Antiangiogenic-specific adverse events in patients with non-small cell lung cancer (NSCLC) treated with nintedanib (BIBF 1120) and docetaxel

#281

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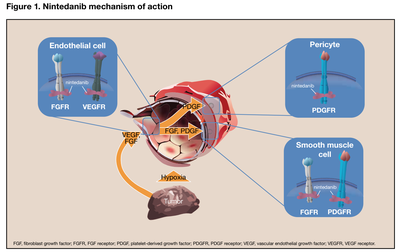
INTRODUCTION

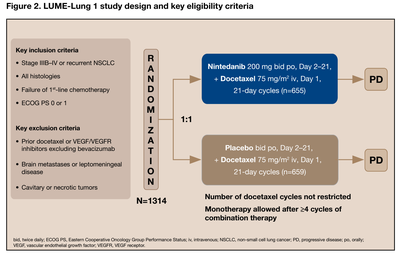
- Antiangiogenic treatments are associated with class-specific side effects, including gastrointestinal and nongastrointestinal perforations; bleeding; thromboembolism (ie, venous and arterial); and hypertension. Non-small cell lung cancer (NSCLC) patients with squamous cell carcinoma (SCC) in particular have a higher incidence of bleeding and are not candidates for treatment with antiangiogenic compounds
- Nintedanib (BIBF 1120) is an oral, twice-daily, triple angiokinase inhibitor targeting vascular endothelial growth factor receptors-1–3, platelet-derived growth factor receptors-α/β, and fibroblast growth factor receptors-1–3 (Figure 1)[1] as well as RET and FLT3
  - nintedanib has negligible drug-drug interactions via CYP450[2]
  - nintedanib has a manageable safety profile in combination with docetaxel, pemetrexed, paclitaxel/carboplatin, gemcitabine/cisplatin, and afatinib[3-7]
  - nintedanib was active as 2nd-, and 3rd-line monotherapy in a Phase II study with NSCLC patients[8]
  - studies with nintedanib have not reported a significantly higher incidence of adverse events (AEs) commonly associated with antiangiogenic treatments relative to baseline, and NSCLC patients with SCC histology showed a manageable safety profile when treated with nintedanib[3,4,9]
- LUME-Lung 1 (NCT00805194; 1199.13) was a randomized, placebo-controlled Phase III trial investigating nintedanib + docetaxel in patients with advanced NSCLC after failure of 1st-line chemotherapy. The study design is shown in Figure 2
  - LUME-Lung 1 demonstrated that nintedanib significantly improved median progression-free survival (PFS) regardless of histology (3.4 vs 2.7 months [mo]; HR 0.79 [95% CI: 0.68–0.92], p=0.0019) and significantly improved clinically meaningful median overall survival (OS) for patients with adenocarcinoma tumor histology (12.6 vs 10.3 mo; HR 0.83 [95% CI: 0.70–0.99], p=0.0359)
  - AEs in the nintedanib arm were manageable with adequate treatment, dose interruptions, and dose reductions
  - the most frequent AEs in the nintedanib arm were diarrhea and reversible increases in alanine and aspartate aminotransferase levels[9]
- This assessment extends our investigation of the LUME-Lung 1 trial and evaluates whether the combination of nintedanib + standard docetaxel increases the frequency of characteristic AEs often associated with antiangiogenic agents versus placebo + docetaxel. In addition, the antiangiogenic safety profile was further characterized in the two main histologies—adenocarcinoma and SCC—in the LUME-Lung 1 patient population

Figure 1. Nintedanib mechanism of action



FGF, fibroblast growth factor; FGFR, FGF receptor; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Figure 2. LUME-Lung 1 study design and key eligibility criteria



bid, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; iv, intravenous; NSCLC, non-small cell lung cancer; PO, progressive disease; po, orally; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

