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PHASE I STUDIES

A phase 1 study of nevanimibe HCl, a novel adrenal-specific sterol O-acyltransferase 1 (SOAT1) inhibitor, in adrenocortical carcinoma

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Summary

Background Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy with very limited treatment options. Nevanimibe HCl (formerly ATR-101), a novel adrenal-specific sterol O-acyltransferase 1 (SOAT1) inhibitor, has been shown in nonclinical studies to decrease adrenal steroidogenesis at lower doses and to cause apoptosis of adrenocortical cells at higher doses. *Methods* This phase 1, multicenter, open-label study assessed the safety and pharmacokinetics (PK) of nevanimibe in adults with metastatic ACC (NCT01898715). A "3 + 3" dose-escalation design was used. Adverse events (AEs), PK, and tumor response based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were evaluated every 2 months. *Results* 63 patients with metastatic ACC, all of whom had previously failed systemic chemotherapy and only 2 of whom were mitotane-naïve, were dosed with oral nevanimibe at doses ranging from 1.6 mg/kg/day to 158.5 mg/kg/day. Subjects who did not experience tumor progression or a dose-limiting toxicity (DLT) could continue to receive additional cycles. No patients experienced a complete or partial response; however, 13 of the 48 (27%) patients who underwent imaging at 2 months had stable disease (SD), and 4 of these had SD > 4 months. In addition, drug-related adrenal insufficiency, considered a pharmacologic effect of nevanimibe, was observed in two patients. The most common treatment-emergent AEs were gastrointestinal disorders (76%), including diarrhea (44%) and vomiting (35%). A maximum tolerated dose (MTD) could not be defined, as very few dose-limiting toxicities (DLTs) occurred. Because the large number of tablets required at the highest dose (i.e., ~24 tablets/day) resulted in low-grade gastrointestinal adverse effects, a maximum *feasible* dose of 128.2 mg/kg/day was established as a dose that could be taken on a long-term basis. *Conclusions* This study demonstrated the safety of nevanimibe at doses of up to ~6000 mg BID. As the total number of tablets required to achieve an MTD exceeded practical administration limits, a maximum *feasible* dose was defined. Given that the expected exposure levels necessary for an apoptotic effect could not be achieved, the current formulation of nevanimibe had limited efficacy in patients with advanced ACC.

Keywords Adrenocortical carcinoma · Nevanimibe · ATR-101 · SOAT1

Introduction

Adrenocortical carcinoma (ACC) is a very rare but frequently aggressive endocrine tumor [1, 2]. The incidence is 1 to 2 cases/million per year. Women are more frequently affected with a male-to-female ratio of 1.0:1.2 [3, 4]. Despite considerable heterogeneity, the overall prognosis is extremely poor in advanced stages: the five-year survival for stages I and IV

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according to the European Network for the Study of Adrenal Tumors (ENS@T) classification are 82% and 13%, respectively [5]. The management of ACC involves a multidisciplinary therapeutic approach as recently clearly indicated by the first international guidelines on the management of this rare disease [6]. Currently, the only potentially curative treatment for stages I to III is surgical resection [2]. However, even where surgery is an option and successful, recurrences occur frequently [7]. Mitotane [an isomer of p,p'-DDD, also known as 1,1-(dichlorodiphenyl)-2,2-dichloroethane (o,p'-DDD)] is the only FDA-approved medical treatment for patients with metastatic/unresectable ACC. Retrospective studies in patients with advanced disease showed 11–24% partial or complete response with mitotane administration [8–10]. However, mitotane has been associated with several adverse events (AEs), primarily endocrine, gastrointestinal (GI) dysfunction and central nervous system (CNS) symptoms [11]. A narrow therapeutic window is another challenge associated with mitotane use. Finally, mitotane has poor absorption, distribution, metabolism and excretion (ADME) properties [12]. Cytotoxic chemotherapy alone or in combination with mitotane is recommended for patients who are at high risk for a recurrence with advanced ACC [13–16]. Therefore, there is a significant interest in finding an effective therapeutic intervention for ACC.

Nevanimibe HCl is an orally administered adrenal-specific inhibitor of sterol O-acyltransferase 1 (SOAT1), which catalyzes the esterification of intracellular free cholesterol. SOAT1 is also known as ACAT1 (acyl-coA:cholesterol acyltransferase 1) and was suggested as one of the targets of mitotane [17]. The chemical name of nevanimibe is N-[2,6-bis(1-methylethyl)phenyl]-N′-[[1-[4-(dimethylamino)phenyl]cyclopentyl]methyl]urea, hydrochloride salt. Nevanimibe has been shown to reduce adrenocortical steroid production at lower doses and to induce cellular apoptosis at higher doses in adrenocortical-derived cells and in the adrenal cortex of dogs [18]. As cytotoxic effects of nevanimibe are restricted to the adrenal cortex, treatment with nevanimibe provides a unique opportunity for the targeted treatment of ACC. The primary objective of this phase 1 study was to assess the safety and tolerability of orally administered nevanimibe in patients with advanced ACC. The secondary objectives included determination of the maximum tolerated dose (MTD), pharmacokinetics (PK), pharmacodynamic (PD) effects, and preliminary efficacy.

