

Final results from ARQ 197-114: a Phase 1b safety trial evaluating the c-MET inhibitor ARQ 197 in cirrhotic patients with hepatocellular carcinoma

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BACKGROUND

- c-MET is the receptor tyrosine kinase for hepatocyte growth factor (HGF),¹ which is involved in liver regeneration and maturation of bone marrow progenitor cells in adults^{2,3}
- Inappropriate c-MET activation and/or dysregulation is implicated in tumor cell proliferation, migration, and invasiveness.¹ c-MET is dysregulated in a broad spectrum of cancers, including hepatocellular carcinoma (HCC)^{4,5}
- ARQ 197 is a selective, non-ATP competitive inhibitor of c-MET phosphorylation and activation.⁶ It has demonstrated anti-tumor activity against a wide range of human tumor cell lines, including synergy with sorafenib *in vitro*,⁷ and in human tumor xenograft models^{8,9}
- As of March 29, 2010, ARQ 197 has been evaluated in over 400 patients with cancer
- ARQ 197 is orally administered; it is well tolerated and active both as monotherapy¹⁰ and in combination with other agents¹¹

OBJECTIVES

- Safety of ARQ 197 monotherapy in HCC patients with cirrhosis progressing on previous therapies
- Pharmacokinetic (PK) and biomarker analysis, time to disease progression (TTP), objective response rate, and disease control rate
- Dynamic changes in HGF, vascular endothelial growth factor (VEGF), and soluble c-MET in peripheral blood associated with ARQ 197 therapy

METHODS

Key inclusion criteria

- Adults (≥18 years) with histologically confirmed HCC
- Barcelona Clinic Liver Cancer Staging Category A, B, or C
- Confirmed cirrhotic status of Child-Pugh Class A (or B by protocol amendment)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- No more than two prior systemic treatments for HCC, with last treatment completed ≥4 weeks prior to first dose of ARQ 197
- Local or loco-regional therapy completed ≥4 weeks prior to first dose of ARQ 197
- Measurable disease defined by revised Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Adequate bone marrow, liver, and renal function

Key exclusion criteria

- Previous or concurrent cancer other than HCC
- History of cardiac disease
- Active, clinically serious infections defined as superior to Grade (G) 2, according to National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0
- Known human immunodeficiency virus (HIV) infection
- History of liver transplant
- Clinically significant gastrointestinal bleeding occurring ≤4 weeks prior to first dose of ARQ 197

Study design

- Multicenter, single cohort, Phase 1b study at the recommended Phase 2 oral dose of 360 mg twice daily (BID) administered continuously until disease progression

- Hematology (complete blood count) and liver function tests checked weekly throughout the study
- Electrocardiogram performed weekly during Cycle 1, then monthly
- PK samples obtained on study Days 1 and 15 of Cycle 1 (cycles were 28 days)
- Anti-tumor activity assessed per RECIST version 1.1 guidelines based on CT scans at 8-week intervals

RESULTS

- As of March 19, 2010, a total of 21 patients were enrolled and treated with ARQ 197 at a dose of 360 mg BID
 - 19 (90.5%) patients were male, and 2 (9.5%) were female (median age: 66.2 years; range 47–80)
 - 8 (38.1%) patients had ECOG performance status 0, and 13 (61.9%) ECOG performance status 1
 - 17 (80.9%) patients had Child-Pugh A status, and 4 (19.1%) had Child-Pugh B status
 - Median plasma alpha-fetoprotein level was 200 mg/mL (range 2–63,918)
 - Median number of prior systemic therapies received was 1 (range 1–5)

