

ARQ 197-215: a randomized, placebo-controlled Phase 2 clinical trial evaluating the c-MET inhibitor, ARQ 197, in 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 is implicated in tumor cell proliferation, migration, and invasiveness (Figure 1).¹ c-MET is dysregulated in a broad spectrum of cancers, including hepatocellular carcinoma (HCC)^{4,5}
 - Overexpression of HGF and c-MET in HCC is associated with poor prognosis in patients with HCC¹
 - Silencing of c-MET expression leads to regression of experimental tumors⁶ and growth inhibition of HCC cell lines⁷
 - Therefore, c-MET inhibition is a potential therapeutic strategy in HCC
- ARQ 197 is a selective, non-ATP competitive inhibitor of c-MET phosphorylation and activation;⁸ it has demonstrated anti-tumor activity against a wide range of human tumor cell lines and in human tumor xenograft models^{9,10}
- ARQ 197 shows synergistic cytotoxicity in vitro when combined with various anticancer drugs, including erlotinib and sorafenib¹¹
- ARQ 197 has been evaluated in over 400 patients with cancer and has been demonstrated to be a clinically well-tolerated, orally available, anticancer drug candidate, exhibiting anti-tumor activity as both monotherapy¹² and in combination¹³
- ARQ 197 continues to demonstrate evidence of clinical efficacy in a number of tumor types, including non-small cell lung cancer (NSCLC). Data from a multinational, randomized, double-blind clinical trial (ARQ 197-209) in NSCLC have been presented at this conference¹⁴

