Adverse events of different PD-1 inhibitors in lung cancer patients: a real-world study

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Background: Programmed death-1 (PD-1) inhibitors have been approved and are currently widely used to treat lung cancer patients. However, comparative data on the adverse events (AEs) associated with different PD-1 inhibitors are very limited.

Methods: Patients with histologically confirmed lung cancer who had been treated with at least 1 dose of PD-1 inhibitors between January 2017 and December 2019 at a tertiary cancer hospital were included in the study. Data on treatment-related AEs (tr-AEs) were collected from their electronic medical records.

Results: A total of 227 lung cancer patients treated with nivolumab (n=83), pembrolizumab (n=65), camrelizumab (n=27), sintilimab (n=31), and toripalimab (n=21) were included. In relation to nivolumab, pembrolizumab, camrelizumab, sintilimab, and toripalimab, the incidence rates of all-grade tr-AEs were 37.34%, 24.62%, 62.96%, 29.03% and 9.52%, respectively (P=0.01), and the incidence rates of grade 3–4 tr-AEs were 2.41%, 3.08%, 22.22%, 3.23% and 0%, respectively (P=0.05). The most common all-grade tr-AEs were capillary hemangioma (22.22%) and abnormal liver function (22.22%) for camrelizumab, pneumonitis for nivolumab (12.05%), pembrolizumab (6.15%) and nausea/vomiting (12.9%) for sintilimab, and pneumonitis (4.76%), rash/pruritus (4.76%) and shingles (4.76%) for toripalimab. Sex, age, PD-1 inhibitors, histology type and PD-1 cycles were significantly associated with tr-AEs.

Conclusions: There were significant differences in the incidence and most common tr-AEs among the different PD-1 inhibitors. Different monitoring priorities should be given to different PD-1 inhibitors during treatment cycles.

Keywords: Programmed death-1 (PD-1); lung cancer; adverse events (AEs)

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Introduction

With an estimated 2,206,771 new cases and an estimated 1,796,144 deaths in 2020, lung cancer is the leading cause of cancer-related death worldwide (1). Programmed death-1 (PD-1) inhibitors, which are recommended for first-line therapy for non-small cell lung cancer (NSCLC) and second-line therapy for small cell lung cancer (SCLC) in the National Comprehensive Cancer Network (NCCN) guidelines, have revolutionized lung cancer therapy. The overall response rate (ORR) and overall survival (OS) were significantly improved compared to standard chemotherapy in both pretreated and treatment-naïve lung cancer patients (2).

However, the treatment-related adverse events (tr-AEs) caused by PD-1 inhibitors, which potentially affect any organ with a very wide occurrence time (from days after first dose to one year after discontinuation) seriously affect drug tolerance and safety (3-5). A meta-analysis revealed that 66% of patients treated with PD-1/programmed death-ligand 1 (PD-L1) inhibitors experienced all-grade tr-AEs, 14.0% experienced grade 3 or higher tr-AEs and 0.45% died from tr-AEs (6). The most commonly tr-AEs mainly involve skin, endocrine glands, gastrointestinal tract, lung, kidney and liver (3-6). In immune checkpoint inhibitor (ICI)-related pneumonitis patients, the mortality rate has been reported to be as high as 18.2% (7). Further, it has been reported that 5–14% of patients discontinue treatment due to tr-AEs (8-10).

Currently, more than 8 PD-1 inhibitors have been approved worldwide and are commonly used to treat lung cancer. Different PD-1 inhibitors were different in immunoglobulin G (IgG) subclasses, fragment antigen-binding (Fab) extracellular domains, Fc receptors and the degree of humanization which result in difference in affinity and specificity to PD-1, antibody dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), IgG-Fc receptors (FcγR) mediate phagocytosis and immunogenicity (11-15). The above biological characteristics may lead to different antitumor activity and tr-AEs of various PD-1 blockers. Capillary hemangioma, a benign proliferation of the capillary endothelial cells, has only been observed in patients treated with camrelizumab (16,17). Besides, incidences of AEs also vary between different PD-1 inhibitors, for example, nivolumab is associated with higher incidences of all-grade AEs [odds ratio (OR) =1.28; 95% confidence interval (CI): 0.97–1.79] and grade 3 or higher AEs (OR =1.30; 95% CI: 0.89–2.00) than pembrolizumab (6).

