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MONOGRAPH

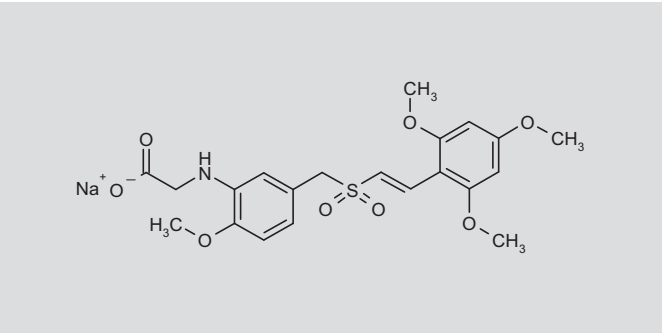
ON 01910.Na

Polo-Like Kinase Inhibitor
Oncolytic

Rigosertib
Estybon®

N-[2-Methoxy-5-[(*E*)-2-(2,4,6-trimethoxyphenyl)vinylsulfonylmethyl]phenyl]glycine sodium salt

InChI: 1S/C21H25NO8S.Na/c1-27-15-10-19(29-3)16(20(11-15)30-4)7-8-31(25,26)13-14-5-6-18(28-2)17(9-14)22-12-21(23)24;/h5-11,22H,12-13H2,1-4H3,(H,23,24);/q;+1/p-1/b8-7+;



$C_{21}H_{24}NNaO_8S$
Mol wt: 473.472
CAS: 592542-60-4
CAS: 592542-59-1 (free acid)
EN: 365104

SUMMARY

ON 01910.Na (rigosertib, Estybon®) is a novel small molecule developed to treat cancer. It has a multitargeted mechanism of action, including polo-like kinase inhibition, resulting in selective blockade of mitosis and death in cancer cells, even those carrying drug-resistant mutations. In preclinical experiments, ON 01910.Na proved active against numerous cancer types both alone and in combination with other chemotherapies. Pharmacokinetic studies show that the compound undergoes rapid plasma elimination ($t_{1/2}$ < 1 hour), with limited evidence of metabolism but extensive biliary excretion. Over 260 patients have been treated with intravenous ON 01910.Na in clinical trials, and the compound showed a good safety profile, with a low incidence of adverse events. The lead indication is myelodysplastic syndrome (MDS), and ongoing studies show favorable results in MDS patients. The U.S. FDA has designated ON 01910.Na as an orphan drug for the treatment of MDS and has provided a Special Protocol Assessment, accepting a pivotal phase III trial design for monotherapy in patients with MDS refractory to hypomethylating agents. Additional hematological and solid tumor (e.g., acute myeloid leukemia, ovarian and pancreatic cancer) indications for ON 01910.Na are being probed, both as a single agent and in combination therapy. An oral formulation of ON 01910.Na is also being tested in patients.

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SYNTHESIS

The company has requested that this information not be divulged, although details on the synthesis of this product can be obtained in references 1-3.

BACKGROUND

Antimitotic agents are widely used to treat both solid tumors and hematological cancers. However, these medications are often associated with dose-limiting toxicities and drug resistance. In the search for the next generation of targeted anticancer drugs, target pathways include those that are overexpressed in tumor cells with minimal expression in normal tissues. Drugs that selectively target these pathways have the potential to have higher safety margins in patients. Moreover, the development of predictive biomarkers for these targets would aid in the identification of those individuals who could respond favorably to therapy (4).

Among the most promising cellular targets that have been identified are the polo-like kinases (PLKs) (4). This family of enzymes is known to play an important role in cell division and checkpoint regulation of mitosis and maintaining DNA integrity (4, 5). PLKs are overexpressed in many human tumors (e.g., breast cancer, pancreatic cancer, non-Hodgkin's lymphoma), and this overexpression has been associated with poor clinical outcomes (6-8). Since PLKs are not overexpressed in normal, nondividing cells, they represent an attractive chemotherapeutic target family (5).

