634P The ave-rec phase II trial of PD-L1/PD-1 blockade with avelumab plus chemoradiotherapy for resectable ESMO high risk rectal cancers

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Background: Long course chemoradiotherapy (LCCRT) for locally advanced rectal cancer (LARC) results in a complete pathological CR in 10-30% of patients (pts). Radiotherapy (RT) is immuno-stimulatory by enhancing tumour cell death, but also immunosuppressive stimulating PDL1 production and myeloid-derived suppressor cells. PDL1 inhibition may be required to enhance RT immuno-stimulatory effects. *Hypothesis:* In pts with resectable LARC, Avelumab given post LCCRT may enhance tumour response rates whilst reducing relapses.

Methods: Phase II single arm trial. Pts had LCCRT (50.4Gy + 5FU [225mg/m^2/day/CI] or Capecitabine [825mg/m^2 BID]/5.5 weeks). Post LCCRT pts received 4 cycles Avelumab (AV) (10mg/kg, q2 weeks), then resection 10-12 weeks post LCCRT. Fresh tumour biopsy/ctDNA sampling taken at pre LCCRT, pre AV and at surgery. Response by FDG PET and pelvic MRI. *Inclusion Criteria*: pts with MRI stage T3b-4/N1-2/M0 LARC , tumoural lower border <12cm from anal verge, measurable disease, ECOG 0-1, adequate organ function. *Endpoints:* (a) *Primary*; Complete pathological response rate (Target $\geq$ 35%) reported centrally, (b) *Secondary*; Imaging responses, Toxicity. (c) *Exploratory;* Tumoural immune cell subsets/checkpoint expression and ctDNA analysis, Distant relapse-free survival and the sites of relapse.

Results: 37 pts entered. Baseline TNM: T3b-d 75%, T4a-b 25%. 33 pts completed LCCRT, 31 pts (83%) had all 4 cycles of AV and 32 pts (86%) had surgery. ORR Pelvic MRI (N=33): 2 CR, 14 PR, 31 DCR. FDG PET: 10 CMR, 18 PMR.. 10 pts Grade 3 AEs, 3 pts with treatment-related G3 and no G4 AEs. No immune-related G3 AEs. Post-operative complications as expected. Pathological response (Modified Ryan Score) (N=32): Complete pathCR (18.7%), near CR (15.7%), in MSI-H (N=4), 50% and 25% resp. Median followup 3.1 yrs: 3 yr est. time to progression 82%, distant relapse free survival 80%, disease free survival 80%.

Conclusions: The Ave-Rec phase II study has shown Avelumab post LCCRT is safe with significant imaging responses and complete/near-complete path response rate of 34.3% in pts with ESMO high risk rectal cancers. Parallel translational studies are ongoing. The addition of immune checkpoint inhibitors warrants further evaluation in LARC.

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635P Avelumab (AVE) combined with cetuximab (CET) and irinotecan (IRI) for the treatment of refractory microsatellite stable (MSS) metastatic colorectal cancer (mCRC): The AVETUXIRI phase II study

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Background: Cetuximab could mediate, independently from RAS mutation, an immunogenic tumor cell death and antitumor immune response. This trial explores the efficacy and safety of AVE, CET and IRI for the treatment of refractory MSS mCRC.

Methods: Chemo-refractory (+anti-EGFR refractory if RAS wt) MSS, mCRC patients (pts) were enrolled in 3 cohorts (A: RAS wt, B & C: RAS mut) and treated with CET (500 mg/m^2/Q2W), IRI (150 mg/m^2/Q2W) and AVE (10 mg/kg/Q2W). Primary endpoints were safety, overall response rate (ORR) (cohorts A-B) and 6 months progression-free survival rate (6m-PFSR) (cohort C). Secondary and exploratory endpoints included disease control rate (DCR), PFS, OS and immunoscore (IS) biomarker. Based on a Simon 2-stage design (α=0.1; β=0.2) for ORR (cohorts A: P0/P1=0.15/0.33 — B: P0/P1=0.09/0.25) and 6m-PFSR (cohort C: P0/P1=0.15/0.31), 10+18 (A); 13+15 (B) and 14+25 (C) pts were needed. At least 2+5 (A); 2+3 (B) and 3+6 (C) pts must reach ORR (A-B) or 6m-PFSR (C) for efficacy objectives. Immunofluorescence (CD3, CD8 densities) was performed on baseline metastasis biopsies to generate IS.

Results: 57 pts (median 62 yrs, 73.7% male, 84.2% left-sided, 86.0% synchr. mCRC) were included and 55 pts treated. Any treatment-emergent adverse event (AE) grade >=3 occurred in 35 pts (63.6%; diarrhea in 11 pts, 20.0%). Immune-related AEs grade >=3 appeared in 2 pts (3.6%; 1 acute kidney injury, 1 cholangitis). Efficacy results are summarized.

Table: 635P

Characteristics	Cohort A (n=28)	Cohort B (n=13)	Cohort C (n=14)
ORR, % (pts)	21.4% (6/28)	0.0% (0/13)	0.0% (0/14)
DCR, % (pts)	50.0% (14/28)	61.5% (8/13)	42.9% (6/14)
6m-PFSR, % (pts)	25.0% (7/28)	38.5% (5/13)	7.1% (1/14)
Median PFS, months (95%CI)	3.6 (2.5-5.6)	3.7 (2.7-6.4)	2.8 (2.4-3.8)
Median OS, months (95%CI)	11.4 (5.3-15.6)	10.1 (6.0-22.8)	6.8 (5.3-9.7)

Independently of RAS mutation, high IS was associated with greater tumor shrinkage (OR=8.3, p<0.01), DCR (OR=8.0, p=0.05), PFS (median 7.1 vs 3.1 months; HR=0.29, p<0.01) and OS (median 12.9 vs 7.2 months; HR=0.62, p=0.19).

Conclusions: Despite good tolerability, AVETUXIRI trial did not reach its efficacy endpoint. IS could be a predictive biomarker for selecting patients with potential treatment benefits.

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