Therefore, it is important to formulate special monitoring plans according to the spectrum of AEs of different PD-1 inhibitors to ensure treatment safety. Although there have been numerous studies on tr-AEs of PD-1 inhibitors, most of them focus on the comparison between a specific PD-1 inhibitor and chemotherapy, or the relationship between tr-AEs and efficacy either in lung cancer or other cancers. There is a lack of literature to study the tr-AEs of multiple PD-1 inhibitors in the same population. Thus, we conducted a real-world study to evaluate the incidence and spectrum of tr-AEs with all available PD-1 inhibitors in a tertiary cancer hospital in lung cancer patients.

We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6899/rc).

Methods

Patients

This retrospective study was conducted at a tertiary cancer hospital in China. Patients with histologically confirmed lung cancer who had been treated with at least 1 dose of PD-1 inhibitors between January 2017 and December 2019 were included in the study (see *Figure 1*). Patients with incomplete information were excluded from the study. Clinical data and tr-AEs were collected independently by 2 pharmacists from the patients' electronic medical records. The sample size was determined by the eligible cases during the study period. The tr-AE grades were evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0). This study was approved by the Ethics Committee of the Zhejiang Cancer Hospital (No. IRB-2020-57), and complied with the principles of the Declaration of Helsinki (as revised in 2013). All patients signed the informed consent form.

Statistical analysis

The data statistician was blinded to the group information. Baseline characteristics and tr-AEs are presented as frequencies and proportions, and were analyzed using χ^2 tests if all the theoretical frequencies were ≥5 and the total sample size was ≥40, otherwise, Fisher's exact test was used. Differences were evaluated with 2-sided tests, with an α level of 0.05. A multivariate logistic regression analysis was conducted to identify potential risk factors for tr-AEs. All

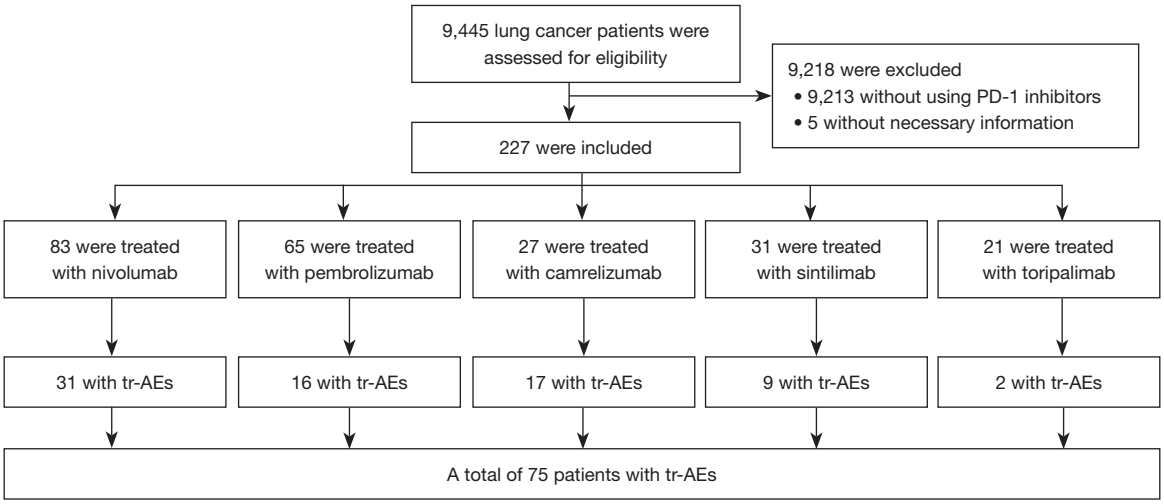

Figure 1 Research flow chart. Lung cancer patients were screened, and 227 eligible patients were included. Treatment-related adverse events (tr-AEs) were collected for each PD-1 inhibitor group.

analyses were performed using SPSS statistical package version 22.0 (IBM, Chicago, IL, USA).

Results

Baseline characteristics

A total of 227 lung cancer patients treated with PD-1 inhibitors were included. The median follow-up period was 2.9 (range, 0.27–24.9) months. Among the 227 patients, 36.56% were treated with nivolumab (n=83), 28.63% with pembrolizumab (n=65), 11.89% with camrelizumab (n=27), 13.66% with sintilimab (n=31), and 9.25% with toripalimab (n=21). Patients had a median age of 63 (range, 34–82) years, and 83.70% (n=190) were male and 16.30% (n=37) were female. In total, 45.81% (n=104) of the patients were treated with PD-1 inhibitors as a monotherapy, and 15.86% (n=36) received more than 10 cycles (see *Table 1*).

