

Phase 1 Study of Cabozantinib in Combination with Topotecan-Cyclophosphamide for Patients with Relapsed Ewing Sarcoma or Osteosarcoma

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Abstract

Purpose Phase 1 study assessing the safety and toxicity of cabozantinib in combination with topotecan and cyclophosphamide for relapsed osteosarcoma and Ewing sarcoma. **Methods** Oral cabozantinib (25mg/m²) was administered daily for 21 (dose level 1) or 14 (dose level -1B) days. Topotecan (0.75mg/m²) and cyclophosphamide (250mg/m²) were administered IV on days 1-5. A modified 3+3 design based upon first cycle dose-limiting toxicities (DLT) was used for dose escalation. **Results** Twelve patients with a median age of 15 (12.9-33.2) years were enrolled (7 with Ewing sarcoma; 5 with osteosarcoma); all were evaluable for toxicity. At dose level 1, three of six patients developed first cycle DLT: grade 3 epistaxis; grade 3 transaminitis; prolonged grade 2 thrombocytopenia. Six patients were enrolled on dose level -1B (interrupted cabozantinib, given days 8-21), with one first cycle DLT (grade 3 pneumothorax) observed. Of the 10 response evaluable patients, one had partial response (Ewing sarcoma), seven had stable disease, and two had progressive disease. **Conclusions** The recommended phase 2 doses and schedules for this combination are topotecan 0.75mg/m² IV days 1-5, cyclophosphamide 250mg/m² IV days 1-5, and cabozantinib 25mg/m² days 8-21. Non-concomitant administration of cabozantinib with cytotoxic therapy in this population has acceptable toxicity while allowing for potential disease control.

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Abbreviations

ALT	alanine aminotransferase
BSA	Body surface area
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DLT	Dose limiting toxicity
EFS	Event free survival
EKG	Electrocardiogram
EWS	Ewing sarcoma
IV	Intravascular
MTD	Maximum tolerated dose
mTKI	multitargeted kinase inhibitors
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RTK	Receptor tyrosine kinase
SD	Stable disease
TRAE	treatment related adverse effect
VEGFR-2	vascular endothelial growth factor receptor 2
ULP-WGS	ultra-low passage whole genome sequencing
UPC	urine protein/creatinine

Abstract

Purpose

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Methods

Oral cabozantinib (25mg/m²) was administered daily for 21 (dose level 1) or 14 (dose level -1B) days. Topotecan (0.75mg/m²) and cyclophosphamide (250mg/m²) were administered IV on days 1-5. A modified 3+3 design based upon first cycle dose-limiting toxicities (DLT) was used for dose escalation.

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Twelve patients with a median age of 15 (12.9-33.2) years were enrolled (7 with Ewing sarcoma; 5 with osteosarcoma); all were evaluable for toxicity. At dose level 1, three of six patients developed first cycle DLT: grade 3 epistaxis; grade 3 transaminitis; prolonged grade 2 thrombocytopenia. Six patients were enrolled on dose level -1B (interrupted cabozantinib, given days 8-21), with one first cycle DLT (grade 3 pneumothorax) observed. Of the 10 response evaluable patients, one had partial response (Ewing sarcoma), seven had stable disease, and two had progressive disease.

Conclusions

The recommended phase 2 doses and schedules for this combination are topotecan 0.75mg/m² IV days 1-5, cyclophosphamide 250mg/m² IV days 1-5, and cabozantinib 25mg/m² days 8-21. Non-concomitant administration of cabozantinib with cytotoxic therapy in this population has acceptable toxicity while allowing for potential disease control.

1 INTRODUCTION

Ewing sarcoma and osteosarcoma are aggressive malignancies of bone and/or soft tissue which most commonly affect adolescents and young adults. Patients with relapsed Ewing sarcoma likewise fare poorly [1-4]. Outcomes for patients with relapsed osteosarcoma are poor, with one analysis reporting 12% event-free survival (EFS) at 4 months [5]. Given these outcomes, new treatment approaches are needed.

