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Background: Immune checkpoint inhibitors have demonstrated poor efficacy in MSS mCRC. Previous research indicate that cetuximab (anti-EGFR chimeric monoclonal antibody) could initiate, independently from RAS mutation, an immunogenic tumor cell death and mediate antitumor immune response. In this trial, we aim to explore the clinical efficacy and safety of anti-PDL1 avelumab (AVE) combined with cetuximab (CET) and irinotecan (IRI) for treatment refractory MSS mCRC. **Methods:** AVETUXIRI (NCT03608046) is a multicenter academic study recruiting MSS, BRAFV600E wt, mCRC patients (pts) refractory to standard treatment (fluoropyrimidine, oxaliplatin, irinotecan and anti-EGFR treatment if RAS wt tumor) in 2 cohorts (cohort A: RAS wt – cohort B: RAS mut). In both cohorts, patients receive CET (400 mg/m2 W1, 250 mg/m2 W2, 500 mg/m2/2 weeks from W3), IRI (180 - 150 mg/m2/2 weeks from W1) and AVE (10 mg/kg/2 weeks starting from W3). Primary endpoints are overall response rate (ORR), defined as partial or complete response (PR or CR) according (i)RECIST1.1, and safety. Secondary endpoints include disease control rate (DCR), PFS and OS. Based on a Simon 2-stage design for ORR in each cohort (cohort A: P0=0.15, P1=0.33 / cohort B: P0=0.09, P1=0.25 / $\alpha = 0.1$, $\beta = 0.2$ in both cohorts), 10 and 13 patients are required in the first stage of cohort A and B respectively. At least 2 pts have to reach PR or CR in each cohort to allow the continuation of the trial in the 2nd stage. **Results:** Between Oct 2018 and Jan 2020, 23 patients (median age 62 y-old, 86.9% male 78.3% left-sided, 91.3% synchronous mCRC) have been included in the first stage of the trial. No major or unexpected safety events were observed. 21.7% (5/23) of pts presented grade 3 diarrhea, all related to IRI, with complete resolution after IRI dose reduction or interruption. A reduced starting dose of IRI (150 mg/m2) was amended (09/2019) for the last included 8 pts without any grade 3-4 diarrhea occurrence. Grade 1-2 hypothyroidism was the only immune-related side effect. 3 PR were observed in cohort A and none in cohort B. DCR was 60.0% (6/10) and 61.5% (8/13) in cohort A and B respectively. Median PFS and OS were respectively 4.2 and 12.7 months (cohort A) and 3.8 and 14.0 months (cohort B). 6 months-PFS rate was 40.0% and 38.5% in cohort A and B. 12 months-OS rate was 53.3% and 57.7% in cohort A and B. The median follow-up of patients was 9.2 months. **Conclusions:** The AVETUXIRI trial met its primary efficacy endpoint for RAS wt mCRC pts justifying the study continuation in cohort A (2nd stage). No PR was observed in RAS-mut cohort. Nevertheless, encouraging data of DCR, PFS and OS observed in RAS mut cohort allow the opening of a new cohort for RAS-mut mCRC (cohort C) with PFS as primary endpoint. Clinical trial information: NCT03608046.

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