European Journal of Cancer 116 (2019) 114–115

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Letter to the Editor

Immune-related adverse events predict the therapeutic efficacy of pembrolizumab in urothelial cancer patients

Taketo Kawai*, Yusuke Sato, Katsuhiro Makino, Yuta Yamada, Akira Nomiya, Masaki Nakamura, Daisuke Yamada, Motofumi Suzuki, Yasuhiko Igawa, Haruki Kume

Department of Urology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Received 9 May 2019; accepted 9 May 2019
Available online 10 June 2019

Dear Editor,

We read with great interest the article published in the *European Journal of Cancer* by Rogado *et al.* [1], 'Immune-related adverse events predict the therapeutic efficacy of anti-PD-1 antibodies in cancer patients'. They clearly showed the relationship between the occurrence of immune-related adverse events (irAEs) and the efficacy of anti–programmed death receptor 1 (PD-1) antibodies in various types of tumours. Recently, we have had similar results in a single tumour type, urothelial cancer.

We reviewed 30 cases with metastatic urothelial cancer, treated with pembrolizumab from February 2018 to April 2019 at our institute. They consisted of 25 males and five females with median age of 70 years (range, 26 to 85). The median follow-up period was 183 days (range, 17 to 430). All cases had been refractory to conventional chemotherapy. Pembrolizumab was administrated as second-line treatment in 28, third-line treatment in one and fourth-line treatment in one.

Objective response rate (ORR) was 16.7% per the response evaluation criteria in solid tumours (version 1.1) [2]: complete response (CR) was achieved in two (6.7%), partial response (PR) in three (10%), stable disease (SD) in seven (23.3%) and progressive disease (PD) in 18 (60%).

We observed 18 irAEs (60%) and seven severe irAEs (23%; grades III to V, Common Terminology Criteria for Adverse Events, version 5.0) [3]. A median of 25 days (range, 2 to 177) elapsed before the onset of irAEs. Severe irAEs included grade V myocarditis associated with myasthenia gravis in one and grade III interstitial pneumonitis in three, adrenal insufficiency in one, type 1 diabetes in one and dermatitis in one.

ORR (CR + PR) was higher in cases with any irAEs (27.8%) than without (0%), but this was not scored as significant following the Fisher's exact test ($p = 0.066$). In contrast, there was a significant difference when comparing CR + PR + SD with PD (any irAEs, 61.1% and no irAEs, 9.1%, $p = 0.007$).

Progression-free survival (PFS) and overall survival (OS) were also better in cases with any irAEs

DOI of original article: https://doi.org/10.1016/j.ejca.2018.10.014.
* *Corresponding author*: Department of Urology, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 1130033, Japan. Fax: +81 3 5800-8917.
E-mail address: taketokawai@yahoo.co.jp (T. Kawai).

https://doi.org/10.1016/j.ejca.2019.05.017

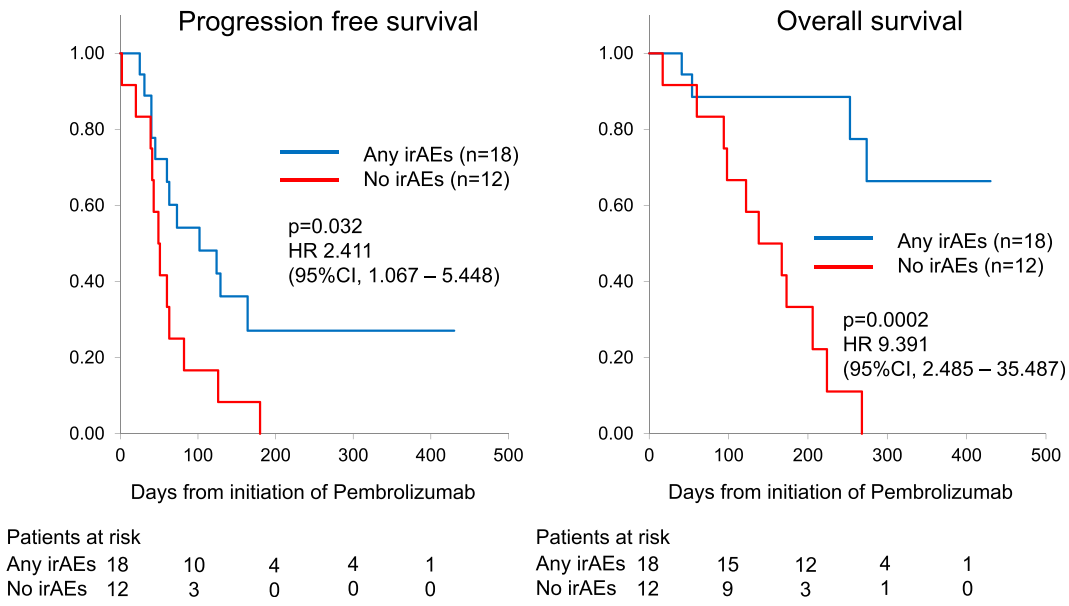

Fig. 1. Progression-free survival and overall survival. Significant survival differences were observed in cases with and without irAEs. HR, hazard ratio; 95% CI, 95% confidence interval; irAEs, immune-related adverse events.

($p = 0.032$, $p = 0.0002$, respectively) as determined by the log rank test (Fig. 1).

Our results were consistent with those of Rogado *et al.* [1], which showed a direct association between irAEs and pembrolizumab efficacy in a Japanese cohort with advanced urothelial cancer, single tumour type.

Furthermore, we also demonstrated survival differences in terms of OS, although OS was not different between cases with and without irAEs in the article by Rogado *et al.* A report from MD Anderson Cancer Center on 290 cases with various types of tumours also showed that cases with grade ≥III irAEs had significantly improved ORR (25% versus 6%; $p = 0.039$) and significantly longer time to progression ($p = 0.004$), but similar OS ($p = 0.10$) [4]. On the other hand, in a retrospective analysis of 148 melanomas treated with nivolumab, OS was significantly better in cases with any grade of irAE ($p < 0.001$) [5]. Another study of 134 patients with non–small-cell lung cancer treated with nivolumab in the second-line setting or later also showed favourable PFS and OS in cases with irAEs ($p = 0.04$ and $p = 0.01$, respectively) [6].

Our study has several limitations, including the small number of cases, its retrospective nature and the short follow-up period. However, accumulating evidence seems to reveal the predictive value of irAEs with regard to anti–PD-1 antibody efficacy, which is a double-edged sword.

Funding

No funding.

Conflict of interest statement

The authors declare no conflict of interest.

References

[1] Rogado J, Sánchez-Torres JM, Romero-Laorden N, Ballesteros AI, Pacheco-Barcia V, Ramos-Leví A, et al. Immune-related adverse events predict the therapeutic efficacy of anti-PD-1 antibodies in cancer patients. Eur J Canc 2019;109:21–7.

[2] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Canc 2009;45:228–47.

[3] https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

[4] Fujii T, Colen RR, Bilen MA, Hess KR, Hajjar J, Suarez-Almazor ME, et al. Incidence of immune-related adverse events and its association with treatment outcomes: the MD Anderson Cancer Center experience. Investig New Drugs 2018;36:638–46.

[5] Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. Clin Cancer Res 2016;22:886–94.

[6] Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of immunerelated adverse events with nivolumab efficacy in non-small-cell lung cancer. JAMA Oncol 2018;4:374–8.