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An Open-Label, Multicenter, Phase I, Dose Escalation Study with Phase II Expansion Cohort to Determine the Safety, Pharmacokinetics, and Preliminary Antitumor Activity of Intravenous TKM-080301 in Subjects with Advanced Hepatocellular Carcinoma

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT02191878
- **Sponsor(s):** Arbutus Biopharma, Inc.
- **Principal Investigator:** Ghassan K. Abou-Alfa
- **IRB Approved:** Yes

LESSONS LEARNED

- TKM-080301 showed a favorable toxicity profile at the studied dose.
- TKM-080301 targeting PLK1 through small interfering RNA mechanism did not demonstrate improved overall survival in patients with advanced hepatocellular carcinoma compared with historical control. Preliminary antitumor activity as shown in this early-phase study does not support further evaluation as a single agent.

ABSTRACT

Background. Polo-like kinase 1 (PLK1) is overexpressed in hepatocellular carcinoma (HCC). Knockdown of PLK1 expression by PLK1 small interfering RNA (siRNA) in an HCC cell line showed reduced expression in RNA-induced silencing complex and a reduction in cell proliferation.

Methods. A 3 + 3 dose escalation plus expansion cohort at the maximum tolerated dose (MTD) was implemented. Patients with HCC, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , and Child-Pugh score A received TKM-080301 as an intravenous infusion once every week for 3 consecutive weeks, repeated every 28 days.

Results. The study enrolled 43 patients. The starting dose of TKM-080301 was 0.3 mg/kg, and MTD was declared at 0.75 mg/kg. Following the development of grade

4 thrombocytopenia in two subjects on the expansion cohort, the MTD was redefined at 0.6 mg/kg. Four patients did not have any evaluable postbaseline scan. Of the other 39 subjects who had received at least 0.3 mg/kg, 18 subjects (46.2%) had stable disease (SD) by independent RECIST 1.1 criteria. By Choi criteria, eight subjects (23.1%) had a partial response (PR). For 37 assessable subjects, with 2 subjects censored, median progression-free survival (PFS) was 2.04 months. Median survival for the whole study population was 7.5 months.

Conclusion. TKM-080301 was generally well tolerated. In this early-phase study, antitumor effect for TKM 080301 was limited. Further evaluation as a single agent in large randomized trials is not warranted. *The Oncologist* 2019;24:747–e218

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DISCUSSION

PLK1 is a validated molecular target in oncology [1] and has been shown to play nonredundant roles in cell cycle regulation [2]. Expression of PLK1 in HCC tumor samples from 56 patients with HCC was shown to be up to 12-fold higher than in controls, and its overexpression is a negative prognostic indicator of patients' outcomes. Inhibition of PLK1 activity in proliferating cancer cells rapidly induces mitotic arrest and apoptosis [3] and can sensitize cancer cells to cytotoxic effects of chemotherapy [4]. TKM-080301 evaluation in patients with HCC was limited by the development of thrombocytopenia in two subjects dosed at 0.75 mg/kg in the initial expansion cohort; thus, the recommended dose was reduced to 0.6 mg/kg. Other than transient delayed infusion reactions that responded to standard therapy, TKM-080301 was well tolerated. No deaths were related to TKM-080301.

We analyzed responses based on the Choi criteria, given that it may be more appropriate than RECIST 1.1 to identify responders in advanced HCC [5], and we observed 23.1% PRs (waterfall plot available online), whereas RECIST 1.1 showed no PR or complete response.

An exploratory assessment of overall survival (OS) was performed, revealing a median OS of 7.5 months (Fig. 1). This compares favorably with the median OS of 6.5 months

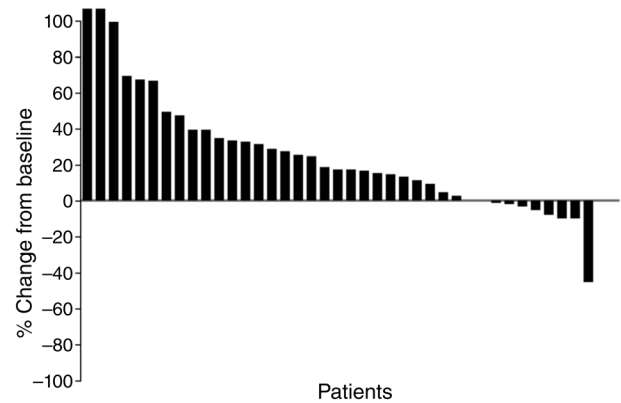


Figure 1. Waterfall plot on percentage change from baseline in target tumor diameter. Best response (RECIST) was assessed by central imaging (intent-to-treat population).

reported for subjects treated with sorafenib in a phase III study in the Asia-Pacific region with similar subject demographics to the current study [6], and with placebo arms in second-line studies. In summary, TKM-080301 was generally well tolerated by most subjects, but with modest anti-tumor activity and insufficient data to support further exploration.

