Anti-PD1/PDL1 antibodies plus chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma

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Research

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Abstract

Background: Patients with advanced esophageal squamous cell carcinoma (ESCC) have a poor prognosis with few treatment options. Immunotherapy was suggested as a promising treatment for ESCC from some clinical trials. Here we collected clinical results from 23 patients who were received anti-PD1/PDL1 antibodies (mAbs) plus chemotherapy as first line therapy with advanced ESCC, to analyze this combined therapy's efficacy on advanced ESCC.

Methods: Results of 23 Patients started treatment from December 15th, 2017 to September 27th, 2019 (12 patients were enrolled in phase II clinical trials, 11 patients were treated by physician's choice regiment) of anti-PD1/PDL1 antibodies (mAbs) plus chemotherapy on advanced ESCC as first line treatment were collected. Regiments were either anti-PD1 or anti-PDL1 mAbs plus traditional chemotherapy (cisplatin/5-fluorouracil (5-FU), Paclitaxel/ cisplatin, Paclitaxel/carboplatin or Paclitaxel/ 5-FU) every 3 weeks for six cycles, followed by maintenance therapy with anti-PD1/PDL1 mAbs. Objective response and safety profiles were observed as well as progression-free survival(PFS), overall survival(OS) and duration of response.

Results: Of the 23 patients, 18 (78.3%) responded to treatment: 15 partial and 3 complete response. 4 patients had stable disease and 1 patient had progressive disease. The median time to response was 1.4 months (range, 1.4 months – 2.8 months). Treatment-related adverse events occurred in all patients but 3-4 grade immune-mediated adverse events occurred in only one patient. As of April 10th, 2020, the Objective response rate was 78.3%, the median PFS was 15.5 months and the median OS was 21.5 months. No treatment-related deaths were observed.

Conclusions: Anti-PD1/PDL1 antibodies plus chemotherapy as the first-line treatment for advanced ESCC showed promising results with manageable adverse events and worthy of further study.

Background

Esophageal cancer is the sixth leading cause of cancer-related death, with an estimated 572,034 new esophageal cancer cases and 508,585 deaths occurred in 2018 worldwide[1]. Compared to western countries where the most esophageal cancer is adenocarcinoma(EAC), the subtype of squamous cell carcinoma exceeds more than 90% of esophageal cancer in Asia, where bearing 70% globule burden of esophageal cancer[23]. Moreover, ESCC is quite different from esophageal adenocarcinoma in terms of etiology, origins of tumor cells, biological behaviors, growth pattern and prognosis. Patients with ESCC have poorer survival than those with EAC[4]. The treatment goal of advanced ESCC is to palliate symptoms and prolong survival. Cisplatin and 5-fluorouracil (5-FU) (CF) have been established as the standard chemotherapy for advanced ESCC for several decades. Other regiments such as triplet, irinotecan-based, oxaliplatin-based and paclitaxel-based regimens and anti-EGFR inhibitors have been conducted in clinical trials to investigate modern therapeutic agents. However, the advantages of these strategies are limited and it often leads to a low qualities of life for patients[5]. Thus, new effective therapeutic approaches for

advanced ESCC are urgently needed. Immune checkpoint PD-1 or its ligand PDL1 inhibitors have demonstrated robust and durable anti-tumor efficiency and manageable toxicity in numerous advanced solid tumors and are approved for the treatment of one or more advanced cancers in more than 60 countries. In esophageal cancer, they also indicated the durable clinical benefits and manageable safety profiles as KEYNOTE-028[6], KEYNOTE-180[7], KEYNOTE-181[8], ONO-4538[9], and ATTRACTION-03[10]clinical trials investigated, which indicated a promising option for advanced ESCC. However, the overall response rate remained low and immunotherapy in these studies were all the second or more lines therapy for esophageal cancer. In addition, these clinical trials not only focused on advanced ESCC, which leads to hard to tell the accurate response reactivity on this specific esophageal cancer subtype. Evidences indicated immunotherapy plus chemotherapy can improve the overall response rate in many cancers. In esophageal cancer, a phase III clinical trial (KEYNOTE-590) will evaluate the anti-tumor activity of two different groups [pembrolizumab + cisplatin + 5-fluoruracil (5-FU) vs. placebo + cisplatin + 5-FU] in patients with previously untreated esophageal carcinama. Early results of PFS and OS of patients will be expected in 2021[11].

