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Safety, tolerability, pharmacokinetics and preliminary antitumour activity of an antisense oligonucleotide targeting STAT3 (danvatirsen) as monotherapy and in combination with durvalumab in Japanese patients with advanced solid malignancies: a phase 1 study

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ABSTRACT

Objectives We assessed the safety, tolerability, pharmacokinetics, preliminary antitumour activity and pharmacodynamics of danvatirsen, an antisense oligonucleotide targeting signal transducer and activator of transcription 3 (STAT3), monotherapy and danvatirsen plus durvalumab, an antiprogrammed cell death ligand 1 monoclonal antibody, in patients with advanced solid malignancies.

Design Phase 1, open-label study with two cohorts.

Setting Two centres in Japan.

Participants Japanese individuals aged ≥20 years, with histologically confirmed solid malignancies, except for hepatocellular carcinoma, refractory to standard therapy.

Interventions In cohort 1, patients received danvatirsen monotherapy; in cohort 2, patients received danvatirsen plus durvalumab combination therapy.

Primary and secondary outcome measures The primary endpoint was safety and tolerability based on adverse events (AEs). Secondary endpoints were pharmacokinetics, immunogenicity, antitumour activity and pharmacodynamics.

Results Eleven patients were assigned to treatment and included in the analysis. Danvatirsen dose reductions were only required in cohort 2 for hepatic function abnormal (alanine aminotransferase (ALT)/ aspartate aminotransferase (AST)/gamma-glutamyl transferase (γGT) increased), neutrophil count decreased and platelet count decreased. One patient experienced grade 3 ALT/AST increased and new appearance of eosinophilia as a dose-limiting toxicity. AEs were reported in 90.9% (10/11) patients. Commonly reported AEs causally related to the danvatirsen were platelet count decreased (60% (3/5)) and ALT/AST/γGT increased (50% (3/6)) in cohorts 1 and 2, respectively; none was causally related to durvalumab. One serious AE occurred in cohort 1 (pancreatitis; unrelated to study treatment). One case of ALT/AST/γGT increased occurred in cohort 2, leading to discontinuation. No AEs led to death. Danvatirsen did not accumulate in plasma after multiple dosing. In cohort 2, three patients had disease control at 12 weeks and one had unconfirmed partial response. STAT3 expression tended to decrease regardless of monotherapy or combination therapy.

Conclusions Danvatirsen was well tolerated by Japanese patients with advanced solid tumours as monotherapy and combined with durvalumab. No new safety signals arose.

Trial registration number NCT03394144; ClinicalTrials.gov.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is the first to report safety and preliminary efficacy data of combination danvatirsen/durvalumab therapy in Japanese patients.
⇒ Based on previous phase 1 study results in Asians, we excluded patients with hepatocellular carcinoma as we hypothesised that by doing so, we would avoid possible confounding factors and facilitate the detection of drug-related hepatoxicity.
⇒ The sample size was small, which limited the interpretation of the antitumour activity and immunogenicity results.

INTRODUCTION

Signal transducer and activator of transcription 3 (STAT3) signalling is considered a driver of cancer development and progression via the transcriptional expression of target genes involved in cell cycle progression and the regulation of apoptosis.[1 2] STAT3 exerts pleiotropic actions in tumorigenesis and regulation of immune responses against cancer. It regulates the expression of many genes critically involved in the survival of tumour cells and also plays a role in the

function of non-tumour cells of the tumour microenvironment involved in immune evasion, angiogenesis and metastasis.[1] Although many attempts have been made to target STAT3, either by direct inhibition with small-molecule inhibitors[3] or pathway inhibition,[4 5] STAT3 has proven difficult to target.[6]

Danvatirsen (AZD9150) is a potent, 16-nucleotide, generation 2.5 antisense oligonucleotide that selectively targets STAT3 by downregulating STAT3 RNA in various cell types.[7] Danvatirsen enhances antigen-presenting cell function and regulates tumour cell proliferation.[8] Several clinical trials have provided early clinical evidence of the antitumour activity and tolerability of danvatirsen among patients with heavily pretreated lymphoma and lung cancer.[9 10] In a recent phase 1/1b study of danvatirsen monotherapy in Asian patients with hepatocellular carcinoma (HCC), danvatirsen was administered in a dose-escalation scheme starting at 1 mg/kg. Hepatic toxicity (elevation of hepatic transaminases) was the dose-limiting toxicity (DLT), and the maximum tolerated dose (MTD) was 2 mg/kg (unpublished data). DLTs were mainly attributed to the HCC-related hepatic compromise in these patients. Baseline hepatic dysfunction possibly made it difficult to consider the relationship between the observed hepatotoxicity and the safety and tolerability of danvatirsen. No significant differences in danvatirsen pharmacokinetics (PK) were observed between these patients and non-Asian patients in previous studies (unpublished data).

