

Phase I Study of Lenalidomide and Sorafenib in Patients With Advanced Hepatocellular Carcinoma

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT01348503
- **Sponsor:** Celgene
- **Principal Investigator:** E. Gabriella Chiorean
- **IRB Approved:** Yes

LESSONS LEARNED

- Combination therapies in patients with hepatocellular carcinoma can be associated with overlapping toxicity and are therefore poorly tolerated.
- Using sorafenib at the maximum tolerated dose can lead to a higher incidence of toxicities. Consequently, combination studies might evaluate sorafenib at alternative schedules or doses to improve tolerance, recognizing this could affect sorafenib efficacy.
- Although this combination was poorly tolerated, it does not exclude further evaluation of new-generation immunomodulator drugs or immune checkpoint inhibitors in the hope of optimizing tolerance and safety.

ABSTRACT

Background. Sorafenib is the standard treatment for advanced hepatocellular carcinoma (HCC), and to date, no combination therapy has demonstrated superior survival compared with sorafenib alone. The immunosuppressive microenvironment in HCC is a negative predictor for survival. Lenalidomide is an immunomodulator and antiangiogenic agent, with limited single-agent efficacy in HCC. Based on these data, we designed a phase I study of sorafenib plus lenalidomide to determine the safety and preliminary antitumor activity of this combination.

Methods. This was an open-label, phase I study with a 3+3 dose escalation/de-escalation design. The starting dose of sorafenib was 400 mg p.o. b.i.d. and of lenalidomide was 15 mg p.o. daily with a planned dose escalation by 5 mg per cohort up to 25 mg daily. Dose de-escalation was planned to a sorafenib dose of 400 mg p.o. daily combined with two doses of lenalidomide: 10 mg p.o. daily for a 28-day cycle (cohort 1) and 10 mg p.o. daily for a 21- or 28-day cycle (cohort 2). Patients with cirrhosis, a Child-Pugh score of A-B7, and no previous systemic therapy were eligible.

Results. Five patients were enrolled. Their median age was 56 years (range 39–61), and the ECOG status was 0–2. Four patients were treated at dose level (DL) 1. Because of the poor tolerance to the combination associated with grade 2 toxicities, one more patient was treated at DL –1. No dose-limiting toxicity was observed as specified per protocol. The most common toxicities were nausea, anorexia, pruritus, elevated liver enzymes, and

elevated bilirubin. Three patients experienced one or more of the following grade 3 toxicities: fatigue (DL 1), increased bilirubin (DL 1), skin desquamation (DL –1), and elevated transaminase levels (DL 1). The median duration of therapy was 1 cycle (range 1–3). All patients discontinued the study, 4 because of progressive disease and 1 by patient preference. The best confirmed response was progressive disease. The median progression-free survival was 1.0 month (95% confidence interval 0.9–2.8), and the median overall survival was 5.9 months (95% confidence interval 3.68–23.4).

Conclusion. In our small study, the combination of lenalidomide and sorafenib was poorly tolerated and showed no clinical activity. Although the study was closed early because of toxicity concerns, future studies assessing combinations of sorafenib with new-generation immunomodulator drugs or other immunomodulatory agents, should consider lower starting doses of sorafenib to avoid excessive toxicity. *The Oncologist* 2016;21:664–665d

DISCUSSION

Patients with HCC have limited therapeutic options. Sorafenib, a multi-tyrosine kinase inhibitor, is the only Food and Drug Administration (FDA)-approved systemic therapy for this disease, with marginal improvement in median overall

Table of Results

Subject	Cycles (n)	DLT	Best response	PFS (mo)	OS (mo)	Treatment after study
1	1	No	PD	0.92	23.4	SBRT
2	3	No	PD	2.76	5.86	
3	1	No	PD	1.02	3.68	
4	1	No	PD	0.95	16.09	Chemotherapy/bland embolization/radioembolization
5	1	No	PD	0.92	5.36	Radioembolization

Abbreviations: DLT, dose-limiting toxicity; PD, progressive disease; PFS, progression-free survival; OS, overall survival; SBRT, stereotactic body radiotherapy.

survival. HCC is commonly associated with chronic inflammation and is thought to be capable of evading local immune surveillance. Tumor infiltration with regulatory T cells (T_{regs}) has been associated with disease progression and a higher risk of relapse after curative therapy.

