Axitinib in Combination with Radiotherapy for Advanced Hepatocellular Carcinoma: A Phase I Clinical Trial

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Research

Keywords: advanced hepatocellular carcinoma, axitinib, maximum tolerated dose, radiotherapy.

Posted Date: June 30th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-38081/v1

Version of Record: A version of this preprint was published on January 20th, 2021. See the published version at https://doi.org/10.1186/s13014-020-01742-w.

Abstract

Background: Axitinib is a selective vascular endothelial growth factor receptors 1–3 inhibitor approved for second-line treatment of advanced renal cell carcinoma. In a randomized, placebo-controlled phase II trial for patients with locally advanced or metastatic hepatocellular carcinoma (HCC), axitinib improved progression-free survival and showed overall response rate of 9.7%. This phase I study aimed at evaluating maximum tolerated dose (MTD) of axitinib in combination with radiotherapy (RT) for advanced hepatocellular carcinoma (HCC).

Methods: This phase I study followed the rule of traditional 3 + 3 design. Major eligibility included: (1) advanced HCC unsuitable for surgery, radiofrequency ablation or transarterial chemoembolization; (2) failure on sorafenib or no grant for sorafenib from health insurance system. Eligible patients with advanced HCC received axitinib for total 8 weeks during and after RT. Three cohorts with axitinib dose escalation were planned: 1 mg twice daily (level I), 2 mg twice daily (level II) and 3 mg twice daily (level III). The prescribed doses of RT ranged from 37.5 to 67.5 Gy in 15 fractions to liver tumor(s) and were determined based on an upper limit of mean liver dose of 18 Gy (intended isotoxic RT for normal liver). The primary endpoint was MTD of axitinib in combination with RT.

Results: Total nine eligible patients received axitinib dose levels of 1 mg twice daily (n = 3), 2 mg twice daily (n = 3) and 3 mg twice daily (n = 3). Dose-limiting toxicity (DLT) did not occur in the 3 cohorts; the MTD was defined as 3 mg twice daily in this study. ORR was 66.7%, including 3 complete responses and 3 partial responses, at 3 months after treatment initiation. With a median follow-up of 16.6 months, median OS was not reached, 1-year OS was 66.7%, and median PFS was 7.4 months.

Conclusions: Axitinib in combination with RT for advanced HCC was well tolerated with an axitinib MTD of 3 mg twice daily in this study. The outcome analysis should be interpreted with caution due to the small total cohort.

Trial registration: ClinicalTrials.gov (Identifier: NCT02814461), Registered June 27, 2016 - Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT02814461

Background

The management of inoperable hepatocellular carcinoma (HCC) is challenging. Local ablation treatments including radiofrequency ablation (RFA) or other ablative approaches can typically achieve excellent local control for tumors less than 3 cm (1, 2). For large or multifocal tumors, regional therapy with transarterial chemoembolization (TACE) are commonly recommended. In randomized studies, patients receiving TACE had better survival than those treated with only symptomatic treatment (3, 4). However, either local ablation or TACE is sometimes contraindications for reasons, such as large tumor size, large number, inadequate location, macrovascular involvement, or impaired liver function.

Radiotherapy (RT) is another treatment option for inoperable HCC (5–18). Advances in RT technique, breathing motion management and image guidance have made RT precise enough to be delivered safely to HCC. Considering tumor size and normal tissue tolerance, radiation doses have ranged widely. Therefore, for advanced HCC treated with RT, the outcomes were reported in a wide range, including local control from 50–70% and median survival from 6 to 18 months. Higher radiation doses, hypofractionated RT or stereotactic body radiotherapy may improve these treatment outcomes. However, first recurrence was usually identified at an intrahepatic site beyond irradiated field. A treatment strategy combining RT with systemic therapy may be reasonable.