Methods

Population

Eligible patients were 18 years of age or older with clinically confirmed ACC that was locally advanced or metastatic and not responsive to surgical resection, and who had been offered and declined or failed mitotane (adjuvant or therapeutic) therapy and a platinum-based chemotherapy regimen. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Patients were excluded if they had plasma mitotane levels >5 μg/mL or had undergone chemotherapy, investigational therapy, hormonal, biological, or targeted agents within 4 weeks or five half-lives (whichever was shorter) before the first dose of study treatment.

Study design

This was a phase 1, multicenter (5 study centers: 4 in the United States, and 1 in Germany), open-label, ascending multiple-dose cohort study of the effects of nevanimibe on adults with advanced ACC who had failed or declined previous therapy (NCT01898715). All enrolled patients signed an IRB-approved informed consent form. The study employed a "3 + 3" dose-escalation design. A minimum of 3 patients were enrolled in a given dose cohort. If no dose-limiting toxicities (DLTs) were observed after 28 days (one cycle), the dose was escalated for the next cohort. Patients with stable disease (SD), partial response (PR), or complete response (CR) were allowed to receive additional 4-week cycles of nevanimibe therapy at the same dose. Each higher dose level of nevanimibe was administered only after the safety of the lower dose was established. However, if one of the patients in a dose cohort developed a DLT, then an additional 3 patients would be recruited at that dose level (i.e., "3 + 3" design). The planned dose escalation schedule was dose-doubling. However, if two patients in a dose cohort experienced an investigational drug-related grade 2 or greater AE, or one DLT, the dose escalation followed a Fibonacci series, specifically, the sum of the previous two doses. Dose escalation continued until a) the MTD was reached; b) an effective dose was established; or c) the amount of study drug needed in each dose exceeded an amount that could be practically taken at one time. The MTD was defined as the highest dose at which no more than one of 6 patients experienced a DLT. The initial dose level was 1.6 mg/kg body weight, administered orally once per day. Each patient was assigned to one dose cohort and did not move between cohorts.

Pharmacokinetic assessments

Plasma concentrations of nevanimibe were obtained at time points shown in Table 1 for cohorts with once daily (QD) dosing (Cohorts 1–7) and Table 2 for cohorts with twice daily (BID) dosing (Cohorts 8–14). The individual concentration-time profiles of plasma nevanimibe was evaluated using model-independent methods as implemented in WinNonlin™, Version 5 or higher.

Table 1 Pharmacokinetic Sampling Time Points – QD Dosing

Visit	Sampling Time Point
Cycle 1 Day 1	Pre-dose and 0.25, 0.5, 1, 2, 4, and 7 h post-dose
Cycle 1 Day 2	Pre-dose
Cycle 1 Day 22	Pre-dose and 0.25, 0.5, 1, 2, 4, and 7 h post-dose
Cycle 1 Day 23	Pre-dose
Cycle N Day 29	Pre-dose and 2 h post-dose
Final/Early Termination Visit	Random sample

All samples were analyzed using a validated assay at a central laboratory

Safety assessments

Safety was assessed by physical examinations, vital signs, electrocardiograms (ECGs), laboratory parameters, and ECOG performance status. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Hematologic DLTs were defined as grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L) lasting >7 days, febrile neutropenia (defined as ANC $< 1.0 \times 10^9$/L and fever ≥38.5 °C) or documented grade ≥ 3 infection with ANC $\leq 1.0 \times 10^9$/L, platelet count $<25 \times 10^9$/L lasting >7 days, and/or clinically significant bleeding and platelet count $<50 \times 10^9$/L. Non-hematologic DLTs were defined as any related grade 3, grade 4, or grade 5 toxicity; however, if AEs of nausea, vomiting, or diarrhea could be reduced to Grade 2 or lower within 72 h, the event was not considered to be a DLT. Patients who experienced a DLT were discontinued from the study. In case of multiple AEs, the presence or absence of a DLT was based on the most severe related AE experienced.

Efficacy assessments

The primary efficacy assessments for nevanimibe included response assessment by cross sectional imaging (computed tomography, CT, or magnetic resonance imaging, MRI) by RECIST 1.1 [19], and assessment of adrenocortical hormones produced by the tumor. Radiologic assessments were performed locally at each study center. Additional assessments included 24-h urine free cortisol levels and urine metabolomics.

