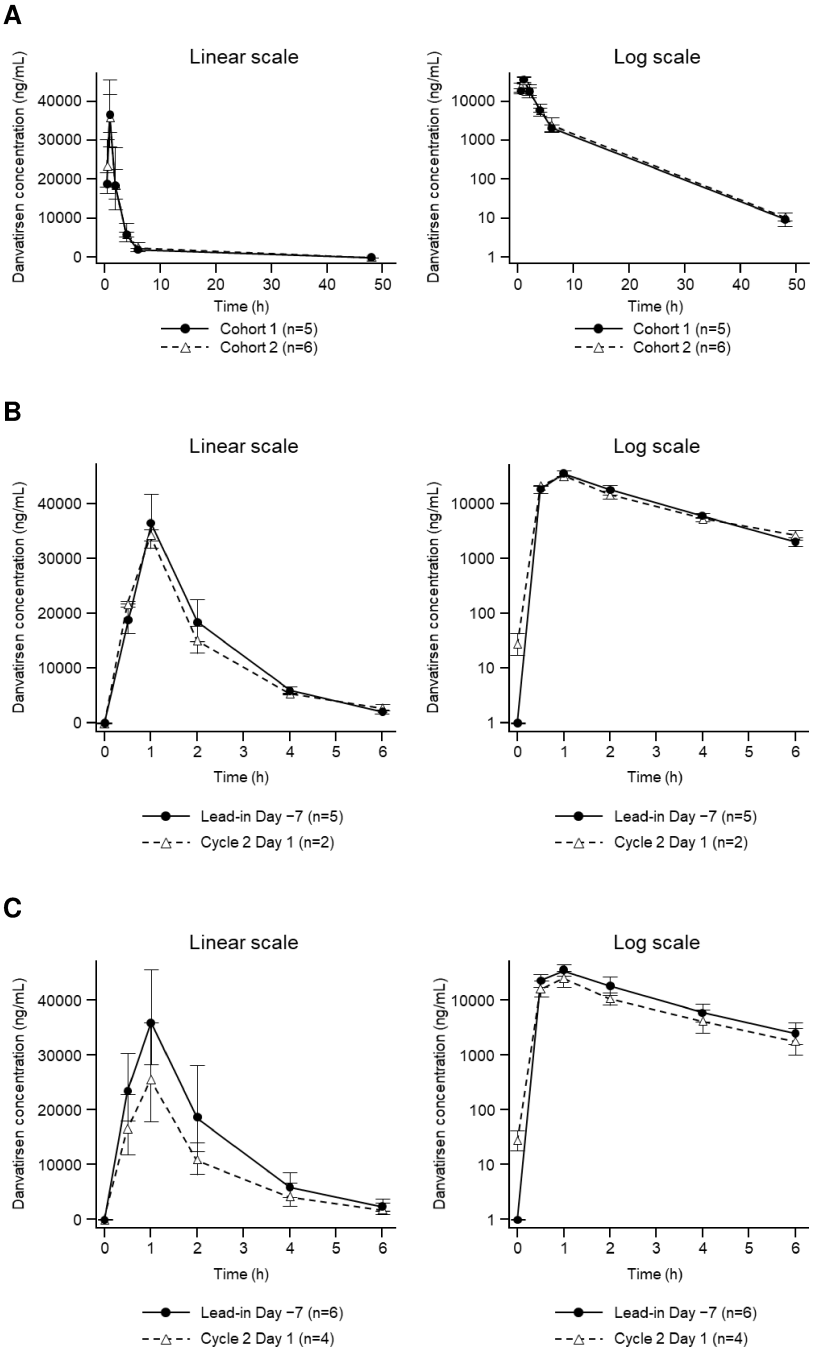
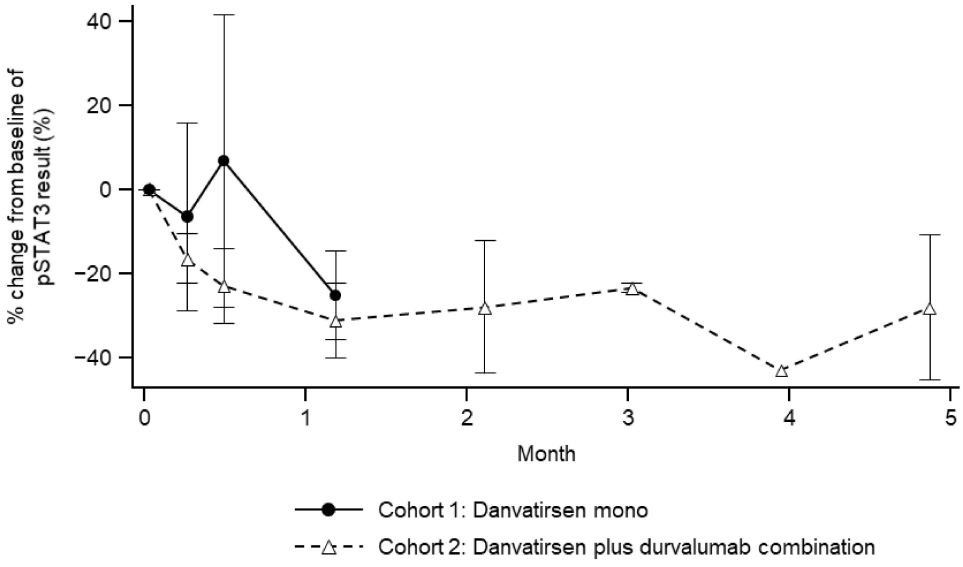
Supplementary materials