Sorafenib, a multi-kinase inhibitor against angiogenesis and tumor proliferation, has become the standard systemic therapy for advanced HCC after two randomized controlled trials proved better survival of patients treated with sorafenib than placebo (19, 20). Regorafenib, another multi-kinase inhibitor similar to sorafenib, was approved as a second-line treatment for HCC after failure from sorafenib (21). Lenvatinib, a new multi-kinase inhibitor, was recently approved as another first-line treatment of HCC after a randomized phase III study proved non-inferiority in term of overall survival compared with sorafenib (22). However, a substantial portion of patients treated with these kinase inhibitors encountered intrahepatic progression eventually. It has been believed that adding local treatment to effective systemic therapy may possibly consolidate at least local therapeutic effect. Sorafenib in combination with RT was considered effective in tumor response (23, 24), but potential hepatic toxicities may undermine the benefit of the strategy (25).

At the timepoint when our present study was initiated, sorafenib was the only approved targeted therapy for advanced HCC. Meanwhile, axitinib, a potent kinase inhibitor selectively inhibiting vascular endothelial growth factor (VEGF) receptors 1, 2 and 3, demonstrated superior outcomes for renal cell carcinoma (RCC) when compared with sorafenib, and thus axitinib was approved as second-line treatment for advanced RCC after failure of prior treatment with sunitinib or a cytokine (26). HCC and RCC are both hypervascular cancers that can be potentially controlled by angiogenesis inhibitor. Axitinib was also studied for HCC in some clinical trials. In a randomized placebo-controlled phase II trial for locally advanced or metastatic HCC who failed from sorafenib, axitinib improved progression-free survival and showed overall response rate of 9.7%, but did not demonstrated benefit in overall survival (27). Another phase II trial also reported second-line axitinib showed encouraging response rate with well tolerability (28).

Axitinib in combination with RT seems to be a potential approach. We hypothesized RT combined with axitinib would be safe and effective for advanced HCC, but the safety profile is not yet established. This phase I study aimed at determining the safety and maximum tolerated dose (MTD) of axitinib in combination with radiotherapy for advanced hepatocellular carcinoma.

Methods

This phase I study was approved by the institutional review board (No. 20150704M) and was registered in ClinicalTrials.gov (Identifier: NCT02814461). Patients with advanced HCC unsuitable for resection, liver transplantation, RFA or TACE, or who failed after prior local-regional treatment were eligible. Other key eligibility criteria included failure on sorafenib or no grant for sorafenib from health insurance system, Child-Pugh score A or B, and ECOG performance status 0–2. Multiple tumors, portal vein thrombosis, nodal metastasis or distant metastasis was allowed. Major exclusion criteria included high risk of bleeding (e.g. active peptic ulcer, unstable esophageal/gastric varices, history of aneurysm, and requirement of anticoagulant therapy) and pre-existing uncontrolled hypertension (systolic > 140 mmHg, diastolic > 90 mmHg) or proteinuria ≥ 500 mg/24 hours.

This phase I study followed the rule of traditional 3 + 3 design, and dose escalation of axitinib was conducted with 3 dose levels: 1 mg twice daily (level I), 2 mg twice daily (level II) and 3 mg twice daily (level III). Because the interaction between axitinib and RT was not well known before this study, the starting dose of axitinib was set at a minimal dose of 1 mg twice daily for the best of safety. The regimen of RT was 37.5 to 67.5 Gy in 15 fractions in 3 weeks (2.5 to 4.5 Gy per fraction) to liver tumor(s) (e.g. portal vein thrombosis, tumors with size ≥ 3 cm, or recurrent/refractory tumors). The final prescribed dose of RT was based on an upper limit of mean liver dose of 18 Gy for all plans (intended isotoxic RT for normal liver). Daily Entecavir 0.5-1 mg or Telbivudine 600 mg was recommended for patients with hepatitis B during and 3 months after RT. The primary endpoint was MTD of axitinib in combination with RT for advanced HCC. Secondary endpoints included overall response rate (ORR), RT in-field response rate, acute and late toxicities, overall survival (OS) and progression free survival (PFS).

