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Running title
Clinical activity of abemaciclib in MCL

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Mantle cell lymphoma (MCL) accounts for ~6% of all non-Hodgkin lymphomas (NHLs) with an aggressive clinical course in patients, especially after early relapse.[1] Lack of cure for relapsed/refractory (R/R) MCL with conventional therapy[1] has resulted in a search for targeted therapies. CDK4 & 6 inhibitors have emerged as therapeutic options for R/R MCL because MCL cell lines and patient-derived samples that express high levels of cyclin D1 are highly sensitive to CDK4 & 6 inhibitors.[2] Oral abemaciclib is a potent and selective CDK4 & 6 inhibitor that reduced tumor growth in human xenograft models with MCL.[3] In a Phase I study of patients with MCL, palbociclib, another CDK4 & 6 inhibitor, was shown to overcome resistance to ibrutinib, a first-in-class BTK inhibitor.[4] Here, we evaluated the efficacy, safety, and pharmacokinetic profile of abemaciclib in patients with R/R MCL in a Phase II trial.

In this multi-center, open-label, single arm trial, patients ≥18 years of age with R/R MCL received 200 mg oral abemaciclib Q12H (every 12 hours) each day of a 28-day cycle (*Online Supplemental Appendix).* The study enrolled 28 patients in 8 centers in France and Germany from March 2013 to September 2015 (*Online Supplemental Figure 1*). Most patients were male (60.7%) and white (96.4%) with a median age of 70 years (range, 53-83) (*Online Supplemental Table 1*). Median number of prior therapies was 3 (range 1-6) and majority of the patients (67.8%) had received ≤3 prior lines of therapies. 7 patients had received prior stem cell transplant and median time to treatment from stem cell transplant was 46 months (range, 18-87 months). During the study, patients completed a median of 6 cycles (range, 1-32).

Fluorescence *in-situ* hybridization (FISH)/cytogenetics showed that all evaluable samples (n=5) from patients had the t(11;14)(q13;q32) translocation, which is a genetic hallmark of MCL and 4 (14.3%) among them overexpressed cyclin D1 (Figure 1A). In addition, cyclin D1 was overexpressed in 16 more patients (57.1%) as evidenced by immunohistochemistry although the t(11;14)(q13;q32) translocation could not be verified in these patients due to lack of evaluable samples.

Primary objective was disease control rate (DCR) based on the Response Criteria for NHL (including bone marrow evaluation).[5] Key secondary objectives included the objective response rate (ORR), duration of response (DoR), progression-free survival (PFS) and overall survival (OS). Single-agent abemaciclib demonstrated a DCR of 71.4% (95% CI; 51.3, 86.8). ORR was 35.7% (95% CI: 18.6, 55.9) including 2 CRs (7.1%) (CR, n=1; CRu, n=1) and 8 PRs (28.6%) (Table 1; Figure 1A). Median time to best response was 110.5 days. At the end of cycle 2, 22 patients were evaluated; 1 patient had CRu, 4 had PR, 15 had SD and 2 had PD. At a median follow up time of 13.8 months, median DoR was 12.39 months (95% CI: 3.19, not reached [NR]), median PFS was 8.18 months (95% CI: 4.34, 16.03) and median OS was 16.03 months (95% CI: 6.77, NR; *Online Supplemental Figure 2*). A correlation could not be made between efficacy, and gene translocation and cyclin D1 expression due to the small number of samples and lack of sufficient information on the biomarkers.

In the subgroup of patients who had received ≤3 prior therapies DCR was higher (84.2%; n=16; 95%CI: 60.4, 96.6) than those who received >3 prior therapies (44.4%; n=4; 95% CI: 13.7, 78.8). A similar trend was observed for ORR (47.4%; 95% CI: 24.5, 71.1 vs 11.1%; 95% CI: 0.3, 48.3), DoR (12.39 vs 6.67 months), PFS (12.85 vs 5.09 months) and OS (NR vs 8.18 months; *Online Supplemental Table 2*). Thus, abemaciclib was more clinically active in patients who had received ≤3 prior therapies than those who received higher numbers of prior therapies. In patients who received temsirolimus, an mTOR inhibitor, as prior therapy (n=14), ORR was 14.3% (95% CI: 1.8, 42.8) vs 57.1% (95% CI: 28.9, 82.3) in those who did not receive temsirolimus.

