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ORIGINAL ARTICLE

Effect of osimertinib in treating patients with first-generation EGFR-TKI-resistant advanced non-small cell lung cancer and prognostic analysis

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Summary

Purpose: *To explore the efficacy and safety of the third-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) Osimertinib in the treatment of patients with first-generation EGFR-TKI-resistant advanced non-small cell lung cancer (NSCLC).*

Methods: *The clinical data of 84 patients with advanced NSCLC treated in our hospital from September 2016 to March 2018 were retrospectively analyzed. All patients had progressive disease (PD) after treatment with first-generation EGFR-TKI, and then they were treated with Osimertinib. The remission of disease was analyzed and evaluated after treatment, and the long-term survival and progression of disease were recorded via follow-up. The influencing factors for the patient's prognosis were explored using univariate and multivariate Cox regression analyses.*

Results: *The efficacy was evaluated in all patients at 4 weeks after treatment. There were 0 cases of complete response (CR), 34 cases (40.5%) of partial response (PR), 38 cases (45.2%) of stable disease (SD) and 12 cases (14.3%) of PD. The objective response rate (ORR) and the disease control rate (DCR) were 40.5% (34/84) and 85.7% (72/84), respectively. The main adverse reactions included diarrhea (34.5%), nausea and vomiting (14.3%), constipation (11.9%), rash (27.4%), skin itch (20.2%), loss of appetite (13.1%), oral ulcer (10.7%), hepatic dysfunction (2.4%) and bone marrow suppression, mostly of grade I-II, which could be significantly relieved after symptomatic treatment. The incidence rate of grade III and above adverse reactions was 9.5% (8/84). The dosage of Osimertinib was reduced in 2 cases due to adverse reactions, while other adverse reactions were improved after symptomatic treatment. The levels of vascular endothelial growth factor (VEGF) and carcinoembryonic antigen (CEA) obviously declined from 247.57±20.72 pg/mL and 11.20±1.38 μg/L before treatment to 134.84±14.37 pg/mL and 6.80±0.54 μg/L after treatment ($p<0.05$). The median overall survival (mOS) and median progression-free survival (mPFS) were 25.3 and 10.6 months, respectively. The 1-year OS rate was 79.8% (67/84), and the OS rate was 52.3% at the end of follow-up. Subgroup analysis showed found that heart disease and thrombosis complicated before treatment had significant impact on mOS ($p=0.007$, $p=0.019$). The results of multivariate Cox regression analysis revealed that heart disease and thrombosis complicated before treatment were independent risk factors affecting the patient's OS [HR=2.339 (95% CI: 1.448-5.674), $p=0.031$, HR=1.977 (95% CI: 1.152-2.365), $p=0.020$].*

Conclusion: *Osimertinib has definite efficacy in the treatment of patients with first-generation EGFR-TKI-resistant advanced NSCLC, with a low incidence rate of tolerable adverse reactions. The presence or absence of heart disease and thrombosis before treatment are independent influencing factors for the patient OS.*

Key words: *osimertinib, epidermal growth factor receptor-tyrosine kinase inhibitor, non-small cell lung cancer, advanced stage, efficacy, prognosis*

Introduction

Non-small cell lung cancer (NSCLC) accounts for 80-85% of all lung cancers. The gene mutation rate of epidermal growth factor receptor (EGFR) is the highest (40-55%) in NSCLC patients in East Asia [1,2]. The efficacy of EGFR-tyrosine kinase inhibitor (EGFR-TKI) has been confirmed in the treat-

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ment of EGFR mutation-positive NSCLC [3-5]. The first-, second- and third-generation TKIs mainly include Gefitinib, Erlotinib, Icotinib, Afatinib and Osimertinib, respectively [6]. Drug resistance occurs in most patients within 1-2 years after treatment, 60% of which is caused by T790M mutation [7,8]. As a kind of third-generation irreversible T790M mutation-selective EGFR-TKI, Osimertinib is used for patients with T790M mutation-positive EGFR-TKI-resistant advanced NSCLC [9,10].

In this paper, the clinical data of 84 patients with EGFR mutation-positive advanced NSCLC and progressive disease (PD) after first-generation EGFR-TKI treatment in our hospital were retrospectively analyzed, and the efficacy of Osimertinib and the influencing factors for the patient prognosis were analyzed, so as to provide a strong basis for the treatment of such patients.

