Multiple immune-related adverse events and anti-tumor efficacy: real-world data on various solid tumors

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Abstract

Background

Immune checkpoint inhibitors have been approved for various types of cancer; however, they cause a broad spectrum of immune-related adverse events (irAEs). The association between the development of irAEs and the clinical benefit remains uncertain. We aimed to evaluate the association of irAEs and the treatment efficacy in the real-world practice.

Methods

We conducted a retrospective study on patients with recurrent or metastatic non-small cell lung cancer, melanoma, renal cell carcinoma, or gastric cancer who received anti-PD-1/PD-L1 antibodies (nivolumab, pembrolizumab, or atezolizumab) at the Keio University Hospital between September 2014 and January 2019. We recorded treatment-related AEs from medical records and graded them using the Common Terminology Criteria for Adverse Events version 4. We performed an overall survival (OS) analysis using a Cox proportional hazards model.

Results

Among 212 patients eligible for this study, 108 experienced irAEs and 42 developed multiple irAEs. OS in patients with multiple irAEs was significantly longer than that in patients with single irAE (42.3 months vs. 18.8 months; hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.25–0.93; P = 0.03). Moreover, OS from the development of a second irAE in those with multiple irAEs was longer than that from the development of the first irAE in patients with single irAEs (median OS, 26.9 months vs. 17.7 months, respectively; HR, 0.59; 95% CI, 0.30–1.14; P = 0.11).

Conclusions

Our single-center retrospective study revealed a remarkable tendency associating the development of multiple irAEs with favorable prognoses.

Background

Immune checkpoint inhibitors (ICIs) have shown a drastic benefit against malignant melanomas [1, 2], and cancer immunotherapy has become a new standard of care for various malignancies [3–12]. ICIs including antibodies to programmed cell death-1 (PD-1), programmed cell death ligand 1 (PD-L1), cytotoxic T-lymphocyte antigen-4 (CTLA-4), and combinations of these [13, 14] have been approved for non-small cell lung cancer (NSCLC), malignant melanoma (MM), renal cell carcinoma (RCC), gastric cancer (GC), and other types of cancers in Japan.

These ICIs are known to cause specific immune-related adverse events (irAEs) [15]. irAEs occur in a variety of organs, causing signs and symptoms such as interstitial pneumonia, enterocolitis,

hypothyroidism, liver dysfunction, skin rash, vitiligo, hypophysitis, type 1 diabetes, renal dysfunction, neurological disorders, or myocarditis. ICIs are often discontinued due to severe irAEs that may lead to life-threatening conditions. Although the mechanisms of irAEs remain to be elucidated, the enhancement of systemic T-cell activity by ICIs causes a loss of immune tolerance in various organs, resulting in irAEs [16, 17].

Some retrospective studies have reported that the development of irAEs is associated with clinical benefits such as better treatment responses or prognoses for certain malignancies [18–23]. However, these retrospective data were affected by an observation time bias due to higher irAEs risks by longer treatment times in responders. Theoretically unbridle T-cell activity causes severe irAEs, which may also enhance anti-tumor immune reactions. If the development of irAEs reflects a systemic immune activation, the number of irAEs in each patient should be associated with anti-tumor ICI effects. Therefore, we conducted a retrospective analysis focused on the association between the number of irAEs and the clinical outcomes.

Methods

Study design

We retrospectively assessed the efficacy and toxicity of anti-PD-1/PD-L1 antibody, nivolumab, pembrolizumab, and atezolizumab, in patients with four major ICI-approved cancer types: NSCLC, MM, RCC, or GC between September 2014 and January 2019 at the Keio University Hospital in Japan. We excluded patients treated with anti-PD1/PD-L1 antibody during clinical trials or under off-label use, and also patients with prior or concurrent treatment with an anti-CTLA-4 antibody. We collected baseline characteristics, clinical outcomes, and irAEs from clinical records. IrAEs were defined as events occurring during PD-1/PD-L1 treatment and events occurring after ICI treatment, including pneumonitis, diarrhea/colitis, hepatitis, rash, neurological disorders, or endocrine abnormalities, diagnosed as being irAEs by the attending doctor. We graded irAEs using the Common Terminology Criteria for Adverse Events version 4.0. The Keio University Hospital Institutional Ethics Committee approved this study.