Dose reductions and dose omissions were reported for 78.6% and 75% of the patients, respectively. Median relative dose intensity was 71.5%. Median time to dose reduction was 28 days (range, 15–117) for those who had received ≤3 prior therapies and 15 days (range, 15–43) for patients who had received >3 prior therapies.

Safety was assessed per Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The most frequent TEAEs of any grade were diarrhea, thrombocytopenia, fatigue and neutropenia (Table 2). Diarrhea was the most common TEAE and was reported by 75% of the patients with most (60.7%) experiencing low grade diarrhea (grade 1 or 2) in cycle 1. Grade 3 diarrhea occurred less frequently (14.3%). Per protocol, diarrhea was managed with over-the-counter medications, such as loperamide, or dose reduction. 12.5% of patients required dose reduction due to diarrhea, and no patient discontinued due to this adverse event. 50% of the patients who experienced diarrhea received anti-diarrheal medication (loperamide). Fatigue was also predominantly of low grade; grade 3 and 4 events were reported for thrombocytopenia (n=11) and neutropenia (n=9) and were likely related to study drug. A total of 42.9% of the patients reported at least 1 serious adverse event (SAE). 5 patients experienced grade ≥3 events, likely related to the study drug (n=1 each of lobar pneumonia and lung infection, dehydration and pyrexia, nausea, grade 5 sepsis, and somnolence). There were 5 fatal events reported that were considered by investigators as due to AEs (1 patient due to grade 5 meningitis that was unrelated to study drug, 1 patient due to grade 5 sepsis possibly related to study drug, 1 patient due to grade 4 sepsis unrelated to study drug, 1 patient due to grade 5 reversible posterior leukoencephalopathy unrelated to study drug, and I patient due to grade 3 lung infection possibly related to study drug; *Online Supplemental Figure 3*).

PK evaluations included assessing plasma concentrations of abemaciclib and its metabolites by LC-MS method. The median abemaciclib t_{max} after a single dose was 5.7 hours (range, 3.9-8.0 hours) (Figure 1B). The mean (coefficient of variation) steady-state abemaciclib trough concentration was 364 ng/mL (85%), indicating a high degree of interindividual variability in exposure. After single and multiple doses of abemaciclib, the mean accumulation ratio based on C_{max} was 2.14 for abemaciclib and 3.91 to 5.17 for its metabolites, LSN2839567, LSN3106726, and LSN3106729 (*Online Supplemental Table 3*).

In this single arm Phase II trial, abemaciclib monotherapy demonstrated clinical activity and a manageable safety profile in patients with R/R MCL. The ORR of 35.7% achieved with abemaciclib was similar to the 33% ORR with bortezomib[6], 28% with lenalidomide,[7] and 47% with temsirolimus[8], which are approved agents for MCL treatment. This study did not investigate the effect of abemaciclib in patients who previously received BTK inhibitors or lenalidomide as these compounds were not approved at the time of enrollment; the results post temsirolimus, however, suggest a potential influence of prior pathway specific treatment. Compared to this, ORR was higher with BTK inhibitors; 81% with alacabrutinib[9] and 68% with ibrutinib[10]. However, *de novo* or acquired resistance to BTK inhibition[11] followed by uncontrolled growth of resistant MCL cells have led to poor prognosis. Therefore, the current challenge in the treatment of R/R MCL is to overcome the resistance to BTK inhibitors by choosing combination therapies targeting non-overlapping pathways.

Simultaneous inhibition of BTK and BCL2 with ibrutinib and venetoclax in a Phase II trial, improved patient outcomes at 16 weeks (CR: 42%) compared to historical controls at the same time point (9%).[12] A CR of 37% was demonstrated in a Phase I trial of R/R MCL patients who were treated with a combination of ibrutinib and palbociclib.[4] Prolonging cell cycle arrest using a CDK4 & 6 inhibitor was reported to have reverted ibrutinib resistance.[13] These data are promising and indicate that abemaciclib may have a potential role in the treatment of R/R MCL. It is important to explore the CDK4 & 6 inhibitors in combination with BTK inhibitors with potential synergistic effects.

