The Oncologist®

Clinical Trial Results

Safety, Pharmacokinetics, Pharmacodynamics, and Antitumor Activity of Necuparanib Combined with Nab-Paclitaxel and Gemcitabine in Patients with Metastatic Pancreatic Cancer: Phase I Results

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT01621243
- **Sponsor(s)**: Momenta Pharmaceuticals
- **Principal Investigator**: Eileen M. O'Reilly
- **IRB Approved**: Yes

Lessons Learned

- Despite the compelling preclinical rationale of evaluating the genetically engineered heparin derivative, necuparanib, combined with standard therapy in metastatic pancreas adenocarcinoma, the results were ultimately disappointing.
- Safety was documented, although dose escalation was limited by the number of subcutaneous injections, the potential for skin toxicity (cellulitis), and low-level anticoagulant effect. Nonetheless, the hypothesis of targeting prothrombotic pathways in pancreas adenocarcinoma remains compelling.

Abstract

Background. Necuparanib is derived from unfractionated heparin and engineered for reduced anticoagulant activity while preserving known heparin-associated antitumor properties. This trial assessed the safety, pharmacokinetics (PK), pharmacodynamics, and initial efficacy of necuparanib combined with gemcitabine ± nab-paclitaxel in patients with metastatic pancreatic cancer.

Methods. Patients received escalating daily subcutaneous doses of necuparanib plus 1,000 mg/m^2 gemcitabine (days 1, 8, 15, and every 28 days). The protocol was amended to include 125 mg/m^2 nab-paclitaxel after two cohorts (following release of the phase III MPACT data). The necuparanib starting dose was 0.5 mg/kg, with escalation via a modified 3 + 3 design until the maximum tolerated dose (MTD) was determined.

Results. Thirty-nine patients were enrolled into seven cohorts (necuparanib 0.5, 1 mg/kg + gemcitabine; necuparanib 1, 2, 4, 6, and 5 mg/kg + nab-paclitaxel + gemcitabine). The most common adverse events were anemia (56%), fatigue (51%), neutropenia (51%), leukopenia (41%), and thrombocytopenia (41%). No deaths and two serious adverse events were potentially related to necuparanib. Measurable levels of necuparanib were seen starting at the 2 mg/kg dose. Of 24 patients who received at least one dose of necuparanib + nab-paclitaxel + gemcitabine, 9 (38%) achieved a partial response and 6 (25%) achieved stable disease (63% disease control rate). Given a cellulitis event and mild activated partial thromboplastin time increases at 6 mg/kg, the 5 mg/kg dose was considered the MTD and selected for further assessment in phase II.

Conclusion. Acceptable safety and encouraging signals of activity in patients with metastatic pancreatic cancer receiving necuparanib, nab-paclitaxel, and gemcitabine were demonstrated.

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Discussion

Heparins are present as cell surface glycosaminoglycans and have crucial regulatory roles in normal physiological processes and pathophysiological conditions, including tumor onset, proliferation, and metastasis [1–4]. Possible antitumor effects of heparin include prevention of metastasis via inhibition of heparanase and interaction with P-selectin [5–14]. Heparin administration is limited by its anticoagulant effects. Necuparanib is a noncytotoxic, glycol-split, heparan sulfate mimetic intended to treat advanced malignancies. Necuparanib is rationally engineered from heparin through a process that reduces anticoagulant activity while preserving activity against a number

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Efficacy outcomes

Efficacy variable	Necuparanib + gemcitabine		Necuparanib + nab-paclitaxel + gemcitabine	
	Completed ≥1 dose ($n = 11$)	Completed ≥1 cycle ($n = 10$)	Completed ≥1 dose ($n = 24$)	Completed ≥1 cycle ($n = 16$)
OS (month) median (95% CI)	10.4 (6.1–21.8)	10.2 (3.4–21.0)	13.1 (4.0–16.6)	15.6 (9.3–17.8)
Survival rate (95% CI)				
6 months	91 (51–99)	90 (47–99)	71 (48–85)	94 (63–99)
12 months	45 (17–71)	40 (12–67)	54 (31–71)	69 (40–86)
18 months	36 (11–63)	30 (7–58)	21 (8–39)	25 (8–47)
24 months	18 (3–44)	10 (1–36)	21 (8–39)	25 (8–47)
Progression-free survival (month) median (95% CI)	7.5 (1.9–12.5)	6.5 (1.6–10.4)	5.9 (2.1–8.7)	7.9 (3.4–11.4)
RECIST best response, unconfirmed or confirmed, (%)				
Complete response	0	0	0	0
Partial response	1 (9)	1 (10)	9 (38)	9 (56)
Stable disease	6 (55)	6 (60)	6 (25)	5 (31)
Progressive disease	3 (27)	3 (30)	2 (8)	2 (13)
Not evaluable	1 (9)	0	7 (29)	0
Disease control rate	7 (64)	7 (70)	15 (63)	14 (88)

Dose-limiting toxicities

Dose level	Dose of drug: necuparanib	Dose of drug: nab-paclitaxel	Dose of drug: gemcitabine	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity	Dose-limiting toxicity information
1	0.5 mg/kg		1,000 mg/m^2	8	8	1	Elevated liver function tests
2	1.0 mg/kg		1,000 mg/m^2	4	4	0	
3	1.0 mg/kg	125 mg/m^2	1,000 mg/m^2	4	4	0	
4	2.0 mg/kg	125 mg/m^2	1,000 mg/m^2	5	5	0	
5	4.0 mg/kg	125 mg/m^2	1,000 mg/m^2	4	4	0	
6	6 mg/kg	125 mg/m^2	1,000 mg/m^2	4	4	1	Cellulitis at injection site; 3 injections required; grade 1–2 aPTT prolongation
7	5 mg/kg	125 mg/m^2	1,000 mg/m^2	10	10	10	

of heparin-binding proteins involved in tumor progression and metastasis. [15–17]

