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Brief Correspondence

Randomized Phase 1 Trial of Pembrolizumab with Sequential Versus Concomitant Stereotactic Body Radiotherapy in Metastatic Urothelial Carcinoma

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Abstract

Preclinical data indicate that radiotherapy works synergistically with pembrolizumab, but the effect and toxicity of this combination may depend on radiotherapy timing. We conducted a randomized phase 1 trial combining pembrolizumab with either sequential (A) or concomitant (B) stereotactic body radiotherapy (SBRT) in metastatic urothelial carcinoma (mUC). No dose-limiting toxicity occurred. Treatment-related adverse events (trAEs; Common Terminology Criteria for Adverse Events v4.0) of grade 1–2 occurred in six of nine and all nine patients in arms A and B, respectively. One grade 3 trAE occurred in arm B. No grade 4–5 trAEs occurred. Overall response rates of 0% and 44.4% were noted in arms A and B, respectively, as per Response Evaluation Criteria in Solid Tumors v1.1. The trial was not powered to compare efficacy between arms. Targeted sequencing of tissue DNA and circulating tumor DNA (ctDNA) revealed high genomic concordance. Treatment response was associated with ctDNA fraction decline. We conclude that sequential and concomitant SBRT can be safely combined with pembrolizumab in mUC and that the effect of SBRT timing on efficacy is worth exploring further.

Patient summary: This study assessed the safety of pembrolizumab combined with radiotherapy at two different time points in metastatic bladder cancer. We conclude that the combination treatment was well tolerated.

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Pembrolizumab improves overall survival (OS) in patients with metastatic urothelial carcinoma (mUC), yet the majority of patients do not respond and OS remains limited [1,2]. Preclinical data indicate that stereotactic body radiotherapy (SBRT) may synergize with pembrolizumab [3], but the timing of SBRT may influence the combination's toxicity and efficacy [4].

We conducted a randomized phase 1 trial in mUC in which pembrolizumab (200 mg, 3 weekly) was combined with SBRT (3 × 8 Gy, to one metastatic lesion), administered either sequentially (prior to the first pembrolizumab cycle, arm A) or concomitantly (prior to the third pembrolizumab cycle, arm B). Safety was the primary outcome, with dose-limiting toxicity (DLT) defined as any grade 3–5 metabolic or hematological toxicity or any grade 3–5 nonhematological toxicity that was (probably or possibly) related to SBRT, and that occurred between the start of SBRT and 12 weeks after the end of SBRT. Secondary endpoints included best overall objective response as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, progression-free survival (PFS), OS, and local response in the irradiated lesion as per RECIST v1.1. Details of the materials and methods can be found in the Supplementary material.

Eighteen patients were enrolled (nine into each arm), and all received at least one dose of pembrolizumab or one fraction of SBRT (Supplementary Fig. 1). Baseline patient characteristics are listed in Supplementary Table 1; details on patient characteristics, treatment, and response are listed in Supplementary Table 2. Treatment-related adverse events (AEs) of grade 1–2 occurred in six of nine patients in arm A and in all nine patients in arm B. One patient in arm B experienced grade 3 treatment-related lymphopenia, 11 months after administration of SBRT (Supplementary Tables 2 and 3). No grade 4–5 treatment-related AEs were observed (Supplementary Tables 3 and 4). No DLT occurred, indicating that the combination of pembrolizumab with sequential or concomitant SBRT is safe in patients with mUC, as previously described in other solid tumors [5].

A response rate of 0% (RECIST v1.1) was observed in arm A, with all patients experiencing progressive disease as the best overall objective response in nonirradiated lesions. Two patients had an initial partial response (PR) at first evaluation, which progressed shortly afterward and therefore does not qualify as a PR according to RECIST v1.1. In arm B, a response rate of 44% was noted in nonirradiated lesions, with three patients experiencing a PR and one patient experiencing a complete response (CR; Fig. 1A and Supplementary Fig. 2). Albeit in a small group, and therefore potentially a chance outcome, the discrepancy in response rates between both arms is intriguing and compels further research; it suggests that timing of SBRT could influence the systemic antitumor immune effect. Our data concur with

