Phase II Study of First-Line Trebananib Plus Sorafenib in Patients with Advanced Hepatocellular Carcinoma

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TRIAL INFORMATION

• ClinicalTrials.gov Identifier: NCT00872014
• Sponsor(s): Amgen
• Principal Investigator: Ghassan K. Abou-Alfa
• IRB Approved: Yes

LESSONS LEARNED

• Trebananib leveraging anti-angiogenic mechanism that is distinct from the classic sorafenib anti-vascular endothelial growth factor inhibition did not demonstrate improved progression-free survival at 4 months in patients with advanced hepatocellular carcinoma (HCC).
• In support of previously reported high Ang-2 levels’ association with poor outcome in HCC for patients, trebananib treatment with lower baseline Ang-2 at study entry was associated with improved overall survival to 22 months and may suggest future studies to be performed within the context of low baseline Ang-2.

ABSTRACT

Background. Ang-1 and Ang-2 are angiopoietins thought to promote neovascularization via activation of the Tie-2 angiopoietin receptor. Trebananib sequesters Ang-1 and Ang-2, preventing interaction with the Tie-2 receptor. Trebananib plus sorafenib combination has acceptable toxicity. Elevated Ang-2 levels are associated with poor prognosis in hepatocellular carcinoma (HCC).

Methods. Patients with HCC, Eastern Cooperative Oncology Group ≤2, and Childs-Pugh A received IV trebananib at 10 mg/kg or 15 mg/kg weekly plus sorafenib 400 mg orally twice daily. The study was planned for ≥78% progression-free survival (PFS) rate at 4 months relative to 62% for sorafenib historical control (power = 80% α = 0.20). Secondary endpoints included safety, tolerability, overall survival (OS), and multiple biomarkers, including serum Ang-2.

Results. Thirty patients were enrolled sequentially in each of the two nonrandomized cohorts. Demographics were comparable between the two arms and the historical controls. PFS rates at 4 months were 57% and 54% on the 10 mg/kg and 15 mg/kg trebananib cohorts, respectively. Median OS was 17 and 11 months, respectively. Grade 3 and above events noted in ≥10% of patients included fatigue, hypertension, diarrhea, liver failure, palmar-plantar erythrodysesthesia syndrome, dyspnea, and hypophosphatemia. One death was due to hepatic failure. Serum Ang-2 dichotomized at the median was associated with improved OS in both cohorts.

Conclusion. There was no improvement in PFS rate at 4 months in either cohort, when compared with sorafenib historical control. The Oncologist 2017;22:780–e65

DISCUSSION

High Ang-2 levels’ association with poor outcome in HCC for patients treated with sorafenib or placebo has been reported [1]. Adding trebananib, which sequesters Ang-1 and Ang-2, preventing their interaction with the Tie-2 receptor [2], to sorafenib treatment on a continuous schedule in two nonrandomized cohorts of two doses of trebananib with comparable demographics between the two arms and the historical control did not show an improvement in progression-free survival (PFS) rate at 4 months, compared with the estimate of historical control sorafenib in patients with advanced HCC. This is, albeit a favorable median PFS of 7.9 for the 10 mg/kg arm, a reminder

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of the difficulty of interpreting these endpoints vis-à-vis the complexity of HCC and the accompanying cirrhosis.

The combination of trebananib plus sorafenib seems relatively well tolerated; however, the relatively higher than anticipated worsening of liver function is a concern and may add some pretext to the relatively poor outcome of the higher dose of 15 mg/kg cohort compared with the lower dose of 10 mg/kg cohort.

The exploratory biomarker analyses showed several patterns, among which the most intriguing finding is the lower baseline Ang-2 at study entry, suggesting an association with improved OS to 22 months (Fig. 1). The association between Ang-2 and survival was previously observed \( p < .006 \) in a phase II trial of trebananib plus sunitinib in renal cancer patients [3].

A relatively improved estimate of 17 months median OS of the 10 mg/kg compared with 11 months of the 15 mg/kg trebananib cohort, which is commensurate with the sorafenib single agent historical control of 10.7 months [4], is noted. We do not believe that the biology of trebananib could explain a lower dose improved efficacy or synergy with sorafenib. This may likely be an artifact of the Kaplan-Meier curve estimation and censoring.