Due to the aggressive nature of malignancies, the aim of danvatirsen treatment is to downregulate phosphorylated STAT3 in tumours relatively quickly. Therefore, an initial loading dose was administered to ensure sufficient tissue accumulation of danvatirsen. Danvatirsen monotherapy at a 3 mg/kg ideal body weight (IBW)-based dose (corresponding to fixed dosing at 200 mg of the starting dose[11]) was tolerable in D5660C00004 (NCT02499328, unpublished data) and ISIS 481464-CS1 trials[10] investigating the safety and tolerability for non-Japanese patients with solid tumours and haematological malignancies. The impact of the IBW-based dose (3 mg/kg) versus fixed dose (200 mg) was evaluated by comparing simulated steady-state parameters using a population PK model. Simulation results demonstrated that IBW-based and fixed dosing regimens yielded similar median steady-state parameters. Therefore, danvatirsen 200 mg weekly is supported by previous trial experience and clinical PK data, except for patients with HCC.

Durvalumab is a fully human monoclonal antibody that inhibits programmed cell death ligand 1 (PD-L1). By binding to the receptors PD-1 and CD80, durvalumab can enhance T-cell recognition and responses against cancer cells.[12] Durvalumab is approved globally for the treatment of locally advanced non-small cell lung cancer following chemoradiation based on data from the PACIFIC trial,[13] and for use in combination with etoposide plus carboplatin or cisplatin as a first-line treatment for extensive-stage small-cell lung cancer based on data from the CASPIAN trial.[14] In addition to these indications, durvalumab has shown clinical antitumour activity in other solid tumours,[13] including breast cancer,[15] and it is currently under extensive study for a broad range of solid tumours and haematological malignancies.[12]

The goal of using both danvatirsen and durvalumab as a complementary antitumour strategy is to impede immune-escape mechanisms in the tumour bed (danvatirsen) while promoting T-cell responses (durvalumab).[9 16] Phase 1b/2 and phase 2 studies for patients with advanced solid malignancies and recurrent or metastatic head and neck squamous cell carcinoma (RM-HNSCC) evaluated the antitumour activity of durvalumab plus danvatirsen may compared with durvalumab monotherapy.[17 18] The phase 1b/2 study reported an objective response rate (ORR) of 26% and the duration of response (DoR) was not reached,[17] whereas the phase 2 study reported an ORR of 16.2% and a DoR of 10.3[18]; both studies were small and had a DoR that was not interpretable or short. Of note, differences in the sample size, patient characteristics and study characteristics preclude direct comparison between studies. To date, the combination of danvatirsen with durvalumab (or any other prior anti-PD-1 and/or PD-L1 therapy) had not been studied in Japanese patients. This study aimed to assess the safety, tolerability, PK, preliminary antitumour activity and pharmacodynamics of danvatirsen monotherapy and danvatirsen in combination with durvalumab in Japanese patients with advanced solid malignancies.

MATERIALS AND METHODS

Study design

This was a phase 1, open-label study conducted between 30 January 2018 and 12 April 2019 at two centres in Japan. Figure 1 shows the study design. In this study, we applied a 3+3 two-cohort dose-escalation scheme in which three to six evaluable patients were enrolled in cohort 1 and six were required for cohort 2. Cohort 1 comprised patients who received danvatirsen monotherapy, and cohort 2 comprised patients who received danvatirsen plus durvalumab combination therapy. A Safety Review Committee (SRC) evaluated the safety and tolerability of danvatirsen monotherapy or in combination with durvalumab during the study. The SRC decided whether to expand cohort 1, proceed to cohort 2 or if it was appropriate to stop study enrollment. The study included a lead-in phase of 7 days, in which loading doses of danvatirsen 200 mg were administered on days −7, −5 and −3. The DLT period consisted of the lead-in phase and cycle 1.

The Institutional Review Board approved the study protocol and related study documents. This study was performed according to the ethical principles stated in the Declaration of Helsinki, which are consistent with the International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements and the sponsor's policy on bioethics. At enrollment, all patients