METHODS

LUME-Lung 1 study design

- Key inclusion and exclusion criteria for LUME-Lung 1 are presented in Figure 2
- Additional important inclusion and exclusion criteria for participation in the LUME-Lung 1 trial are listed below:
  - included patients with SCC and stable asymptomatic brain metastases
  - excluded the following patients:
    - radiographic evidence of cavitary or necrotic tumors
    - centrally located tumors with radiographic evidence (computed tomography or magnetic resonance imaging) of local invasion of major blood vessels
    - history of clinically significant hemoptysis within the past 3 months
    - therapeutic anticoagulation (except for low-dose heparin and/or heparin flush as needed for maintenance of indwelling intravenous device) or antiplatelet therapy (except for chronic low-dose therapy with acetylsalicylic acid ≤325 mg daily)
    - history of major thrombotic or clinically relevant major bleeding event in the past 6 months
    - known inherited predisposition to bleeding or thrombosis

Assessment

- The incidence and intensity of antiangiogenic-associated AEs according to the common terminology criteria for AEs (CTCAE version 3.0) were evaluated in all patients who received at least one dose of nintedanib, docetaxel, or placebo
- AEs of interest were categorized by pooling MedDRA terms and by using Standardized MedDRA Queries, and were tabulated by the antiangiogenic AE category, preferred term, and worst CTCAE grade
- AEs that were analyzed include perforations (gastrointestinal and nongastrointestinal), hypertension, bleeding (including respiratory bleeding), and thromboembolic events (in particular arterial thromboembolism and venous embolism)
- Populations that were analyzed include all patients (overall), as well as those with adenocarcinoma and SCC
- The safety analyses compared the nintedanib arm against the placebo arm and were based on the concept of treatment-emergent AEs
  - AEs with onset between the first administration of study drug (docetaxel or nintedanib/placebo) until 28 days after the last administration of study drug were considered to be on treatment

RESULTS

Patients

- Patient baseline demographics and disease characteristics were balanced between the groups (Table 1)

Table 1. Demographics and baseline disease characteristics (randomized set)

	Overall		Adenocarcinoma		Squamous cell carcinoma	
	Nintedanib (N=655)	Placebo (N=659)	Nintedanib (n=533)	Placebo (n=536)	Nintedanib (n=276)	Placebo (n=278)
Mean age, years (SD)	59.7 (9.7)	59.8 (9.0)	58.5 (10.1)	58.6 (9.5)	60.7 (8.0)	61.3 (8.2)
Age ≥65 years, n (%)	200 (30.5)	214 (32.5)	90 (16.9)	96 (17.9)	85 (30.8)	104 (37.4)
Gender, n (%)						
Male	476 (72.7)	479 (72.7)	203 (63.2)	208 (61.9)	234 (84.8)	242 (86.7)
Female	179 (27.3)	180 (27.3)	119 (37.0)	128 (38.1)	42 (15.2)	37 (13.3)
Race, n (%)						
White	533 (81.4)	530 (80.4)	253 (78.6)	253 (75.3)	235 (85.1)	237 (84.9)
Asian	116 (17.7)	123 (18.7)	65 (20.2)	78 (23.2)	39 (14.1)	41 (14.7)
Black/African American	4 (0.6)	5 (0.8)	3 (0.9)	4 (1.2)	1 (0.4)	1 (0.4)
American Indian/Alaska native	2 (0.3)	1 (0.2)	1 (0.3)	1 (0.3)	1 (0.4)	0
ECOG PS,[a] n (%)						
0	187 (28.5)	189 (28.7)	96 (29.8)	99 (29.5)	75 (27.2)	75 (26.9)
1	467 (71.3)	470 (71.3)	226 (70.2)	237 (70.5)	201 (72.8)	204 (73.1)
Smoking history, n (%)						
Currently or ex-smoker	490 (74.8)	498 (75.6)	207 (64.3)	221 (65.8)	235 (85.1)	246 (88.2)
Never	165 (25.2)	161 (24.4)	115 (35.7)	115 (34.2)	41 (14.9)	33 (11.8)
Clinical stage at diagnosis (UICC/AJCC),[b,c] n (%)						
Stage <IIIB	105 (16.0)	105 (15.9)	50 (15.6)	54 (16.1)	46 (16.6)	46 (16.5)
Stage IIIB	148 (22.6)	146 (22.2)	55 (17.1)	45 (13.3)	85 (30.8)	91 (32.6)
Stage IV	399 (60.9)	408 (61.9)	215 (66.8)	237 (70.6)	144 (52.2)	142 (50.9)
Missing	3 (0.5)	0	2 (0.6)	0	1 (0.4)	0
Metastases at screening, n (%)	588 (89.8)	605 (91.8)	320 (99.3)	330 (93.2)	255 (95.1)	244 (87.5)
Brain metastases at baseline, n (%)	38 (5.8)	38 (5.8)	26 (8.1)	24 (6.8)	6 (2.2)	11 (3.9)

ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; UICC/AJCC, Union Internationale Contre le Cancer/American Joint Committee on Cancers (6th or 7th edition).
[a]One patient randomized to nintedanib + docetaxel had an ECOG performance status of 2. [b]The 6th edition was used to stage 709 of 1314 patients (54%) and the 7th edition was used to stage 602 of 1314 patients (45.8%).

Adverse events

General overview

- Table 2 provides a general overview of all AEs that occurred during the on-treatment period in all patients
- Almost all patients in both arms experienced an AE (Overall: nintedanib, 93.6% vs placebo, 93.0%; Adenocarcinoma: nintedanib, 96.3% vs placebo, 94.3%; SCC: nintedanib, 90.5% vs placebo, 90.6%)
- The incidences of patients with AEs of CTCAE Grade ≥3 were slightly higher among all patients and histologies in the nintedanib arm compared with the placebo arm (Overall: nintedanib, 71.3% vs placebo, 64.3%; Adenocarcinoma: nintedanib, 75.9% vs placebo, 68.4%; SCC: nintedanib, 66.6% vs placebo, 58.6%)

Table 2. Common non-hematologic AEs, all CTCAE grades (≥15% incidence) or CTCAE Grade ≥3 (≥1% incidence)

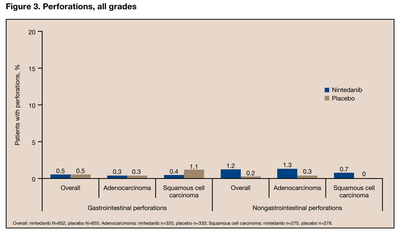
	Nintedanib + docetaxel (N=655)		Placebo + docetaxel (N=659)	
Adverse events, n (%)	All grades	Grade ≥3	All grades	Grade ≥3
Diarrhea	276 (42.3)	43 (6.6)	143 (21.8)	17 (2.6)
Neutrophil count decreased	242 (37.1)	209 (32.1)	235 (35.9)	196 (29.9)
Fatigue	198 (30.4)	37 (5.7)	156 (23.8)	24 (3.7)
ALT increased	186 (28.5)	51 (7.8)	55 (8.4)	6 (0.9)
Nausea	158 (24.2)	5 (0.8)	118 (18.0)	6 (0.9)
AST increased	147 (22.5)	22 (3.4)	43 (6.6)	3 (0.5)
Appetite decreased	145 (22.2)	9 (1.4)	102 (15.6)	8 (1.2)
Dyspnea	124 (19.0)	32 (4.9)	110 (16.8)	35 (5.3)
Vomiting	115 (17.6)	3 (0.5)	61 (9.3)	3 (0.5)
Alopecia	107 (16.4)	1 (0.2)	119 (18.2)	0
Cough	99 (15.2)	6 (0.9)	110 (16.8)	4 (0.6)
Pyrexia	93 (12.7)	5 (0.8)	66 (10.0)	2 (0.3)
Asthenia	88 (8.9)	16 (2.3)	64 (9.8)	10 (1.5)
Chest pain	56 (8.6)	9 (1.4)	62 (9.4)	14 (2.1)
Constipation	54 (8.2)	1 (0.2)	52 (7.9)	3 (0.5)
Pneumonia	33 (5.1)	23 (3.5)	26 (3.9)	22 (3.4)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