Statistical analysis

We defined overall survival (OS) as the time between the initiation of immunotherapy and death from any cause, and we measured time to treatment failure (TTF) as the time from the first administration of ICIs to that of treatment discontinuation for any cause, including disease progression, adverse events, patient preference, or death. We defined the survival post development of irAEs the survival from the development of irAEs to death from any cause. We used the Cox proportional hazard model to calculate hazard ratios (HRs) and adjusted all of them according to primary tumor types. We performed all statistical analyses using the JMP version 14.2.0 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics and irAEs

A total of 219 patients were treated with anti-PD-1/PD-L1 antibody monotherapy between September 2014 and January 2019 in the real-world practice (Fig. 1). We excluded 6 patients with MM or RCC who received combined nivolumab and ipilimumab and 1 patient with MM who received ipilimumab prior to PD-1 antibody monotherapy because we could not rule out the possibility of their irAE being due to ipilimumab. Thus, we analyzed data from 212 patients with NSCLC (n = 112), MM (n = 37), RCC (n = 34), or GC (n = 29). The median follow-up time was 11.3 months (range, 0.04–53.0) as of July 31st, 2019, the analysis cutoff date.

We found 163 irAEs in 108 patients during the treatment or after ICIs discontinuation. The most commonly observed irAEs were included increased alanine transaminase (ALT) (n = 43), rash (n = 31), diarrhea (n = 26), pneumonitis (n = 23), and hypothyroidism (n = 21). We found irAEs with grade ≥ 3 in 36 patients (33%). The baseline characteristics of patients with any irAE (irAEs group) were similar to those of patients without irAEs (no-irAE group) (Table 1). The duration of ICI administration in the irAEs group was significantly longer than that in the no-irAE group (median, 5.0 months vs. 2.7 months, P = 0.021).

Association of irAEs with treatment efficacy

The median OS was significantly longer in the irAEs than in the no-irAE group (median OS, 28.1 months vs. 12.7 months; HR, 0.49; 95% confidence interval [CI], 0.33–0.73; P = 0.0004) (Fig. 2). The TTF was also significantly longer in the irAEs group than in the no-irAE group (median TTF, 5.2 months vs. 2.7 months; HR, 0.49; 95% CI, 0.49–0.90; P = 0.0098).

In the subgroup of patients who had received ICIs over 60 days, OS in the irAEs group (n = 76) tended to be longer than that in the no-irAE group (n = 57) (median OS, 42.3 months vs. 23.1 months; HR, 0.63; 95% CI, 0.35–1.11; P = 0.114). In addition, even in patients who had received ICIs for less than 60 days, the median OS was significantly longer in those in the irAEs group (n = 32) than in those in the no-irAE group (n = 47) (13.3 months vs. 3.4 months; HR, 0.46; 95% CI, 0.25–0.84; P = 0.012).

Association between the number of irAEs in each patient and treatment efficacy

Of 108 patients who experienced any irAE, we found 42 with multiple irAEs (median number of irAEs, 2; range, 2–4). We evaluated the efficacy and safety of ICIs according to the number of irAEs. Table 2 lists characteristics of patients in the multiple irAEs group (n = 42) and the single irAE group (n = 66). We found no significant difference in terms of the baseline characteristics between the two groups. The median durations of ICI administration were 8.6 months (range, 0.04–46.0) in the multiple irAEs group and 4.0 months (range, 0.04–44.5) in the single irAE group (P = 0.13).

Table 3 shows the number of irAEs in the multiple irAEs group and in the single irAE group. We found no specific tendency in the multiple irAEs group. The most commonly observed grade ≥ 3 irAEs in the multiple irAEs group (those with incidence ≥ 5%) were pneumonitis (21%), increased ALT (12%), and adrenal insufficiency (7%); and that in the single irAE group was pneumonitis (6%). The most frequently observed combinations of first and second irAEs were increased ALT and diarrhea (n = 5), and increased ALT and hypothyroidism (n = 5) (Fig. 3).

