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ORIGINAL ARTICLE

Nintedanib for the treatment of patients with refractory metastatic colorectal cancer (LUME-Colon 1): a phase III, international, randomized, placebo-controlled study

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Background: Angiogenesis is critical to colorectal cancer (CRC) growth and metastasis. Phase I/II studies have demonstrated the efficacy of nintedanib, a triple angiokinase inhibitor, in patients with metastatic CRC. This global, randomized, phase III study investigated the efficacy and safety of nintedanib in patients with refractory CRC after failure of standard therapies.

Patients and methods: Eligible patients (Eastern Cooperative Oncology Group performance status 0–1, with histologically/cytologically confirmed metastatic/locally advanced CRC adenocarcinoma unamenable to surgery and/or radiotherapy) were randomized 1 : 1 to receive nintedanib (200 mg twice daily) or placebo (twice daily), until disease progression or undue toxicity. Patients were stratified by previous regorafenib, time from onset of metastatic disease to randomization, and region. Co-primary end points were overall survival (OS) and progression-free survival (PFS) by central review. Secondary end points included objective tumor response and disease control by central review.

Results: From October 2014 to January 2016, 768 patients were randomized; 765 were treated (nintedanib $n = 384$; placebo $n = 381$). Median follow-up was 13.4 months (interquartile range 11.1–15.7). OS was not improved [median OS 6.4 months with nintedanib versus 6.0 months with placebo; hazard ratio (HR), 1.01; 95% confidence interval (CI), 0.86–1.19; $P = 0.8659$]. There was a significant but modest increase in PFS with nintedanib versus placebo (median PFS 1.5 versus 1.4 months, respectively; HR 0.58; 95% CI 0.49–0.69; $P < 0.0001$). There were no complete or partial responses. Adverse events (AEs) occurred in 97% of 384 nintedanib-treated patients and 93% of 381 placebo-treated patients. The most frequent grade ≥3 AEs were liver-related AEs (nintedanib 16%; placebo 8%) and fatigue (nintedanib 9%; placebo 6%).

Conclusions: The study failed to meet both co-primary end points. Nintedanib did not improve OS and was associated with a significant but modest increase in PFS versus placebo. Nintedanib was well tolerated.

ClinicalTrials.gov number: NCT02149108 (LUME-Colon 1).

Key words: chemorefractory metastatic colorectal cancer, angiogenesis inhibition, nintedanib

Introduction

While combination cytotoxic therapy remains the backbone of treatment in metastatic colorectal cancer (CRC), inhibition of angiogenesis via the vascular endothelial growth factor (VEGF) pathway is now also a well-established treatment approach in CRC. A number of angiogenesis-targeting agents are approved, either in combination with fluoropyrimidine-based chemotherapy in first- or second-line (bevacizumab, aflibercept, ramucirumab), or as monotherapy in the last-line setting (regorafenib) [1, 2]. Owing to these advances, patients with metastatic CRC typically achieve an overall survival (OS) of ~30 months [1].

Regorafenib and trifluridine/tipiracil (TAS-102) have both been shown to improve survival compared with best supportive care (BSC) in patients who had previously received all available standard therapies; they are approved for use in refractory CRC [3, 4]. However, both agents are associated with adverse events (AEs) that may be dose limiting [4, 5]. As such, there remains a need for active and better-tolerated treatments that prolong survival while maintaining patient quality of life (QoL).

Nintedanib is an oral, twice-daily, triple angiokinase inhibitor of VEGF receptors 1–3, platelet-derived growth factor receptor-α/β, and fibroblast growth factor receptors 1–3, which also inhibits the kinases RET, FLT3, Lck and Lyn [6, 7], and has been shown to delay or arrest tumor growth in xenograft models of solid tumors [6]. In the clinic, nintedanib monotherapy has been shown to exert an antiangiogenic effect in 67% of patients with advanced, refractory CRC in a phase I study, while stabilizing disease and maintaining a manageable safety profile [7]. On the basis of these results, the manageable tolerability profile expected with nintedanib [8], and the unmet need in this patient population, we hypothesized that nintedanib would be a suitable treatment of patients with CRC who had failed all currently approved therapies but could benefit from additional treatment. Here, we present the results of the phase III LUME-Colon 1 study that assessed the efficacy and safety of nintedanib in patients with refractory CRC after failure of standard therapies.