A number of PLK inhibitors are presently undergoing preclinical and clinical development, including ON 01910.Na (rigosertib), a small-molecule styryl benzyl sulfone (5). Styryl benzyl sulfones are a novel family of non-ATP-competitive compounds that induce selective G_2/M arrest of tumor cells, characterized by spindle abnormalities

leading to their apoptosis (9). ON 01910.Na shows selective cytotoxicity towards tumor cells with minimal effects on normal cells in vitro. The compound is also active against multidrug-resistant (MDR) cells, which are resistant to many commercially available chemotherapeutic agents (10).

The lead indication for ON 01910.Na, based on mechanistic rationale and proof-of-concept studies, is myelodysplastic syndrome (MDS). MDS is a group of chronic diseases of bone marrow dysfunction characterized by persistent peripheral blood cytopenia (11). The overall incidence of MDS in the U.S. is 4.3 cases per 100,000 people, with an estimated 11,000 newly diagnosed cases in 2010 (12). There are relatively few treatment options for high-risk MDS patients who have relapsed after initial treatment with hypomethylating agents, and ON 01910.Na represents a promising therapy for this condition. The U.S. FDA has designated ON 01910.Na as an orphan drug for the treatment of MDS and has provided a Special Protocol Assessment (SPA), accepting a pivotal phase III trial design for monotherapy in patients with MDS.

In addition to MDS, ON 01910.Na is being investigated in patients suffering from hematological and solid tumor indications, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL) and pancreatic cancer, both as a single agent and as combination therapy.

PRECLINICAL PHARMACOLOGY

Preclinical in vitro experiments have demonstrated that ON 01910.Na is highly effective against a broad spectrum of cancers, including drug-resistant cancer cell lines. This compound shows activity either alone or in combination with other anticancer agents. In vitro and in vivo studies demonstrate that ON 01910.Na has a low toxicity profile. Moreover, experiments have identified multiple mechanistic targets for this new chemical entity.

ON 01910.Na belongs to a family of styryl benzyl sulfones. Some analogues are novel small-molecule kinase inhibitors that do not compete with ATP (13). ON 01910.Na, the most advanced development candidate from this class, has been evaluated against more than 100 tumor lines in vitro. The compound induced apoptosis across all tumor cells tested, with IC_{50} values ranging between 20 nM and 250 nM (10, 13). Studies in drug-resistant human tumor cell lines demonstrated that ON 01910.Na is not a multidrug resistance protein 1 or multidrug resistance-associated protein substrate, and is not cross-resistant to many drug-resistant tumor cells. ON 01910.Na is active against a range of drug-resistant tumor cell lines, including human uterine sarcoma MES-SA/Dx5 and acute lymphoblastic leukemia (ALL) CEM/CX, which are known to overexpress multidrug resistance protein 1/P-glycoprotein and confer resistance to an array of anticancer medications (13). ON 01910.Na has also demonstrated activity against other drug-resistant cell lines, including paclitaxel-resistant ovarian cancer 1A9, vincristine-resistant epidermoid carcinoma KB and doxorubicin-resistant breast adenocarcinoma MCF7 cells, with IC_{50} estimates almost identical to those found with the parent (nonresistant) cell lines (10). Further studies showed no evidence of cross-resistance of ON 01910.Na to cells resistant to methotrexate (ALL MOLT cells), vinblastine (KB cells, Burkitt's lymphoma Daudi/MDR20 cells), etoposide (HEK 293/pcDNA3.1-MRP1 cells) and mitoxantrone (HEK 293/ABCG2 cells). These studies collectively suggest that ON 01910.Na is not a substrate for multidrug-resistant transporters (P-glycoprotein, multidrug resistance-associated protein 1) (14).

Antitumor activity for ON 01910.Na has also been demonstrated in vivo in nude mice bearing human tumor xenografts, including hepatoma BEL-7402, breast adenocarcinoma MCF7 and pancreatic carcinoma MIA PaCa-2. The compound readily inhibited tumor growth in these models, and outperformed oxaliplatin (BEL-7402 model), doxorubicin (MCF7 model) and gemcitabine (MIA PaCa-2 model). Moreover, the drug showed no evidence of toxicity (weight loss) at the dose tested (200 mg/kg i.p. every 2 days) (10, 15).

