Efficacy and Safety of PD-1 Immune Checkpoint Inhibitors in Locally Advanced and Advanced NSCLC Patients With Chronic Viral Infection

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Abstract

Introduction

Immune checkpoint inhibitors (ICIs) have become new research hotspots in the treatment of non-small cell lung cancer, but the efficacy and safety of immunotherapy for patients with chronic viral infection are still unclear, because existing clinical trials often exclude those patients.

Methods

We identified 78 locally advanced or advanced NSCLC patients with chronic viral infection treated with PD-1/PD-L1 inhibitors alone or combined with the chemotherapy/bevacizumab therapy, of whom 60 with hepatitis B, 2 with hepatitis C, and 16 with syphilis. Objective response rates were assessed using the RECIST v1.1. Adverse events were graded following the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

Results

Objective responses were observed in 19 out of 78(24.36%) patients, and the disease control rate (DCR) was 69.23% (54/78). No patient achieved a complete response. The median progression-free survival (PFS) was 6.49 months (95% CI:3.71-9.27). PFS was 1.44 months (95%CI:0.00-4.34) for monotherapy versus 7.34 months (95%CI:4.50-10.18) for combination therapy (P=0.053). Patients in the first-line treatment group revealed relatively higher ORR and longer PFS (ORR: 48.00% vs. 13.20%, P = 0.001; PFS: 7.67 months vs. 5.57 months, P = 0.129). Patients with combined radiotherapy showed longer PFS than those without combined radiotherapy (14.07 vs.4.62, P=0.027). The incidence of adverse events of any grade was 73.07% (57/78), among which there were 7 cases of grade 4 adverse events. The incidence of leukopenia was the highest (57.69%), followed by anemia (25.64%) and elevated hepatic transaminase (24.36%). Hepatic transaminase increased in 26.7% (16/60) of HBV patients, and remained unchanged in 65.0% (39/60) patients.

Conclusions

The PD-1 inhibitor showed an acceptable toxicity profile and moderate efficacy on locally advanced and advanced NSCLC patients with chronic viral infection, but still has the potential to increase the incidence of hepatitis. We recommend that those patients be monitored closely and treated with antiviral therapy.

Introduction

Lung cancer is one of the leading causes of cancer-related deaths worldwide [1], and non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers. Despite the existence of various treatment methods such as new chemotherapeutics and gene-targeted drugs, NSCLC patients with lung cancer have below 5-year survival rate and high mortality rate. In recent years, immunotherapy, especially PD-1/PD-L1 immune checkpoint inhibitors, has achieved a great success in the clinical application of various tumor entities by inhibiting the PD-1/PD-L1 signaling pathway and activating the immune system. Therefore, it has fetched much attention of the researchers recently. However, existing clinical trials often exclude patients with viral infections (patients with hepatitis B, hepatitis C, syphilis, etc.), and the efficacy and safety of immunotherapy for such patients are still unclear. There is a high occurrence of hepatitis B in China and the current hepatitis B surface antigen carrying rate of people under 60 is 7.2% [2]. There are about 93 million chronic HBV infections, of which more than 20 million are patients with active hepatitis B [3]. The purpose of this investigation is to retrospectively analyze the efficacy and safety of PD-1 immune checkpoint inhibitors for locally advanced and advanced NSCLC patients with chronic viral infection, to provide a reference for clinical decision-making.

Patients And Methods

Patients

We studied the medical records of all locally advanced and advanced NSCLC patients treated at the Jiangsu Cancer Hospital between May 2018 and July 2021 and identified patients who received the PD-1 inhibitor alone or in combination with the chemotherapy and/or the bevacizumab therapy and screened patients who met one or more of the following criteria: positive for hepatitis B surface antigen; HCV - RNA positive; Syphilis antibody positive. All patients included in this study had at least one measurable disease. This study was approved by the Academic Ethics Committee of Jiangsu Cancer Hospital.