Table 1. Baseline characteristics of the studied patients

Parameters	*n=84* *n (%)*
Age (years)	60.6±9.9
Gender (Male/ Female)	54/30
Pathologic type	
Adenocarcinoma	80 (95.2)
Adenosquamous carcinoma	4 (4.8)
Initial EGFR status	
19 del	57 (67.9)
21 L858R	27 (32.1)
T790M status	
+	74 (88.1)
-	10 (11.9)
Brain metastasis	
Yes	23 (27.4)
No	61 (72.6)
Number of metastatic sites	
<3	21 (25.0)
≥3	63 (75.0)
Smoking history	
Yes	37 (44.0)
No	47 (56.0)
KPS score	
70-90	45 (53.6)
60-70	39 (46.4)
Systemic disease	
Hypertension	31 (36.9)
Heart disease	20 (23.8)
Thrombosis	6 (7.1)

EGFR: epidermal growth factor receptor; KPS: Karnofsky performance status

Methods

Objectives of the study

The patients who were diagnosed with advanced NSCLC and used Osimertinib in our hospital from September 2016 to March 2018 were analyzed.

Inclusion criteria: 1) patients who were diagnosed with advanced NSCLC *via* histological or cytological examination, and used Osimertinib due to PD after first-line or multi-line treatment with first-generation EGFR-TKI, 2) those with EGFR gene (exon 19 or 21) mutation, 3) those with a Karnofsky performance scale (KPS) score ≥60 points, 4) those aged above 18 years old, 5) those with measurable lesions shown in CT or MRI scan, and 6) those with stable asymptomatic brain metastasis after treatment.

Exclusion criteria: 1) patients complicated with other tumors, 2) those who used to take other targeted drugs for T790M mutation before using Osimertinib, 3) those with severe dysfunction of heart, liver, kidney or other vital organs, 4) those with severe uncontrolled medical diseases or acute infection, 5) those with severe coagulation disorders or bleeding tendency, or 6) those with a history of neurological or mental disorders. Among the 84 patients, there were 54 males and 30 females aged 41-77 years old with an average of 60.6±9.9 years. Brain metastasis occurred in 23 cases, but did not occur in 61 cases. The number of metastatic sites was <3 in 21 cases, and ≥3 in 63 cases. There were 46 cases of malignant pleural effusion, 37 cases of bone metastasis and 13 cases of liver metastasis. Besides, 74 cases had EGFR-TKI-resistant positive T790M mutation, and the EGFR 19del mutation and 21 L858R mutation were found in 57 cases and 27 cases, respectively (Table 1). The present study was performed according to the *Declaration of Helsinki* and with the approval the Ethics Committee of Shanxi Tumor Hospital, and all patients enrolled signed the informed consent.

Treatment methods

Osimertinib was used once a day (80 mg/time), 3 weeks taken as a course of treatment. After 6 weeks, the efficacy was evaluated. When severe side reactions occurred, corresponding symptomatic treatment should be performed, and the dosage of Osimertinib should be reduced or the drug should be withdrawn. During treatment, the hepatic-renal function examination, blood routine tests, electrocardiography and CT were regularly performed, and adverse reactions were observed and evaluated. None of patients underwent other systemic anti-tumor treatment during treatment with Osimertinib.

Observation indexes

The efficacy was evaluated based on the *Response Evaluation Criteria in Solid Tumors (RECIST) 1.1*: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The objective response rate (ORR) [(CR+PR)/total cases × 100%] and disease control rate (DCR) [(CR+PR+SD)/total cases × 100%] were cal-

culated. Progression-free survival (PFS) refers to the duration from Osimertinib treatment to PD or death of any cause, and overall survival (OS) refers to the duration from Osimertinib treatment to death. According to the *National Cancer Institute-Common Toxicity Criteria 4.0*, the adverse reactions, including anemia, leukopenia, thrombocytopenia, hepatic dysfunction, rash, diarrhea, pruritus, constipation and oral ulcer, were evaluated.