Recently, there has been tremendous interest in a range of multitargeted tyrosine kinase inhibitors (mTKIs) in patients with bone sarcoma. Cabozantinib is an oral small molecule potent mTKI of proinvasive receptor tyrosine kinases (RTKs), most notably VEGFR-2 and MET, important mediators of tumor growth and angiogenesis. [6, 7] [6, 7] [6, 7] [11, 12] Ewing sarcoma and osteosarcoma both over-express MET and this expression is associated with an aggressive phenotype and poor prognosis [8-10]. The pediatric phase 1 study of cabozantinib identified 40 mg/m²/day continuous dosing as the recommended phase 2 dose [11]. Importantly, a European phase 2 single agent study of cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma reached its primary efficacy endpoint in both the Ewing sarcoma and osteosarcoma cohorts. Specifically, single agent cabozantinib yielded an objective response in 25.6% of Ewing sarcoma patients and 33.3% of osteosarcoma patients had 6-month non-progression[12]. Efforts to build upon this activity have been limited. Preclinical studies have demonstrated that targeting proangiogenic mechanisms in combination with cytotoxic chemotherapy may overcome chemoresistance and inhibit growth of sarcomas [13]. Prior studies in adult patients with high-grade gliomas and advanced pancreatic cancer combined cabozantinib with other cytotoxic agents and/or radiotherapy with acceptable adverse effect profiles [14, 15].

Cyclophosphamide and topotecan have shown activity against Ewing sarcoma and osteosarcoma in both phase 1 and phase 2 trials. In initial testing, the recommended phase 2 dose was cyclophosphamide 250mg/m² and topotecan 0.75mg/m²each IV on Days 1-5 of a 21-day cycle. This combination was overall well tolerated with primarily hematologic toxicities. In the phase 1 study, 1 (20%) patient with osteosarcoma had partial response and 2 (40%) had stable disease, while 3 (60%) of Ewing sarcoma patients had stable disease [16]. In

a phase 2 study, 36% of patients with Ewing sarcoma and 11% of patients with osteosarcoma had objective responses [17].

While cabozantinib and separately topotecan/cyclophosphamide are active in patients with Ewing sarcoma and osteosarcoma, they have not previously been studied in combination. In our trial, we aimed to determine the safety and toxicity of oral cabozantinib in combination with IV topotecan and cyclophosphamide, and to select the recommended phase 2 doses (RP2D) and schedules for this combination in pediatric patients with relapsed or refractory Ewing sarcoma or osteosarcoma.

2 METHODS

2.1 Patient Population

Patients 6-40 years of age with a histologically confirmed diagnosis of relapsed or refractory Ewing sarcoma or high-grade osteosarcoma with evaluable or measurable disease were eligible. Molecular evidence of translocation involving *EWSR1* or *FUS* was required for patients with Ewing sarcoma. A body surface area (BSA) $\geq 1.25\text{m}^2$ and $< 2\text{m}^2$ was required due to potential deviations due to rounding given available size of cabozantinib tablets. In addition, Lansky (< 16 years of age) or Karnofsky (≥ 16 years of age) performance score of ≥ 50 was required. Prior treatment with TKIs other than cabozantinib was allowed. Prior use of topotecan and cyclophosphamide was allowed. If this regimen immediately preceded enrollment to the trial, then no more than two prior cycles were allowed, and the patient must not have progressed on this combination. Patients with unhealed and/or chronic wounds were not eligible, and patients had to be ≥ 2 weeks from prior major surgical procedures.

The trial was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board. All patients (or parent/guardian) provided informed consent for participation.

2.2 Study Design

This was a prospective, open-label, single arm, phase 1 clinical trial (NCT04661852). The primary objective was to determine the maximum tolerated dose (MTD) and/or recommended phase 2 doses (RP2D) of cabozantinib when combined with topotecan and cyclophosphamide in patients with relapsed or refractory Ewing sarcoma and osteosarcoma. Secondary objectives were to describe the toxicities of the combination administered on this schedule, and to estimate the objective response rate.

