A phase I study of anlotinib combined with platinum-pemetrexed in untreated non-squamous non-small cell lung cancer

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Research Article

Keywords: anlotinib, phase I study, non-small cell lung cancer, first-line therapy

Posted Date: July 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-698041/v1

Abstract

Background

Anlotinib hydrochloride is an oral small molecule multi-target tyrosine kinase inhibitor, and it has been approved as third-line therapy for patients with advanced non-small cell lung cancer (NSCLC) in China. This dose-exploration study was designed to investigate the feasibility of anlotinib in combination with chemotherapy in patients with non-squamous NSCLC.

Methods

This phase I study followed a 3 + 3 dose reduction design with three dose levels of anlotinib (12mg, 10mg, 8mg). Anlotinib was given at an initial dose of 12mg with pemetrexed (500mg/m^2) plus cisplatin (75mg/m^2) or carboplatin (AUC = 5) on 21-day cycles for 4 cycles. The primary goal of the study was to identify the maximum tolerated dose (MTD) and secondary endpoints included progression free survival (PFS) and overall survival (OS).

Results

A total of eight participants were enrolled. DLTs were observed in two patients (pts) at anlotinib 12mg (grade 3 hand-foot syndrome and grade 3 appetite loss). No DLTs occurred at anlotinib 10mg and the MTD was 10mg. Among seven pts evaluable, four achieved confirmed partial response (PR) and three had stable disease (SD). With a median follow-up of 10.05 months, the median PFS was 7.00 months (95%CI: 2.76 to NE). Grade 3 treatment-related adverse events (TRAEs) included appetite loss (n = 2), hypertension (n = 2), thrombocytopenia (n = 1), diarrhea (n = 1) and hand-foot syndrome (n = 1). No grade 4 or grade 5 TRAEs observed during the treatment.

Conclusion

The feasible dose of anlotinib in combination with platinum-pemetrexed as first-line therapy was 10 mg, which was well tolerated and showed promising antitumor activity in advanced non-squamous NSCLC.

Introduction

In recent years, various antiangiogenic therapies have been evaluated in combination with platinum-based chemotherapy as first-line therapy for advanced NSCLC without driver gene mutations[1, 2]. However, only Bevacizumab, a humanized monoclonal antibody that binds vascular endothelial (VEGF), has been approved in the clinic [3–5]. Small molecule tyrosine-kinase inhibitors (TKIs) with antiangiogenic activity such as sorafenib, cediranib and vandetanib et al. have also been investigated in

this setting, while no significant survival improvement was observed. In addition, most of these oral TKIs result in added toxicities. Therefore, clinical trials about antiangiogenic TKIs in combination with chemotherapy for untreated NSCLC are worthy of further exploration.

Anlotinib is an oral angiokinase inhibitor that blocks VEGFR 1 to 3, platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1 to 4 [6, 7]. Besides, receptor kinases of RET, c-Kit and c-Met are also inhibited. With low half maximal inhibitory concentration (IC_{50}), anlotinib has shown promising anti-tumour activity in various tumors including NSCLC in previous studies[6, 8], and it is the only CFDA-approved angiokinase inhibitor for advanced NSCLC [9]. Based on the pharmacokinetics of anlotinib, limited drug-drug interactions allow its combination with cytotoxic drugs. Therefore, anlotinib-platinum-pemetrexed (APP) regimen was investigated in this trial. Considering the toxicity profile of anlotinib monotherapy as well as the predicted intolerance of the combination therapy, a dose-reduction design was employed, reducing anlotinib from 12 mg to 10mg and 8mg.

Patients And Methods

Study population

Eligible patients had histologically or cytologically confirmed stage IIIB/IIIC/IV non-squamous NSCLC; negative mutations of EGFR\ALK\ROS1; age range from 18 to 70; never received any systematic treatment (including immunotherapy); Eastern Cooperative Oncology Group (ECOG) performance status 0–1; survival time expected ≥ 3 months; and no major organ dysfunction. Patients were excluded if they had active brain metastases, uncontrolled hypertension, severe cardiovascular diseases, and coagulation abnormalities.

This study was reviewed and approved by the Institutional Review Board of West China Hospital, Sichuan University. Written informed consent was obtained from all participants. This study is registered with ClinicalTrials.gov, number NCT04012619.