Before and after treatment, 5 mL of fasting venous blood was drawn in both groups, and centrifuged at 3000 rpm for 10 min. Then the serum was taken to detect the levels of carcinoembryonic antigen (CEA, normal reference value ≤5.90 μg/L) and vascular endothelial growth factor (VEGF, normal reference value <127 pg/mL) *via* enzyme-linked immunosorbent assay.

The T790M mutation status was detected in all patients using tissue biopsy (21 cases), peripheral blood (60 cases), and tissue biopsy + peripheral blood (3 cases). The detection methods included polymerase chain reaction (PCR), amplification refractory mutation system (ARMS), droplet digital PCR (ddPCR), Cobas and next-generation sequencing (NGS).

Statistics

SPSS 22.0 software was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test or Fisher's exact probability test were performed for comparison. T-test was used for the intragroup comparison of paired data, and two-way analysis of variance (ANOVA) for the intergroup comparison. The survival curves were plotted using the Kaplan-Meier method, and log-rank test was performed to compare survival differences. The influencing factors for the patient survival were analyzed *via* univariate and multivariate Cox regression analyses. P<0.05 suggested statistically significant difference.

Results

Efficacy

The efficacy was evaluated in all patients at 4 weeks after treatment. It was found that there were 0 cases of CR, 34 cases (40.5%) of PR, 38 cases (45.2%) of SD and 12 cases (14.3%) of PD. The ORR and DCR were 40.5% (34/84) and 85.7% (72/84), respectively (Table 2).

Adverse reactions

The main adverse reactions included diarrhea (34.5%), nausea and vomiting (14.3%), constipation (11.9%), rash (27.4%), pruritus (20.2%), poor appetite (13.1%), oral ulcer (10.7%), hepatic dysfunction (2.4%) and bone marrow suppression, mostly of grade I-II, which could be significantly relieved after symptomatic treatment. In terms of bone marrow suppression, there were 7 cases (8.3%) of anemia, 1 case (1.2%) of leukopenia, and 4 cases (4.8%) of thrombocytopenia. The incidence rate of adverse reactions of grade III and above was 9.5% (8/84), including 4 cases (4.8%) of diarrhea, 3 cases (3.6%) of rash and 1 case (1.2%) of thrombocytopenia. Among them, the dosage of Osimertinib was reduced in 2 cases due to adverse reactions, while other adverse reactions were improved after symptomatic treatment, without affecting treatment (Table 3).

Changes in expressions of serum CEA and VEGF

The levels of VEGF and CEA obviously declined from 247.57±20.72 pg/mL and 11.20±1.38 μg/L before treatment to 134.84±14.37 pg/mL and 6.80±0.54 μg/L after treatment, and the differences were statistically significant (p<0.05) (Figure 1).

Recurrence and patient survival

As of December 31, 2019, the median follow-up time was 25.7 months, and the median OS (mOS)

Table 2. Clinical effective rates of the two studied groups

	n=84 *n (%)*
CR	0 (0)
PR	34 (40.5)
SD	38 (45.2)
PD	12 (14.3)
ORR	34 (40.5)
DCR	72 (85.7)

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate

Table 3. Adverse reactions of Osimertinib in 62 patients with advanced lung z

Parameters	*n=84*	
	Grade I-II *n (%)*	*Grade III-IV* *n (%)*
Nausea / Vomiting	12 (14.3)	0 (0)
Diarrhea	29 (34.5)	4 (4.8)
Constipation	10 (11.9)	0 (0)
Rash	23 (27.4)	3 (3.6)
Pruritus	17 (20.2)	0 (0)
Poor appetite	11 (13.1)	0 (0)
Oral ulcer	9 (10.7)	0 (0)
Hepatic dysfunction	2 (2.4)	0 (0)
Anemia	7 (8.3)	0 (0)
Leukopenia	1 (1.2)	0 (0)
Thrombocytopenia	3 (3.6)	1 (1.2)