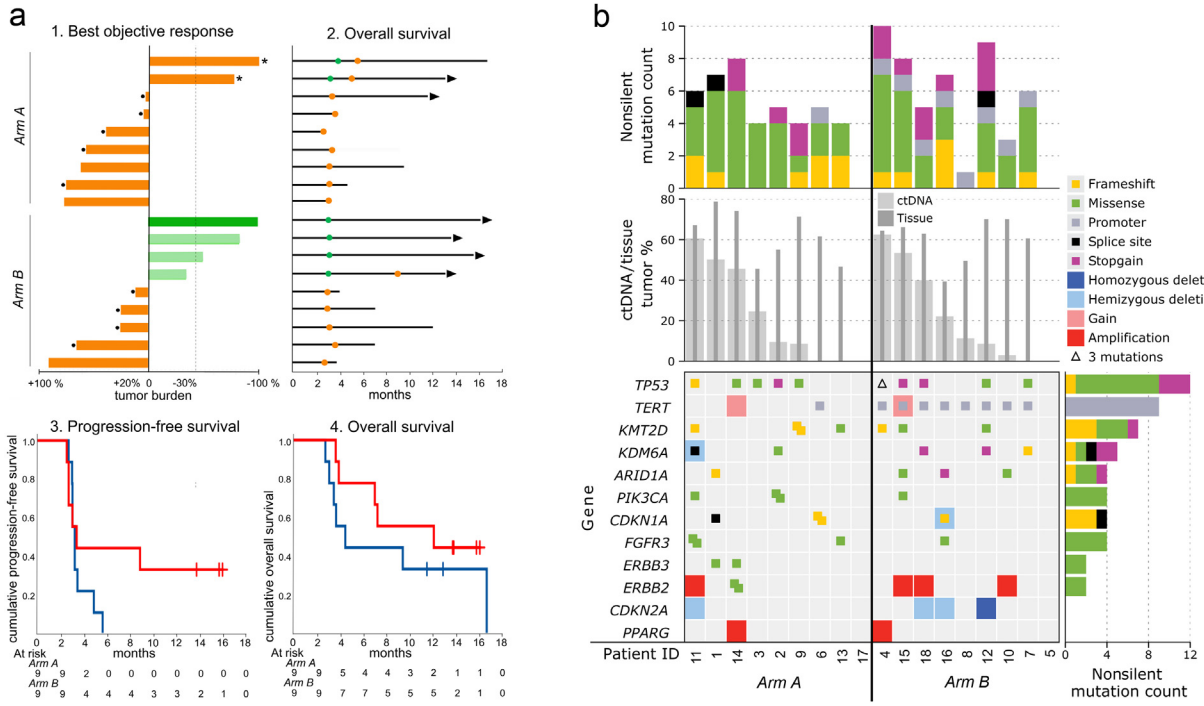

Fig. 1 – (A) (1) Horizontal waterfall plots indicating the best objective response in tumor burden according to RECIST v1.1. The top shows response of arm A; the bottom shows response of arm B. Orange bars indicate progressive disease, light green bars indicate partial response, and dark green bar indicates a complete response. Black dots indicate appearance of new lesion(s) at first evaluation. An asterisk indicates that the patient had initial partial response, yet progressive disease at subsequent evaluation and thus progressive disease as the best objective response according to RECIST v1.1. (2) Corresponding overall survival in months. Green dots represent first partial or complete response, orange dots represent first progressive disease, and black triangles indicate that the patient was alive at data cutoff on April 2, 2018. Bottom panels show Kaplan-Meier plots comparing arm A (blue) with arm B (red) for progression-free survival (3) and overall survival (4); crosses indicate censored patients. (B) Key somatic alterations detected in 18 metastatic urothelial carcinoma patients. Mutation and copy number results are a composite of tissue and baseline circulating tumor DNA (ctDNA) genomics. The top panel provides the nonsilent mutation count for each patient (TERT promoter mutations included). Represented below are the ctDNA fraction and percent tumor-derived DNA for tissue samples. Results from 12 frequently altered driver genes are shown, sorted by alteration frequency (as depicted in the bar plot on the right-hand side). RECIST: Response Evaluation Criteria in Solid Tumors.