While the results described above illustrate the broad-spectrum activity of ON 01910.Na as a single-use anticancer agent, preclinical studies also demonstrated the utility of this compound as part of a combination therapy with other medications. In vitro cytotoxic experiments with BEL-7404 cells found synergistic effects when ON 01910.Na was coadministered with 5-fluorouracil or when therapy was followed by doxorubicin, cisplatin or flavopiridol (16). Studies in xenograft models (BEL-7402, MCF7) found that when ON 01910.Na was combined with other drugs (irinotecan, paclitaxel, doxorubicin or vincristine), superior activity was achieved compared to monotherapy (15).

The combination of ON 01910.Na and oxaliplatin has also yielded promising results. In vitro experiments with BEL-7404 and prostate carcinoma DU 145 cells showed that enhanced cell killing effects of ON 01910.Na and oxaliplatin occur after DNA synthesis is complete, which is secondary to potentiating effects of G_2/M arrest and apoptosis (17). These findings have been confirmed in xenograft models, where ON 01910.Na enhanced the in vivo cancericidal effect of oxaliplatin against human hepatoma, melanoma, pancreas and prostate cancers (18).

An array of preclinical testing has been done to establish target mechanistic pathways for drug activity. The results show that ON 01910.Na produces the following major abnormalities in tumor cell lines: 1) aberrant cell division, including irregular chromosomal segregation and cytokinesis; 2) G_2/M arrest and apoptosis in many tumor cells; and 3) decreased expression of dual specificity phosphatase Cdc25C (19). Key molecular targets for the compound include the PLK1 pathway, cyclin-dependent kinase (CDK1; a mitotic regulator) and the phosphoinositide 3-kinase (PI3K) pathway (20).

Early investigations indicated that ON 01910.Na inhibited PLK1, a kinase known to be overexpressed in many tumor cells (10). In vitro studies in gemcitabine-resistant pancreatic cancer cells found that the combination of ON 01910.Na and gemcitabine induced synergy in resistant cell lines that were also found to be sensitive to PLK1 siRNA knockdown (21). Whereas other studies did not confirm that ON 01910.Na is a direct PLK1 inhibitor, the compound is thought to inhibit a PLK pathway, presumably PLK3 (19).

Preclinical investigations have also demonstrated a potential role for ON 01910.Na in the treatment of patients with trisomy 8 MDS. Trisomy 8 $CD34^+$ cells have been found to persist and even expand in individuals with bone marrow failure, despite a potent specific immune response. In these patients, increased cyclin D1 causes upregulation of survivin, resulting in resistance of $CD34^+$ cells to apoptosis. In vitro experiments showed a favorable response to ON

01910.Na, where the compound decreased cyclin D1 accumulation in cultured bone marrow from patients with high-risk trisomy 8 MDS and monosomy 7 patients (who also show upregulation of cyclin D1), while selectively decreasing blasts and aneuploidy (22-24).

Cyclin D1 overexpression is a hallmark characteristic of MCL, and in vitro studies showed a rapid decrease in cyclin D1 levels in MCL cells following exposure to ON 01910.Na. The compound appears to work by inhibiting the PI3K/Akt/mTOR/elF4E-BP signaling pathway, which in turn blocks cyclin D1 mRNA translation. Correspondingly, ON 01910.Na was found to trigger cytochrome c-dependent apoptosis in MCL cells (9).

Chronic lymphocytic leukemia (CLL), the most common form of leukemia, is characterized by the accumulation of B-cell lymphocytes in the bloodstream. The disease is incurable with chemotherapy, and few agents show activity against refractory CLL (25). In vitro studies demonstrated that 48-hour exposure to ON 01910.Na induced apoptosis of CLL cells, with limited toxicity to T or B cells from normal donors. The drug showed activity against a variety of CLL subtypes, including IgVH unmutated (more progressive cells) and mutated cells, and those carrying p53 deletions. Gene expression profiling elucidated a dual mechanism of action for ON 01910.Na against CLL that involves inhibition of the PI3K/Akt survival pathway with BIM upregulation and induction of oxidative stress secondary to upregulation of Noxa (26, 27).