Data collection and response assessment

Medical records were examined and separated on clinical pathologic features and treatment histories. Data and follow-up records were updated as of July 1, 2020. The best response to PD-1 inhibitor-based therapy, defined as a complete or partial response and stable disease achieved at least once during therapy, was assessed using the RECIST v 1.1 criteria. The PFS was defined from the time of treatment initiation to clinical or radiographic progression or death. Adverse events (AEs) were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

Statistical analysis

Survival data were estimated using the Kaplan–Meier method and compared using the log-rank test in the overall cohort and other subgroups. Statistical analyses were performed using the SPSS version 25.0 (SPSS, Inc). $P \leq 0.05$ was considered to indicate statistical significance.

Results

Patients' characteristics

In this study, we considered 78 patients with chronic viral infection who were treated at Jiangsu Cancer Hospital with the PD-1 inhibitor alone or in combination with the chemotherapy and/or the bevacizumab therapy, and their clinical and pathological baseline characteristics are shown in Table 1. The median age of the 78 patients was 65 years, including 62 males and 16 females. Adenocarcinoma was the most common pathological type (56.4%), followed by squamous cell carcinoma (35.9%). Most of the patients (88.5%) were clinically diagnosed with stage IV lung cancer. Out of 78 patients, 60 were suffering from NSCLC with a history of hepatitis B (including 57 patients with past HBV infection and 3 patients with chronic HBV), 2 NSCLC patients had the record of hepatitis C, and 16 with syphilis. All patients received PD-1/PD-L1 immune checkpoint inhibitors, including 10 patients were treated with monotherapy and 68 patients were prescribed with the combination chemotherapy/bevacizumab. Most of the patients (67.9%) received the PD-1 inhibitor-based therapy as second- or late-line therapy and most of the patients (87.2%) did not received combined radiotherapy. Most patients (85.9%) had an ECOG performance status of 0 or 1.

Overall clinical outcomes

As shown in Figure 1A, Objective Radiographic Responses (ORR) was observed in 19 of 78(24.36%) patients, and the disease control rate (DCR) was 69.23% (54/78). No patient achieved a complete response. The median PFS was 6.49 months with a 95% CI of 3.71-9.27 months (Figure 1B). Among those 19 patients who achieved a partial response, 17

were treated with the combination chemotherapy/bevacizumab and only 2 had the PD-1 inhibitor monotherapy, but the results showed no statistically significant difference.

Subgroup analyses

As displayed in Figure 1C , all 10 patients in the combined radiotherapy group were in a more stable condition than that in the non-combined radiotherapy group (DCR=100.00%) ($P < 0.05$) ,and patients with better performance status exhibited a trend of higher DCR than those with poorer performance status (88.23% vs.74.00% vs.18.18%) ($P < 0.05$). Patients in the first-line treatment group (ORR=48.0%) revealed relatively higher ORR and longer PFS than those treated with the PD-1 inhibitor-based therapy as second- or late-line therapy (ORR: 48.00% vs. 13.20%, $P = 0.001$, Figure 1D ; PFS: 7.67 months vs. 5.57 months, $P = 0.129$, Figure 2A). As shown in Figure 2B, PFS was 1.44 months (95%CI:0.00-4.34) for monotherapy versus 7.34 months (95%CI:4.50-10.18) for combination therapy ($P=0.053$), which was not statistically significant, but it was worth observing that 17 out of the 19 (89.47%) patients who achieved a partial response were on combination therapy. Significant difference was observed in the PFS of different combination groups (PD-1 antibody alone vs. PD-1 antibody combined with the chemotherapy vs. PD-1 antibody combined with the bevacizumab vs. PD-1 antibody combined with the chemotherapy and the bevacizumab groups: 1.44 vs.5.67 vs.1.67 vs.14.13, Figure 2C). Patients with combined radiotherapy showed longer PFS than those without combined radiotherapy (14.07 vs.4.62, $P=0.027$) (Figure 2D). The evaluation of lesion for the efficacy of ICI therapy and irradiation site were the same sites in all the patients treated with radiotherapy, and the treatment processes are presented in Table 2.

Safety

As shown in the Table 3, the incidence of any grade treatment-related AEs was 73.07% (57/78), including 7 cases of grade 4 adverse reactions, 3 cases of myelosuppression, 2 cases of pneumonia, 1 case of superior vena cava occlusion, and 1 case of ketoacidosis. No fatal effects happened. Among the treatment-related AEs, the incidence of leukopenia was the highest (57.69%), followed by anemia (25.64%), elevated alanine aminotransferase or aspartate aminotransferase (24.36%) and fatigue (24.59%).