Here, we report results from 23 patients with advanced esophageal squamous cell carcinoma which was unresectable or incurable by radiotherapy received anti-PD1 /PDL1 mAbs combined with traditional chemotherapy as first line treatment. These data were reported of immunotherapy plus chemotherapy as first line treatment for advanced ESCC for the first time.

Methods

Patients

Results of 23 patients started treatment from December 15th, 2017 to September 27th, 2019 (12 patients were enrolled in phase II clinical trials, 11 patients were treated by physician's choice regiment) of anti-PD1/PDL1 antibodies (mAbs) plus chemotherapy on advanced ESCC as first line treatment were collected. Patients aged ≥ 18 years with a diagnosis of unresectable advanced or recurrent esophageal squamous cell carcinoma (American Joint Committee on Cancer, 7th edition) were collected. Previous chemotherapy or radiotherapy were not permitted. In clinical trials, all studies were performed in accordance with the International Conference on Harmonisation Good Clinical Practices guideline and in compliance with their studies protocols. For the rest 11 patients treated by physician's choice, study was performed in compliance with the study protocol, which was approved by the Ethics Committee of the first affiliated hospital of Zhejiang University. All patients were provided with written informed consent before enrollment. All authors have access to the data and participated in the written, reviewed or edit the draft of the article and ensure the integrity of the accuracy data analysis.

Study Design

In this study, patients received 3 mg/kg (weight ≤ 60 kg) or 200 mg (weight 60 kg) of anti-PD1 or anti-PDL1 mAbs plus traditional chemotherapy (cisplatin/5-fluorouracil (5-FU), Paclitaxel/ cisplatin, Paclitaxel/carboplatin or Paclitaxel/ 5-FU) every 3 weeks for six cycles, followed by maintenance therapy with anti-PD1 or anti-PDL1 mAbs respectively until progression, death or unacceptable toxicity. The specific indications of chemotherapy were 5-FU 750 mg/m2, cisplatin 75 mg/m2, paclitaxel 175 mg/m2 and carboplatin 75 mg/m2. The primary outcomes of this trial were objective response and safety. Key secondary outcomes including PFS, OS and tolerability, duration of response.

Assessments

Tumor imaging was performed every 2 cycles (1.4 months). Response was assessed per RECIST v1.1 and per irRC by investigator. PFS was calculated as the time between day1 (treatment started) and disease progression defined by RECIST v1.1 or last follow-up date. Patients were followed up for survival until death or study closure. Adverse events (AEs) were assessed for up to 30 days after treatment (90 days for serious AEs) and were graded according to Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analyses

Safety and efficacy analyses were performed in all patients. The response rate was assessed by point estimate. Duration of response, progression-free survival, and overall survival was estimated using the Kaplan-Meier method. 95% CIs were calculated using the Clopper-Pearson method.

Results

Patients

From December 15th, 2017, to September 27th, 2019, 23 patients with advanced esophageal squamous cell carcinoma which was unresectable or incurable by radiotherapy were collected (Fig. 1). Baseline characteristics were list in Table 1. All patients received anti-PD1/PDL1 mAbs plus chemotherapy as first line therapy. The median duration of follow-up time (defined as the time from start of treatment to death or the date of data cutoff for those who were alive) was 11.9 months (range, 6.0-27.2 months) as of April 10th, 2020. As of April 10th, 2020, 7 patients (30.4%) had completed at least 12-months treatment, 12 patients (52.2%) had discontinued treatment because of progressive disease or death, one patient (4.3%) discontinue treatment because of other diseases (tuberculosis), and 10 patients remained on treatment (Fig. 1).

Table 1
Baseline characteristics

Characteristic	N (N = 23)	%
Median age, years (range)	63(46–69)	
Male	23	100
Female	0	0
Tumor location		
Upper thoracic	6	26.1
Mid-thoracic	5	21.7
Lower thoracic	12	52.2
TNM stage		
IVa	8	34.8
IVb	15	65.2
ECOG PS		
0	7	30.4
1	15	65.2
2	1	4.3
1^{ST} line of therapy	23	100
Abbreviation: ECOG PS, Eastern cooperative oncology group performance status.		

