Anti-angiogenic-specific adverse events in patients with non-small cell lung cancer treated with nintedanib and docetaxel

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Abstract

Objectives: LUME-Lung 1 was a randomized, placebo-controlled, Phase III trial investigating nintedanib + docetaxel versus placebo + docetaxel in patients with advanced NSCLC progressing after first-line chemotherapy. Progression-free survival was significantly improved with nintedanib + docetaxel in the overall population and overall survival was significantly improved in the pre-specified analysis of patients with adenocarcinoma. We evaluated the frequency of characteristic adverse events (AEs) commonly seen with existing anti-angiogenic agents.

Materials and methods: The incidence and intensity of AEs were evaluated in all patients who received at least one dose of study medication (N = 1307) and for the two main histologies: adenocarcinoma (n = 653) and squamous cell carcinoma (SCC; n = 553). AEs of special interest were analyzed by category, preferred term, and worst CTCAE grade and included perforation, hypertension, bleeding, thromboembolic events, and skin disorders.

Results and conclusions: The incidence of patients with all-grade gastrointestinal (GI) perforations was low and balanced between arms (0.5% in both) and across histologies; the incidence of non-GI perforations was 1.2% with nintedanib + docetaxel versus 0.2% with placebo + docetaxel. The incidence of some events was higher with nintedanib + docetaxel versus placebo + docetaxel: hypertension (3.5% vs 0.9%), rash (11.0% vs 8.1%), and cutaneous adverse reactions (13.0% vs 10.7%). Rash and cutaneous adverse reactions were predominantly Grade 1–2 with both treatments. The incidence of all-grade bleeding was also slightly higher in nintedanib + docetaxel-treated patients (14.1% vs 11.6%) driven by between-treatment differences in the SCC subpopulation; most events were Grade 1–2. The proportion of patients with a thromboembolic event was low and comparable between arms for all grades (5.1% vs 4.6%) and Grade ≥3 (2.1% vs 3.1%). Safety evaluation of the LUME-Lung 1 study showed that the frequency of AEs commonly associated with other anti-angiogenic agents was lower with nintedanib + docetaxel. Survival benefits from addition of nintedanib to docetaxel in patients with adenocarcinoma after first-line therapy can be achieved alongside a manageable safety profile.

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1. Introduction

Vascular endothelial growth factor (VEGF) plays the most important role in regulating tumor-related angiogenesis and is often highly expressed in human cancers making it a preferred target for antitumor therapy [1,2]. With the introduction of VEGF inhibitors for cancer treatment, new class-specific adverse events (AEs) for these drugs have been observed, including perforations, bleeding, thromboembolic events, hypertension, and proteinuria [3,4]. Skin-related AEs are also often associated with the anti-VEGF small-molecule tyrosine kinase inhibitors sorafenib and sunitinib although these effects are not related directly to VEGF inhibition [3,5].

In addition to VEGF, various other signaling pathways mediate tumor angiogenesis, growth, and metastasis (e.g., platelet-derived growth factor [PDGF], fibroblast growth factor [FGF]) [6]. Nintedanib is an oral, twice-daily, triple angiokinase inhibitor targeting VEGF receptors 1–3 (VEGFR-1 to -3), PDGF receptors α/β (PDGFR-α and -β), and FGF receptors 1–3 (FGFR-1 to -3), as well as rearranged during transfection (RET) receptor tyrosine kinase and fms-like tyrosine kinase receptor-3 (FLT3) [7,8]. Nintedanib has negligible drug–drug interactions via cytochrome P450 (CYP450) [9], and a manageable safety profile in combination with docetaxel, pemtrexed, carboplatin/paclitaxel, and afatinib [8,10–12]. LUME-Lung 1 (NCT00805194; 1199.13), a randomized, placebo-controlled, Phase III trial that investigated nintedanib plus docetaxel in patients with advanced non-small cell lung cancer (NSCLC) progressing after first-line chemotherapy, demonstrated that nintedanib plus docetaxel significantly improved median progression-free survival regardless of histology (median 3.4 vs 2.7 months; hazard ratio [HR] = 0.79 [95% confidence interval [CI]: 0.68–0.92], p = 0.0019) [8]. The addition of nintedanib to docetaxel also significantly improved median overall survival in the pre-specified population of patients with adenocarcinoma histology (12.6 vs 10.3 months; HR = 0.83 [95% CI: 0.70–0.99], p = 0.0359). AEs with nintedanib plus docetaxel were manageable with adequate treatment, dose interruptions, and dose reductions, and the most frequently reported Grade ≥3 AEs were diarrhea and reversible increases in alanine and aspartate aminotransferase levels. The outcomes of the LUME-Lung 1 study contributed to nintedanib in combination with docetaxel being approved in the European Union for the treatment of patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology after first-line chemotherapy [13].

