Association between immune-related adverse events and survival in patients with renal cell carcinoma treated with nivolumab plus ipilimumab: Immortal time bias-corrected analysis.

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Abstract

Background: Immune-related adverse events (irAEs) in patients treated with immune check inhibitors are associated with favourable response rate and survivals in multiple cancers, including renal cell carcinoma (RCC). The aim of this study was to investigate how irAEs were associated with improved survivals in advanced RCC patients treated with nivolumab plus ipilimumab.

Materials and methods: This retrospective study included patients who received nivolumab plus ipilimumab between September 2018 and February 2022 at six centres. We assessed associations of the development and the number of irAEs with overall survival (OS) and progression-free survival (PFS). To eliminate immortal time bias, landmark analysis and a Cox model with time-dependent variables were used.

Results: This study included 129 patients with a median follow-up of 12.3 months. The 2-year OS and PFS rates were 55% and 42%, respectively. Ninety six patients experienced irAEs. The development of irAEs was positively associated with OS and PFS rates (hazard ratio [HR] 0.328, 95% confidence interval [CI] 0.165–0.648, p = 0.001; HR 0.334, 95% CI 0.151–0.737, p = 0.007). Patients who experienced multiple irAEs had longer OS (HR 0.507, 95% CI 0.235–1.097, p = 0.085 or HR 0.245, 95% CI 0.110–0.544, p < 0.001) and PFS (HR 0.572, 95% CI 0.316–1.036, p = 0.085 or HR 0.267, 95% CI 0.113–0.628, p = 0.002) compared with those who experienced single or zero irAE.

Conclusions: Developing irAEs, particularly multiple irAEs, is associated with favourable survivals in advanced RCC patients treated with nivolumab plus ipilimumab.

Introduction

Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape for patients with advanced malignancies, including renal cell cancer (RCC). Programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) are checkpoint proteins that have been successfully targeted by antagonist antibodies. The CheckMate 214 trial demonstrated benefits of nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4) in patients with intermediate- and high-risk disease according to the International Metastatic RCC Database Consortium (IMDC) risk score [1].

ICIs may lead to immune-related adverse events (irAEs) that involve overstimulation of the immune system and consequently inflammation of organs and tissues [2]. The irAEs target multiple organs and tissues, including the endocrine, dermatological, gastrointestinal, hepatic, and respiratory systems [3, 4]. Combination ICI therapy of nivolumab plus ipilimumab is associated with a higher incidence and severity of irAEs compared with single ICI therapy [5]. The irAEs are not only adverse events but also an antitumor response to ICIs. Patients who experience irAEs on anti-PD-1 and anti-PD-L1 antibody therapy have improved response and survival rates [6–11]. The development and number of irAEs that involve multiple organ systems were also associated with survival [12, 13]. Multiple small retrospective studies have

demonstrated prolonged survival after irAEs in RCC patients who experienced irAEs compared with those who did not experience them [13–17]. However, these findings must be verified in larger populations.

Immortal time bias often affects the results of observational studies. Patients with irAEs may have longer survival compared with those without irAEs because they must live long enough to develop them. To correct for immortal time bias, appropriate statistical analyses, such as landmark analysis (LMA) and Cox model with time-dependent variable (CMTD), should be used [18]. However, most studies that assessed the association between irAEs and survival did not correct for immortal time bias [6–9, 11–16].

In this retrospective, multicentre study, we performed LMA and CMTD to evaluate the associations between irAEs and survival rate in 129 RCC patients treated with nivolumab plus ipilimumab as first-line therapy.

Patients and Methods

Patients

We used the Musashino Study Group database, which consists of 132 consecutive patients who received nivolumab plus ipilimumab for previously untreated metastatic or locally advanced RCC of IMDC intermediate or high risk at six institutions between September 2018 and February 2022. We excluded three patients without a pathological diagnosis. Therefore, 129 patients were included in this study. The patients received nivolumab plus ipilimumab as first-line systemic therapy for their RCC. Nivolumab (240 mg) and ipilimumab (1 mg/kg) were administered intravenously every 3 weeks for four doses, followed by nivolumab monotherapy at a dose of 240 mg every 2 weeks or 480 mg every 4 weeks. This study was approved by the institutional review board of each study institution and carried out according to the Declaration of Helsinki and its amendments.