Progress has also been made in the preclinical development of a predictive biomarker for ON 01910.Na in the treatment of pancreatic cancer. The compound showed activity against pancreatic tumor cells both in vitro and in vivo, and this activity was linked to downregulation of cyclin B1, which plays a key role in cell cycle regulation. A follow-up experiment was conducted with nine patient-derived pancreatic tumors. The tumors were tested for cyclin B1 mRNA, and two tumor samples were identified as potential responders to ON 01910.Na. The predicted activity was confirmed in vivo in mouse tumor xenografts, where efficacy was demonstrated. Overall, this investigation suggests that a cyclin B1-based ex vivo assay may be able to identify those patients with pancreatic cancer who are more likely to respond to ON 01910.Na chemotherapy (28).

Collectively, the results from preclinical pharmacological studies suggest multiple potential uses for ON 01910.Na in anticancer therapy. These studies provided the motivation to advance this drug to clinical trials in patients suffering from an array of solid tumors and hematological cancers.

PHARMACOKINETICS AND METABOLISM

The pharmacokinetic profile of ON 01910.Na has been evaluated in various preclinical and clinical studies. In vitro studies demonstrated that the compound is extensively bound in plasma (> 97%) across most species (rats, dogs, humans), with lower binding in mouse plasma (29). Cytotoxicity studies in DU 145 cells showed reduced activity for ON 01910.Na against cells incubated in medium supplemented with human serum albumin. Drug binding was associated with a 20-fold decrease in IC_{50} values (30). Experiments in Daudi human lymphoma cells likewise demonstrated reductions in the cell kill effect of ON 01910.Na as albumin levels increased. Adding protein binding displacers (e.g., warfarin, aspirin) restored the drug's activity (31). These results are important to consider in the development of dosing regimens for a highly protein-bound anticancer agent, as only unbound drug is capable of extravascular distribution.

The preclinical pharmacokinetics of ON 01910.Na have been studied in mice, rats and dogs (30). The compound is rapidly eliminated from the plasma following i.v. administration, with an elimination $t_{1/2}$ of < 1 hour. This is followed by a prolonged secondary phase, where plasma levels are < 1% of the observed peak concentration. ON 01910.Na displayed nonlinear kinetics with increasing dose, consistent with saturation of elimination pathways.

There is limited evidence for metabolism of ON 01910.Na based on nonclinical testing conducted in vivo. Tissue distribution studies in mice do indicate extensive liver uptake of drug, and biliary excretion is the predominant route of elimination (30). These in vivo results were confirmed ex vivo in the isolated perfused rat liver model. In those experiments, the drug was extensively excreted in bile and clearance decreased with increasing dose. Studies using livers from multidrug resistance-associated protein 2-deficient rat donors pointed to a role for that transport system in ON 01910.Na disposition by the liver (32).

The clinical pharmacokinetics of ON 01910.Na have been characterized in a series of phase I studies. A first-in-man study was performed on 20 cancer patients. ON 01910.Na was administered as a 2-hour i.v. infusion over a range of doses of 80-3120 mg. Systemic exposure (plasma AUC) increased with dose, albeit in a nonlinear fashion. ON 01910.Na clearance ranged from 1.6 to 22.8 L/h in the patients studied, consistent with a low hepatic extraction ratio for compound (33).

ON 01910.Na was next evaluated in a multicenter study, where the effect of dose and administration schedule on pharmacokinetics was determined. Three general protocols were evaluated: a 72-hour infusion (dose range: 50-1375 mg/m^2), a 24-hour infusion (dose range: 250-4450 mg/m^2) and 2-, 4- or 8-hour infusions (dose range: 240-3200 mg/m^2). A total of 81 patients were evaluated. ON 01910.Na was rapidly eliminated from the plasma ($t_{1/2}$ ~ 2 hours), and drug concentrations reached steady state quickly following administration by prolonged infusion. Drug clearance was inversely correlated with dosing rate (mg/m^2/h), consistent with nonlinear kinetics (34).