The current analysis extends our investigation of the LUME-Lung 1 trial and evaluates the frequency of characteristic AEs commonly seen with existing agents that target angiogenesis. In addition, the safety profile is further characterized in the two main histologies in the LUME-Lung 1 trial – adenocarcinoma and squamous cell carcinoma (SCC).

2. Materials and methods

2.1. Study design

Complete details of the LUME-Lung 1 study design have been reported previously [8]. All patients provided written informed consent and the study protocol was approved by independent ethics committees or institutional review boards at each center. Patients with tumors of all histologies who had stable (<4 weeks) asymptomatic brain metastases were permitted. Key exclusion criteria included: radiographic evidence of cavitary or necrotic tumors; centrally located tumors with radiographic evidence (computed tomography [CT] or magnetic resonance imaging [MRI]) of local invasion of major blood vessels; history of clinically significant hemoptysis within the past 3 months; use of 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; and known inherited predisposition to bleeding or thrombosis.

2.2. Assessment

The incidence and intensity of AEs according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 were evaluated in all patients who received at least one dose of study medication: nintedanib/placebo or docetaxel. AEs were categorized by pooling Medical Dictionary for Regulatory Activities (MedDRA) terms and by using standardized MedDRA queries or tailored special search categories, and were tabulated by the AE of special interest (AESI) category, preferred term, and worst CTCAE grade. AESIs that were analyzed included perforation (i.e., gastrointestinal [GI] and non-GI), hypertension, bleeding (including respiratory bleeding), thromboembolic events (in particular, arterial and venous thromboembolisms), and skin reactions (including rash, cutaneous adverse reactions [Standardized MedDRA Queries term: severe cutaneous adverse reactions), and hand–foot syndrome [HFS]).

In addition to an analysis of the overall population, patients with adenocarcinoma and SCC were analyzed to determine the presence of histology-specific AEs. Safety analyses compared the nintedanib arm to the placebo arm, and were based on the concept of treatment-emergent AEs. AEs with onset between the first administration of the study drug (docetaxel or nintedanib/placebo) until 28 days after the last administration were considered to be ‘on-treatment’ AEs.

3. Results

3.1. Patient population

Baseline demographics and disease characteristics for the overall population (N = 1314) have been reported previously and were balanced between the two treatment groups. Of the overall population, 658 patients had tumors of adenocarcinoma histology and 555 had tumors of SCC histology; demographics and baseline characteristics, including predefined stratification factors, were also balanced across treatment groups (Table A1). On the randomized population, 1307 patients went on to receive at least one dose of study drug, and comprised the safety population (adenocarcinoma n = 653; SCC n = 553).

3.2. Perforation

GI perforations were infrequent, and were balanced between both treatment arms and across histologies (Table 1). In the overall population, a total of six patients had GI perforations (any grade) (nintedanib n = 3 and placebo n = 3); of these, one patient in the nintedanib group and three patients in the placebo group experienced an intestinal or gastric perforation, while the remaining two nintedanib-treated patients experienced an anal or perirectal abscess. Grade ≥3 GI perforations were infrequent in both treatment arms and across histologies, and lower in the nintedanib arm.