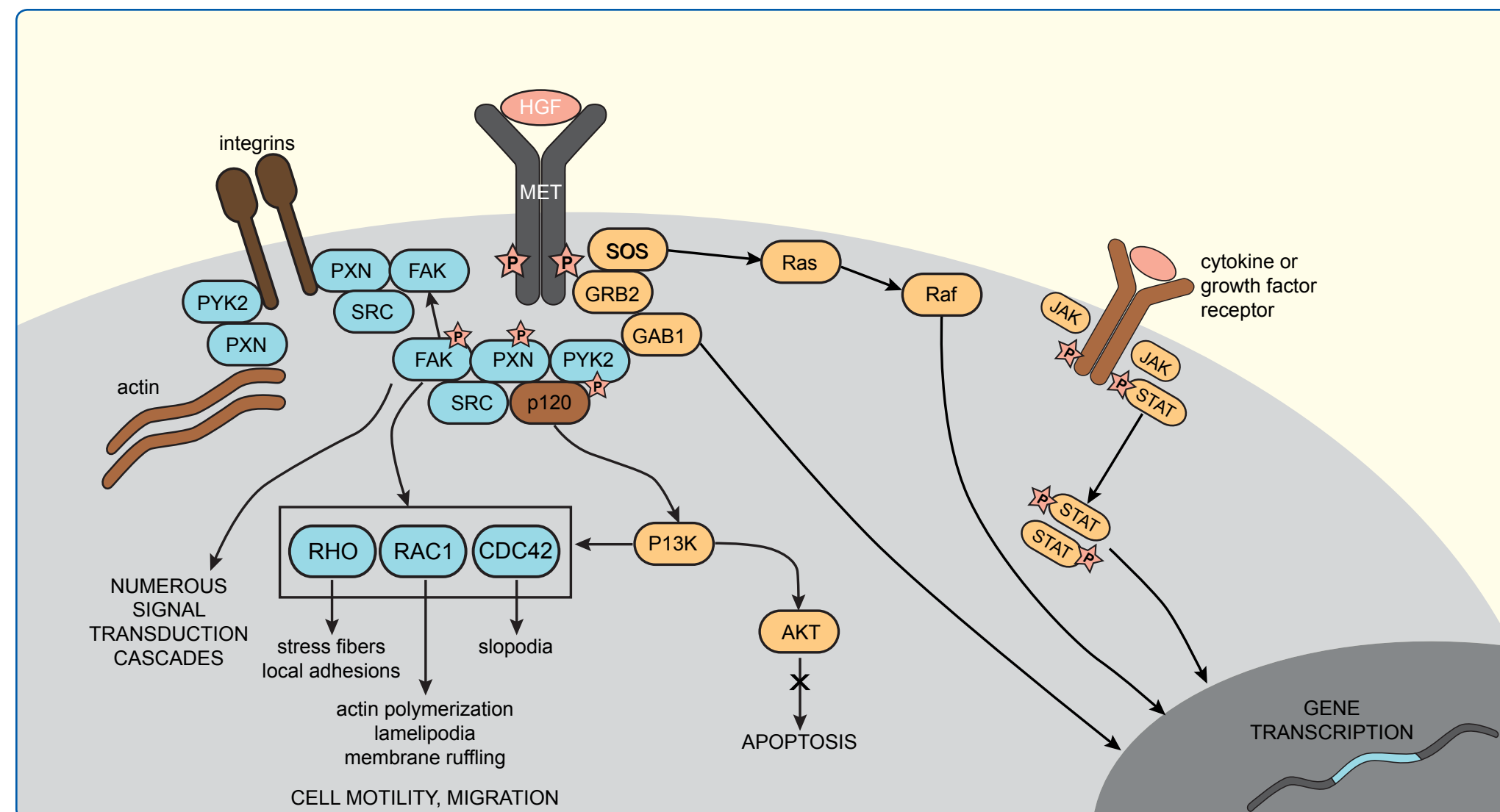


Figure 1: c-MET signaling pathway

RESULTS FROM PRIOR PHASE 1 CLINICAL TRIAL IN CIRRHOTIC PATIENTS WITH HCC

- ARQ 197-114 was a Phase 1b study conducted as a multicenter, single-cohort run-in for a subsequent randomized, controlled Phase 2 trial^{15,16}
 - Full results for this study are presented in another poster at this conference¹⁶
- A total of 21 patients were treated at a dose of 360 mg twice daily (BID)^{15,16}
 - Mean age of patients was 66.2 years (47-80); 19 patients were male
 - 8 patients presented with ECOG PS0, 13 with PS1
 - 17 patients presented with Child-Pugh status A, and 4 with Child-Pugh status B
 - The median alpha-fetoprotein (AFP) value was 200 (2-63,918); the median number of prior systemic therapies was 1 (1-5)
- 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 (43%), anemia (43%), neutropenia (38%), leukopenia (33%), diarrhea (29%), anorexia (29%), and fatigue (24%)
 - Interestingly, once early neutropenia resolved, patients were able to remain on a lower dose of ARQ 197 generally without further reoccurrence for long periods of time
- Preliminary pharmacokinetic (PK) data showed that plasma concentrations did not decline within 12 hours after the first dose and reached steady state by Day 15
- Among 18 patients evaluable for response, 10 (56%) had stable disease at 2 months by RECIST (best response) and 5 (28%) continued to have stable disease at 4 months by RECIST (best response)
- Median time on study for evaluable patients was 13 weeks (range 2.2-56 weeks)
- Median time to progression (TTP; radiographic) was 107 days (95% CI: 54; Figure 2)
- This Phase 1b study of ARQ 197 in patients with HCC and cirrhosis showed no worsening of liver function, confirming the manageable safety profile of the molecule and preliminary evidence of efficacy
 - Hematologic toxicity may be expected, considering the involvement of c-MET in the maturation of bone marrow progenitors^{2,3}