This is the first clinical evaluation of necuparanib, a novel therapeutic agent, which was conducted in patients with metastatic pancreatic adenocarcinoma. Necuparanib in combination with nab-paclitaxel and gemcitabine demonstrated acceptable tolerability. No clear dose-proportional trends in individual adverse events (AEs) were observed. The most common AEs had comparable rates, when necuparanib was administered with gemcitabine with or without nab-paclitaxel, to what would be expected with chemotherapy alone. The grade 3/4 hematological toxicities observed in this study in the necuparanib + nab-paclitaxel and gemcitabine cohort were similar to those observed in the Von Hoff phase III MPACT trial (neutropenia, 3% vs. 38%; anemia, 3% vs. 13%; and thrombocytopenia, 0% vs. 13%, respectively). No grade 3/4 AEs of leukocytosis, febrile neutropenia, epistaxis, pulmonary embolism, deep vein thrombosis, phlebitis, or hematuria were reported with the necuparanib + nab-paclitaxel and gemcitabine regimen.

Based on collective safety and on PK, progressive disease (PD), biomarker, and efficacy data, a 5 mg/kg necuparanib dose, with capping at 450 mg, providing for a reasonable injection volume (i.e., two injections daily), was selected for further clinical evaluation in part B (randomized phase II trial). Pharmacodynamic data (i.e., hepatocyte growth factor) showed saturation with necuparanib 5 mg/kg and subtherapeutic levels of anticoagulation, which may be beneficial for thrombosis prevention. Promising antitumor activity was observed, as evidenced by survival and response data, with an overall disease-control rate of 63% when all dose cohorts were pooled. Similarly, promising effects on reduction in Carbohydrate antigen 19-9 (CA19.9) levels from baseline with necuparanib treatment were observed. The median overall survival for patients who received at least one dose (13.1 months) and at least one cycle (15.6 months) of necuparanib + nab-paclitaxel + gemcitabine compared favorably with the phase III data for nab-paclitaxel + gemcitabine (8.5 months), differences in sample sizes and study populations notwithstanding [18].

These encouraging phase I results supported further clinical investigation in part B of this two-part study; however, the phase II portion of the trial was discontinued following a planned interim futility analysis, which did not show a sufficient level of efficacy to warrant continuation of study accrual. The phase II results will be reported separately.

Trial Information	
Disease	Pancreatic cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study – 1	Phase I
Type of Study – 2	3 + 3
Primary Endpoint	Safety
Primary Endpoint	Tolerability
Secondary Endpoin	MTD
Secondary Endpoint	Recommended phase II dose
Secondary Endpoint	PK
Secondary Endpoint	PD

Additional Details of Endpoints or Study Design
This was a phase I, open-label, multiple ascending-dose study of necuparanib given as monotherapy and then in combination with nab-paclitaxel and gemcitabine for patients with newly diagnosed untreated metastatic pancreas adenocarcinoma. Following completion of the first two cohorts (0.5 and 1.0 mg/kg necuparanib + gemcitabine), a protocol amendment in 2013 added nab-paclitaxel to the regimen following the presentation of MPACT study results supporting the combination. Dose escalation was conducted via a modified 3 + 3 design and occurred if all patients in the studied cohort completed cycle 1 without a dose-limiting toxicity (DLT). If a DLT was observed in one patient in the initial cohort of three to four patients, the cohort was expanded to six or seven patients. Dose escalation continued until the maximum tolerated dose (MTD) was defined. The protocol was modified during cohort 6 dosing to specify a maximum necuparanib dose of 450 mg (maximum of two injections of 225 mg/1.5 mL for each injection) following indications that daily doses greater than this were associated with elevated coagulation parameters. Dose escalation was to be terminated if two patients in the same cohort experienced a DLT in cycle 1. A DLT was defined as any AE judged by the investigator to be drug-related and assessed as grade $\geq$3 according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
Safety data in patients who received at least one dose of at least one of the study drugs were summarized by treatment group, and descriptive statistics were calculated for quantitative data and differences from baseline, as appropriate. Pharmacokinetic and PD parameters were calculated using noncompartmental methods and summarized by treatment group using descriptive statistics.

Investigator's Analysis	Activity and safety demonstrated. Proceeded to randomized phase II, but futility met in phase II

Drug Information for Phase I Control	
Drug 1	
Generic/Working name	Necuparanib
Company name	Momenta Pharmaceuticals
Drug type	Biological
Drug class	Other: heparan sulfate mimetic
Dose	0.5–5 milligrams (mg) per kilogram (kg)
Route	Other: subcutaneous
Schedule of administration	Daily subcutaneous doses in cohorts from 0.5 to 5 mg/kg; dose capped at 450 mg
Drug 2	
Generic/Working name	Nab-paclitaxel
Trade name	Abraxane
Company name	Celgene
Drug type	Small molecule
Drug class	Tubulin/Microtubules targeting agent
Dose	125 mg/m^2
Route	IV
Schedule of administration	Days 1, 8, and 15 of a 28-day cycle
Drug 3	
Generic/Working name	Gemcitabine

Trade name	Gemzar
Company name	Eli Lilly
Drug type	Small molecule
Drug class	Antimetabolite
Dose	1,000 mg/m^2
Route	IV
Schedule of administration	Days 1, 8, and 15 of a 28-day cycle
Drug 4	
Generic/Working name	New drug
Company name	Momenta Pharmaceuticals
Drug type	Biological
Drug class	Other
Dose	0.5 mg/kg
Route	Subcutaneous

Patient Characteristics for Phase I Control

Number of Patients, Male	12
Number of Patients, Female	27
Stage	IV pancreas adenocarcinoma
Age	Median (range): 63 years
Number of Prior Systemic Therapies	Median (range): 0
Performance Status: ECOG	0 — 21
	1 — 18
	2 —
	3 —
	Unknown —