The incidence of non-GI perforations was also low overall but higher in nintedanib-treated patients (1.2% vs 0.2%; see Table 1). The non-GI perforations in the nintedanib arm were due to bladder perforation (one patient), laryngeal fistula (one patient), periproctitis abscess (one patient), and lung or chest wall abscess (five patients). Four of the five patients who reported lung or chest wall...
<table>
<thead>
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<th>Adverse event</th>
<th>Overall n (%)</th>
<th>Nintedanib + docetaxel (n=275)</th>
<th>Placebo + docetaxel (n=278)</th>
<th>Nintedanib (n=320)</th>
<th>Placebo (n=333)</th>
<th>Placebo + docetaxel (n=333)</th>
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<tbody>
<tr>
<td>Adenocarcinoma, n(%)</td>
<td></td>
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<tr>
<td>Overall</td>
<td>3 (0.5)</td>
<td>3 (0.5)</td>
<td>4 (1.3)</td>
<td>6 (0.9)</td>
<td>1.1 (0.7)</td>
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<td>Grade 1</td>
<td>3 (0.5)</td>
<td>1 (0.3)</td>
<td>6 (3.5)</td>
<td>11 (3.3)</td>
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<td>Grade 2</td>
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<td>3 (1.2)</td>
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<td>2 (0.6)</td>
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<td>Grade 3</td>
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<td>Squamous cell carcinoma, n (%)</td>
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<tr>
<td>Overall</td>
<td>92 (14.1)</td>
<td>15 (2.3)</td>
<td>76 (11.6)</td>
<td>12 (1.8)</td>
<td>35 (10.3)</td>
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<tr>
<td>Grade 1</td>
<td>52 (8.0)</td>
<td>10 (1.5)</td>
<td>46 (7.0)</td>
<td>7 (1.1)</td>
<td>37 (11.1)</td>
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<tr>
<td>Grade 2</td>
<td>32 (5.1)</td>
<td>14 (2.1)</td>
<td>30 (4.6)</td>
<td>20 (3.1)</td>
<td>11 (3.4)</td>
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<tr>
<td>Grade 3</td>
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<td>5 (0.7)</td>
<td>30 (4.6)</td>
<td>7 (1.1)</td>
<td>20 (6.0)</td>
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<tr>
<td>Hemoptysis</td>
<td>18 (2.8)</td>
<td>8 (1.2)</td>
<td>10 (1.5)</td>
<td>7 (1.1)</td>
<td>7 (2.1)</td>
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<tr>
<td>Non-GI</td>
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<td>GI</td>
<td>5 (0.7)</td>
<td>2 (0.7)</td>
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The percentage of patients with hypertension (all grades) was low in both treatment arms for all patients and independent of histology, albeit higher in patients receiving nintedanib treatment (3.5% vs 0.9%; Table 1). The majority (24 of 29) of patients with hypertension had Grade 1 or 2 events; no patients had hypertension of Grade 4 or 5, and there were no cases of posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome.

Blood pressure remained stable during treatment in both treatment arms. Median systolic blood pressure was 125 mmHg at screening and 120 mmHg at the end of treatment in both treatment arms. Median diastolic blood pressure was 80 mmHg in both treatment arms at screening and 70 mmHg in the nintedanib group and 76 mmHg in the placebo group at the end of treatment. Similar results were observed in patients with adenocarcinoma and SCC.

### 3.4. Bleeding

The percentage of patients with bleeding (all grades) was slightly higher in the nintedanib arm than in the placebo arm (14.1% vs 11.6%; Table 1). The difference between treatments in the overall study population was driven by patients with SCC (nintedanib 17.1% vs placebo 10.8%). The frequency of bleeding was similar in the two treatment groups in patients with adenocarcinoma histology (nintedanib 10.9% vs placebo 11.1%). The majority of cases of bleeding were Grade 1 or 2 with few patients experiencing Grade ≥3 bleeding events. The number of patients with Grade ≥3 bleeding events was similar between treatment arms in all study populations (see Table 1). There were no imbalances in the number of patients with respiratory bleeding (all grades and Grade ≥3) events between the treatment arms for the overall study population and for patients with adenocarcinoma. In patients with SCC, respiratory bleeding was more frequent in the nintedanib arm than in the placebo arm (10.9% vs 8.6%).

As shown in Table 2, the most common bleeding events in the overall population were epistaxis and respiratory bleeding. There was no clustering of bleeding events in any organ system other than the respiratory tract. No AEs indicating intracerebral bleeding were reported. Similar results were seen in patients with adenocarcinoma and SCC.