The trial used a modified 3+3 design which permitted dose de-escalation in addition to escalation (**Supplemental Table 1**) ; the MTD was defined as per the standard 3+3 design. If dose level 1 was not tolerable, dose de-escalation depended upon the toxicity profile observed to decide whether to evaluate dose level -1A (dose reduced chemotherapy due primarily to hematologic toxicity) or dose level -1B (interrupted cabozantinib dosing due primarily to non-hematologic toxicity).

Treatment

Patients received therapy in 21-day cycles as shown in **Supplemental Table 1**. The cabozantinib tablet dose began at 62.5% of the recommended pediatric phase 2 monotherapy dose ($25\text{mg}/\text{m}^2/\text{day}$ PO instead of $40\text{mg}/\text{m}^2/\text{day}$) while topotecan and cyclophosphamide began at their standard pediatric doses ($0.75\text{mg}/\text{m}^2/\text{day}$ IV and $250\text{mg}/\text{m}^2/\text{day}$ IV, respectively). Likewise, a step-up dosing regimen was employed in cycle 1 for all dose levels in an effort to improve mTKI tolerability (**Supplemental Table 2**). Myeloid growth factor (filgrastim or pegfilgrastim) was started on days 6-8 of each cycle.

Patients were allowed local control measures (surgery and/or radiotherapy to sites of disease) after a minimum of four cycles of protocol therapy without disease progression. Protocol therapy was held for at least 1 week prior to surgery and for a minimum of 2 weeks following surgery, at least 24 hours prior to radiation, during radiation, and for a minimum of 1 week following radiation.

Dose-Limiting Toxicities

The primary endpoint was the occurrence of a dose-limiting toxicity (DLT) within the cycle 1 DLT observation window (from the first dose in cycle 1 until the first dose of cycle 2). DLTs were defined as events that were possibly, probably or definitely attributable to the treatment regimen. DLTs occurring in the first cycle were used to guide dose escalation decisions. Hematologic DLT was defined as not meeting neutrophil or platelet criteria for subsequent cycle within 14 days of planned cycle start date. For non-hematological toxicity, any toxicity [?] grade 3 attributable to the treatment regimen was classified as a DLT with the exceptions of the following: grade 3 nausea, vomiting, anorexia, diarrhea or dehydration resolving to [?] grade 2 within 72 hours; grade 3 weight loss unless persistent for >21 days despite optimal nutrition support; grade 3 liver enzyme elevation that returns to levels that meet eligibility criteria within 7 days of holding cabozantinib and that do not recur upon re-challenge; asymptomatic grade 3 lipase or elevation that returns to levels that meet the eligibility criterion within 7 days of holding cabozantinib and that does not recur upon re-challenge; grade 3 febrile neutropenia in the absence of clinical or laboratory documentation of infection; grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation; grade 3 proteinuria (urine protein/creatinine (UPC) ratio >1.9) unless it is confirmed with a second measurement within 72 hours; and QTc prolongation >500ms unless it persists beyond 72 hours despite correction of serum electrolyte abnormalities. In addition, non-hematologic toxicities that delayed start of subsequent cycle by > 14 days were considered DLTs.

2.5 Safety and Efficacy Assessments

Routine clinical and laboratory assessments, physical examinations, EKGs, echocardiograms, and tibial growth plate x-rays were conducted at baseline and prespecified intervals. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5. Imaging studies and tumor assessments were obtained at baseline, after cycle 2, after cycle 4, and then every 4 cycles until documented progression for patients with complete response (CR), partial response (PR), or stable disease (SD). Response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Patients with an overall best objective response of CR or PR prior to any local measures were categorized as responders, and all other patients as non-responders.