Previous PK assessments performed in Colo-205 xenograft tumors showed that continuous inhibition of CDK4 & 6 and the resulting cell-cycle arrest were associated with an abemaciclib plasma concentration of approximately 200 ng/mL.[14] In this study, although the mean steady state trough abemaciclib plasma concentrations in patients were higher than the levels associated with durable cell cycle arrest in preclinical models, the range of the observed

concentrations was consistent with patients with solid tumors.[14] Similar to abemaciclib, its major metabolites, LSN2839567 and LSN3106726, also inhibit CDK4 & 6 with similar potencies in *in vitro* biochemical and cell-based assays and the metabolite exposure achieved in patients with MCL at a dosage of 200 mg twice daily exceeds the 50% inhibition concentration (IC_{50}) for CDK4/cyclin D1 and CDK6/cyclin D1.[15] Thus, the exposure of abemaciclib and its active metabolites is consistent with what is expected to yield biological activity. However, the optimal abemaciclib dose in MCL based on the relationship between exposure, efficacy, and safety requires further elucidation.

In conclusion, this study demonstrated that single-agent abemaciclib dosed on a continuous schedule has clinical activity in patients with R/R MCL who received multiple prior systemic therapies. The safety profile of abemaciclib in this patient group is generally consistent with other abemaciclib studies on advanced breast cancer except for higher thrombocytopenia. Additional clinical trials of abemaciclib in combination with current preferred therapies such as a BTK inhibitors are needed to determine the synergistic effects and positioning of CDK4 & 6 inhibitors in MCL.

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Table 1. Summary of Overall best response

Best Overall Response	**Abemaciclib** (N=28), n (%) (95% CI)
Disease control rate (CR+CRu+PR+SD)	20 (71.4) (51.3, 86.8)
Overall response rate (CR+CRu+PR)	10 (35.7) (18.6, 55.9)
Complete response (CR)	1 (3.6) (0.1, 18.3)
Complete response unconfirmed (CRu)	1 (3.6) (0.1, 18.3)
Partial response (cPR)	8 (28.6) (13.2, 48.7)
Stable disease (SD)	10 (35.7) (18.6, 55.9)
Progressive disease, n (%) (95% CI)	2.0 (11.8) (0.9, 23.5)
Not assessed,[a] n (%)	6.0 (21.4)
Time to events	**Abemaciclib** (N=28), n (%) (95% CI)
Median progression-free survival, months (95% CI)	8.2 (4.34, 16.03)[b]
Median overall survival, months (95% CI)	16.0 (6.77, NR)[c]

[a]Patients without post-baseline tumor assessment values at the time of data base lock
[b]Number of PFS events were 19
[c]Number of OS events were 17

Table 2. Treatment-emergent adverse events

Events occurring in ≥20% of patients (N=28)	**All Grades n (%)**	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Diarrhea	21 (75.0)	7 (25.0)	10 (35.7)	4 (14.3)	0
Thrombocytopenia	14 (50.0)	2 (7.1)	1 (3.6)	6 (21.4)	5 (17.9)
Fatigue	12 (42.9)	4 (14.3)	7 (25.0)	1 (3.6)	0
Neutropenia	11 (39.3)	0	2 (7.1)	2 (7.1)	7 (25.0)
Anemia	10 (35.7)	2 (7.1)	6 (21.4)	1 (3.6)	2 (7.1)
Nausea	9 (32.1)	6 (21.4)	1 (3.6)	2 (7.1)	0
Vomiting	8 (28.6)	6 (21.4)	2 (7.1)	0	0
Creatinine increased	7 (25.0)	3 (10.7)	3 (10.7)	1 (3.6)	0

Figure Legends

Figure 1. Anti-tumor Activity and Pharmacokinetics of abemaciclib. **A.** Change in Tumor Size at Best Response. Best overall response was based on investigator assessment. Number above or below each bar is the number of treatment regimens prior to study entry. Cyclin D1 expression and t(11;14)(q13;q32) translocation in each patient is shown below the response. Abbreviations: CR, complete response; CRu, complete response unconfirmed; PD, progressive disease; PR, partial response; SD, stable disease. **B.** Abemaciclib plasma concentration-time profiles following oral administration of single (left panel) and multiple (right panel) doses of 200 mg abemaciclib every 12 hours, depicted as individual (gray continuous lines) and geometric mean (black broken line).

