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Research Letters

An Open-label Randomized Phase 2 study of Durvalumab Alone or in Combination with Tremelimumab in Patients with Advanced Germ Cell Tumors (APACHE): Results from the First Planned Interim Analysis

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There is growing interest in the potential antitumor effects of immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway. Data from two independent groups have demonstrated that the majority of patients with germ cell tumors (GCTs) express PD-L1 [1,2]. Furthermore, our analysis of the Foundation Medicine database revealed that a small subset of nonseminomatous GCTs featured a high tumor mutation burden (TMB) or microsatellite instability (MSI) that could make these tumors sensitive to immune checkpoint inhibitor therapy [3].

APACHE (NCT03081923) is an open-label randomized phase 2 study. Patients were randomized 1:1 to receive 1500 mg of durvalumab intravenously (arm A) or 1500 mg of durvalumab plus 75 mg of tremelimumab intravenously (arm B) for four cycles followed by durvalumab alone. Treatment was administered every 4 wk in both study arms until disease progression (PD), unacceptable toxicity onset, or a maximum of 12 mo was achieved. The primary endpoint was the objective response rate (according to Response Evaluation Criteria in Solid Tumor [RECIST] version 1.1). The total sample size was divided into a three-stage design. In stage 1, each arm is terminated if no responses are observed in 11 patients (details on the study design are provided in the Supplementary material). Biomarker analyses of the available pretherapy tumor samples included PD-L1 expression (Ventana SP142 assay, details provided in the Supplementary material) and genomic sequencing (FoundationONE assay, Foundation Medicine, Cambridge, MA, USA).

From February 2017 to April 2018, 22 patients were randomized at a single center (11 per arm, Supplementary Table 1). The median follow-up (calculated using the reverse Kaplan-Meier method) was 7.5 mo. No grade 3–4 adverse events occurred in either arm (Supplementary Table 2).

One patient (in arm B, 9.1%) experienced a partial response of multiple lung metastases that was confirmed at the time of data analysis (+8 mo, Supplementary Table 3). The patient was a 43-yr-old male with pure seminomatous testicular GCT who had received two prior lines, including high-dose chemotherapy (Fig. 1A). Another patient in arm B had stable disease (SD) with a decrease in serum tumor markers (STMs) of >10% from baseline and developed PD 3 mo later. All the remaining patients had experienced progression of the primary tumor. Among these patients, hyperprogression features were observed in eight cases in arm A (72.7%) and four cases in arm B (36.4%). These features were reflected in an increase in tumor burden (that we arbitrarily set as an increase of >100% in the sum of the diameters of target lesions, Fig. 1C) or an unequivocal increase in STMs during treatment when compared to two measurements within the 2 mo preceding randomization (Fig. 1D).

Response and progression occurred regardless of tumor molecular features and PD-L1 expression (Supplementary Table 4). One case in arm B experienced PD even though his tumor exhibited MSI. This case was one of the two GCT patients reported to have MSI in the Foundation Medicine database, and the TMB was elevated in both patients (18 and 23.4 mutations/Mb) [3].

Finally, four patients received further paclitaxel, cisplatin, and gemcitabine chemotherapy after experiencing PD on immunotherapy. One patient experienced a near complete response (in the fifth line; Supplementary Fig. 1), and