2.6 Correlative Biology Evaluations

Serial plasma samples were obtained to quantify and characterize ctDNA over time in response to protocol therapy. Peripheral blood samples were collected in cell-stabilizing tubes at baseline, Cycle 1 Day 3, Cycle 1 Day 5, Cycle 2 Day 1, and then at times of subsequent of disease evaluation. Plasma was isolated and processed to collect cell free DNA as previously described [18]. TranSS-Seq to detect *EWSR1* and *FUS* fusions was used to quantify ctDNA for patients with Ewing sarcoma and ultra-low passage whole genome sequencing (ULP-WGS) to detect aneuploidy was used for patients with osteosarcoma. Detailed methods are as previously reported [18].

2.7 Statistical Analyses

The safety and response evaluable populations were composed of all patients who received at least 1 dose of any of the three study agents. The dose-determining analysis population consisted of all patients from the safety population who either met the minimum exposure criterion and completed the cycle 1 DLT evaluation period without experiencing a DLT or received at least 1 dose of any of the three study agents and experienced a first-cycle DLT. The minimum exposure criterion was defined as receiving at least 80% of the planned doses of each of the three study agents (cabozantinib, topotecan and cyclophosphamide) in the first cycle. A 95% exact two-sided confidence interval was placed on the proportion of responders. Analyses were performed using R version 4.0.2.

3 Results

3.1 Patient Characteristics

Twelve patients enrolled: seven with Ewing sarcoma and five with osteosarcoma (**Table 1**). Most patients were male (75%, n=9) and the median age at study entry was 15.0 years (range 12.9-33.2). Patients enrolled

on trial a median 14.4 months (range 8.0–76.5) from initial diagnosis. The number of prior systemic therapy regimens varied from 1 to 10, with a median of 1.5 prior regimens.

3.2 Dose-Limiting Toxicities and Dose Determination

At dose level 1, three of six patients developed first cycle DLT: grade 3 epistaxis; prolonged grade 2 increased alanine aminotransferase (ALT); prolonged grade 2 thrombocytopenia that delayed the start of the second cycle. Therefore, dose level 1 was considered not tolerable. Two of three DLTs were non-hematologic DLTs and dose level -1B with interrupted cabozantinib dosing was evaluated. Six patients were enrolled on dose level -1B, with one first cycle DLT (grade 3 pneumothorax) observed. This established dose level -1B as the MTD and RP2D.

3.3 Subsequent Cycle Toxicities

Ten of 12 patients (83.4%) patients continued past cycle 1. Of these, 5 (50%) had subsequent cycle DLTs. Post-cycle 1 DLTs included prolonged thrombocytopenia (n=2), typhlitis (n=1), and hematuria (n=1). In response to these post-cycle 1 DLTs, patients either had dose modifications (n=4) or were removed from protocol therapy (n=1).

3.4 Other Toxicities

Treatment related adverse events (TRAEs) that occurred in >10% of patients are shown in **Table 2**. All patients experienced some degree of anemia, lymphopenia, neutropenia, thrombocytopenia, leukopenia and nausea. Other common TRAEs included sinus tachycardia (83%), fatigue (83%), increased alanine aminotransferase (75%), anorexia (75%), vomiting (67%), increased alkaline phosphatase (67%) and hypertension (67%).

3.5 Treatment Duration and Efficacy

The median duration of treatment on protocol was 1.5 months (range 0.4-7.2; **Figure 1**). Due to travel constraints, three patients were removed from protocol therapy but elected to continue to be treated as per the clinical trial protocol guidelines at their home institution (starred in **Figure 1**). These three patients were followed for an additional 30 days after being removed from protocol therapy and all were alive with disease at the end of this follow-up period.

Of the 12 patients, 10 (83%) patients were evaluable for objective response by investigator assessment (RECIST 1.1) and two (17%) were inevaluable. The two inevaluable patients did not complete disease evaluations before coming off protocol therapy due to toxicity and were classified as non-responders. Of the 10 patients evaluable for response, one patient with Ewing sarcoma had a partial response (PR), seven patients had stable disease (SD) and two patients had progressive disease (PD). Three patients with RECIST non-measurable disease were coded as having responses or non-complete response / non-progressive disease (non-CR/non-PD). **Figure 2** shows a waterfall plot of the maximal change in tumor size from baseline for the five patients with measurable disease.