Study objectives

As primary objective we aimed to assess whether the development and the number of irAEs were associated with improved overall survival (OS) and progression-free survival (PFS). We also assessed OS and PFS in patients who discontinued nivolumab plus ipilimumab therapy due to irAEs. The radiological response was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 [19]. OS and PFS were defined as the interval from the initiation of treatment to death from any cause and first Response Evaluation Criteria in Solid Tumors-defined progression, respectively. All adverse events were recorded in accordance with the Common Terminology Criteria for Adverse Events (version 5.0) [20]. IrAEs were defined as inflammatory adverse effects that enhance immune system activity.

Statistical analysis

PFS and OS were estimated using the survival analysis. In the analysis, we used three analytical approaches (Cox model with time-independent variable [no immortal time bias correction], LMA, and LMA plus CMTD) to compare the survival between patients who experienced and those who did not experience

irAEs. In LMA, the landmark was specified as 3 months. In CMTD, time-dependent variable was defined by considering the occurrence of irAEs as each time point after the landmark. All Cox models included age and the IMDC-risk at the start of treatment, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The schematic diagrams of the definition of exposure were presented in supplementary Fig. 1. All statistical analysis were carried out with a two-sided significance level of 5% and performed using R software version 4.0.2 (www.r-project.org).

Results

Patient characteristics

The median age of the study participants was 67 (range: 28–87) years, and 92 patients (71%) were males (Table 1). In total, 78 and 51 patients had IMDC intermediate and high risks, respectively. Clear cell and non-clear cell RCC were present in 107 and 22 patients, respectively. The most common site of metastasis was the lungs (66%), followed by bones (22%). The median follow-up was 12.3 (0.1–36.3) months.

Efficacy of nivolumab plus ipilimumab therapy

In total, 76 patients received four doses of nivolumab plus ipilimumab, whereas the remaining 53 received three doses or less due to irAEs or disease progression. The median duration of nivolumab plus ipilimumab therapy was 3.5 (range: 0.1–32.2) months.

Tumor reduction was assessed in 125 patients (Fig. 1a). In total, 15 (12%) and 47 (36%) patients achieved achieved complete and partial responses, respectively, and the objective response rate (ORR) was 48%. The overall 2-year OS and PFS rates were 55% and 42%, respectively (Fig. 1b and 1c).

Incidence of irAEs

In total, 96 patients experienced irAEs, of whom 88 and 59 experienced irAEs of grades ≥ 2 and ≥ 3, respectively. Endocrine irAEs were common. Hypopituitarism, thyroiditis/hyperthyroidism, and hypothyroidism were observed in 36 (28%), 24 (19%), and 24 (19%) patients, respectively (Fig. 2a and supplementary Table 1). Among non-endocrine irAEs, the most commonly affected organ was the skin (n = 31, 24%), followed by the liver (n = 19, 15%) and lungs (n = 12, 9%). In total, 86% of the irAEs occurred within 4 months, whereas only 1% occurred after 1 year (Fig. 2b). High-dose glucocorticoids (≥ 40 mg prednisone or equivalent) were required to treat irAEs in 25 (19%) patients. One patient died of treatment-related pneumonitis.