Primary Assessment Method for Phase I Control

Title	Necuparanib, nab-paclitaxel, gemcitabine ($n = 24$)
Number of Patients Enrolled	39
Number of Patients Evaluable for Toxicity	39
Number of Patients Evaluated for Efficacy	24
Evaluation Method	RECIST 1.1
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 9$ (38%)
Response Assessment SD	$n = 6$ (25%)
Response Assessment PD	$n = 2$ (8%)
(Median) Duration Assessments PFS	5.9 months, CI: 2.1–8.7
(Median) Duration Assessments OS	13.1 months, CI: 4.0–16.6

Phase I Control Adverse Events

AE	Necuparanib + gemcitabine			Necuparanib + gemcitabine + nab-paclitaxel						Necuparanib + gemcitabine ± nab-paclitaxel
	Co 1 0.5 mg/kg (*n* = 8)	Co 2 1 mg/kg (*n* = 4)	Co 1 + 2 total (*n* = 12)	Co 3 1 mg/kg (*n* = 4)	Co 4 2 mg/kg (*n* = 5)	Co 5 4 mg/kg (*n* = 4)	Co 6 6 mg/kg (*n* = 4)	Co 7 5 mg/kg (*n* = 10)	Co 3–7 total (*n* = 27)	Co 1–7 total (*n* = 39)
Most common AEs (>30% of patients receiving necuparanib + gemcitabine + nab-paclitaxel)										
Anemia	5 (63)	3 (75)	8 (67)	3 (75)	4 (80)	2 (50)	2 (50)	3 (30)	14 (52)	22 (56)
Fatigue	4 (50)	2 (50)	6 (50)	2 (50)	3 (60)	3 (75)	2 (50)	4 (40)	14 (52)	20 (51)
Neutropenia	4 (50)	3 (75)	7 (58)	1 (25)	3 (60)	3 (75)	2 (50)	4 (40)	13 (48)	20 (51)
Leukopenia	3 (38)	1 (25)	4 (33)	2 (50)	3 (60)	2 (50)	3 (75)	2 (20)	12 (44)	16 (41)
Thrombocytopenia	2 (25)	2 (50)	4 (33)	2 (50)	2 (40)	4 (100)	2 (50)	2 (20)	12 (44)	16 (41)
ALT ↑	1 (13)	1 (25)	2 (17)	2 (50)	2 (40)	3 (75)	3 (75)	1 (10)	11 (41)	13 (33)
Nausea	1 (13)	2 (50)	3 (25)	3 (75)	3 (60)	2 (50)	1 (25)	2 (20)	11 (41)	14 (36)
Abdominal pain	1 (13)	—	1 (8)	3 (75)	1 (20)	2 (50)	1 (25)	3 (30)	10 (37)	11 (28)
Diarrhea	2 (25)	2 (50)	4 (33)	1 (25)	2 (40)	3 (75)	2 (50)	1 (10)	9 (33)	13 (33)
AEs grade 3 or higher, probably/definitely related to necuparanib (patients receiving >1 necuparanib + nab-paclitaxel + gemcitabine)										
ALT ↑	1 (13)	1 (25)	2 (17)	1 (25)	1 (20)	1 (25)	1 (25)	—	4 (15)	6 (15)
Anemia	—	—	—	—	—	—	1 (25)	—	1 (4)	1 (3)
Blood ALP ↑	—	—	—	—	—	—	—	1 (10)	1 (4)	1 (3)
AST ↑	1 (13)	—	1 (8)	—	—	—	1 (25)	—	1 (4)	2 (5)
Injection site cellulitis	—	—	—	—	—	—	1 (25)	—	1 (4)	1 (3)
Lymphopenia	—	—	—	—	—	1 (25)	—	—	1 (4)	1 (3)
Neutropenia	—	—	—	—	1 (20)	—	—	—	1 (4)	1 (3)

n (%) patients are shown. Adverse events have been sorted by necuparanib + gemcitabine + nab-paclitaxel (cohort 3–7 total) results.
Abbreviations: —, no adverse event; ↑, increased; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Co, cohort.

Dose-Limiting Toxicities Table

Dose level	Dose of drug: necuparanib	Dose of drug: nab-paclitaxel	Dose of drug: gemcitabine	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity	Dose-limiting toxicity information
1	0.5 mg/kg		1,000 mg/m^2	8	8	1	Elevated LFTs
2	1.0 mg/kg		1,000 mg/m^2	4	4	0	
3	1.0 mg/kg	125 mg/m^2	1,000 mg/m^2	4	4	0	
4	2.0 mg/kg	125 mg/m^2	1,000 mg/m^2	5	5	0	
5	4.0 mg/kg	125 mg/m^2	1,000 mg/m^2	4	4	0	
6	6 mg/kg	125 mg/m^2	1,000 mg/m^2	4	4	1	Cellulitis at injection site; 3 injections required; grade 1–2 aPTT prolongation
7	5 mg/kg	125 mg/m^2	1,000 mg/m^2	10	10	10	

Abbreviations: aPTT, activated partial thromboplastin time; LFT, liver function test.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Activity and safety demonstrated. Proceeded to randomized phase II, but futility met in phase II

This was the first clinical evaluation of necuparanib, a novel therapeutic agent, which was conducted in patients with metastatic pancreatic adenocarcinoma. Necuparanib in combination with nab-paclitaxel and gemcitabine demonstrated acceptable tolerability. No clear dose-proportional trends in individual adverse events (AEs) were observed. The most common AEs had comparable rates, when necuparanib was administered with gemcitabine with or without nab-paclitaxel, to what would be expected with chemotherapy alone. With the exception of anemia, the grade 3/4 hematological toxicities observed in this study in the necuparanib + nab-paclitaxel and gemcitabine cohort were similar to those observed in the Von Hoff et al. phase III study (neutropenia, 3% vs. 38%; anemia, 3% vs. 13%; and thrombocytopenia, 0% vs. 13%, respectively). No grade 3/4

AEs of leukocytosis, febrile neutropenia, epistaxis, pulmonary embolism, deep vein thrombosis, phlebitis, or hematuria were reported with the necuparanib + nab-paclitaxel and gemcitabine regimen.