In conclusion, the combination of sorafenib and trebananib did not demonstrate improved control of tumor growth at 4 months, the primary endpoint of this trial. Any further studies of this combination or similar in HCC should be studied within the context of low baseline Ang-2 and possibly other markers reported herein.

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**Trial Information**

| Disease            | Hepatocellular carcinoma |
|--------------------|--------------------------|
| Stage of Disease/Treatment | Metastatic/Advanced |
| Prior Therapy      | None                     |
| Type of Study - 1  | Phase II                 |
| Type of Study - 2  | Randomized               |
| ORR                | RECIST 1.0 objective response rates were 3% and 7%, for the 10 mg/kg and 15 mg/kg cohorts, respectively. |
| PFS                | PFS rates at 4 months were 57% and 54% for the 10 mg/kg and 15 mg/kg trebananib cohorts, respectively. |
| TTP                | Median TTP was 9 months (95% CI: 3.4, 16.4) and 6.9 months (95% CI: 3.6, 12.7) in the 10 mg/kg and 15 mg/kg trebananib cohorts, respectively. |
| Response Duration  | There was no significant difference in the rate of durable stable disease at \( \geq 16 \) weeks from study day 1 (46.7% and 40% on the 10 mg/kg and 15 mg/kg trebananib cohorts, respectively). This translated into a disease controlled rate of 50% and 46.7% in the 10 mg/kg arm and 15 mg/kg arm, respectively. |
| Primary Endpoint   | Progression-free survival at 4 months |
| Secondary Endpoint | Toxicity                  |
| Secondary Endpoint | Overall survival           |
| Secondary Endpoint | Progression-free survival  |
| Secondary Endpoint | Time to progression        |
| Secondary Endpoint | Overall response rate      |
### Secondary Endpoint: Pharmacokinetics

### Secondary Endpoint: Correlative endpoint

### Additional Details of Endpoints or Study Design

The study consisted of two sequentially enrolled cohorts of trebananib 10 mg/kg and trebananib 15 mg/kg, each dosed weekly in combination with sorafenib given at the standard dose of 400 mg twice daily in an every-4-weeks dosing schedule. Based on an estimated 4-month progression-free survival rate of 62% for sorafenib single agent [5], and assuming a 4-month progression-free survival rate of 78% in each cohort, 30 patients in each cohort were required to accrue to satisfy a power of 80% with the one-sided exact test for single proportion at $\alpha = 0.20$. Survival curves were estimated using the Kaplan-Meier methodology.

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### Drug Information for Phase II Trebananib 10 mg/kg + Sorafenib

**Drug 1**
- **Generic/Working name**: Trebananib
- **Company name**: Amgen
- **Drug type**: Peptibody
- **Dose**: 10 milligrams (mg) per kilogram (kg)
- **Route**: Intravenous (IV)

**Drug 2**
- **Generic/Working name**: Sorafenib
- **Trade name**: Nexavar
- **Company name**: Bayer
- **Drug type**: Small molecule
- **Dose**: 400 milligrams (mg) per flat dose
- **Route**: Oral (PO)

### Drug Information for Phase II Trebananib 15 mg/kg + Sorafenib

**Drug 1**
- **Generic/Working name**: Trebananib
- **Company name**: Amgen
- **Drug type**: Peptibody
- **Dose**: 15 milligrams (mg) per kilogram (kg)
- **Route**: Intravenous (IV)

**Drug 2**
- **Generic/Working name**: Sorafenib
- **Trade name**: Nexavar
- **Company name**: Bayer
- **Drug type**: Small molecule
- **Dose**: 400 milligrams (mg) per flat dose
- **Route**: Oral (PO)

### Patient Characteristics for Phase II Trebananib 10 mg/kg + Sorafenib

| Characteristic                | Count       |
|------------------------------|-------------|
| Number of patients, male     | 50          |
| Number of patients, female   | 10          |