Figure 1A

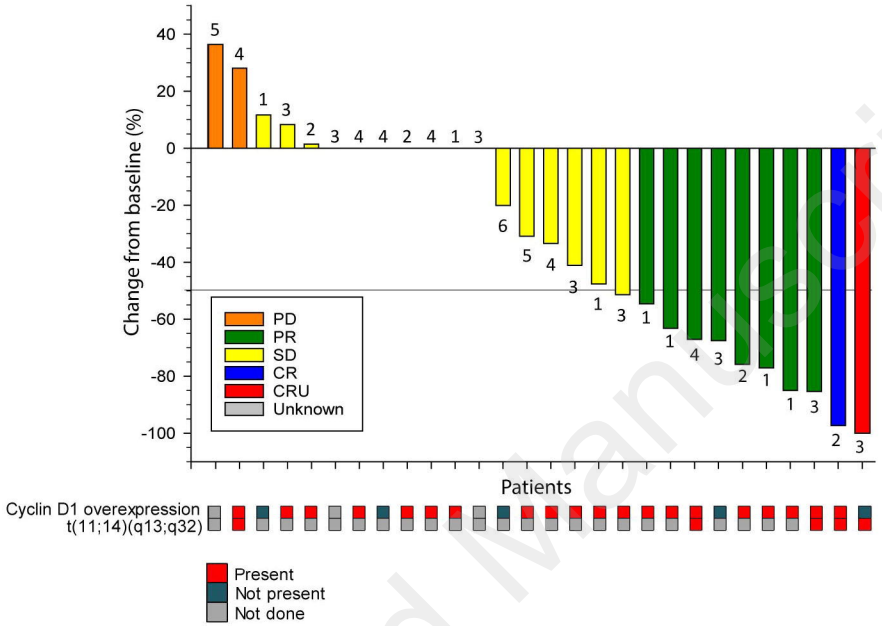
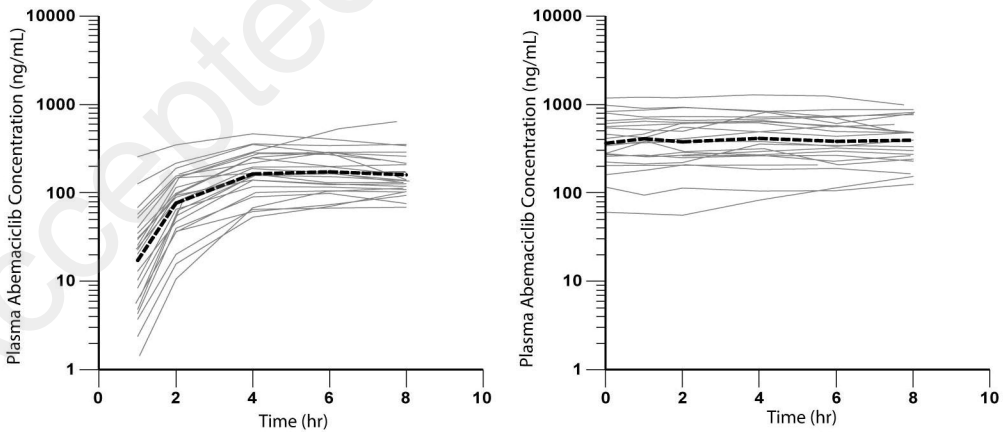


Figure 1B



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Supplemental Methods

Patients

Patients ≥18 years of age with R/R MCL to standard therapy were eligible. Additional inclusion criteria included assessable disease based on the Response Criteria for NHL[13], an Eastern Cooperative Oncology Group performance status (ECOG PS) score ≤2 and adequate organ function (absolute neutrophil count ≥1.5 × 10^9/L, platelets ≥75 × 10^9/L, hemoglobin ≥8 g/dL, bilirubin ≤1.5 times upper limits of normal [ULN], alanine aminotransferase ≤3 times ULN, aspartate aminotransferase ≤ 3 times ULN, and estimated creatinine clearance ≥50 ml/min).[14] Key exclusion criteria included any serious medical condition that precluded participation, symptomatic CNS metastasis, recipient of autologous or allogenic stem-cell transplant ≤75 days prior to receiving treatment, pregnant or lactating female patients, and the presence of any active infection. The institutional review boards of the participating institutions approved the study protocol. Written informed consent was obtained from all participants before entering the study, and ethical principles of the Declaration of Helsinki and Good Clinical Practice were followed.