Based on collective safety and on pharmacokinetic, progressive disease, biomarker, and efficacy data, a 5 mg/kg necuparanib dose, with capping at 450 mg, providing for a reasonable injection volume (i.e., two injections daily), was selected for further clinical evaluation in part B. Progressive disease data (i.e., hepatocyte growth factor) showed saturation with necuparanib 5 mg/kg and subtherapeutic levels of anticoagulation, which may be beneficial for thrombosis prevention. Promising antitumor activity was observed, as evidenced by survival and response data, with an overall disease-control rate of 63% when all dose cohorts were pooled. Similarly, promising effects on reduction in CA19.9 levels from baseline with necuparanib treatment were observed. The median OS for patients who received at least one dose (13.1 months) and at least one cycle (15.6 months) of necuparanib + nab-paclitaxel + gemcitabine compared favorably with the phase III data for nab-paclitaxel + gemcitabine (8.5 months), differences in sample sizes and study populations notwithstanding.

These encouraging phase I results supported further clinical investigation in part B of this two-part study; however, the phase II portion of the trial was discontinued following a planned interim futility analysis, which did not show a sufficient level of efficacy to warrant continuation of study accrual. The phase II results will be documented in a separate publication.

Acknowledgments

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Disclosures

Eileen M. O'Reilly: Celgene, MedImmune, Halozyme (C/A), Celgene, MabVax, Roche, Momenta Pharmaceuticals, Sanofi, Oncomed, MedImmune, AstraZenica, Bristol-Meyers Squibb (RF); **James Roach:** Momenta Pharmaceuticals (E, OI [former]); **Molly Rosano:** Momenta Pharmaceuticals (E, OI); **Silva Krause:** Momenta Pharmaceuticals (E, OI); **William Avery:** Momenta Pharmaceuticals (E); **Julie Wolf:** Novella Clinical (E); **Keith Flaherty:** Momenta (C/A); **Darrell Nix:** Momenta (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/ inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

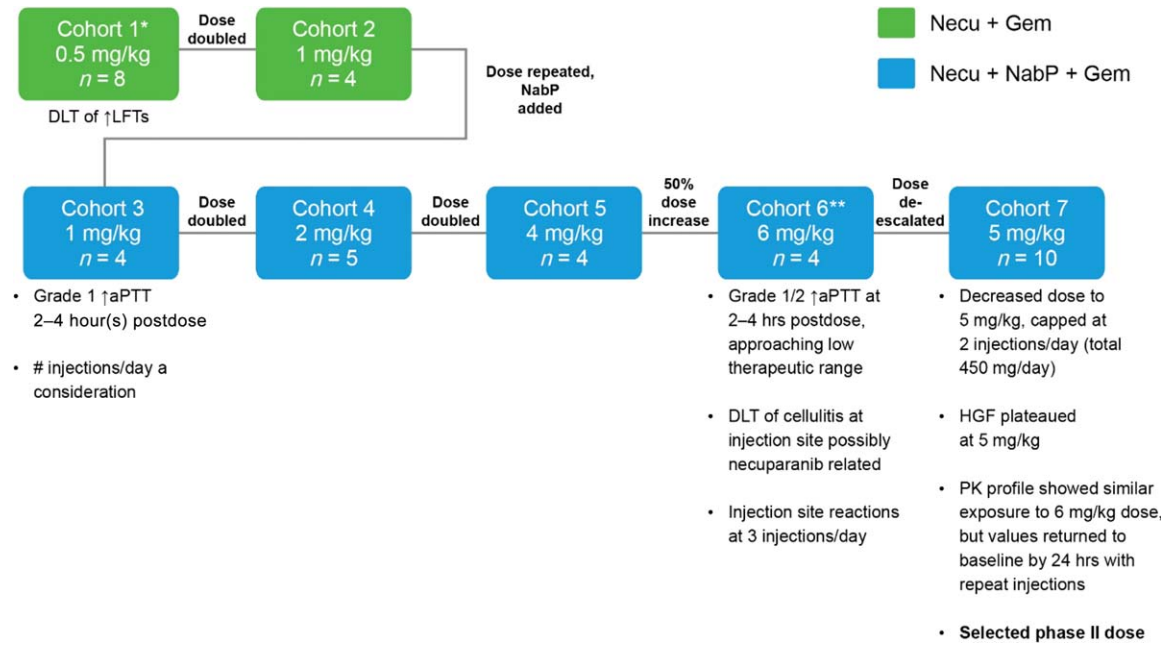

Figure 1. Dose escalation and disposition in patients receiving at least one dose of necuparanib.

Abbreviations: aPTT, activated partial thromboplastin time; DLT, dose-limiting toxicity; Gem, gemcitabine; HGF, hepatocyte growth factor; LFTs, liver function tests; NabP, nab-paclitaxel; Necu, necuparanib; PK, pharmacokinetics.