Table 2
Regiments

Chemotherapy	Anti-PD1 /PDL1 mAbs	No.
5-FU [a]+Cisplatin	Tislelizumab	6
	Nivolumab	2
	CS1001 [b]	5
Paclitaxel + Cisplatin	Sintilimab	5
	Camrelizumab	2
Paclitaxel + Carboplatin	Toripalimab	1
5-FU + Cisplatin	Camrelizumab	1
Paclitaxel + 5-FU	Sintilimab	1
Abbreviation: 5-FU, 5-fluorouracil		
[b] CS1001: Anti-PDL1 antibody;		
Tislelizumab, Nivolumab, Sintilimab, Camrelizumab and Toripalimab: Anti-PD1 antibodies		

Efficacy

The objective response rate by central review per International Working Group 2007 criteria was 78.3% (95% CI, 56–92%). And the disease control rate (DCR) was 95.7% (95%CI, 78%-100%). Overall, 3 patients (13.0%) achieved a complete response (CR) and 15 patients (65.2%) achieved a partial response (PR), 4 patients (17.4%) achieved a stable disease (SD) and the another 1 patient (4.3%) had a progression disease (PD) by Lugano criteria (Table 3). Early and durable responses were observed (Fig. 3B, C), the median time to response was 1.4 months (range, 1.4 months – 2.8 months). The median duration of response of these patients was not reached, although was anticipated to extend beyond the range 5.1–23.8 months, and the 6 months disease control rate was 91.3% (Table 3). Twenty two (95.7%) of 23 evaluable patients had target lesion size reduced from baseline (Fig. 3A, B). One of these patients, while on study treatment, had partial response (according to criteria pre investigator) 1.4 months after treatment, discontinued treatment because of tuberculosis. At data cutoff, among 3 CR patients, 1 patient still on the treatment with its PFS of 25.2 months, another 2 CR patients had cancer recrudesced in retroperitoneum and adrenal gland, defined as disease progression with its PFS of 17.3 and 18.4 months respectively. At data cutoff, the median PFS was 15.5 months, the median OS was 21.5 months (Table 3). At data cutoff, 7 patients (30.4%) had died, and the overall survival of them were 27.2, 21.5, 18.3, 15.5, 9.8, 9.2, 6.0 months respectively.

Table 3
Antitumor activity (based on Response Evaluation Criteria in Solid Tumors version 1.1)

Response, % (95% CI)	
Overall response	78.3 (56–92)
Complete response	13.0 (3–34)
Partial response	65.2 (43–84)
Stable disease	17.4 (5–39)
Disease control rate	95.7 (78–100)
Progressive disease	4.3 (0–22)
Median time to response, months (range)	1.4(1.4–2.8)
Median duration of response, months (range)	7.5+ (5.1 + to 23.8+)
Median PFS, months	15.5
Median OS, months	21.5
6 months disease control rate n(%)	21 (91.3%)
Abbreviation: PFS, Progression-free survival	

Safety

Treatment-related adverse events of any grade occurred in all patients. Grade 3 or 4 treatment-related adverse events occurred in 16 patients (69.6%) (Table 4). The most common adverse events were neutropenia, gastrointestinal reaction, Alopecia and fatigue. No patient died as a result of treatment-related adverse events.

Immune-mediated adverse events of any grade occurred in 19 patients (82.6%) (Table 4). One patient had grade 4 rash which was considered related to immunotherapy and discontinued treatment, other immune mediated adverse events were all grade 1 or 2 events.

Table 4
Incidence of Treatment-related adverse events

Treatment-Related Events				
Any		23 (100)		
Grade 3–4		16 (69.6)		
Led to discontinuation		0		
Led to death		0		
≥ 0% incidence	Grade 1–2	Grade 3	Grade 4	Grade 5
Diarrhoea	7 (30.4)	0	0	0
Decreased appetite	17 (73.9)	2 (8.7)	0	0
Fatigue	20 (87.0)	3 (13.0)	0	0
Nausea	18 (78.3)	2 (8.7)	2 (8.7)	0
Alopecia	19 (82.6)	4 (17.4)		0
Neutropenia	12 (52.2)	8 (34.8)	2 (8.7)	0
Anaemia	20 (87.0)	0	0	0
White blood cell count decreased	16 (69.6)	6 (26.1)	0	0
Peripheral sensory neuropathy	16 (69.6)	2 (8.7)	0	0
Fever	6 (26.1)			
Immune-mediated adverse events				
Any		19 (82.6)		
Grade 3–4		1 (4.3)		
Led to discontinuation		1 (4.3)		
Led to death		0		
≥ 0% incidence	Grade 1–2	Grade 3	Grade 4	Grade 5
Rash	12 (52.2)	0	1 (4.3)	0
Hypothyroidism	10 (43.5)	0	0	0
Capillary hyperplasia	3 (13.0)	0	0	0
NOTE. Data presented as No. (%).				