The median time-to-onset of the first irAE was 2.7 months in the single irAE group (range, 0.04–29.8) and 1.5 months in the multiple irAEs group (range, 0.04–32.4) (P = 0.46, Additional file 1). The median time-to-onset of the second irAEs was 3.8 months in the multiple irAEs group (range, 0.07–34.4), which was significantly longer than that of the first irAE in the single irAE group (P = 0.014).

Patients with multiple irAEs showed significantly longer OSs compared with patients with single irAE (42.3 months vs. 18.8 months; HR 0.48; 95% CI, 0.25–0.93; P = 0.03) (Fig. 4a). The TTF in the multiple irAEs group (although not significantly different) was longer than that in the single irAE group (median TTF, 9.5 months vs. 4.0 months; HR, 0.69; 95% CI, 0.43–1.10; P = 0.12) (Additional file 2). The survival from the development of the second irAEs in the multiple irAEs group was longer than the survival from the development of the first irAE in the single irAE group (median OS, 26.9 months vs. 17.7 months, respectively; HR, 0.59; 95% CI, 0.30–1.14; P = 0.11) (Fig. 4b).

Discussion

This retrospective study shows a unique insight into the association between the number of irAEs in each patient and the efficacy of ICIs. The frequency of irAEs in our hospital was comparable to those in clinical trials [3–6, 24]. Further, patients with any irAE showed longer OSs than those without irAEs as reported [25]. Interestingly, our study revealed that development of multiple irAEs was associated with longer survivals in patients with various types of malignancies. To assess our hypothesis that higher systemic immune activation by ICIs induces multiple irAEs and better anti-tumor effects, we focused on the association between the number of irAEs and the anti-tumor response. As we expected, OS was significantly better in patients with multiple irAEs than in those with a single irAE. In addition, we observed longer survivals from the development of the second irAEs development in patients in the multiple irAEs group compared to the survivals from the development of the first irAE development in patients in the single irAE group. Although it is difficult to exclude the possibility that longer treatment durations increase the chance of second irAEs, our results suggest that development of multiple irAEs may be a predictive biomarker for improved prognoses. Whether patients develop multiple irAEs or not could reflect an association between the efficacy of ICIs and the degree of immune activation by them. Patients who develop single irAE are probably predisposed to the development of the specific irAE, but the irAE does not reflect the systemic immune activation strength after administration of ICIs. On the other hand, development of multiple irAEs may represent a high systemic immune activation induced by ICIs. ICIs target not only tumor-specific T cells but also other T cells, and they may cause the unintended activation of non-tumor-specific T cells, resulting in irAEs in a variety of organs [17]. Of note, we found no specific

irAE type being associated with longer survival, contrary to some reported results [26, 27]. Thus, more clinical evidence is required to elucidate the association mechanisms between irAEs and ICIs efficacy.

Since irAEs are often severe, responsible for ICIs discontinuation, and often life-threatening if not properly managed, strategies to detect the development of irAEs in the early stages and appropriate interventions to counteract them are necessary to strengthen the efficacy and benefit of ICIs. However, no biomarkers for predicting the efficacy of ICIs and the development of irAEs exist [28, 29]. Our results on the association between the presence of multiple irAEs and better prognoses suggest that maintaining ICIs therapy in patients who develop irAEs should be a priority.

We are aware of some limitations of our study due to its retrospective nature. First, we could not define irAEs diagnostic criteria, and some irAEs were diagnosed by exclusion, which could have led to inaccuracies. Second, grade 1 to 2 irAEs could have been underestimated or overlooked in cases in which medical records lacked concrete descriptions; however, we believe most severe irAEs were detected without omission. Finally, since our analysis included four cancer types, the ICI administration regimens varied. To account for this, we evaluated HRs for death adjusting for cancer types.

Conclusions

The development of multiple irAEs may be intimately connected with increased survival. Further research on a larger population is warranted to confirm our results and to elucidate the mechanisms of this association.