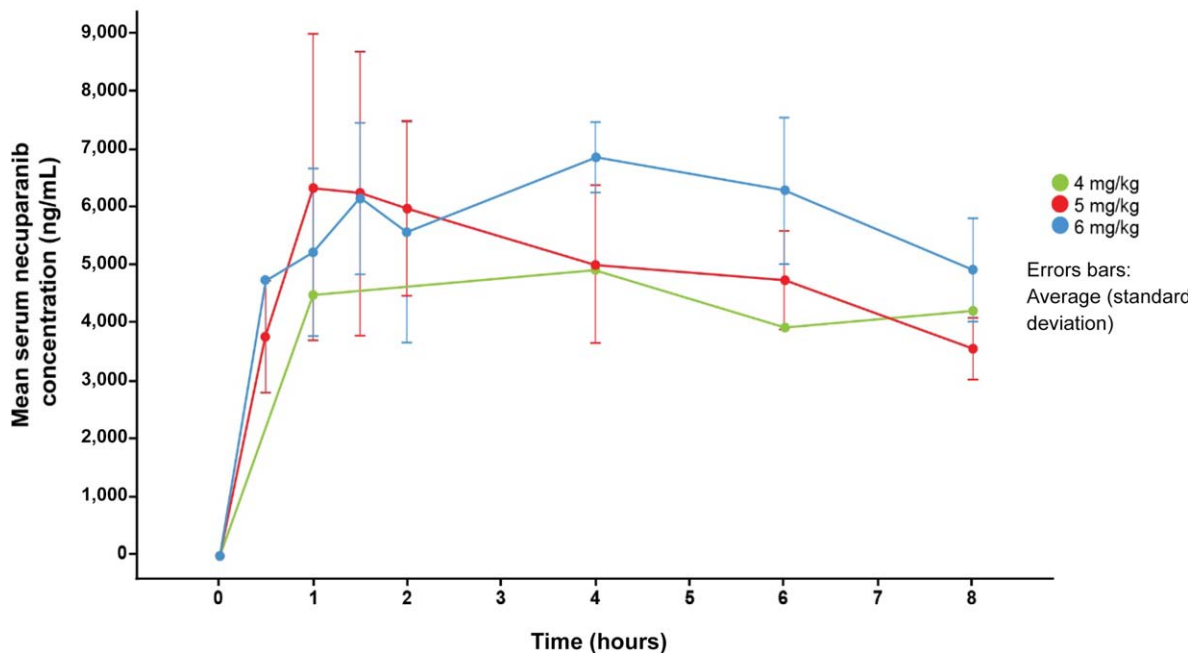

Figure 2. Concentration of necuparanib for patients with at least three measurable levels on day 1.

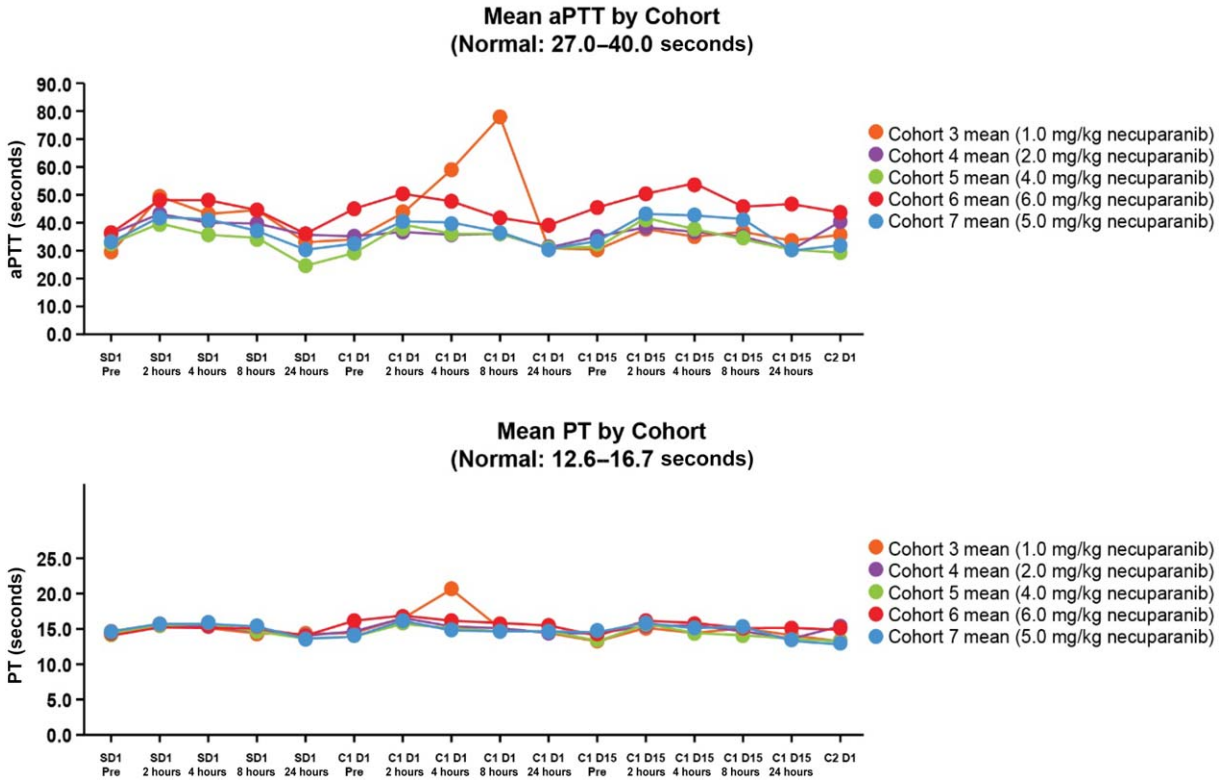

Figure 3. Activated partial thromboplastin time and prothrombin time in patients who received necuparanib in combination with nab-paclitaxel and gemcitabine (cohorts 3–7).

Abbreviations: aPTT, activated partial thromboplastin time; PT, prothrombin time.