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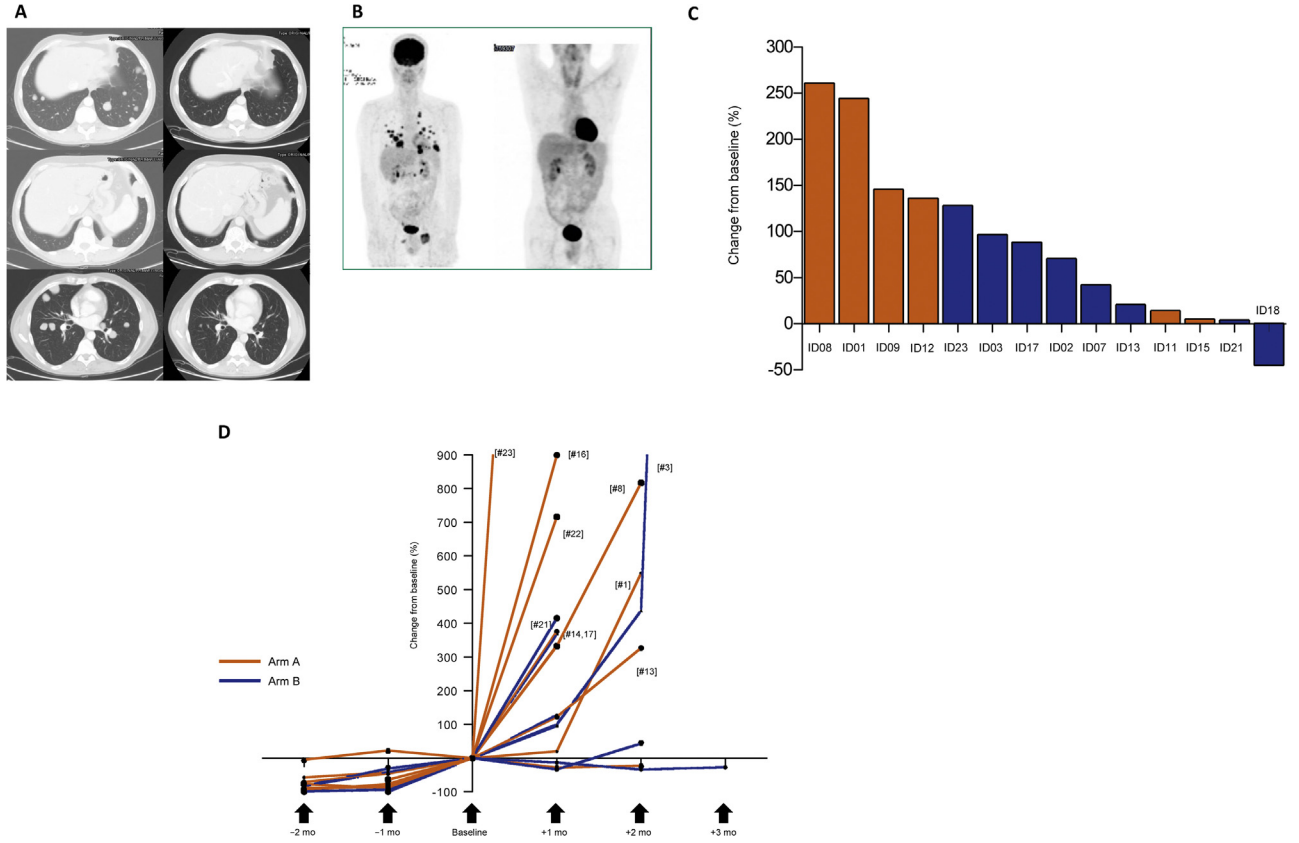

Fig. 1 – (A) Outstanding RECIST response and (B) decrease in fluorodeoxyglucose uptake for multiple lung metastases from testicular seminoma observed in patient ID 18 after two courses of durvalumab and tremelimumab. The response was maintained at the time of last follow-up (+6 mo) while the patient was receiving maintenance durvalumab therapy. This patient had received four cycles of bleomycin + etoposide + cisplatin chemotherapy and three high-dose chemotherapy courses according to the TI-CE protocol (paclitaxel and ifosfamide, followed by carboplatin and etoposide). Analyses of archival tumor from this patient revealed PD-L1 negative staining on immune cells, low tumor mutational burden score, and microsatellite stable tumor. RECIST = Response Evaluation Criteria in Solid Tumors. (C) Waterfall plot showing the percentage change from baseline for the sum of the diameters of the target lesions according to RECIST v.1.1 criteria for arm A (blue bars) and arm B (red bars. (D) Percentage change from baseline (day of randomization) in serum tumor markers throughout the study treatment, and during the 2 mo before randomization. Study identification numbers are shown for patients with a hyperprogressive phenotype, whose characteristics are further described in Supplementary Table 4.

another patient had SD with an STM decline. The remaining patients had no response.

