75% of the patients, followed by nausea and vomiting 33.3%, diarrhea 20.8%, stomatitis 8.3%. Hematologic adverse events occurred, such as anemia grade $\geq$ 3 in 4.2% and neutropenia grade $\geq$ 3 in 33.4%. 12.5% of patients required admission for febrile neutropenia. In 58.3% of patients it was necessary to delay treatment and 62.5% required dose reductions mainly due to hematological adverse events.

Conclusion: Comparing our data with those of the RECOURSE study, we can say that the SG and PFS of our patients were significantly lower. This may be due to the fact that we included patients with ECOG 2, rapid progressors, as well as a higher percentage of patients who required hospital admission due to toxicity. The adverse events of our patients were similar to those described in the RECOURSE study, except for asthenia and febrile neutropenia, which were significantly higher in our study.

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P-148 Molecular characterisation of gastric tumours in a South Indian cohort and their clinical correlation

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Background: Gastric cancer is amongst the leading causes of cancer and cancer-related mortality worldwide. The prevalence of gastric cancer is particularly high in Eastern Asia with nearly 70 % incidence in developing countries. In this population, there remains a wide heterogenicity observed in the cancer aggressiveness and treatment outcomes, the plausible explanation being the molecular heterogenicity in