Discussion

In this retrospective study, we have evaluated the efficacy and the safety of the PD-1 inhibitor on locally advanced and advanced NSCLC patients with chronic viral infection. Results show that the PD-1 inhibitor-based therapy, especially combined with chemotherapy and bevacizumab, had moderate efficacy on this population. Notably, the incidence of elevated hepatic transaminase was higher in them than those without chronic viral infection and other toxicity profile was acceptable.

Recently, immunotherapy, especially PD-1/PD-L1 immune checkpoint inhibitors, has brought new hope for lung cancer patients by activating the autoimmune system to achieve the effect of killing tumors. Successful anti-PD-1 / PD-L1 immunotherapy requires an adequate number of specific T cells in the tumor microenvironment. Similar to the tumor microenvironment, the chronic viral infection is a strong immunosuppression environment, leading to specific T cells exhausting [4], in theory, it may influence the effect of ICI which has reversed the role of T cell failure at the same time and undermine the balance between the host immune system and virus control that has caused the risk of liver damage. In China the incidence of hepatitis B is higher. At present, the hepatitis B surface antigen carrying rate among people aged 1-59 is 7.2%. There are about 93 million chronic HBV infected people in China, among which more than 20 million active hepatitis B patients require proper treatment. The efficacy and safety of immunotherapy for these

patients need to be clarified, but existing clinical trials tend to exclude patients with co-viral infection [5].Thus there is not any consensus yet and appropriate strategy of ICIs in this population needs in depth assessment.

In the existing published articles about safety and efficacy of ICIs in patients with chronic viral infection and advanced-stage cancer, the types of cancer involved are not comprehensive, with liver cancer and melanoma accounting for the majority and NSCLC accounting for less than five percent [6]. In one retrospective study of PD-1 inhibitors for NSCLC with special issues involving 32 HBV-infected patients, four of nine patients experienced severe AST/ALT elevation (grade 3 or higher) were HBV patients. And three patients developed viral reactivations or flares, despite receiving anti-HBV therapy prior to the immunotherapy[7]. In another retrospective study, no patients experienced grade 3 or 4 hepatic immune-related adverse events or required ICI discontinuation or corticosteroid administration for management of hepatic toxicity[8]. In our study, the incidence of elevated ALT/AST and increased virus-load was lower than those of the first study and higher than those of the second study. Differences in ECOG performance status, prior lines of therapy, and agents combined with PD-1 antibody of the patients may contribute to the differences among the three studies. Given the unavailability of such information and the limited number of patients in those studies, the results of the three studies were not comparable. Therefore, our study expanded the sample size and detailed the relevant information. There are no existing studies on this population in China (China has the highest prevalence of hepatitis B in the world), and the impact of racial differences on treatment outcomes cannot be ignored. Our study is the first study on the efficacy and safety of ICIs in NSCLC with chronic viral infection in Chinese population.

Among 78 patients included in the study, the objective response rate (ORR) was 24.36% (19/78), and the disease control rate (DCR) was 69.23% (54/78). Comparing the phase III clinical trial Keynote-042 in the Chinese subgroup study[9], the exclusion criteria of which included patients with a history of infectious diseases, the overall objective response rate of the immunotherapy group was similar to the results of this study (24.36% vs. 32.80%) (P=0.250), indicating that the history of infectious diseases does not affect the short-term efficacy. In terms of long-term efficacy, the median progression-free survival (PFS) reached 6.49 months (95% CI :3.71-9.27). Among them, the first-line treatment shows better efficacy than the second-line and later treatment (7.67 months vs. 5.57 months, P = 0.129). Previous studies have proved that the median progression-free survival of advanced NSCLC who received pembrolizumab as the first-line immunotherapy was about 8 months[10, 11], which is similar to our study, and that of advanced NSCLC who received nivolumab as the second-line immunotherapy was about 3 months[12, 13]. In our study, the median PFS of second- and later-line treatment group seems improved than the previous studies. This phenomenon may be because the patients' constitutions are different. In our study, 11.5% of patients were clinically diagnosed with stage IIIB lung cancer, which may have improved the results.