Table 2 Pharmacokinetic Sampling Time Points – BID Dosing

Visit	Sampling Time Point
Cycle 1 Day 1, Dose 1	Pre-dose and 0.5, 1, 2, 4, and 8 h post-dose
Cycle 1 Day 1, Dose 2	Pre-dose and 0.5, 1, 2, 4, 8, and 12 h post-dose
Cycle 1 Day 22	Pre-dose and 0.5, 1, 2, 4, 8, and 12 h post-dose
Cycle N Day 29	Pre-dose and 2 h post-dose
Final/Early Termination Visit	Random sample

All samples were analyzed using a validated assay at a central laboratory

Statistical methods

Study populations The Enrolled Population included all patients who signed an informed consent form and completed an inclusion/exclusion criteria evaluation. The Safety Population included all patients who received at least one dose of nevanimibe. The modified Intention-to-Treat (mITT) Population included all patients who received at least one dose of nevanimibe and had at least one efficacy evaluation following baseline. Patients who experienced a DLT were included in the mITT Population. The Per Protocol (PP) Population included all patients who completed at least 4 weeks of nevanimibe treatment and received at least 75% of the assigned dose for Cycle 1.

Data summarization Descriptive analysis was performed using SAS version 9.3 or higher.

The PK analysis was performed on plasma concentration versus time data for each individual patient using the Phoenix WinNonlin non-compartmental analysis function (linear-up log-down trapezoidal rule for the area under the curve (AUC) calculations). The PK analysis included maximum observed plasma concentration (C_{max}), T_{max}, AUC_{last}, $AUC_{0–24}$ (Cohorts 1 through 7), $AUC_{0–12}$ (Cohorts 8 through 14), terminal half-life of the drug ($t_{1/2}$), and mean residence time (MRT). Any concentration reported as Below the Limit of Quantitation (BLQ) was set equal to zero. For all safety data, continuous variables were summarized by the number of observations (n), the mean, SD, median, min and max. No formal statistical analysis of the safety data was conducted. Safety summaries were based on observed values only. The number of doses of study drug received per cycle and throughout the study was summarized by dose cohort and overall for the Safety Population.

Results

Demographics All dosed patients had metastatic ACC at the time of enrollment (38% lung, 35% liver, 27% lymph nodes, 19% retroperitoneal spread, 16% kidney, and 22% other sites). The average age of patients was 47 years and the mean body weight was 80 kg (SD 22 kg). The majority were white (91%) and approximately half were women (54%). Summaries of demographic and baseline characteristics of patients are provided in Table 3 by dose cohort and overall. A total of 61 of 63

Table 3 Summary of Demographic and Baseline Characteristics by Cohort – Safety Population

Characteristic Category/ Statistic	Cohort 1 (*N* = 3)	Cohort 2 (*N* = 3)	Cohort 3 (*N* = 5)	Cohort 4 (*N* = 4)	Cohort 5 (*N* = 6)	Cohort 6 (*N* = 3)	Cohort 7 (*N* = 4)	Cohort 8 (*N* = 5)	Cohort 9 (*N* = 6)	Cohort 10 (*N* = 5)	Cohort 11 (*N* = 4)	Cohort 12 (*N* = 6)	Cohort 13 (*N* = 4)	Cohort 14 (*N* = 5)	Overall *N* = 63
Age at informed consent (years)															
Mean (SD)	41.7 (10.0)	61.3 (11.0)	43.4 (12.8)	32.0 (3.6)	49.0 (11.1)	50.7 (25.3)	48.0 (20.2)	50 (12.8)	45.5 (9.9)	47.2 (15.1)	51.5 (7.8)	42.5 (11.7)	50.8 (18.4)	50.2 (15.6)	47.1 (13.5)
Sex, n (%)															
Male	1 (33)	2 (67)	2 (40)	1 (25)	0	2 (67)	2 (50)	2 (40)	4 (67)	2 (40)	2 (50)	4 (67)	3 (75)	2 (40)	29 (46)
Female	2 (67)	1 (33)	3 (60)	3 (75)	6 (100)	1 (33)	2 (50)	3 (60)	2 (33)	3 (60)	2 (50)	2 (33)	1 (25)	3 (60)	34 (54)
Race, n (%)															
White	3 (100)	3 (100)	5 (100)	2 (50)	6 (100)	3 (100)	4 (100)	4 (80)	6 (100)	4 (80)	4 (100)	6 (100)	4 (100)	3 (60)	57 (90.5)
Asian	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (40)	2 (3.2)
Black	0	0	0	2 (50)	0	0	0	0	0	0	0	0	0	0	2 (3.2)
Other	0	0	0	0	0	0	0	1 (20)	0	1 (20)	0	0	0	0	2 (3.2)
Baseline weight (kg)															
n	3	3	5	3	6	3	4	5	6	5	4	6	4	5	62
Mean (SD)	87.83 (22.62)	111.77 (36.75)	78.80 (23.64)	85.77 (34.77)	61.65 (11.34)	69.17 (10.56)	83.48 (28.06)	81.82 (15.69)	85.95 (23.66)	77.48 (20.71)	92.68 (15.09)	67.98 (17.48)	89.43 (17.38)	68.24 (18.38)	79.86 (22.22)