Overall, the results from preclinical and clinical pharmacokinetic studies show that ON 01910.Na exhibits high plasma binding and is rapidly eliminated from the plasma across various species, including humans. Administration by continuous infusion may be required to maintain sufficient exposure to the drug, although this requires further evaluation.

SAFETY

Preclinical studies point to a favorable safety profile for ON 01910.Na. Whereas the drug is cytotoxic against numerous human tumor cell lines in vitro, normal cells are not affected (13). Likewise, the compound shows significant activity against leukemia cells, with minimal effects on normal blood cells or bone marrow cells (35). Toxicology studies in rats showed no evidence of significant myelotoxicity, neurotoxicity or cardiotoxicity. The maximum tolerated doses (MTD) in rats for single- and repeat-dose (28 days)

studies were > 1200 mg/m^2 and 450 mg/m^2, respectively. For dogs, MTD estimates of > 4000 mg/m^2 (single dose) and > 1000 mg/m^2 were obtained (10).

Over 260 patients with solid or blood tumors or MDS have been treated in phase I and phase II clinical trials. Table I provides a summary of the clinical trial results published to date, including adverse effects observed in patients treated with ON 01910.Na. The compound is associated with remarkably low toxicity, even in individuals treated for 6 months or longer who received multiple sequential cycles of drug. The first-in-man study established an MTD of 3120 mg (2-hour infusion) for the compound. The dose-limiting toxicity observed at this dose level was abdominal pain. Infusion of 4200 mg over 2 hours was not considered feasible because of the occurrence of grade 2 toxicity (33). The toxicity profile was considered acceptable for phase II development (34). Longer continuous infusion times (up to 72 hours) were also investigated. Fatigue was the most common side effect reported following ON 01910.Na administration by continuous i.v. infusion over 24 hours (2750 mg/m^2 given weekly) or 72 hours (250 mg/m^2/day every 2 weeks) (36, 37).

CLINICAL STUDIES

The results from preclinical studies suggested multiple potential uses for ON 01910.Na, either as a single agent or as combination therapy, and these findings are guiding studies in humans. A number of clinical trials have been completed or are currently under way to establish the safety profile of the compound, and to evaluate drug response against a number of solid tumors and hematological malignancies. The studies can be found on the ClinicalTrials.gov website (38), and the results are summarized in Table I.

Hematological malignancies

The lead indication for ON 01910.Na is MDS. This is based on mechanistic rationale and proof-of-concept studies. In an early phase I study involving MDS patients with refractory anemia, ON 01910.Na demonstrated efficacy with respect to improved cytopenia and decreased blast counts at a dose of 800 mg/m^2 administered for 3 or 5 days (23).

Currently, four separate trials with MDS patients are being carried out and preliminary results have been reported. This includes a phase I study (ClinicalTrials.gov Identifier: NCT00854646), with data collected from 10 patients with MDS or refractory leukemia. Patients received escalating doses of ON 01910.Na (650-1700 mg/m^2) by continuous infusion over 3-6 days every 2 weeks for four cycles, with subsequent treatments every 3-4 weeks. Biological activity for the compound (reduced blasts, eradication of MDS clone, improved peripheral counts) was noted in several patients, and this correlated with increased survival (39).

In another study, the safety and efficacy of ON 01910.Na are being evaluated in a broad population of MDS patients (ClinicalTrials.gov Identifier: NCT00854945). The drug is being dosed by continuous infusion over 48 hours once a week for 3 weeks of a 4-week cycle. In an initial report, 13 high- or intermediate-risk patients received ON 01910.Na at doses of 800 or 1500 mg/m^2/day. Drug response has been observed in several patients based on hematological improvements, pain relief and overall well-being (40).