List Of Abbreviations

ALT Alanine aminotransferase

CI Confidence interval

CTCAE Common Terminology Criteria for Adverse Events

CTLA-4 Cytotoxic T lymphocyte-associated protein 4

ECOG Eastern Cooperative Oncology Group

GC Gastric cancer

HR Hazard ratio

irAE Immune-related adverse event

ICI Immune checkpoint inhibitor

MM Malignant lymphoma

NSCLC Non-small cell lung carcinoma

OS Overall survival

PD-1 Programmed cell death protein 1

PD-L1 Programmed cell death ligand 1

RCC Renal cell carcinoma

TTF Time to treatment failure

Declarations

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This retrospective study was approved by the Keio University Hospital Institutional Ethics Committee (IRB code: 20180202). It was determined to be a retrospective analysis of de-identified data, and thus was determined to be exempt from requiring written informed consent.

Consent for publication

This manuscript contains no individual person's data.

Availability of data and materials

The datasets generated during the current study are not publicly available due to ethical restrictions, however they are available from the corresponding author on reasonable request.

Competing interests

Dr. Sukawa is affiliated to the department funded by Ono Pharmaceutical Co. Ltd., and has received honoraria from Ono Pharmaceutical Co. Ltd. Dr. Mizuno has received honoraria from Ono Pharmaceutical Co. Ltd., and Bristol-Myers Squibb outside the submitted work. Dr. Suzuki has received honoraria from Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb, MSD Co. Ltd., and Chugai Pharmaceutical Co. Ltd., outside the submitted work. Dr. Funakoshi has received honoraria from Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb, and MSD Co. Ltd., and grants from Ono Pharmaceutical Co. Ltd., outside the submitted work. Dr. Hamamoto has received honoraria from Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb, and Chugai Pharmaceutical Co. Ltd., outside the submitted work. Dr. Kanai has received honoraria from Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb, MSD Co. Ltd., and Chugai Pharmaceutical Co. Ltd, and has received designated donations from Ono Pharmaceutical Co. Ltd., and

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Authors' contributions

KS and YS made substantial contributions to the conception and design, acquisition of data, and data analysis. KS drafted the manuscript. YS made substantial contributions to the study design and revision of the manuscript. TK approved the submitted version. NB, KS, SS, RM, TF, SI, KT, KT, KK, KH, HH, YH and HT have contributed to the acquisition of data. All authors have read and approved the final manuscript.

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Additional Files

Additional file 1. Box plot of time-to-onset by any irAEs.

Additional file 2. Kaplan–Meier estimates of time to treatment failure.

Kaplan–Meier estimates of time to treatment failure in the multiple irAEs and single irAE groups (HR adjusted according to the primary tumor) are shown.

Tables

Table 1. Baseline Characteristics of Patients in the study		
Characteristic (n = 212)	**irAEs (n = 108)**	**No-irAE (n = 104)**
Age—years		
Median (range)	66 (34–94)	69 (30–92)
Male gender—n (%)	71 (66)	75 (72)
ECOG performance status—n (%)		
0	36 (33)	31 (30)
1	64 (59)	54 (52)
≥2	8 (8)	19 (18)
Treatment line—n (%)		
1st line	22 (20)	16 (15)
2nd line	40 (37)	34 (33)
Salvage-line	46 (43)	54 (52)
Cancer types—n (%)		
Non-small cell lung cancer	63 (58)	49 (47)
Malignant melanoma	18 (17)	19 (18)
Renal cell cancer	16 (15)	18 (17)
Gastric cancer	11 (10)	18 (17)
Types of ICIs—n (%)		
Nivolumab	83 (77)	90 (87)
Pembrolizumab	23 (21)	10 (10)
Atezolizumab	2 (19)	4 (4)
Median duration of ICI administration —months (range)	5.0 (0.04–46)	2.7 (0.04–44)
ICIs administration over 60 days—n (%)	76 (70)	57 (55)