Study design

This was a multi-center, open-label, single arm Phase II study of patients with R/R MCL. Patients received the maximum tolerated dose of 200 mg oral abemaciclib Q12H (every 12 hours) on Days 1 through 28 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, or patient or physician withdrawal. Dose adjustments in the form of treatment suspension or reduction were allowed both within a cycle and between cycles. Dose suspensions and reductions were required if a patient experienced grade 3 or 4 nonhematologic or grade 4 hematologic toxicity possibly related to abemaciclib. If patient had

persistent or recurrent grade 2 nonhematologic toxicity that did not resolve to baseline or grade 1 within 7 days with supportive care, dose can be reduced or suspended. Supportive care and concomitant medications were allowed. Any concurring anticancer therapy was not allowed.

Efficacy and safety measurements

Radiological tumor assessments were made by computed tomography (CT) and magnetic resonance imaging (MRI) at baseline (≤28 days before the first dosing of abemaciclib) and at the end of every 2 cycles for the initial 6 cycles and thereafter at the end of every 3 cycles until objective progression was observed. Patient's survival status was followed until death or study completion.

Pharmacokinetics

For PK evaluations, blood samples were collected on Days 1 and 15 pre-dose and 1, 2, 4, 6, and 8 hours post-dose. Plasma concentrations of abemaciclib and its metabolites were determined using a validated LC-MS method (Charles River Laboratories, Montreal, Canada). Maximum concentration (C_{max}), time of maximum concentration (t_{max}), steady state trough concentration (C_{trough}), area under the concentration-time curve from time zero until the last observed concentration ($AUC_{0\text{-}last}$), and accumulation ratio based on C_{max} were computed by non-compartmental methods using WinNonlin Professional Edition.

Statistical methods

The study tested the assumption that the true DCR was significantly different from a pre-specified null DCR (25%). If the observed DCR was 50%, then a sample size of 20 patients was estimated to provide a 95% confidence interval (CI) that the DCR will be between 27% and 73%

excluding a 25% or lower DCR. DCR and its 95% CI were estimated using the Clopper-Pearson method. DoR, PFS, and OS were analyzed using Kaplan-Meier methods.

Supplemental Table 1. Patient and disease characteristics

Characteristic	Abemaciclib treatment (N=28)
Age in years, median (range)	70.0 (53.0-83.0)
Male, n (%)	17 (60.7)
Race White, n%	27 (96.4)
MCL Stage at initial diagnosis, n%	
I	2 (7.1)
III	6 (21.4)
IV	20 (71.4)
Bulky mass (tumor size ≤10 cm), n (%)	3 (10.7)
ECOG PS, n (%)	
0	12 (42.9)
1	14 (50.0)
2	2 (7.1)
Simplified MIPI at baseline, n (%)	
Low risk	6 (21.4)
Intermediate risk	11 (39.3)
High risk	7 (25.0)
Not available	4 (14.3)
Number of prior regimens, n (%)	
1	6 (21.4)
2	5 (17.9)
3	8 (28.6)
>3	9 (32.1)
Prior systemic therapies, n (%)	
Rituximab	28 (100.0)
Doxorubicin-based therapy	24 (85.7)
Cytarabine-based therapy	20 (71.4)
Temsirolimus	14 (50.0)
Bendamustine	9 (32.1)
Stem cell transplantation (autologous)	7 (25.0)
Bortezomib	3 (10.7)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; MIPI = simplified mantle-cell lymphoma international prognostic index; N = total population size; n = number of patients.

Supplemental Table 2. Subgroup analysis based on number of prior systemic therapies

	≤3 prior therapies (n=19)	>3 prior therapies (n=9)
Best Overall Response n (%) (95% CI)		
Disease Control Rate	16 (84.2) (60.4, 96.6)	4 (44.4) (13.7, 78.8)
Overall Response Rate (CR+CRu+PR)	9 (47.4) (0.2, 0.7)	1 (11.1) (0.003, 0.5)
Complete Response	1 (5.3) (0.1, 26.0)	0
Complete Response Unconfirmed	1 (5.3) (0.1, 26.0)	0
Partial Response	7 (36.8) (16.3, 61.6)	1 (11.1) (0.3, 48.2)
Stable Disease	7 (36.8) (16.3, 61.6)	3 (33.3) (7.5, 70.1)
Time to Best Overall Response, days (range)	112 (55, 25)	109 (109, 109)
Median Time to Events (months, 95% CI)		
Duration of Response	12.39 (3.19, NR)	6.67 (NR)
Time to Progression	16.16 (5.45, NR)	5.09 (0.72, 10.2)
Disease-free Survival	14.36 (3.19, NR)	6.67 (NR)
Progression-free Survival	12.85 (4.34, 16.2)	5.09 (0.72, 10.2)
Overall Survival	NR (6.47, NR)	8.18 (1.12, 16.3)
Event-free Survival	11.79 (5.45, 16.3)	10.22 (NR)
MCL Stage at diagnosis, n (%)		
Stage I	0	2 (22.2)
Stage III	4 (21.1)	2 (22.2)
Stage IV	15 (78.9)	5 (55.5)

