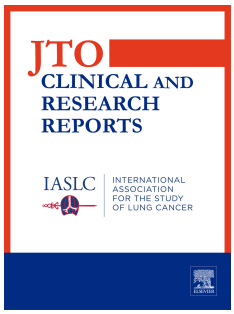

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Brief Report

Phase I Study of Ceritinib combined with Trametinib in Patients with Advanced ALK- or ROS1-Positive Non-Small Cell Lung Cancer

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Running title: Ceritinib and Trametinib in NSCLC

Key words: Ceritinib, Trametinib, ALK-rearrangement, ROS1-rearrangment, Non-small cell lung cancer, MEK inhibition

Abstract

Introduction: In patients with non-small cell lung cancers (NSCLC) harboring oncogenic ALK or ROS1 rearrangements, tyrosine kinase inhibitors have yielded high response rates and improvements in progression-free survival compared to cytotoxic chemotherapy, however, acquired resistance eventually develops. In preclinical models, ALK and MEK co-inhibition was able to overcome ALK inhibitor resistance.

Methods: A phase I study of the ALK/ROS1 inhibitor ceritinib and the MEK inhibitor trametinib in patients with refractory NSCLC harboring ALK or ROS1 fusions was initiated. A 3 + 3 dose escalation scheme was employed. Two dose levels were investigated. The primary endpoint was to determine the safety and tolerability of the combination.

Results: Nine patients (n = 8 ALK+, n = 1 ROS1+) were enrolled in the study and completed at least 1 cycle of therapy. The most common adverse events (AE, all grades) were diarrhea (n = 9; 100%), rash (n = 8; 89%), abdominal pain (n = 5; 56%), and elevated AST/ALT (n = 4; 44%). The overall response rate was 22% while disease control rate was 56%. Median duration of response was 7.85 months. The median progression free survival (PFS) was 3.0 months (95% CI: 1.5 – 7.0 months). The median overall survival (OS) was 8.9 months (95% CI: 2.0 - N.R.)

Conclusions: Data from this trial indicates that the combination of ceritinib and trametinib revealed no unexpected toxicities and that a tolerable dose could be identified. A subset of patients appeared to obtain clinical benefit from this treatment after progression on prior ALK/ROS1 inhibitor treatment.

Introduction

Oncogenic ALK-rearrangements are present in approximately 3-7% of NSCLC adenocarcinomas[1]. Oncogenic rearrangements in ROS1, which shares structural similarity with ALK, occur in approximately 2-3% of NSCLC adenocarcinomas[1]**.** Tumors harboring ALK-or ROS1-rearrangements are dependent on these molecular alterations for growth and survival. As a result, monotherapy with ALK/ROS1-tyrosine kinase inhibitors often leads to significant initial response in ALK- or ROS1-rearranged NSCLC. Unfortunately, resistance to ALK- or ROS1-directed monotherapy ultimately develops[2-4]**.** Furthermore, up to 30% of these patients do not experience an initial response to therapy. Identifying and targeting potential mechanisms of resistance to ALK or ROS1 inhibition may lead to longer disease control and patient survival.

Preclinical studies in EML4-ALK NSCLC models showed that EML4-ALK-driven lung cancers are dependent on RAS-mitogen-activated protein kinase (MAPK) signaling[5]. Furthermore, combined ALK and MEK inhibition with ceritinib and trametinib resulted in decreased tumor cell proliferation and survival, and increased depth and duration of tumor regression compared with monotherapy treatment both *in vitro* and *in vivo*[5]. ROS1 fusions have also been found to activate the MAPK signaling pathway and a constitutively active form of MEK (MEK-DD) was sufficient to rescue ROS1 expressing lung cancer cells from crizotinib treatment, suggesting that co-inhibition of ROS1 and MEK may overcome ROS1 inhibitor resistance[6].

We sought to evaluate the combination of the second-generation ALK/ROS1 inhibitor ceritinib[7] with the MEK1/2 inhibitor trametinib[8] in a phase I study of patients with advanced ALK or ROS1 rearranged NSCLC who had progressed on prior treatment with at least one prior ALK/ROS1 inhibitor.