Dose-limiting toxicity (DLT) was defined as, according CTCAE version 4.0, any of the following when considered related to protocol treatment: any grade 4 or 5 toxicities, grade 3 gastrointestinal toxicity despite the use of medical intervention and/or prophylaxis, grade 3 anemia, or grade 3 nonhematologic toxicities except nausea, vomiting, diarrhea, constipation, pain, and hypertension controlled with medication. In the beginning of the study, the first 3 patients were treated at starting dose of axitinib with 1 mg twice daily, and the next step would follow the rule described here. In order to observe any acute or delayed toxicities, our investigators waited for at least 3 months before moving to subsequent dose levels. If DLT was observed in 0 of 3 patients at a given dose level, the study would enter the next higher dose level. If DLT developed in ≥ 2 of 3 patients, the study would return to the next lower dose level if any. If DLT was noticed in 1 of 3 patients at a given dose level, additional 3 patients would be needed at this dose level. If DLT was noticed in 1 patient of the expanded 6-patient cohort, the study proceeded to the next higher level. If DLT developed in ≥ 2 patients of the expanded 6-patient cohort, the trial would proceed to the next lower dose level if any. When there were only 3 patients in the next lower dose level, 3 additional patients would be enrolled; while 6 patients are already there, the phase I trial would be stopped. MTD is defined as the dose at which ≤ 1/6 encounters DLT. It was estimated that about 9 to 18 patients would be enrolled in the phase I study. At least 3 months of follow-up after completion of protocol treatment should be performed to allow an adequate observation of DLT occurrence.

The descriptive statistics were summarized as percentages for proportions and as median (with ranges in parentheses) for continuous values. By response evaluation criteria in solid tumors (RECIST), the response rates were calculated 3 months after treatment initiation. Survival curves were analyzed by Kaplan-Meier method, using Log-rank test when determining statistical significance of difference between subgroups. A p value < 0.05 (two-tailed) would be considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences software (SPSS, Inc, Chicago, IL).

Results

During the phase I study, total nine patients were enrolled (Table 1). Each 3 subsequently entered cohorts of axitinib dose levels: 1 mg twice daily (n = 3), 2 mg twice daily (n = 3) and 3 mg twice daily (n = 3). Dose-limiting toxicity (DLT) did not occur in the 3 cohorts (Table 2), and the MTD was defined as 3 mg twice daily in this study. The most common adverse events (AEs) occurring in patients receiving axitinib (all grades) were hypertension, proteinuria, increased alanine transaminase (ALT), increased alkaline phosphatase (ALK-P), and increased bilirubin. The most common grade 3 AEs were hypertension, which could be managed by anti-hypertensive agents. Other grade 3 AEs included nausea, vomiting and diarrhea, which were all manageable. Among all patients, no grade 4 or 5 AEs occurred.

Table 1
Patient and disease characteristics (n = 9)

Age, years, median (range)	**72 (37–83)**
Gender (Male : Female)	8:1
ECOG performance status	
0	1 (11%)
1	8 (89%)
Child-Pugh Score	
5 (class A)	4 (45%)
6 (class A)	3 (33%)
7 (class B)	2 (22%)
Etiology of HCC	
Hepatitis B virus (HBV)	5 (56%)
Hepatitis C virus (HCV)	1 (11%)
Non-HBV, Non-HCV	3 (33%)
BCLC staging	
B	1 (11%)
C	8 (89%)
RT doses, Gy, median (range)	45 (37.5–53)