Discussion

Clinical outcomes are poor for patients with advanced ESCC. For stage IV ESCC, effective therapies are limited. The median OS of conventional chemotherapy for stage IV ESCC was just 7.7 months (231 days)[12]. And conventional treatments often lead to low life qualities of these patients.

In esophageal carcinoma, the clinical trials results of anti-PD1/PDL1 mAbs were all came from 2 or more lines of therapy, the ORR ranges from 6.7%-30%, median PFS ranges from 1.4 to 3.4 months and the OS ranges from 5.6 to 11.1 months as previously KEYNOTE-028[6], KEYNOTE-180[7], KEYNOTE-181[8], ONO-4538[9], and ATTRACTION-03[10]clinical trials investigated. For advanced esophageal carcinoma, conventional chemotherapy includes cisplatin and 5-fluorouracil (5-FU) (CF), triplet, irinotecan-based, oxaliplatin-based and paclitaxel-based regimens. The efficacy of these strategies was limited (ORR 15%-62.5%, median PFS 3.9-7 months, median OS 7–13 months) and the incidence of toxicities was high.

In this analysis of 23 patients with advanced esophageal squamous cell carcinoma which is unresectable or incurable by radiotherapy, we established the clinical benefit and safety of anti-PD1 /PDL1 mAbs combined with chemotherapy in this patient population. The safety profile of this combination was acceptable and manageable. The response rate was up to 78.3% (18 of 23), 3 patients (13.0%) achieved a complete response and 15 patients (65.2%) achieved a partial response. As data cutoff of April 10th, 2020, the median PFS was 15.5 months, the median OS was 21.5 months, which largely exceeded the median OS (7.7 months) of the similar conditions' patients in conventional chemotherapy as first line therapy. As data cutoff, 7 patients (3 CR and 4 PR) PFS exceeded 15 months and 1 patient (CR) with its PFS of 25.2 months remained in treatment without progression. The time to initial response was 2 cycles after initial treatment (1.4 months) in 18 patients and another 1 patient achieved confirmed PR 4 cycles after initial treatment (2.8 months), and the median duration of response was not reached, although was anticipated to extend beyond the range 5.1–23.8 months

Although it is difficult to make direct comparisons among several trials since which had some different clinicopathological patient characteristics, with the median PFS of 15.5 months (which even exceeded the median OS for the similar conditions' ESCC patients in other trials) and ORRs of 78.3% (which exceeded more than twice of which in almost all other trials with the similar conditions' ESCC patients), our study showed comparable efficacy and outcomes. In addition, 7 patients died, 6 of these 7 patients' original ECOG performance status were 1, which means these patients' original conditions were poor. And the patient excluded because of tuberculosis responded pretty well and reached partial response criteria and even remained partial response for 1 year. These promising data demonstrated potent anti-tumor efficiency of the combination therapy.

Recent studies have shown that chemotherapy can induce favorable immunogenic compounds and stimulated immune system [13,14]. The mechanism of efficacy of chemotherapy for tumor is it can destroy rapidly growing cells in the body. The neoantigens caused by platinum salts can be added to de novo mutations caused by tobacco smoke and other carcinogens in ESCC[15,16]. And evidence showed that mutation landscape can determine sensitivity to PD1/PDL1 blockade, the presence of these neoantigens

can increase the effectiveness of anti- PD1/PDL1 mAbs and thus affect tumor regresssion[17,18]. Chemotherapy combined with immunotherapy, can help improve tumor antigens' cross-presentation, thus reverse the immunosuppression to some extent, promote the proliferation of effector T cells, and enhances the anti-tumor function of the immune system[19–21].

For patients with metastatic/recurrent or advanced ESCC, the primary treatment goal is to alleviate cancer-related symptoms, minimize treatment-related toxicity, prolong survival time, and improve quality of life[22]. In our study, the life quality of patients was good and at the data cutoff of April 10th, 2020, in 12 patients (the patient with tuberculosis was excluded) who have received the combination treatment more than 12 months, they all completed 6 cycles of chemotherapy, which is hard to achieve in conventional chemotherapy. It is partial because of the shrinking of the major lesion of esophageal promoted patients' nutrition conditions since they can eat more.