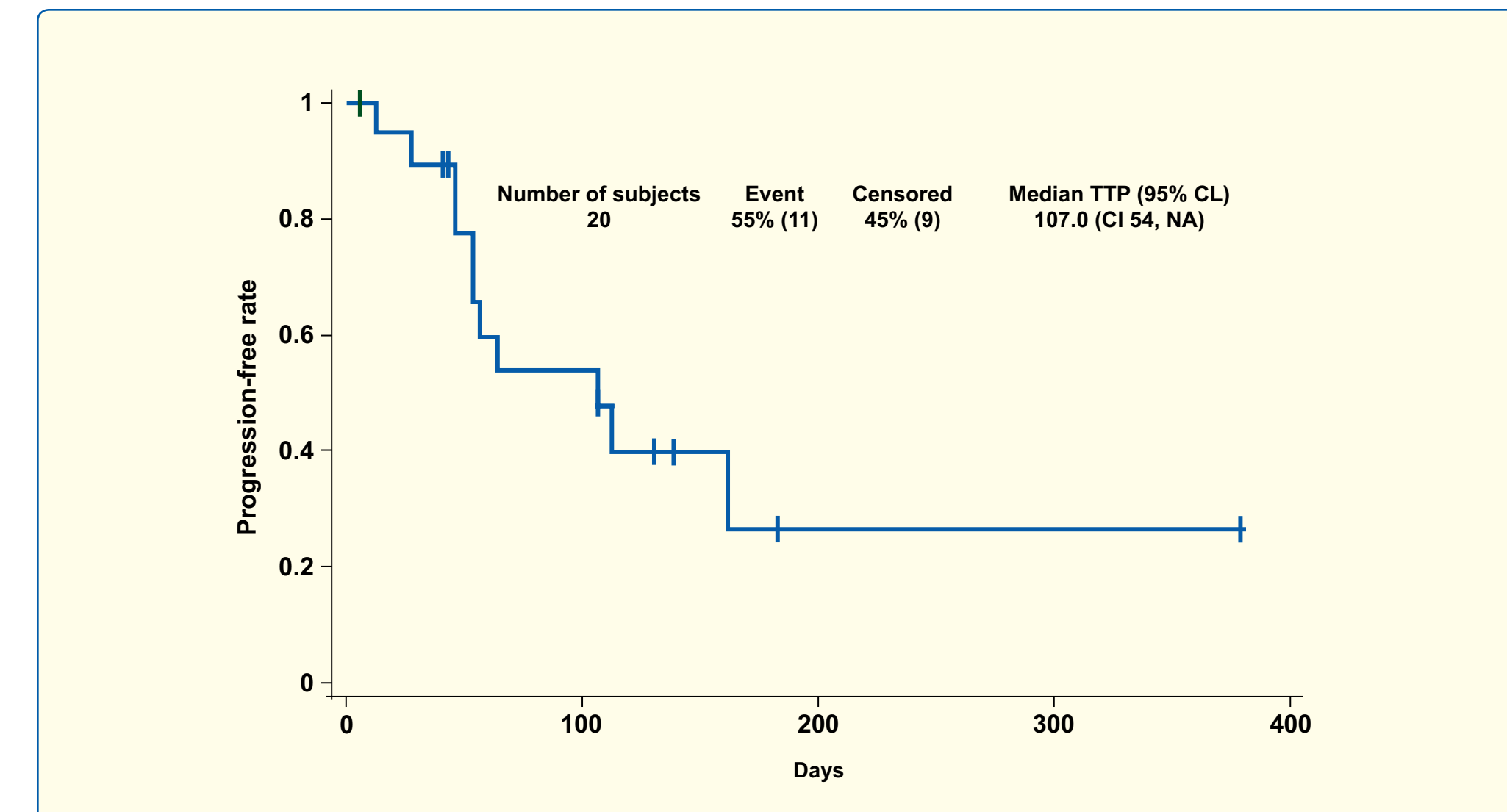


Figure 2: Median time to progression (radiographic)