Table 2. Baseline Characteristics of the Patients grouped by the number of irAEs			
Characteristic	**Multiple (n = 42)**	**Single (n = 66)**	**P value***
Age at administration—years			
Median (Range)	66 (34–86)	67 (36–94)	0.39
Male gender—n (%)	23 (55)	48 (73)	0.06
ECOG performance status—n (%)			
0–1	40 (95)	60 (91)	0.51
≥2	2 (5)	6 (9)	
Treatment line—n (%)			
1st line	10 (24)	12 (18)	0.62
2nd line or later	32 (76)	54 (82)	
Cancer types—n (%)			
Non-small cell lung cancer	25 (60)	38 (58)	0.82
Malignant melanoma	8 (19)	10 (15)	
Renal cell cancer	6 (14)	10 (15)	
Gastric cancer	3 (7)	8 (12)	
Type of ICIs—n (%)			
Nivolumab	30 (71)	53 (80)	0.56
Pembrolizumab	11 (26)	12 (18)	
Atezolizumab	1 (2)	1 (2)	
Median duration of ICI administration —months (range)	8.6 (0.04–46.0)	4.0 (0.04–44.5)	0.13

* A t-test for difference in means was used to compare ages and median durations of ICI administration; all other variables were compared using Chi-Square and Fisher's Exact tests.

Table 3. Summary of Adverse Events				
Variables	Multiple irAEs (n = 42)		Single irAE (n = 66)	
	Any Grade	Grade≥3	Any Grade	Grade≥3
Increased ALT	23 (55%)	5 (12%)	20 (30%)	2 (3%)
Rash	16 (38%)	0	15 (23%)	1 (2%)
Diarrhea	16 (38%)	2 (5%)	10 (15%)	2 (3%)
Pneumonitis	15 (36%)	9 (21%)	8 (12%)	4 (6%)
Hypothyroidism	17 (40%)	1 (2%)	4 (6%)	0
Adrenal insufficiency	5 (12%)	3 (7%)	3 (5%)	2 (3%)
Neurological disorders	3 (7%)	1 (2%)	3 (5%)	2 (3%)
Others[a]	2 (5%)	2 (5%)	3 (5%)	0

[a]Other irAEs include G2 arthritis, 2 G2 nephritis in the single irAE group, G3 Sjogren syndrome, and G3 thrombocytopenia in the multiple irAEs group.