Patients and methods

Study design and participants

LUME-Colon 1 was a randomized, double-blind, placebo-controlled, global, phase III trial. Eligible patients had histologically or cytologically confirmed metastatic or locally advanced colorectal adenocarcinoma not amenable to curative surgery and/or radiotherapy. Patients were required to have progressed on approved standard therapies or have experienced unacceptable toxicity. Full inclusion and exclusion criteria have been reported previously [9], and are shown in the protocol (supplementary appendix, available at *Annals of Oncology* online). Previous treatment with regorafenib and trifluridine/tipiracil was permitted; however, the proportion of regorafenib-naïve patients was limited (maximum 70%).

The protocol was approved by health authorities and independent ethics committees or institutional review boards based on local regulations.

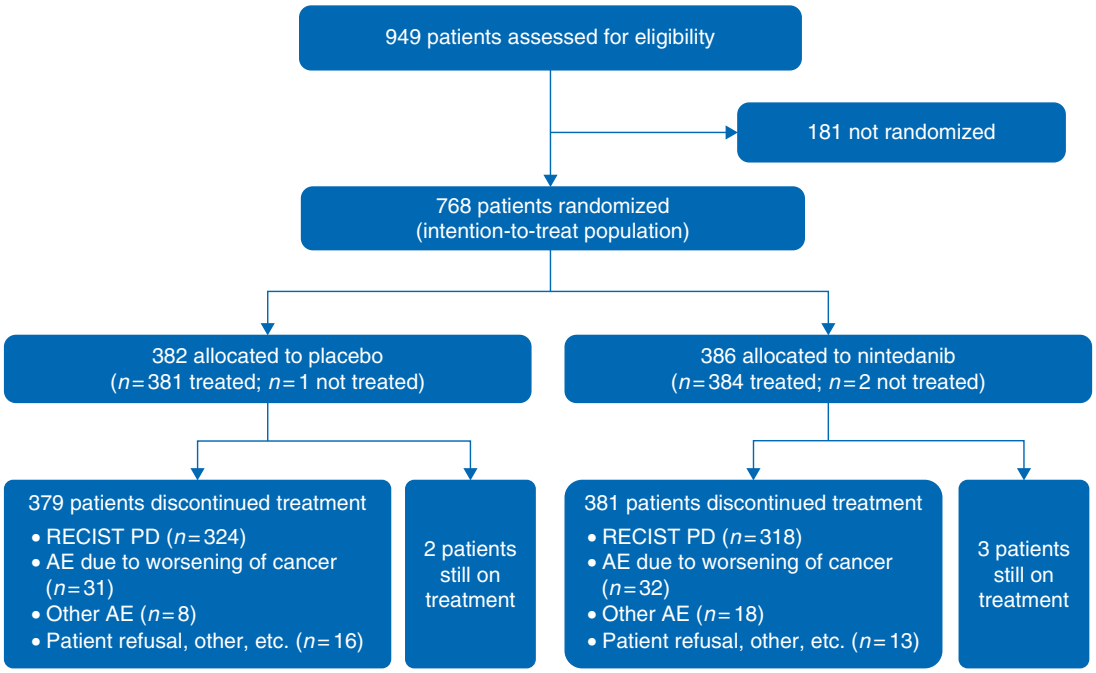

Figure 1. Patient disposition. Three patients were randomized but not treated in the study, two patients (placebo *n* =1; nintedanib *n*=1) due to worsening of underlying disease and one (nintedanib) due to noncompliance with the study protocol. AE, adverse event; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 1. Baseline characteristics and previous treatments

