Final Results of the AIO 0307 Study: A controlled, randomized, double-blind phase II study of FOLFOX6 or FOLFIRI combined with sorafenib (S) vs placebo (P) in 2nd-line metastatic colorectal carcinoma (mCRC) treatment.

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Background: The oral multikinase inhibitor Sorafenib (S) inhibits angiogenesis and tumor growth in preclinical models of CRC. This study investigated the addition of S to standard 2nd line chemotherapy (CTX).

Methods: Patients (pts) with mCRC and progression after first-line therapy with an oxaliplatin- or irinotecan based fluoropyrimidine containing regimen ± Bevacizumab (Bev), were randomized to receive chemotherapy (CTX) (FOLFOX6 or FOLFIRI) + S (400 mg bid) or CTX + placebo (P). 240 pts were planned to be enrolled to ensure a power of 80% if median progression-free survival (PFS) with S is increased by 2 months compared to P.

Results: Between 04/09 and 10/11, 101 pts were enrolled. Recruitment was stopped prematurely due to slow accrual. 97 pts were evaluable in the full analysis set. Median age was 65 years, 60 pts were male, 97% with ECOG 0 or 1. Median PFS was 5.2 months (mths) in S and 5.6 mths in P (HR 0.84, 90% CI 0.58, 1.22, p=0.439). Best response rate was 25.6% and 12.2% (p=0.106), respectively. Disease control rates were comparable. Median overall survival (OS) was 9.6 mths with S compared to 12.7 mths with P (HR 1.57, 90% CI 1.03, 2.41, p = 0.076). Difference in OS was even more pronounced in subgroup (n=41) with FOLFOX6 backbone (9.6 vs. 13.8 mths, HR 2.37, 90% CI 1.22, 4.60, p=0.026). In 69 Bev-pretreated pts OS was 8.4 vs. 14.9 mths (HR 2.30; 90% CI 1.36, 3.88, p=0.007) compared to 13.1 vs. 7.4 mths (HR=0.61; 90% CI 0.28, 1.36, p=0.308) in 28 pts without Bev pretreatment. Adverse events (AEs) were consistent with the known safety profiles. Most frequent grade

3/4 AEs affected the gastrointestinal tract (diarrhea, mucositis/stomatitis, nausea); other frequent severe AEs included neutropenia and leukopenia, fatigue, fever, sensory neuropathy, and thrombosis.

Conclusions: No unexpected safety concerns occurred during the course of the study. S did not lead to improved PFS. There was a detrimental effect of S on OS in patients with Bev pretreatment.