Methods

This was an investigator-initiated phase I trial of ceritinib plus trametinib in patients with ALK or ROS1-rearranged NSCLC who had progressed on prior ALK/ROS1-targeted therapy. Institutional review boards at UC Davis and UCSF approved the study, and all patients provided written informed consent. Eligible patients were ≥18 years with histologically or cytologically confirmed stage IIIB or IV NSCLC (AJCC v7) and documented ALK- or ROS1-rearrangement by CLIA approved next generation sequencing (NGS) or

fluorescence in situ hybridization (FISH) test . Disease progression after treatment with ≥ 1 prior ALK/ROS1 inhibitor was required. Patients with a history of pneumonitis, clinically significant heart disease, impaired GI function, or prior systemic treatment within three weeks were excluded.

The primary endpoint of the study was to determine the safety, tolerability, and recommended phase 2 dose (RP2D) of the combination. Secondary endpoints included objective response rate (ORR) determined by investigator assessment, disease control rate (DCR), duration of response (DOR), progression free survival (PFS) and overall survival (OS). Adverse events were assessed by CTCAE v5. A standard 3 + 3 dose escalation scheme was employed. Two dose levels (DLs) were investigated (Level 1: ceritinib 300 mg PO daily with food + trametinib 1.5 mg PO daily without food, Level 2: ceritinib 450 mg PO daily with food + trametinib 1.5 mg PO daily without food. A Level 3 cohort of ceritinib 450 mg PO daily with food + trametinib 2.0 mg PO daily without food was planned, but not enrolled to due to closure of the trial. Cycle length was defined as 28 days. Dose limiting toxicities (DLTs) were defined as any treatment-related toxicity occurring within the first cycle of therapy as grade 3 or 4 clinically evident non-hematologic toxicity; grade 4 neutropenia or thrombocytopenia lasting > 7 days or febrile neutropenia. Patients were followed for safety evaluation until 30 days post their last dose of study drugs. A minimum of 6 and maximum of 18 patients were planned to be enrolled in the phase 1 study.

A phase Ib study was planned based on the RP2D determined after dose escalation complete, however the study was stopped early due to low accrual. Here we report the safety and efficacy data from the phase 1 dose escalation portion of the trial.

Results

A total of nine patients were enrolled. Six patients were enrolled and treated at DL 1 and 3 patients were enrolled and treated at DL 2. The baseline characteristics of patients treated are summarized in **Table 1**. Median age was 55 years (range 45-77). There were 4 male and 5 females. Eight ALK-rearrangement^{+} and one ROS1-rearrangement^{+} patients were enrolled (fusion partners indicated in Table 1). The median number of prior lines of therapy was 4, the median number of prior lines of ALK/ROS1 inhibitor therapy was 2.

The most common adverse events (AEs) and grade 2 or higher AEs are summarized in **Table 2**. The most common AEs of any grade were diarrhea (n = 9; 100%), rash (n = 8; 89%), nausea (n = 6; 67%), abdominal pain (n = 5; 56%) and elevated AST/ALT (n = 4; 44%). The most common study-attributable grade 3 or higher AE was elevated AST/ALT (n = 3; 33%). There were no significant differences in the frequency or grade of AEs between dose level 1 and dose level 2, nor were there any significant differences in AEs based on line of therapy at the time of enrollment. We observed only one dose-limiting toxicity (grade 3 rash) in dose level 1. There were no treatment related deaths.

Two patients with ALK+ NSCLC experienced confirmed partial response (PR) for an overall response rate of 22%. One responder experienced an 88% reduction in tumor size by RECIST 1.1 (**Figure 1A)**. Both responders were in dose level 1 and both had received only one prior line of ALK inhibitor therapy **(Figure 1B)**. Three patients (33%, all in dose level 1) experienced stable disease (SD) for an overall DCR (PR + SD) of 56%. Four of the five patients with either PR or SD had received only one prior ALK inhibitor **(Figure 1B)**. The remaining four patients (44%, 1 in DL 1 and 3 in DL 2) experienced progression of their disease, including the sole ROS1+ patient. All patients who experienced disease progression had been treated with three or more prior ALK/ROS1 inhibitors **(Figure 1B)**. The median progression PFS was 3.0 months (95% CI: 1.5 – 7.0 months) (**Figure 1B**). The median overall survival OS was 8.9 months (95% CI: 2.0 - N.R.) (**Figure 1C**). The median DOR among the two patients who achieved a PR was 7.85 months.

