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Clinical Trial Results

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

Ghassan K. Abou-Alfa,[a,b] Jean-Frederic Blanc,[c] Steven Miles,[d] Tom Ganten,[e] Jörg Trojan,[f] Jonathan Cebon,[g] Andre K. Liem,[h] Lara Lipton,[i] Charu Gupta,[j] Benjamin Wu,[j] Michael Bass,[j] Ellen Hollywood,[a] Jennifer Ma,[a] Margaret Bradley,[a] Jason Litten,[j] Leonard B. Saltz[a,b]

[a]Memorial Sloan Kettering Cancer Center, New York, New York, USA; [b]Weill Cornell Medical College, New York, New York, USA; [c]Hôpital Saint-André, Bordeaux, France; [d]Cedars Sinai Hospital, Los Angeles, California, USA; [e]University of Heidelberg, Heidelberg, Germany; [f]Johann Wolfgang Goethe University, Frankfurt, Germany; [g]Olivia Newton-John Cancer Research Institute, Austin Health, Melbourne, Victoria, Australia; [h]Translational Oncology Research International, Long Beach, California, USA; [i]Western Hospital, Footscray, Victoria, Australia; [j]Amgen Inc., Thousand Oaks, California, USA

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 $\leq$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 $\geq$78% progression-free survival (PFS) rate at 4 months relative to 62% for sorafenib historical control (power = 80% $\alpha = 0.20$). 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 $\geq$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

Correspondence: Ghassan K. Abou-Alfa, M.D., Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, New York 10065, USA. Telephone: 646-888-4184; e-mail: abou-alg@mskcc.org Received January 15, 2017; accepted for publication April 5, 2017; published Online First on June 7, 2017. http://dx.doi.org/10.1634/theoncologist.2017-0058

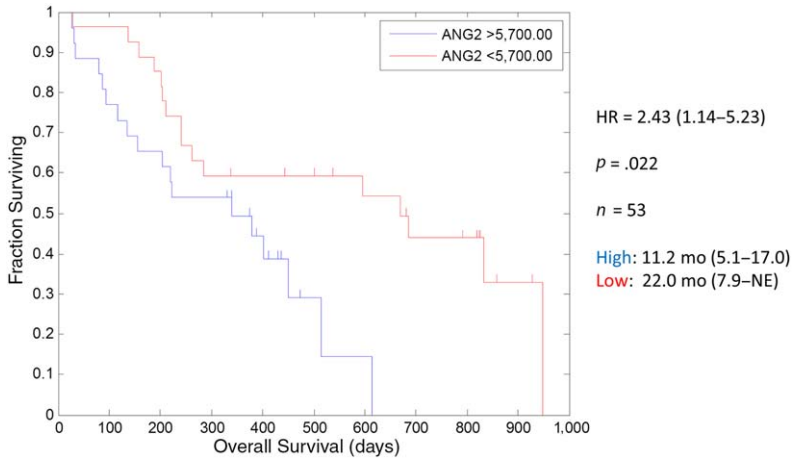

Figure 1. Kaplan-Meier curves depicting overall survival in the Ang-2 >5,700 ng/mL and <5,700 ng/mL dichotomized 10 mg/kg trebananib arm.

Abbreviations: HR, hazard ratio; NE, not evaluable.

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.

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 ≥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. The

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)
Schedule of Administration	Once a week
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)
Schedule of Administration	Twice daily

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)
Schedule of Administration	Once a week
Drug 2	
Generic/Working name	Sorafenib
Trade name	Nexavar
Company name	Bayer
Drug type	Small molecule
Drug class	
Dose	400 milligrams (mg) per flat dose
Route	Oral (PO)

Patient Characteristics for Phase II Trebananib 10 mg/kg + sorafenib

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)

Age	Median (range): 64 and 60 per arm
Number of prior systemic therapies	Median (range): 0
Performance Status: ECOG	0 — 1 — 57 (0–1) 2 — 3 — unknown — 3

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.