Supplemental Table 3. Pharmacokinetics of abemaciclib and its metabolites in relapsed or refractory MCL

		Geometric Mean (CV%)				
Dose	**Analyte**	**C_{max} ng/mL, (%) (n=26)**	**t_{max}[a] (hr) (n=26)**	**$AUC_{(0\text{-last})}$ (hr*ng/mL) (n=26)**	**C_{trough} (ng/mL) (n=21)**	**RA, C_{max} (n=20)**
Single	Abemaciclib	189 (59)	5.70 (3.92 – 8.00)	978 (61)	NA	NA
	LSN2839567	42.6 (58)	4.06 (3.33 – 8.00)	221 (59)	NA	NA
	LSN3106726	54.4 (55)	6.04 (3.97 – 8.00)	275 (64)	NA	NA
	LSN3106729	13.8 (90)	6.00 (3.92 – 8.00)	68.0 (97)	NA	NA
Multiple[b]	Abemaciclib	449 (71)[c]	4.00 (0.00 – 8.00)[c]	3090 (77)[c]	364 (85)	2.14 (74)
	LSN2839567	198 (42)[c]	4.00 (1.05 – 8.00)[c]	1350 (45)[c]	156 (53)	3.91 (70)
	LSN3106726	323 (45)[c]	2.00 (0.00 – 8.00)[c]	2280 (48)[c]	282 (55)	5.17 (68)
	LSN3106729	86.2 (60)[c]	3.97 (0.00 – 8.00)[c]	585 (61)[c]	64.9 (71)	5.02 (79)

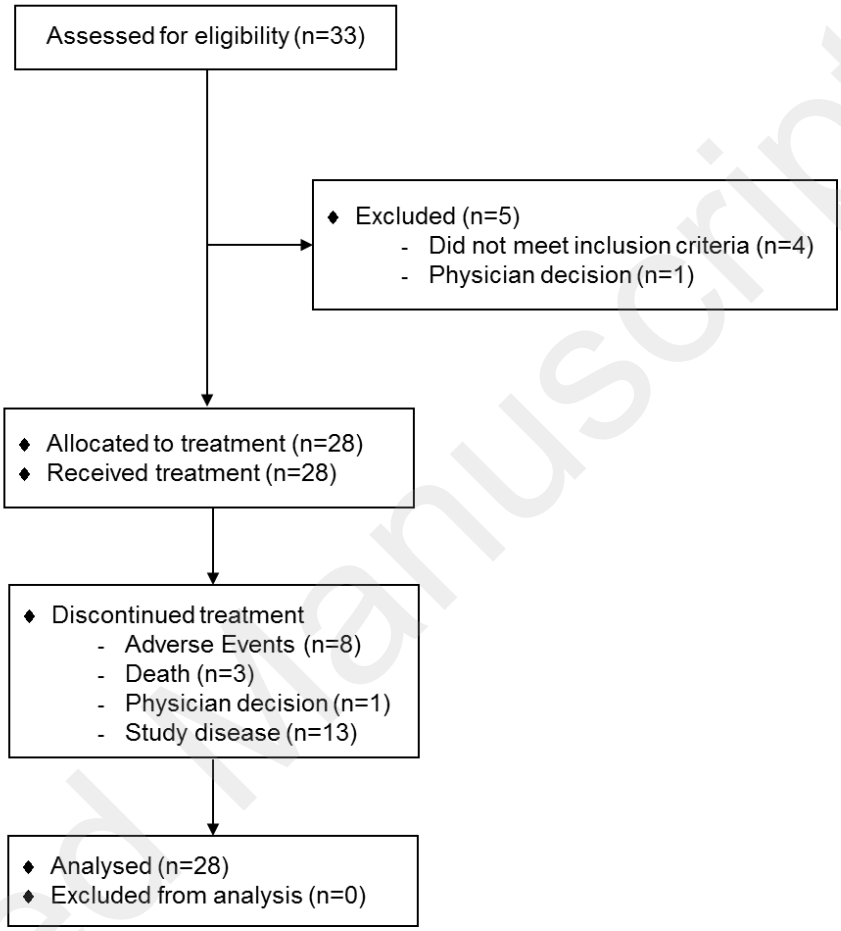
Abbreviations: C_{max} = maximum observed plasma concentration; t_{max} = time of maximum observed drug concentration; AUC(0-last) = area under the concentration time curve from time 0 to last observed concentration; C_{trough} = observed plasma concentration prior to next dose; RA, C_{max} = accumulation ratio based on C_{max}; n = number of observations