Percentages were calculated using the number of patients in the column heading as the denominator. Baseline measurements for each dose level refer to data collected at Cycle 1 Day 1 pre-dose. If a value at Cycle 1 Day 1 pre-dose was not available, the last measurement prior to the first dose of nevanimibe was used as the baseline value

SD standard deviation

(97%) patients previously received mitotane and 53 of 63 (84%) patients had previously received mitotane and chemotherapy, most commonly etoposide/doxorubicin/cisplatin (EDP). Very few patients were mitotane-naïve although this was permitted in the protocol.

Dose cohorts A total of 63 patients were dosed in 14 separate cohorts, and 47 (70%) patients completed four weeks of treatment (Cycle 1) with nevanimibe. For Cohorts 1–7, the assigned dose of nevanimibe was administered orally in a fasting condition, once daily. Subsequent cohorts (8-14)were dosed BID under different administration conditions in an attempt to increase exposure. For Cohorts 8–11, the assigned dose was administered to fasted patients twice daily by mouth with non-diet cola. For Cohorts 12–14, the assigned dose was administered immediately following the morning and evening meals with a beverage of their choice. The dose escalation is shown in Table 4.

Pharmacokinetics Since for Cohorts 1–7 (single daily dose) 24-h PK assessment was performed, in Cohorts 8–14, PK sampling was conducted over a 12-h period with extrapolation of data to 24 h for comparison with Cohorts 1–7. In Cohorts 12–14 (BID dosing with food) nevanimibe exposure was statistically not different from Cohort 11 and lower than expected based on the results of a healthy volunteer food-effect study. The highest individual exposure occurred at the highest dose level (Cohort 13, 158.5 mg/kg/day, Patient 220 Cycle 1 Day 22 AUC_{0-12} = 45,500 ng·hr/mL [extrapolated AUC_{0-24} = 91,000 ng·hr/mL]), while the highest mean exposures occurred in Cohorts 11 and 13. Mean 24-h AUC values are shown in Fig. 1.

Exposure Sixty-three patients received at least one dose of nevanimibe. During Cycle 1 and over the course of the study, 47 (75%) and 39 (62%) patients, respectively, received 75% or more of the assigned dose. The median duration of treatment for Cycle 1 was 28 days, with a minimum of 2 days and a maximum of 31 days. Overall, the median duration of treatment was 45 days, with a minimum of 2 days and maximum of 386 days (Fig. 2).

Disposition Sixty-three patients received at least 1 dose of nevanimibe and were thus included in the Safety Population. Forty-eight patients met criteria for the mITT population, and 44 met criteria for the Per Protocol Population. Patients who did not experience tumor progression or a dose-limiting toxicity (DLT) could continue to receive additional 28-day cycles of nevanimibe. Thirty-four patients (51%) ultimately discontinued from the study because of progressive disease by RECIST 1.1 or other objective criteria (Table 5).

Table 4 Dose Escalation Schedule

Cohort	Number of Patients (N)	Nevanimibe dose (mg/kg/day)	Formulation	Administration Conditions
1	3	1.6	Powder-in-capsule	Fasted with water
2	3	3.2	Powder-in-capsule	Fasted with water
3	5	6.4	Powder-in-capsule	Fasted with water
4	4	12.8	Powder-in-capsule	Fasted with water
5	6	25.6	Powder-in-capsule	Fasted with water
6	3	51.2	Powder-in-capsule	Fasted with water
7	4	102.4	Powder-in-capsule	Fasted with water
8	5	23.3	Tablets	Fasted with non-diet cola
9	6	37.3	Tablets	Fasted with non-diet cola
10	5	60.6	Tablets	Fasted with non-diet cola
11	4	97.9	Tablets	Fasted with non-diet cola
12	6	97.9	Tablets	With food
13	4	158.5	Tablets	With food
14	5	128.2	Tablets	With food

Safety results

Dose-limiting toxicities (DLTs) Two patients (3.2%) experienced DLTs, which however were not the primary reason for study discontinuation: 1 patient in Cohort 7 (102.4 mg/kg/day) with pre-existing liver disease experienced an AE of reversible asymptomatic grade 3 elevation of liver enzymes (ALT 6.8 x upper limit of normal) on Day 29, which resolved approximately 1 week after discontinuation of study drug; and 1 patient in Cohort 9 (37.3 mg/kg/day) experienced SAEs of grade 3 vomiting and diarrhea following the third dose of study drug. As few DLTs were reported, an MTD could not be determined; instead, a maximum *feasible* dose was defined as the number of tablets that could reasonably be taken daily, over an extended period of time.