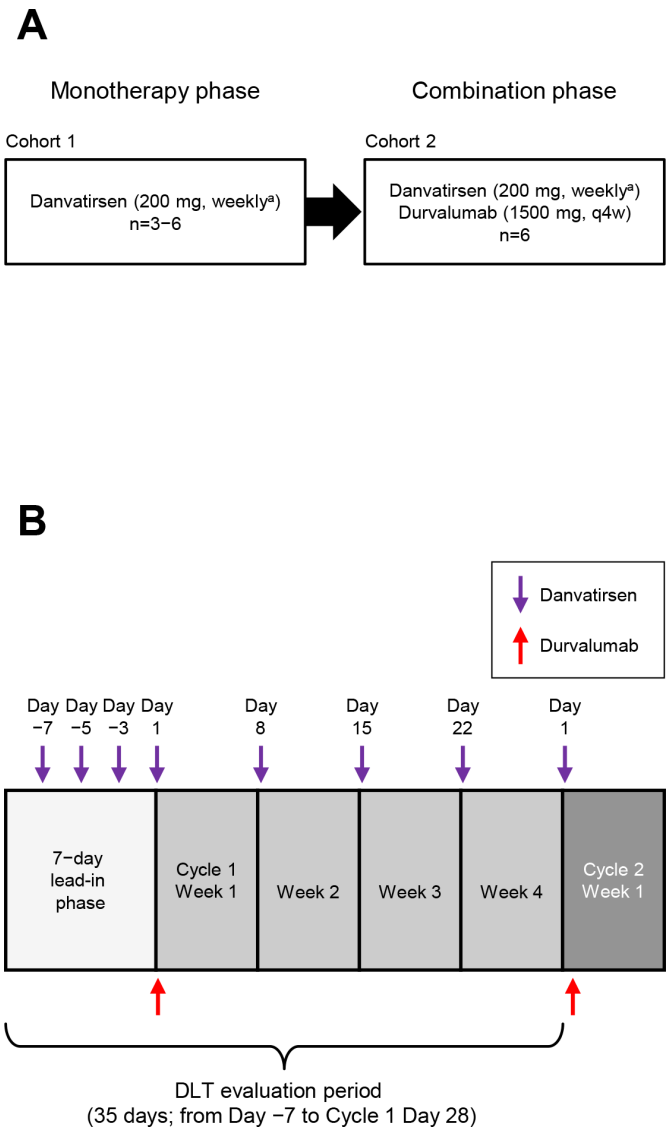

Figure 1 (A) Study design. (B) Dosing schedule. [a]Loading doses on days −7, −5, −3 of cycle 1 day 1. DLT, dose-limiting toxicity; q4w, every 4 weeks.

provided written informed consent to participate in the study. The study was registered at ClinicalTrials.gov.

Treatment

Danvatirsen (cohorts 1 and 2) was administered via weekly 200 mg 1-hour infusions (day 1) in 4-week cycles after the initial 7-day lead-in phase. Durvalumab (cohort 2 only) 1500 mg was infused every 4 weeks after the administration of danvatirsen.

Regarding dose modification criteria for danvatirsen, if a patient experienced a clinically significant and/or unacceptable toxicity (including a DLT related to danvatirsen during the assessment period), drug administration was interrupted or the dose was reduced, and supportive therapy was administered as required. A recovery period of 21 days was allowed given the long half-life of danvatirsen in tissue. If the toxicity resolved or reverted to a lower Common Terminology Criteria for Adverse Events (CTCAE) grade within 21 days of onset and the patient showed clinical benefit, study treatment could be restarted using the following dose modification criteria. For CTCAE grade 3 adverse events (AEs), if the AE reverted to grade 2 within 21 days, the dose level was reduced to 200 mg every 2 weeks. If a second interruption was needed, the dose level was decreased to 150 mg every 2 weeks. If patients started treatment with an abnormal baseline laboratory value, treatment could restart once the laboratory value returned to pretreatment levels. For grade 4 AEs, if the AE reverted to grade 2 within 21 days, the dose level was reduced to 150 mg every 2 weeks. If a second grade 4 AE occurred, or grade 3/4 AEs persisted longer than 21 days, the treatment was permanently discontinued, and the patient was followed up for safety. A maximum of two dose reductions was allowed for an individual patient. If the second dose reduction was not tolerated, study treatment was permanently discontinued, and the patient was followed up for safety. For durvalumab, dose modification was not allowed. Durvalumab administration was scheduled on day 1 of each 4-week cycle.

All medications (including study treatments) were recorded in electronic case report forms. Other medications necessary for the patients' safety and well-being were given at the discretion of the investigator. Patients could continue to receive the study treatment as long as they continued to show clinical benefit (as judged by the investigator) unless the patient had confirmed progressive disease, clinical deterioration and/or no further benefit from treatment, experienced unacceptable toxicity or discontinued for any other reason.

Patients

Eligible participants were male or female Japanese patients, aged ≥20 years, with histologically confirmed solid malignancies (except for HCC) that were refractory to standard therapy or for which no standard of care regimen existed, had a body weight >30 kg, Eastern Cooperative Oncology Group performance status score of 0 or 1, measurable disease, life expectancy >12 weeks, adequate organ and bone marrow function, were women or men willing to use effective contraception before study entry and 20 weeks after study end, and women with childbearing potential who had a negative pregnancy test.