Tr-AE incidence rates of different PD-1 inhibitors

In relation to nivolumab, pembrolizumab, camrelizumab, sintilimab, and toripalimab, the total incidence rates of all-grade tr-AEs were 37.34% (31/83), 24.62% (16/65), 62.96% (17/27), 29.03% (9/31), and 9.52% (2/21), respectively (P=0.01), and the total incidence rates of grade 3–4 tr-AEs were 2.41% (2/83), 3.08% (2/65), 22.22% (6/27), 3.23% (1/31), and 0%, respectively (P=0.05). Further, comparisons between each 2 groups after Bonferroni adjustment showed that camrelizumab had a higher incidence of all-grade tr-AEs than pembrolizumab and toripalimab, and a higher incidence of grade 3–4 tr-AEs than nivolumab and pembrolizumab. Tr-AEs led to permanent discontinuation (6.02% for nivolumab, 1.54% for pembrolizumab, 3.70% for camrelizumab, 3.23% for sintilimab and 0% for toripalimab), and dose interruptions (7.23% for nivolumab, 3.08% for pembrolizumab, 7.41% for camrelizumab, 12.90% for sintilimab and 4.76% for toripalimab) did not differ significantly between the different PD-1 inhibitors (see *Table 2*).

Pneumonitis was the most common all-grade tr-AE for nivolumab and pembrolizumab (12.05% and 6.15%, respectively). Conversely, capillary hemangioma (22.22%) and abnormal liver function (22.22%) were the most common tr-AEs for camrelizumab, while nausea/vomiting (12.9%) was the most common tr-AE for sintilimab. In the toripalimab group, the most common tr-AEs were pneumonitis (4.76%), rash/pruritus (4.76%), and shingles (4.76%) (see *Table 2*). Fisher's exact tests showed that there were significant differences between PD-1 inhibitors in relation to capillary hemangioma (P=0.000). Further, a comparison between each 2 groups after Bonferroni adjustment showed that the incidence of capillary hemangioma was higher in the camrelizumab group than the nivolumab and pembrolizumab groups. Pneumonitis was the most common grade 3–4 tr-AE in the nivolumab (2.41%) and pembrolizumab groups (3.08%), while abnormal liver function was the most common grade

Table 1 Baseline characteristics

Variables	Number (%) (N=227)
Sex	
Male	190 (83.70)
Female	37 (16.30)
Age	
>60 years	138 (60.79)
≤60 years	89 (39.21)
Smoke	
Yes	174 (76.65)
No	53 (23.35)
ECOG-PS	
0	87 (38.33)
1	103 (45.37)
2	37 (16.30)
Clinical stage	
I	6 (2.64)
III	52 (22.90)
IV	169 (74.45)
Histology type	
Adenocarcinoma	92 (40.53)
Squamous	104 (45.81)
Other non-small cell lung cancer	12 (5.29)
Small cell lung cancer	19 (8.37)
Lung surgery history	
Yes	12 (5.29)
No	215 (94.71)
Thoracic radiotherapy history	
Yes	118 (51.98)
No	109 (48.02)
Treatment line	
1	82 (36.12)
2	88 (38.77)
3–	57 (25.11)
PD-1 cycles	
1	22 (9.69)
2	28 (12.33)
3	44 (19.38)
4	30 (13.22)
5–10	67 (29.52)
>10	36 (15.86)
Treatment	
PD-1 inhibitor monotherapy	104 (45.81)
Nivolumab	42 (18.50)
Pembrolizumab	33 (14.54)
Camrelizumab	17 (7.49)
Sintilimab	9 (3.96)
Toripalimab	2 (0.88)
PD-1 inhibitor + chemotherapy	79 (34.80)
Nivolumab + chemotherapy	26 (11.45)
Pembrolizumab + chemotherapy	26 (11.45)
Camrelizumab + chemotherapy	1 (0.44)
Sintilimab + chemotherapy	10 (4.41)
Toripalimab + chemotherapy	16 (7.05)
PD-1 inhibitor + antiangiogenic drugs	36 (15.86)
Nivolumab + anlotinib/apatinib/endostatin	7 (3.08)
Pembrolizumab + anlotinib/bevacizumab	5 (2.20)
Camrelizumab + apatinib/bevacizumab	9 (3.96)
Sintilimab + anlotinib/bevacizumab	12 (5.29)
Toripalimab + anlotinib	3 (1.32)
Other combined therapy	9 (3.96)
Nivolumab + ipilimumab	4 (1.76)
Nivolumab + ipilimumab + chemotherapy	2 (0.88)
Nivolumab + bevacizumab + chemotherapy	2 (0.88)
Pembrolizumab + bevacizumab + chemotherapy	1 (0.44)

ECOG-PS, Eastern Cooperative Oncology Group-performance status; PD-1, programmed death-1.