Adverse events Overall, 60 (95.2%) patients experienced 768 treatment-emergent AEs (TEAEs) (Table 6) of which 330 in 41 patients (65%) were considered drug-related. The most common TEAEs by system organ class (SOC) were GI disorders (76%), including diarrhea (44%), vomiting (35%), nausea (32%), abdominal pain (24%), constipation (22%), abdominal distention (21%) and gastro-esophageal reflux disease (GERD) (11%), especially at higher doses. These AEs were controlled with medication and tended to improve over time with continued dosing of nevanimibe. Other common TEAEs included fatigue (30%), dysuria (22%), dyspnea (16%), pyrexia (16%), insomnia (16%), decreased appetite (14%), hypokalemia (14%), headache (14%), peripheral edema (14%), urinary tract infection (14%), elevated AST level (13%), dizziness (13%), hypertension (13%), back pain (11%), and dehydration (10%) (Table 7). Subjects also

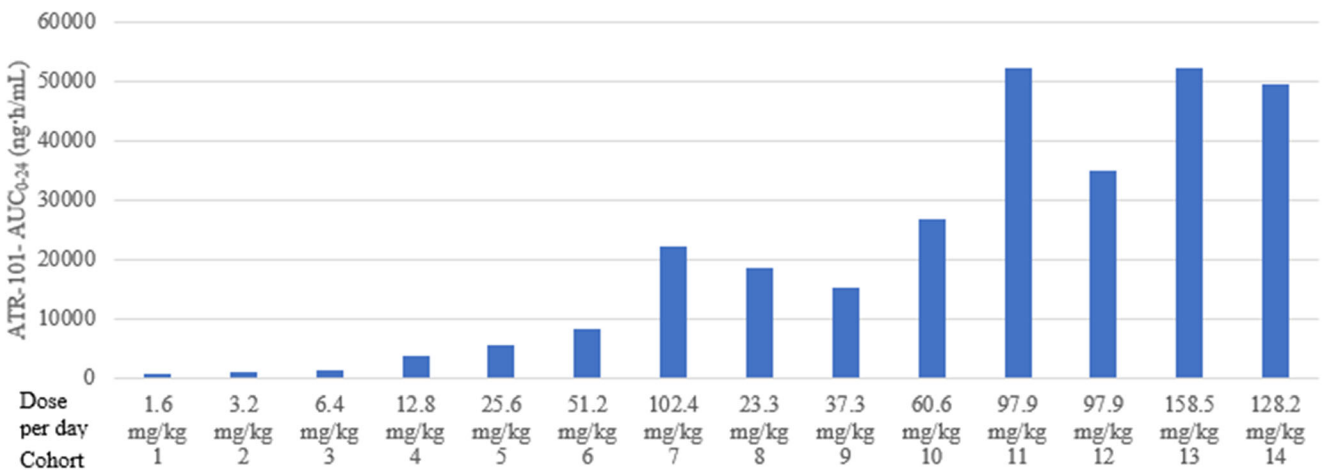

Fig. 1 Nevanimibe Mean 24-h AUC Values – Safety Population

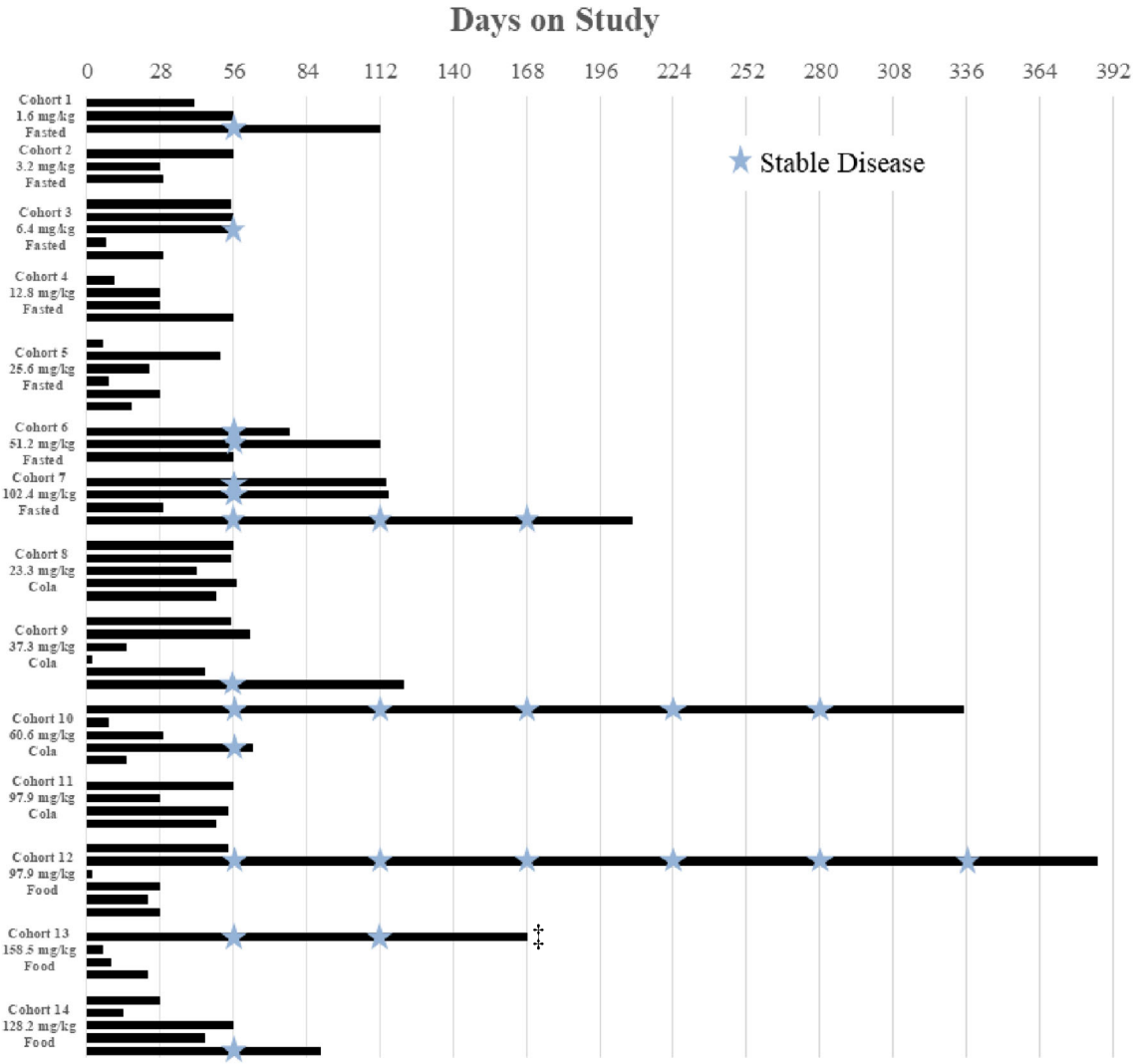

Fig. 2 Nevanimibe Doses and Exposure Duration by Dose Cohort – Safety Population

experienced a skin rash (5%) or pruritis (8%) that was either self-limited or improved with topical corticosteroids. Nine (14.3%) deaths were reported in this study, all unrelated to nevanimibe. Three deaths were due to disease/tumor progression, 3 due to sepsis/pulmonary sepsis, 2 due to respiratory failure, and 1 due to upper GI bleeding.

