Phase I Study of Oral Nintedanib Combined with Docetaxel in Previously Treated Japanese Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

#P415

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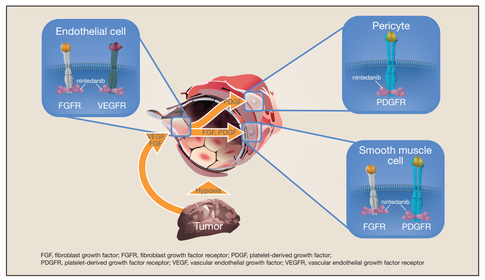
INTRODUCTION

- More effective, well-tolerated drugs are required for the second-line treatment of advanced NSCLC, as current standard therapies (docetaxel, pemetrexed or erlotinib) – while efficacious – only provide modest survival benefits in eligible patients[1-3]
- Angiogenesis, supported by vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) signalling,[4-7] plays an integral role in the progression and differentiation of NSCLC[8]
- Nintedanib is an oral, small molecule, angiokinase inhibitor of VEGF receptor (VEGFR)-1–3, PDGF receptor (PDGFR)-α/β and FGF receptor (FGFR)-1–3 (Figure 1), as well as RET and Flt3, which has demonstrated potent antitumourigenic and antiangiogenic activity in preclinical models of human cancer, including NSCLC[9]

Figure 1. Mode of action of nintedanib.



- As monotherapy, nintedanib was well tolerated at doses up to 200 mg twice daily (bid) and showed encouraging antitumour activity in a Phase I trial of 21 Japanese patients with advanced, refractory solid tumours[10]
- This Phase I dose-escalation study (NCT00876460) aimed to define the maximum tolerated dose (MTD) of nintedanib plus docetaxel, and to confirm its safety/tolerability profile in Japanese patients with advanced NSCLC who had failed prior first-line, platinum-based combination chemotherapy

METHODS

Study endpoints

Primary endpoint

- MTD of nintedanib in combination with standard-dose docetaxel (60 or 75 mg/m²)
  - MTD was defined as the highest dose at which incidence of dose-limiting toxicities (DLTs) in Cycle 1 was ≤33.3% (0/3, 1/6 or 2/6)
  - DLTs were defined as the following drug-related adverse events (AEs):
    - non-haematological toxicities ≥grade 3, except transient electrolyte abnormalities and isolated elevations of gamma glutamyl transpeptidase (γGT); gastrointestinal toxicities and hypertension ≥grade 3 were only counted if they persisted despite optimal supportive care/intervention
    - alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations ≥grade 2, combined with bilirubin elevations ≥grade 2
    - grade 4 haematological toxicities; grade 4 non-febrile neutropenia and/or leucopenia were only counted if they persisted for >7 days despite adequate supportive treatment
    - grade 4 febrile neutropenia
  - an inability to resume nintedanib dosing within 14 days after stopping due to treatment-related AEs, was counted as a DLT
- Incidence and intensity of AEs according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

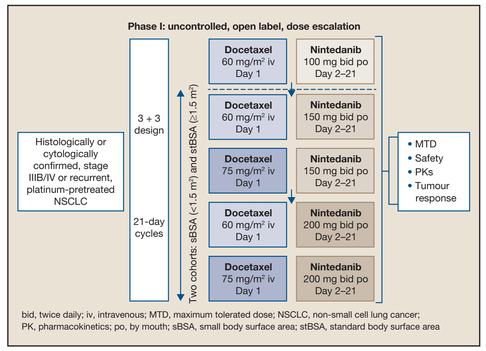
Key secondary endpoints

- Pharmacokinetic (PK) profiles of nintedanib and its metabolites when combined with docetaxel
- PK profile of docetaxel when combined with nintedanib
- Best tumour response according to Response Criteria in Solid Tumors (RECIST) version 1.0

Study design

- Phase I, open-label, dose-escalation study of nintedanib plus docetaxel utilising a standard 3 + 3 design (3–6 patients per dose level) based on reporting of DLTs during Cycle 1 (Figure 2)
- Patients received intravenous docetaxel at a dose of 60 mg/m² (recommended dose in Japan) or 75 mg/m² (dose used in global Phase III trials[11]) on Day 1, followed by continuous, oral nintedanib bid on Days 2–21 in 21-day cycles
- After testing the first dose of nintedanib (100 mg bid) plus docetaxel 60 mg/m² without consideration of body surface area (BSA), standard 3 + 3 dose escalations were performed separately in two patient cohorts with a small (<1.5 m²) BSA (sBSA) and standard (≥1.5 m²) BSA (stBSA), respectively
  - this protocol amendment was made following an initial observation of DLTs in sBSA patients
- Tumour imaging by computerised tomography or magnetic resonance imaging scan was performed at screening and after every 6 cycles
- Treatment was continued for as long as patients tolerated the combination without clinical signs of tumour progression

Figure 2. Study design.