Patient Characteristics for Phase II Trebananib 15 mg/kg + sorafenib	
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)
Age	Median (range): 64 and 60 per arm
Number of prior systemic therapies	Median (range): 0
Performance Status: ECOG	0 — 1 — 57 (0–1) 2 — 3 — unknown — 3

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	
Number of patients enrolled	30
Number of patients evaluable for toxicity	30
Number of patients evaluated for efficacy	30

Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 1$ (3%)
Response assessment SD	$n = 14$ (47%)
Response assessment PD	$n = 15$ (50%)
Response assessment OTHER	$n = 0$ (0%)
(Median) duration assessments PFS	7.9 months, 95% CI: 3.1–12.6
(Median) duration assessments TTP	9 months, 95% CI: 3.4–16.4
(Median) duration assessments OS	17 months, 95% CI: 8.6–27.4
(Median) duration assessments duration of treatment	5.5 months

Primary Assessment Method for Phase II Trebananib 15 mg/kg + sorafenib

Assessment	
Number of patients enrolled	30
Number of patients evaluable for toxicity	30
Number of patients evaluated for efficacy	30
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 2$ (7%)
Response assessment SD	$n = 12$ (40%)
Response assessment PD	$n = 16$ (53%)
Response assessment OTHER	$n = 0$ (0%)
(Median) duration assessments PFS	5.5 months, 95% CI: 3.9–9
(Median) duration assessments TTP	6.9 months, 95% CI: 3.6–12.7
(Median) duration assessments OS	The median overall survival was 17 months (95% CI: 8.6, 27.4) and 11 months (95% CI: 6.7, not evaluable).
(Median) duration assessments duration of treatment	3.5 months
Assessment	
Number of patients enrolled	30
Number of patients evaluable for toxicity	30
Number of patients evaluated for efficacy	30
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 2$ (7%)
Response assessment SD	$n = 12$ (40%)
Response assessment PD	$n = 16$ (53%)
Response assessment OTHER	$n = 0$ (0%)
(Median) duration assessments PFS	5.5 months, 95% CI: 3.9–9
(Median) duration assessments TTP	6.9 months, 95% CI: 3.6–12.7
(Median) duration assessments OS	11 months, 95% CI: 6.7, not evaluable
(Median) duration assessments duration of treatment	3.5 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 Erythrodysasthesia Syndrome	83%	0%	0%	17%	0%	0%	17%

Grade 3 or greater treatment-emergent adverse events that occurred in at least 10% of patients in either or both cohorts.
*NC/NA, no change from baseline/no adverse event.

Pharmacokinetics/Pharmacodynamics

Cmax and Cmin of the trebananib and sorafenib at the end of infusion of week 1, 5 and 9; predose, week 2, 5, and 9, as well as at 48 and 96 hours of week 5, showed no clear dose proportionality in exposure between the 10 and 15 mg/kg dose groups.

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics/Pharmacodynamics	Correlative endpoints met
Investigator's Assessment	Correlative endpoints met but not powered to assess activity

Trebananib is a first-in-class anti-angiogenic agent that 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 trebananib therapy was 3.5 months (range 1 day to 21 months), with a median dose and relative dose intensity of 15.2 mg/kg and 99%, respectively.

The median duration of sorafenib therapy was 3.7 months (range 0.3–28 months), and the median dose was 744 mg daily with relative intensity of 87% for the 10 mg/kg trebananib cohort. 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 outcome of this study may be explained in different ways. An alleged ceiling of benefit from anti-angiogenic therapy may exist [6]. In order to improve on existing approaches, combination studies that inhibit alternative targets or pathways will be required. The investigation of multiple novel approaches is underway [7], including immunotherapeutic therapies [8].

The combination of trebananib plus sorafenib seems relatively well tolerated. However, within the realm of this small, 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); **Benjamin Wu:** Amgen (E, OI); **Michael Bass:** 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)

Table 1 (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.