TRIAL INFORMATION

Disease	Hepatocellular carcinoma
Stage of Disease / Treatment	Metastatic / advanced
Prior Therapy	No designated number of regimens
Type of Study – 1	Phase I
Type of Study – 2	3 + 3
Primary Endpoint	Safety
Primary Endpoint	Tolerability
Primary Endpoint	Pharmacokinetics
Secondary Endpoint	Efficacy
Investigator's Analysis	Drug tolerable, efficacy indeterminant

DRUG INFORMATION

Drug 1	
Generic/Working Name	New drug
Trade Name	TKM-080301
Company Name	Arbutus Biopharma, Inc.
Drug Type	Biological
Drug Class	siRNA
Dose	0.3 milligrams (mg) per kilogram (kg)
Route	Intravenous
Schedule of Administration	Once every week for 3 consecutive weeks, repeated every 28 days

DOSE ESCALATION TABLE

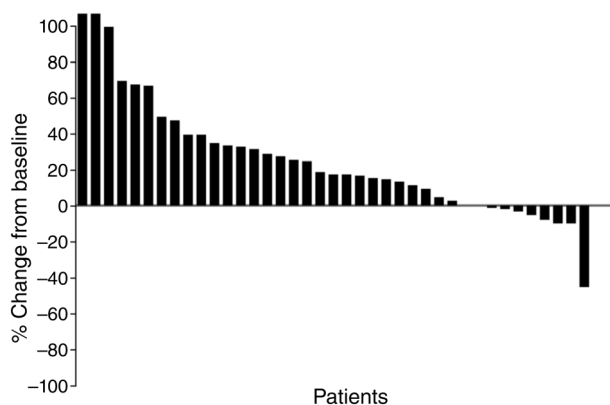
Dose level	Dose of drug: new drug, mg/kg	Number enrolled	Number evaluable for toxicity
1	0.3	3	3
2	0.6	9	9
3	0.75	15	15
Added to 0.6 at MTD	0.6	16	16

PATIENT CHARACTERISTICS

Number of Patients, Male	36
Number of Patients, Female	7
Stage	IV
Age	Median (range): 62 years
Number of Prior Systemic Therapies	Median (range): 1
Performance Status: ECOG	0 — 23 1 — 20 2 — 3 — Unknown —
Cancer Types or Histologic Subtypes	Hepatocellular carcinoma, 43

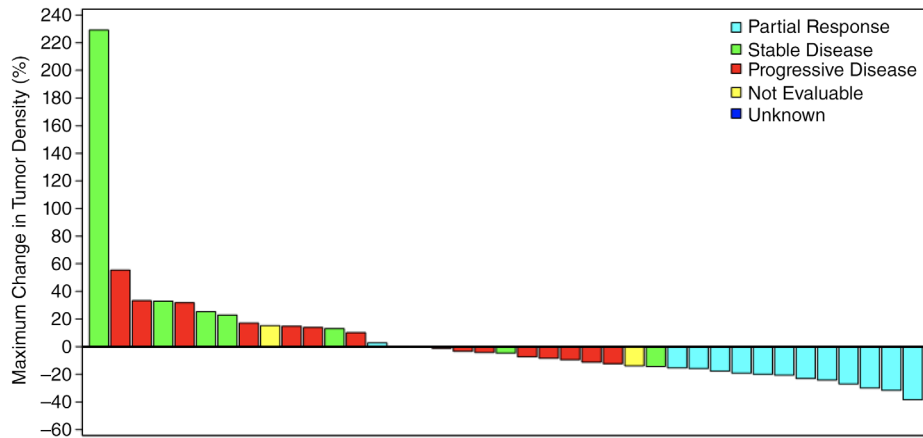
PRIMARY ASSESSMENT METHOD

Title	Response assessment by RECIST
Number of Patients Screened	43
Number of Patients Enrolled	43
Number of Patients Evaluable for Toxicity	43
Number of Patients Evaluated for Efficacy	39
Response Assessment – PR	<i>n</i> = 1
Response Assessment – SD	<i>n</i> = 20
Response Assessment – PD	<i>n</i> = 18
(Median) Duration Assessments – PFS	2 months
(Median) Duration Assessments – OS	8 months



Waterfall plot on percentage change from baseline in target tumor diameter. Best response (RECIST) was assessed by central imaging (intent-to-treat population).