Key eligibility criteria

Inclusion criteria

- Histologically or cytologically confirmed, stage IIIB–IV or recurrent NSCLC (all histologies)
- Receipt of one prior platinum-based chemotherapy regimen (not containing docetaxel); one additional regimen was allowed for adjuvant and/or neoadjuvant therapy in recurrent NSCLC
- Age ≥20 and ≤74 years
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1
- Life expectancy of ≥3 months
- Adequate organ function

Exclusion criteria

- Active brain metastases
- Pulmonary fibrosis or interstitial lung disease
- History of major thrombotic or clinically relevant major bleeding event in the past 6 months

PK analysis

- Blood samples for PK analysis were taken during Cycles 1 and 2
  - Day 1: 0, 1, 1.5, 2, 3, 4 and 7 hours after the start of docetaxel administration
  - Day 2: 0, 1, 2, 3, 4, 6, 7 and 10 hours after nintedanib morning administration
  - Day 3: just before the morning nintedanib intake
- Trough concentrations of nintedanib and its metabolites were measured on Days 8 and 15, prior to administration of the morning dose of nintedanib

RESULTS

Patients

- Forty-two patients, including 17 with sBSA (<1.5 m²) and 25 with stBSA (≥1.5 m²), were treated with nintedanib plus docetaxel (Table 1)
  - three patients (one with sBSA and two with stBSA) received nintedanib 100 mg bid plus docetaxel 60 mg/m² before the protocol amendment to carry out dose escalations according to BSA
  - three patients were excluded from MTD confirmation due to: early consent withdrawal before completion of Cycle 1, low compliance with study treatment resulting from a non-DLT AE, and insufficient data to confirm a DLT non-occurrence
- All baseline characteristics, except for gender, were well balanced between the two cohorts

Table 1. Patient demographics and baseline characteristics.

	sBSA (<1.5 m²) (n=17)	stBSA (≥1.5 m²) (n=25)	All patients (n=42)
Median age, years (range)	65 (45–72)	62 (47–73)	64 (45–73)
Male, n (%)	6 (35.3)	23 (92.0)	29 (69.0)
ECOG PS 0 / 1, n (%)	6 (35.3) / 11 (64.7)	8 (32.0) / 17 (68.0)	14 (33.3) / 28 (66.7)
Stage IIIB / IV, n (%)	1 (5.9) / 16 (94.1)	6 (24.0) / 19 (76.0)	7 (16.7) / 35 (83.3)
Adenocarcinoma / squamous / large cell histology, n (%)	14 (82.4) / 3 (17.6) / 0 (0.0)	19 (76.0) / 5 (20.0) / 1 (4.0)	33 (78.6) / 8 (19.0) / 1 (2.4)

ECOG PS, Eastern Cooperative Oncology Group performance status; sBSA, small body surface area; stBSA, standard body surface area

Maximum tolerated dose

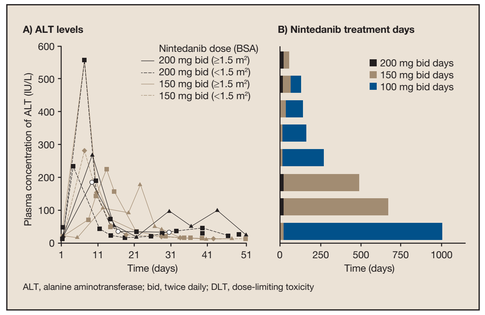
- DLTs occurred in 12 patients during Cycle 1: six patients each in the sBSA and stBSA cohorts, respectively (Table 2)
  - all DLTs were grade 3 liver enzyme (particularly ALT) elevations
  - all liver enzyme increases were fully reversible and manageable through dose reduction or treatment discontinuation
    - in the eight patients who required dose reduction, ALT levels recovered rapidly following nintedanib withdrawal (Figure 3); nintedanib was successfully reintroduced in all eight patients and only one required a further dose reduction
- The MTD of nintedanib, given in combination with docetaxel 60 or 75 mg/m², was 150 mg bid in the sBSA cohort and 200 mg bid in the stBSA cohort

Table 2. Observed DLTs at each nintedanib dose among patients with sBSA (<1.5 m²) or stBSA (≥1.5 m²).