RANDOMIZED CONTROLLED PHASE 2 STUDY DESIGN – ARQ 197-215

- A global, randomized, double-blind, placebo-controlled, Phase 2 study
- Approximately 99 patients will be enrolled from multiple study sites
- Patients are being randomized in a 2:1 fashion to receive either oral ARQ 197 360 mg BID or placebo (Figure 3)
- Patients are seen weekly for the first month of treatment and then monthly for safety visits
- Computed tomography (CT)/magnetic resonance imaging (MRI) scans are performed every 6 weeks
- Patients randomized to placebo are eligible for crossover to open-label ARQ 197 360 mg BID following radiographic confirmation of progression of disease (PD)
- All patients will continue in the study until confirmed PD, unacceptable toxicity, or withdrawal from the study for other reasons
- The primary endpoint is TTP
- Secondary endpoints include comparisons of the study arms for median PFS, overall survival, biomarker analyses, PK analysis, and safety

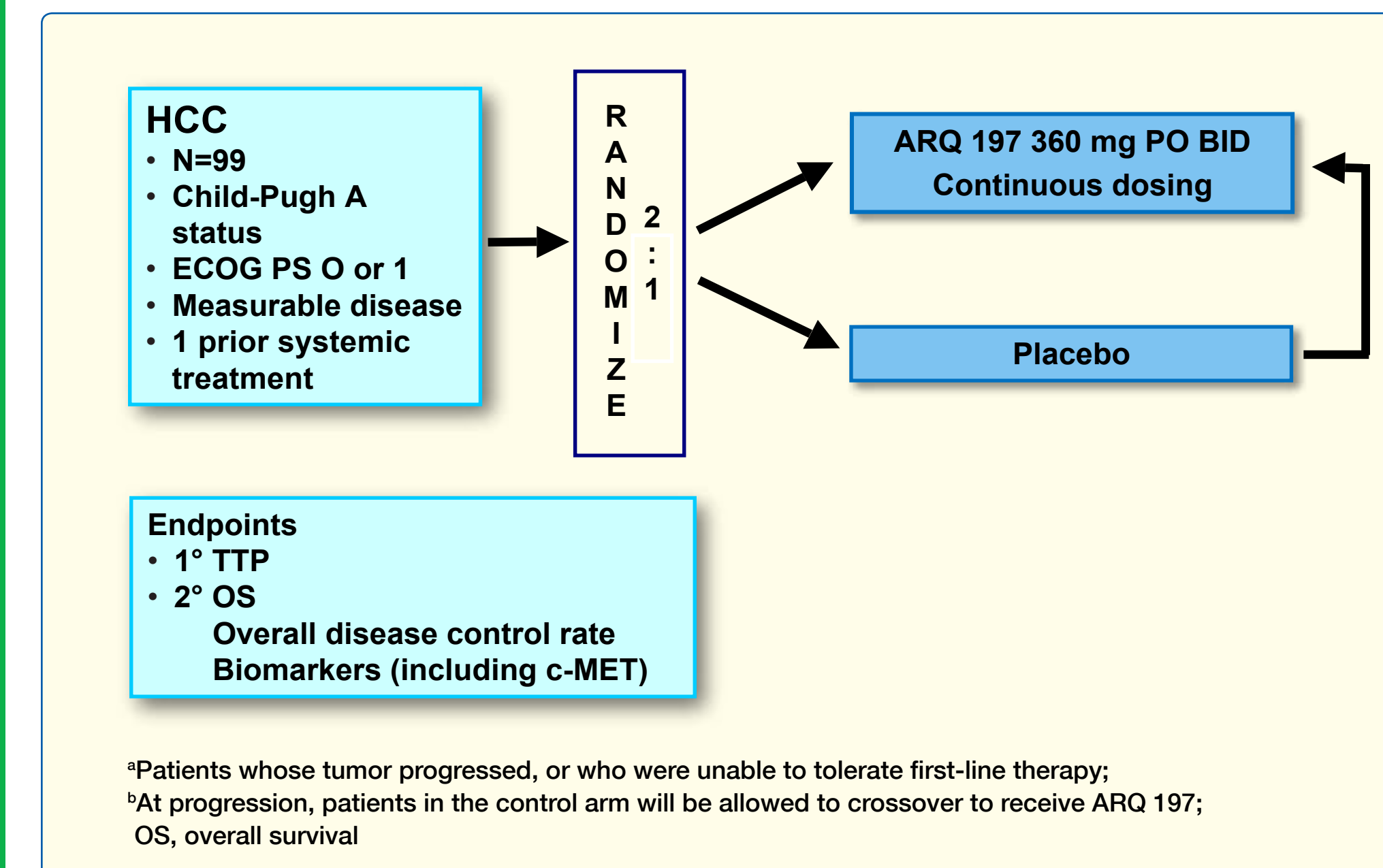


Figure 3: ARQ 197-215 study design

Key inclusion criteria

- Histologically or cytologically confirmed HCC (with archival or fresh biopsy samples available)
- At least 1 cycle of prior systemic therapy with radiographic disease progression or inability to tolerate therapy