The main exclusion criteria were untreated/unstable central nervous system involvement; any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic, or hormonal therapy for cancer; toxicity related to prior treatment, except for alopecia and anorexia; immune-mediated AEs while receiving prior immunotherapy; immune disease that required systemic treatment for the past 2 years; inflammatory bowel disease; primary immunodeficiency; cardiovascular disease; severe systemic diseases or other severe or uncontrolled comorbidities; ascites or pleural effusion; other malignancies; bowel obstruction; active infections or any other condition that, in the opinion of the investigator, could interfere with patient safety or study evaluations.

Primary endpoints: safety and tolerability

Safety was assessed according to AEs, serious AEs (SAEs), laboratory findings, vital signs and ECG data. Deaths, AEs leading to discontinuation of study treatment, other significant AEs and AEs of special interest were also evaluated. AEs were classified by the Medical Dictionary for Regulatory Activities V.22.0, system organ class (SOC), preferred term (PT) and CTCAE grade.

Tolerability was assessed based on DLTs, which were generally defined as drug-related AEs occurring from the initiation of danvatirsen until the end of cycle 1 and assessed as grade ≥3 according to the National Cancer Institute CTCAE. Exceptions are listed in online supplemental information.

Secondary endpoints

Pharmacokinetics

The measures assessed were the concentration of danvatirsen and non-compartmental pharmacokinetic parameters, such as area under the curve, maximum plasma concentration and concentration at the end of a dosing interval. The same evaluations were done for the danvatirsen plus durvalumab combination therapy. The PK parameters were evaluated following the initial dose (day −7 of the lead-in phase) and following the repeated doses (day 1 of cycle 2). In the loading period, plasma concentrations were not determined after the second and third dose on days −5 and −3, respectively.

Immunogenicity

Immunogenicity was assessed based on the number and percentage of patients who developed detectable antidanvatirsen antibodies and antidurvalumab antibodies. Venous blood samples were collected predose on day 1 of cycle 1, cycle 2 and subsequent even-numbered cycles. Samples were evaluated for the presence of antidanvatirsen using a quantitative ELISA method and for antidurvalumab antibodies using a validated bridging immunoassay (Discovery SECTOR Imager equipped with Discovery Workbench 2006 MSD V.4.0; Meso Scale, Rockville, Maryland).

Antitumour activity

Antitumour activity was assessed based on the ORR, disease control rate and DoR. Tumour responses were evaluated according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1,[19] modified to account for unique responses to immunotherapy that may occur after progressive disease.[20] Tumour assessments were performed at screening, on cycle 1 day 1, every 6 weeks until week 12, and then every 8 weeks until the end of treatment visit.

Pharmacodynamics

Pharmacodynamic response was assessed by STAT3 RNA knockdown in blood. Blood samples (2.5 mL) for the evaluation of STAT3 RNA knockdown (danvatirsen) were collected from patients at screening, day −7 of the lead-in phase, day 1 and day 8 of cycle 1, day 1 of all subsequent cycles, and at the end of treatment visit. RNA expression of STAT3 was measured using the nanoString nCounter system (NanoString Technologies, Seattle, Washington).

Patient and public involvement statement

Neither the patients nor the public were involved in the design, conduct, reporting or dissemination plans of this research.

Statistical analysis

Approximately 12 patients were planned for enrollment: three to six evaluable Japanese patients with advanced solid malignancies were required for cohort 1, and six evaluable patients were required for cohort 2. The total number of patients depended on the available data in each cohort and the decision of the SRC.

The safety analysis set included all patients who received at least one dose of danvatirsen or durvalumab. The efficacy analysis set included all patients with unidimensional measurable disease at baseline as per the RECIST V.1.1 criteria who received at least one dose of study treatment. The PK analysis set included all treated patients with reportable danvatirsen or durvalumab plasma concentrations and no important AEs or protocol deviations that could have impacted PK. The pharmacodynamic analysis set included all patients who provided biological samples for pharmacodynamic research.

No inferential testing was performed on safety data. Safety data were summarised using descriptive statistics. Summary statistics of mean, arithmetic mean (PK), median, SD, minimum, maximum and number of observations were used. Pharmacokinetic, immunogenicity and pharmacodynamic variables were analysed for all patients with available data; missing data were not imputed or carried forward. For the antitumour activity evaluation, if the target lesion measurements were missing, the response was classified as not evaluable. The statistical software used for the analysis was SAS V.9.4 or higher (SAS Institute, Cary, North Carolina). Biostatistics Group, AstraZeneca conducted statistical analysis.

