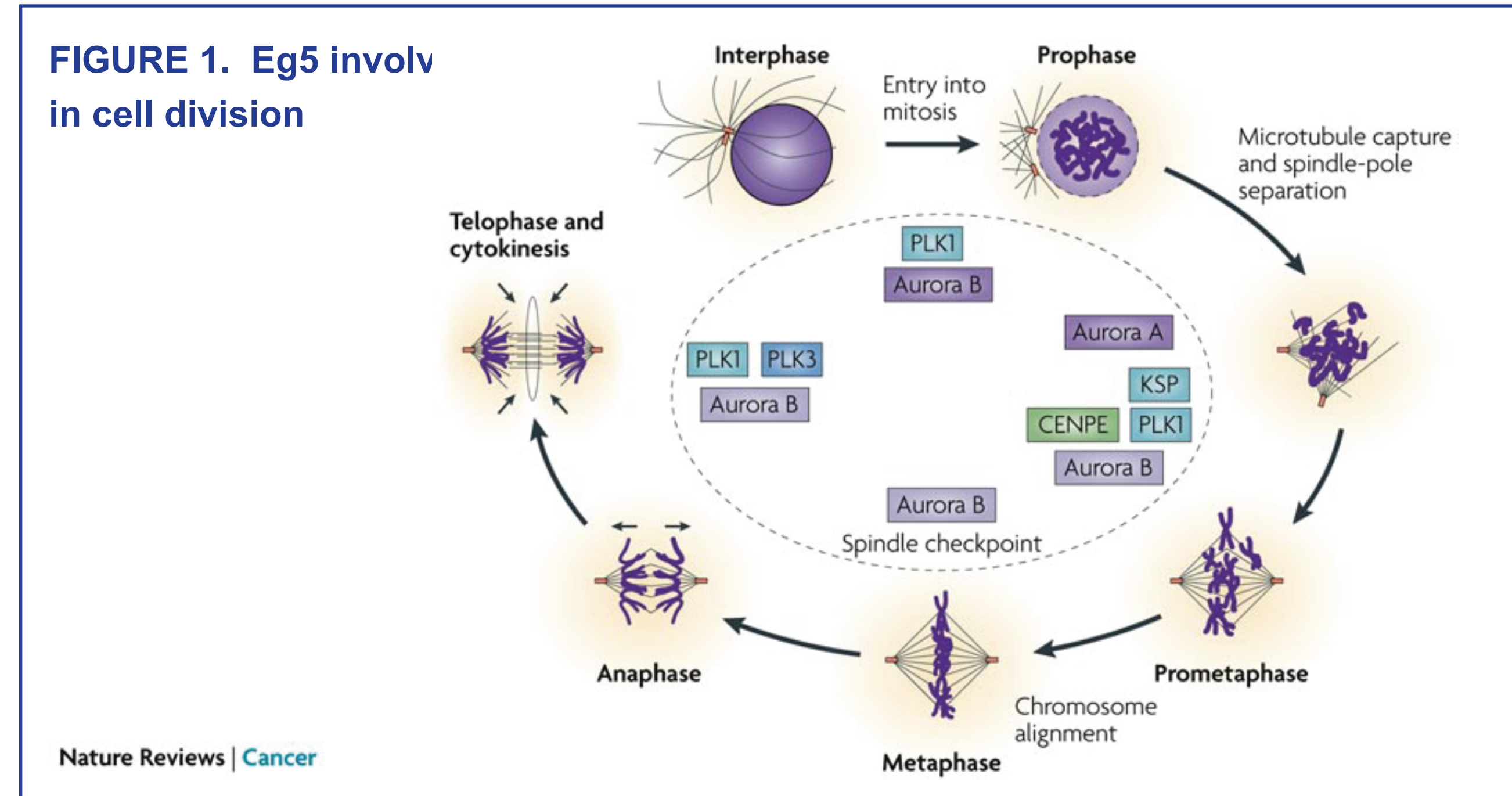


BACKGROUND

Eg5 (KSP; kinesin spindle protein) is a microtubule-based ATPase motor protein involved in cell division (see Figure 1) (1). Pharmacologic inhibition of Eg5 is recognized as a potential therapeutic strategy in cancer supported by the observation that over-expression of Eg5 causes genomic instability and tumor formation in mice (2) and that tumor cell tetraploidy or aneuploidy may render cancer cells more sensitive to Eg5 inhibition than normal cells (3). ARQ 621 is a potent and selective inhibitor of the Eg5 mitotic motor protein, and shown its anti-tumor activity against a range of human cancer cell lines *in vitro* and in a number of xenografts grown in athymic mice. The 621-101 clinical trial evaluated the safety and pharmacokinetics of ARQ 621 in patients with solid and hematologic tumors. Final results from the solid tumors cohort are reported here.



PRECLINICAL RESULTS

As previously reported, ARQ 621 demonstrated anti-tumor activity against a wide range of human cancer cell lines *in vitro*, including colon, lung, endometrial, bladder, and hematologic cancer cell lines and in a number of xenografts grown in athymic mice, including pancreatic, breast, prostate, and ovarian carcinomas. Compared to ispinesib, a previously characterized Eg5 inhibitor, ARQ 621 demonstrated comparable potency and proved to be a non-DNA damaging agent. Furthermore, for ARQ 621, no evidence of bone marrow toxicity was documented in pre-clinical mouse efficacy models or safety studies in rats and dogs (4-7).

METHODS

Patients (pts) were enrolled into this multi-cohort Phase 1 trial at the initial dose of 10 mg/m². Drug was administered weekly intravenously over 1-2 hours. Cohorts of 3 or 6 patients were based on a 3+3 dose escalation schedule, and dose was increased according to a modified Fibonacci scheme. Treatment continued until disease progression or unacceptable toxicity.