Adverse events

- Study drug-related adverse events (AEs) were reported in 20 (95.2%) of 21 patients
- The most commonly reported study drug-related AEs were asthenia, anemia, neutropenia, leukopenia, diarrhea, anorexia, and fatigue (**Table 1**)
 - Patient 001 developed G4 then G3 neutropenia; ARQ 197 dose was first reduced to 300 mg BID, then held for 1 week after the second event with growth factors treatment before restarting ARQ 197 at 240 mg BID for the duration of the study
 - Patient 002 had two dose reductions (240 mg BID, then 120 mg BID) and two courses of growth factor treatment due to multiple episodes of neutropenia (one G2, one G3, and two G4) and anemia (two G3 and one G4). Treatment was temporarily withheld on four occasions
 - Patient 013 experienced two episodes of G3 bradycardia on Days 13 and 35. This patient was also being treated with beta-blockers, which were then given at a reduced dose following the AE. The patient subsequently continued ARQ 197 at a reduced dose (240 mg BID, then 120 mg BID) after resolution of bradycardia, until discontinuation due to progressive disease
 - Patient 016 developed G3 neutropenia; treatment was withheld for 2 weeks, then resumed at full dose without any further growth factor treatment. Patient developed G4 neutropenia/leukopenia again on Day 57 and was discontinued due to progressive disease
 - In two patients, bone marrow toxicity led to study drug discontinuation: Patient 0017 developed G4 leukopenia on Day 17, and Patient 0008 developed G4 neutropenia on Day 23 and G3 leukopenia on Day 30

Table 1. Most common^a study drug-related adverse events (N=21)

Adverse event	Patients (N %)		
	Any grade	Grade 3	Grade 4
Anemia	9 (43)	4 (19)	1 (5)
Asthenia	9 (43)	1 (5)	–
Neutropenia	8 (38)	1 (5)	4 (19)
Leukopenia	7 (33)	2 (10)	1 (5)
Anorexia	6 (29)	–	–
Diarrhea	6 (29)	–	–
Fatigue	5 (24)	1 (5)	–
Alopecia	4 (19)	–	–
Thrombocytopenia	3 (14)	–	–
Vomiting	3 (14)	–	–
Bradycardia	2 (10)	1 (5)	–

^aOccurring in ≥10% of patients

- Four patients (19%) experienced study drug-related SAEs, including G3 anemia (n=2), G4 neutropenia (n=2), G4 leukopenia (n=1), G5 pneumonia (n=1), and septic shock (n=1)
 - The septic shock occurred during untreated drug-related G4 leukopenia and caused the death of the patient
- No drug-related worsening of liver function was observed

Pharmacokinetic analysis

- PK analyses were performed on Day 1 (n=10) and Day 15 (n=7) of Cycle 1
- Mean maximum concentration (C_{max}) ± standard deviation (SD) was 1714 ± 771 ng/mL on Day 1, and 3926 ± 1508 ng/mL on Day 15
- Mean area under the concentration time curve (AUC₍₀₋₁₂₎) ± SD was 15,693 ± 6842 hr.ng/mL on Day 1, and 36,882 ± 15,887 hr.ng/mL on Day 15
- Analysis showed that plasma concentrations did not decline within 12 hours after the first dose and reached steady state by Day 15

Tumor response

- ARQ 197 shows preliminary signs of activity (**Figure 1**)
- Progression-free rate at 2 months based on Kaplan-Meier estimate was 59.7%, and rate at 4 months was 39.8%
- Median time on study for evaluable patients was 13 weeks (range 2.2–56 weeks)
 - One patient was taken off the study for alpha-fetoprotein increase at 4 months, although radiographic imaging at the time of discontinuation showed stable disease
 - One patient remains stable for >13 months, with a decrease in tumor density at CT scan with i.v. contrast
- Median TTP (radiographic) was 107 days (95% CI: 54, NA; **Figure 2**)