RESULTS

Patient disposition and characteristics

Of the 12 patients enrolled, 11 (cohort 1, five patients; cohort 2, six patients) were assigned to receive the study treatment (figure 2). One patient was not assigned to receive the study treatment because of screening failure. Study treatment was discontinued due to disease progression for five (100%) patients in cohort 1 and five (83.3%) patients in cohort 2. In cohort 2, one (16.7%) patient discontinued study treatment due to a grade 3 AE of hepatic function abnormal (alanine aminotransferase (ALT)/aspartate aminotransferase (AST)). Five patients in cohort 1 and six patients in cohort 2 were included in the safety, PK, immunogenicity, antitumour activity and pharmacodynamics analysis sets.

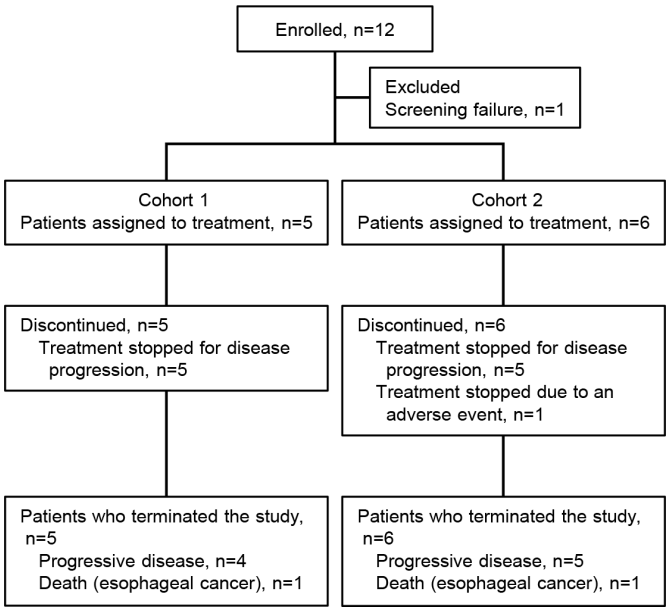

Figure 2 Patient disposition.

Regarding the demographic and clinical characteristics at baseline (table 1), more male than female patients were enrolled in both cohorts. Patients had a median age of 68 years (41–77), a median body weight of 64.3 kg (44.5–91.6) and a median body mass index of 25.7 kg/m^2 in cohort 1 and 22.3 kg/m^2 in cohort 2. The most commonly reported tumour locations were the colon (two (40%) patients in cohort 1; one (16.7%) patient in cohort 2) and oesophagus (two (40%) patients in cohort 1; three (50%) patients in cohort 2). All oesophageal tumours were squamous cell carcinomas. Body weight, age and body mass index were comparable between cohorts, but disease characteristics were less evenly distributed between cohorts regarding tumour grades.

Study endpoints

Safety and tolerability

There were no dose reductions for danvatirsen in cohort 1. In cohort 2, dose reductions of danvatirsen were reported for three (50%) patients: one patient (16.7%) with grade 3 hepatic function abnormal (ALT/AST/gamma-glutamyl transferase (γGT) increased), one patient (16.7%) with grade 3 neutrophil count decreased, and one patient (16.7%) with grade 3 platelet count decreased. The relative dose intensity (RDI) of danvatirsen in cohort 1 was 100%, and that in cohort 2 was 91%. As there were no dose interruptions, reductions or modifications for durvalumab in cohort 2, the RDI of durvalumab was 100%. Regarding tolerability, a single DLT was reported for one (16.7%) patient in cohort 2 with a grade 3 hepatic function abnormal event (ALT/AST/γGT increased) and new appearance of eosinophilia (>5%), indicating danvatirsen monotherapy with fixed dosing and its combination with durvalumab were tolerable in this Japanese population.

A total of 18 AEs were reported for four (80%) patients in cohort 1, and 28 AEs were reported for six (100%) patients in cohort 2 (online supplemental table 1). Six AEs considered to be causally related to study treatment were reported for three (60%) patients in cohort 1, and 19 AEs considered causally related to study treatment were reported for six (100%) patients in cohort 2. At least one AE of CTCAE grade ≥3 was reported for three (60%) patients in cohort 1 and six (100%) patients in cohort 2.

One SAE of pancreatitis, considered unrelated to study treatment, was reported for one (20%) patient in cohort 1, and one grade 3 AE (hepatic function abnormal (ALT/AST/γGT increased)) leading to discontinuation was reported for one (16.7%) patient in cohort 2. No AEs leading to death or other significant AEs were reported. One patient died in each cohort, and the cause of death in both cases was disease progression.

By SOC, the most commonly reported AEs in cohort 1 were investigations (four (80%) patients) and in cohort 2, investigations and general disorders and administration site conditions (four (66.7%) patients, each). By PT, the most commonly reported AE was platelet count decreased for three (60%) patients in cohort 1 and hepatic function abnormal (ALT/AST/γGT increased) for three (50%) patients in cohort 2.