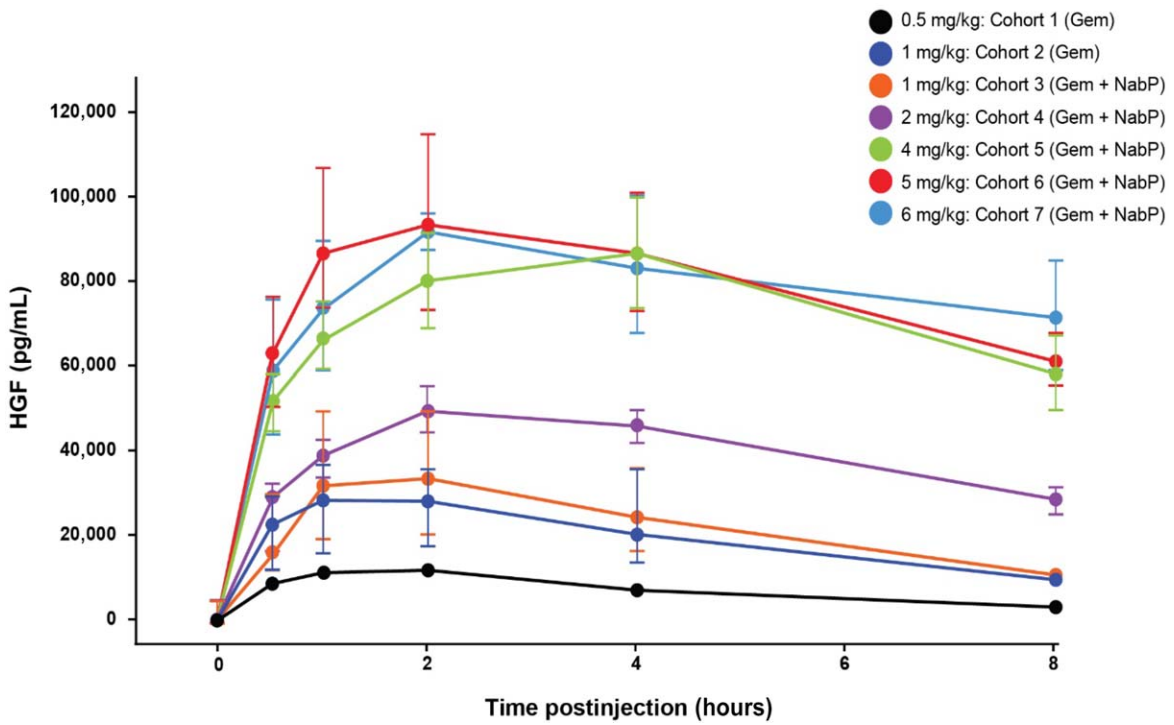

Figure 4. Mean (standard deviation) serum hepatocyte growth factor levels by dose group

Abbreviations: Gem, gemcitabine; HGF, hepatocyte growth factor; NabP, nab-paclitaxel; necu, necuparanib.

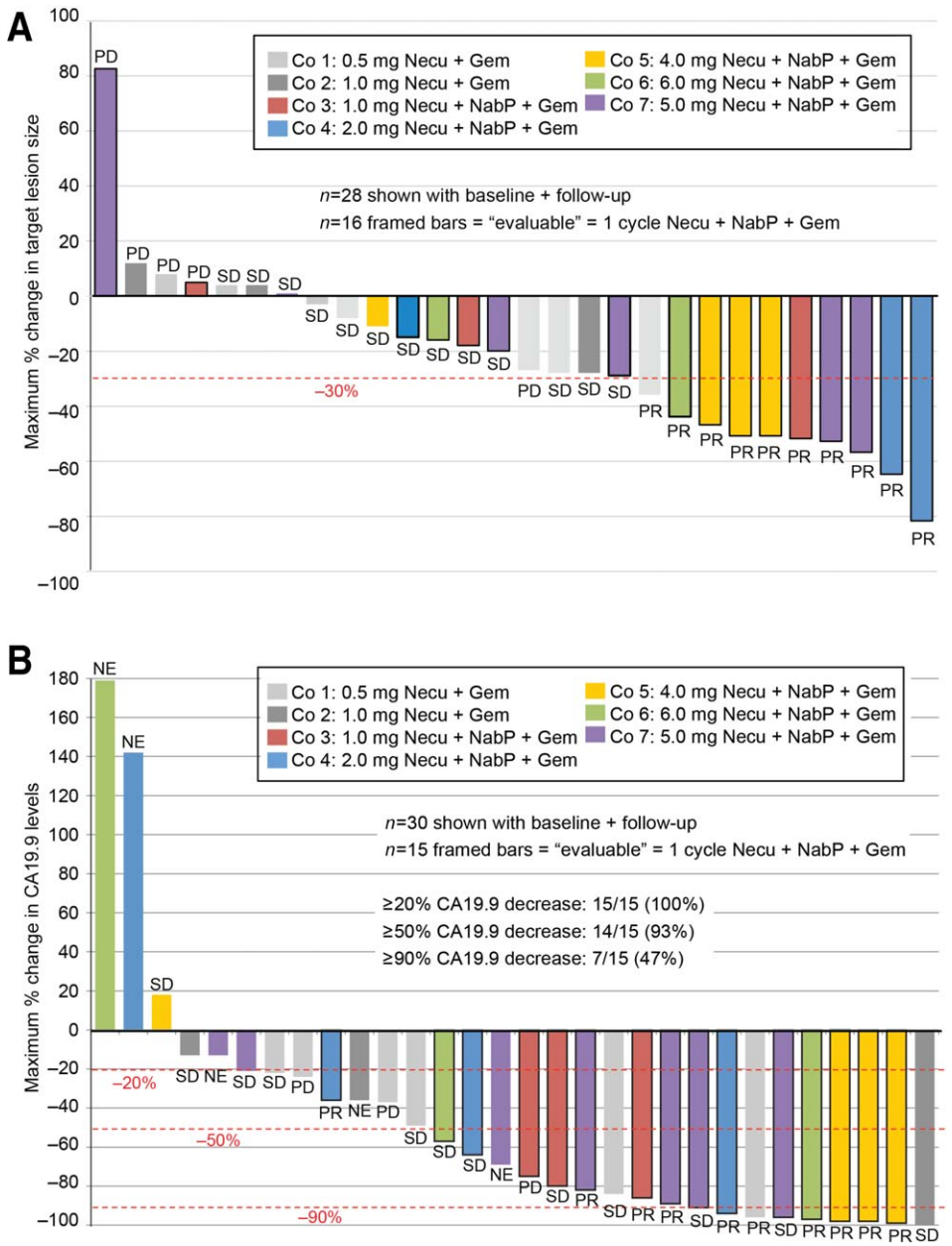

Figure 5. Patient time on study for patients receiving necuparanib + gemcitabine (cohorts 1 and 2; **A**) or necuparanib + nab-paclitaxel + gemcitabine (cohorts 3–7; **B**).