Table 2
Toxicities

	Total (n = 9)		Level I cohort (n = 3)		Level II cohort (n = 3)		Level III cohort (n = 3)	
	Grade 1–3	Grade 3	Grade 1–3	Grade 3	Grade 1–3	Grade 3	Grade 1–3	Grade 3
Leucopenia	4	0	0	0	2	0	2	0
Anemia	1	0	1	0	0	0	0	0
Thrombocytopenia	4	0	0	0	2	0	2	0
Increased ALT	5	0	2	0	1	0	2	0
Increased alkaline-P	6	0	3	0	0	0	3	0
Increased total bilirubin	6	0	2	0	1	0	3	0
Increased creatinine	2	0	1	0	1	0	0	0
Hypothyroidism	3	0	1	0	0	0	2	0
Proteinuria	6	0	2	0	1	0	3	0
Skin rash	1	0	0	0	0	0	1	0
Hand numbness	1	0	1	0	0	0	0	0
Hypertension	9	5	3	1	3	2	3	2
Nausea/Vomiting	1	1	1	1	0	0	0	0
Diarrhea	3	2	1	1	1	1	1	0
Constipation	2	0	1	0	1	0	0	0

Among all 9 patients, overall response rate by RECIST criteria was 66.7%, including 3 complete responses (CR) and 3 partial responses (PR), at 3 months after treatment initiation (Table 3). RT in-field response rate was 77.8% (4 CR and 3 PR) (Table 3). The axitinib dose levels were not associated with tumor response ($p = 0.406$). Figure 1 illustrated one patient with CR with CT scans before and after RT in combination with axitinib 1 mg twice daily.

Table 3
Tumor response to axitinib in combination with radiotherapy (n = 9)

	Overall response	RT in-field response
Complete response (CR)	3 (33.3%)	4 (44.4%)
Partial response (PR)	3 (33.3%)	3 (33.3%)
Stable disease (SD)	0 (0%)	0 (0%)
Progressive disease (PD)	3 (33.3%)	2 (22.2%)
Response rate (CR + PR)	6 (66.7%)	7 (77.8%)

With a median follow-up of 16.6 months, median overall survival (OS) was not reached, 1-year OS was 66.7% (Fig. 2), and median progression-free survival (PFS) was 7.4 months (Fig. 3). On univariate analysis, responders ($p = 0.024$) and Child-Pugh A ($p = 0.018$) were associated with favorable OS. Responders ($p = 0.002$) and Child-Pugh A ($p = 0.002$) were also associated with favorable PFS.

Discussion

Previously, a phase I study determined the MTD of axitinib monotherapy was 5 mg twice daily (29). Therefore, in the phase II and phase III trials for advanced RCC with progression after first-line treatment (26, 30), the staring dose of axitinib was set as 5 mg twice daily. It was mentioned the axitinib dose could be adjusted according to individual tolerance within the range from 2 mg twice daily to 10 mg twice daily. However, the safety of axitinib in combination with RT was not yet established before our study. We had not known the potential interaction between axitinib and RT. Following a principle of the best safety, the starting dose of axitinib in our present phase I study was set as a minimal practicable dose of 1 mg twice daily, and the dose would be escalated by a relatively safe dose interval when moving to the next dose levels. In addition, we intended to deliver isotoxic and safe RT to normal liver with similar mean liver doses approaching 18 Gy for each patient. Although this caused heterogeneous prescribed RT dose in our study, this would be a necessary measure to make RT toxicities relatively constant and could enable appropriate evaluation of tolerability regarding axitinib MTD in combination with RT.

Our study successfully proved that axitinib in combination with RT is safe at least up to the dose of axitinib 3 mg twice daily, which was considered as the MTD in this study. The dose is already within the recommended dose range of axitinib: 2 mg twice daily to 10 mg twice daily. According to our data, no additional toxicities were induced by the combination of RT and axitinib. All the AEs did not exceed grade 3 and were all manageable. We did not further escalate the dose because we had only limited resources for this study. If any other study groups want to conduct another similar phase I study, a starting dose with axitinib 3 mg twice daily can be considered. A determined MTD will facilitate design of a phase II study evaluating efficacy.