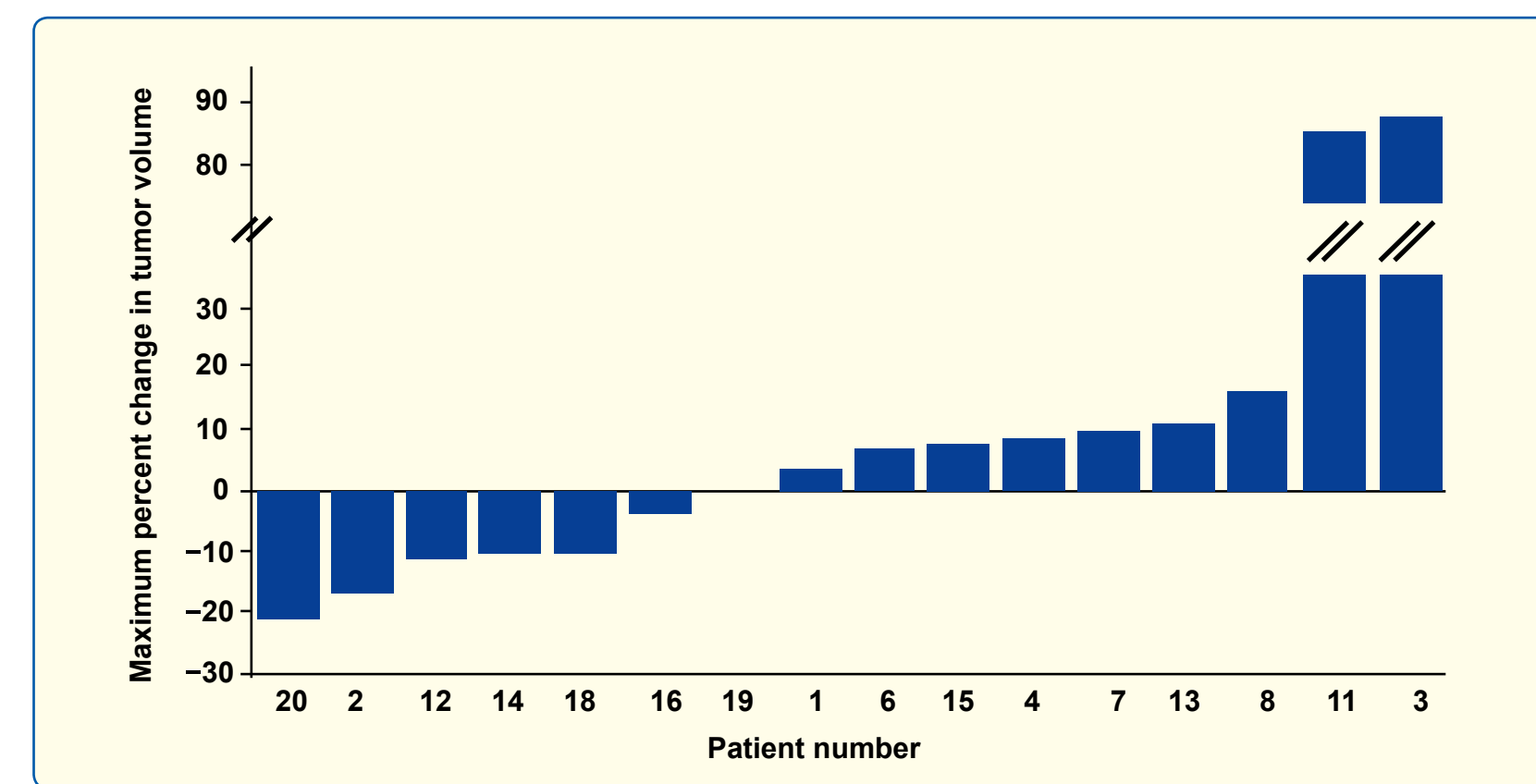


Figure 1: Maximum percent change in tumor volume in evaluable patients (n=16)