Association between irAEs and survival rates

We used three approaches, Cox model with time-independent variable (no immortal time bias correction), LMA, and LMA plus CMTD, to assess the associations between irAEs and survival rates. The differences in OS and PFS between the irAE and non-irAE groups were greater in the Cox model with time-independent variable (HR 0.218, 95% CI 0.119–0.400, $p < 0.001$ and HR 0.135, 95% CI 0.079–0.231, $p < 0.001$,

respectively) than in LMA alone (HR 0.485, 95% CI 0.259–0.908, p = 0.024 and HR 0.697, 95% CI 0.386–1.256, p = 0.230, respectively) or LMA plus CMTD (HR 0.328, 95% CI 0.165–0.648, p = 0.001 and HR 0.334, 95% CI 0.151–0.737, p = 0.007, respectively) (supplementary Fig. 2). Based on LMA alone, four patients who experienced irAEs after the landmark were grouped into the non-irAE group, and the differences in survival rates were smaller than those in LMA plus CMTD, suggesting that LMA alone may underestimate the difference. Therefore, we used LMA plus CMTD for immortal time bias correction in subsequent analyses.

The number of irAEs was positively associated with favourable OS and PFS rates. Patients who experienced multiple irAEs had longer OS (HR 0.507, 95% CI 0.235–1.097, p = 0.085 or HR 0.245, 95% CI 0.110–0.544, p < 0.001, respectively) and PFS (HR 0.572, 95% CI 0.316–1.036, p = 0.085 or HR 0.267, 95% CI 0.113–0.628, p < 0.002, respectively) compared with those who experienced single or zero irAE (Fig. 3a and 3b). A similar trend was observed for grade ≥ 2 irAEs (supplementary Fig. 3). The OS and PFS rates were not significantly different in patients who experienced grade 1–2 versus ≥ 3 irAEs (OS: HR 1.226, 95% CI 0.539–2.787, p = 0.628; PFS: HR 0.934, 95% CI 0.521–1.673, p = 0.818) (Fig. 3c and 3d). Patients who experienced both endocrine and non-endocrine irAEs exhibited longer OS and PFS compared with those who experienced endocrine or non-endocrine irAEs (supplementary Fig. 4). Pituitary and thyroid irAEs were associated with OS as organ-specific irAEs (supplementary Table 2).

Survival rates in patients who discontinued nivolumab plus ipilimumab therapy due to irAEs

In total, 49 (38%) patients discontinued nivolumab plus ipilimumab therapy due to irAEs, of whom 14 received molecular-targeted therapies, including cabozantinib and axitinib, and/or nivolumab rechallenge, as second- or later-line therapies following disease progression, whereas the remaining 35 patients did not receive any systemic therapy for RCC (Fig. 4a). Four and three patients underwent nephrectomy and metastasectomy, respectively, while three patients underwent radiation therapy for metastases (Fig. 4a). A total of 23 patients experienced on-going responses in the treatment-free status with a median duration of 12.6 (range: 2.3–30.5) months following discontinuation of nivolumab plus ipilimumab therapy. Seven patients died from RCC progression, whereas one patient each died from drug-induced pneumonitis or sepsis. The 2-year OS and PFS rates were 72% and 54%, respectively (Fig. 4b and 4c).

Discussion

The present study demonstrated that the development and the number of irAEs were positively associated with the survival rates. In total, 38% of patients required discontinuation of ICI combination therapy due to irAEs. However, half of such patients experienced durable responses without any therapy.

The response and survival rates (ORR: 48%; 2-year OS and PFS rates: 55% and 42%, respectively) were mainly consistent with those from previous studies [21, 22]. Previous studies have demonstrated the associations between irAEs and oncological outcomes in multiple cancers, including RCC [6–17]. The development of irAEs is an independent predictor of longer PFS in RCC treated with nivolumab plus

