Predictive assay for anti-angiogenic agents (AADx) identifies a molecular subgroup of RAS wt mCRC with low efficacy of FOLFIRI plus bevacizumab – analysis of the FIRE-3 (AIO KRK-0306) trial

S. Stintzing1, B. Price2, L. Knight2, A. McCavigan2, S.M. Walker2, D.P. Harkin3, R.D. Kennedy4, D. Neureiter5, S. Held6, A. Jung7, T. Kirchner8, V. Heinemann1

1Department of Medicine III, University Hospital, LMU Munich, Germany; 2ALMAC Diagnostics Ltd, Glasgow, United Kingdom; 3Institute of Pathology, SALK Salzburg, Austria; 4CliniAssure GmbH, Leverkusen, Germany, Institute of Pathology University of Munich, Germany

Background:

The FIRE-3 trial compared 1st-line therapy of FOLFIRI plus either cetuximab or bevacizumab in 582 KRAS exon 2 wildtype (wt) mCRC patients. The subgroup of extended RAS wt patients consisted of 400 patients. The AADx molecular assay has previously been shown to identify a strong prognostic angiogenic subgroup across multiple cancer types including ovarian and lung cancer. Both, bevacizumab (through inhibition of VEGF-activation) and cetuximab (through inhibition of EGFR-signaling) are expected to have anti-angiogenic effects in colorectal cancer. The predictive role of AADx in FOLFIRI plus bevacizumab or cetuximab treated in colorectal cancer patients remains unclear.

Methods:

Transcriptional profiling of 501 formalin fixed embedded pre-treatment samples from the ITT population was performed using the A mascot Diagnostics XIO™ array. Patients were classified by the AADx assay as ANGIO ON or ANGIO OFF based on a predefined score. ORRs were compared using Fisher’s exact test. Progression-free survival (PFS) and Overall survival (OS) times were compared using Kaplan-Meier estimation and log-rank tests. Hazard ratios (HR) were estimated according to the Cox proportional hazard model.

Results:

- AADx has developed an angiogenic diagnostic (AADx) gene expression assay in ovarian cancer that:
  - identifies angiogenic molecular subtypes
  - is defined by activation/repression of genes associated with angiogenic processes
  - demonstrates prognostic performance in ovarian, colorectal and lung cancers
  - predicts response to bevacizumab in ovarian cancer
  - Angiogenesis active v. AADx negative v. ANGIO ON (C1 and C2):
    - Angiogenesis biology switched on in the patient tumour
    - Angiogenesis inactive v. AADx positive v. ANGIO OFF (C2): Angiogenesis biology switched off in the patient tumour

- In Patients Treated with FOLFIRI + Cetuximab:
  - FOLFIRI + Bevacizumab vs. FOLFIRI + Cetuximab:
    - HR = 0.49 (0.27 - 0.88)
    - Log-rank test p = 0.017

- In Patients Treated with FOLFIRI + Bevacizumab:
  - HR = 0.98 (0.62 - 1.52)
  - Log-rank test p = 0.55

- In Patients Treated with FOLFIRI + Cetuximab:
  - HR = 0.96 (0.54 - 1.7)
  - Log-rank test p = 0.8

Overall Response Rates According to AADx Score (ORR)

- FOLFIRI + Bevacizumab vs. FOLFIRI + Cetuximab:
  - HR = 0.54
  - Log-rank test p = 0.0306

Conclusions:

The data suggests that the AADx assay interacts with RAS mutation and may define RAS wt mCRC patients that respond differently to cetuximab or bevacizumab in combination with FOLFIRI. One potential explanation of the data is that Cetuximab is a more effective treatment for the poor prognosis ANGIO ON subtypes.