Discussion

This study sought to characterize the safety and efficacy of the combination of the ALK/ROS1-inhibitor ceritinib with the MEK-inhibitor trametinib in patients with pretreated ALK+ or ROS1+ NSCLC. The most common adverse events observed were rash, diarrhea, and elevated AST and ALT, none of which were unexpected, with only rash being a DLT. These results suggest that this treatment regimen – particularly the regimen defined by DL 1 of ceritinib 300 mg (with food) + trametinib 1.5 mg (without food) both administered daily may be safe for further clinical investigation. While we did not observe any DLTs at DL 2, we only enrolled 3 patients to this cohort, thus the safety of this dose level remains incompletely explored.

We explored the efficacy of the ceritinib + trametinib combination as a secondary endpoint of the study. Two responses were observed out of 8 patients treated with ALK+ disease. We also observed a disease control rate of 56%. One ALK-positive demonstrated substantial clinical benefit with an 88% reduction in tumor size by RECIST and a 12-month PFS; however, tissue was not available for NGS or other analyses. The number of lines of prior ALK/ROS1 inhibitor therapy may correlate with response, as the two patients with a PR had only received one prior ALK/ROS1 inhibitor, while the four patients with disease progression as their best response had received 3-5 prior ALK/ROS1 inhibitors. This observation suggests that ALK and MEK-targeted co-treatment has the potential to be a therapeutic option for a select subset of patients with ALK-driven NSCLC but would likely only be effective if used as an earlier line of therapy. Several other studies are underway assessing the safety and efficacy of this approach with different ALK/ROS1 inhibitor and MEK inhibitor combinations (Alectinib + Cobimetinib, NCT03202940; Brigatinib + Binimetinib, NCT04005144; and Lorlatinib + Binimetinib, NCT04292119).

The limitations of this trial include its early closure that ultimately led to a small sample size and the inability to explore further dose levels or expansion cohorts in specific patient subsets. Pre-treatment biopsies were also unavailable to perform correlative studies that may have provided insight into the molecular mechanisms underlying response or resistance to treatment. This study was closed to accrual prior to completion due to the changing landscape of ALK+ NSCLC treatment and availability of newer FDA-approved agents and during the study period (e.g., alectinib, lorlatinib and brigatinib). Further studies would be required to determine the maximum tolerated dose (MTD) for the combination, although it would be reasonable to consider ceritinib 300 mg + trametinib 1.5 mg PO daily as the RP2D given its tolerability and efficacy profile.

In summary, co-targeting of ALK/ROS1 and MEK remains a rational strategy to overcome resistance to ALK-targeted therapy. The combination of ALK/ROS1 and MEK inhibition in the limited experience reported here suggests that such a strategy is clinically feasible and may be effective in patients with limited prior exposure to ALK/ROS1 inhibitors and/or in combination with next-generation ALK/ROS1 inhibitors in clinical development.

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Figure Legends

Figure 1. Efficacy of ceritinib + trametinib in ALK and ROS1 rearranged NSCLC. A. Waterfall plot for best percentage change in target lesion size by RECIST 1.1 criteria by investigator assessment are shown for patients who received of ceritinib + trametinib. * Indicates patients who received dose level 1 of ceritinib 300 mg PO daily with food plus trametinib 1.5 mg PO daily without food. ** Indicates patients who received dose level 2 of ceritinib 450 mg PO daily with food plus trametinib 1.5 mg PO daily without food. **B.** Swimmer's plot for patients treated with ceritinib + trametinib with the genotype and dose level as indicated in (A)**.** Prior ALK/ROS1 inhibitor therapies for each patient were as follows: 1) crizotinib, ceritinib, alectinib, and brigatinib; 2) crizotinib, ceritinib, and lorlatinib; 3) crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib; 4) alectinib; 5) crizotinib and alectinib; 6) alectinib, brigatinib, and lorlatinib; 7) alectinib; 8) crizotinib; 9) alectinib. # Indicates patients who discontinued treatment due to toxicity. **C.** Progression-free and **D.** overall survival of patients treated with ceritinib plus trametinib. Kaplan-Meier analysis of investigator assessed progression-with 95% confidence intervals are indicated by the dashed lines.