ipilimumab [17]. The organ systems affected by irAEs may affect the ICI benefit differently. The ORR for nivolumab was positively correlated with the incidence rates of skin, gastrointestinal, and endocrine irAEs, whereas the ORR for nivolumab plus ipilimumab was positively correlated with the incidence rates of skin and gastrointestinal irAEs in a meta-analysis of patients with solid tumours [23]. A retrospective study of RCC treated with nivolumab or nivolumab plus ipilimumab demonstrated that thyroid irAEs were an independent predictor of favourable PFS [13]. In the present study, pituitary and thyroid irAEs were associated with a favourable OS (supplementary Table S2). The association between organ-specific irAEs and an ICI benefit varied among previous studies, which may be due to the rarity of organ-specific irAEs and differences in the treatment regimen and tumor type among studies. The present (Figs. 3a, 3b, supplementary Fig. 4) and previous [12, 13] studies demonstrated associations of the number and occurrence of multi-organ irAEs with improved survival in RCC or non-small cell lung cancer treated with ICIs. It is unclear whether the severity of irAEs is associated with the survival rates. In the present study, the survival rates were similar between patients with mild to moderate irAEs and those with severe irAEs (Fig. 3c, 3d), suggesting that the severity of irAEs does not affect survival. However, these results should be interpreted with caution because patients who experience severe irAEs often discontinue the ICI treatment and receive glucocorticoid therapy, which may affect the tumor status. By contrast, patients who experience mild to moderate irAEs often continue ICI treatment. Taken together, the number of irAEs and/or occurrence of multi-organ irAEs have a stronger association with favourable survivals compared with organ-specific irAEs or the severity of irAEs.

Patients who experience severe irAEs may need to discontinue the ICIs. The oncological outcomes in such patients are unclear. In the present study, discontinuation of ICI combination therapy due to irAEs were required in one third of patients. Interestingly, half of these patients experienced long-term on-going responses without any additional systemic therapy (Fig. 4a and 4c). The immunological effects appeared to persist for a substantial time after ICI discontinuation in such patients.

Although the precise mechanisms underlying irAEs are not clear, they may involve the bystander effect from activated T cells, which is consistent with the mechanism of action of ICIs [24]. In a post-mortem study of melanoma patients who developed fulminant myocarditis after ICI combination therapy, infiltrating T cells and macrophages were found in the myocardial tissue, and high-frequency T cell receptors were found in the cardiac muscle, skeletal muscle, and tumor [25]. Immune toxicities elicited by CTLA-4 blockade are associated with early diversification of the T cell repertoire [26], which may be associated with several multi-organ irAEs and, in turn, with favourable antitumor efficacy. Other studies have suggested an association between T cells and irAEs involving the gut microbiome. In a study of melanoma patients treated with ipilimumab, those with a high abundance of Faecalibacterium in the gut microbiota at baseline had longer PFS and OS, and higher rates of ICI-induced colitis, compared with other patients [27]. Microbial diversity and composition may modify the antitumor effect and irAE risk in patients treated with ICIs.

A potential confounding factor when assessing the association between irAEs and survival is that patients with irAEs, particularly late-onset irAEs, may have longer survival because only patients who live

long enough will develop irAEs. We corrected for this immortal time bias using established analytical techniques, i.e. LMA and CMTD [28, 29]. In LMA, the irAE status is determined for all patients at a certain predefined point in time (landmark). Immortal time bias is corrected before the landmark using this approach, whereas any change in irAE status after the landmark is ignored. CMTD links longitudinal and survival data to quantify the association between a longitudinal process and survival outcome. Statistical performance is improved in models that include time as a covariate [30].

The strengths of the present study were the relatively large number of participants, all of whom received nivolumab plus ipilimumab therapy as first-line systemic therapy, and use of appropriate statistical analysis techniques. However, the present study had several limitations, including its retrospective design and lack of central radiological review of the treatment response. Additionally, the follow-up duration was short, and the follow-up strategies differed among institutions.

Conclusions

In patients with advanced RCC treated with nivolumab plus ipilimumab, the development and the number of irAEs are positively associated with favourable survival. Discontinuation of ICI combination therapy due to irAEs may be required in one-third of patients; however, half of such patients can experience durable responses without any additional therapy. The present study will help with counselling and management of this patient population.

Declarations

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Author contributions: Satoshi Washino 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: Satoshi Washino.

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Ethics statement

This study was approved by the institutional review board of each study institution and carried out according to the Declaration of Helsinki and its amendments. Informed consent was obtained from all patients via posters and/or websites using the opt-out method. Sugure Shirotake received lecture fees from Bristol Meyers Squibb and Ono Pharmaceutical. Yuji Miura received lecture fees from Takeda Pharmaceutical, Bristol Meyers Squibb and Eisai, and research grants from MSD and Ono

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Table

Table 1 is available in the Supplementary Files section.

