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Randomized phase 1 trial of pembrolizumab with neo-adjuvant versus concomitant stereotactic body radiotherapy in metastatic urothelial carcinoma: Clinical and translational results

Eur Urol Suppl 2019; 18(1);e2105

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Introduction & Objectives: Preclinical data indicates that stereotactic body radiotherapy (SBRT) works synergistically with pembrolizumab, but the effect and potential toxicity might depend on the timing of SBRT. The current study assessed the safety of two different SBRT schedules in combination with pembrolizumab for metastatic urothelial carcinoma (mUC), and explored correlative biomarkers including circulating tumor DNA (ctDNA).

Materials & Methods: An open-label phase 1 trial was conducted at Ghent University Hospital in patients with mUC to assess the dose-limiting toxicity (DLT) of the combination of pembrolizumab (200mg intravenously, 3-weekly) and SBRT (3x8Gy to the largest lesion). Patients were randomized (1:1) to receive SBRT either prior to the first (arm A) or the third (arm B) cycle of pembrolizumab. Blood was collected throughout the trial for biomarker analysis. Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events version 4.0. Secondary endpoints included best overall response measured per Response Evaluation Criteria in Solid Tumors v1.1 (RECISTv1.1). The trial was approved by the Ethical Committee of Ghent University Hospital and is registered on ClinicalTrials.gov (NCT02826564). Funding was provided by Merck Sharp & Dohme.

Results: Eighteen patients were randomized (nine to each arm) and started trial treatment. No DLT occurred. Treatment-related AEs grade 1-2 occurred in 6/9 and 9/9 patients in arm A and B respectively. One patient in arm B experienced lymphopenia grade 3, unrelated to SBRT. No treatment-related AEs grade 4-5 occurred. An objective response rate as per RECISTv1.1 of 0% and 44-4% was noted in arm A and B respectively. Targeted sequencing of tissue DNA and ctDNA revealed high genomic concordance. A decline in ctDNA was observed in responding patients.

Conclusions: Neo-adjuvant and concomitant SBRT combined with pembrolizumab is safe, with potentially superior responses in the latter. ctDNA monitoring is feasible during disease evolution and suggests a shared driver gene status throughout disease progression.