HCC is known as a hypervascular cancer supplied majorly from hepatic artery, while normal liver tissue is supplied by portal vein. Therefore, transarterial therapies are relatively specific for HCC rather than normal liver. Medical anti-angiogenic agents also proved clinical therapeutic value for HCC. Combination of some anti-angiogenic agents and RT showed potential benefit at both pre-clinical and clinical level (31–34). A pre-clinical study demonstrated that axitinib can improve tumor control of RT by radiosensitizing tumor endothelial cells (35). Anti-angiogenesis may allow better maturation of cancer blood vessels, and could potentially improve tumor oxygenation and thus tumoricidal effect of RT (36, 37). In our study, the response rate of axitinib in combination with RT is encouraging compared with RT alone. High rate of complete response was observed. This could be contributed by radiosensitization effect from addition of axitinib.

Spatial cooperation may exist between local treatment (e.g. RT) and systemic therapy. In addition to extrahepatic progression, many patients with advanced HCC treated by sorafenib eventually also progressed in liver, with a median time to progression 5.5 months according to SHARP study (19). On the other hand, from the experience of RT, outfield recurrence is the most common site of first recurrence. RT in combination with effective systemic therapy possibly exert the effect of spatial cooperation which may be translated to improved PFS and even OS. Our present study showed an acceptable PFS and impressive OS for advanced HCC treated with the combination strategy. However, because the phase I trial enrolled only small numbers of patients, it is difficult to conclude that axitinib in combination with RT could offer benefits compared with RT alone based on the data presented. Further phase II or even phase III study is required to adequately evaluate the efficacy.

Clinical experiences with RT and anti-angiogenic agent are few but still exist with encouraging results. For example, one retrospective study treated advanced HCC with RT and sunitinib (another multi-kinase inhibitor), reported objective response rate of 74% and a median survival of 16 months, and concluded hypofractionated RT can be delivered safely concomitantly with sunitinib (38), which was compatible with the result of several phase I or II studies using sorafenib plus RT (25, 39). In our present study, combining axitinib and RT were safe and effective with results comparable to other study with similar combination approach.

The use of anti-HBV medicines during RT can prevent re-activation of hepatitis B virus. In a phase II clinical trial, the combination of sorafenib and RT carries fair local regional control, but still suggested that the combination therapy should be used with caution due to a relatively higher hepatic toxicity (25). Lacking routine use of anti-HBV medicine may be at least part of the reason that the study encountered the issue. In our study, we prespecified the use of anti-HBV medicine for any patient with confirmed hepatitis B. We did not observe worse liver toxicity nor re-activation of hepatitis B.

Since regorafenib and lenvatinib were both proved as effective treatment for HCC, the combination of RT with these relatively new agents could also be studied in the setting of clinical trial. Adverse effects caused by regorafenib are serious concern because a substantial portion of HCC patients cannot well tolerate even regorafenib monotherapy. Lenvatinib could be a better candidate to try a combination

treatment with RT because many patients can better tolerate lenvatinib monotherapy as compared with sorafenib. Several other new treatments for advanced HCC emerge recently, including ramucirumab or immunotherapy with immune checkpoint inhibitors. Various combination treatments are worthy of further research.

This study had some limitations as stated below. Shortness of resources for further dose escalation limited the axitinib MTD at 3 mg twice daily in our study setting. The real MTD of axitinib in combination of RT may possibly be higher. The nature of phase I study escalating doses only allow determination of MTD but not for efficacy. Due to only 9 cases, we can only pool all patients together to get a mixed efficacy data involving all dose levels. The efficacy reported in our phase I study should be interpreted with caution.

Conclusions

Axitinib in combination with RT for advanced HCC is well tolerated with an axitinib MTD of 3 mg twice daily in this study. Some patients experienced tumor response to the protocol treatment, even with low dose of axitinib. However, the outcome analysis should be interpreted with caution due to the small total cohort.