**Stage**
- Macroscopic Vascular Invasion: trebananib 10 mg/kg + sorafenib, $n = 30$: 8 (26.7)
- Macroscopic Vascular Invasion: trebananib 15 mg/kg + sorafenib, $n = 30$: 8 (26.7)
- Extrahepatic Spread: trebananib 10 mg/kg + sorafenib, $n = 30$: 10 (33.3)
- Extrahepatic Spread: trebananib 15 mg/kg + sorafenib, $n = 30$: 10 (33.3)
### Patient Characteristics for Phase II Trebananib 15 mg/kg + Sorafenib

| Parameter                        | Trebananib 10 mg/kg + Sorafenib (n = 30) | Trebananib 15 mg/kg + Sorafenib (n = 30) |
|----------------------------------|-----------------------------------------|-----------------------------------------|
| Hepatitis B                      | 6 (20)                                  | 8 (27)                                  |
| Hepatitis C                      | 5 (17)                                  | 10 (33)                                 |
| Alcohol                          | 10 (33)                                 | 5 (17)                                  |
| NASH/other                       | 4 (13)                                  | 6 (20)                                  |
| Unknown                          | 7 (23.3)                                | 7 (23.3)                                |

Abbreviations: NASH, nonalcoholic steatohepatitis.

### Primary Assessment Method for Phase II Trebananib 10 mg/kg + Sorafenib

| Assessment                         | Trebananib 10 mg/kg + Sorafenib (n = 30) | Trebananib 15 mg/kg + Sorafenib (n = 30) |
|------------------------------------|-----------------------------------------|-----------------------------------------|
| Number of patients enrolled       | 30                                      |                                         |
| Number of patients evaluable for toxicity | 30                                      |                                         |
| Number of patients evaluated for efficacy | 30                                      |                                         |
### PRIMARY ASSESSMENT METHOD FOR PHASE II TREBANANIB 15 MG/KG + SORAFENIB

| Assessment | Number of patients enrolled | Number of patients evaluable for toxicity | Number of patients evaluated for efficacy | Response assessment CR | Response assessment PR | Response assessment SD | Response assessment PD | Response assessment OTHER | (Median) duration assessments PFS | (Median) duration assessments TTP | (Median) duration assessments OS | (Median) duration assessments duration of treatment |
|------------|-----------------------------|---------------------------------------|----------------------------------------|----------------------|----------------------|-----------------------|----------------------|----------------------|----------------------------------|----------------------------------|-------------------------------|----------------------------------|
|            | 30                          | 30                                    | 30                                     | 0 (0%)               | 2 (7%)               | 12 (40%)              | 16 (53%)             | 0 (0%)               | 7.9 months, 95% CI: 3.1–12.6    | 9 months, 95% CI: 3.4–16.4       | 17 months, 95% CI: 8.6–27.4     | 5.5 months                      |

### ADVERSE EVENTS: PHASE II TREBANANIB 10 MG/KG + SORAFENIB

| Name                                                  | *NC/NA | 1     | 2     | 3     | 4     | 5     | All grades |
|-------------------------------------------------------|--------|-------|-------|-------|-------|-------|------------|
| Fatigue (asthenia, lethargy, malaise)                 | 90%    | 0%    | 0%    | 10%   | 0%    | 0%    | 10%        |
| Hypertension                                         | 80%    | 0%    | 0%    | 20%   | 0%    | 0%    | 20%        |
| Diarrhea                                             | 80%    | 0%    | 0%    | 20%   | 0%    | 0%    | 20%        |
| Dyspnea (shortness of breath)                        | 93%    | 0%    | 0%    | 7%    | 0%    | 0%    | 7%         |
| Dermatology/Skin - Palmar-Plantar Erythrodyasthesia Syndrome | 83%    | 0%    | 0%    | 17%   | 0%    | 0%    | 17%        |

*NC/NA, no change from baseline/no adverse event.

Grade 3 or greater treatment-emergent adverse events that occurred in at least 10% of patients in either or both cohorts.
Overall survival beyond the 10.7 months that sorafenib has previously demonstrated, and better therapies are needed. We therefore evaluated the combination of trebananib plus sorafenib, which sequesters Ang-1 and Ang-2, preventing their interaction with the Tie-2 receptor [1, 2]. Elevated serum Ang-2 levels have been associated with a poor prognosis in hepatocellular carcinoma (HCC) [3]. Furthermore, leveraging an anti-angiogenic mechanism that is distinct from the classic anti-vascular endothelial growth factor inhibition (VEGF), trebananib might be expected to provide a synergistic anti-angiogenic effect when combined with anti-VEGF therapies. The combination of trebananib plus sorafenib has been previously studied in renal cell carcinoma, where it showed a similar toxicity profile to that of sorafenib as single agent [4]. While sorafenib remains the sole standard treatment of advanced HCC [5], its efficacy is marginal, and better therapies are needed. We therefore evaluated the safety and efficacy of the combination of trebananib plus sorafenib in HCC.