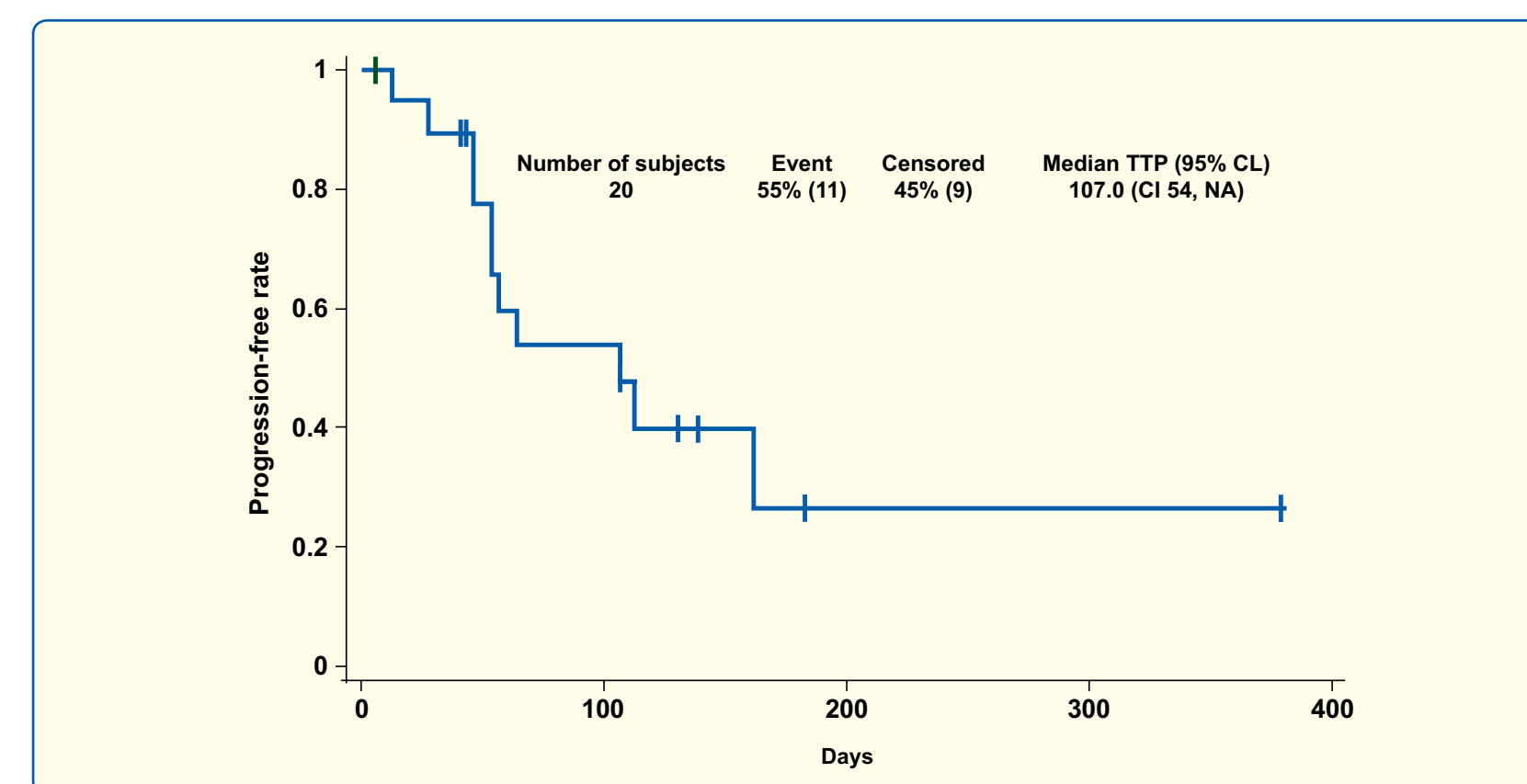


Figure 2: Kaplan-Meier estimate of time to disease progression (TTP)

Tumor biomarker analysis

- All patients' biopsies were positive for total c-MET and at least weakly positive for HGF, while only one patient showed activation of c-MET

Plasma biomarker analysis

- HGF plasma levels (median 2400 ng/mL) were higher than in previous treated patient populations
- Neutropenia may correlate with reductions in plasma HGF (more than plasma c-MET) which, in turn, is generally related to efficacy (tumor response) (**Figures 3 and 4**)
 - c-MET plays an important role in the maturation of bone marrow progenitors;^{2,3} therefore, reductions in plasma HGF may have consequences on neutrophil counts
- Conversely, VEGF plasma levels do not seem to correlate with ARQ 197 activity (**Figure 5**)