Table 1: Baseline Characteristics of Patients

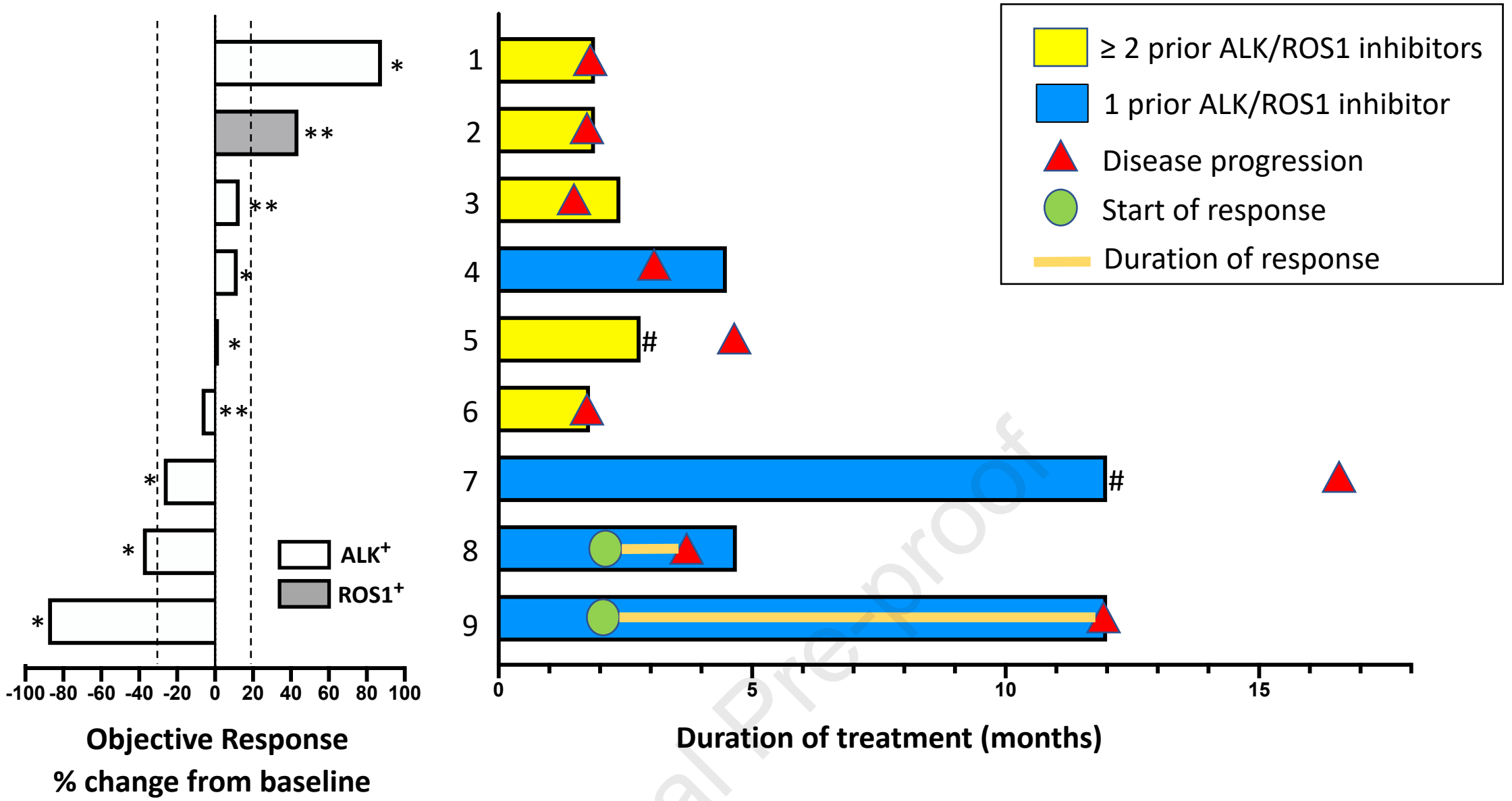
Patient Characteristic	Number of patients (%)
Age, median (range)	55 (45 – 77)
Sex	
M	4 (44)
F	5 (56)
Race	
White	5 (56)
Asian	3 (33)
Unknown	1 (11)
History of Smoking	
Current/Former	1
Never	8
Prior Lines of therapy	
1	2 (22)
2	1 (11)
3	1 (11)
4	2 (22)
5	2 (22)
6	1 (11)
Prior Lines of ALK/ROS1 inhibitor therapy	
1	4 (44)
2	1 (11)
3	1 (11)
4	2 (22)
5	1 (11)
ALK Rearrangement	8 (88)
EML4-ALK V1	2 (25)
EML4-ALK V3a/b	2(25)
ALK intron 19 rearrangement	1 (12.5)
FISH+ Only (no NGS)	3 (37.5)
ROS1 Rearrangement	1 (11)
LRIG2-ROS1	1 (100)