Since the advent of sorafenib as a standard treatment of patients with advanced HCC [5], improved anti-angiogenic agents remain an attractive approach for the treatment of advanced HCC. Efforts to identify new agents have, however, been rather disappointing, with no evidence so far of improved overall survival beyond the 10.7 months that sorafenib has previously demonstrated [5]. Herein, we studied the novel approach of targeting a non-VEGF-associated biological axis in angiogenesis, adding trebananib, which sequesters Ang-1 and Ang-2, preventing their interaction with the Tie-2 receptor, to sorafenib treatment on a continuous schedule [1]. This did not show an improvement in progression-free survival (PFS) rate at 4 months, compared with the estimate of sorafenib in the historical registration study control, with similar demographics when compared with the present study (Table 1). This is, albeit a favorable median PFS of 7.9 for the 10 mg/kg arm, a reminder of the difficulty of interpreting these endpoints vis-à-vis the complexity of HCC and the accompanying cirrhosis. This, add to the length of time on therapy or of observation that may be needed before one may be able to discern any improved efficacy outcome.

The median duration of trebananib therapy given in the 10 mg/kg trebananib cohort was 5.5 months, with a range of 0.3–24.7 months, a median dose of 10.2 mg/kg, and a relative dose intensity of 99%. These figures were similar for the 15 mg/kg trebananib cohort: the median duration of therapy was 3.7 months (range 0.13–21 months), with a median daily dose and relative intensity of 781 mg and 95%, respectively. The biomarker analyses showed several patterns that are exploratory in nature and would require further validation and confirmation. The most intriguing finding is the lower baseline Ang-2 at study entry, suggesting an association with improved OS to 22 months. High Ang-2 levels’ association with poor outcome in HCC for patients treated with sorafenib or placebo has already been reported [9]. The association between Ang-2 and survival was previously observed (p < .006) in a phase II trial of trebananib in combination with sunitinib in renal cancer patients [4]. The higher Ang-2 levels may indicate greater tumor angiogenic activity or metastatic potential [10].

A relatively improved estimate of 17 months median OS of the 10 mg/kg compared with 11 months of the 15 mg/kg trebananib cohort, which is commensurate with the sorafenib single agent historical control of 10.7 months [5], is noted. These values, however, have to be interpreted with caution given the uncontrolled, sequentially enrolled study, the relatively higher than anticipated worsening of liver function is a concern and may add some pretext to the relatively poor outcome of the 15 mg/kg cohort compared with the 10 mg/kg cohort, raising the question of whether a higher dose would be necessary to achieve the potential synergy between trebananib and sorafenib. In support of this statement, the renal carcinoma study evaluated the combination of trebananib and sorafenib at 10 mg/kg and 3 mg/kg trebananib dose levels [4]. The adverse event profiles of the studies have lot of similarities but differ in the degree of liver toxicity, which is reported at a higher rate in the present study, even at the 10 mg/kg dose. This is another reminder of the dual nature of HCC and the accompanying cirrhosis that may well render subjects more prone to certain toxicities that are not necessarily of concern otherwise. Liver failure was the cause of death in one patient in the HCC study and in none of the four adverse events-related deaths on the renal study [4].

The biomarker analyses showed several patterns that are exploratory in nature and would require further validation and confirmation. The most intriguing finding is the lower baseline Ang-2 at study entry, suggesting an association with improved OS to 22 months. High Ang-2 levels’ association with poor outcome in HCC for patients treated with sorafenib or placebo has already been reported [9]. The association between Ang-2 and survival was previously observed (p < .006) in a phase II trial of trebananib in combination with sunitinib in renal cancer patients [4]. The higher Ang-2 levels may indicate greater tumor angiogenic activity or metastatic potential [10].