Cohort	Nintedanib dose (mg bid)	Docetaxel dose (mg/m²)	No. of DLTs/ patients	Nature of DLT
–	100	60	0 / 3*	–
sBSA (<1.5 m²)	150	60	2 / 6	ALT and AST increase
				ALT increase
		75	1 / 6	ALT and AST increase
	200	60	3 / 3	ALT, AST and γGT increase
				ALT, AST and γGT increase
				ALT and AST increase
		75	–	–
stBSA (≥1.5 m²)	150	60	0 / 3	–
		75	2 / 6	ALT and γGT increase
				ALT increase
	200	60	2 / 6	ALT and AST increase
				ALT increase
		75	2 / 6	ALT, AST and γGT increase
				ALT increase

*BSA in 100 mg bid group: <1.5 m², n=1; ≥1.5 m², n=2
ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; DLT, dose-limiting toxicity; γGT, gamma glutamyltransferase; sBSA, small body surface area; stBSA, standard body surface area

Figure 3. Change in plasma concentrations of (A) ALT and (B) treatment days in the eight patients with ALT DLTs during Cycle 1 who had a dose reduction of nintedanib from an initial dose of 150 or 200 mg bid.



Safety and tolerability

- AEs with nintedanib plus docetaxel were generally manageable irrespective of BSA (Table 3).
- The most common drug-related AEs were neutropenia, leucopenia, fatigue, alopecia, decreased appetite, ALT elevations, AST elevations, diarrhoea and γGT elevations
  - the high incidence of neutropenia and leucopenia was assumed to be related to docetaxel treatment
- Major grade 3–4 drug-related AEs were neutropenia (95.2%), leucopenia (64.3%), ALT elevations (28.6%), γGT elevations (16.7%), AST elevations (16.7%), febrile neutropenia (16.7%) and lymphopenia (16.7%)
  - only one patient experienced grade 3 gastrointestinal toxicity (diarrhoea), which was managed with symptomatic treatment without dose reduction
  - liver enzyme elevations were most common grade 3 non-haematological AEs, but all were asymptomatic and manageable

Table 3. Frequency of patients with drug-related AEs (≥20% incidence overall) across all dose groups in all treatment cycles by BSA.

	sBSA (<1.5 m²) (n=17)		stBSA (≥1.5 m²) (n=25)		All patients (n=42)	
Cohort	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4	All grades
Haematological						
Neutropenia	17 (100)	17 (100)	23 (92.0)	23 (92.0)	40 (95.2)	40 (95.2)
Leucopenia	10 (58.8)	14 (82.4)	17 (68.0)	21 (84.0)	27 (64.3)	35 (83.3)
Anaemia	–	4 (23.5)	–	6 (24.0)	–	10 (23.8)
Non-haematological						
Fatigue	–	15 (88.2)	–	17 (68.0)	–	32 (76.2)
Alopecia	–	12 (70.6)	–	18 (72.0)	–	30 (71.4)
Decreased appetite	1 (5.9)	13 (76.5)	–	15 (60.0)	1 (2.4)	28 (66.7)
Diarrhoea	–	6 (35.3)	1 (4.0)	16 (64.0)	1 (2.4)	22 (52.4)
Dysgeusia	–	6 (35.3)	–	11 (44.0)	–	17 (40.5)
Rash	–	8 (47.1)	–	9 (36.0)	–	17 (40.5)
Nausea	–	7 (41.2)	–	8 (32.0)	–	15 (35.7)
Vomiting	–	9 (52.9)	–	5 (20.0)	–	14 (33.3)
Stomatitis	–	4 (23.5)	–	8 (32.0)	–	12 (28.6)
Peripheral sensory neuropathy	1 (5.9)	3 (17.6)	–	7 (28.0)	1 (2.4)	10 (23.8)
Oedema	–	5 (29.4)	–	4 (16.0)	–	9 (21.4)
Laboratory abnormalities						
ALT increased	6 (35.3)	13 (76.5)	6 (24.0)	14 (56.0)	12 (28.6)	27 (64.3)
AST increased	5 (29.4)	13 (76.5)	2 (8.0)	14 (56.0)	7 (16.7)	27 (64.3)
γGT increased	3 (17.6)	10 (58.8)	4 (16.0)	12 (48.0)	7 (16.7)	22 (52.4)
ALP increased	1 (5.9)	9 (52.9)	–	9 (36.0)	1 (2.4)	18 (42.9)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, gamma glutamyltransferase; sBSA, small body surface area; stBSA, standard body surface area

PK analysis

- Despite inter-patient variability, nintedanib AUC and maximum concentration (C_{max}) increased in an almost dose-proportional manner following single-dose administration of nintedanib 100, 150 or 200 mg (Table 4)
- Plasma concentrations of nintedanib reached maximum levels 2–3 hours post-administration and then declined with half-life of 8–9 hours
- The PK analysis revealed no interactions between nintedanib and docetaxel
  - the PK parameters were similar to those observed in a previous Japanese study that evaluated single-agent nintedanib in patients with advanced solid tumours.[10]
  - co-administration of nintedanib did not affect docetaxel exposure, as indicated by comparing C_{max} and AUC before (Cycle 1) and after (Cycle 2) nintedanib administration (Figure 5)

Table 4. Mean PK parameters of nintedanib (+ docetaxel) following single oral administration of nintedanib 100, 150 or 200 mg.