Perforation

- Gastrointestinal and nongastrointestinal perforations were not common and were balanced between both treatment arms (Figure 3)
- Gastrointestinal perforations occurred in three patients (0.5%) in the nintedanib arm and three patients (0.5%) in the placebo arm
  - one patient in the nintedanib group and three patients in the placebo group experienced an intestinal or gastric perforation; the remaining two patients in the nintedanib arm experienced an anal or perirectal abscess
- Nongastrointestinal perforations occurred in eight patients (1.2%) treated with nintedanib and in one patient (0.2%) treated with placebo
  - the patient in the placebo arm experienced a skin abscess associated with a fistula at the site of a previous intercostal drain
  - nongastrointestinal perforations in the nintedanib arm were due to bladder perforation (one patient), laryngeal fistula (one patient), periprocritic abscess (one patient), and lung or chest wall abscess (five patients)
- Overall, there was no relevant difference between the treatment arms or across the different histologies in gastrointestinal and nongastrointestinal perforations and fistulae

Figure 3. Perforations, all grades

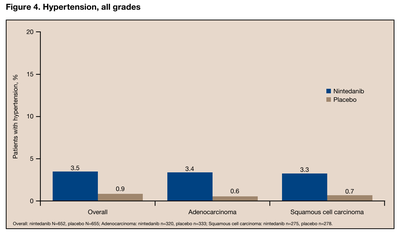


Overall: nintedanib N=652, placebo N=655; Adenocarcinoma: nintedanib n=320, placebo n=333; Squamous cell carcinoma: nintedanib n=275, placebo n=278.

Hypertension

- The percentage of patients with hypertension (all grades) was low in both treatment arms (Figure 4), albeit numerically greater in the nintedanib arm in the overall patient population (3.5% vs 0.9%) as well as those with adenocarcinoma (3.4% vs 0.6%), and SCC (2.3% vs 0.7%)
  - four patients in the nintedanib group and one patient in the placebo group experienced Grade 3 hypertension
  - no patients had hypertension of Grade 4 or 5
  - there were no cases of posterior reversible encephalopathy syndrome or reversible posterior leukoencephalopathy syndrome
- The median values for systolic and diastolic blood pressure from baseline remained stable during the course of the trial for patients in both the nintedanib and placebo arms
  - at screening, median values for systolic blood pressure were 125 mm Hg in both treatment arms; at the end of treatment, median values were 120 mm Hg
  - at screening, median diastolic blood pressure was 80 mm Hg in both treatment arms, and at the end of treatment, 70 mm Hg in the nintedanib group and 76 mm Hg in the placebo group
- No relevant differences were noted between the main study populations in both treatment arms

Figure 4. Hypertension, all grades



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Bleeding

Overall patients

- The percentages of patients with bleeding were 14.1% in the nintedanib arm and 11.6% in the placebo arm (Figure 5)
  - when taking exposure into account, there was no relevant difference in the percentage of patients with bleeding events between the treatment groups (incidence rate ratio of nintedanib vs placebo: 1.10 [95% CI: 0.81-1.49])
  - the difference in percentages between treatments in the overall study population was driven by patients with SCC, where bleeding was more pronounced in the nintedanib arm versus the placebo arm (17.1% vs 10.8%)
- Most cases of bleeding were CTCAE Grade 1 or 2 in both treatment arms, and fatal bleeding (CTCAE Grade 5) was low (<1.5%) and not relevantly different between the treatment arms (Table 3)
- The most common bleeding event was epistaxis (nintedanib 4.9% vs placebo 2.7%), which was primarily of CTCAE Grade 1 (Table 4)
- No AEs indicating intracerebral bleeding were reported for the study population
- Most fatal bleeding events were tumor-associated, and none in the nintedanib arm were considered study drug-related by the investigator
- There was no apparent correlation between bleeding and thrombocytopenia as an AE

Patients with tumors of adenocarcinoma histology

- The percentages of patients with bleeding were similar in the two treatment groups (nintedanib 10.9% vs placebo 11.1%)
- Most cases of bleeding were CTCAE Grade 1 or 2, and fatal bleeding (CTCAE Grade 5) was low (<1%) and balanced between the arms
- Fatal bleeding occurred in three patients treated with nintedanib and in two patients treated with placebo
- The most common bleeding events reported for nintedanib versus placebo were epistaxis (5.0% vs 3.6%) and hemoptysis (4.2% vs 2.5%)