	Nintedanib ($n = 386$)	Placebo ($n = 382$)
Median age, years (range)	62 (22–85)	62 (23–83)
Sex (%)		
Male	236 (61.1)	218 (57.1)
Race[a] (%)		
Caucasian	279 (72.3)	268 (70.2)
Asian	97 (25.1)	104 (27.2)
Other	5 (1.3)	3 (0.8)
Missing	5 (1.3)	9 (2.4)
ECOG PS at baseline[b] (%)		
0	162 (42.0)	142 (37.2)
1	223 (57.8)	240 (62.8)
Region (%)		
Western Europe, North America, Australia	231 (59.8)	227 (59.4)
Asia	95 (24.6)	98 (25.7)
Other	60 (15.5)	57 (14.9)
Time from onset of metastatic disease until randomization (%)		
<24 months	108 (28.0)	110 (28.8)
≥24 months	278 (72.0)	272 (71.2)
Primary site of disease[c] (%)		
Colon	256 (66.3)	227 (59.4)
Rectum	130 (33.7)	154 (40.3)
Unknown	0	1 (0.3)
>1 metastatic site at screening (%)	345 (89.4)	319 (83.5)
Presence of liver metastases (%)		
Yes	277 (71.8)	266 (69.6)
No	109 (28.2)	116 (30.4)
Previous treatments		
Mean (SD) number of lines of previous systemic anticancer therapies (%)	3.9 (1.8)	3.9 (1.8)
≥3 lines of previous systemic anticancer therapies (%)	297 (76.9)	296 (77.5)
Previous systemic anticancer therapies (%)		
Oxaliplatin	386 (100.0)	382 (100.0)
Fluoropyrimidine	386 (100.0)	382 (100.0)
Irinotecan	386 (100.0)	382 (100.0)
Bevacizumab or aflibercept	382 (99.0)	381 (99.7)
Bevacizumab	368 (95.3)	370 (96.9)
Aflibercept	48 (12.4)	47 (12.3)
Regorafenib	141 (36.5)	144 (37.7)
Trifluridine/tipiracil	55 (14.2)	53 (13.9)
Previous radiotherapy (%)	104 (26.9)	132 (34.6)
KRAS wild-type and other *RAS* wild-type patients only	Nintedanib ($n = 158$)	Placebo ($n = 176$)
Prior cetuximab or panitumumab (%)	158 (100.0)	175 (99.4)

Data are *n* (%) unless otherwise specified.
[a]One patient indicated the races American Indian or Alaska Native, Black or African American and White.
[b]One patient in the nintedanib arm had an ECOG PS >1.
[c]One patient in the placebo arm had primary site 'Other/unknown'.
ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

LUME-Colon 1 followed the guiding principles of the Declaration of Helsinki and was conducted in accordance with good clinical practice as well as local laws and regulations. All patients provided written informed consent. The database cut-off date for these analyses was 14 June 2016.

Patients were randomized 1 : 1 to receive oral nintedanib 200 mg twice daily plus BSC or matching placebo twice daily plus BSC in 21-day courses until disease progression, undue toxicity, or withdrawal of consent. Randomization was stratified by previous treatment with regorafenib (yes versus no), time from the onset of metastatic disease until randomization in the trial (<24 versus ≥24 months), and geographical region (Western Europe, North America and Australia; Asia; and rest of the world). Predefined dose reductions were permitted to manage AEs (supplementary appendix, available at *Annals of Oncology* online). Patients were followed up every 3 weeks during treatment; tumor

response was assessed by computed tomography/magnetic resonance imaging every 6 weeks using Response Evaluation Criteria in Solid Tumors v1.1.

Outcomes

Co-primary end points were OS and progression-free survival (PFS) by central review. Secondary end points were objective tumor response and disease control by central review, and PFS by investigator assessment. Health-related QoL (HRQoL) was evaluated and results will be published in detail separately. Safety was assessed according to the US National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistical analysis

Full details of the statistical analysis are provided in the protocol (supplementary appendix, available at *Annals of Oncology* online). Co-primary end points and additional efficacy outcomes were analyzed on an intention-to-treat basis. A stratified log-rank test was used for primary efficacy analysis of both co-primary end points at a two-sided 5% level of significance in all randomized patients. Assuming a median OS of 5 months in the control group [3], recruitment of about 50 patients per month, and 20% loss to follow-up, 764 patients were to be randomized; 611 OS events were needed for the primary OS analysis to detect a hazard ratio (HR) of 0.77 (median OS difference of 1.5 months) with 90% power. It was assumed that nintedanib would increase median PFS by 2.7 weeks to 10.7 weeks versus 8 weeks with placebo (HR 0.75). As co-primary end points, it was planned to analyze OS and PFS at the same time once the required number of OS events had been reached. As expected, there were more PFS than OS events, and therefore no formal power calculation for PFS was done and as many PFS events as possible were included in the analysis. At the time of the OS analyses, it was estimated that 595 analyzable PFS events would have occurred, which would yield a power of 95% for the PFS analysis.

HRQoL analyses were not adjusted for multiple testing. Safety data were analyzed descriptively in all treated patients.

Results

Patient disposition is shown in Figure 1. Between 14 October 2014 and 18 January 2016, 768 patients were randomized to receive treatment with nintedanib ($n = 386$) or placebo ($n = 382$); these comprised the efficacy population. The safety population comprised 765 treated patients (nintedanib, $n = 384$; placebo, $n = 381$). Most baseline characteristics were well balanced between arms, with some slight differences in primary disease site, previous radiotherapy and number of metastatic sites between treatment groups (Table 1).