In our group analysis, the short-term efficacy of patients in the first-line treatment group was significantly better than that in the second-and multi-line treatment groups (48.00% vs. 13.20%) (P<0.05). The reason may be that patients in the first-line treatment group have not received other treatments, and there are more specific T cells in the tumor microenvironment than in second-line and multi-line patients, which promote the immune system to recover to a greater extent. The ECOG score of group 0 and group 1 was significantly higher than that of group 2 (88.23% vs.74.00% vs.18.18%) (P<0.05), indicating that patients with better physical conditions are more likely to benefit. The ECOG score of group 2 has poor efficacy, but no deaths related to adverse reactions of immunotherapy occurred, and the safety was fair. The 10 patients in the combined radiotherapy group were all in stable condition, which was better than the non-radiotherapy group, and the PFS was also significantly longer than the patients without combined radiotherapy (14.07 vs.4.62, P=0.027). Because local radiotherapy has a synergistic effect with immunotherapy by enhancing the uptake of antigen by APC, promoting DC activation and migration, and tumor-associated antigen cross-presentation [14]. We divided patients into four groups in accordance with the different agents that were used to combine with the PD-1 inhibitor, drawing the conclusion that patients who received the PD-1 inhibitor in combination with the chemotherapy

and the bevacizumab therapy obtained the longest PFS (PD-1 antibody alone vs. PD-1 antibody combined with the chemotherapy vs. PD-1 antibody combined with the bevacizumab vs. PD-1 antibody combined with the chemotherapy and the bevacizumab groups: 1.44 vs.5.67 vs.1.67 vs.14.13, P=0.002), which is consistent with previous research.

The incidence of adverse events of any group among 78 patients was 73.07% (57/78), including 7 cases of grade 4 adverse reactions, 3 cases of bone marrow suppression, 2 cases of pneumonia, 1 case of superior vena cava obstruction, and 1 case of ketoacidosis. 3 patients who died due to respiratory failure after receiving immunotherapy for 2 months were considered to be affected by rapid tumor progression. The incidence of leukopenia in any grade of adverse reactions was the highest (57.69%), followed by anemia (25.64%), hepatic transaminase elevating (24.36%) and fatigue (21.79%). There is no big difference between the adverse reaction spectrum and the incidence of adverse reactions in patients with infectious diseases and those of patients without infectious diseases, but it is worth observing that the proportion of hepatic transaminase elevating was increased. In the clinical phase III trials of Keynote001, the proportion of alanine aminotransferase (ALT) elevating and aspartate aminotransferase (AST) elevating were respectively 2.2% and 3.0% in the treatment of pembrolizumab.[15] Compared with patients without a history of infectious diseases, the patients in this study displayed a higher incidence of hepatotoxicity. Hepatic transaminase increased in 26.7% (16/60) of hepatitis B patients, of which 5% were Grade 3/4 increased and 65.0% (39/60) remained unchanged, as is shown in Table 4. Among the 3 patients with active hepatitis B, two had a Grade1 elevation of aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) before treatment, one of which decreased to normal after 8 weeks of treatment, and the other had Grade1 elevation of liver transaminase in the first week, and then rapidly rose to Grade3 in the second week, and there was an increase in Grade3 bilirubin. This patient had an increase in hepatitis B virus titer and a progressive increase in the spleen before receiving immunotherapy. Therefore, the change in liver enzymes of this patient was not an immune-related adverse event. Among 57 cases of past HBV infection, 15 patients had increased hepatic transaminase, of which 2 were Grade3 elevated. One case was liver cirrhosis, and the virus titer was high before receiving immunotherapy. The patient did not achieve antiviral therapy. Grade3 hepatic transaminase increased after receiving immunotherapy for 4 weeks. The other patient received antiviral therapy within the first 12 weeks of immunotherapy. The HBV viral load was in a controlled state and he had good liver function. Entecavir was stopped without following the doctor's advice, and a Grade3 increase in hepatic transaminase appeared. The above three patients with Grade3 adverse events were all reversed the adverse events with steroids and ICI was not discontinued, so the adverse reactions were considered acceptable. Compared with patients with previous viral infections, patients with active chronic viral hepatitis had no increased risk of higher-grade liver function tests abnormalities at ICI initiation (P=1.000). Of these 78 patients, 9 patients had baseline liver function abnormalities before treatment (all of them had elevated Grade1 transaminase and elevated Grade1 total bilirubin), and six of them were receiving antiviral therapy, including 5 ALT More than twice the upper limit of normal value and a patient whose ALT did not reach twice the upper limit of normal value but had progressive enlargement of the spleen. Of the 9 patients with abnormal liver function at baseline, 4 had increased hepatic transaminase, of which 2 had Grade 3 increases (mentioned above), and the remaining 2 had Grade2 increases. It is worth noting that 5 hepatitis B patients have decreased liver transaminases, of which 2 patients started receiving entecavir within 2 months before treatment, and 1 patient increased the dose of lamivudine due to the increase in viral titer during treatment. , The other 2 cases received other treatments to improve liver function without antiviral treatment due to a mild increase in ALT, such as polyene phosphatidylcholine, monoammonium cysteine glycyrrhizate, it is considered that the above-mentioned drugs contribute to the reduction of liver transaminase. Among 60 patients with hepatitis B, the viral load of 53 cases remained unchanged, the viral load of 2 cases increased, and the viral load of 5 cases decreased. All 5 patients with reduced viral load received antiviral therapy.