There were also some limitations of this study. The sample size was too small and the patients enrolled were all Asian and male, which could lead to selection basis. A phase III of large data sets and muti-centre were warranted in the future and the results of KEYNOTE-590/MK-3475-590 were expected. Our study also did not focus on biomarkers to predict the effect of this combination therapy. PD-L1 overexpression is associated with worse clinical outcomes in ESCC[23–25]. However, the higher ORR of anti-PD1 mAb and longer median OS were also observed in PD-L1 overexpression patients when compared to the patients with low PD-L1 expression[7,8,26]. Further investigation should be done to analyze the potential biomarkers for this combination therapy.

Conclusion

In summary, this is the first report of immunotherapy plus chemotherapy as the first line treatment of advanced ESCC. These data demonstrated that treatment with anti-PD1/PDL1 mAbs combined with chemotherapy is an effective and safe option in patients with advanced ESCC. It tremendously prolonged the PFS and OS of these patients and patients had better life quality when compared with treatment by conventional treatments. These combined treatments are worthy of further study.

Abbreviations

ESCC
Esophageal squamous cell carcinoma
mAbs
Monoclonal antibodies
PFS
Progression free survival
OS
Overall survival
EAC

Adenocarcinoma
AEs
Adverse events
DCR
Disease control rate
CR
Complete response
PR
Partial response
SD
Stable disease
PD
Progression disease
5-FU
5-fluorouracil
CF
Cisplatin and 5-fluorouracil
ECOG PS
Eastern cooperative oncology group performance status

Declarations

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Availability of data and materials

The datasets generated during the current study are available

Authors' contributions

JQ, WL, HW, LT and NX were involved in the conception and design of the work. CM and HJ collected the data. JQ, WL, HW, LT and NX did the data analysis and interpretation. JQ, WL and HW were major

contributors in writing the manuscript, and CM revised the manuscript. All authors approved the final manuscript. JQ, WL and HW contributes equally, LT and NX are the Co-corresponding authors.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the first affiliated hospital of Zhejiang University. All patients were provided with written informed consent before enrollment.