Median treatment duration was 2.1 [interquartile range (IQR), 1.4–3.3] months in the nintedanib group and 1.4 (IQR, 1.3–2.1) months in the placebo group. Patients treated with nintedanib received 93.0% of the planned dose during the study, compared with 98.4% in the placebo group. Dose reductions were required in 19% of nintedanib-treated patients (58 required one and 14 required two dose reductions) and 3% of placebo-treated patients (12 single dose reductions). The most common reasons for nintedanib dose reduction were increased alanine aminotransferase (ALT) levels, increased aspartate aminotransferase (AST) levels and diarrhea. Dose reductions were required owing to AEs, except in one patient receiving placebo. Treatment interruption of >14 days was required in 12 nintedanib-treated patients (3%) and one placebo-treated patient (0.3%). Systemic therapy after progression is shown in supplementary Table S1, available at *Annals of Oncology* online (supplementary appendix, available at *Annals of Oncology* online).

At the analysis of the co-primary end points of OS and PFS, 613 OS events and 687 PFS events had occurred and median follow-up was 13.4 months (IQR, 11.1–15.7). Median OS was 6.4 months with nintedanib and 6.0 months with placebo [HR 1.01; 95% confidence interval (CI) 0.86–1.19; $P = 0.8659$; Figure 2A]. Median PFS was 1.5 versus 1.4 months (HR 0.58; 95% CI 0.49–0.69; $P < 0.0001$) (Figure 3A). Although not a co-primary end point, median PFS by investigator review was 2.6 months (95% CI 2.0–2.7) with nintedanib versus 1.4 months (95% CI 1.4–1.4) with placebo (HR 0.57; 95% CI 0.49–0.67; $P < 0.0001$; supplementary Figure S1, available at *Annals of Oncology* online).

Analysis of OS by treatment arm and prespecified subgroup showed that baseline number of metastatic sites (1 versus >1), rectum as site of primary tumor (yes versus no) and Eastern Cooperative Oncology Group performance status (0 versus ≥1) all had interaction P values ≤0.1 (Figure 2B). The effect of nintedanib on PFS was consistent in most prespecified subgroup

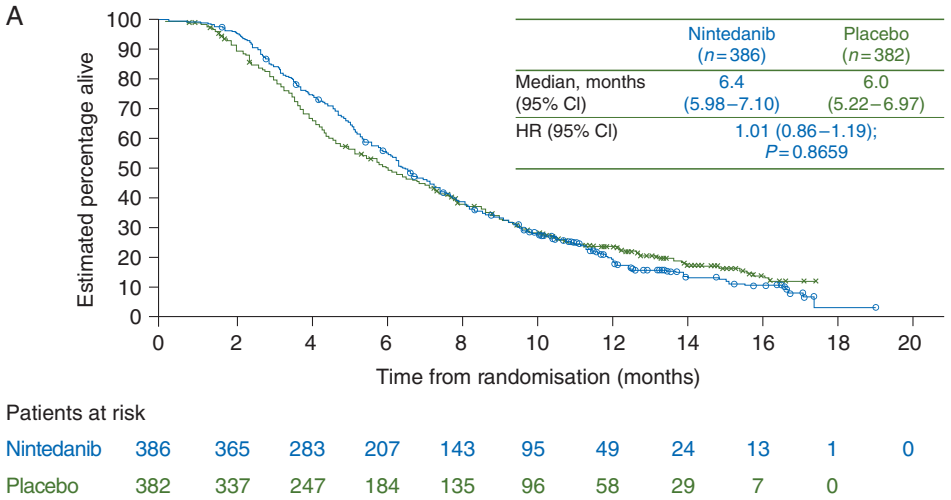

Figure 2. Overall survival. (A) Kaplan–Meier curves for intention-to-treat population. (B) Subgroup analyses (forest plot). CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival. *Exploratory analysis.