3.6 Circulating Tumor DNA

Figure 3 shows change in ctDNA levels over time for patients with osteosarcoma (panel **A**) and Ewing sarcoma (panel **B**). All four patients with osteosarcoma and available baseline samples had detectable ctDNA >10% (median 16.9%, range 12.4% – 35.5%). Levels decreased during therapy in two osteosarcoma patients and increased during therapy in the other two patients. Of these two patients, one had stable disease at re-evaluation and one was not able to be re-evaluated. A fifth patient without a baseline sample had detectable ctDNA at cycle 1 day 3 that subsequently decreased during therapy. ctDNA was detectable in 5/7 patients with Ewing sarcoma, with a median percent ctDNA level of 2.11 (range 0.31 – 54.08) among those 5 patients. Of the five patients with detectable ctDNA at baseline, levels increased in one patient with clinical progression. In the other four patients, levels either decreased and remained low throughout therapy or were low at baseline and remained low throughout therapy. The sole patient with Ewing sarcoma who had a partial response did not have detectable ctDNA at baseline or during therapy.

4 Discussion

This study is the first combination trial of cabozantinib, topotecan and cyclophosphamide in patients with relapsed or refractory Ewing sarcoma or osteosarcoma. Concomitant therapy was not tolerable but an interrupted schedule was tolerable. The recommended phase 2 schedule administers cabozantinib only on days 8-21 of each cycle. Most patients had stable disease with this combination, including three patients with disease control for more than 4 months. One partial response was observed in a patient with Ewing sarcoma. Decreasing ctDNA levels were observed in patients with stable disease.

Discontinuous dosing of cabozantinib was necessary with this combination based upon the observed toxicity profile with concomitant dosing. Previous studies involving mTKIs and cytotoxic therapies in pediatric patients with solid tumors have shown mixed results with regard to schedule. A phase 1 study of pazopanib in combination with irinotecan and temozolomide in relapsed/refractory sarcomas found concomitant dosing was not tolerable[19]. Likewise, in a phase 1 study of regorafenib in combination with vincristine/irinotecan, concomitant dosing of regorafenib with the cytotoxic backbone was discontinued due to toxicity. Discontinuous administration of regorafenib during weeks without vincristine/irinotecan was the recommended phase 2 schedule[20]. In contrast, a randomized phase 2 study of pazopanib added to doxorubicin and ifosfamide for patients with soft tissue sarcoma found concomitant dosing to be tolerable. While grade 3/4 toxicity rates were higher in the pazopanib arm and 60% of patients on the pazopanib arm experienced a pazopanib-related serious adverse event, the regimen met predefined feasibility rules[21]. A phase 2 study of lenvatinib in combination with ifosfamide and etoposide for patients with relapsed or refractory osteosarcoma also found that concomitant dosing was feasible[22]. Our results add to this growing body of literature that suggest that considerations for scheduling mTKIs around chemotherapy is likely dependent upon the specific chemotherapy regimen and specific mTKI. In prior adult studies, concomitant cabozantinib was tolerable with temozolomide but not with gemcitabine[14, 15]. It now seems clear that it should not be assumed that mTKIs can simply be added to backbone chemotherapy.

Previous studies have demonstrated efficacy of cabozantinib monotherapy and separately of the topotecan plus cyclophosphamide regimen in this same population. The primary objective of this phase 1 trial was safety and the study was not designed to evaluate efficacy. Further, as both cabozantinib monotherapy and topotecan plus cyclophosphamide have shown activity in this patient population, the individual contribution or possible synergy of the agents is unclear. In particular, prior experience with topotecan/cyclophosphamide in Ewing sarcoma demonstrated ~20-30% response rate compared to the 14% observed in the current dose finding study [17] [23]. Nevertheless, this novel combination may warrant further exploration given the observed disease control, including stable disease for >4 months in 3 patients. In addition, several patients with stable disease had reductions in ctDNA burden by ULP-WGS and TranSS-Seq, suggesting possible benefit in these patients.