RESPONSE ASSESSMENT BY CHOI CRITERIA	
Response Assessment – PR	n = 17
Response Assessment – SD	n = 6
Response Assessment – PD	n = 14
Response Assessment – Other	n = 2



Waterfall plot on percentage change from baseline in target tumor density (Choi).

SERIOUS ADVERSE EVENTS		
Name	Grade	Attribution
Leucocytosis	3	Probable
Thrombocytopenia	4	Probable
Cardiac disorder not otherwise defined	3	Probable
Abdominal pain	3	Possible
Ascites	3	Probable
Gastric ulcer hemorrhage	4	Probable
Peritoneal hemorrhage	4	Probable
Pyrexia	3	Probable
Noncardiac chest pain	3	Possible
Hepatic failure	3	Possible
Cholangitis	4	Possible
Infections	3	Probable
Sepsis	4	Probable
Infusion-related reaction	3	Definite
Hypercalcemia	3	Probable
Musculoskeletal pain	3	Possible
Tumor hemorrhage	4	Possible
Acute kidney injury	3	Possible
Pulmonary embolism	3	Probable
Deep vein thrombosis	3	Probable
Hypotension	3	Probable

DOSE-LIMITING TOXICITIES				
Dose level	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity	Dose-limiting toxicity information
0.3	3	3		
0.6	9	9	1	Grade 1 chills
0.75	15	15	4	Grade 2 chills, thrombocytopenia
Added to 0.6 MTD	16	16		

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion

Study completed

Investigator's Assessment

Drug tolerable, efficacy indeterminant

Knockdown of polo-like kinase 1 (PLK1) expression by PLK1 small interfering RNA (siRNA) in hepatocellular carcinoma (HCC) cell lines showed a reduction in PLK1 protein expression of 96% and up to 92% reduction in a multiprotein complex, specifically a ribonucleoprotein, which incorporates one strand of a single-stranded RNA fragment, such as microRNA, or double-stranded siRNA, also called RNA-induced silencing complex [7]. PLK1 overexpression has also been associated with metastatic disease [8] and poor prognosis in HCC. Studies with TKM-080301 in preclinical models of human cancer have demonstrated that TKM-080301 has robust anticancer activity in both subcutaneous and orthotopic liver tumor models in mice [9]. TKM-080301 is a lipid nanoparticle (LNP) formulation comprising four lipids and a synthetic, double-stranded siRNA directed against human PLK1 mRNA. Synthetic siRNAs are a duplex of complementary RNA oligonucleotides designed to achieve post-transcriptional gene suppression through the RNA interference mechanism [10].

TKM-080301 was designed for systemic intravenous delivery of siRNA to solid tumors and has been prepared in the form of LNPs, which can accumulate within tumors taking advantage of the "enhanced permeation and retention" effect [11, 12]. The lipid components of TKM-080301 also protect the siRNA from degradation by plasma and tissue nucleases, prevent rapid clearance of the siRNA, and enable effective intracellular uptake of the PLK1-targeting siRNA into cancer cells [13].

Pharmacology studies evaluating single- and multiple-dose pharmacodynamic evaluations of TKM-080301 in various subcutaneous tumor models and in an orthotopic mouse model of human liver cancer have demonstrated human PLK1 mRNA silencing, significant survival benefit, and significant tumor growth inhibition in orthotopic mouse models and various subcutaneous models of human cancer.

Liver is the primary tissue of distribution of TKM-080301, along with spleen, and to a lesser extent the adrenals. Approximately 66%–83% and 1.5%–3.2% of a total injected dose of TKM-080301 accumulates in the liver and spleen of mice, respectively.

This was a multicenter, open-label, nonrandomized, dose escalation phase I/II study conducted at 15 sites in six countries (the U.S., Canada, Hong Kong, the Republic of Korea,

Singapore, and Taiwan). The study was designed to determine the safety, tolerability, pharmacokinetics, and antitumor activity of TKM-080301 in adult subjects with metastatic or locally advanced inoperable HCC that is refractory to, or unsuitable for standard therapy. A conservative starting dose of 0.3 mg/kg was selected for this study to establish the safety of TKM-080301 in subjects with locally advanced or metastatic HCC. The study was restricted to patients with HCC with preserved hepatic function classified as Child-Pugh A. Subsequent dose escalations to 0.6 mg/kg and 0.75 mg/kg were planned. The maximum planned dose in this study was 0.75 mg/kg. Treatment cycles consisted of a single intravenous infusion of TKM-080301 over 60 minutes once weekly for 3 consecutive weeks, followed by a rest week, repeated every 4 weeks. To minimize the risk of infusion-related reactions, all subjects received a steroid prophylaxis regimen prior to each dose of TKM-080301, which was reduced according to a prescribed schedule if TKM-080301 was well tolerated.