Table 2 tr-AEs of difference PD-1 inhibitors

Tr-AEs	Nivolumab (n=83)	Pembrolizumab (n=65)	Camrelizumab (n=27)	Sintilimab (n=31)	Toripalimab (n=21)	Total (n=227)	P value
All-grade tr-AEs	31 (37.34)[a,b,c]	16 (24.62)[c]	17 (62.96)[b]	9 (29.03)[a,b,c]	2 (9.52)[a,c]	75 (33.04)	0.001
Grade 3–4 tr-AEs	2 (2.41)[a]	2 (3.08)[a]	6 (22.22)[b]	1 (3.23)[a,b]	–[a,b]	11 (4.85)	0.005
Tr-AEs led to permanent discontinuation	5 (6.02)	1 (1.54)	1 (3.70)	1 (3.23)	–	8 (3.52)	0.634
Tr-AEs led to dose interruption	6 (7.23)	2 (3.08)	2 (7.41)	4 (12.90)	1 (4.76)	15 (6.61)	0.300
Hypothyroidism	5 (6.02)	1 (1.54)	–	1 (3.23)	–	7 (3.08)	0.503
Hyperthyroidism	1 (1.20)	–	–	1 (3.23)	–	2 (0.88)	0.657
Pneumonitis	10 (12.05)	4 (6.15)	2 (7.41)	–	1 (4.76)	17 (7.49)	0.256
Abnormal renal function	2 (2.41)	1 (1.54)	3 (11.11)	2 (6.45)	–	8 (3.52)	0.135
Abnormal liver function	5 (6.02)[a,b]	1 (1.54)[b]	6 (22.22)[a]	3 (9.68)[a,b]	–[a,b]	15 (6.61)	0.008
Leukopenia/neutropenia/ thrombocytopenia	4 (4.82)	1 (1.54)	1 (3.70)	–	–	6 (2.64)	0.610
Nausea/vomiting	1 (1.20)	1 (1.54)	3 (11.11)	4 (12.9)	–	9 (3.96)	0.009
Rash/Pruritus	7 (8.43)	–	1 (3.70)	–	1 (4.76)	9 (3.96)	0.055
Capillary hemangioma	–[a]	–[a]	6 (22.22)[b]	–[a, b]	–[a,b]	6 (2.64)	0.000
Fatigue	4 (4.82)	3(4.62)	2 (7.41)	1 (3.23)	–	10 (4.41)	0.882
Shingles	–	–	–	–	1 (4.76)	1 (0.44)	0.093
Hypoalbuminemia	1 (1.20)	1 (1.54)	–	–	–	2 (0.88)	1.000
Phlebitis	2 (2.41)	–	–	–	–	2 (0.88)	0.790
Transient epilepsy	–	–	–	1 (3.23)	–	1 (0.44)	0.348
Hiccup	–	–	1 (3.70)	–	–	1 (0.44)	0.211
Hypomagnesemia	1 (1.20)	–	–	–	–	1 (0.44)	0.561
Lipase elevation	–	–	1 (3.70)	–	–	1 (0.44)	0.211
Drowsiness	1 (1.20)	–	–	–	–	1 (0.44)	1.000
Tongue mucositis	1 (1.20)	–	–	–	–	1 (0.44)	1.000
Hoarseness	1 (1.20)	–	–	–	–	1 (0.44)	1.000
Insomnia	–	1 (1.54)	–	–	–	1 (0.44)	0.629
Diarrhea	–	2 (3.08)	–	–	–	2 (0.88)	0.463
Tears in wind	–	1 (1.54)	–	–	–	1 (0.44)	0.629
Hypokalemia	–	1 (1.54)	1 (3.70)	–	–	2 (0.88)	0.238
Memory loss	–	1 (1.54)	–	–	–	1 (0.44)	0.629
Hiccup	–	–	1 (3.70)	–	–	1 (0.44)	0.210
Oral mucositis	–	–	1 (3.70)	–	–	1 (0.44)	0.210
Albuminuria	–	–	1 (3.70)	–	–	1 (0.44)	0.210

There was no significant difference between groups with the same letter of superscript (a, b, c), but there was a significant difference between the groups with different letters of superscript (a, b, c). Tr-AEs, treatment-related adverse events; PD-1, programmed death-1.