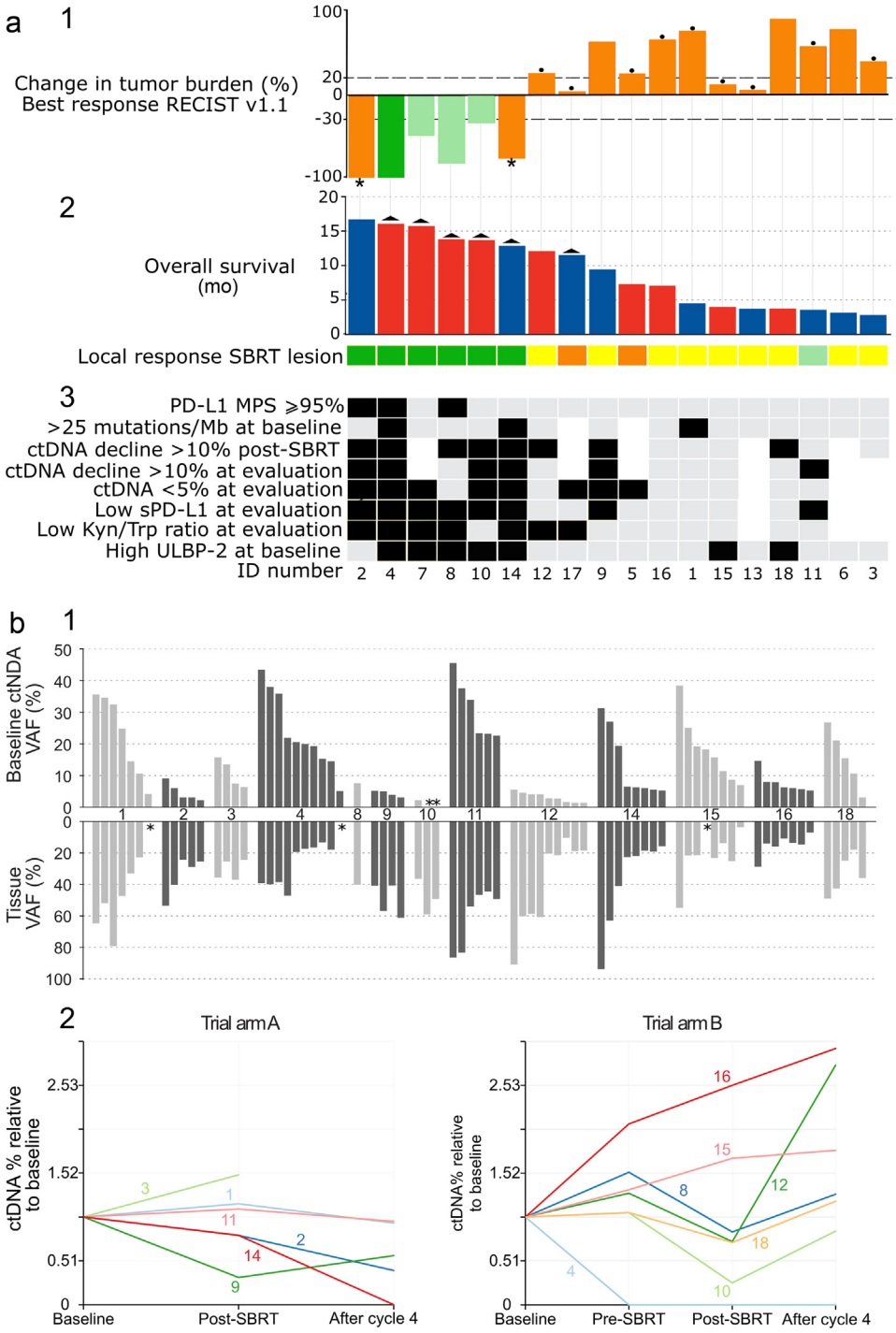

Fig. 2 – (A) (1) Best change in tumor burden as per RECIST v1.1. Orange bars indicate progressive disease, light green bars indicate partial response, and dark green bar indicates a complete response. Black dots indicate appearance of new lesion(s) at first evaluation. An asterisk indicates that the patient had initial partial response, yet progressive disease at subsequent evaluation and thus progressive disease as the best objective response according to RECIST v1.1. (2) Overall survival of patients per arm (arm A: blue bars; arm B: red bars; black triangle: alive at data cutoff) with corresponding local response of the irradiated lesion (dark green: complete response; light green: partial response; yellow: stable disease; orange: progressive disease). (3) Selected genomic and immune markers. Division of low versus high for mutations/Mb, sPD-L1, Kyn/Trp, and ULBP-2 was based on the median value of all measurements; cutoffs are 0.24 pg/ml for sPD-L1, 6.15 nM for Kyn/Trp ratio, and 101.24 pg/ml for ULBP-2. Black boxes represent positive analysis, grey boxes negative analysis, and white boxes no analysis available. (B) Mirror plot (1) and minor allele frequency (MAF) graphs (2). (1) Mutation call concordance between cell-free DNA (cfDNA) and tissue biopsy. Top bar plots show the variant allele frequency (VAF) of mutations in baseline cfDNA, mirrored below by the VAF in matched tissue. Asterisks annotate mutations that were not called independently in both samples. All patients with ctDNA detected and tumor tissue content of >8% are included; all nonsilent mutations are shown, grouped by patients. (2) Evolution of circulating tumor DNA (ctDNA) fraction (%) over the course of treatment. Median relative MAF change is plotted relative to baseline for each of the three time points in arm A, and four time points in arm B. Results for individual patients are shown in unique colors. ctDNA = circulating tumor DNA; Kyn/Trp = kynurenine/tryptophane; Mb = megabase; PD-L1 MPS = tumor programmed death-ligand 1 modified percent score; RECIST = Response Evaluation Criteria in Solid Tumors; sPD-L1 = soluble programmed death-ligand 1; SBRT = stereotactic body radiotherapy; ULBP-2 = UL16 binding protein 2.