Table 2: Summary of most common toxicities observed

Toxicity Observed	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Total, Any Grade (%)
Diarrhea	6 (67)	2 (22)	1 (11)	9 (100)
Rash	3 (33)	4 (44)	1 (11)*	8 (89)
Nausea	5 (56)	1 (11)		6 (67)
Abdominal pain	4 (44)	1 (11)		5 (56)
Elevated AST/ALT		1 (11)	3 (33)	4 (44)
Vomiting	3 (33)			3 (33)
Dizziness	3 (50)			3 (50)
Fatigue	2 (22)			2 (22)
GERD		2 (11)		2 (22)
Weight loss	2 (22)			2 (22)
Pneumonia	1 (11)		1 (11)	2 (11)
Mouth sores		1 (11)		1 (11)
Serum amylase elevation		1 (11)		1 (11)
Encephalopathy			1 (11)	1 (11)
Dyspnea		1 (17)		1 (17)
Mouth sores		1 (11)		1 (11)
Sinusitis			1 (11)	1 (11)
Encephalopathy			1 (11)	1 (11)
Serum Amylase Increased		1 (17)		1 (11)
Bilirubin Increased		1 (33)		1 (11)
Proteinuria			1 (11)	1 (11)
Malaise		1 (33)		1 (11)
Edema		1 (33)		1 (11)
Hypertension		1 (33)		1 (11)
Hypoalbuminemia		1 (33)		1 (11)

*Rash was the only treatment emergent >Grade 3 adverse event observed (Dose Level 1)

