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Clinical Trial Results

CF102 for the Treatment of Hepatocellular Carcinoma: A Phase I/II, Open-Label, Dose-Escalation Study

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Author Summary

Abstract

Background. The A_3 adenosine receptor (A_3AR) is overexpressed in the tumor and in the peripheral blood mononuclear cells of patients with hepatocellular carcinoma (HCC). The orally active drug candidate CF102, an A_3AR agonist, induces apoptosis of HCC cells via deregulation of the Wnt signaling pathway. In this open label phase I/II trial, the safety and clinical effects of CF102 were assessed in patients with advanced unresectable HCC.

Methods. The primary objectives of this trial were to examine the safety and pharmacokinetic (PK) behavior of CF102 given orally (1, 5, and 25 mg BID) in 28-day cycles. Evaluation of anti-tumor effects and the utilization of A_3AR as a biological predictive marker of response to CF102 were the secondary objectives.

Results. Eighteen patients received CF102—six at each dose level. No serious drug-related adverse events or dose-limiting toxicities were observed. CF102 demonstrated good oral bioavailability and linear PK behavior. Median overall survival in the study population, 67% of whom had received prior sorafenib, was 7.8 months, and for Child Pugh B patients (28%) it was 8.1 months. Stable disease by RECIST was observed in four patients for at least 4 months. CF102 maintained liver function over a 6-month period. A correlation between receptor overexpression levels at baseline and patients' overall survival was found. One of the patients who presented with skin nodules that were biopsy-proven to be HCC metastases prior to the trial showed complete metastasis regression during three months of treatment with CF102.

Conclusions. CF102 is safe and well-tolerated, showing favorable PK characteristics in Child Pugh A and B HCC patients, justifying further clinical development.

Overall survival data

Subject number	Starting dose (mg BID)	Months from diagnosis to CF102	Months previously on sorafenib	Entry Child-Pugh class	Survival from start of CF102 (months)
302	1	27	—	A	8.2
303	1	8	—	A	27.3
304	1	5	—	A	7.1
305	5	18	8.2	A	4.1
306	5	14	7.0	A	7.1
307	5	24	1.4	A	10.6
308	25	14	10.8	A	8.3
309	25	1	—	B	8.1
310	25	1	—	B	7.6
312	5	20	—	B	10.7
313	25	14	3.3	B	7.0
314	1	53	4.8	A	5.6
315	5	22	8.0	A	3.5
316	25	78	2.3	A	12.6
317	1	26	5.0	B	13.2
318	1	33	24.2	A	7.0
319	5	19	2.6	A	4.2
320	25	19	6.0	A	8.4
Median			**All**		**7.8**
			Sorafenib failures		**7.0**
			Child Pugh B		**8.1**

Discussion

The current study demonstrates that CF102 is safe and well tolerated, with a linear PK at the dose range used during the study. The adverse events that were observed are expected in a population of patients with advanced HCC.

ClinicalTrials.gov Identifier: NCT00790218
Sponsor: Canfite Biopharma Ltd

Principal Investigators: Pnina Fishman, Salomon M. Stemmer
IRB Approved: Yes

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The median OS of the 18 subjects to date is 7.8 months, with one subject continuing on CF102 as of the date of this report. These results are encouraging in light of the fact that 67% of the patient population in the current study had experienced disease progression on sorafenib and that, for these patients, CF102 treatment was second-line therapy. An additional finding was the 8.1-month median OS of the five Child-Pugh B patients. Previous experience with comparable patient populations has shown an OS for Child Pugh B patients in the range of 3.5–5.5 months [1–3]. Considering that Child Pugh B patients treated with sorafenib generally have poor outcomes due to underlying liver dysfunction, CF102 also may be considered as a drug to be developed for this patient sub-population.

CF102 had no adverse effect on routine measures of liver function over a 6-month period in 12 patients treated for at least that duration. These findings corroborate clinical CF102 data published earlier that show a protective effect on normal liver tissue in an experimental model of liver inflammation [4] and suggest that CF102 could be used in patients with cirrhosis and/or hepatic impairment. Other A3AR agonists have likewise been found to act as anti-cancer agents and concomitantly induce liver protective effects, as well as cardioprotective, neuroprotective, and myeloprotective effects [4–7].

Previous studies have reported that A3AR is up-regulated in tumor tissues of both tumor-bearing animals and humans. High receptor expression is also mirrored in patients' peripheral blood mononuclear cells, possibly reflecting receptor levels in neoplastic tissue. An increase in A3AR expression levels was also found during colorectal tumor progression, suggesting it may be possible to utilize the receptor as a biological follow-up marker [8, 9]. Further studies will be required to evaluate these possibilities. ***The Oncologist*** 2013;18:25–26

Disclosures
Author disclosures available online.

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