Figures

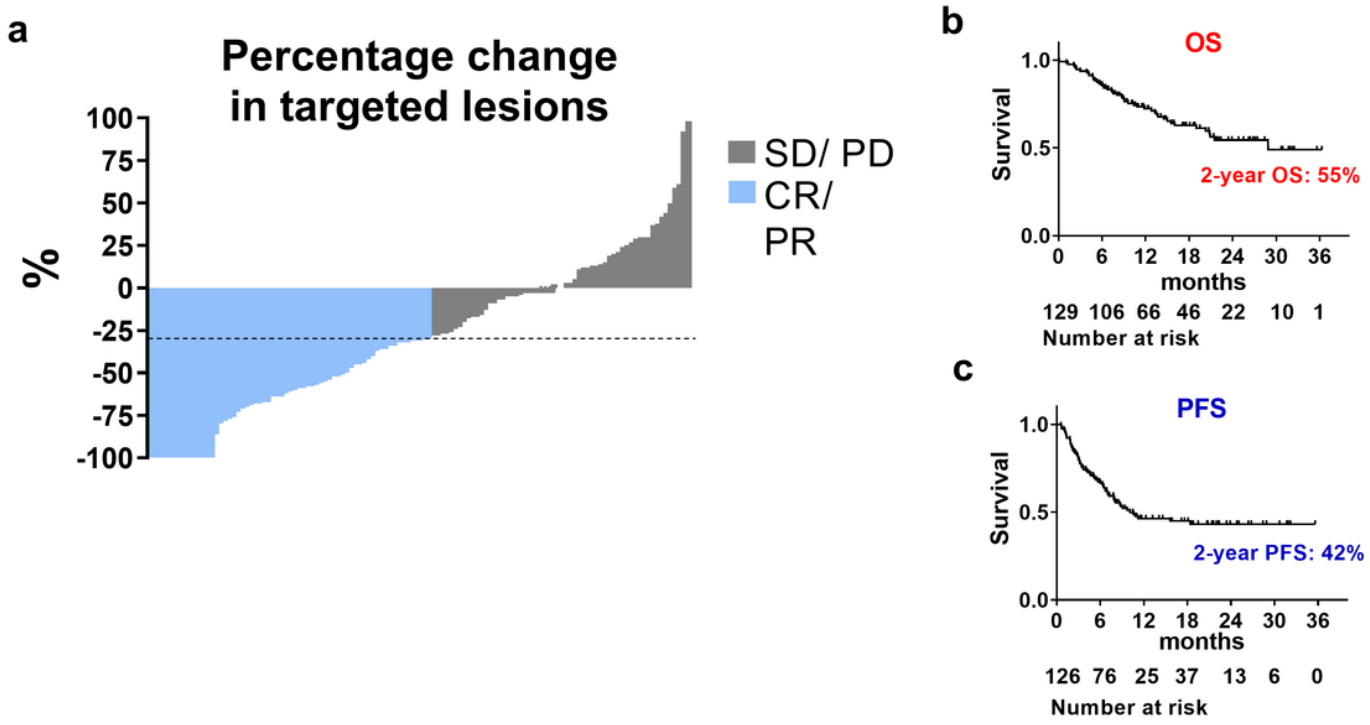

Figure 1

Tumor responses and survival

(a) Representative waterfall plot of the maximum percentage change in targeted lesions compared with the baseline measurement. Blue and grey bars indicate complete or partial responses and stable or progressive disease, respectively. Overall survival (b) and progression-free survival (c) following nivolumab plus ipilimumab therapy.

SD: stable disease; PD: progressive disease; CR: complete response; PR: partial response; OS: overall survival; PFS: progression-free survival.

