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382O Inhibition of WEE1 is effective in TP53 and RAS mutant metastatic colorectal cancer (mCRC): A randomised phase II trial (FOCUS4-C) comparing adavosertib (AZD1775) with active monitoring

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Background: Outcomes in RAS-mutant metastatic colorectal cancer (mCRC) remain poor and patients have limited therapeutic options. Adavosertib is the first small molecule inhibitor of WEE1 kinase. We hypothesised that aberrations in DNA replication seen in mCRC with both RAS and TP53 mutations would sensitise tumours to WEE1 inhibition.

Methods: Patients with newly diagnosed mCRC were registered into FOCUS4 and tested for TP53 and RAS mutations. Those with both mutations who were stable or responding after 16 weeks of chemotherapy were randomised 2:1 between Adavosertib or active monitoring (AM). The primary outcome was progression-free-survival (PFS).

Results: Between Jul 2017 and Mar 2020 718 patients were registered into FOCUS4; 247 (34%) were RAS/TP53-mutant. 69 patients were randomised from 25 UK hospitals (44 to Adavosertib; 25 to AM) and recruitment terminated early due to COVID-19 and following DMEC review of efficacy data. Adavosertib was associated with a PFS improvement over AM (median 3.61 vs 1.87 months; HR=0.35[95% CI 0.18-0.68], p=0.0022). In pre-specified subgroup analysis, Adavosertib activity was greater in left-sided tumours HR=0.24 [95% CI 0.11−0.51], versus right-sided HR=1.02 [95% CI 0.41−2.56] (interaction p=0.043). Adavosertib activity was limited to tumours with KRAS12/13 mutations, rather than mutations in extended KRAS or NRAS (interaction p=0.01). Overall survival (OS) was not improved with Adavosertib vs AM (median 14.0 vs 12.8 months; HR=0.92[95%CI 0.44-1.94], p=0.93); however in left-sided tumours, median OS was 14.1 vs 11.3 months (HR=0.37 [95%CI 0.15-0.87]) and 6.5 vs 15.5 months in right-sided (HR=2.15 [95%CI 0.72-6.43], interaction p=0.0047). Adavosertib was well tolerated; grade 3 toxicities were diarrhoea (9%), nausea (5%) and neutropenia (7%).

Conclusions: In this phase II randomised trial, Adavosertib improved PFS compared with AM and demonstrates potential as a well-tolerated therapy for RAS/TP53-mutant mCRC. Activity was greater in patients with left-sided tumours, with potential impact on OS. Further testing is required in this sizable population of unmet need.

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383O MAYA trial: Temozolomide (TMZ) priming followed by combination with low-dose ipilimumab and nivolumab in patients with microsatellite stable (MSS), MGMT silenced metastatic colorectal cancer (mCRC)

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Background: The activity of TMZ in patients with mCRC is modest, but restricted to those with MSS status and MGMT silencing (negative IHC + *MGMT* methylation). In this hyperselected population, acquired resistance to TMZ is linked to emergence of mutations in mismatch repair genes and hypermutation. Thus, TMZ may be used as priming agent for immune-sensitization of MSS CRCs.

Methods: MAYA was a multicenter, single-arm phase II trial enrolling patients with pretreated MSS mCRC and MGMT silencing as centrally assessed by IHC + pyrosequencing (NCT03832621). The trial was designed to evaluate the safety and efficacy of 2 priming cycles of TMZ 150 mg/sqm d1-5q4w followed in absence of disease progression by its combination with ipilimumab 1 mg/kg q8w/nivolumab 480 mg q4w. Primary endpoint: 8-month progression-free survival rate (8m PFS). Secondary endpoints: overall survival (OS), overall response rate (ORR), safety, patient-reported outcomes. According to a single-stage design, 27 patients were required to increase 8m PFS from 5% to 20% with α- and β-error of 5% and 20%.

Results: Among 703 patients prescreened from March 2019 to November 2020, 204 (29%) were molecularly eligible and 135 started the priming phase, of whom 33 (24%) reached the second treatment phase. For these, median age: 58 years, M/F 52/48%, *RAS* mutated/wild-type 76/24% (no BRAF mutated); 1/2/$\geq$3 previous lines 6/45/49%. Overall, 10 were alive and progression free after 8 months, 21 had PFS $<$8 months (2 too early). The primary endpoint was met: 8m PFS was 32%; median PFS and OS: 7.1 and 18.5 months; ORR 39%, with delayed/gradual responses consistent with efficacy of immunotherapy. The rate of any grade/grade $\geq$3 immune-related adverse events was 48/6%, all easily manageable with protocol guidelines. On/post-therapy re-biopsies were analyzed in 9 cases with emergence of either TMB$>$10 mut/mb or MGMT expression, which predicted 8m PFS status.

Conclusions: MAYA study proved the immune-sensitizing role of TMZ in MSS/MGMT silenced mCRC. The safety and efficacy of TMZ priming followed by ipilimumab/nivolumab combo strategy is worthy of further development and extensive biomarker analyses are ongoing.

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