Abbreviations: Gem, gemcitabine; NabP, nab-paclitaxel; NE, not evaluable; Necu, necuparanib; PD, progressive disease; PR, partial response; SD, stable disease.

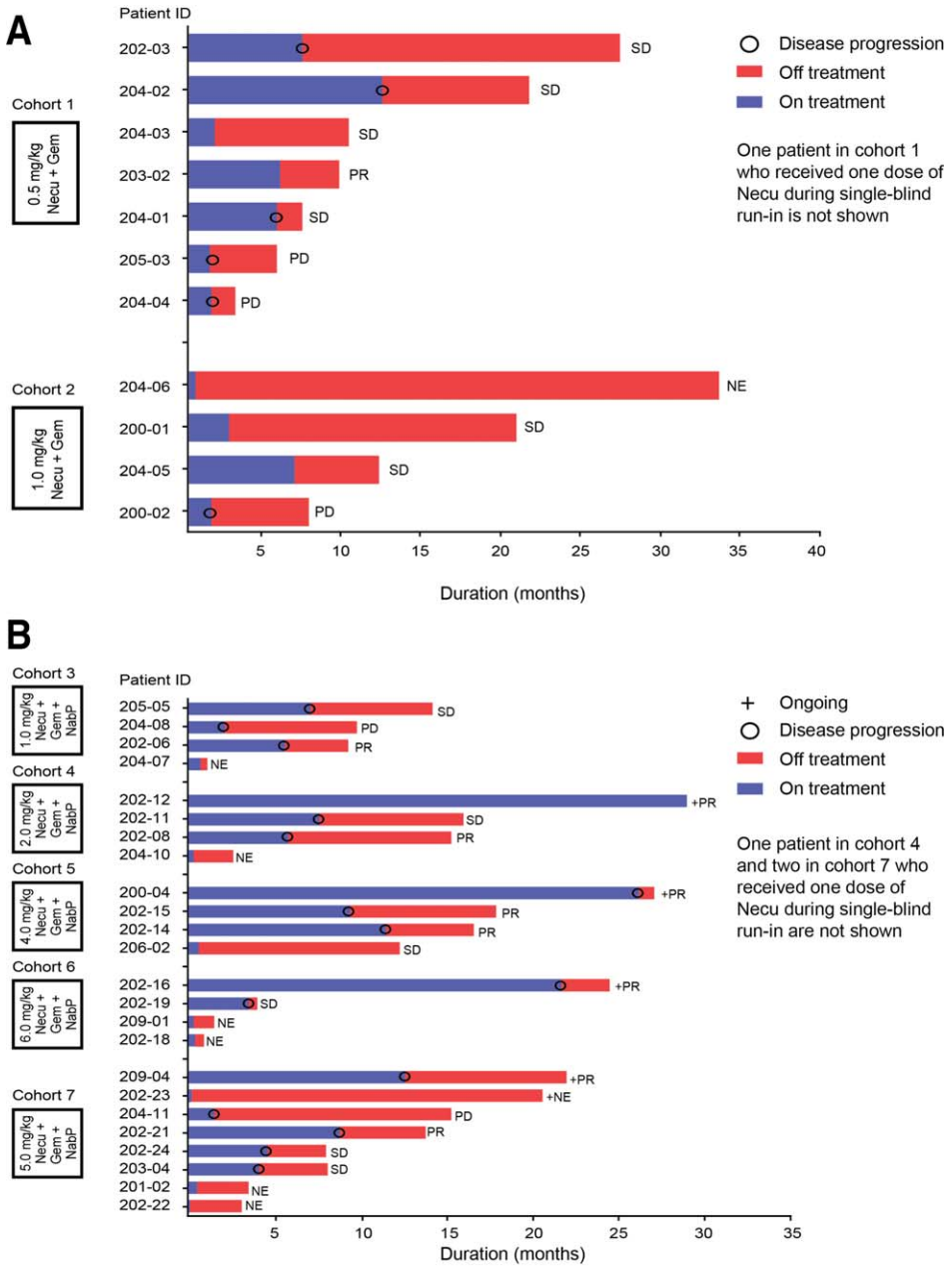

Figure 6. Patient time on study for patients receiving necuparanib + gemcitabine (cohorts 1 and 2; A) or necuparanib + nab-paclitaxel + gemcitabine (cohorts 3–7; B).

Abbreviations: Gem, gemcitabine; NabP, nab-paclitaxel; NE, not evaluable; Necu, necuparanib; PD, progressive disease; PR, partial response; SD, stable disease.

Table 1. Baseline patient and disease characteristics

Characteristics	All patients ($n = 39$)	Necuparanib + gemcitabine ($n = 12$)	Necuparanib + nab-paclitaxel + gemcitabine ($n = 27$)
Mean age, years	63.0	65.6	61.9
Gender, *n* (%)			
Female	27 (69)	9 (75)	18 (67)
Male	12 (31)	3 (25)	9 (33)
Race, *n* (%)			
White	35 (90)	11 (58)	24 (89)
Black or African American	2 (5)	0	2 (74)
Not available	2 (5)	1 (8)	1 (4)
Ethnicity, *n* (%)			
Hispanic or Latino	6 (15)	4 (33)	2 (7)
Not Hispanic or Latino	31 (80)	7 (58)	23 (85)
Not available	2 (5)	1 (8)	1 (4)
BMI	26.0	27.0	25.6
ECOG			
0	7	7	14
1	4	17	21
Tumor location, *n*			
Liver	28	9	19
Lung	14	5	9
Lymph nodes	6	2	4
Peritoneum	7	1	6
Number of metastatic sites, *n*			
1	13	4	9
2	11	6	5
3	5	1	4
>3	6	1	5
Mean CA19.9 levels, U/mL[a]	34,612.2	54,798.6	27,883.4

Data were available for the following numbers of patients (necuparanib + gemcitabine, necuparanib + nab-paclitaxel + gemcitabine): ECOG (11, 24); tumor location and number of metastatic sites (12, 23); CA19.9 (9, 27).
[a]Not available for three patients.
Abbreviations: BMI, body mass index; CA, cancer antigen; ECOG, Eastern Cooperative Oncology Group.