Subjects who demonstrated clinical benefit without progression might have continued up to six complete cycles and might have received treatment beyond six cycles with the approval of the sponsor's medical monitor if the investigator considered it in the best interests of the subject. Subjects would then have continued TKM-080301 therapy until withdrawal of consent, disease progression, or unacceptable toxicity occurred.

The study was divided into two phases. The dose escalation phase was to enroll three cohorts of three to six subjects each, with each cohort assigned to receive successive increases of a predefined TKM-080301 dose escalation based on prior clinical experience with TKM-080301 in advanced solid tumors.

The starting dose of TKM-080301 was 0.3 mg/kg per dose (Cohort 1), and sequential cohorts were to receive TKM-080301 0.6 mg/kg per dose (Cohort 2) and 0.75 mg/kg per dose (Cohort 3), provided that dose-limiting toxicities (DLTs) were seen in none or no more than one subject during the preceding cycle. Once the maximum tolerated dose (MTD) had been established, ongoing subjects receiving a dose lower than the MTD might have had their dose increased to the MTD or an intermediate dose level if in the opinion of the

investigator and sponsor the subject may receive additional clinical benefit. Dose escalation proceeded without incident for Cohort 2 (0.6 mg/kg) and Cohort 3 (0.75 mg/kg). Safety was assessed during each cycle, including liver function tests and electrocardiograms. The potential for immune-related toxicities and infusion reactions were investigated during the first dose of cycle 1. Serial pharmacokinetic sampling was taken for cycle 1, doses 1 and 2, and for cycle 2, dose 1. A preinfusion sample was collected prior to dose 1 in each subsequent cycle. DLTs were defined as grade 4 toxicity considered possibly, probably, or definitely related to TKM 080301.

Assessment for preliminary evidence of antitumor activity (response rate according to RECIST 1.1 criteria) was a secondary objective of the study. Overall tumor response was assessed at the end of cycle 2 and every two cycles thereafter, and/or upon study discontinuation by the investigator. Clinical benefit rate was assessed in the expansion cohort and was defined as the sum of all subjects with RECIST 1.1 defined complete response (CR), partial response (PR), minor response (MR; $\geq 20\%$ decrease of target tumors but $< 30\%$ decrease), stable disease (SD) lasting ≥ 16 weeks, and $\geq 50\%$ decrease in alpha-fetoprotein (AFP) from baseline.

A total of 12 subjects (three subjects at 0.3 mg/kg, five subjects at 0.6 mg/kg, and four subjects at 0.75 mg/kg) had been dosed. Two subjects in the 0.3 mg/kg group remained on therapy. No DLTs were observed in Cohort 1 (0.3 mg/kg) or Cohort 2 (0.6 mg/kg). Review of subsequent adverse events (AEs) for subjects in those groups revealed that approximately 90% of the reported AEs were mild to moderate in severity, and most AEs were assessed to be unrelated or unlikely related to study drug by the investigator. A total of six subjects reported a total of 11 serious AEs (SAEs), but none of the SAEs was assessed as serious, unexpected, and treatment related. With no DLTs noted in Cohort 3, 0.75 mg/kg was declared as the MTD by the Safety Review Panel (SRP). The SRP also approved the opening of the phase II expansion cohort at the MTD of 0.75 mg/kg per week. After the development of grade 4 thrombocytopenia in two subjects, a recommended dose reduction to 0.6 mg/kg followed. The dose reduction was applicable for all subjects on study and any new subjects enrolled.