On the basis of these results, the monotherapy arm of the APACHE study has been closed to accrual. The evidence we have accumulated using single-agent immunotherapy is even more negative than that already reported with pembrolizumab in GCT [4] because a significant number of patients exhibited features of hyperprogressive disease under durvalumab therapy. Interestingly, none of these patients harbored *MDM2* amplification, a molecular signature linked to hyperprogression to immunotherapy in other tumor types [5].

Durvalumab and pembrolizumab study results should prompt cessation of the development of immune checkpoint inhibitors as single agents for GCT. Regarding combination immunotherapy, encouraging signs suggest that this therapeutic option might be viable in selected cases, although predictive biomarkers are lacking. In fact, the responding seminoma case harbored a PD-L1–negative tumor with a very low TMB (4 mutations/Mb).

The second stage of the APACHE trial and the results of the ongoing studies of combination immunotherapy (NCT02834013 and NCT03158064) will hopefully shed light on the critical issue of predictive biomarkers.

The APACHE trial is registered at ClinicalTrials.gov as NCT03081923.

This work was presented in poster sessions at the 2018 Annual Meeting of the American Association for Cancer Research, April 14–18, 2018, Chicago, IL, USA and the 2018 Annual Meeting of the American Society of Clinical Oncology, June 1–5, 2018, Chicago, IL, USA.

Conflicts of interest: Andrea Necchi is a consultant for Merck, AstraZeneca, Janssen, Incyte, Roche, Bioclin Therapeutics, Clovis Oncology, Bayer, and Astellas/Seattle Genetics; has received grant/research support from Merck and AstraZeneca; and has received travel expenses/honoraria from Roche, Merck, AstraZeneca, and Janssen. Siraj M. Ali, Jeffrey S. Ross, and Jon H. Chung are employees of Foundation Medicine Inc. The remaining authors have nothing to disclose.

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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.2018.09.010.

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A Dedicated Prostate MRI Teaching Course Improves the Ability of the Urologist to Interpret Clinically Significant Prostate Cancer on Multiparametric MRI

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Multiparametric magnetic resonance imaging (MRI) plays an increasingly important role in the diagnosis and treatment of men with prostate cancer. It is important for urologists to be able to interpret prostate MRI to a high standard so that they can perform accurate targeted prostate biopsy and prostate cancer treatments [1]. The objectives of this study were to assess whether the accuracy of urologists in identifying the presence of clinically significant cancer based on a standardised multiparametric MRI set could be improved by completion of a 2-d training course.

A 2-d national training course in prostate MRI for urologists was delivered in September 2016. A total of 25 urologists (17 attendees, 8 residents) independently reported 32 prostate MRI scans under test conditions. Attendees had some prior exposure to prostate MRI; however, this ranged from very limited exposure to more substantial exposure. Scans were chosen at random from men who had previously undergone pre-biopsy MRI, transperineal template, and targeted prostate biopsies at our institution [2]. MRIs included T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences. A test was conducted at the start of the course where participants, blinded to pathology findings, recorded the likelihood of 16 MRIs harbouring clinically significant cancer (defined as Gleason grade 3 + 4 or greater and/or maximum cancer core length $\geq$4 mm) on a 1–5 Likert scale of suspicion. Teaching was then given over 2 d in the form of lectures, practical reporting sessions, and case-based discussions on prostate MRI interpretation. At the end of the course, the participants assessed a different set of 16 randomly chosen scans.

The primary outcome was the cohort's change in average area under the curve (AUC) for detection of clinically significant cancer before and after teaching. Receiver operating characteristic (ROC) curves were based on generalised linear mixed models with random effects on readers and cases. This approach generalises the Obuchowski-Rockette method [3] and is described by Liu et al. [4]. For each ROC curve and AUC value, 95% confidence interval (CI) was computed by stratified bootstrap (B = 50 000 samples) and adjusted percentile.

MRIs were performed in men with no prior biopsy (14/32, 44%) or men with a prior negative biopsy (18/32, 56%).