A total of 59 SAEs were reported in 31 (49%) patients, including abdominal pain, sepsis, adrenal insufficiency, chest pain, disease progression, dehydration, hyponatremia, respiratory failure, vomiting, and diarrhea. Events that were considered by the investigator to be definitely related to nevanimibe included vomiting and diarrhea in 1 patient, and rash in 1 patient; events that were considered by the investigator to be probably related included general deterioration of health in 1 patient, and adrenal insufficiency and increased hepatic enzymes in 1 patient; and events that were considered by the investigator to be possibly related included adrenal insufficiency in 1 patient. One patient had SAEs of jejunal obstruction (probably related) and myelitis caused by varicella-zoster virus reactivation (possibly related). One patient had SAEs of weakness (probably related) and hematuria (possibly related).

Nine (14%) patients experienced AEs that led to discontinuation from the study; 8 (13%) patients discontinued due to treatment-related AEs. Six (10%) patients, some of whom had liver metastases of ACC, experienced reversible asymptomatic elevated ALT; 4 were considered severe. Three ALT events were related to nevanimibe. Eight (13%) patients experienced elevated AST. Four AST events were related to nevanimibe. Three (5%) patients had increased bilirubin, blood creatinine, and/or C reactive protein; 3 (5%) patients had sepsis. In addition, 2 patients experienced treatment-related AEs of adrenal insufficiency.