- Measurable disease as defined by a modified version of RECIST version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Adequate bone marrow, liver, and renal function

Key exclusion criteria

- More than one prior systemic regimen
- Child-Pugh B or C cirrhotic status
- Previous or concurrent cancer other than HCC in primary site or histology, except cervical carcinoma *in situ*, treated basal cell carcinoma, superficial bladder tumors. Any cancer curatively treated for more than 3 years is permitted
- History of cardiac disease occurring ≤ 6 months prior to study entry
- Active, clinically serious infections defined as \geq Grade 3 according to National Cancer Institute-Common Terminology Criteria for Adverse Events, version 4.0
- History of liver transplant

CURRENT ENROLLMENT

- As of May 10, 2010, 33 of the required 99 patients were enrolled and treated with ARQ 197 (Figure 4)
- Participating centers are located in Belgium, Canada, Germany, Italy, and the United States

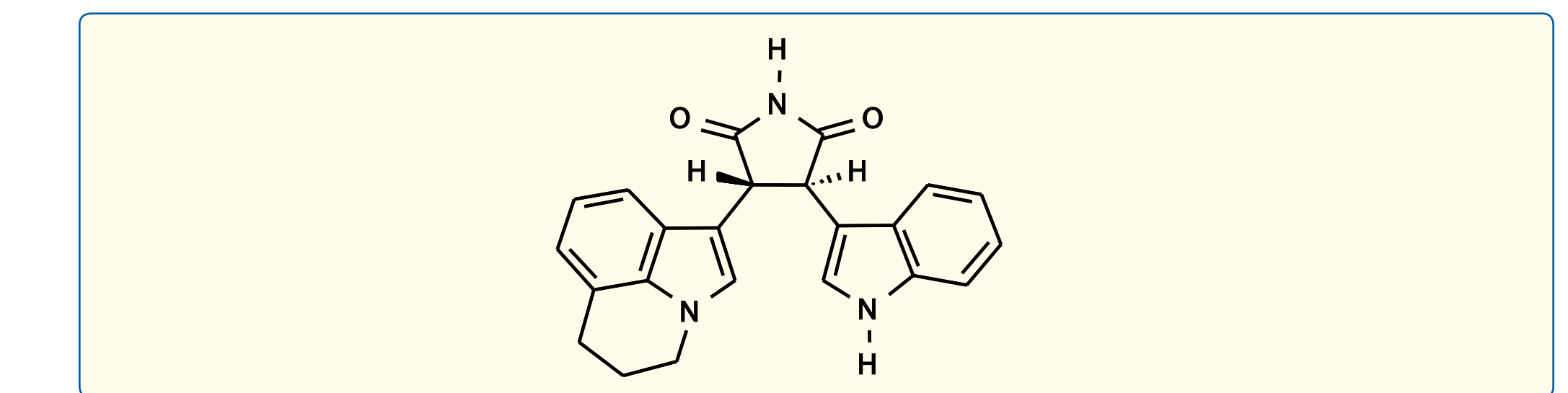


Figure 4: Molecular structure of ARQ 197

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Disclosure

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