List Of Abbreviations

HCC: hepatocellular carcinoma

MTD: maximum tolerated dose

RT: radiotherapy

DLT: dose-limiting toxicity

RFA: radiofrequency ablation

TACE: transarterial chemoembolization

VEGF: vascular endothelial growth factor

RCC: renal cell carcinoma

ORR: overall response rate

OS: overall survival

PFS: progression free survival

RECIST: response evaluation criteria in solid tumors

ALK-P: alkaline phosphatase

CR: complete responses

PR: partial responses

Declarations

Ethics approval and consent to participate:

This phase I study was approved by the institutional review board of Shin Kong Wu Ho-Su Memorial Hospital (No. 20150704M).

Consent for publication:

Consent for publication was obtained.

Availability of data and materials:

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

Competing interests:

The authors declare no conflicts of interest.

Funding:

This study was supported by grants from the Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan (No. SKH-8302-106-DR-27).

Authors' contributions:

KLY, YML and KHC conceived the study; KLY, MSC, HLK and YYH collected data; KLY and SCH performed statistical analyses and interpreted data; KLY wrote manuscript; KHC provided critical review and revision of manuscript. All authors reviewed and approved the final manuscript.

Acknowledgment:

We would like to thank all the investigators and patients.

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Figures

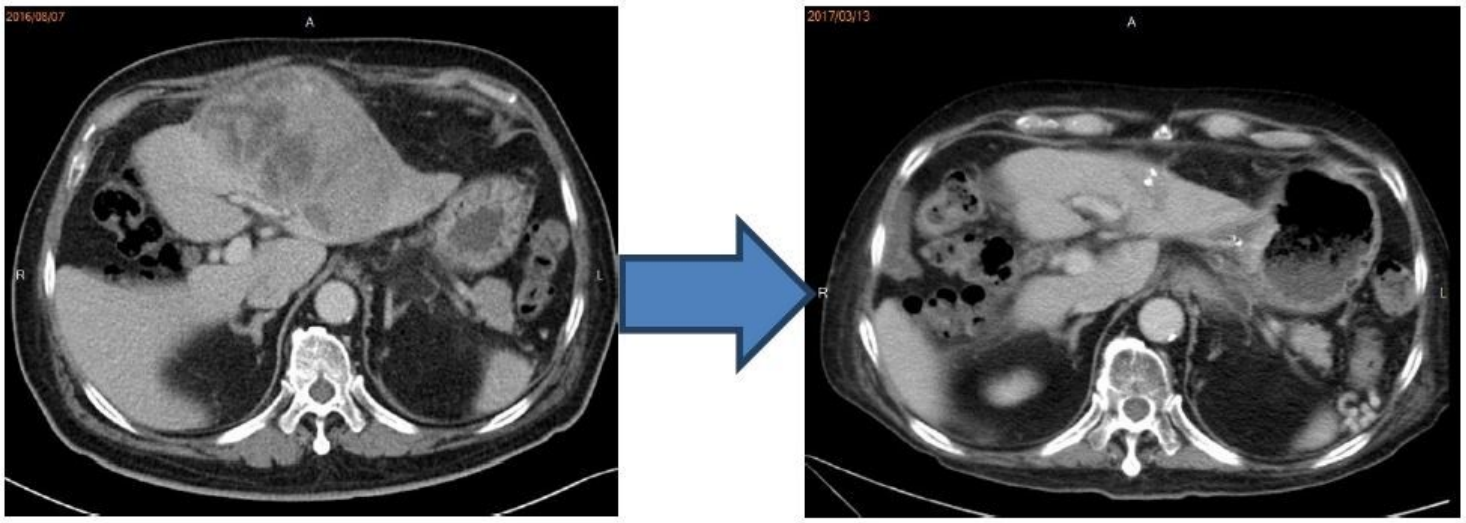

Figure 1

A case presentation (complete response, long-term alive, no recurrence) CT scan before and after RT 45 Gy in 15 fractions + axitinib 1mg twice daily