Table 2 summarises the most common grade ≥3 AEs. The most common SOC (CTCAE grade ≥3) was metabolism and nutrition disorders for cohort 1 and investigations for cohort 2. More patients in cohort 2 reported CTCAE grade ≥3 AEs than in cohort 1. No significant safety abnormalities were reported concerning grade 3 laboratory shifts, ECGs and vital signs.

Pharmacokinetics

After a single intravenous infusion at 200 mg over 1 hour on day −7 of the lead-in phase, plasma concentrations of danvatirsen in cohort 1 and cohort 2 declined in a bi-phasic fashion, with a fast distribution phase and a slow elimination phase (online supplemental figure 1A). The geometric mean plasma concentration of danvatirsen (cohort 1) declined rapidly after the end of the infusion, similarly to the single-dose pharmacokinetic profile determined in the lead-in phase on day −7 (online supplemental figure 1B), suggesting no accumulation of danvatirsen in plasma after administration of multiple doses. The geometric mean plasma concentrations of danvatirsen were slightly lower for cycle 2, day 1 than those of the lead-in period (online supplemental figure 1C). We compared the pharmacokinetic parameters of danvatirsen between cohorts 1 and 2 (online supplemental table 2). Individual values in cohort 1 were within the range of corresponding values in cohort 2, suggesting no remarkable drug interaction between danvatirsen and durvalumab.

Immunogenicity

Out of 23 samples, four were identified as potentially positive at the screening assay, two of which were confirmed positive for antibodies to danvatirsen. Of note, the two positive samples were from the same

Table 1 Baseline patient characteristics and demographics

	Danvatirsen monotherapy (cohort 1) N=5	Danvatirsen+durvalumab (cohort 2) N=6	Total N=11
Sex			
Male	4 (80.0)	4 (66.7)	8 (72.7)
Age, median (range), years	68.0 (41–73)	67.0 (63–77)	68.0 (41–77)
Weight, median (range), kg	64.8 (61.4–91.6)	63.9 (44.5–71.1)	64.3 (44.5–91.6)
Body mass index, median (range), kg/m^2	25.7 (21.9–34.7)	22.3 (19.5–28.1)	22.7 (19.5–34.7)
ECOG PS			
0	3 (60.0)	5 (83.3)	8 (72.7)
1	2 (40.0)	1 (16.7)	3 (27.3)
Primary tumour location			
Oesophagus	2 (40.0)	3 (50.0)	5 (45.3)
Colon	2 (40.0)	1 (16.7)	3 (27.3)
Rectum	1 (20.0)	0	1 (9.1)
Uterine corpus	0	1 (16.7)	1 (9.1)
Unknown	0	1 (16.7)	1 (9.1)
Tumour grade			
Well-differentiated	1 (20.0)	1 (16.7)	2 (18.2)
Moderately differentiated	3 (60.0)	2 (33.3)	5 (45.5)
Poorly differentiated	0	1 (16.7)	1 (9.1)
Not assessable	0	2 (33.3)	2 (18.2)
High grade	1 (20.0)	0	1 (9.1)
Histology type			
Squamous cell carcinoma of the oesophagus	2 (40.0)	3 (50.0)	5 (45.5)
Tubular adenocarcinoma of the colon	2 (40.0)	1 (16.7)	3 (27.3)
Adenocarcinoma*	1 (20.0)	1 (16.7)	2 (18.2)
Endometrioid adenocarcinoma	0	1 (16.7)	1 (9.1)
Overall disease classification†			
Metastatic	5 (100.0)	6 (100.0)	11 (100.0)
Locally advanced	1 (20.0)	1 (16.7)	2 (18.2)
No evidence of disease	0	0	0
Missing	0	0	0

Data are n (%).
*One case of adenocarcinoma of the rectum in cohort 1 and one case of adenocarcinoma located in 'other' in cohort 2.
†Classifications were not mutually exclusive.
ECOG PS, Eastern Cooperative Oncology Group Performance Status.

patient in cohort 2. There was an eightfold titre increase from day 1 of cycle 4 (titre: 100) to day 1 of cycle 6 (titre: 800). This patient did not have any SAEs but did present a grade 3 AE of platelet count decreased. Predose plasma concentrations of danvatirsen in this patient were 37.7, 46.2, 41.1 and 80.4 ng/mL on day 1 of cycles 1, 2, 3 and 5, respectively. The best objective response of this patient was stable disease for ≥6 weeks. All 17 samples assessed for antibodies to durvalumab were negative.

Antitumour activity

Efficacy parameters are summarised in online supplemental table 3. No confirmed complete response (CR) or partial response (PR) was recorded during the study. No patient achieved an objective response, and three (50%) patients in cohort 2 had disease control at 12 weeks.