Study design

This study employed a standard 3 + 3 dose reduction design (Fig. 1) and eligible patients received anlotinib-chemotherapy regimen on 21-day cycles for 4 cycles. Pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) or carboplatin (AUC = 5) were intravenously given on day 1 of each cycle. According to the ALTER0303 study, the initial dose of anlotinib was set as 12 mg/day with a 2-week on/1-week off schedule and was reduced to 10 mg/day and 8 mg/day in sequence depending on DLTs in cycle 1. Patients who had disease control after the combination regimen continued to receive anlotinib maintenance until disease progression.

Assessments

Adverse events (AEs) were monitored during the study and summarized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. Based on Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, tumor response was evaluated by computerized tomography (CT) or magnetic resonance imaging (MRI) at baseline and subsequently every 6 weeks until study termination. Patients who had complete response (CR) and partial response (PR) were required to have efficacy confirmation at least 4 weeks after the initial evaluation.

The primary endpoint was the MTD of anlotinib, at which less than 33% of patients experienced a DLT in the first treatment cycle. DLT was defined as grade 4 and above hematological toxicity, grade 2 and above liver and kidney function injury and grade 3 and above non-hematological toxicity. The secondary endpoints included PFS and OS. PFS was defined as the time from the date of randomization to the date of disease progression or death. OS was defined as the time from the date of randomization to the date of death.

Statistical analysis

Recruitment of a minimum of 3 patients and a maximum of 18 patients was planned in accordance with the 3 + 3 study design. Analyses were based on Apr 10, 2020, database lock. All patients who received at least one dose of the investigational drug were included in safety assessment and those who completed at least one cycle of the treatment were eligible for efficacy evaluation. The baseline demographic characteristics and frequency of adverse events were summarized with descriptive statistics. Two-sided 95% exact CIs were calculated for ORR and DCR using the Clopper-Pearson method, and estimated time-to-event endpoints were calculated with the Kaplan-Meier method with two-sided 95% CIs for medians. All statistical analyses were carried out with SAS 9.1.3 software.

Results

Demographic characteristics

A total of 8 patients enrolled in this trial between April 2019 and November 2019. All patients were untreated before and had histological confirmation of adenocarcinoma without sensitizing EGFR/ALK/ROS1 alterations (Table 1). Their median age was 62 years (39.0–69.0) and 7 of them had an ECOG performance status of 1.

Table 1
Patient characteristics at baseline

Characteristics	Anlotinib (n = 8)
Age, median (range), years	62.0 (39.0–69.0)
Gender, n (%)	
Male	5 (62.5)
Female	3 (37.5)
ECOG, n (%)	
0	1 (12.5)
1	7 (87.5)
Stage, n (%)	
IVA	5 (62.5)
IVB	3 (37.5)
Smoking history, n (%)	
Ever	4 (50.0)
Never	4 (50.0)

DLT and MTD

In the study, two DLTs were observed in two pts separately at anlotinib 12mg (grade 3 hand-foot syndrome and grade 3 appetite loss). No DLTs occurred at 10mg and the MTD was determined as 10mg, at which less than 33% of pts experienced a DLT when treated with anlotinib-platinum-pemetrexed combination.

Safety

AEs were monitored throughout the treatment until 30 days after termination of the trial. AEs occurred in all patients and 5 of them experienced grade 3 AEs (Table 2). The most frequently AEs were appetite loss (87.5%), alanine transaminase elevation (62.5%), aspartate transaminase elevation (62.5%), thrombocytopenia (50%), nausea (50%), hypertension (50%) and fatigue (50%). Grade 3 treatment-related adverse events (TRAEs) included appetite loss (n = 2), hypertension (n = 2), thrombocytopenia (n = 1), diarrhea (n = 1) and hand-foot syndrome (n = 1) (Table 3). No grade 4 or grade 5 TRAEs were observed during the treatment.

Table 2
Overview of adverse events and discontinuations

n (%)	Anlotinib (n = 8)
Total patients with ≥ 1 AE	8 (100.0)
Serious AE	3 (37.5)
Severe AE (grade ≥ 3)	5 (62.5)
AE leading to death	0 (0.0)
AE leading to withdrawal from treatment	2 (25.0)
AE leading to dose modification/interruption	5 (62.5)
Treatment-related AE	8 (100.0)
Treatment-related serious AE	3 (37.5)

