

Session PO.TB01.05 - Mechanisms and Models of Gastrointestinal Malignancies

4093 / 21 - Preclinical evaluation of novel treatment strategies in patient-derived xenograft (PDX) models of pancreatic cancer

April 17, 2018, 1:00 PM - 5:00 PM Section 4

Presenter/Authors

D. Behrens¹, B. Büttner¹, R. L. Lawlor², C. Heeschen³, M. Buchholz⁴, J. Siveke⁵, A. M. Wengner⁶, A. Saluja⁷, J. Hoffmann¹; ¹EPO GMBH, Berlin, Germany, ²ARC-NET Univ. of Verona, Verona, Italy, ³QMUL, Barts Cancer Inst., London, United Kingdom, ⁴Philipps Univ. Marburg, Marburg, Germany, ⁵DKFZ, Univ. Hosp. Essen, Essen, Germany, ⁶Bayer AG, Berlin, Germany, ⁷Univ. of Miami, Miami, FL

Abstract

Pancreatic cancer (PC) remains a lethal disease with only 3 - 8% of patients surviving 5 years after diagnosis of the tumor (WHO, 2012). Within the EU project “CAM-PaC” a comprehensive panel of thirty patient-derived PC xenografts (PDX) was established and used for the efficacy screening of new therapeutic options. Within this study, responders to the MPS-1 inhibitor BAY1161909, the Super Enhancer disrupting agent Minnelide and the MEK inhibitor Trametinib were identified and analyzed for potential biomarkers. Patient tumors were collected during surgery and circulating tumorigenic cancer stem cells were isolated from the peripheral blood using VAR2CSA-coated magnetic beads. Both were transplanted subcutaneously into NOD/SCID/IL2y⁻ mice and propagated in NMRI:nu/nu mice after engraftment. These were morphologically and molecularly characterized by histopathological revision and with NGS panels, designed based on pathway aggregated genes identified with the International Cancer consortium (described by Bailey et al., Nature 531, 2016). Standard drugs were applied using clinically relevant dosages and schedule. MPS-1 inhibitor BAY1161909 was given in monotherapy and in combination with Abraxane. Minnelide (MTD) was applied second line after three cycles of chemotherapy (Cisplatin, Abraxane, Gemcitabine) and Trametinib was tested as monotherapy.

All PDX correlated with histopathological and molecular characteristics of patient tumours. BAY1161909 monotherapy showed moderate anti-tumor efficacy with an average tumor growth inhibition of 30% ($p > 0.05$). However, tumor relapse after the end of chemotherapy was delayed in mice treated with the combination of BAY1161909 and Abraxane compared to Abraxane alone. 13 out of 22 PDX models tested to date were identified as responders (tumor growth inhibition $> 50\%$) to Minnelide and 5 out of 11 to Trametinib. While Minnelide induced tumor growth inhibition above 80% in 32% of the models, Trametinib achieved the same efficacy in only 9% of the tested PDX models. The described PDX panel clearly reflects clinical situation of pancreatic cancer due to their histologic growth and detection of inherent and acquired treatment resistance as well as recurrent disease. In a few cases, the tested drugs induced complete remissions. We are currently analyzing the molecular data to determine response markers. Our approach may offer personalized treatment options for PC patients.