Figures

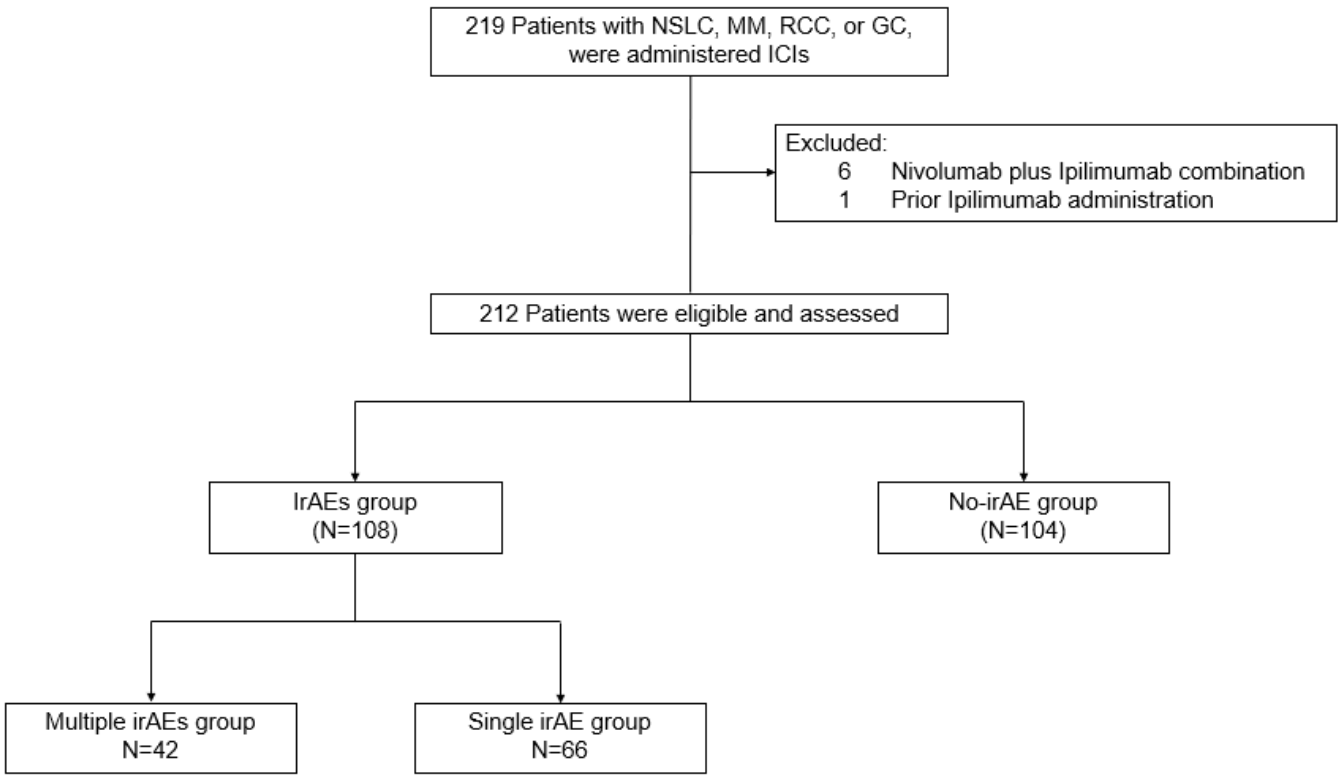

Figure 1

Flow diagram of patient selection and analysis according to the development of irAEs