Patients with tumors of SCC histology

- The percentage of patients with bleeding was greater in the nintedanib group (17.1%) than in the placebo group (10.8%)
- Most cases of bleeding were CTCAE Grade 1 or 2
- The most common bleeding events were hemoptysis (nintedanib 6.9% vs placebo 5.8%) and epistaxis (nintedanib 4.7% vs placebo 1.4%)
- The percentages of patients with drug-related bleeding, bleeding of Grade ≥3, serious bleeding, fatal bleeding, and bleeding resulting in permanent discontinuation of last study medication were balanced between treatment groups in patients with SCC
  - five patients with SCC in both the nintedanib and the placebo treatment groups died because of bleeding (hemoptysis: one vs three patients; pulmonary hemorrhage: two vs two patients; hemorrhage: two vs 0 patients)

Figure 5. Bleeding

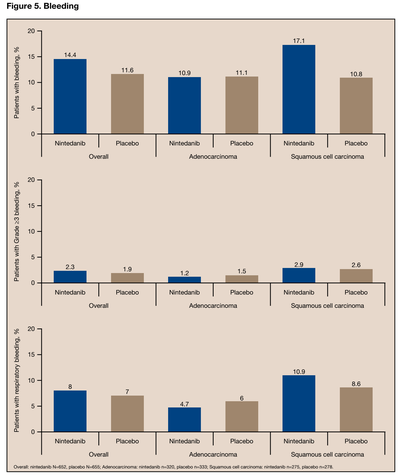

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Table 3. Patients with bleeding by worst CTCAE grade

	Overall		Adenocarcinoma		Squamous cell carcinoma	
	Nintedanib (N=652)	Placebo (N=655)	Nintedanib (n=320)	Placebo (n=333)	Nintedanib (n=275)	Placebo (n=278)
CTCAE Grade, n (%)						
Grade 1	59 (9.0)	43 (6.6)	34 (10.6)	23 (6.9)	20 (10.9)	15 (5.4)
Grade 2	33 (5.1)	33 (5.0)	15 (4.7)	14 (4.2)	15 (5.5)	13 (4.7)
Grade 3	6 (0.9)	4 (0.6)	1 (0.3)	3 (0.9)	3 (1.1)	1 (0.4)
Grade 4	0	1 (0.2)	0	0	0	1 (0.4)
Grade 5	9 (1.4)	7 (1.1)	3 (0.9)	2 (0.6)	5 (1.8)	5 (1.8)