Table 3 Risk factors of treatment-related adverse events

Variable	Univariate			multivariate		
	OR	95% CI	P	OR	95% CI	P
Sex (male/female)	2.277	1.456–3.562	0.000	2.993	1.296–6.912	0.010
Age (>60/≤60 years)	1.661	1.139–2.420	0.008	1.688	1.090–2.613	0.019
Pd-1 inhibitors			0.000			0.000
N/C	0.351	0.203–0.606	0.000	0.260	0.135–0.503	0.000
P/C	0.192	0.115–0.320	0.000	0.167	0.087–0.322	0.000
S/C	0.241	0.146–0.398	0.000	0.168	0.089–0.317	0.000
T/C	0.062	0.030–0.280	0.000	0.043	0.018–0.107	0.000
Clinical stage (IV/II–III)	3.148	1.892–5.237	0.000	1.652	0.895–3.049	0.109
Histology			0.000			0.000
Squamous/adenocarcinoma	0.723	0.498–1.050	0.088	1.406	0.851–2.323	0.183
Other NSCLC/adenocarcinoma	0.135	0.031–0.582	0.007	0.134	0.028–0.636	0.011
SCLC/adenocarcinoma	1.919	1.145–3.217	0.013	5.674	2.690–11.551	0.000
ECOG-PS			0.625			
1/0	0.839	0.585–1.203	0.340	–	–	–
2/0	0.951	0.562–1.607	0.850	–	–	–
Treatment line			0.008			0.095
2/1	0.677	0.427–1.073	0.097	0.609	0.325–1.140	0.121
3–/1	1.277	0.847–1.925	0.244	1.025	0.531–1.980	0.941
Combine treatment (yes/no)	1.752	1.248–2.459	0.001	1.311	0.805–2.136	0.277
PD-1 cycles (≥10/<10)	2.104	1.277–3.466	0.004	2.607	1.450–4.687	0.001
Smoking (yes/no)	0.669	0.454–0.985	0.043	1.787	0.802–3.984	0.156
Drink alcohol (yes/no)	0.659	0.467–0.930	0.017	0.869	0.555–1.361	0.541
Lung surgery history (yes/no)	1.736	0.682–4.415	0.228	–	–	–
Thoracic radiotherapy history (yes/no)	1.914	1.364–2.686	0.000	1.528	0.991–2.357	0.055

N, nivolumab; C, camrelizumab; P, pembrolizumab; S, sintilimab; T, toripalimab; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ECOG-PS, Eastern Cooperative Oncology Group-performance status; PD-1, programmed death-1.

3–4 tr-AE in the camrelizumab (11.11%) and sintilimab groups (3.22%). There was no grade 3–4 tr-AEs in patients treated with toripalimab.

Risk factors for tr-AEs

The univariate analysis revealed that sex (P=0.000), age (P=0.008), PD-1 inhibitors (P=0.000), clinical stage (P=0.000), histology (P=0.000), treatment line (P=0.008), combined treatment (P=0.001), PD-1 inhibitor cycles (P=0.004), smoking (P=0.043), drinking alcohol (P=0.017), and thoracic radiotherapy history (P=0.000) were significantly associated with tr-AEs (see *Table 3*). The multivariate analysis revealed that male (OR =2.993; 95% CI: 1.296–6.912; P=0.001), an age >60 years (OR =1.688; 95% CI: 1.090–2.613; P=0.019), SCLC (OR =5.674; 95% CI: 2.690–11.551; P=0.000), and ≥10 PD-1 cycles (OR =2.607; 95% CI: 1.450–4.687; P=0.001) were independent risk factors for tr-AEs (see *Table 3*). PD-1 inhibitors (P=0.000) were also significantly associated with tr-AEs.