STUDY OBJECTIVES

Primary

- Safety, tolerability and recommended Phase 2 dose (RP2D) of ARQ 621 administered intravenously in pts with metastatic solid tumors

Secondary/Exploratory

- Pharmacokinetic (PK) profile of ARQ 621
- Pharmacodynamic profile of ARQ 621
- Preliminary assessment of antitumor activity of ARQ 621

IMPORTANT ELIGIBILITY CRITERIA

- 18 years of age or older
- Locally advanced or metastatic solid tumors
- Measurable disease per RECIST version 1.1
- ECOG performance status ≤ 2
- Adequate bone marrow, liver, and renal function
- Stable brain metastases within 8 weeks of study entry
- No anticancer therapy within 4 weeks of study entry
- No history of thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, or HUS-spectrum syndrome

CLINICAL RESULTS

As of April 21, 2011, 48 pts (22 male; median age 60.5 yrs, ECOG PS 0 (N=11), PS 1 (N=36), PS 2 (N=1)) with solid tumors were enrolled. The most common tumors treated with ARQ 621 were colorectal (N=12), pancreatic (N=5) and breast (N=4).

TABLE 1. Baseline Patient Characteristics (N = 48)

Median age, years (range)	60.5 (28-82)
Sex	
Male	22 (46%)
Female	26 (54%)
Race	
Caucasian	43 (90%)
Black	2 (4%)
Other	3 (6%)
ECOG	
0	11 (23%)
1	36 (75%)
2	1 (2%)
Median number of prior systemic therapies (range)	5 (1-13)

Treatment-emergent adverse events (TEAEs) were reported in 48 (100%) pts. The most common (>10%) include: fatigue 20 (42%), nausea 16 (33%), anemia 9 (19%), vomiting 12 (25%). Seventeen pts experienced 29 serious AEs (including: anemia, sepsis, pneumonia, pleural effusion, DVT), 24 were reported as not drug related. Five drug-related SAEs were anemia (70 mg/m²), DVT (140 mg/m²), fatigue, nausea, and acute intravascular hemolysis (400 mg/m²).