Table 2. Summary of adverse events

AE	Necuparanib + gemcitabine			Necuparanib + gemcitabine + nab-paclitaxel						Necuparanib + gemcitabine ± nab-paclitaxel
	Co 1 0.5 mg/kg (*n* = 8)	Co 2 1 mg/kg (*n* = 4)	Co 1 + 2 total (*n* = 12)	Co 3 1 mg/kg (*n* = 4)	Co 4 2 mg/kg (*n* = 5)	Co 5 4 mg/kg (*n* = 4)	Co 6 6 mg/kg (*n* = 4)	Co 7 5 mg/kg (*n* = 10)	Co 3–7 total (*n* = 27)	Co 1–7 total (*n* = 39)
Most common AEs (>30% of patients receiving necuparanib + gemcitabine + nab-paclitaxel)										
Anemia	5 (63)	3 (75)	8 (67)	3 (75)	4 (80)	2 (50)	2 (50)	3 (30)	14 (52)	22 (56)
Fatigue	4 (50)	2 (50)	6 (50)	2 (50)	3 (60)	3 (75)	2 (50)	4 (40)	14 (52)	20 (51)
Neutropenia	4 (50)	3 (75)	7 (58)	1 (25)	3 (60)	3 (75)	2 (50)	4 (40)	13 (48)	20 (51)
Leukopenia	3 (38)	1 (25)	4 (33)	2 (50)	3 (60)	2 (50)	3 (75)	2 (20)	12 (44)	16 (41)
Thrombocytopenia	2 (25)	2 (50)	4 (33)	2 (50)	2 (40)	4 (100)	2 (50)	2 (20)	12 (44)	16 (41)
ALT ↑	1 (13)	1 (25)	2 (17)	2 (50)	2 (40)	3 (75)	3 (75)	1 (10)	11 (41)	13 (33)
Nausea	1 (13)	2 (50)	3 (25)	3 (75)	3 (60)	2 (50)	1 (25)	2 (20)	11 (41)	14 (36)
Abdominal pain	1 (13)	—	1 (8)	3 (75)	1 (20)	2 (50)	1 (25)	3 (30)	10 (37)	11 (28)
Diarrhea	2 (25)	2 (50)	4 (33)	1 (25)	2 (40)	3 (75)	2 (50)	1 (10)	9 (33)	13 (33)
AEs grade 3 or higher, probably/definitely related to necuparanib (patients receiving >1 necuparanib + nab-paclitaxel + gemcitabine)										
ALT ↑	1 (13)	1 (25)	2 (17)	1 (25)	1 (20)	1 (25)	1 (25)	—	4 (15)	6 (15)
Anemia	—	—	—	—	—	—	1 (25)	—	1 (4)	1 (3)
Blood ALP ↑	—	—	—	—	—	—	—	1 (10)	1 (4)	1 (3)
AST ↑	1 (13)	—	1 (8)	—	—	—	1 (25)	—	1 (4)	2 (5)
Injection site cellulitis	—	—	—	—	—	—	1 (25)	—	1 (4)	1 (3)
Lymphopenia	—	—	—	—	—	1 (25)	—	—	1 (4)	1 (3)
Neutropenia	—	—	—	—	1 (20)	—	—	—	1 (4)	1 (3)

n (%) patients are shown. Adverse events have been sorted by necuparanib + gemcitabine + nab-paclitaxel (cohort 3–7 total) results.
Abbreviations: —, no adverse event; ↑, increased; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Co, cohort;

Table 3. Efficacy outcomes

Efficacy variable	Necuparanib + gemcitabine		Necuparanib + nab-paclitaxel + gemcitabine	
	Completed ≥1 dose (*n* = 11)	Completed ≥1 cycle (*n* = 10)	Completed ≥1 dose (*n* = 24)	Completed ≥1 cycle (*n* = 16)
OS (mo) median (95% CI)	10.4 (6.1–21.8)	10.2 (3.4–21.0)	13.1 (4.0–16.6)	15.6 (9.3–17.8)
Survival rate (95% CI)				
6 months	91 (51–99)	90 (47–99)	71 (48–85)	94 (63–99)
12 months	45 (17–71)	40 (12–67)	54 (31–71)	69 (40–86)
18 months	36 (11–63)	30 (7–58)	21 (8–39)	25 (8–47)
24 months	18 (3–44)	10 (1–36)	21 (8–39)	25 (8–47)
PFS (mo) median (95% CI)	7.5 (1.9–12.5)	6.5 (1.6–10.4)	5.9 (2.1–8.7)	7.9 (3.4–11.4)
RECIST best response, unconfirmed or confirmed, (%)				
CR	0	0	0	0
PR	1 (9)	1 (10)	9 (38)	9 (56)
SD	6 (55)	6 (60)	6 (25)	5 (31)
PD	3 (27)	3 (30)	2 (8)	2 (13)
NE	1 (9)	0	7 (29)	0
Disease control rate	7 (64)	7 (70)	15 (63)	14 (88)

Abbreviations: CI, confidence interval; CR, complete response; mo, Month; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; OS, overall survival; RECIST, Response Evaluation Criteria In Solid Tumors; SD, Stable disease.