A total of 43 subjects were enrolled in the study at different dose levels: 3 subjects in the 0.3 mg/kg group, 9 subjects in the 0.6 mg/kg group, 15 subjects in the 0.75 mg/kg group, and 16 subjects in the reduction from 0.75 to 0.6 mg/kg group. All 43 subjects (100.0%) were included in the intention-to-treat (ITT) and per protocol analysis sets. Overall, 36 subjects (83.7%) were male and seven subjects (16.3%) were female. The race of most subjects was Asian (27 subjects; 62.8%) or white (14 subjects; 32.6%), and the ethnicity of most subjects was "not Hispanic or Latino" (38 subjects; 88.4%). The mean (range) age was 62 years (39–79). Body mass index ranged between 18.05 and 36.32 kg/cm². Overall, the different dose levels were generally similar regarding demographic characteristics. Life expectancy was more than 3 months for all 43 subjects (100%). No subjects had a New York Heart Association classification of grade II or greater. A total of 25 subjects

(58.1%) were at risk for hepatitis B, 6 subjects (14.0%) were at risk for hepatitis C, and 9 subjects (20.9%) had no risk factors. Most of the subjects (31 subjects; 72.1%) were classified at the C stage in the Barcelona Clinic Liver Cancer classification, with eight subjects (18.6%) classified at the B stage. The Eastern Cooperative Oncology Group performance status at screening for the overall population was 0 for 23 subjects (53.5%) and 1 for 20 subjects (46.5%).

A total of 39 subjects (90.7%) of the 43 enrolled subjects had an evaluable postbaseline scan. Overall, as assessed by the investigator, in subjects who received at least 0.3 mg/kg, 20 subjects (50.0%) had stable disease. Overall, as assessed by the central imaging center, in subjects who received at least 0.3 mg/kg, 18 subjects (46.2%) had stable disease and 20 subjects (51.3%) had progressive disease.

No subjects at any dose level met RECIST 1.1 criteria for CR, PR, or MR. Five subjects (11.6%) overall met RECIST 1.1 criteria for SD lasting ≥ 16 weeks. Three subjects (7.0%) demonstrated $\geq 50\%$ decrease in AFP from baseline. Overall, for eight subjects (18.6%) with a clinical benefit, the benefit was statistically significant ($p = .0012$). A total of 37 (86.0%) events were assessed. Six subjects (14.0%) were censored. The median progression-free survival was 2.04 months overall with a range of 0.0 to 13.3 months (95% confidence interval, 1.61; 3.42). Overall, 22 subjects (51.2%) in the ITT population died, and 21 subjects (48.8%) were censored at last contact. Three subjects' deaths during study treatment were reported as treatment-emergent AEs. The median follow-up time was 7.66 months. The median survival was 7.52 months. Overall as assessed by the investigator, in subjects who received at least 0.3 mg/kg, 20 subjects (50.0%) had stable disease. As assessed by Choi criteria, in subjects who received at least 0.3 mg/kg, 9 subjects (23.1%) had PR; 9 subjects (23.1%) of the 43 subjects assessed had SD. The mean duration of best response as assessed by Choi criteria was 18.7 ± 35.56 days for target response.

Treatment with TKM-080301 was generally safe and well tolerated in subjects with HCC during this study. A total of 41 of the 43 subjects (95.3%) of the ITT population experienced at least one AE. A reduction in spleen volume was observed in three subjects and was likely due to an on-target siRNA effect of PLK1 inhibition. In these subjects, the decline in splenic volume was not associated with clinically significant functional hyposplenism. TEAEs reported in more than one subject were pyrexia (20 subjects; 46.5%); fatigue (16 subjects; 37.2%); chills (15 subjects; 34.9%); peripheral edema (8 subjects; 18.6%); noncardiac chest pain (3 subjects; 7.0%); and malaise, edema, and pain in two subjects (4.7%) each. A total of 17 subjects (39.5%) had at least one infusion-related TEAE. No SAE of TKM-080301-related hepatic disease was noted. No fatal TEAE was assessed as being possibly, probably, or definitely related to TKM-080301. Overall, 22 subjects died (including censoring at last contact). Three of these subjects who died during the course of study treatment were reported as TEAEs. All three fatal TEAEs were assessed as unlikely or not related to TKM-080301.

In conclusion, TKM-080301 was safe and well tolerated in this population of patients with advanced HCC and adequate

liver function. Single-agent TKM-080301 did not demonstrate clinically meaningful antitumor activity, the secondary endpoint of this trial. Any further studies of this drug in HCC should be designed within the context of these results.

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Imane El Dika is currently at Weill Cornell Medical College, New York, New York, USA.

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DISCLOSURES

Jung-Hwan Yoon: Astra-Zeneca (RF); **Robin K. Kelley:** Agios, Bristol-Meyers Squibb, AstraZeneca, Target Pharma Solutions, Genentech/Roche (C/A), Agios, Astra Zeneca, Bayer, Bristol-Meyers Squibb, Exelixis, Eli Lilly, Novartis, Taiho, Merck, Tekmira (RF); **Thomas Yau:** Bristol-Meyers Squibb, Merck Sharpe & Dohme, Blueprint (C/A). 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

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