Supplementary Figure 1. Geometric mean (±standard deviation) plasma concentrations (ng/mL) of danvatirsen versus time (pharmacokinetic analysis set). (A) In lead-in phase, Day −7 of Cohort 1 and Cohort 2. (B) In lead-in phase, Day −7 and Cycle 2, Day 1 of Cohort 1. (C) In lead-in phase, Day −7 and Cycle 2, Day 1 of Cohort 2.



Supplementary Figure 2. Pharmacodynamics of danvatirsen (% change from baseline of STAT3) by treatment cycle (pharmacodynamics analysis set)



Supplementary Table 1. Incidence of adverse events overall and by system organ class and preferred term

	Danvatirsen monotherapy (Cohort 1) N=5	**Danvatirsen plus durvalumab (Cohort 2) N=6**
AE category	Number of patients[a] (%)	
Any AE	4 (80.0)	6 (100.0)
AE causally related to treatment[b]	3 (60.0)	6 (100.0)
AE causally related to danvatirsen only[b]	3 (60.0)	5 (83.3)
AE causally related to durvalumab only[b]	NA	0
AE causally related to danvatirsen and durvalumab[b]	NA	2 (33.3)
AE of CTCAE Grade ≥3	3 (60.0)	6 (100.0)
AE of CTCAE Grade ≥3, causally related to treatment[b]	0	5 (83.3)
AE of CTCAE Grade ≥3, causally related to danvatirsen only[b]	0	5 (83.3)
AE of CTCAE Grade ≥3, causally related to durvalumab only[b]	NA	0
AE of CTCAE Grade ≥3, causally related to danvatirsen and durvalumab[b]	NA	0
AE with outcome = death	0	0
AE with outcome = death, causally related to treatment[b]	0	0
SAE (including events with outcome = death)	1 (20.0)	0
SAE (including events with outcome = death), causally related to treatment[b]	0	0
SAE causing discontinuation of danvatirsen	0	0
SAE causing discontinuation of danvatirsen, causally related to treatment[b]	0	0
AE leading to discontinuation of danvatirsen	0	1 (16.7)
AE leading to dose modification of danvatirsen	1 (20.0)	4 (66.7)
AE leading to dose reduction of danvatirsen	0	3 (50.0)
AE leading to dose interruption of danvatirsen	1 (20.0)	1 (16.7)
Other significant AEs[c]	0	0

System organ class / Preferred term		
Hepatobiliary disorders	0	3 (50.0)
Hepatic function abnormal	0	3 (50.0)
General disorders and administration site conditions	1 (20.0)	4 (66.7)
Malaise	1 (20.0)	2 (33.3)
Pyrexia	1 (20.0)	1 (16.7)
Fatigue	0	1 (16.7)
Investigations	4 (80.0)	4 (66.7)
Platelet count decreased	3 (60.0)	2 (33.3)
Gamma-glutamyltransferase increased	1 (20.0)	2 (33.3)
Neutrophil count decreased	0	2 (33.3)
Alanine aminotransferase increased	1 (20.0)	1 (16.7)
Aspartate aminotransferase increased	1 (20.0)	1 (16.7)
Blood bilirubin increased	1 (20.0)	0
Blood lactate dehydrogenase increased	0	1 (16.7)
Weight increased	1 (20.0)	0
Blood alkaline phosphatase increased	0	1 (16.7)

[a]Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

[b]As assessed by the Investigator, and derived from individual causality assessments for combination studies.

[c]Significant AEs, other than SAEs and those AEs leading to discontinuation of the study.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; SAE, serious adverse event

Supplementary Table 2. Summary of danvatirsen pharmacokinetic parameters after a single and multiple intravenous infusions in Cohorts 1 and 2