A limitation to this study was the lack of long-term efficacy and adverse effects data. Given that all agents were commercially available, multiple patients opted to come off trial once their dose was established to be treated as per this regimen at an institution closer to home, limiting our ability to report on longer term toxicity or disease control. An additional limitation of this trial was the lack adequate sample size within each disease group to assess efficacy. However, a strength is establishing a dose that is applicable to both relapsed Ewing sarcoma and osteosarcoma.

In summary, we demonstrate the safety and tolerability of interrupted dosing cabozantinib, cyclophosphamide and topotecan for patients with relapsed Ewing sarcoma and osteosarcoma. Combinations of mTKIs with chemotherapy are either being studied or under development as part of front-line therapy for newly diagnosed Ewing sarcoma and osteosarcoma.

Tables Guide:

Table 1. Characteristics of patients with relapsed or refractory Ewing sarcoma and osteosarcoma (n=12)

Table 2. Adverse events that either occurred in >10% of patients at any grade, or occurred at grade [?]³

in patients with relapsed or refractory Ewing sarcoma and osteosarcoma treated with the combination of cabozantinib, topotecan and cyclophosphamide (n=12). Adverse events considered unrelated or unlikely related to protocol therapy are excluded.

Table 3. Summary of objective best response in patients with relapsed or refractory Ewing sarcoma and osteosarcoma treated with a combination of cabozantinib, topotecan and cyclophosphamide (n=12).

Figures Guide:

Figure 1 . Duration of treatment with a combination of cabozantinib, topotecan and cyclophosphamide in patients with relapsed or refractory Ewing sarcoma and osteosarcoma (n=12).

Figure 2. Best percent change in tumor size from baseline for patients with relapsed or refractory Ewing sarcoma and osteosarcoma with measurable disease (n=5)

Figure 3. Spider plots demonstrating ctDNA levels throughout study duration for A) patients with osteosarcoma and B) patients with Ewing sarcoma

Supplemental Tables Guide:

Supplemental Table 1. Planned dose escalation schema

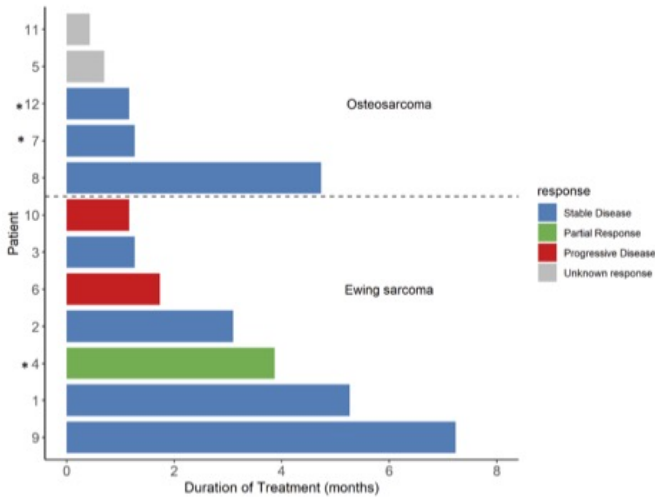
Supplemental Table 2 : Cabozantinib dose ramp-up schedule according to dose level (Cycle 1 only). Grayed out dose levels were not evaluated.