Lenalidomide is a second-generation immunomodulator drug (IMiD) and has been approved by the FDA for the therapy of multiple myeloma and 5q deletion myelodysplastic syndrome. Lenalidomide exhibits its antitumor effects through antiangiogenic and immunomodulating properties. Lenalidomide modulates mononuclear and activated macrophage secreted cytokines and increases the secretion of the T-cell lymphokines that stimulate clonal T-cell proliferation. In preclinical models, lenalidomide enhanced the antitumor activity of sorafenib, presumably through immune modulation and increased $CD8^+$ in tumor infiltrating lymphocytes (TILs) and decreased T_{regs} among TILs. Lenalidomide as a single agent demonstrated preliminary efficacy in phase II clinical trials with a partial response (PR) rate of 15%, including 2 patients with durable responses of 32 and 36 months. In another study, the PR and stable disease (SD) rates were 5% and 36%, respectively.

On the basis of these data, we designed a phase I “3+3” dose escalation/de-escalation study to evaluate the safety, maximum tolerated dose, and preliminary activity of the combination of sorafenib and lenalidomide. In the present phase I study, 3 of 5 patients experienced symptomatic

progressive disease (PD) within the first cycle (Table of Results). Poor tolerability was evident, even at substandard treatment doses in 1 patient (sorafenib 400 mg and lenalidomide 10 mg daily). Because of the high toxicity, especially fatigue and elevated transaminase levels, potentially attributed to both study agents, the study was discontinued early. Although no responses were seen on our study, the small sample size precluded the ability to judge the efficacy of this combination.

The prognosis remains poor for patients with advanced HCC, with a median overall survival of less than 12 months. The lack of predictive biomarkers, resistance to cytotoxic chemotherapy, and the underlying liver disease continue to be major challenges in successfully treating HCC. No sorafenib-based combination therapies have shown superior results to sorafenib alone. Although the combination with lenalidomide was intolerable, an ongoing clinical trial is evaluating a newer generation IMiD (CC-122) combined with sorafenib (ClinicalTrials.gov identifier, NCT02323906). As novel combinations are being considered for this disease, it is crucial that we better understand the biology associated with different HCC etiologies and any overlapping toxicity with sorafenib. The recent success with immune checkpoint inhibitors in HCC is encouraging, but still, only 20% of patients benefited. With the evolving field of genomically and other biomarker-driven precision therapeutics, patients with HCC will benefit from rational combinations to further improve their outcome.

TRIAL INFORMATION

Disease	Hepatocellular Carcinoma
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	None
Type of study - 1	Phase I
Type of study - 2	3+3 Dose Escalation/De-escalation
Primary Endpoint	Maximum Tolerated Dose
Secondary Endpoint	Toxicity
Secondary Endpoint	Safety
Secondary Endpoint	Recommended Phase II Dose
Investigator's Analysis	Poorly Tolerated/Not Feasible

DRUG INFORMATION

Drug 1	
Generic/Working name	Sorafenib
Trade name	Nexavar
Company name	Bayer

Drug type	Small molecule
Drug class	Angiogenesis - VEGF
Dose	Milligrams per flat dose
Route	Oral (p.o.)
Schedule of Administration	Cohort: Dose level – 2: Sorafenib 400 mg daily Cohort: Dose level – 1: Sorafenib 400 mg daily Cohort: Dose level 1: Sorafenib 400 mg b.i.d. Cohort: Dose level 2: Sorafenib 400 mg b.i.d. Cohort: Dose level 3: Sorafenib 400 mg b.i.d.
Drug 2	
Generic/Working name	Lenalidomide
Trade name	Revlimid
Company name	Celgene
Drug type	Biological
Dose	Milligrams per flat dose
Route	Oral (p.o.)
Schedule of Administration	Cohort: Dose level – 2: Lenalidomide dose level, 10 mg p.o. on days 1–21 Cohort: Dose level – 1: Lenalidomide dose level, 10 mg p.o. daily Cohort: Dose level 1: Lenalidomide dose level, 15 mg p.o. daily Cohort: Dose level 2: Lenalidomide dose level, 20 mg p.o. daily Cohort: Dose level 3: Lenalidomide dose level, 25 mg p.o. daily