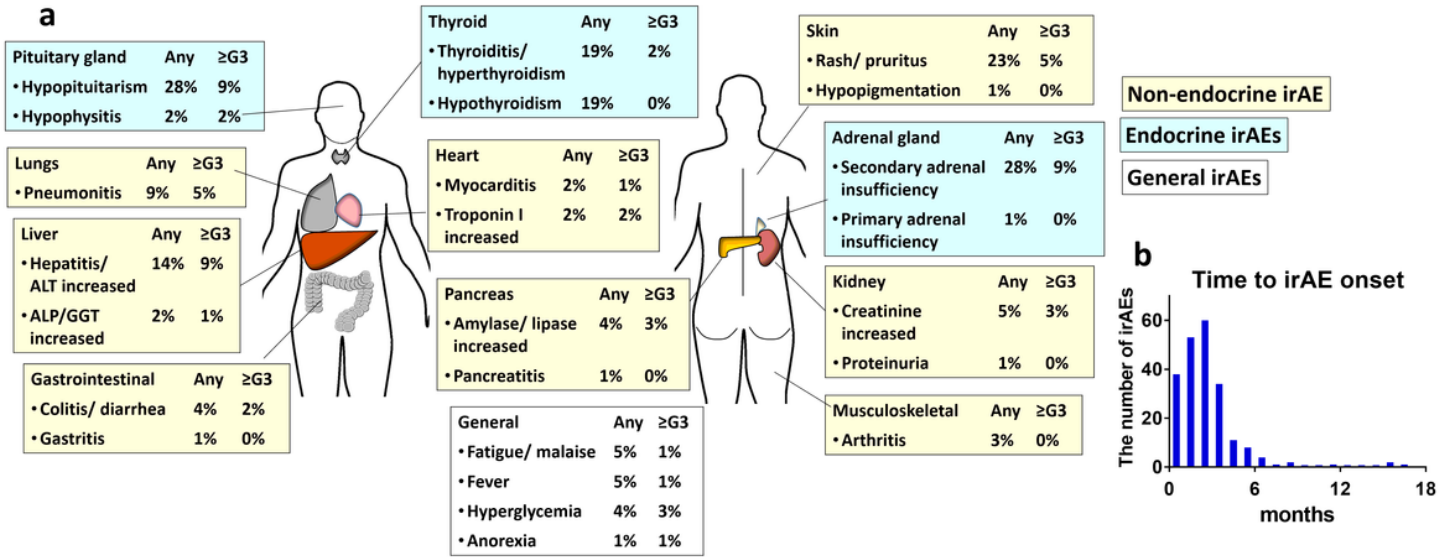

Figure 2

Incidence rates and onset of irAEs

(a) Incidence rates of irAEs in each organ. Non-endocrine and endocrine irAEs are presented in orange and blue, whereas general irAEs are presented in grey. (b) Time of onset of irAEs.

ALT: *alanine aminotransferase;* ALP: alkaline phosphatase; GGT: gamma glutamyl transferase; irAE: immune-related adverse event