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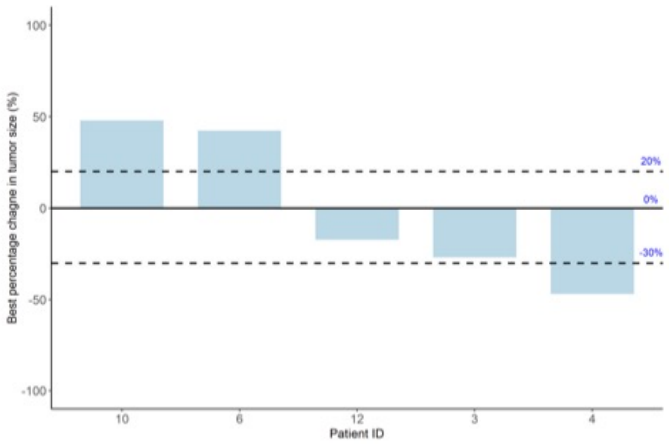
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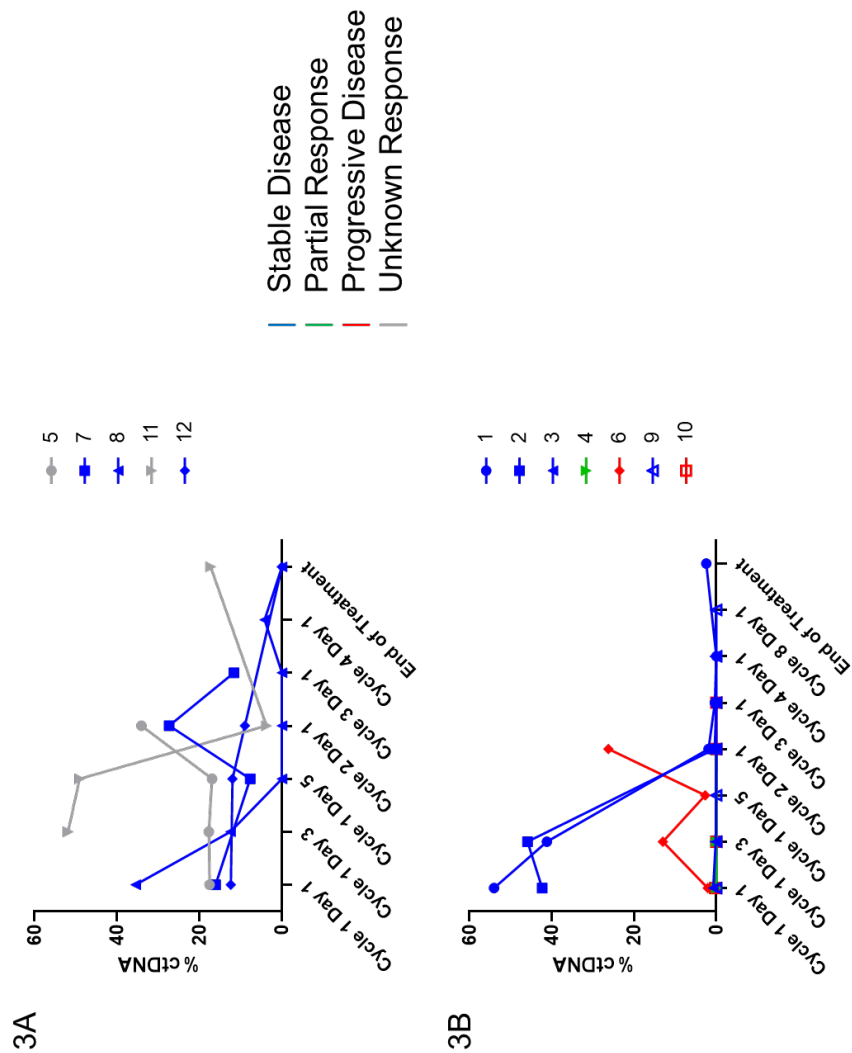
Figure 1. Duration of treatment with a combination of cabozantinib, topotecan and cyclophosphamide in patients with relapsed or refractory Ewing sarcoma and osteosarcoma (n=12).



*Indicates patient removed from clinical trial however continued to be treated as per at home institution after the time point at which the swimmer lane ends, and was followed for at least 30 days during which no change in response category occurred.

Figure 2. Best percent change in tumor size from baseline for patients with relapsed or refractory Ewing sarcoma and osteosarcoma with measurable disease (n=5).





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