Parameter	Nintedanib 100 mg (n=3)	Nintedanib 150 mg (n=23)	Nintedanib 200 mg (n=16)
$AUC_{0-12,}$ ng•h/mL	124 (54.1)	152 (65.0)†	249 (26.2)
$AUC_{0-12,\ norm}$, ng•h/mL/mg	1.24 (54.1)	1.01 (65.0)†	1.24 (26.2)
$AUC_{0-\infty,}$ ng•h/mL	169 (56.1)	260 (50.1)‡	349 (25.6)
$AUC_{0-\infty,\ norm}$, ng•h/mL/mg	1.69 (56.1)	1.73 (50.1)‡	1.75 (25.6)
$C_{max,}$ ng/mL	29.3 (60.0)	33.4 (91.1)	59.9 (43.9)
$C_{max,\ norm,}$ ng/mL/mg	0.293 (60.0)	0.223 (91.1)	0.299 (43.9)
t_{max}*, h	2.00 (1.98–3.02)	3.00 (1.95–7.00)	2.00 (1.98–6.00)
$t_{1/2,}$ h	9.25 (17.5)	7.89 (24.1)‡	7.52 (12.7)
CL/F, mL/min	9,840 (56.1)	9,630 (50.1)‡	9,550 (25.6)
Vz/F, L	7,800 (37.7)	6,580 (62.0)‡	6,210 (25.9)

Values are given as geometric means (% geometric coefficient of variation) unless otherwise specified; *median (range); †n=22; ‡n=18.
$AUC_{0-12,}$ area under the concentration–time curve (0–12 hours); $AUC_{0-12,\ norm,}$ normalised $AUC_{0-12,}$; $AUC_{0-\infty,}$ area under the concentration–time curve (0–∞ hours); $AUC_{0-\infty,\ norm,}$ normalised $AUC_{0-\infty,}$; CL/F, oral clearance; $C_{max,}$ peak concentration; $C_{max,\ norm,}$ normalised C_{max}; t1/2, elimination half life; $t_{max,}$ time to C_{max}; Vz/F, apparent volume of distribution.

- Nintedanib exposure (geometric mean normalised AUC and C_{max}) was slightly higher in sBSA patients than in stBSA patients (Figure 4); however, individual values overlapped and no clinically meaningful differences were observed

Efficacy

- Among 38 evaluable patients, 10 (26.3%) had a partial response (PR) and 18 (47.4%) had stable disease
  - PRs were only seen in patients with non-squamous histology receiving nintedanib 150 or 200 mg bid plus docetaxel
- Median progression-free survival among all 42 patients was 174 days

Figure 4. (A) $C_{max,}$ norm, (B) $AUC_{0-12,\ norm,}$ and (C) $AUC_{0-\infty,\ norm}$ of nintedanib following single oral administration of nintedanib 100, 150 or 200 mg in patients with sBSA (<1.5m²) or stBSA (≥1.5m²).

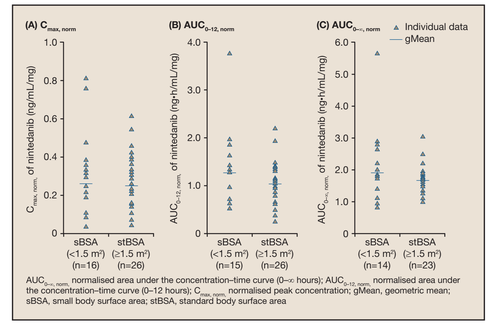
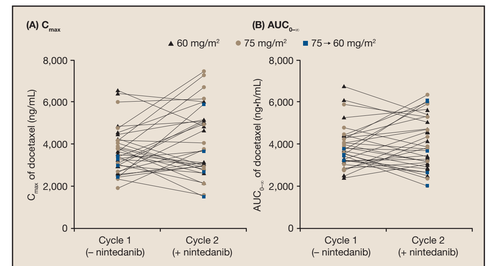


Figure 5. Intra-individual comparisons of C_{max} (A) and $AUC_{0-\infty}$ (B) of docetaxel (60 or 75 mg/m²) before (Cycle 1) and after (Cycle 2) administration of nintedanib 100, 150 or 200 mg bid.



CONCLUSIONS

- Continuous daily treatment with nintedanib combined with docetaxel was manageable and showed promising signs of efficacy in previously treated Japanese patients with advanced NSCLC
- The MTD of nintedanib, given in combination with docetaxel 60 or 75 mg/m², was 150 mg bid in the sBSA cohort and 200 mg bid in the stBSA cohort
  - reasons for the differences in MTD are under evaluation as the median dose adjusted exposure for nintedanib was similar for both BSA cohorts
- Based on these findings, further study of the combination of nintedanib and docetaxel in pretreated Japanese NSCLC patients is warranted

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