O-12 Phase II study of preoperative chemoradiotherapy plus avelumab in patients with locally advanced rectal cancer: The AVANA study

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Background: Preoperative (preop) chemoradiotherapy (CTRT) is considered the standard of care in the management of locally advanced rectal cancer (LARC). RT can induce antigen release from a low neoantigen-burden tumor (such as a mismatch repair proficient colorectal cancer) and activate dendritic cells leading to a CD8+ T lymphocyte-mediated anticancer immune response. In LARC patients (pts), neoadjuvant CTRT increases PD-L1 expression in tumor cells, strongly suggesting a neoadjuvant combinatory strategy with RT and PD-1/PD-L1 pathway blockade. Based on such considerations, we have designed the AVANA study to investigate the role of avelumab (Ave) in combination with preop CTRT in LARC.

Methods: This is an Italian multi-center, phase II study. Pts with resectable LARC, defined by the presence of at least one of the following features: cN+, cT4, high risk cT3, received standard preop CTRT (capecitabine 825 mg/sqm/bid 5 days/week+ 50.4 Gy in 28 fractions over 5.5 weeks) plus 6 cycles of Ave 10 mg/Kg every 2 weeks. Surgery with total mesorectal excision was performed at 8-10 weeks after the end of CTRT. The primary end-point was the pCR rate, defined as complete histological regression with no available tumor cells. Secondary end-points were R0 resection rate, tumor downstaging, local recurrence, sphincter preservation rate, progression-free survival, overall survival, safety profile, and the evaluation of exploratory predictive and/or prognostic biomarkers. Assuming as null hypothesis p0 a pCR rate of 15%, a significance level of 5% (one-side), and a power of 80%, a sample size of 101 pts was needed to detect an absolute increment of 10% in pCR rate (from 15% to 25%). The experimental regimen is considered for further studies if, in at least 22 pts, we observe a pCR.

Results: From April 2019 to November 2020, a total of 101 resectable LARC pts were enrolled in 10 Italian Centers. The median age was 63 years (23-82), 62 (61.4%) pts were male, 93 (92%) had ECOG PS 0. At baseline, 94 (93%) and 16 (16%) pts had cN+ and cT4 LARC, respectively. All pts completed the induction phase. Out of 96 pts evaluable for pathological response, 22 (23%) pts achieved a pCR and 59 (61.5%) pts a major pathological response (a central review is ongoing). At this time, microsatellite status is available only in 39 pts, of which only one was instable. The rate of grade 3-4 non-immune and immune-related adverse events was 8% and 4%, respectively. Avelumab was early interrupted in 9 pts out 101, mainly due to toxicity.

Conclusions: The combination of preop CTRT plus Ave showed promising activity and a feasible safety profile. According to our statistical considerations, the experimental regimen will be considered for further studies. Updated results will be presented during the Congress.

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Legal entity responsible for the study: The author.

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