In summary, there was no significant increase in the incidence of these adverse events in patients with a history of infectious diseases. Considering the retrospective nature of our study and small sample size, data from phase IV

studies with relaxed inclusion criteria or from further prospective series are needed to shed more light on the safety and efficacy of ICIs in this challenging population.

Conclusions

In this retrospective analysis, the efficacy of PD-1/PD-L1 immune checkpoint inhibitors on locally advanced and advanced NSCLC patients with chronic viral infection was acceptable, safe, and the clinical outcome was not affected by the history of infectious diseases. Such patients can benefit from immunotherapy. However, considering that the incidence of hepatic transaminase elevating has increased, we recommend close monitoring for such patients in consultation with a hepatologist and to treat those with active viral hepatitis with antiviral therapy prior to the immunotherapy.

Declarations

Ethics approval and consent to participate

The study was approved by the Academic Ethics Committee of Jiangsu Cancer Hospital. (NO. (2020)160) and individual consent for this retrospective analysis was waived.

Consent for publication

All the authors consent to publish it.

Availability of data and material

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

All authors declare no conflict of interest.

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This work received no funding.

Authors' contributions

Conception and design: Shaorong Yu; (II) Administrative support: Jianwei Lu; (III) Provision of study materials or patients: Jifeng Feng; (IV) Collection and assembly of data:Zhiting Zhao; (V) Data analysis and interpretation: Zhiting Zhao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Tables

Table 1 clinical characteristics of patients and clinical activity of anti-PD-1 therapy

Characteristic	Patients number	CR	PR	SD	PD	ORR	P	DCR	P
Age	35(44.9%)	0	10	14	11	28.6%	0.435	68.6%	0.909
≤60	43(55.1%)	0	9	21	13	20.9%		69.8%	
60									
Sex									
male	62(79.5%)	0	17	26	19	27.4%	0.190	69.4%	0.963
female	16(20.5%)	0	2	9	5	12.5%		68.8%	
Histology									
adenocarcinoma	44(56.4%)	0	10	20	14	22.7%	0.118	68.2%	0.949
Squamous	28(35.9%)	0	9	11	8	32.1%		71.4%	
Other	6(7.7%)	0	0	4	2	0.0%		66.7%	
Stage of cancer	9(11.5%)	0	4	2	3	44.4%	0.319	66.7%	0.860
Stage III B	69(88.5%)	0	15	33	21	21.7%		69.6%	
Stage IV									
History of Infectious Diseases									
hepatitis B	60 (76.9%)	0	15	26	19	25.0%	0.567	68.3%	0.867
hepatitis C	2 (2.6%)	0	0	2	0	0.0%		100%	
syphilis	16 (20.5%)	0	4	7	5	25.0%		68.8%	
ECOG performance status									
0	17 (21.8%)	0	6	9	2	35.3%	0.256	88.2%	**0.001**
1	50 (64.1%)	0	12	25	13	24.0%		74.0%	
2	11 (14.1%)	0	1	1	9	9.1%		18.2%	
Prior lines of therapy									
1	25 (32.1%)	0	12	7	6	48.0%	**0.001**	76.0%	0.367
≥2	53 (67.9%)	0	7	28	18	13.2%		66.0%	
Combined with radiotherapy									
Yes	10 (12.8%)	0	3	7	0	30.0%	0.663	100.0%	**0.005**