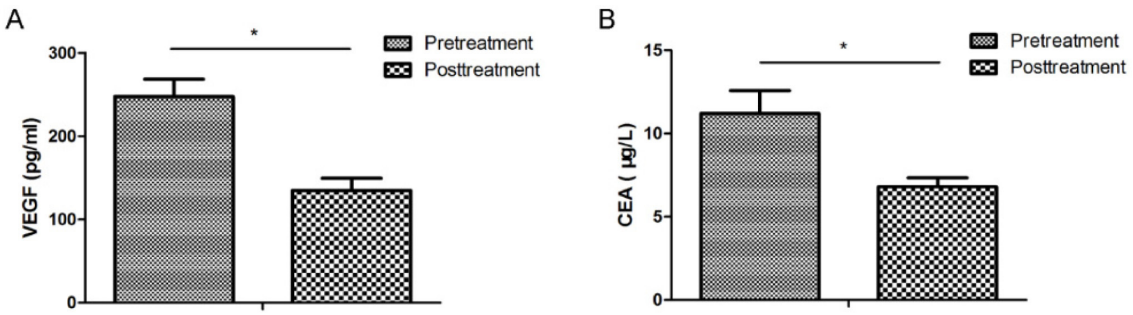

Figure 1. Comparison of pretreatment and posttreatment serum tumor markers of the studied patients. The serum VEGF **(A)** and CEA **(B)** levels of the studied patients were significantly decreased after treatment (*p<0.05).

Table 4. Univariate analysis of predictors for mOS (months) and mPFS (months) in advanced non-small cell lung cancer patients

Parameters	*Cases*	*mOS (months)*	*p value*	*mPFS (months)*	*p value*
Age (years)			0.292		0.365
≤60	49	24.5±3.6		9.43±1.56	
>60	35	26.3±3.9		10.81±1.89	
Gender			0.130		0.289
Male	54	23.9±3.1		10.90±1.77	
Female	30	26.0±3.4		9.67±1.58	
Pathologic type			0.352		0.438
Adenocarcinoma	80	26.1±3.6		10.73±1.86	
Adenosquamous carcinoma	4	24.7±3.7		9.96±1.44	
Initial EGFR status			0.101		0.141
19 del	57	25.9±3.8		10.79±1.51	
21 L858R	27	23.8±3.9		8.94±1.32	
T790M status			0.451		0.116
+	74	26.3±4.0		10.68±1.78	
-	10	25.6±3.3		8.59±1.28	
Brain metastasis			0.129		0.244
Yes	23	25.1±3.4		9.73±1.17	
No	61	27.0±3.9		10.66±1.69	
Number of metastatic lesions			0.091		0.217
<3	21	27.1±4.2		10.74±1.81	
≥3	63	25.2±2.8		8.99±1.29	
Smoking history			0.108		0.187
Yes	37	23.8±2.7		9.45±1.15	
No	47	25.6±3.1		11.57±1.67	
KPS score			0.124		0.463
70-90	45	26.0±3.8		10.87±1.84	
60-70	39	24.2±3.8		9.19±1.22	
Hypertension			0.315		0.383
Yes	31	24.1±3.1		9.06±1.26	
No	53	25.9±3.5		10.80±1.80	
Heart disease			0.007		0.205
Yes	20	22.8±2.8		8.93±1.07	
No	64	27.0±4.0		10.73±1.86	
Thrombosis			0.019		0.438
Yes	6	23.7±2.9		9.18±1.36	
No	78	26.9±3.6		10.90±1.79	

OS: overall survival; PFS: progression-free survival; KPS: Karnofsky performance status; EGFR: epidermal growth factor receptor

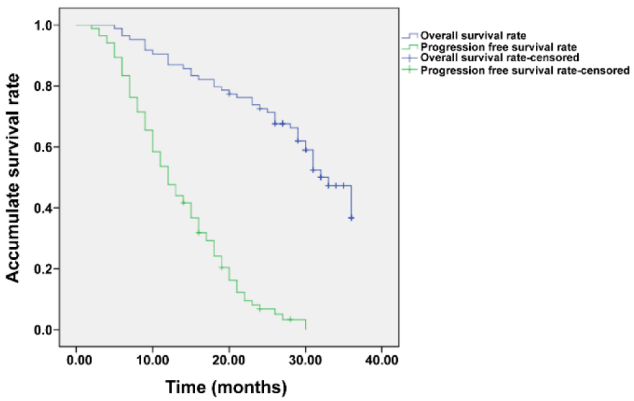

Figure 2. Kaplan-Meier survival curves of advanced non-small cell lung cancer patients. The Figure shows the overall survival rate and progression free survival rate of advanced non-small cell lung cancer patients (p<0.05).