ON 01910.Na is also being evaluated in a phase II study in high-risk MDS patients who are unresponsive to hypomethylating agent therapy (ClinicalTrials.gov Identifier: NCT01241500). The study aims to determine whether ON 01910.Na combined with best supportive care improves overall survival compared to supportive care alone in a population of MDS patients with excess blasts (5-30% bone marrow blasts) who have failed azacitidine or decitabine treatment. Preliminary findings have been reported in 10 patients, including 8 who were on a dosing regimen of 1800 mg/day by continuous infusion over 3 days every 2 weeks for 2 months, followed by monthly dosing. A substantial number of patients showed a favorable response to ON 01910.Na therapy based on hematological improvement and other response indicators. Given that the life expectancy of this patient population is approximately 4 months (41), these preliminary results are encouraging (42).

Survival of MDS patients who transition to acute myeloid leukemia (AML) is dramatically shortened. A fourth clinical trial is currently evaluating the safety and efficacy of ON 01910.Na in MDS patients with refractory AML with trisomy 8 (ClinicalTrials.gov Identifier: NCT00533416). The motivation for this study comes from in vitro experiments indicating a favorable response to ON 01910.Na, namely decreased cyclin D1 accumulation, in cultured bone marrow from patients with high-risk trisomy 8 MDS. Results from this trial have not yet been reported.

Investigators are analyzing bone marrow response and overall survival in patients enrolled in the four ongoing clinical trials in MDS patients. Blood and marrow samples collected in those trials are being tested to determine the rate and duration of objective hematological and marrow responses, and duration of progression-free survival in MDS patients treated with ON 01910.Na (ClinicalTrials.gov Identifier: NCT00987584). Preliminary results in 48 patients found a strong correlation between bone marrow blast response and overall survival in high-risk MDS patients (43).

ON 01910.Na is also undergoing clinical evaluation to treat leukemia. This particular study will evaluate the safety and efficacy of the compound following administration by continuous infusion over 3 or 5 days in patients with AML and ALL (ClinicalTrials.gov Identifier: NCT01167166). Although responses to standard chemotherapy regimens do occur in some AML or ALL patients, durable remissions are achieved infrequently. The study aims to determine whether ON 01910.Na has potential benefits in treating these conditions. The drug will be dosed at 2400 mg/24 hours by continuous i.v. infusion for 72 or 120 hours every 2 weeks for the first 8 weeks and every 4 weeks afterwards. Primary outcome measures are dose-related toxicities and change in bone marrow blast cell and peripheral blood counts. Results have not been reported.

The favorable results from preclinical studies demonstrating cytotoxic activity for ON 01910.Na against CLL and MCL cell lines via cyclin D1 suppression provide a rationale for clinical evaluation of this compound in patients with these and other lymphoid malignancies (ClinicalTrials.gov Identifier: NCT01167166). The study objectives are to establish the MTD for ON 01910.Na and to assess the activity of the drug in patients suffering from MCL, CLL and multiple myeloma. These are incurable diseases that mainly affect people over 65 years of age. The first cohort of patients was dosed at 1200 mg/m^2/day over 48 hours, with planned escalations to 2100 mg/m^2/day. In addition to the drug's toxicity profile, pharmacody-

Table I. *Summary of ON 01910.Na clinical studies*[1].