Other safety assessments Clinical laboratory values were reported within-study, end-of-study, and change-from-baseline,

Table 5 Patient Disposition

Patient Status	Total n (%)
Enrolled	**67 (100%)**
Dosed with nevanimibe	63 (94%)
Completed Cycle 1	47 (70%)
Discontinued	**67 (100%)**
Progressive disease	34 (51%)
Dose-limiting toxicity	0
Investigator judged administration of study drug detrimental to health	3 (5%)
Withdrew consent	6 (9%)
Noncompliance	0
Pregnancy	0
Death	3 (5%)
Lost to follow-up	1 (2%)
Adverse event	11 (16%)
Other	9 (13%)

including hematology, PT/aPTT, blood chemistry, steroid hormones, and urinalysis values. Safety laboratory results, vital signs, and physical examination results were typical of an ACC population. ECG findings at a trough and predicted peak drug levels were normal or not clinically significant.

Efficacy results

Tumor response No cases of objective tumor response (CR or PR) were observed. Thirteen of the 48 (27%) patients who underwent imaging at the first assessment (2 months) had stable disease (SD), with only 4 of these confirmed at 4 months. Maximum duration of stable disease was 12 months. Two patients did have particularly compelling changes in their ACC lesions during the study that might have been due to

Table 6 Summary of Adverse Events – Safety Population

Patients dosed with nevanimibe	n (%) [#] (*N* = 63)
Patients with at least one TEAE [a]	60 (95.2%) [768]
Deaths	9 (14.3%) [9]
Patients with SAEs	31 (49.2%) [59]
Patients with AEs leading to study discontinuation	9 (14.3%) [10]

[a] TEAE: Treatment-emergent adverse event, defined as adverse events that happen for the first time after the first dose (Dose Day 1) of study drug, or exist before but get worse in severity or relationship to study drug after dosing. A drug-related TEAE is defined as TEAE with relatedness of Possible, Probable, or Definite

% = 100*n/N, where n is the number of patients in the specified category and N is the number of patients in the Safety Population per column

= Number of adverse events in the specified category

Table 7 Treatment-Emergent Adverse Events that Occurred in ≥5% of Patients – Safety Population

SYSTEM ORGAN CLASS Preferred Term	OVERALL (N = 63) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	11 (17.5)
Anemia	4 (6.3)
CARDIAC DISORDERS	8 (12.7)
Tachycardia	4 (6.3)
EYE DISORDERS	13 (20.6)
Dry eye	4 (6.3)
Vision blurred	4 (6.3)
GASTROINTESTINAL DISORDERS	48 (76.2)
Diarrhoea	28 (44.4)
Vomiting	22 (34.9)
Nausea	20 (31.7)
Abdominal pain	15 (23.8)
Constipation	14 (22.2)
Abdominal distension	13 (20.6)
Gastroesophageal reflux disease	7 (11.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	39 (61.9)
Fatigue	19 (30.2)
Pyrexia	10 (15.9)
Oedema peripheral	9 (14.3)
INFECTIONS AND INFESTATIONS	19 (30.2)
Urinary tract infection	9 (14.3)
INVESTIGATIONS	20 (31.7)
Aspartate aminotransferase increased	8 (12.7)
Alanine aminotransferase increased	6 (9.5)
Weight decreased	6 (9.5)
Metabolism and Nutrition Disorders	29 (46.0)
Decreased appetite	9 (14.3)
Hypokalaemia	9 (14.3)
Dehydration	6 (9.5)
Hyponatraemia	5 (7.9)
Hypomagnesaemia	4 (6.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	22 (34.9)
Back pain	7 (11.1)
MUSCULAR WEAKNESS	5 (7.9)
Arthralgia	4 (6.3)
NERVOUS SYSTEM DISORDERS	23 (36.5)
Headache	9 (14.3)
Dizziness	8 (12.7)
PSYCHIATRIC DISORDERS	19 (30.2)
Insomnia	10 (15.9)
RENAL AND URINARY DISORDERS	23 (36.3)
Dysuria	14 (22.2)
Nocturia	4 (6.3)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	24 (38.1)
Dyspnoea	10 (15.9)
Cough	6 (9.5)
Pleural effusion	4 (6.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	21 (33.3)
Pruritis	5 (7.9)
Hyperhidrosis	4 (6.3)
VASCULAR DISORDERS	13 (20.6)
Hypertension	8 (12.7)

MedDRA version 16.0 was used for coding

TEAE treatment-emergent adverse event. A treatment-emergent adverse event is an adverse event with a starting date on or after the first day on which study drug was taken

effects of study drug: one patient in Cohort 10 (60.6 mg/kg/day, BID, non-diet cola) presented with a documented history of doubling of the sum of the longest diameters of target lesions in the 5 months prior to entering the study. This patient, who only had lung metastases, remained in the study with SD by RECIST criteria for approximately 1 year before developing progressive disease. One patient in Cohort 13 (158.5/128.2 mg/kg/day, BID, food) had documented acute adrenal insufficiency following 3 doses of study drug (158.5 mg/kg/day). This patient also experienced 20% shrinkage in the sum of the longest diameters of target lesions after approximately 2 months on treatment with nevanimibe. An additional patient, who was in Cohort 12 (97.9 mg/kg/day, BID, food) and had kidney and liver metastases as well as retroperitoneal spread, had SD for more than a year and only discontinued after 387 days on study due to issues with health insurance.