Consent for publication

Consent for publication was obtained from the participants

Competing interests

The authors declare no conflicts of interest

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Figures

Figure 1

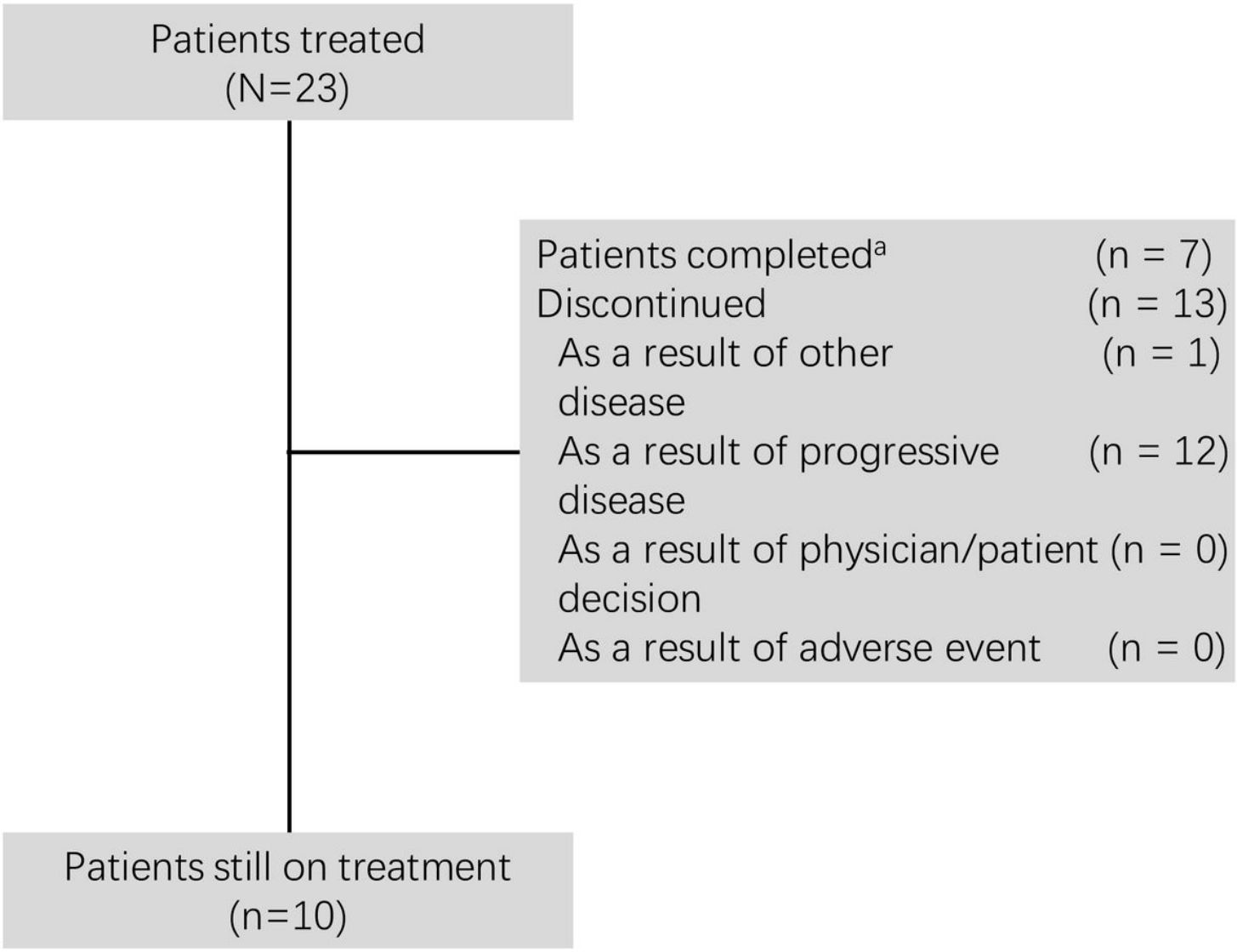

Figure 1

Study design

Figure 2

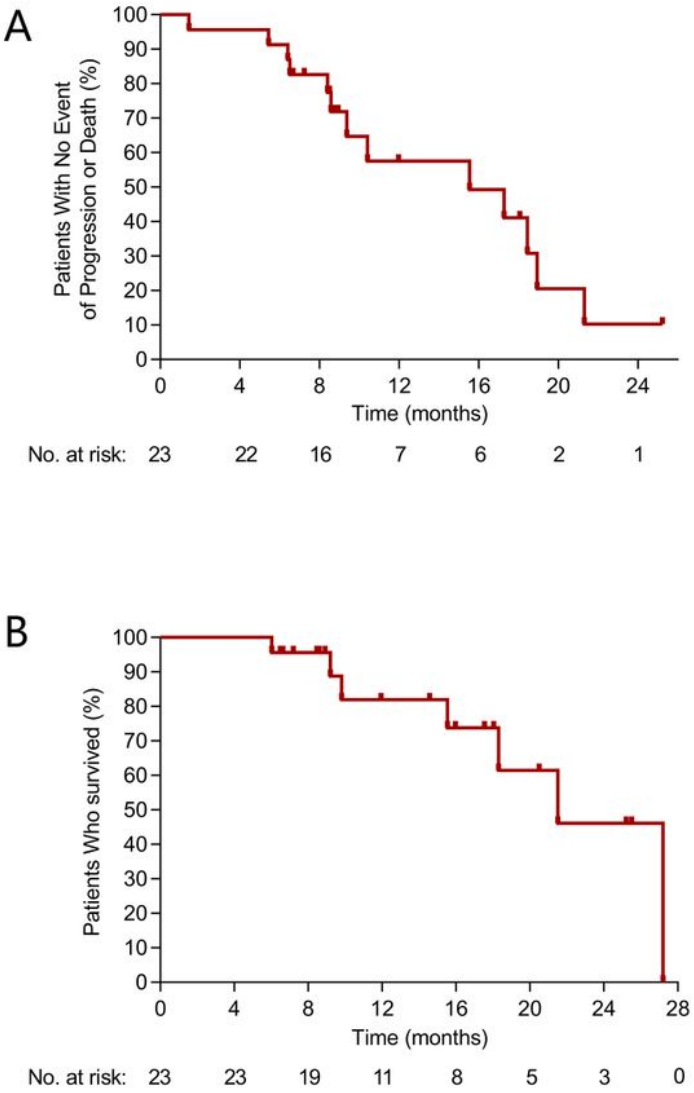

Figure 2

Kaplan–Meier estimates of progression-free survival (A) and overall survival (B)