Study title[2]	Dosing regimen	# Patients	# Responders	Response details	Adverse events (n)[3]	Ref.
Safety of ON-01910.Na in patients with myelodysplasia (NCT00533416)	800 or 1500 mg/m^2/day by continuous i.v. infusion for 2, 3 or 5 days every 3-4 weeks	15	7	Survival observed up to 14 mo post-treatment	Not reported	23, 24
Phase I study (first-in-man)	80-4370 mg infused over 2 hours	20	1	Progression-free > 24 mo	Fatigue (11), pain (12), nausea (6), vomiting (5), ↑ AST/ALT (5) (all were grade 1-2)	33
Phase 1 study in patients with refractory leukemia or MDS (NCT00854646)	650-1700 mg/m^2 by continuous i.v. infusion over 3-6 days	48	19	50%↓ in bone marrow blasts @ wk 4-8 associated with ↑ overall survival	Not reported	39
Study of 72-hour infusion of ON 01910.Na in patients with MDS or AML (NCT00854945)	800 or 1500 mg/m^2/day by continuous i.v. infusion for 2 days weekly for 3 weeks of a 4-week cycle	13	2	Significant %↓ in bone marrow blasts compared to pretreatment values	Most frequently reported were thrombocytopenia, neutropenia, anemia, fatigue and nausea. One serious case of neutropenia observed	40
Efficacy and safety of ON 01910.Na in myelodysplastic syndrome (MDS) patients with trisomy 8 or classified as intermediate-1, -2 or high risk (NCT00906334)	800 mg/m^2/day by continuous i.v. infusion for 2 days for 3 wks/mo 1800 mg/day by continuous i.v. infusion for 3 days every 2 wks/mo	10	5	Median survival after therapy initiation = 5.4 months (range 2.5-13+ mo)	Grade 3/4 nonhematological toxicities occurred in 4 pts: gastrointestinal (1), dysuria (1), fatigue (1), epistaxis (1)	42
Safety study of ON 01910.Na in combination with irinotecan or oxaliplatin (NCT00861328, NCT00861783)	Oxaliplatin: 85 mg/m^2 infused over 2 hours biweekly; ON-01910.Na: 250-1350 mg/m^2 by continuous i.v.	30	2 (partial response) 6 (stable disease)	Chemo-refractory ovarian cancer (duration 11 wks); metastatic breast cancer (duration 13 wks)	Grade 3+ toxicities included pain (3), lethargy (1), pneumonia (1), hyponatremia (1), anemia (1), transient ischemic attack (1), vomiting (1), urinary tract infection (1), shortness of breath & myocardial infarction (1); no dose-limiting toxicity observed	44[4]
Dose escalation study of gemcitabine (G) and ON 01910.Na (ON) in solid tumors (NCT01125891)	G/ON doses: 750/600; 1000/600, 750/1200, 1000/1200 or 1000/1800 mg/m^2 over 30 minutes (G) or 2 hours (ON) 28-Day cycle G: days 1, 8, 15; ON days 1, 4, 8, 11, 15 and 18	36	13	Based on 16 patients with metastatic pancreatic cancer treated with ON-01910.Na (1200, 1800 mg/m^2) Mean progression-free survival 19 weeks; overall survival 48 weeks	Thrombocytopenia, neutropenia, elevated AST/ALT, nausea, vomiting and fatigue observed with combination therapy, but commonly seen with G therapy One case of dose-limiting toxicity documented (death at day 18 at the 1800 mg/m^2 ON dose)	N/A[5]

[1]Table includes summary of study results that have been published to date; [2]where available, title and study number obtained from ClinicalTrials.gov database (http://clinicaltrials.gov); [3]where indicated, frequency of adverse events is reported in parentheses in terms of number of patients; [4]final study findings listed in the table have not yet been published, but will be presented at the 2011 ASCO Annual Meeting, Chicago, IL, June 4-7, 2011, Abst 80890; [5]these findings will be presented at the 2011 ASCO Annual Meeting, Chicago, IL, June 4-7, 2011, Abst 80933.

namic endpoints include reduction in lymph nodes, levels of circulating lymphoma cells and assessment of extranodal disease sites. Results from this study are not yet available.

Solid tumors

In addition to hematological cancers, ON 01910.Na is also undergoing clinical evaluation in patients with solid tumors, either as a single agent or as combination therapy, at study sites in the U.S. and India. Early phase I studies showed an objective response to the medication in 2 patients with advanced ovarian cancer, who remained progression-free for 9 months (35) and 24 months (33), respectively. A phase II study was initiated to evaluate ON 01910.Na therapy in a larger population of patients with progressive ovarian cancer that is resistant to platinum-based therapy (ClinicalTrials.gov Identifier: NCT00856791). The drug is being administered as a 2-hour infusion (2400 or 3200 mg) twice weekly for 3 weeks of a 28-day cycle. The primary endpoint is progression-free survival. This study is currently closed to enrollment. However, a similar study (4-hour infusion) is ongoing in India.