TABLE 2. Most Common Drug-Related AEs (>10%)

MedDRA SOC Preferred Term	Any Grade N All Pts (N=48) N (%)	Grade 1 & 2	Grade 3 & 4
At Least one related TEAE	36 (75.0%)		
Gastrointestinal Disorders			
Nausea	8 (16.7%)	8 (16.7%)	
Vomiting	7 (14.6%)	7 (14.6%)	
Diarrhoea	6 (12.5%)	6 (12.5%)	
General Disorders and Administration Site Conditions			
Fatigue	10 (20.8%)	10 (20.8%)	

TABLE 3. Drug-Related SAEs

MedDRA SOC Preferred Term	Any Grade (N = 48)	Grade 1 & 2	Grade 3 & 4
Blood and Lymphatic System Disorders			
Anemia	1 (2%)	1 (2%)	
Intravascular Hemolysis	1 (2%)		1 (2%)
General Disorders and Administration Site Conditions			
Fatigue	2 (4%)	1 (2%)	1 (2%)
Gastrointestinal Disorders			
Nausea	1 (2%)		1 (2%)
Vascular Disorders			
Deep Vein Thrombosis	1 (2%)		1 (2%)

At the weekly dose of 400 mg/m², drug-related AEs were reported for all enrolled pts (N=7), including three DLT events (nausea, fatigue and acute intravascular hemolysis). Even though protocol-defined DLTs were observed in 2/7 pts, 400 mg/m² was deemed to be not tolerable, and the prior dose level of 280 mg/m² was recommended as MTD.

TABLE 4. Dose-limiting Toxicity

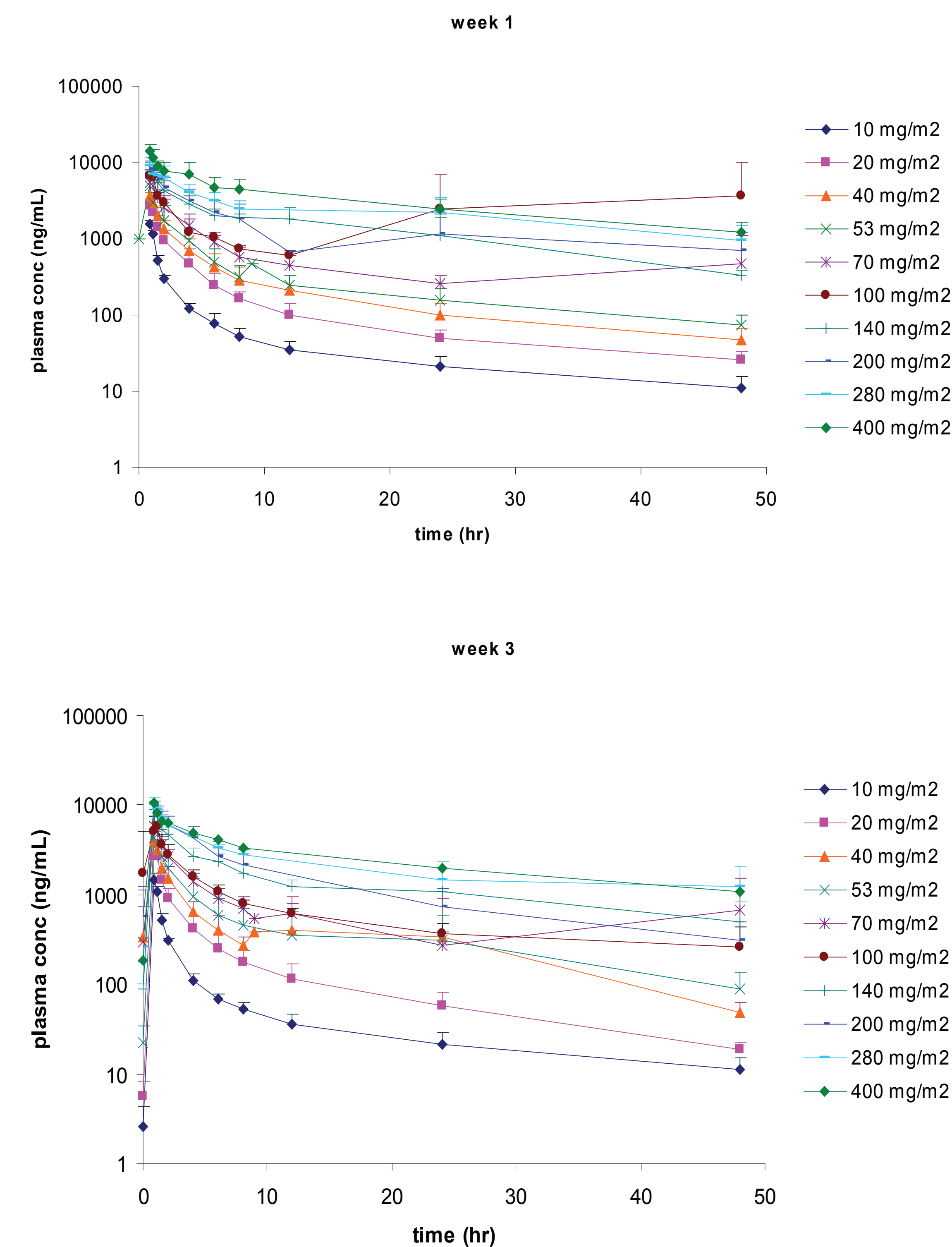
MedDRA SOC Preferred Term	Any grade (N = 48)	Grade 1 & 2	Grade 3 & 4
Blood and Lymphatic System			
Intravascular Hemolysis	1 (2%)		1 (2%)
General Disorders and Administration Site Conditions			
Fatigue	2 (4%)	1 (2%)	1 (2%)
Gastrointestinal Disorders			
Nausea	1 (2%)		1 (2%)
Nervous System Disorders			
Headache	1 (2%)	1 (2%)	
Peripheral Sensory Neuropathy	2 (4%)	2 (4%)	