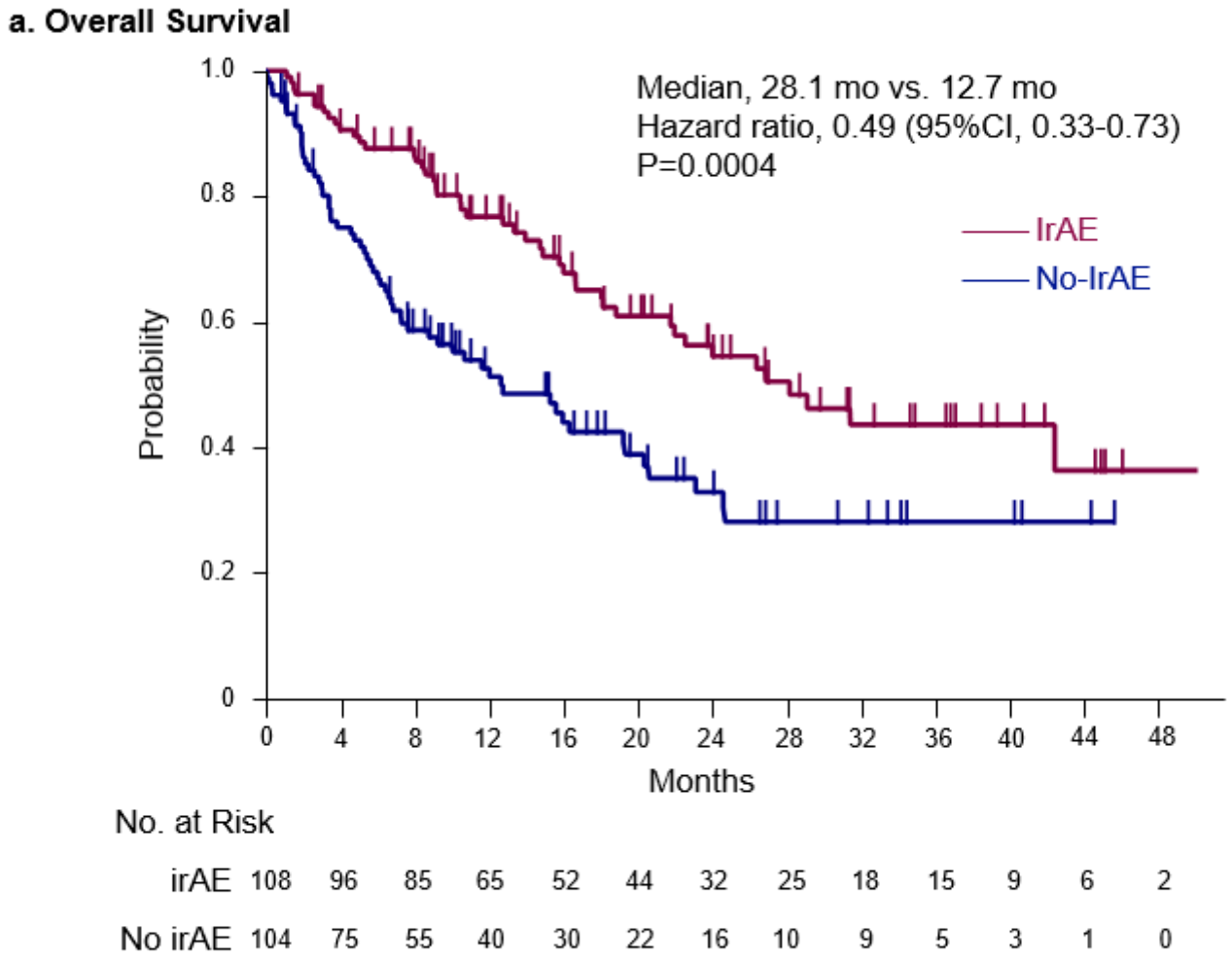

Figure 2

Kaplan–Meier estimation of overall survival. Kaplan–Meier estimates of overall survival in the irAEs and no-irAE groups. We adjusted the hazard ratio for death according to the primary tumor type.