		Danvatirsen monotherapy (Cohort 1) N=5	Danvatirsen plus durvalumab (Cohort 2) N=6
Single intravenous infusion of danvatirsen 200 mg over 1 hour on Day −7 of the lead-in period			
C_{max}, ng/mL	Geometric mean (CV%)	36570 (13.28)	35960 (24.18)
t_{max}, h	Median (range)	1.00 (0.97–1.08)	0.985 (0.95–1.05)
$AUC_{(0-6)}$, ng·h/mL	Geometric mean (CV%)	73930 (7.92)	77270 (31.75)
$AUC_{(0-48)}$, ng·h/mL	Geometric mean (CV%)	90110 (8.179)	95940 (32.8)
$AUC_{(0-t)}$, ng·h/mL	Geometric mean (CV%)	90120 (8.201)	95930 (32.8)
$AUC_{(0-\infty)}$, ng·h/mL	Geometric mean (CV%)	90190 (8.189)	96010 (32.78)
CL, L/h	Mean (SD)	2.223 (0.1798)	2.176 (0.7228)
V_z, L	Mean (SD)	16.27 (1.199)	15.76 (5.885)
MRT, h	Mean (SD)	3.604 (0.4443)	3.705 (0.2352)
Once weekly intravenous infusion at danvatirsen 200 mg over 1 hour on Cycle 2 Day 1			
$C_{ss\ max}$, ng/mL	Geometric mean (range)	34470 (33700–35200)	34470 (18400–36900)
$t_{ss\ max}$, h	Median (range)	1.05 (1.03–1.07)	1.00 (0.95–1.05)
$AUC_{(0-6)}$, ng·h/mL	Geometric mean (range)	69850 (67100–72700)	51090 (37100–74900)
$AUC_{(0-t)}$, ng·h/mL	Geometric mean (range)	69900 (67300–72600)	50830 (37000–74100)
C_{trough}, ng/mL	Geometric mean (range)	28.02 (20.4–38.5)	27.92 (18.1–46.2)
R_{AC}	Mean (range)	0.941 (0.887–0.995)	0.7402 (0.582– 0.947)

AUC, area under the plasma concentration-time curve; $AUC_{(0-6)}$, AUC from zero to 6 hours; $AUC_{(0-48)}$, AUC from zero to 48 hours; $AUC_{(0-6)}$, AUC from zero to 6 hours; $AUC_{(0-t)}$, AUC from zero to the time of the last measurable concentration; $AUC_{(0-\infty)}$, AUC from zero to infinity; CL, plasma clearance; C_{max}, maximum plasma concentration; $C_{ss\ max}$, maximum plasma concentration at steady state; CV, coefficient of variation; max, maximum; min, minimum; MRT, mean residence time; R_{AC}, extent of accumulation on multiple dosing; SD, standard deviation; t_{max}, time to maximum plasma concentration; $t_{ss\ max}$, time to maximum plasma concentration at steady state; Vz, volume of distributionrs

Supplementary Table 3. Summary of antitumor activity results

		Danvatirsen monotherapy (Cohort 1) N=5	Danvatirsen plus durvalumab (Cohort 2) N=6
Best objective response			
Response	Total	0	0
	Complete response[a]	0	0
	Partial response[a]	0	0
Non-response	Total	5 (100.0)	6 (100.0)
	Stable disease ≥6 weeks	0	5 (83.3)
	Progression	5 (100.0)	1 (16.7)
	RECIST progression	4 (80.0)	1 (16.7)
	Death	1 (20.0)	0
	Not evaluable	0	0
Disease control rate			
Disease control at 12 weeks[b]	Yes	0	3 (50.0)
	No	5 (100.0)	3 (50.0)

[a] Response required confirmation.

[b] Disease control = confirmed complete response + confirmed partial response + stable disease at or after 12 weeks.

RECIST, Response Evaluation Criteria in Solid Tumors

Supplementary information

Dose-limiting toxicity (DLT) was defined as any ≥Grade 3 adverse event per the National Cancer Institute Common Terminology Criteria for Adverse Events, with the following exceptions:

- Increase in transaminase level (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) was considered a DLT if:
    - AST and/or ALT increased to >15× the upper limit of normal [ULN] at any time;
    - AST and/or ALT increased to >10× to 15×ULN over 14 consecutive days; and/or
    - AST and/or ALT increased to >5×ULN, and one or more of the following conditions was met and not explained by other causes:
        1. Total bilirubin increased to >2×ULN
        2. New appearance of eosinophilia (>5%)
        3. Clinical signs of functional liver impairment
- Nausea, vomiting, and diarrhea were considered DLTs only if assessed as ≥Grade 3 after optimal prophylactic or treatment measures have been prescribed.
- Fatigue was not considered a DLT.
- Neutropenia was considered a DLT only in the case of:
    - Grade 3 febrile neutropenia (i.e., absolute neutrophil count [ANC] <1,000/mm^3) with a single temperature reading of >38.3ºC or a sustained temperature of ≥38ºC for more than 1 hour);
    - Grade 4 febrile neutropenia (i.e., ANC <1,000/mm^3) with life-threatening consequences indicating urgent intervention;
    - ≥Grade 3 (i.e., ANC <1,000/mm^3) associated with an infection that was clinically severe, associated with sepsis, or requiring hospitalization. Grade 3 non-febrile

neutropenia with clinically minor infection (as judged by the investigator) was not considered a DLT; or

- Grade 4 (i.e., ANC <500/mm^3) sustained for more than 5 days.

- Thrombocytopenia was considered a DLT only in the case of:
  - ≥Grade 3 thrombocytopenia (i.e., platelet count <50,000/mm^3) associated with bleeding; or
  - Grade 4 thrombocytopenia (i.e., platelet count <25,000/mm^3).
- Any toxicity judged by the Investigator to be drug that required study treatment to be interrupted for more than 10 consecutive days was considered a DLT.
- Any other Grade 3 or Grade 4 laboratory evaluations that were asymptomatic but assessed by the Investigator as clinically significant were considered DLTs.