PK data analysis showed that on day 1 at 280 mg/m² the mean C_{max} (n=4) was 9185 ± 2512 ng/mL and AUC(0-48hr) was 108435 ± 39127 hr*ng/mL (Figure 1).

TABLE 5. Dose proportionality of AUC

Week	Dose	10	20	40	53	70	100	140	200	280	400
Week 1	Dose Ratio	1	2	4	5.3	7	10	14	20	28	40
	AUC _{inf} Ratio	1	2.5	3.8	5.5	7.2	9.6	18	25	29	53
Week 3	Dose Ratio	1	2	4	5.3	7	10	14	20	28	40
	AUC _{inf} Ratio	1	2.5	5.6	6.5	7.5	9.1	19	22.3	33	45

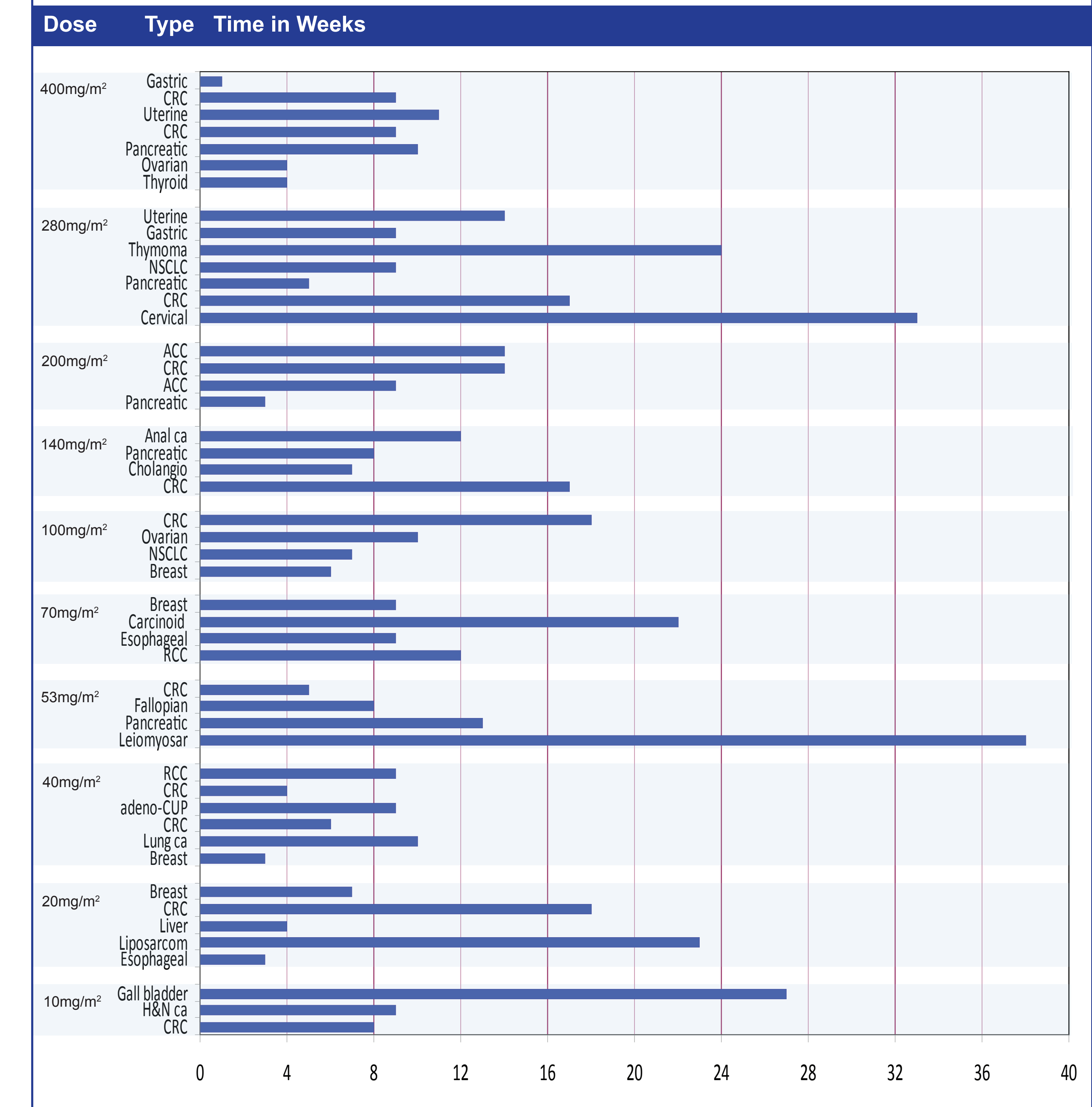
FIGURE 2. Comparison of Mean Concentration-Time Profiles for 10 to 400 mg/m² Dose Groups



- For dose levels ranging from 10 to 400 mg/m², C_{max} was less than dose proportional and AUC_{inf} was very close to dose proportional.
- Over this dose range, mean half-life and mean clearance ranged from 12.2 to 22.2 hr and 1.8 to 3.9 L/hr/min, respectively.

Twenty nine pts were evaluable for response per RECIST (v. 1.1). Best response of stable disease was obtained in 11 pts at 2 mo and 5 pts at 4 mo. Time on study for evaluable pts ranged from 8 to 38 (median 17.5, mean 19) weeks (Figure 3). Six pts (cholangiocarcinoma, liposarcoma, leiomyosarcoma, cervical, carcinoid and colorectal carcinoma) remained stable for > 4 months.

FIGURE 3. Time on Study



CONCLUSIONS

- MTD/RP2D is defined as 280 mg/m².
- PK profiles show that AUC_{inf} is nearly dose proportional and C_{max} is less than dose proportional.
- ARQ 621 appeared to be well-tolerated and demonstrated a favorable safety profile with manageable adverse events and low bone marrow toxicity at weekly doses up to 280 mg/m².
- SD longer than 4 months was observed in 6 patients.

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