A relatively improved estimate of 17 months median OS of the 10 mg/kg compared with 11 months of the 15 mg/kg trebananib cohort, which is commensurate with the sorafenib single agent historical control of 10.7 months [5], is noted. These values, however, have to be interpreted with caution given the
limited sample size and the fact that these were sequentially accrued cohorts. We do not believe that the biology of trebananib could explain a lower dose improved efficacy or synergy with sorafenib. This may likely be an artifact of the Kaplan-Meier curve estimation and censoring. The similar 4-month PFS in the two arms of the study, plus the same duration and dose intensity, argue against any enhanced drug exposure advantage and thus against a treatment effect resulting in improved survival, except a delayed one that is not discernible except beyond 4 months, albeit with lack of any biologic argument to support it. An imbalance that is not accounted for may have influenced the point estimate of OS, which in both arms exceeds the single agent sorafenib estimate of 10.7 months.

In conclusion, the combination of sorafenib and trebananib did not demonstrate improved control of tumor growth at 4 months, the primary endpoint of this trial. Any further studies of this combination or similar in HCC should be studied within the context of low baseline Ang-2 and possibly other markers reported herein.

**DISCLOSURES**

Ghassan K. Abou-Alfa: Amgen, Bayer (C/A, RF);
Jean-Frederic Blanc: Bristol-Myers Squibb, Bayer SP (C/A);
Jörg Trojan: Amgen, Bayer, Bristol-Myers Squibb, Eli Lilly & Co., Merck Serono, Merck Sharp & Dohm, Roche (C/A), Amgen, Bayer, Bristol-Myers Squibb, Eli Lilly & Co., Merck Serono, Roche (H);
Charu Gupta: Amgen (E);
Michael Bass: Amgen (E, OI);
Benjamin Wu: Amgen (E, OI);
Leonard B Saltz: Taiho (RF). The other authors indicated no financial relationships.

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**Figures and Tables**

**Table 1. Demographics (n = 60)**

| Parameter                   | Trebananib 10 mg/kg + sorafenib (n = 30, n (%)) | Trebananib 15 mg/kg + sorafenib (n = 30, n (%)) |
|-----------------------------|-------------------------------------------------|-------------------------------------------------|
| Median age (years)          | 64                                              | 60                                              |
| Males                       | 23 (77)                                         | 27 (90)                                         |
| Race                        |                                                 |                                                 |
| White                       | 23 (77)                                         | 19 (63)                                         |
| Black                       | 0                                               | 4 (13)                                          |
| Hispanic or Latino          | 2 (7)                                           | 2 (7)                                           |
| Asian                       | 3 (10)                                          | 5 (17)                                          |
| Japanese                    | 1 (3)                                           | 0                                               |
| Native Hawaiian or other Pacific Islander | 1 (3) | 0 |
| Etiology (subjects with more than one etiology are cited for every etiology) |                                                 |                                                 |
| Hepatitis B                 | 6 (20)                                          | 8 (27)                                          |
| Hepatitis C                 | 5 (17)                                          | 10 (33)                                         |
| Alcohol                     | 10 (33)                                         | 5 (17)                                          |
| NASH/Other                  | 4 (13)                                          | 6 (20)                                          |
| Unknown                     | 7 (23.3)                                        | 7 (23.3)                                        |
| ECOG 0–1                    | 29 (97)                                         | 28 (93)                                         |
| Extent of disease           |                                                 |                                                 |
| Macroscopic vascular invasion | 8 (26.7) | 8 (26.7) |
| Extrahepatic spread         | 10 (33.3)                                       | 10 (33.3)                                       |

(continued)
| Parameter                              | Trebananib 10 mg/kg + sorafenib (n = 30), n (%) | Trebananib 15 mg/kg + sorafenib (n = 30), n (%) |
|----------------------------------------|------------------------------------------------|------------------------------------------------|
| Prior therapy (subjects with more than one prior therapy are cited for each) |                                                 |                                                 |
| Prior surgical therapy                 | 6 (20)                                          | 5 (17)                                          |
| Locoregional therapy                   | 9 (30)                                          | 6 (20)                                          |
| Radiation therapy                      | 1 (3.3)                                         | 1 (3.3)                                         |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NASH, nonalcoholic steatohepatitis.