In cohort 2, PR was observed in one patient and stable disease for ≥6 weeks was reported for five (83.3%) patients. Progression was reported for five (100%) patients in cohort 1. Of these, four (80%) patients had RECIST progression, and one (20%) patient died of disease progression.

A patient in cohort 2 presented with a 49.1% reduction from baseline in target lesion size (hepatic metastasis), which was assessed as unconfirmed PR (figure 3). This patient had oesophageal carcinoma and metastatic lesions to hepatic lymph and gall bladder lymph nodes. The patient died during

Table 2 Incidence of grade ≥3 AEs

System organ class MedDRA preferred term	Danvatirsen monotherapy (cohort 1) N=5	Danvatirsen+durvalumab (cohort 2) N=6
Patients with any AE	3 (60.0)	6 (100.0)
Metabolism and nutrition disorders	2 (40.0)	1 (16.7)
Hypermagnesaemia	1 (20.0)	0
Hypertriglyceridaemia	0	1 (16.7)
Hypokalaemia	1 (20.0)	0
Gastrointestinal disorders	1 (20.0)	0
Pancreatitis	1 (20.0)	0
Hepatobiliary disorders	0	2 (33.3)
Hepatic function abnormal (ALT/AST/γGT increased)	0	2 (33.3)
Investigations	1 (20.0)	3 (50.0)
Neutrophil count decreased	0	2 (33.3)
ALT increased	1 (20.0)	0
AST increased	1 (20.0)	0
Blood bilirubin increased	1 (20.0)	0
γGT increased	1 (20.0)	1 (16.7)
Platelet count decreased	0	1 (16.7)

Data are n (%).
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, gamma-glutamyl transferase.

the study follow-up period from disease progression (liver and distant lymph nodes). In cohort 2 (n=5), the median per cent change from baseline at 12 weeks in target lesion size was 17.59 (min: −40.4%, max: 90.0%).

Pharmacodynamics

The mean (SD) for percent change from baseline of STAT3 at day 1 of cycle 2, when steady-state drug concentrations were achieved, was −25.14 (10.6) for cohort 1 (only two of five patients in cohort 1 were on treatment long enough to measure STAT3 levels at day 1 of cycle 2), and −31.1 (8.8) for cohort 2 (online supplemental figure 2).

An overall trend in decreased STAT3 expression was consistently observed, regardless of whether patients received danvatirsen alone or in combination with durvalumab. Reduced STAT3 expression by danvatirsen was observed on day 1 of cycle 1 and the effect continued through the administration period.

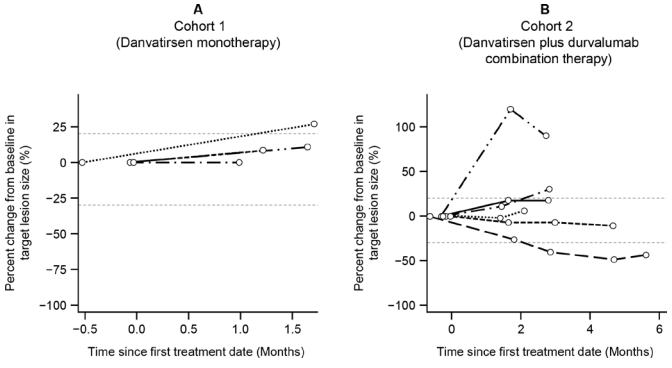

Figure 3 Percent change in target lesion size in treated patients. (A) Cohort 1 (danvatirsen monotherapy). (B) Cohort 2 (danvatirsen plus durvalumab combination therapy).

DISCUSSION

This is the first study to assess the safety, antitumour activity, PK and pharmacodynamics of danvatirsen monotherapy administered at a fixed dose, and of danvatirsen in combination with durvalumab in Japanese patients with advanced solid tumours. Danvatirsen monotherapy and danvatirsen plus durvalumab combination therapy were well tolerated by this study population. No new AEs for danvatirsen or durvalumab were detected. The combination was found to be safe for Japanese patients, which is consistent with findings reported in a phase 1b/2 study of patients with RM-HNSCC.[17] A phase 1/1b study of Asian/Japanese patients with HCC, in which danvatirsen was administered in per-body weight dosing via a 3-hour infusion, reported that the MTD of danvatirsen was 2 mg/kg dose (unpublished data). Of note, patients in the present study received danvatirsen via a 1-hour infusion and had an MTD of 200 mg (ie, corresponding to a 3 mg/kg dose). Furthermore, based on the previous phase 1/1b study results, we hypothesised that by excluding patients with HCC from the present study, we would remove confounding factors to evaluate study drug-related hepatotoxicity. Although hepatotoxicity was a DLT in this phase 1 study, patients had a lower frequency of hepatotoxicity compared with patients with HCC in the previous study. The difference in toxicity was attributed to the already compromised hepatic function of patients

with HCC in the previous study (unpublished data). As the safety and tolerability of the danvatirsen 200 mg fixed dose were confirmed, we infer that fixed dosing does not impact safety.