[a] Median and range

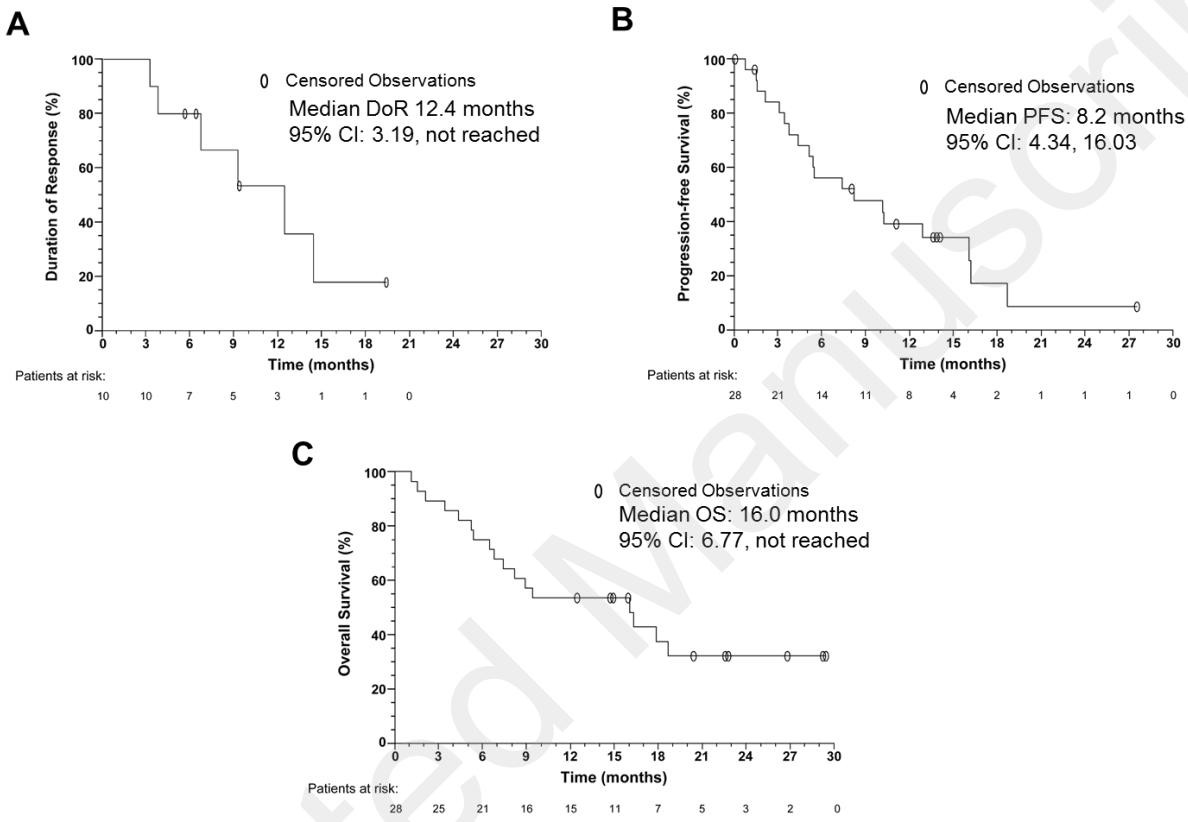
[b] In multiple dose, PK values were calculated on days 12 (n=1), 14 (n=10), 15 (n=9), or 16 (n=1)

[c] n=21

Supplemental Figure 1. CONSORT diagram



Supplemental Figure 2. Kaplan-Meier curves of duration of response (A), progression-free survival (B) and overall survival (C)



Supplemental Figure 3. Duration of treatment and reason for discontinuation by patient