Table 4. Bleeding

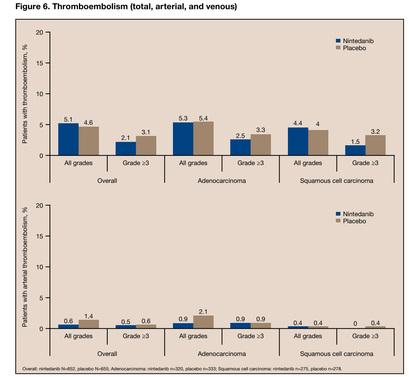
	Overall		Adenocarcinoma		Squamous cell carcinoma	
	Nintedanib (N=652)	Placebo (N=655)	Nintedanib (n=320)	Placebo (n=333)	Nintedanib (n=275)	Placebo (n=278)
Bleeding by preferred term, n (%)	92 (14.1)	76 (11.6)	35 (10.9)	37 (11.1)	47 (17.1)	30 (10.8)
Epistaxis	32 (4.9)	18 (2.7)	16 (5.0)	12 (3.6)	13 (4.7)	4 (1.4)
Hemoptysis	31 (4.8)	31 (4.7)	8 (2.5)	14 (4.2)	19 (6.9)	16 (5.8)
Pulmonary hemorrhage	14 (2.1)	12 (1.8)	3 (0.9)	4 (1.2)	8 (2.9)	7 (2.5)
Respiratory tract hemorrhage	5 (0.8)	4 (0.6)	1 (0.3)	1 (0.3)	4 (1.5)	3 (1.1)
Bronchial hemorrhage	4 (0.6)	0	3 (0.9)	0	1 (0.4)	0
Rectal hemorrhage	3 (0.5)	1 (0.2)	2 (0.6)	0	0	0
Disseminated intravascular coagulation	2 (0.3)	0	1 (0.3)	0	1 (0.4)	0
Hematemesis	2 (0.3)	0	1 (0.3)	0	1 (0.4)	0
Hematuria	2 (0.3)	3 (0.5)	1 (0.3)	2 (0.6)	0	1 (0.4)
Hemorrhoidal hemorrhage	2 (0.3)	2 (0.3)	0	0	1 (0.4)	0
Hemorrhagic diarrhea	1 (0.2)	0	0	0	1 (0.4)	0
Duodenal ulcer hemorrhage	1 (0.2)	0	0	0	1 (0.4)	0
Gingival bleeding	1 (0.2)	0	0	0	0	0
Hemodialysis	1 (0.2)	0	0	0	1 (0.4)	0
Hematoma	1 (0.2)	1 (0.2)	1 (0.3)	NR	NR	NR
Hemorrhage	1 (0.2)	3 (0.5)	0	0	1 (0.4)	2 (0.7)
Lower gastrointestinal hemorrhage	1 (0.2)	0	0	0	1 (0.4)	0
Pharyngeal hemorrhage	1 (0.2)	0	1 (0.3)	0	0	0
Pleural hemorrhage	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)	0	0
Scrotal hematoma	1 (0.2)	0	1 (0.3)	0	0	0
Anal hemorrhage	0	2 (0.3)	0	2 (0.6)	0	0
Contusion	0	1 (0.2)	0	1 (0.3)	0	0
Hemarthrosis	0	1 (0.2)	0	1 (0.3)	0	0
Injection-site hematoma	0	1 (0.2)	0	0	0	1 (0.4)
Intestinal hemorrhage	0	1 (0.2)	0	0	0	1 (0.4)
Mouth hemorrhage	0	2 (0.3)	0	2 (0.6)	0	0
Esophageal hemorrhage	0	1 (0.2)	0	1 (0.3)	0	0
Postprocedural hemorrhage	0	1 (0.2)	0	0	0	1 (0.4)
Tracheal hemorrhage	0	1 (0.2)	0	0	0	1 (0.4)

NR, not reported.
The non-respiratory bleeding events occurred in various locations. Except for the respiratory tract, there was no clustering of bleeding events in any other organ system.

Thromboembolic events

- The overall percentage of patients with thromboembolic events was low (overall populations: nintedanib 5.1% vs placebo 4.6%) and comparable across all main study populations (Figure 6)
  - the incidence of patients with any CTCAE grade and of those with Grade ≥3 was comparable in both treatment arms across all main study populations
  - five patients in the nintedanib group (one myocardial infarction [adenocarcinoma], one disseminated intravascular coagulation [adenocarcinoma], one ischemic stroke [adenocarcinoma], one superior vena caval occlusion [SCC], and one venous thrombosis [SCC]) and four patients in the placebo group (one cerebrovascular accident [adenocarcinoma] and three pulmonary embolisms [SCC]) experienced a fatal thromboembolic event
- The percentage of patients with arterial thromboembolism occurred in fewer patients in the nintedanib group than in the placebo group in the overall (0.6% vs 1.4%) and adenocarcinoma (0.9% vs 2.1%) study populations
- The percentage of patients with venous thromboembolism occurred in more patients in the nintedanib group than in the placebo group in the overall (2.8% vs 1.5%) and adenocarcinoma (2.8% vs 1.2%) study populations, with notably more deep vein thrombosis events (Table 5)

Figure 6. Thromboembolism (total, arterial, and venous)



Overall: nintedanib N=652, placebo N=650; Adenocarcinoma: nintedanib n=320, placebo n=333; Squamous cell carcinoma: nintedanib n=275, placebo n=278.