Table 5. Multivariate Cox regression analysis of OS predictors for advanced non-small cell lung cancer patients

Parameters	*HR*	*95%CI*	*p value*
Heart disease	2.339	1.448-5.674	0.031
Thrombosis	1.977	1.152-2.365	0.020

OS: overall survival; HR: hazard ratio; CI: confidence interval

and median PFS (mPFS) were 25.3 and 10.6 months, respectively. The 1-year OS rate was 79.8% (67/84), and the OS rate was 52.3% at the end of follow-up. The OS and PFS curves plotted using the Kaplan-Meier method are shown in Figure 2.

Analysis of prognostic factors affecting patient survival

In the subgroup analysis, the mOS and mPFS were 25.9±3.8 months and 10.79±1.51 months, respectively, in patients with 19del mutation before Osimertinib treatment. The mOS and mPFS were 23.8±3.9 months and 8.94±1.32 months, respectively, in patients with 21 L858R mutation. T790M mutation-positive patients had mOS 26.3±4.0 months and mPFS 10.68±1.78 months, while T790M mutation-negative patients had mOS of 25.6±3.3 months and mPFS of 8.59±1.28 months. Patients with brain metastasis had mOS 25.1±3.4 months and mPFS 9.73±1.17 months, while those without brain metastasis had mOS of 27.0±3.9 months and mPFS 10.66±1.69 months. The mOS and mPFS were 27.1±4.2 months and 10.74±1.81 months, respectively, in patients with ≥3 metastatic lesions. The mOS and mPFS were 25.2±2.8 months and 8.99±1.29 months, respectively, in patients with <3 metastatic lesions. The mOS was 24.1±3.1 months and 25.9±3.5 months, and the mPFS was 9.06±1.26 months and 10.80±1.80 months, respectively, in patients with and without hypertension. The mOS was 22.8±2.8 months and 27.0±4.0 months, and the mPFS was 8.93±1.07 months and 10.73±1.86 months, respectively, in patients with and without heart disease. The mOS was 23.7±2.9 months and 26.9±3.6 months, and the mPFS was 9.18±1.36 months and 10.90±1.79 months, respectively, in patients with and without thrombosis. It can be seen that gender, age, pathological type, EGFR mutation, T790M mutation, brain metastasis, number of metastatic lesions, smoking status, KPS score and hypertension had no obvious impact on mOS and mPFS (p>0.05). Heart disease and thrombosis complicated before treatment had significant impact on mOS (p=0.007, p=0.019), while they had no significant impact on mPFS (Table 4).

Heart disease and thrombosis complicated before treatment were included into the Cox multivariate analysis. The results revealed that heart disease and thrombosis complicated before treatment were independent risk factors affecting the patient OS [HR=2.339 (95% CI: 1.448-5.674), p=0.031; HR=1.977 (95% CI: 1.152-2.365), p=0.020] (Table 5).

Discussion

T790M mutation is the most common mechanism of drug resistance to the first- and second-generation EGFR-TKI [11]. As a third-generation EGFR-TKI selectively acting on T790M-sensitive mutation and secondary T790M-resistant mutation, Osimertinib has exhibited excellent safety and efficacy in early clinical trials (AURA1 and AURA2) [12,13]. In AURA1 involving 239 patients with evaluable efficacy, objective response was realized in 123 cases (51%), including 122 cases of PR and 1 case of CR, and the DCR and mPFS were 84% and 8.2 months, respectively [12]. In later AURA2, a multi-center single-course study, 210 patients with T790M mutation-positive locally advanced or metastatic NSCLC were enrolled and orally took 80 mg of Osimertinib every day. Among 199 patients with evaluable efficacy, the ORR, CR, DCR, mPFS and 1-year survival rate were 70%, 3%, 92%, 9.9 months (95%CI: 8.5-12. 3) and 81%, respectively, but the data about OS were imperfect [13]. In the later extending study of AURA2, it has also been confirmed that EGFR-sensitive T790M-positive NSCLC patients benefit from Osimertinib treatment [14]. Moreover, in AURA3, 419 patients enrolled were randomly divided at 2:1 into experimental group (Osimertinib, 80 mg/d) and control group (pemetrexed + carboplatin or cisplatin, once every 3 weeks, 6 times at most, pemetrexed maintenance therapy allowed). It was found that both mPFS and ORR were significantly improved in the experimental group compared with those in the