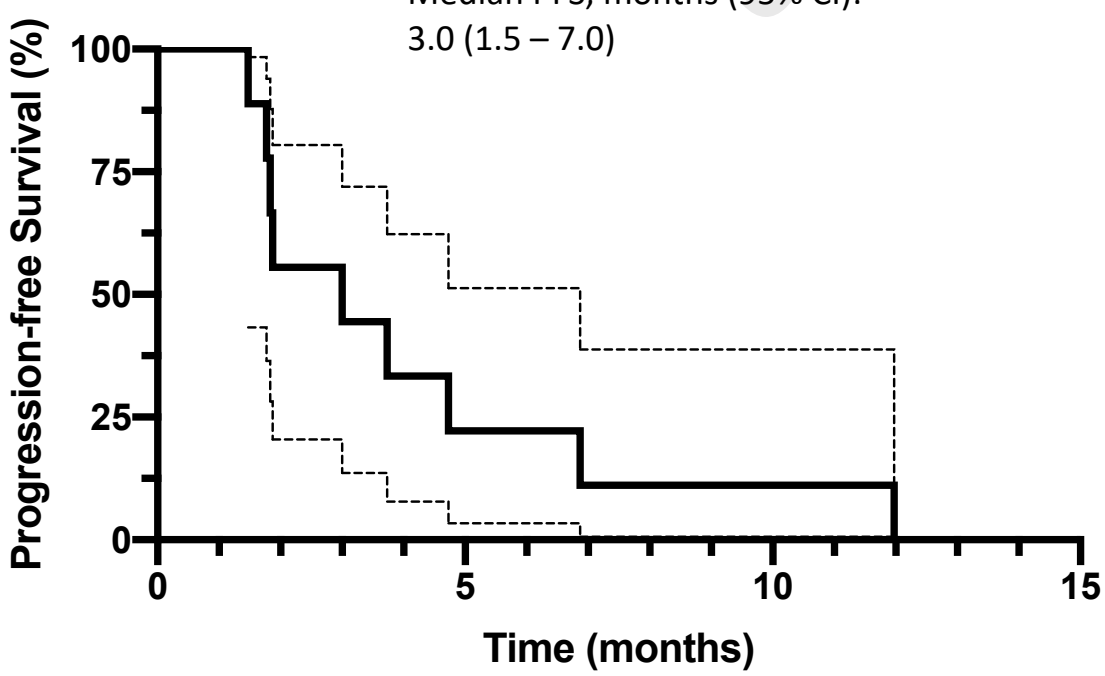
A



C

Progression Free Survival (PFS)

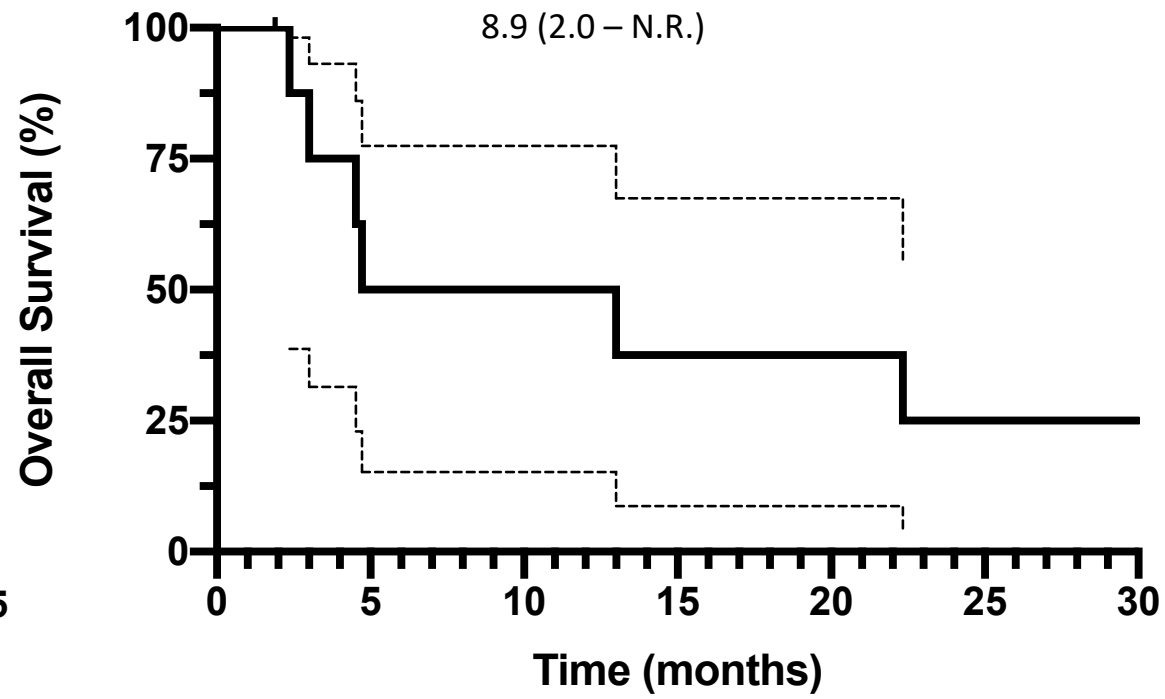
Median PFS, months (95% CI):
3.0 (1.5 – 7.0)



D

Overall Survival (OS)

Median OS, months (95% CI):
8.9 (2.0 – N.R.)



Matthew Lara: Data curation, Formal analysis, Writing - Original draft preparation. Matthew Gubens: Investigation, Writing – Reviewing and Editing. Bianca Bacaltos: Data curation, Project Administration. Lea Daran: Data curation. Steffany Lim: Data curation, Project Administration. Tianhong Li: Investigation. David Gandara: Investigation, Writing – Reviewing and Editing. Trever Bivona: Conceptualization, Writing - Reviewing and Editing. Jonathan Riess: Data curation, Formal analysis, Conceptualization, Methodology, Investigation, Supervision, Writing - Reviewing and Editing. Collin Blakely: Data curation, Formal Analysis, Conceptualization, Funding acquisition, Investigation, Supervision, Methodology, Writing – Reviewing and Editing.