**Abstract:**

**ABT-165 plus FOLFIRI vs bevacizumab plus FOLFIRI in patients with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine/oxaliplatin and bevacizumab - Trial in progress**

Z Wainberg1, L Wang2, H Yue3, M Motwani4, S Kasichayanula4, M Blaney5, L Naumovski6, J Strickler7

1Ronald Reagan UCLA Medical Center, Los Angeles, California, USA; 2Oncology Early Development, AbbVie Inc., Redwood City, California, USA; 3Oncology Early Development, AbbVie Inc., North Chicago, Illinois, USA; 4Clinical Pharmacology and Pharmacoanalytics, AbbVie Inc., Redwood City, California, USA; 5Duke University Medical Center, Durham, North Carolina, USA.

**Introduction:** The dual variable domain immunoglobulin ABT-165 targets human vascular endothelial growth factor (VEGF) and delta-like ligand 4 (DLL4). Combined VEGF and DLL4 blockade increased inhibition of subcutaneous xenograft growth of human colon cancer-derived cell lines vs blockade of either axis alone. In vivo, ABT-165 plus chemotherapy (CT) induced tumor regression with improved efficacy, vs anti-VEGF monoclonal antibody plus CT. In a phase 1 study, a tolerable recommended phase 2 dose was identified for ABT-165 plus FOLFIRI and showed promising efficacy. This phase 2 trial in progress assesses the efficacy/safety of ABT-165 plus FOLFIRI vs bevacizumab (bev) plus FOLFIRI in patients with second-line mCRC.

**Methods:** This is an open-label, multicenter, phase 2 randomized (1:1) trial (NCT03368859) in patients (≥18 years; Eastern Cooperative performance status: 0–1) with histologically/cytologically confirmed mCRC who progressed after fluoropyrimidine/oxaliplatin and bev. ABT-165 (2.5 mg/kg) plus FOLFIRI (irinotecan: 180 mg/m2; leucovorin: 400 mg/m2; fluorouracil bolus: 400 mg/m2, infusion: 2400 mg/m2) or bev (5 mg/kg) plus FOLFIRI are given intravenously on day 1 of each 14-day cycle, until disease progression/ intolerable toxicity. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival (OS), objective response rate (ORR), and safety. Exploratory endpoints include biomarkers predictive for efficacy/safety, correlation of DLL4 levels with PFS, OS, and ORR, pharmacodynamic effects, and the efficacy/safety-exposure relationships in the ABT-165 arm. The hazard ratios of PFS and OS comparing the 2 groups are estimated using the Cox proportional hazard model. Kaplan-Meier methodology is used to estimate the PFS and OS curves, median
PFS and OS, and their 90% confidence intervals. Safety is assessed by ABT-165 exposure, adverse events (AEs), serious AEs, all deaths, and changes in laboratory data and vital signs. Archival tissue is collected and evaluated for DLL4 expression and angiogenesis signature. Approximately 100 patients are planned to be enrolled, with recruitment initiated in January 2018.