Discussion

PD-1 inhibitors are widely used in lung cancer patients, but there is still a lack of head-to-head research on the differences between efficacy and adverse events. Clinical studies on individual drugs have shown that the incidence and spectrum of tr-AEs are seems to be different in different PD-1 inhibitor. The incidence rates of all-grade tr-AEs with nivolumab, pembrolizumab, camrelizumab, sintilimab and toripalimab were (48–92.3%) (18-23), 51–93% (24-27), 89–100% (28-30), 43.2–93% (31,32) and 77.6–93.8% (33-35), respectively. Conversely, our study reported much lower incidence rates of 37.34%, 24.62%, 62.96%, 29.03% and 9.52%, respectively. This may be because this was a retrospective study, and tr-AEs that were not recorded in the electronic medical system were not able to be included. In addition, traditional Chinese medicine (TCM) was commonly used to treat our patients, which may reduce the occurrence of tr-AEs. Studies have shown that TCM can reduce chemotherapy-related toxicities, such as thrombocytopenia, vomiting, diarrhea, fatigue, and loss of appetite (36-39). Additionally, TCM can affect gut microbiome and T lymphocytes subsets in cancer patients (40). In relation to toripalimab, there was another possible reason for the lower incidence: previous studies have mainly been conducted in patients who had been heavily pretreated, but in our study, 42.86% (9/21) of the patients were treatment naïve. Thus, the physiological and psychological conditions related to AEs should have been better in our study, which may be associated with tr-AEs.

Reports on the most common tr-AEs of PD-1 inhibitors differ among previous studies (30-35). This may be related to whether chemotherapy or other targeted drugs are combined, disease status, patients' conditions, and concomitant medication. In our study, a higher incidence of pneumonitis was observed in the nivolumab group (12.05%) compared to that previously reported (3–6%) (19,41,42). This may be because 51.80% (43/83) of patients in the nivolumab group had a previous history of radiotherapy in our study. Additionally, the incidence of capillary hemangioma was lower in our study (22.22%) than that reported previously (80–97.3%) (30-32,43). This may be because 37.04% (10/27) of patients received combined therapy, 25.93% (7/27) received apatinib, 7.41% (2/27) received bevacizumab, and 3.70% (1/27) received pemetrexed plus cisplatin. Studies have shown that the incidence of capillary hemangioma decreased sharply to 8.9% and 22% when the therapy was combined with apatinib (44) or gemcitabine plus cisplatin (32).

Mechanisms of tr-AEs caused by PD-1 inhibitors have not been fully elucidated, but it is known that tr-AEs may result from some combination of autoreactive T cells, autoantibodies, and proinflammatory cytokines (45,46). The underlying mechanisms of why different PD-1 inhibitors have different tr-AEs are still unclear. The difference of biological characteristics maybe is associated with that. Camrelizumab, a potent agonist of human VEGFR-2, can drive hemangioma development by activating vascular endothelial cell proliferation and lead to high incidence of capillary hemangioma (47).

The risk factors for tr-AEs remain unclear and reports are very inconsistent in different articles. One study reported that concomitant chemotherapy, a higher body mass index, and the presence of epidermal growth factor receptor mutation were predictors for irAEs (48). Another study found that serum albumin ≥3.6 g/dL [hazards ratio (HR) =1.62; 95% CI: 1.10–2.39; P=0.015] and a history of type I hypersensitivity reactions (HR =1.48; 95% CI: 1.02–2.14; P=0.037) were risk factors for irAEs (49). Our research found that sex, age, PD-1 inhibitors, histology type, and PD-1 inhibitor cycles were significantly associated with tr-AEs.

Our results should be interpreted with caution in light of the limitations of the study. First, this was a retrospective study; thus, information bias cannot be excluded, and unrecorded adverse events could not be counted, which may have led to the underestimation of tr-AEs. Second, the incidence rates of tr-AEs with PD-1 inhibitor monotherapy and in combination were not statistically significant separately due to the small sample size. Thus, further studies need to be conducted to clarify the characteristics of the immune-related AEs associated with different PD-1 inhibitors.

In this study, only cases with incomplete data were excluded, and there were no restrictions in relation to age, previous treatment, or the combined use of drugs in the included population; thus, it has good external applicability. Based on results of our research, it is suggested that: (I) differentiated monitoring plan should be made according to different PD-1 inhibitors, for example, capillary hemangioma and liver function should been closely monitored when camrelizumab adopted; (II) special attention should be paid to patients with male sex, age >60 years, SCLC and use PD-1 inhibitor 10 or more cycles.

Conclusions

There was significant differences in the incidence and

spectrum of tr-AEs with different PD-1 inhibitors.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of the Zhejiang Cancer Hospital (No. IRB-2020-57). All patients signed the informed consent form. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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