Table 3
Summary of most common TRAEs reported in ≥ 20% of patients

AE, n(%)	Anlotinib (n = 8)	
	Total	≥ Grade III
TRAEs	8 (100.0)	5 (62.5)
Appetite down	7 (87.5)	2 (25.0)
Hypertriglyceridemia	5 (62.5)	0 (0.0)
Alanine transaminase elevation	5 (62.5)	0 (0.0)
Aspartate transaminase elevation	5 (62.5)	0 (0.0)
Hypertension	4 (50.0)	2 (25.0)
Thrombocytopenia	4 (50.0)	1 (12.5)
Nausea	4 (50.0)	0 (0.0)
Fatigue	4 (50.0)	0 (0.0)
Neutropenia	3 (37.5)	0 (0.0)
Hypercholesterolemia	3 (37.5)	0 (0.0)
Leukopenia	3 (37.5)	0 (0.0)
Dizziness	3 (37.5)	0 (0.0)
Hand-foot syndrome	2 (25.0)	1 (12.5)
Diarrhea	2 (25.0)	1 (12.5)
Vomiting	2 (25.0)	0 (0.0)
Gum pain	2 (25.0)	0 (0.0)
Proteinuria	2 (25.0)	0 (0.0)
Hypothyroidism	2 (25.0)	0 (0.0)
Anemia	2 (25.0)	0 (0.0)
Hoarseness	2 (25.0)	0 (0.0)
Thyroid stimulating hormone elevation	2 (25.0)	0 (0.0)
AE: adverse event; TRAEs: treatment-related adverse events		

Efficacy

Tumor response was assessed in 7 cases, for one patient withdrew the consent before completing the first cycle. Among the evaluable cases, 6 exhibited tumor shrinkage (Fig. 2). Four had confirmed PR and 3

were SD while no PD was reported (Table 4). At data cut-off on Apr. 10, 2020, six of them had terminated the treatment, predominantly due to disease progression. With a median follow-up of 10.05 months, the median PFS time was 7.00 months (2.76 to NE) (Table 4).

Table 4
Clinical activity

Best overall response	**Anlotinib (n = 7)**
Confirmed objective response (%), (95%CI)	57.14 (18.41, 90.10)
Confirmed disease control (%), (95%CI)	100.00 (59.04, 100.00)
Complete response, n (%)	0
Partial response, n (%)	4 (57.14%)
Stable disease, n (%)	3 (42.86%)
Progressive disease, n (%)	0
Survival time	**Anlotinib (n = 7)**
Median follow-up time (months), (95%CI)	10.05 (5.59, 11.40)
Median progression-free survival (months), (95%CI)	7.00 (2.76, NE)

In detail, of four responders, three were in 12mg group and another one was in 10mg group (Fig. 2). The responder who experienced the maximum tumor shrinkage was in the high-dose group with a response by the first scan (Fig. 3). At the time of the analysis, one subject in 12mg group was still in this trial and showed sustained remission after 4 cycles of the combination treatment and 10 cycles of anlotinib maintenance (Fig. 3).

Discussions

The tolerability, safety and efficacy of anlotinib combined with chemotherapy were explored in the study and it was demonstrated that anlotinib-platinum-pemetrexed regimen was well tolerated at the dose of anlotinib 10 mg in advanced NSCLC patients. Meanwhile, the combination therapy demonstrated promising anti-tumor activity in these patients with an acceptable safety profile.

Overall, AEs in our study were mild and the majority were of grade 1 or 2 severity. Specific adverse events related to anlotinib such as hypertension and hand-foot syndrome were in the range of incidence reported in previous trials involving anlotinib[10]. On the other side, the combination therapy resulted in higher occurrence of hematological toxicities such as neutropenia, thrombocytopenia, leukopenia and anemia when compared with platinum-pemetrexed alone, indicating an additive myelosuppressive effect of anlotinib, which had been mentioned by other investigators [11]. However, the hematological events significantly declined in 10mg group, and the majority of these events were fully resolved. Overall, there

was no evidence that anlotinib potentiated chemotherapy toxicity and each individual drug could be administered in combination with the recommended dosage.

Remarkably, tumor response of anlotinib-platinum-pemetrexed in this trial (57.14%) was encouraging, since pemetrexed-cisplatin alone only showed a response rate of 30.6% in JMDB study, indicating a synergistic effect of anlotinib. Furthermore,we reported a median PFS of 7.00 months, and as far as we know this was the first reported PFS of APP regimen for treatment-naive NSCLC. These favorable results were mainly attributed to the high selectivity and potent inhibition to VEGFR2 as well as broad inhibitory effect on other pro-angiogenic pathways of anlotinib [12, 13]. In addition to the anti-angiogenic activity, research revealed that anlotinib suppressed tumor cell growth and migration via blockading c-Kit, c-Met and RET [14]. Collectively, our findings suggested that the combined treatment was efficacious and could be an alternative option for non-squamous NSCLC.