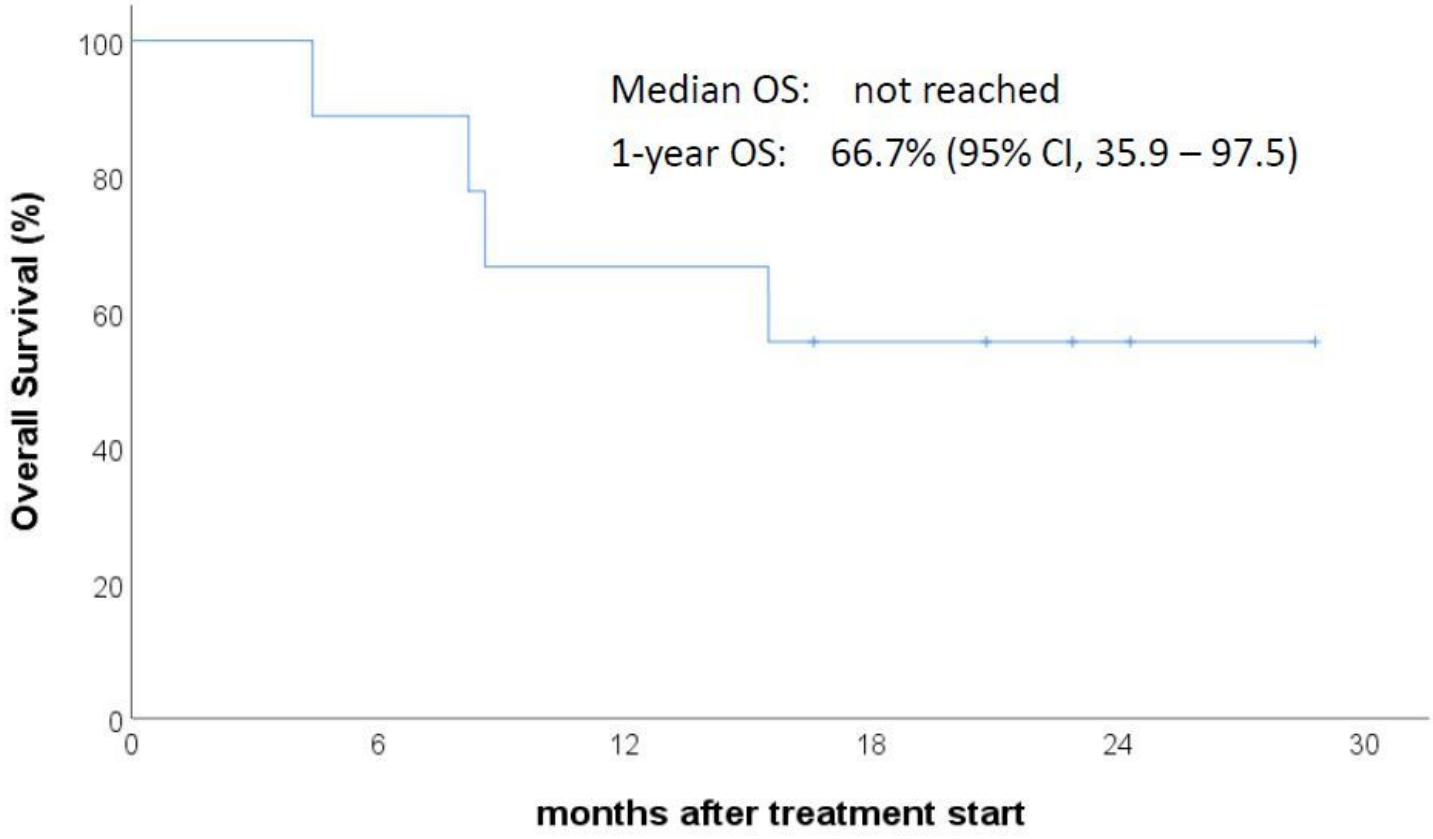

Figure 2

Overall Survival