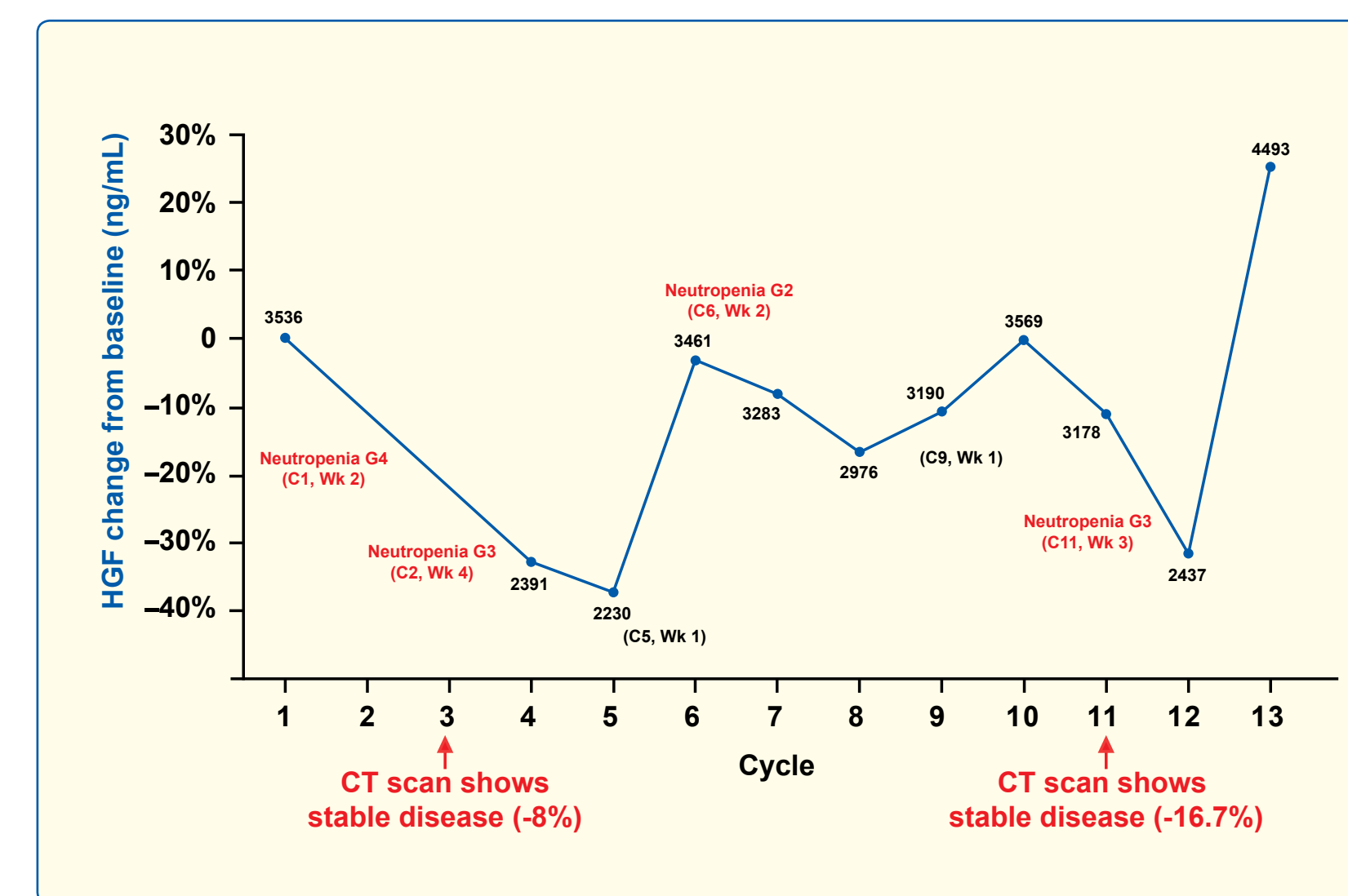


Figure 3: Plasma HGF levels may correlate with neutropenia; HGF by cycle, Patient #2