preclinical data, which showed that only radiotherapy administered during—and not prior to—checkpoint inhibition entailed a synergy between both treatments [4].

Interestingly, the four responding patients in arm B, as well as the two patients in arm A with an initial PR, all had a CR in the irradiated lesion. Median PFS was 3.3 and 3.5 months in arms A and B, respectively; median OS was 4.5 and 12.1 months in arms A and B, respectively (Fig. 1A).

In order to assess the effect of the combination treatment on the genomic tumor profile and the immune profile, blood samples were collected at baseline, prior to the first fraction of SBRT, 7 days after the last fraction of SBRT, and at evaluation after the fourth cycle of pembrolizumab. Programmed death-ligand 1 (PD-L1) was quantified on tissue via immunohistochemistry, and selected immune markers were measured in the blood (Fig. 2A and Supplementary material). Circulating tumor DNA (ctDNA) and tissue DNA from formalin-fixed paraffin-embedded tumor tissue were sequenced and analyzed together to generate a composite mutational landscape (Fig. 1B and Supplementary Tables 5–9). Two tissue samples showed no evidence for somatic alterations, likely due to low tumor cellularity in the cored region. At baseline, 13/18 patients had detectable ctDNA, and a comparison with matched tissue revealed high concordance for driver alterations (Fig. 2B). Specific mutations detected in ctDNA were consistent over time within patients, and emergence or regression of subclones was not observed at evaluation. The high concordance between archival tissue and contemporary ctDNA suggests a shared driver gene status throughout disease progression, consistent with recent research in other tumor types [6]. While this finding should be confirmed in larger studies, it implies that either tissue or ctDNA can provide a snapshot of the tumor molecular subtype. Additionally, we observed large changes in overall ctDNA fraction within patients. Notably, all patients with CR of the SBRT lesion experienced declines in ctDNA fraction after SBRT. In patient 4 (with an overall CR), ctDNA dropped to undetectable levels prior to SBRT and remained undetectable at evaluation (Fig. 2B and Supplementary Fig. 3). To our knowledge, this trial is the first to show that monitoring ctDNA fraction during treatment could be useful in predicting treatment response in mUC. The rapid ctDNA fraction decline in responding patients, compared with stable or increased fractions in nonresponders, suggests that ctDNA sampling could identify hyperprogressors early—prior to any imaging. Similarly, monitoring ctDNA might help resolve cases of pseudoprogression.

Our translational results corroborate with current literature, indicating that predicting a response to checkpoint inhibitors is intricate, with no single marker, such as PD-L1 or tumor mutational burden, being sufficient to explain the response or survival [2,7,8]. Our data suggest that a multifactorial approach (Fig. 2A), combining tumor-specific and immune markers, might be the key to identify who will benefit from treatment. Albeit in a limited patient population, our findings provide a framework for future testing of predictive integrated immune- and tumor-specific signatures.

We conclude that pembrolizumab can be safely combined with SBRT both sequentially and concomitantly. With an objective response rate of 44.4%, concomitant SBRT seems most promising. Finally, ctDNA fraction could serve as a surrogate for monitoring disease evolution.

Author contributions: Nora Sundahl had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ost, Rottey, Reynders, Goetghebeur.
Acquisition of data: Sundahl, Decaestecker, Fonteyne, De Maeseneer, Brochez, Vandekerkhove, Meireson, Annala, Wyatt, Ost, De Visschere, Van Dorpe, Verbeke, Van der Eecken.
Analysis and interpretation of data: Sundahl, Vandekerkhove, Meireson, Annala, Wyatt, Brochez, Ost.
Drafting of the manuscript: Sundahl, Vandekerkhove, Wyatt, Ost.
Critical revision of the manuscript for important intellectual content: All authors.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.01.009.

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