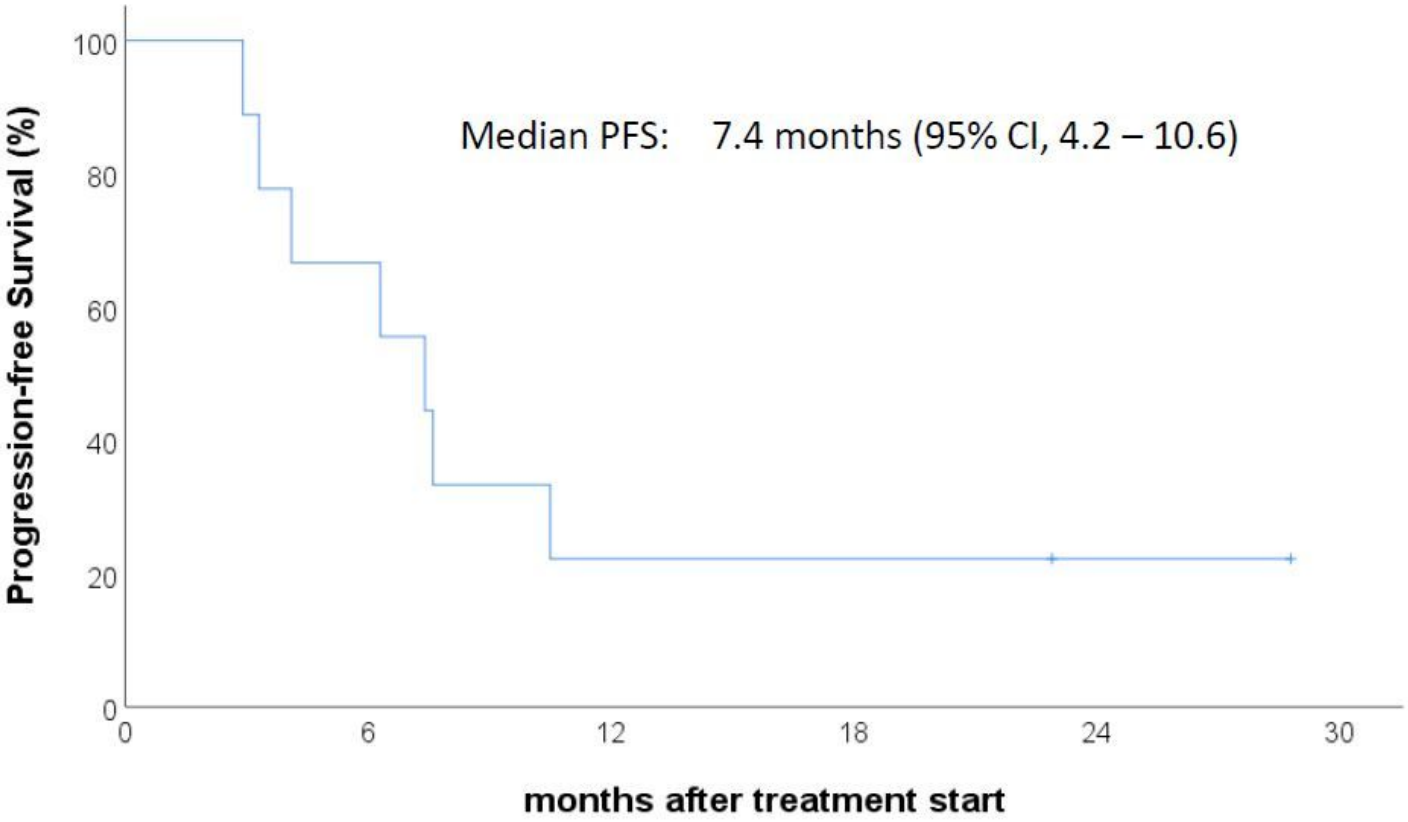

Figure 3

Progression-free survival