Limitations to the findings included the small size of the study sample, by which it was difficult to draw firm conclusions on the anti-tumor efficacy. Besides, the single-arm design of the trial limited its ability to directly compare results with chemotherapy alone. Considering these, the APP regimen could be further validated by controlled trials in the future.

Declarations

Funding

None.

Conflicts of interests

The authors declare that there were no conflicts of interest in the study.

Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Author contributions

M.J.H and Y.L were responsible for the conception and design of the study. M.J.H, Y.M.L, M.Y were responsible for acquisition and analysis of data; furthermore, Y.Y.L conducted statistical analysis. M.J.H drafted the manuscript; Y.L revised and commented the draft, and all authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Our study was approved by the Ethics Committee of West Hospital of China, Sichuan University. Written informed consent of the patient was obtained.

Consent for publication

Not applicable.

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Figures

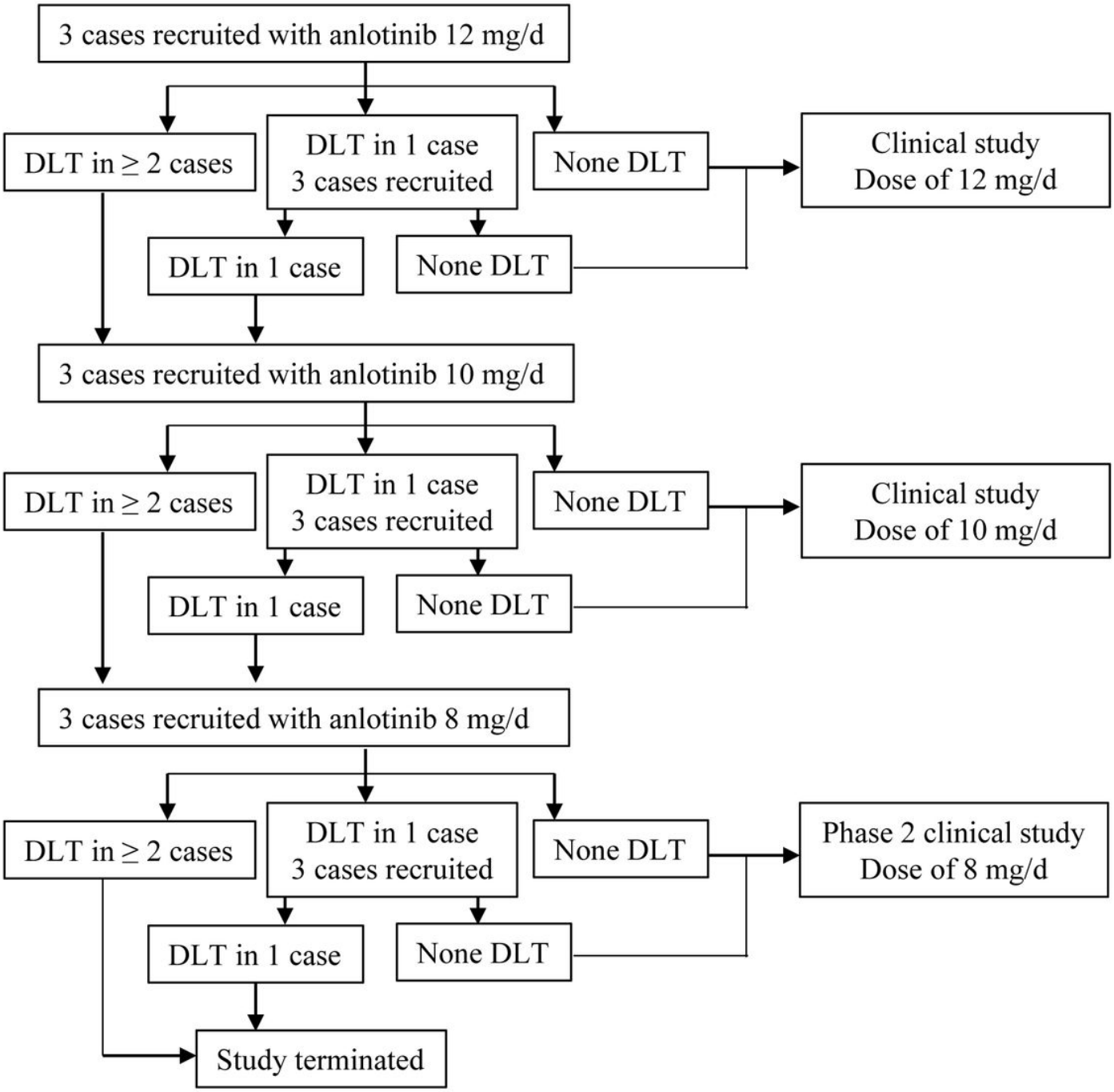

Figure 1

3+3 dose reduction design and process

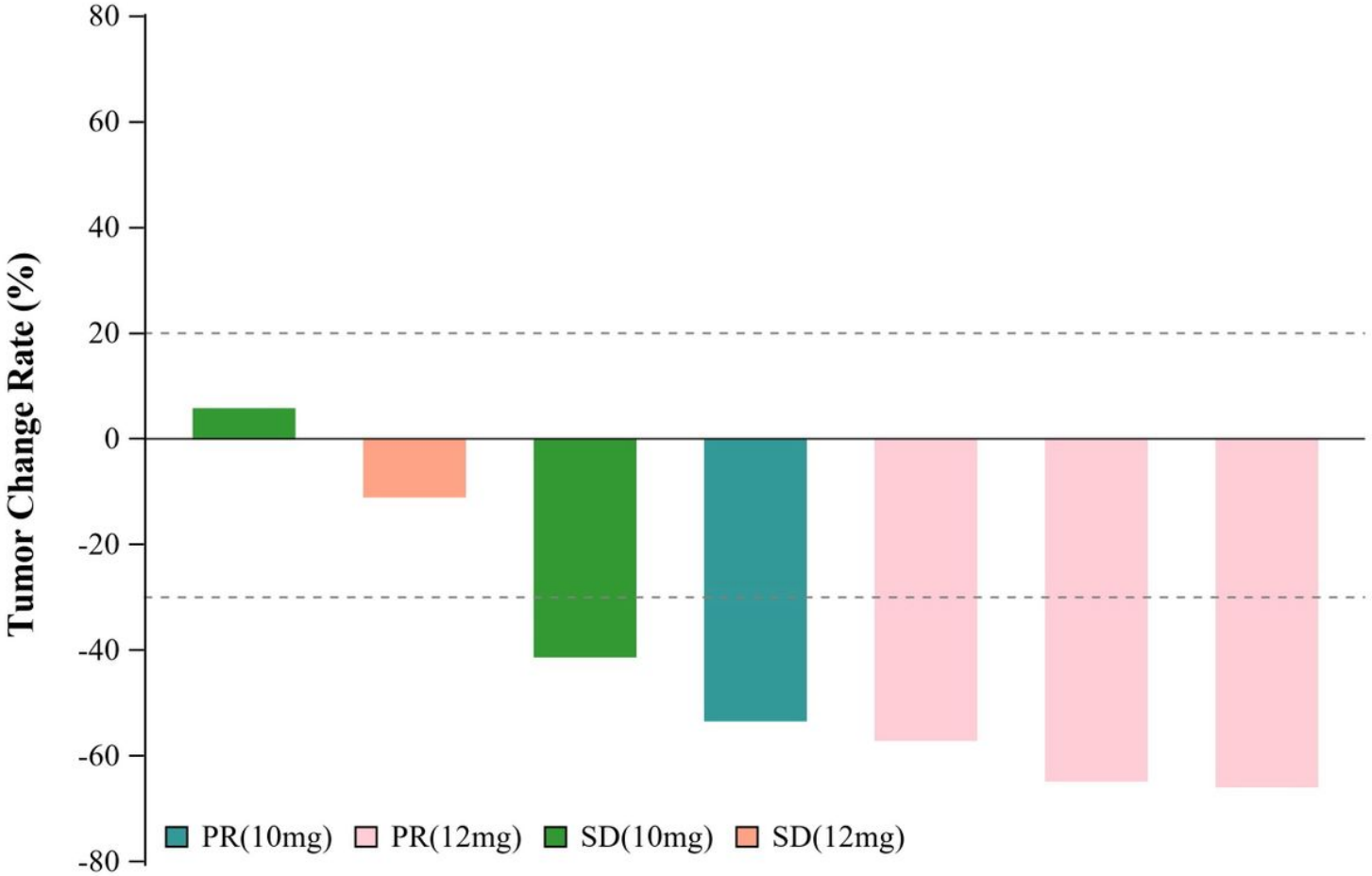

Figure 2

Best change from baseline in sum of longest target lesion diameter per patient

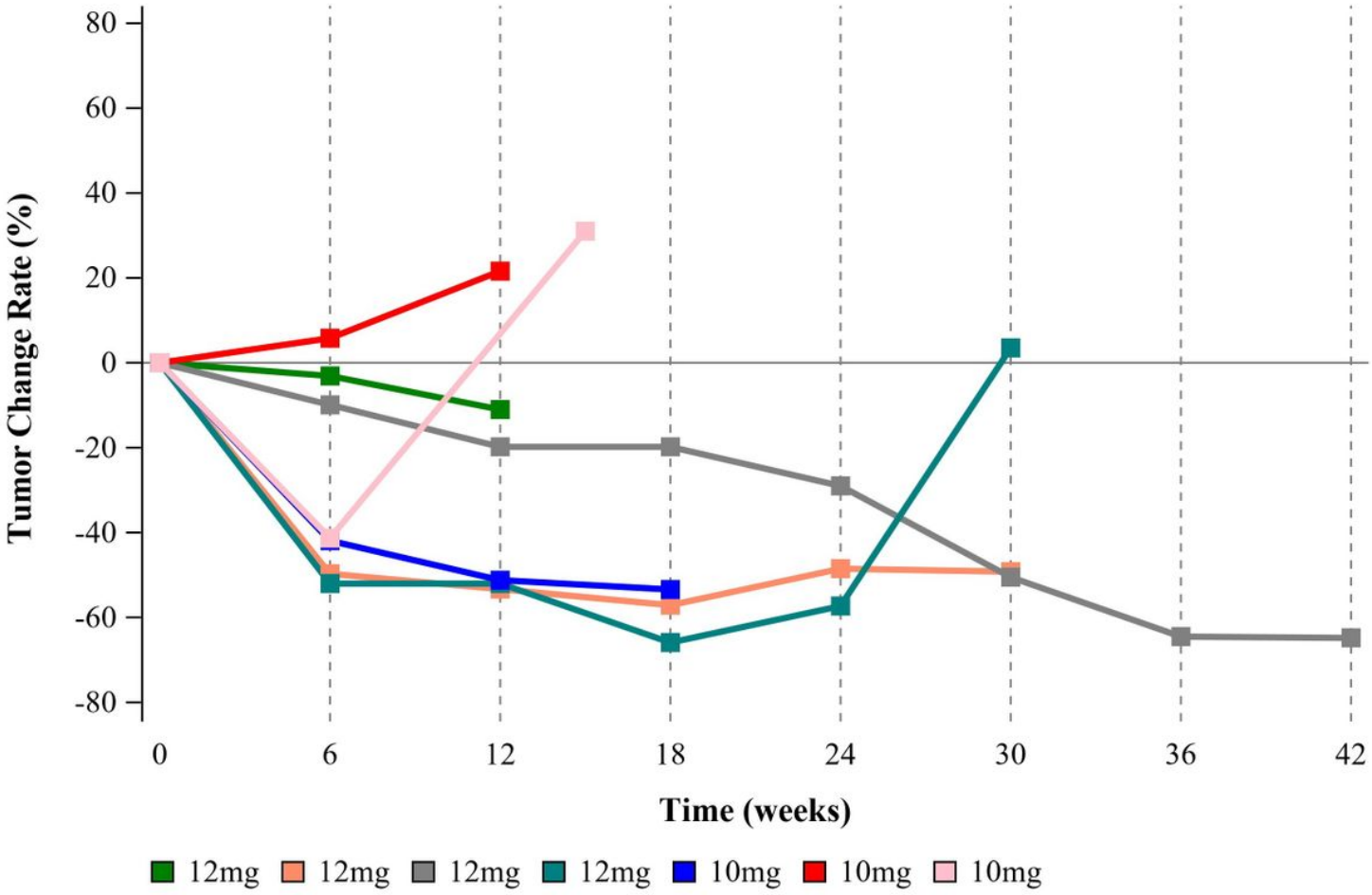

Figure 3

The change curve with time in sum of longest target lesion diameter per patient