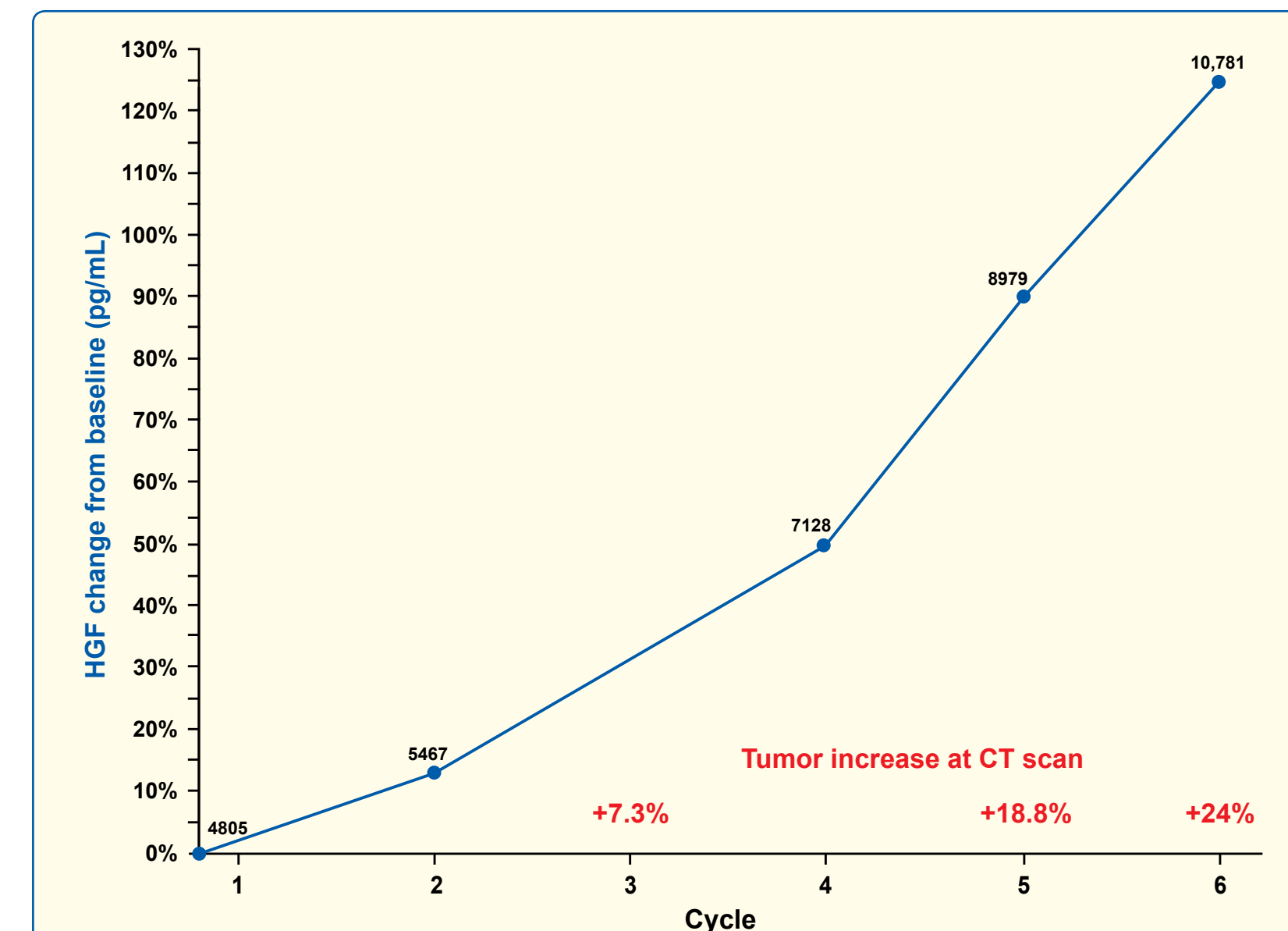


Figure 4: Example of a patient in whom increase in plasma HGF correlates with tumor growth; HGF by cycle, Patient #6