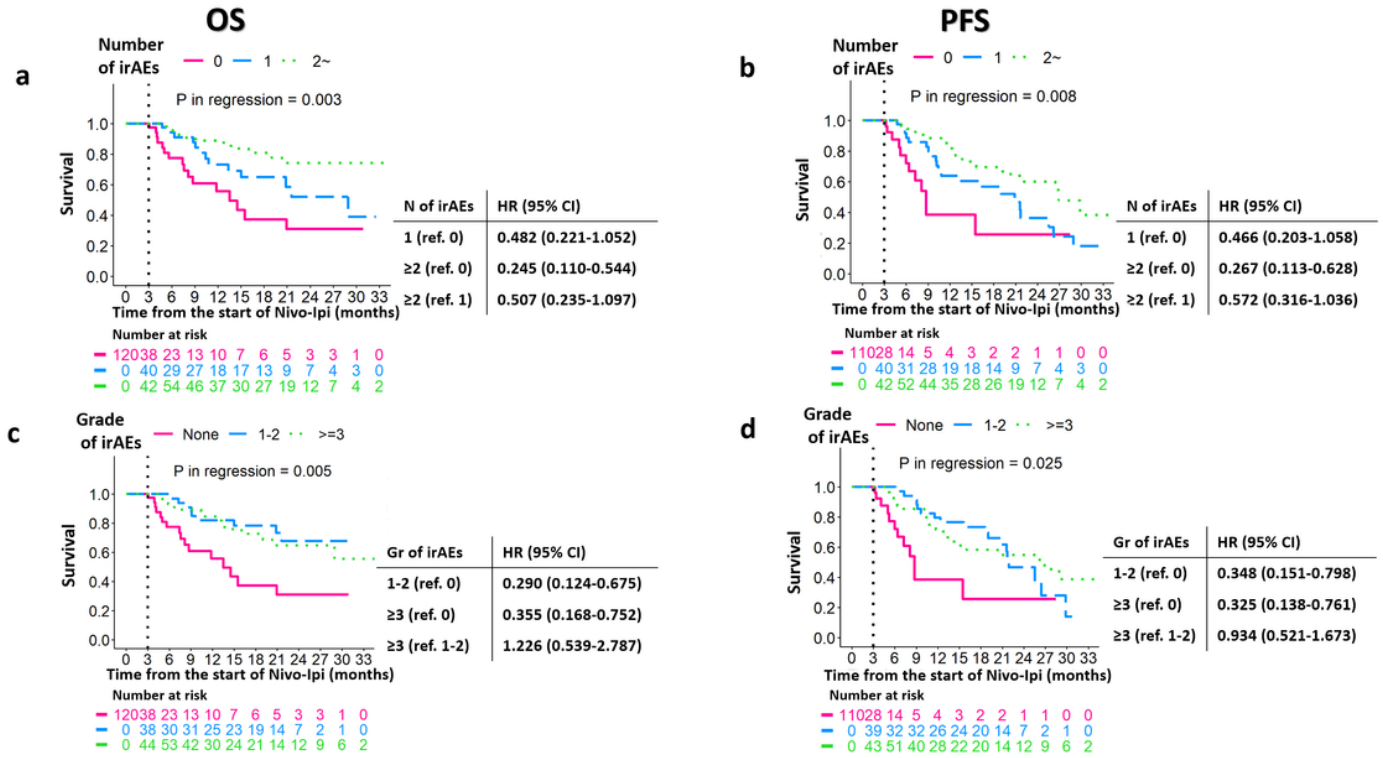

Figure 3

Associations of the number and grade of irAEs with survival.

Associations of the number and grade of irAEs with overall survival (a, c) or progression-free survival (b, d) assessed using landmark analysis plus a Cox model with time-dependent variable. (a, b) Pink lines indicate patients who did not develop irAEs, whereas blue- and green-dashed lines indicate those who developed single and multiple irAEs, respectively. (c, d) Pink lines indicate patients who did not develop irAEs, whereas blue- and green-dashed lines indicate those who developed irAEs of grades 1–2 and ≥ 3 irAEs, respectively.

OS: overall survival; PFS: progression-free survival; N: number; Gr: grade; irAEs: immune-related adverse events; HR: hazard ratio; CI: confidence interval; Nivo-Ipi: nivolumab plus ipilimumab therapy