The most common AEs possibly related to danvatirsen were platelet count decreased in cohort 1 and hepatic function abnormal, defined as ALT/AST/γGT increased, in cohort 2. Other danvatirsen studies have also reported reductions in platelet counts and elevated transaminases.[9 10 17] Although a few other antisense oligonucleotides have also been associated with thrombocytopenia,[21–23] the thrombocytopenia caused by danvatirsen treatment is considered to be associated with the on-target inhibition of STAT3, as a similar effect is observed with Janus kinase inhibitors.[24] Of note, these AEs were reversible when managed with dose interruptions and discontinuations as reported in a phase 1b/2 study of danvatirsen combined with durvalumab for advanced solid malignancies and recurrent metastatic HNSCC.[17]

Danvatirsen plasma concentrations declined in a biphasic manner, with a fast distribution phase and slow elimination phase. After multiple dosing of danvatirsen, there was no accumulation in plasma. No remarkable drug interactions were noted between danvatirsen (antisense oligonucleotide) and durvalumab (monoclonal antibody), likely because these drugs have different elimination routes. It should be noted that a population PK analysis of danvatirsen supporting flat dosing switch reported that race was not a significant covariate on the PK of danvatirsen.[11]

One patient developed antidanvatirsen antibodies. Of note, this patient's predose plasma concentrations of danvatirsen on day 1 of cycles 1, 2, 3 and 5 were higher than the overall geometric means in cohort 1. Although this patient presented with a grade 3 decrease in platelet count, no SAEs were reported. Thus, the presence of antidanvatirsen antibody did not seem to affect the patient's safety and PK.

In the present study, no cases of confirmed CR or PR were reported. At 12 weeks, none of the patients in cohort 1 achieved disease control, while three patients in cohort 2 did achieve disease control. A patient in cohort 2 with advanced oesophageal carcinoma and metastatic tumours in the liver and distant lymph nodes had an unconfirmed PR, presented the maximum decrease (over 49% reduction) in target lesion (hepatic metastasis) size from baseline and had a DoR of approximately 6 weeks. The patient died during study follow-up owing to disease progression. These findings indicate that while STAT3 inhibition was sustained in this patient (data not shown), the antitumour activity was not.

STAT3 knockdown by danvatirsen was observed regardless of whether patients received danvatirsen monotherapy or in combination with durvalumab. The reduction of STAT3 expression by danvatirsen was observed from day 1 of cycle 1, and the effect was maintained during the administration period in some cases. This finding implies that the sustained downregulation of STAT3 may augment the antitumour activity of durvalumab via modulation of immune suppressive mechanisms in the tumour microenvironment. However, as none of the patients achieved disease control, either the STAT3 knockdown was insufficient or other immunosuppressive mechanisms interfered with the sustained effect of danvatirsen and prevented efficacy.

Although we have not explored specific resistance mechanisms that could make danvatirsen ineffective, many immunosuppressive mechanisms have been reported in the literature.[25] Possible resistance mechanisms to consider are cancer cell–intrinsic biology, the phenotype of the tumour microenvironment, and the biology of the patient,[25] which may act independently or be inter-related in a complex manner, causing drug resistance. Further research is needed to identify the mechanism of therapeutic resistance[25] to STAT3 inhibition.

The main limitation of this study was that the patient sample was small, which may affect the interpretation of the results. Additionally, patients had different types of solid tumours and were heavily pretreated. Finally, we did not evaluate progression-free survival in this study and could not further evaluate treatment efficacy in the patient who presented unconfirmed PR.

CONCLUSIONS

Danvatirsen was well tolerated by Japanese patients with advanced solid tumours both as monotherapy and in combination with durvalumab. No new safety signals were raised for danvatirsen or durvalumab. The combination treatment with durvalumab did not result in relevant interactions nor did it largely affect the PK of danvatirsen. Antibodies to danvatirsen were only detected in one patient, but definitive conclusions cannot be drawn given the small sample size. Although there was no clinical benefit in patients receiving danvatirsen monotherapy, some benefit was observed in one patient receiving danvatirsen in combination with durvalumab. STAT3 knockdown was confirmed in this patient, consistent with a potential contribution of danvatirsen to the patient's clinical response. The combination of danvatirsen and durvalumab was tolerable. Inhibition of STAT3 in combination with inhibition of PD-L1 may be a complementary antitumour strategy.

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