DOSE ESCALATION TABLE

Dose level	Dose of drug		Enrolled (n)	Evaluable for toxicity (n)
	Sorafenib	Lenalidomide		
1	400 mg p.o. b.i.d.	15 mg p.o. daily	4	Undefined
–1	400 mg p.o. daily	10 mg p.o. daily	1	1

PATIENT CHARACTERISTICS

Number of patients, male	4
Number of patients, female	1
Stage	Advanced or metastatic
Age	Median (range): 56 (39–61)
Number of prior systemic therapies	Median (range): 0
Performance Status: ECOG	0 – 3 1 – 2 2 – 3 – Unknown –
Other	Not Collected

PRIMARY ASSESSMENT METHOD

Control Arm: Total Patient Population	
Number of patients screened	5
Number of patients enrolled	5
Number of patients evaluable for toxicity	5
Number of patients evaluated for efficacy	5
Response assessment PD	n = 5 (100)
(Median) duration assessments PFS	1.0 months
(Median) duration assessments OS	5.9 months
(Median) duration assessments duration of treatment	28 days

ADVERSE EVENTS							
Adverse Events At All Dose Levels, Cycle 1							
Name	*NC/NA	1	2	3	4	5	All Grades
Fatigue	60%	20%	0%	20%	0%	0%	40%
Nausea	40%	40%	20%	0%	0%	0%	60%
Pruritus	40%	40%	20%	0%	0%	0%	60%
Anorexia	60%	20%	20%	0%	0%	0%	40%
Blood bilirubin increased	60%	20%	0%	20%	0%	0%	40%
Alanine aminotransferase increased	60%	20%	0%	20%	0%	0%	40%
Aspartate aminotransferase increased	60%	20%	0%	20%	0%	0%	40%
Platelet count decreased	60%	20%	20%	0%	0%	0%	40%
Palmar-plantar erythrodysesthesia syndrome	60%	20%	20%	0%	0%	0%	40%
Diarrhea	80%	0%	20%	0%	0%	0%	20%
Hypertension	80%	0%	20%	0%	0%	0%	20%
Mucositis oral	80%	20%	0%	0%	0%	0%	20%
Rash acneiform	80%	0%	0%	20%	0%	0%	20%
Dysgeusia	80%	20%	0%	0%	0%	0%	20%
Neutrophil count decreased	80%	20%	0%	0%	0%	0%	20%
Dehydration	80%	0%	20%	0%	0%	0%	20%

Adverse Events Legend
*No Change From Baseline/No Adverse Event

DOSE-LIMITING TOXICITIES				
Dose level	Dose of drug		Enrolled (n)	Evaluable for toxicity (n)
	Sorafenib	Lenalidomide		
1	400 mg p.o. b.i.d.	15 mg p.o. daily	4	Undefined
-1	400 mg p.o. daily	10 mg p.o. daily	1	1

ASSESSMENT, ANALYSIS, AND DISCUSSION	
Completion	Study terminated before completion
Terminated reason	Toxicity
Pharmacokinetics / Pharmacodynamics	Not Collected
Investigator's Assessment	Poorly Tolerated/Not Feasible

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide [1]. For patients with advanced disease, few effective options exist. Sorafenib is a multi-tyrosine kinase inhibitor against the vascular endothelial growth factor (VEGF) receptor and rapidly accelerated fibrosarcoma. In a randomized controlled clinical trial, sorafenib improved overall survival compared with placebo, 10.7 versus 7.9 months [2]. HCC is an inflammation-associated malignancy with an ability that is thought capable of evading local immune surveillance [3]. Indirect evidence suggests the immune microenvironment plays an important role in tumor progression [4–7]. Tumor infiltration with regulatory T cells (T_{regs}) has been associated with disease progression [4] and with a higher risk of relapse after curative therapy [5–7].