Figure 6. Thromboembolism (total, arterial, and venous) (cont'd)

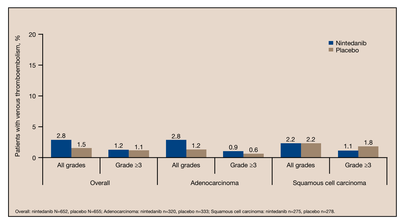


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Table 5. Arterial and venous thromboembolisms

	Overall			Adenocarcinoma			Squamous cell carcinoma		
	Nintedanib (N=652)		Placebo (N=655)	Nintedanib (n=320)		Placebo (n=333)	Nintedanib (n=275)		Placebo (n=278)
CTCAE Grade	1/2	≥3	1/2 ≥3	1/2	≥3	1/2 ≥3	1/2	≥3	1/2 ≥3
Arterial thromboembolism, n (%)	1 (0.2)	3 (0.5)	5 (0.8) 4 (0.6)	0	3 (0.9)	4 (1.2)	3 (0.9)	1 (0.4)	0 1 (0.4)
Ischemic stroke	0	1 (0.2)	0 0	0	1 (0.3)	0 0	0	0	0 0
Myocardial infarction	0	1 (0.2)	1 (0.2) 2 (0.3)	0	1 (0.3)	1 (0.3) 2 (0.6)	0	0	0 0
Pulmonary artery thrombosis	1 (0.2)	0	0 0	0	0	0 0	1 (0.4)	0	0 0
Transient ischemic attack	0	1 (0.2)	1 (0.2) 0	0	1 (0.3)	1 (0.3) 0	0	0	0 0
Acute myocardial infarction	0	0	0 1 (0.2)	0	0	0 1 (0.3)	0	0	0 0
Aortic thrombosis	0	0	1 (0.2) 0	0	0	1 (0.3) 0	0	0	0 0
Transient blindness	0	0	1 (0.2) 0	0	0	1 (0.3) 0	0	0	0 0
Subclavian artery thrombosis	0	0	1 (0.2) 0	0	0	1 (0.3) 0	0	0	0 0
Venous thromboembolism, n (%)	16 (2.5)	4 (1.2)	9 (1.5) 7 (1.1)	6 (1.9)	3 (0.9)	2 (0.6) 3 (1.1)	9 (3.3)	1 (0.4)	5 (1.8) 3 (1.8)
Pulmonary embolism	1 (0.2)	4 (0.6)	1 (0.2) 5 (0.8)	1 (0.3)	3 (0.9)	1 (0.3) 2 (0.6)	0	1 (0.4)	0 3 (1.1)
Deep vein thrombosis	3 (0.5)	1 (0.2)	0 1 (0.2)	1 (0.3)	0	0 1 (0.3)	1 (0.4)	0	0 0
Superior vena cava syndrome	1 (0.2)	2 (0.3)	2 (0.3) 2 (0.3)	0	0	1 (0.3) 0	1 (0.4)	1 (0.4)	1 (0.4) 2 (0.7)
Thrombophlebitis	2 (0.3)	0	0 0	2 (0.6)	0	0 0	0	0	0 0
Venous thrombosis	1 (0.2)	1 (0.2)	0 0	1 (0.3)	0	0 0	0	0	0 0
Venous thrombosis limb	1 (0.2)	1 (0.2)	0 0	1 (0.3)	0	0 0	0	0	0 0
Axillary vein thrombosis	1 (0.2)	0	0 1 (0.2)	0	0	0 0	0	0	0 0
Post-thrombotic syndrome	1 (0.2)	0	0 0	0	0	0 0	1 (0.4)	0	0 0

CTCAE, Common Terminology Criteria for Adverse Events.

CONCLUSIONS

- In the LUME-Lung 1 trial, the combination of nintedanib + standard docetaxel does not greatly increase the frequency of characteristic AEs associated with antiangiogenic agents, except for bleeding, hypertension, and venous thromboembolism in SCC patients compared with placebo + docetaxel
- The nature, frequency, and severity of AEs were consistent with the underlying disease of NSCLC, concomitant chemotherapy with docetaxel, and expected AEs of nintedanib
- The antiangiogenic AE profile of nintedanib appears less pronounced than what has been described for other antiangiogenic therapies in NSCLC, especially in patients with SCC
- Nintedanib in combination with docetaxel meets the medical need for 2nd-line treatment of patients with adenocarcinoma with a manageable safety profile

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