Fatal bleeding events were balanced between the arms for the overall population (nintedanib 1.4% vs placebo 1.1%), the adenocarcinoma population (nintedanib 0.9% [n=31] vs placebo 0.6% [n=2]), and the SCC population (nintedanib 1.8% [n=5] vs placebo 1.8% [n=5]). Fatal bleeding in patients with adenocarcinoma resulted from hemorrhage (nintedanib n=1 vs placebo n=1), pulmonary hemorrhage (nintedanib n=1 vs placebo n=1), and disseminated intravascular coagulation (nintedanib n=1 vs placebo n=0). Fatal bleeding in patients with SCC resulted from hemorrhage (nintedanib n=3 vs placebo n=1), pulmonary hemorrhage (nintedanib n=2 vs placebo n=2), and hemorrhage (nintedanib n=0 vs placebo n=2). One additional nintedanib-treated patient of unknown tumor histology suffered a fatal hemorrhage. The majority of fatal bleeding events were tumor-associated and no deaths in the nintedanib arm were considered related to nintedanib treatment.
3.5. Thromboembolic events

The overall percentage of patients with thromboembolic events was low and comparable across all main study populations (Table 1). The incidence of Grade ≥3 thromboembolic events was also comparable in both treatment arms across all main study populations. As shown in Table 1, the number of patients with arterial thromboembolism was lower in the nintedanib group than in the placebo group in the overall population and the adenocarcinoma population, but did not differ between these groups in the SCC population. The number of patients with venous thromboembolism was higher in the nintedanib group than in the placebo group in the overall population and the adenocarcinoma population, but did not differ between these groups in the SCC population. Reported rates of Grade ≥3 arterial and venous thromboembolism were comparable across study populations.

There was no pattern in the type of arterial thromboembolism events between treatment groups although, for venous thromboembolism events, deep vein thrombosis was slightly more common in the nintedanib (0.6% [n = 4]) than the placebo treatment arm (0.2% [n = 1]). There was no difference in the rate of pulmonary embolism between the treatment arms (0.8% [n = 5] vs 0.9% [n = 6]).

Fatal thromboembolic events were balanced between the arms (nintedanib 0.8% [n = 5] vs placebo 0.6% [n = 4]). Fatal thromboembolic events in patients with adenocarcinoma resulted from cerebrovascular accident (placebo n = 1), myocardial infarction (nintedanib n = 1), ischemic stroke (nintedanib n = 1), and disseminated intravascular coagulation (nintedanib n = 1), while fatal thromboembolic events in patients with SCC resulted from pulmonary embolism (placebo n = 3), superior vena caval occlusion (nintedanib n = 1), and venous thrombosis (nintedanib n = 1).

3.6. Skin toxicity

The percentages of patients with rash and cutaneous adverse reactions were slightly higher with nintedanib than with placebo in all populations (although most events were Grades 1–2). The frequency of patients with cutaneous adverse reactions was slightly higher in the nintedanib arm compared with the placebo arm of the adenocarcinoma population (15.6% vs 10.5%), whereas no differences were observed between treatment arms in the SCC population (9.5% vs 9.0%; Table 3). The most common events by preferred term contributing to the grouped terms of rash were rash (2.9% vs 2.7% in the overall population) and dermatitis acneiform (2.5% vs 2.1%), and stomatitis (9.7% vs 8.7%) was the most common cutaneous adverse reaction (Table 3). The percentages of patients with HFS were low (<1%) and similar in the two treatment arms across populations. No patients experienced Stevens–Johnson syndrome or toxic epidermal necrolysis.