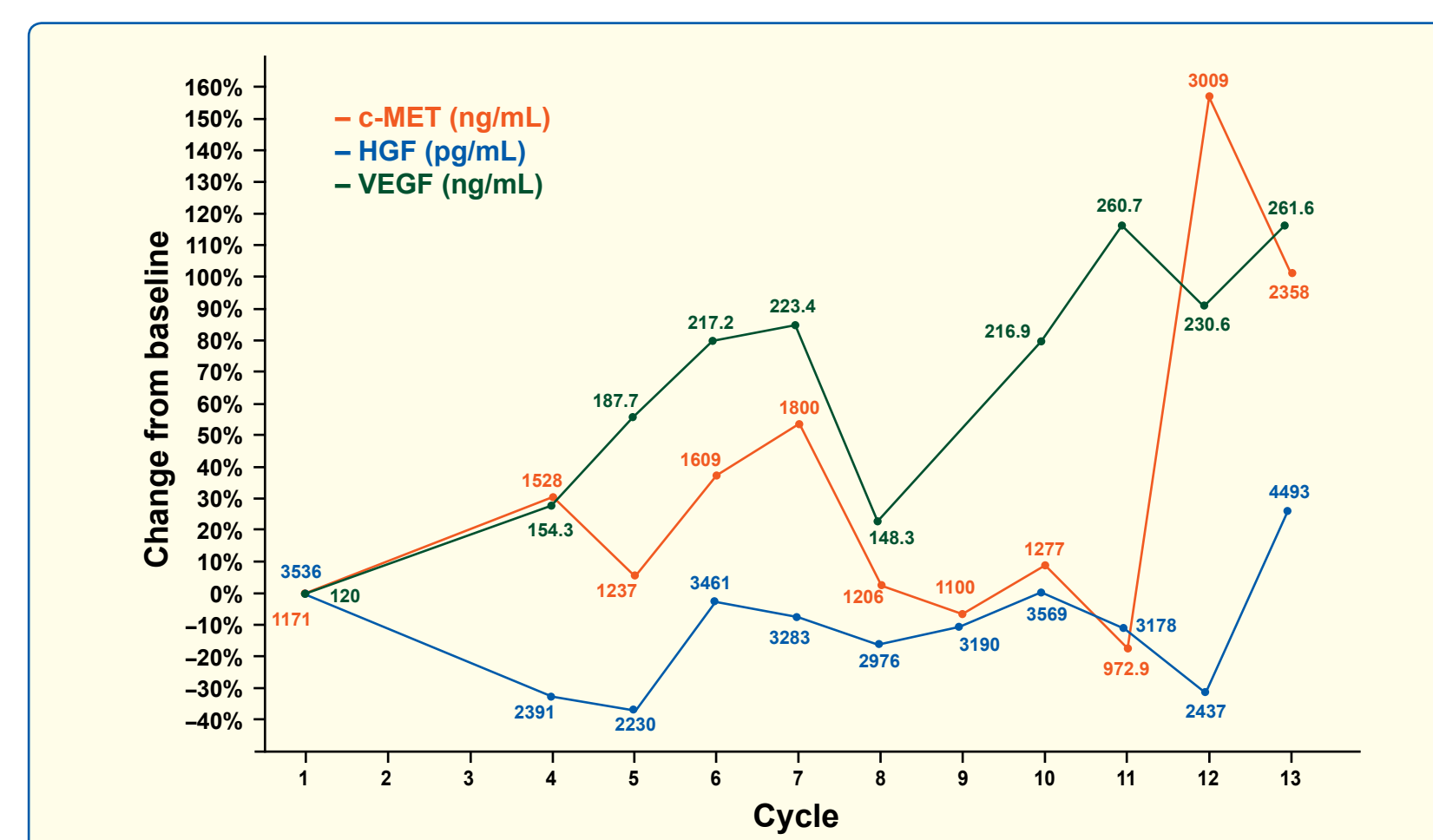


Figure 5: Comparison of changes in plasma concentrations of soluble c-MET, HGF, and VEGF by cycle, Patient #2

CONCLUSIONS

- In patients with HCC and concurrent cirrhosis, the safety profile of ARQ 197 is manageable
 - Treatment with ARQ 197 is primarily associated with manageable hematologic toxicity, which may be expected, given the involvement of c-MET in the maturation of bone marrow progenitor cells
 - In this study, incidence of reported neutropenia was higher than in previous studies with ARQ 197
 - Neutropenia may correlate with reductions in plasma HGF
 - These reductions, in turn, are generally related to tumor response
- No drug-related worsening of liver function has been reported to date
- Preliminary single-agent activity was observed
- Tumor biomarker analysis showed that all patients were positive for total c-MET, and at least weakly positive for HGF
- Enrollment is completed, with 2 subjects still on study
- ARQ 197 is currently being investigated in patients with HCC at the recommended Phase 2 dose of 360 mg BID in two studies:
 - A Phase 1 study in combination with sorafenib
 - A global, randomized, placebo-controlled, single-agent, Phase 2 study in patients who have failed first-line therapy for HCC

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Disclosure

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