The synergistic effects that were obtained in in vitro and in vivo preclinical experiments with ON 01910.Na and other chemotherapeutic agents (gemcitabine, irinotecan, oxaliplatin) have prompted phase I evaluation of these combination therapies in humans. Two studies were initiated to study the safety of ON 01910.Na in combination with irinotecan or oxaliplatin in patients with hepatoma and other solid tumors (ClinicalTrials.gov Identifier: NCT00861783 and NCT00861328). The principal goal of these studies is to determine safe and tolerable doses of ON 01910.Na when combined with these other medications. ON 01910.Na is administered by 24-hour i.v. infusion weekly for 6 weeks, starting at a dose of 250 mg/m^2. Irinotecan (180 mg/m^2 over 1.5 hours) or oxaliplatin (85 mg/m^2 over 2 hours) is administered every 2 weeks during this period. Preliminary results have been reported in 13 patients receiving ON 01910.Na/oxaliplatin. Toxicities from the combined therapy were tolerable at the highest ON 01910.Na dose tested (1350 mg/m^2), and a favorable response was observed in a patient with chemotherapy-refractory ovarian cancer (44).

Studies are also under way to evaluate ON 01910.Na in combination with gemcitabine in patients with solid tumors. The goal is to identify the largest safe dose of ON 01910.Na that can be used in this dual therapy. In one study (ClinicalTrials.gov Identifier: NCT01125891) patients receive a fixed dose of gemcitabine (1000 mg/m^2 infused over 0.5 hours) on days 1, 8 and 15 every 28 days. The starting dose of ON 01910.Na 600 mg/m^2 infused over 2 hours on days 1, 4, 8, 11, 15 and 18 of a 28-day course. In another trial (ClinicalTrials.gov Identifier: NCT01165905), ON 01910.Na is administered by continuous infusion over 24 hours at a starting dose of 250 mg/m^2. The results have not been reported.

Each of the clinical studies described above involves ON 01910.Na administration by the i.v. route. In addition, an oral formulation of ON 01910.Na is being investigated. A phase I study to assess the tolerability of orally administered ON 01910.Na in patients with MDS is under way (ClinicalTrials.gov Identifier: NCT01048619). Single and multiple dose escalations and effects of food and bioavailability are being examined. A second proof-of-concept clinical trial has been initiated to evaluate the safety, pharmacokinetics and clinical activity of ON 01910.Na upon oral dosing (capsule formulation) to patients with solid tumors (ClinicalTrials.gov Identifier: NCT01168011). The aim of this phase I study is to determine the highest oral dose of drug that can be safely administered. This is a dose-escalation study, with an initial dose of 70 mg administered twice daily. Outcome measurements include adverse events (MTD determination), plasma exposure of drug (AUC) and tumor response. The findings from these studies have not yet been reported.

DRUG INTERACTIONS

Studies to date have provided limited evidence of drug:drug interactions involving ON 01910.Na. The drug is extensively plasma bound (> 98%) in humans, and in vitro experiments found that ON 01910.Na binding is displaced by medications such as warfarin and aspirin, resulting in favorable cytotoxic activity (28). While competitive binding displacement would be expected to increase free drug concentrations in the plasma, the clinical implication is limited since increasing the unbound fraction of drug in the plasma will result in increased clearance of ON 01910.Na.

There is no evidence of extensive metabolism of ON 01910.Na, thereby minimizing the risk for drug interactions stemming from enzyme induction and inhibition. The potential exists, however, for hepatobiliary transporter-based drug interactions involving ON 01910.Na, and this warrants further investigation.

SOURCE

Onconova Therapeutics, Inc. (US).

DISCLOSURES

A.M. Gillum and M. Maniar are full-time employees of Onconova Therapeutics; D.R. Taft's research activities have been sponsored in part by Onconova Therapeutics, but he has received no financial benefit from this relationship. R. Dave states no conflicts of interest.

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