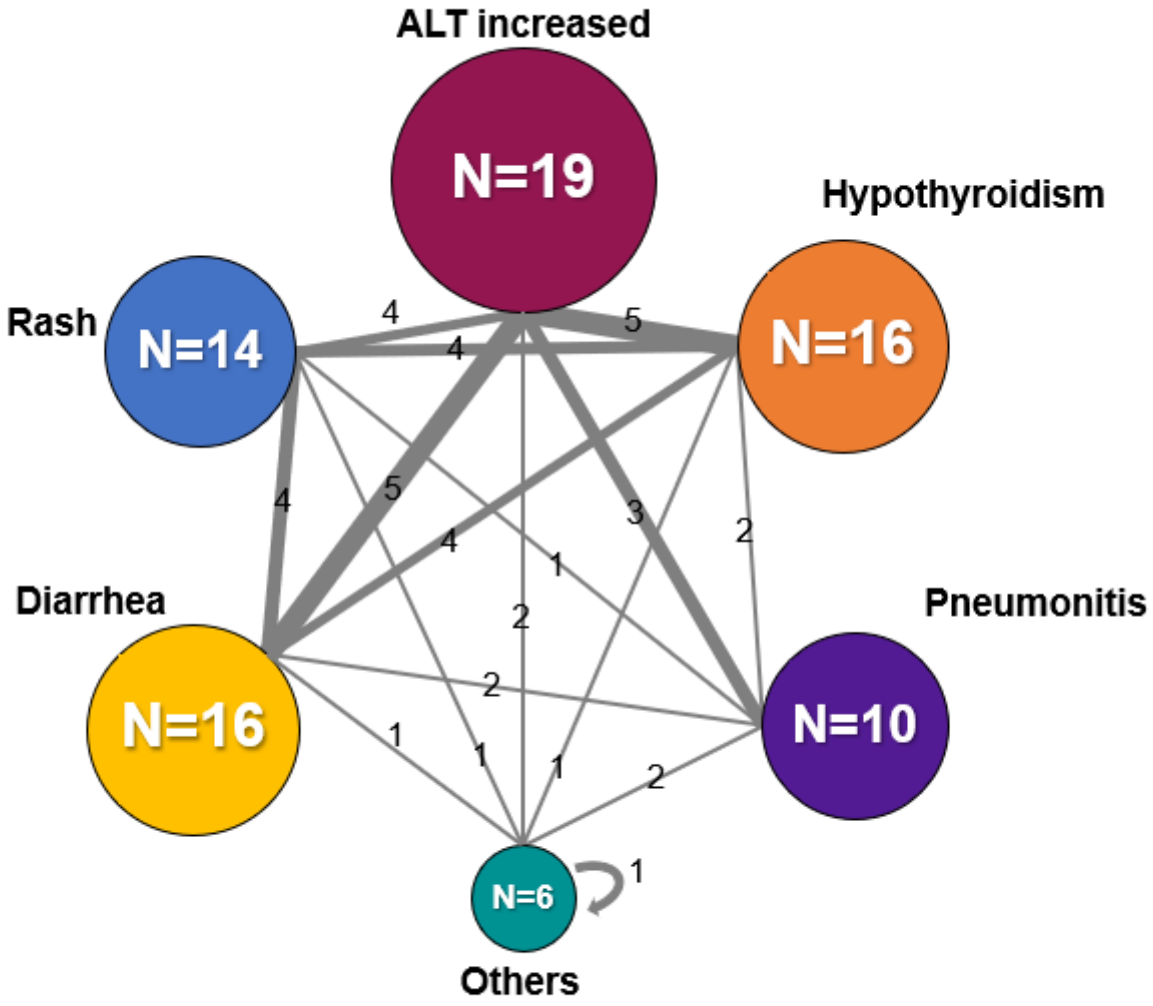

Figure 3

First and second irAE combination profiles in the multiple irAEs group. Numbers may not match the number of irAEs listed in Table 2 because some patients developed three or more irAEs. Others included adrenal insufficiency, neurological disorders, myocarditis, and thrombocytopenia.

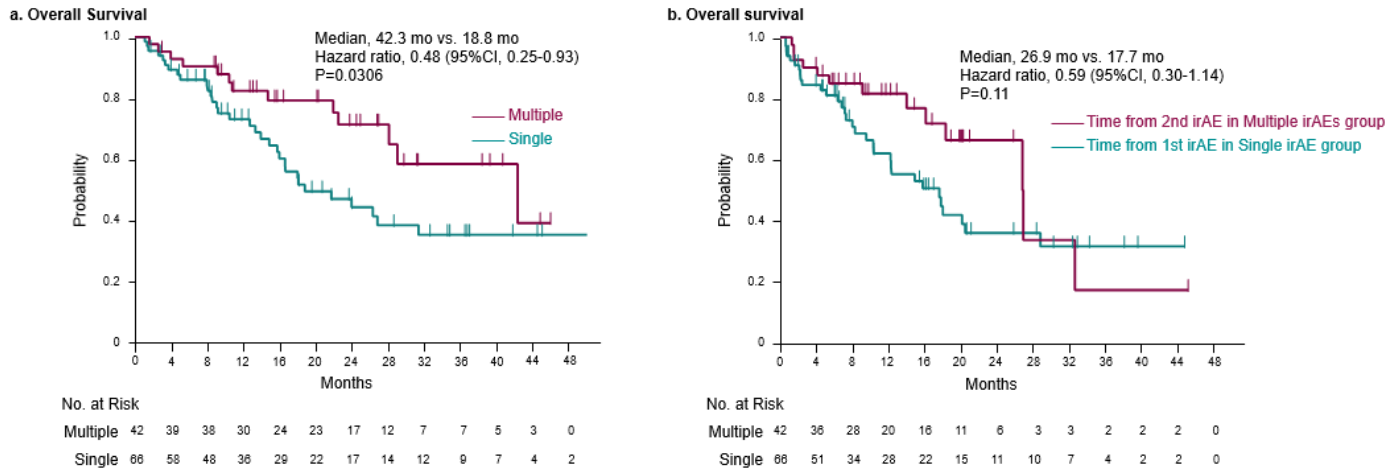

Figure 4

Kaplan–Meier estimation of overall survival in multiple irAEs and single irAE groups. Panel a shows the Kaplan–Meier estimates of overall survival in the multiple irAEs and single irAE groups. Panel b shows the Kaplan–Meier estimates of survival from the development of the second irAEs in the multiple irAEs group, and the survival from development of irAE in the single irAE group. We adjusted the hazard ratio for death according to the primary tumor type.

Supplementary Files

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

- SupplementaryFigure1IRAEANDEFFICACY.pptx
- SupplementaryFigure2IRAEANDEFFICACY.pptx