No	68 (87.2%)	0	16	28	24	23.5%		64.7%	
Agents combined with PD-1 antibody									
anti-PD-1/PD-L1 monotherapy	10 (12.8%)	0	2	3	5	20.0%	0.285	50.0%	**0.001**
combined with chemotherapy	43 (55.1%)	0	14	16	13	32.6%		69.7%	
combined with bevacizumab	6 (7.7%)	0	0	1	5	0.00%		16.7%	
combined with chemotherapy and bevacizumab	19 (24.4%)	0	3	15	1	15.8%		94.7%	
Total	78	0	19	35	24	24.4%		69.2%	

PD-1, programmed death-1.

Table 2. Clinical characteristics, treatment process, clinical activity of patients treated with radiotherapy

Patient	Metastases	Irradiation target	Irradiation area	Irradiation dose	Irradiation times	Clinical activity
1	mediastinum	PTV	mediastinum	40Gy	10f	SD
2	brain	PTV	brain	48Gy	6f	SD
	mediastinum	PTV	mediastinum	36Gy	12f	SD
3	pleura	CTV	pleura	40Gy	10f	SD
4	lung	PTV	lung	50Gy	5f	PR
5	mediastinum	PTV	mediastinum	60Gy	20f	PR
6	lung	PTV	lung	45Gy	15f	SD
7	liver	GTV	liver	40Gy	10f	SD
8	adrenal gland	PTV	adrenal gland	48Gy	12f	SD
9	lung	PTV	lung	30Gy	10f	PR
10	cervical spine	PTV	cervical spine	30Gy	10f	

PTV, planning target volume; CTV, clinical target volume; PD, progressive disease; SD, stable disease; PR, partial response.

Tables 3 Treatment-related adverse events

Event	Total patients (n=78)	
	Any grade	Grade 3 or 4
any event	57(73.07)	23(29.49)
leukopenia	45(57.69)	7(8.97)
anemia	20(25.64)	2(2.56)
elevated ALT or AST	19(24.36)	3(3.85)
fatigue	17(21.79)	0(0.00)
decreased appetite	14(17.95)	0(0.00)
thrombocytopenia	14(17.95)	3(3.85)
nausea	12(15.38)	0(0.00)
rash	9(11.54)	0(0.00)
pyrexia	7(8.97)	2(2.56)
canker sore	7(8.97)	0(0.00)
pneumonitis	6(7.69)	2(2.56)
gingival bleeding	4(5.13)	1(1.28)
nasal bleeding	4(5.13)	0(0.00)
hypothyroidism	3(3.85)	0(0.00)
superior vena cava syndrome	1(1.28)	1(1.28)
ketoacidosis	1(1.28)	1(1.28)

Number of patients with an event (percent). ALT, alanine aminotransferase; AST, aspartate transaminase.

Table 4 The virus load and liver function tests in HBV/HCV patients

virus type	**numbers of patients**	**antivirus therapy**	**virus-load**		
			increase	unchanged	decrease
HBV	60	6	2	53	5
HCV	2	0	0	2	0

follow the table above

change of liver transaminase (%)			
increase		unchanged	decrease
any grade	grade3/4		
16(26.7%)	3(5.0%)	39(65.0%)	5(8.3%)
0(0.0%)	0(0.0%)	2(100.0%)	0(0.0%)

Figures

Figure 1

Clinical outcomes. A, ORR (objective response rate) and DCR (disease control rate) of all patients. B, PFS (progression-free survival) of all patients. C, DCR of patients with or without radiotherapy and DCR of patients with different ECOG performance status. D, ORR of patients treated with ICIs as first-line or later treatment. *: $p<0.05$

Figure 2

Kaplan-Meier curves. A, PFS of patients treated with ICIs as first-line or later treatment. B, PFS of patients treated with ICIs alone or in combination with other drugs. C, PFS of different combination groups. D, PFS of patients with or without radiotherapy.