Lenalidomide is a second-generation immunomodulator drug (IMiD) that modulates mononuclear and activated macrophage secreted cytokines such as tumor necrosis factor- α and interleukin (IL)-1, IL-6, and IL-12 [8]. Lenalidomide

also increases the secretion of the T-cell lymphokines interferon- γ and IL-2, which stimulate clonal T-cell proliferation [9]. IMiDs also exhibit antiangiogenic activity by decreasing the secretion of VEGF and fibroblast growth factor from tumor and stromal cells [10]. VEGF has a significant role in impairing dendritic cell differentiation and their role as antigen-presenting cells. VEGF blockade can improve dendritic cell differentiation [11] and synergize with immunotherapy [12]. In preclinical models, lenalidomide enhanced the antitumor activity of sorafenib, presumably through immune modulation and increased $CD8^+$ of tumor infiltrating lymphocytes (TILs) and decreased T_{regs} among TILs [13].

In a phase II study of thalidomide in advanced HCC, activity included 5% with partial responses (PRs), 5% with minor responses, and 31% with stable disease (SD) [14]. A retrospective analysis of low-dose thalidomide (100 mg/day) showed PR and SD rates of 5% and 21%, respectively, with an overall survival (OS) of 3.2 months [15]. Lenalidomide is a potent thalidomide analog with antiangiogenic and

immunomodulating effects and has been approved by the Food and Drug Administration for therapy for multiple myeloma and 5q deletion myelodysplastic syndrome. It has been studied in 40 HCC patients (35 each with Child-Pugh A and B) with progression or intolerance to sorafenib, at a dose of 25 mg p.o. daily \times 21 days in 28-day cycles. Lenalidomide was well tolerated, with rare grade 3 toxicities. The PR rate was 15%, including 2 patients with a durable response of 32 and 36 months [16].

Based on these data, we designed a phase I “3+3” dose escalation study to evaluate the safety, maximum tolerated dose, and preliminary activity of the combination of sorafenib and lenalidomide. In this phase I study, 3 of 5 patients experienced symptomatic PD within the first cycle. Poor tolerability was evident, even at substandard treatment doses in 1 patient (sorafenib 400 mg and lenalidomide 10 mg daily). Because of the high toxicity, especially fatigue and elevated transaminase levels, potentially attributed to both study agents, and no preliminary signs of efficacy, our study was discontinued early, without further attempts to reduce the sorafenib dose.

The prognosis remains poor for patients with unresectable, advanced HCC, with a median OS of less than 12 months. The lack of predictive biomarkers, relative resistance to cytotoxic chemotherapy, and the underlying liver disease continue to be major challenges in successfully treating HCC. No sorafenib-based combination therapies to date have shown superior results to sorafenib alone [17]. Sorafenib is currently used at the maximum tolerated dose; therefore, combining sorafenib

with novel agents that have overlapping toxicities will likely be unsuccessful. Although the combination with lenalidomide was intolerable and ineffective in our small study, an ongoing clinical trial is evaluating a newer generation IMiD (CC-122) combined with sorafenib (ClinicalTrials.gov identifier, NCT02323906). As novel combinations and therapies are being considered for this disease, it is crucial that we better understand the biology associated with different HCC etiologies (i.e., hepatitis B and C, alcohol-related cirrhosis versus nonalcoholic steatohepatitis) because these could be associated with differential responses to molecularly or immunologically targeted therapies [18]. The recent success with immune checkpoint inhibitors in HCC is encouraging, but still, only 20% of the patients benefited [19]. With the evolving field of genomically and other biomarker-driven precision therapeutics, patients with HCC will benefit from rational combinations or, rather, select therapeutics to further improve outcomes.

ACKNOWLEDGMENT

We thank Celgene Corporation for sponsoring the study and providing the investigational agent, lenalidomide

DISCLOSURES

Romnee S. Clark: Endocyte, Eli Lilly (formerly employed) (E); **E. Gabriella Chiorean:** Celgene Pharmaceutical (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES

- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5–29.
- Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–390.
- Willimsky G, Schmidt K, Loddenkemper C et al. Virus-induced hepatocellular carcinomas cause antigen-specific local tolerance. *J Clin Invest* 2013;123:1032–1043.
- Fu J, Xu D, Liu Z et al. Increased regulatory T cells correlate with CD8 T-cell impairment and poor survival in hepatocellular carcinoma patients. *Gastroenterology* 2007;132:2328–2339.
- Gao Q, Qiu SJ, Fan J et al. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. *J Clin Oncol* 2007;25:2586–2593.
- Ormandy LA, Hillemann T, Wedemeyer H et al. Increased populations of regulatory T cells in peripheral blood of patients with hepatocellular carcinoma. *Cancer Res* 2005;65:2457–2464.
- Unitt E, Marshall A, Gelson W et al. Tumour lymphocytic infiltrate and recurrence of hepatocellular carcinoma following liver transplantation. *J Hepatol* 2006;45:246–253.
- Knight R. IMiDs: A novel class of immunomodulators. *Semin Oncol* 2005;32(suppl 5):S24–S30.
- Corral LG, Haslett PA, Muller GW et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF- α . *J Immunol* 1999;163:380–386.
- Dredge K, Marriott JB, Macdonald CD et al. Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects. *Br J Cancer* 2002;87:1166–1172.
- Fricke I, Mirza N, Dupont J et al. Vascular endothelial growth factor-trap overcomes defects in dendritic cell differentiation but does not improve antigen-specific immune responses. *Clin Cancer Res* 2007;13:4840–4848.
- Gabrilovich DI, Ishida T, Nadaf S et al. Antibodies to vascular endothelial growth factor enhance the efficacy of cancer immunotherapy by improving endogenous dendritic cell function. *Clin Cancer Res* 1999;5:2963–2970.
- Ou DL, Chang CJ, Jeng YM et al. Lenalidomide can improve the anti-tumor activity of sorafenib in hepatocellular carcinoma through immune modulation. *J Gastroenterol Hepatol* 2014;29:2021–2031.
- Patt YZ, Hassan MM, Lozano RD et al. Thalidomide in the treatment of patients with hepatocellular carcinoma: A phase II trial. *Cancer* 2005;103:749–755.
- Yau T, Chan P, Wong H et al. Efficacy and tolerability of low-dose thalidomide as first-line systemic treatment of patients with advanced hepatocellular carcinoma. *Oncology* 2007;72(suppl 1):67–71.
- Safran H, Charpentier KP, Kaubisch A et al. Lenalidomide for second-line treatment of advanced hepatocellular cancer: A Brown University oncology group phase II study. *Am J Clin Oncol* 2015;38:1–4.
- Zhu AX, Rosmorduc O, Evans TR et al. SEARCH: A phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2015;33:559–566.
- Block TM, Mehta AS, Fimmel CJ et al. Molecular viral oncology of hepatocellular carcinoma. *Oncogene* 2003;22:5093–5107.
- El-Khoueiry AB, Melero I, Crocenzi TS et al. Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040. *J Clin Oncol* 2015;33(suppl):LBA101a.

TABLES

Table 1. Patient characteristics

Subject	Age (yr)	Gender	Underlying liver disease	CPS	BCLC	Previous therapies
1	56	Male	Cirrhosis/Hep C	B-7	C	None
2	61	Male	Cirrhosis/Hep C	A-5	B	Chemoembolization/radioembolization
3	53	Male	Cirrhosis/Hep C	A-5	C	SBRT
4	57	Male	Cirrhosis/Hep B	A-5	C	Radioembolization
5	39	Female	None	A-6	C	DEB/bland embolization/radioembolization

Abbreviations: BCLC, Barcelona Clinic Liver Cancer Score; CPS, Child-Pugh score; DEB, drug eluting beads; Hep B, hepatitis B; Hep C, hepatitis C; SBRT, stereotactic body radiotherapy.

Table 2. Results

Subject	Cycles (n)	DLT	Best response	PFS (mo)	OS (mo)	Treatment after study
1	1	No	PD	0.92	23.4	SBRT
2	3	No	PD	2.76	5.86	
3	1	No	PD	1.02	3.68	
4	1	No	PD	0.95	16.09	Chemotherapy/bland embolization/radioembolization
5	1	No	PD	0.92	5.36	Radioembolization

Abbreviations: DLT, dose-limiting toxicity; PD, progressive disease; PFS, progression-free survival; OS, overall survival; SBRT, stereotactic body radiotherapy.

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