control group (4.4 months *vs.* 10.1 months, 31% *vs.* 71%) (HR=0.30 and 5.39), and the median duration of response was 4.1 months *vs.* 9.7 months, respectively, in the two groups [15]. The above findings demonstrate the status of Osimertinib in the standard first-line treatment of disease progression after first-generation EGFR-TKI treatment and patients with T790M-resistant mutation.

In this study, in the efficacy analysis of Osimertinib it was found that the ORR, DCR mOS and mPFS were 40.5%, 85.7%, 25.3 months and 10.6 months, respectively. Compared with those in previous studies, the ORR was lower but PFS was similar [15, 16]. The possible reason is that some patients opted to undergo third-line or further treatment, after which they had larger tumor burden and poor general condition. However, the DCR also reached a satisfactory level (85.7%), which may be related to the tumor and individual heterogeneity, and acquired resistance mechanism of EGFR-TKI [17,18].

In a previous study, Osimertinib exhibited controllable toxicity characteristics, and the most common treatment-related adverse reactions were diarrhea (41%), rash (34%), dry skin (23%) and paronychia (22%) [19]. In this study, Osimertinib showed good safety with tolerable adverse reactions. The incidence rate of adverse reactions of grade III and above was 9.5% (8/84), including 4 cases (4.8%) of diarrhea, 3 cases (3.6%) of rash and grade case (1.2%) of thrombocytopenia. Among them, the dosage of Osimertinib was reduced in 2 cases due to adverse reactions, while other adverse reactions were improved after symptomatic treatment, without affecting the treatment.

After oral administration of Osimertinib, the symptoms and brain lesions of 23 patients with brain metastasis were effectively controlled, and the mOS and mPFS were 25.1±3.4 months and 9.73±1.17 months, respectively. It can be seen that Osimertinib can achieve better efficacy in first-generation EGFR-TKI-resistant advanced NSCLC patients with brain metastasis. In the study of Wu et al, the efficacy of Osimertinib on the central nervous system (CNS) metastasis in T790M-positive advanced NSCLC was deeply analyzed based on the data in AURA3. The results revealed that the ORR was 40% (30/75, 95%CI: 29-52%) and 17% (7/41, 95%CI: 7-32%), respectively, in patients with measurable and/or non-measurable CNS lesions (p=0.014). Among those patients, the median duration of response was 8.9 months (95%CI: 4.3 months - incalculable) and 5.7 months (95%CI: 4.4-5.7 months), and the mPFS was 11.7 months and 5.6 months, respectively, in Osimertinib group and platinum + pemetrexed group (p=0.004). Despite the small sample size in this study, the definite efficacy of Osimertinib was still proved in the treatment of CNS metastasis in T790M-positive advanced NSCLC patients.

In this study, it was found that the presence or absence of heart disease and thrombosis was an independent influencing factor for the OS of EGFR-TKI-resistant advanced NSCLC patients. According to a retrospective analysis involving 18 advanced NSCLC patients with deep vein thrombosis and 87 advanced NSCLC patients without deep vein thrombosis, deep vein thrombosis indicated poor prognosis of patients, and the possible reason was that the tumor progression was accelerated after activation of the coagulation system [20,21].

In this retrospective study, the sample size was limited, the follow-up period was short, the follow-up content was not comprehensive enough, and the influencing factors for ORR and DCR of patients after treatment were not analyzed. In the future, the conclusion of this study needs to be verified by more rigorous large-sample prospective multicenter randomized studies.

Conclusions

Osimertinib has definite efficacy in the treatment of patients with first-generation EGFR-TKI-resistant advanced NSCLC, with a low incidence rate of tolerable adverse reactions. The presence or absence of heart disease and thrombosis before treatment are independent influencing factors for the patient OS.

Conflict of interests

The authors declare no conflict of interests.

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