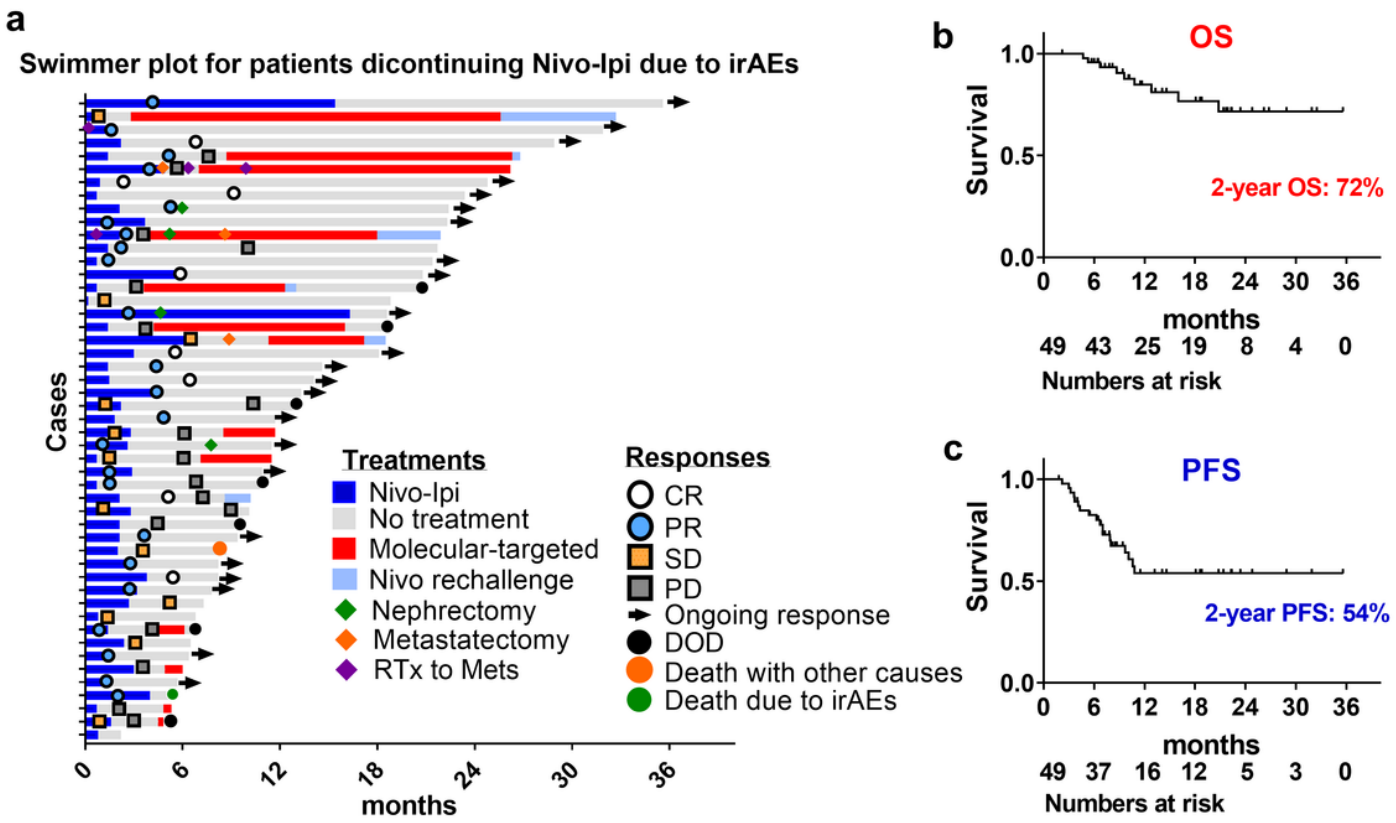

Figure 4

Survival of patients who discontinued nivolumab plus ipilimumab therapy due to irAEs.

(a) Swimmer plot for 49 patients who discontinued nivolumab plus ipilimumab therapy due to irAEs. Blue and gray bars indicate nivolumab plus ipilimumab therapy and no treatment, respectively; red and light blue bars indicate molecular-targeted therapies as a second- or later-line therapy and nivolumab rechallenge following disease progression, respectively. Green, orange, and purple diamonds indicate

nephrectomy, metastasectomy, and radiation therapy for metastases, respectively. White and blue open circles indicate complete and partial responses, respectively, whereas orange and grey open squares indicate stable and progressive disease, respectively. Arrows indicate ongoing responses, whereas black, orange, and green circles indicate death due to disease, other causes, and irAEs, respectively. (b) Overall survival and (c) progression-free survival.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- IJCOSupplementarymaterials.docx