Figure 3

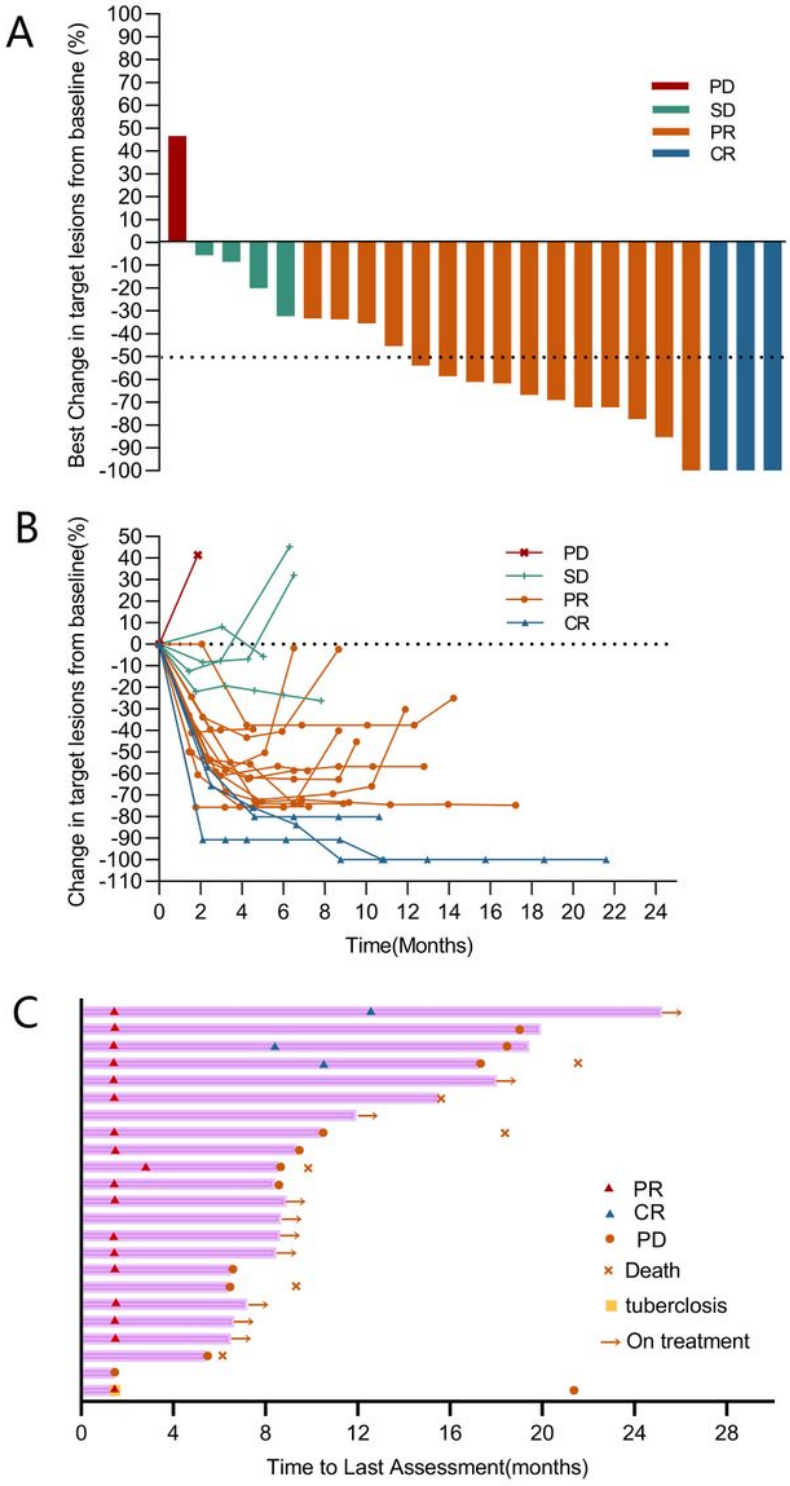

Figure 3

Best change from baseline in target lesion size (A) Change in sum of target lesion diameters over time (B) and treatment exposure and duration of response (C) for evaluable patients.