Pharmacodynamics During the study, biomarker data were collected from urine and blood. However, many of the study patients were taking supplemental glucocorticoids and mineralocorticoids, which confounded the results. Consequently, as summarization of the blood and urine hormone results (including steroid fingerprinting results) was of indeterminate value, these data were excluded from the efficacy assessment that was initially planned.

Discussion

Patients with ACC were dosed with oral nevanimibe across 14 cohorts under multiple conditions to increase drug exposure. In order to attempt to achieve therapeutic exposures while maintaining a volume per dose that would be acceptable to patients, it was ultimately necessary to compress the study drug in a tablet format. The tablet formulation of nevanimibe resulted in increased exposure compared to similar doses of the powder-in-capsule formulation. Administration with an acidic beverage (i.e., non-diet cola) had minimal impact on increasing exposure levels relative to administration with water; and administration with food did not appear to increase exposures relative to administration with an acidic beverage (i.e., non-diet cola), despite the results of a food-effect study in healthy volunteers showing increased absorption with food. The highest exposure occurred at the highest dose level (Cohort 13, 158.5 mg/kg/day), in which the most compelling evidence of the anti-tumor activity of nevanimibe was observed. Using the RECIST 1.1 score, 13 of the 48 (27%) patients who underwent imaging at 2 months had documented SD, including 4 patients with SD > 4 months.

Nevanimibe was generally safe over the entire dosage range for this study. At the highest dose (158.5 mg/kg/day), an MTD could not be defined as a DLT did not occur. Because of the large number of tablets required at the highest dose (i.e., ~24 tablets per day), which resulted in low-grade GI side effects, a maximum *feasible* dose that could be taken on a long-term basis was established at 128.2 mg/kg/day. Thus, nevanimibe exposure levels required to elicit an apoptotic or adrenolytic effect based on nonclinical studies were not achieved in the large majority of patients in the study.

This is the first-in-human study to evaluate the safety and tolerability of nevanimibe in adults with ACC. This study demonstrates the safety of nevanimibe at doses of up to approximately 6000 mg BID for a 75-kg individual. Given that the expected exposure levels of the drug necessary for an apoptotic effect could not be achieved, nevanimibe had limited efficacy in patients with advanced ACC. Further development of nevanimibe for the treatment of ACC is not currently being pursued.

Authors' contributions PJN and VHL authored substantial sections of the manuscript and incorporated reviewer comments. DCS, MF, EK, MAH, MK, MMI, PM, and AN reviewed and edited the manuscript, and provided many helpful comments.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest David C. Smith received research funding for this project from Millendo Therapeutics, formerly Atterocor. David C. Smith received research funding from Bayer, Bristol-Myers Squibb (Medarex), Eli Lilly, Genentech, Astellas, MedImmune, Seattle Genetics, Millenium, Incyte, Novartis, F. Hoffman-La Roche, ESSA, and OncoMed. Matthias Kroiss received research support from Ipsen. Electron Kebebew declares no conflict of interest. Mouhammed Amir Habra received research funding from Exelixis. Mouhammed Amir Habra is a consultant and on the advisory board of Corcept Therapeutics and HRA Pharma. Rashmi Chugh declares no conflict of interest. Bryan J. Schneider received institutional research funding from Incyte, Genentech and Bristol-Meyers Squibb. Martin Fassnacht declares no conflict of interest. Pegah Jafarinasabian is a former employee of Millendo Therapeutics. M. Marian Ijzerman is a current employee of Millendo Therapeutics. Vivian H. Lin is a current employee of Millendo Therapeutics. Pharis Mohideen is a former employee of Millendo Therapeutics and currently owns shares in Millendo Therapeutics. Aung Naing received research funding from NCI, EMD Serono, MedImmune, Healios Onc. Nutrition, Atterocor, Amplimmune, ARMO BioSciences, Karyopharm Therapeutics, Incyte, Novartis, Regeneron, Merck, Bristol-Meyers Squibb, Pfizer, CytomX Therapeutics, Neon Therapeutics, Calithera BioSciences, TopAlliance BioSciences, Eli Lilly, Kymab, PsiOxus, and Immune Deficiency Foundation (spouse). Aung Naing is on the advisory board for CytomX Therapeutics and Novartis and received reimbursement for travel and accommodation from ARMO BioSciences, a wholly owned subsidiary of Eli Lilly and Company.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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