4. Discussion

VEGF-targeted therapies have demonstrated significant efficacy across a range of tumor types; however, there are concerns about treatment–related toxicity when using antibodies targeted to VEGF signaling, such as monoclonal antibodies (e.g., bevacizumab, ramucirumab) or VEGFR tyrosine kinase inhibitors (TKIs; e.g., sunitinib, sorafenib) [14]. As expected, there is overlap in the safety profiles associated with agents that inhibit one or more steps in the angiogenesis signaling pathway; however, there are also differences, which give each compound a characteristic safety profile. We evaluated the anti-angiogenic AEs associated with the angiogenesis inhibitor nintedanib, and found differences compared to other inhibitors of angiogenesis.
Bevacizumab, which targets VEGF, was the first approved anti-angiogenic agent for the treatment of NSCLC, although it is not approved for use in patients with SCC histology because of the increased risk of pulmonary hemorrhage [15,16]. Indeed, bleeding is one of the most severe and potentially life-threatening toxicities of VEGF inhibitors, with a wide range of incidence and severity reported in different studies [17]. Although a pooled analysis of three randomized trials failed to demonstrate a significantly higher incidence of severe hemorrhages of CTCAE Grade 3 or 4 [16], the incidence of mild bleeding episodes was increased in the experimental arm of most trials using bevacizumab (up to 40%) [17]. In both the AVAIL (AVAstin in Lung cancer) and E4599 trials, patients with advanced non-squamous NSCLC who received bevacizumab in combination with chemotherapy experienced significantly higher rates of Grade ≥3 bleeding (~4%) compared to chemotherapy alone [18,19]. Bleeding or hemorrhage (all grades) has also been more frequently reported in patients treated with ramucirumab compared to those treated with placebo in the REVEL study (29% vs 15%) [20]. Life-threatening or fatal bleeding episodes have also been reported with bevacizumab [15]. Grade ≥3 bleeding events in the nintedanib arm of LUME-Lung 1 (2.3%) were comparable to ramucirumab in REVEL (2.4%) and lower than bevacizumab in the AVAIL study (4.2–4.3%) [18,20]. Bleeding events do not appear to be commonly associated with nintedanib treatment; although more nintedanib plus docetaxel-treated patients experienced bleeding compared to placebo plus docetaxel-treated patients, the magnitude of the difference between the nintedanib and placebo arms was lower than with bevacizumab or ramucirumab in NSCLC [18,20]. Moreover, the frequency of fatal bleeding events was low (<1.5%) in the nintedanib arm and was balanced between the treatment arms for all toxicities, suggesting a low risk of fatal bleeding with nintedanib in patients with NSCLC.

Hypertension is another frequently reported AE of VEGF inhibition. Thus far, the mechanisms by which VEGF inhibitors may induce hypertension have not been fully elucidated; however, it is speculated that treatment-induced hypertension reflects the effect of anti-VEGF agents on multiple VEGFRs present on the vasculature throughout the body, and the affinity of an anti-VEGF agent for specific VEGFR subtypes [17]. Despite the recognized association between anti-VEGF agents and hypertension, the frequency and intensity of hypertension as an AE varies between studies, depending on the tumor type and other patient-related factors, and even within the same indication with the same anti-angiogenic agent [17,21]. Meta-analyses have shown that the incidence of hypertension (all grades) in patients receiving bevacizumab was 24%, with 8% of events being Grades 3–4; rates significantly higher compared to controls [22]. Other antiangiogenesis inhibitors are also associated with hypertension and meta-analyses have found similarly high rates of hypertension in patients treated with sorafenib (all grades, 19%; Grades ≥3, 4%) [23], sunitinib (all grades, 22%; Grades 3–4, 7%) [24], vandetanib (all grades, 24%; Grades 3–4, 6%) [25], pazopanib (all grades, 36%; Grades 3–4, 7%) [26], and axitinib (all grades, 40%; Grades 3–4, 13%) [27]. Treatment-related hypertension appears to be dose-dependent with some anti-angiogenic agents, e.g., sunitinib and axitinib [28,29], and a direct relationship between total drug dose and blood pressure has been reported for some agents (e.g., sunitinib) [28]. Consistent with findings for other VEGF inhibitors, a higher frequency of hypertension was reported in LUME-Lung 1; however, the percentage of nintedanib-treated patients who experienced all-grades (3.5%) and Grade ≥3 (0.6%) hypertension was relatively lower than would be commonly expected with VEGF inhibitors. Although nintedanib has not been directly compared to an anti-angiogenic agent in NSCLC, a Phase II study in previously untreated patients with renal cell carcinoma (RCC) compared nintedanib to sunitinib. In this study, 3% of patients...
treated with nintedanib experienced any-grade hypertension compared to 16% in patients treated with sunitinib [30].

Although meta-analyses have shown that bevacizumab treatment is associated with a significantly increased risk of developing GI perforation [31], a similar risk was not shown in a meta-analysis of Phase II and III studies in patients treated with VEGFR TKIs other than nintedanib [32]. Results from the LUME-Lung 1 study suggest that this is also the case for nintedanib, as the rate of GI perforations was not increased by the addition of nintedanib to chemotherapy. Non-GI perforations did occur more commonly in the nintedanib arm than in the placebo arm, but the overall incidence was low.

Anti-angiogenic agents are also associated with an increased risk of arterial and venous thromboembolism [33]. Meta-analyses have shown that bevacizumab is associated with an increased risk of both arterial thromboembolism [34] and venous thromboembolism in patients with solid tumors [35]. Generally, the risk of venous thromboembolism appears lower with VEGFR TKIs, and is often comparable with that of patients treated with standard chemotherapy. A meta-analysis evaluating US Food and Drug Administration-approved VEGFR TKIs ( pazopanib, sunitinib, sorafenib, and vandetanib) across different tumor types, found that the incidence of venous thromboembolism events was 3% (95% CI: 1.7–5.1%) and not significantly increased versus controls [26]. Consistent with this, data from LUME-Lung 1 show a similar frequency of increased venous thromboembolism in the nintedanib arm (2.8%) compared to the placebo arm (1.5%). The increased frequency in the nintedanib arm occurred predominantly among patients with adenocarcinoma histology. There was no increase in arterial thromboembolism with nintedanib treatment relative to placebo.

VEGFR- and multi-kinase inhibitors are also associated with skin toxicities, with hand–foot skin reaction (HFSR), a distinct variant of HFS, and rash being two of the more frequently reported AEs with sorafenib and sunitinib [36]. The exact mechanism of these side effects is poorly understood but different mechanisms have been proposed [37,38]. HFSR is considered one of the most clinically significant dermatologic side effects and can have a deleterious impact on quality of life [39]. Recent meta-analyses of Phase II and Phase III studies in RCC have indicated that the Grade 1–3 HFSR incidence rate was 33.8% with single-agent sorafenib and 18.9% with single-agent sunitinib [38,40]. Although we found that the frequencies of skin-related AEs in LUME-Lung 1 were higher in patients treated with nintedanib than with placebo (cutaneous adverse reactions: 13.0% vs 10.7%; rash: 11.0% vs 8.1%), they were generally lower than reported for other agents and HFS was rare (<1% in either treatment arm). This observation is in line with data for nintedanib versus sunitinib from a Phase II study in first-line RCC patients, where no patients on nintedanib had HFS compared to 31.3% of patients on sunitinib [30].

5. Conclusions

Extensive safety evaluation of the LUME-Lung 1 study showed that the frequency of AEs commonly associated with anti-angiogenic agents was lower with nintedanib plus docetaxel than with other anti-angiogenic agents. The significant survival benefits demonstrated with the addition of nintedanib to docetaxel in LUME-Lung 1 in patients with adenocarcinoma can be achieved alongside a manageable safety profile.

Conflicts of interest

M. Reck has received honoraria for advice and lectures from Hoffmann-La Roche, Eli Lilly, Pfizer, Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca and Boehringer Ingelheim. A Mellemgaard has participated in advisory boards, received honoraria for lectures and support for participation in congresses from Boehringer Ingelheim. J. von Pawel has participated in advisory boards for Clovis Oncology, Novartis, Pfizer, AbbVie, Daiichi Sankyo and Bristol-Myers Squibb. J. Bennouna has participated in advisory boards and received honoraria from Boehringer Ingelheim, Hoffmann-La Roche and AstraZeneca. J.-Y. Douillard has received honoraria for participating in advisory boards or lectures in educational symposia from Boehringer Ingelheim, AstraZeneca, Hoffmann-La Roche and Novartis. J. Barrueco, H. Aboshady and J. Hocke are employees of Boehringer Ingelheim. R. Kaiser is an employee of and a patent holder with Boehringer Ingelheim. M. Gottfried, I. Bondarenko, Y. Cheng, K. Zarogoulidis and A. Luft declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2015.08.003.

References

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