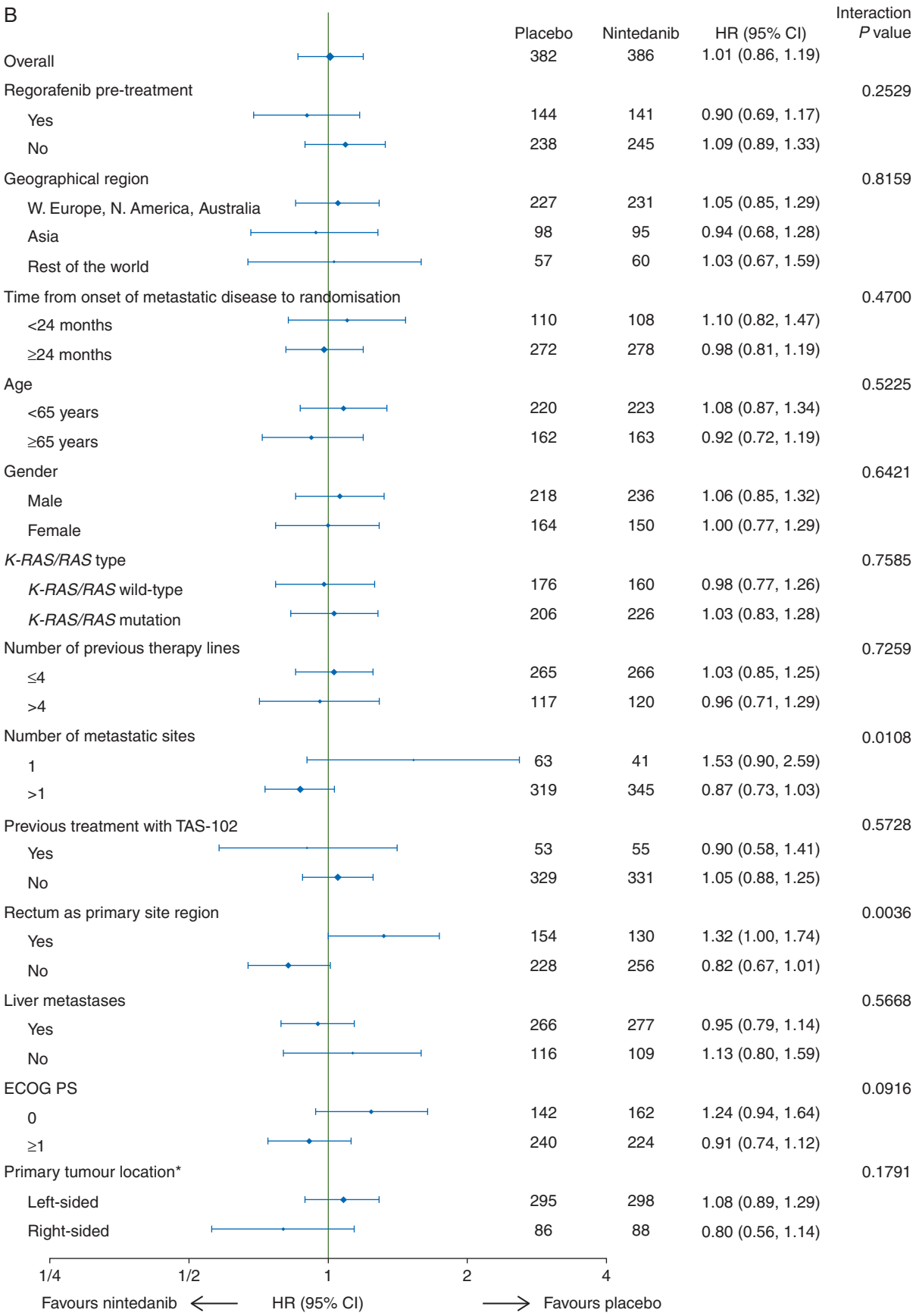

Figure 2. Continued.

analyses (Figure 3B). Exploratory analysis of OS and PFS by primary tumor location (left versus right) showed no treatment interaction (Figures 2B and 3B).

There were no complete or partial responses. The disease control rate was 26% in the nintedanib arm and 11% in the placebo arm (odds ratio, 3.0; 95% CI 2.0–4.5; $P < 0.0001$). Median duration of disease control was 4.0 months (IQR, 2.8–4.5) with nintedanib and 4.1 months (IQR, 3.0–9.6) with placebo.

Mean treatment difference (nintedanib versus placebo) was 2.66 (95% CI 0.97–4.34) for physical functioning and 1.6 (95% CI −0.04–3.27) for global health status/QoL.

The majority of patients in both treatment groups experienced an AE (Table 2). AEs were considered treatment related in 291 patients (76%) treated with nintedanib and 195 patients (51%) treated with placebo. The most frequent grade ≥3 AEs in the nintedanib group were liver-related AEs, mainly increased ALT (8%) and AST (8%) levels, and fatigue.

Serious AEs were reported in 149 patients treated with nintedanib (39%) and 133 patients treated with placebo (35%). Of the 106 deaths due to serious AEs during the study [nintedanib $n = 55$ (14%); placebo $n = 51$ (13%)], most ($n = 94$) were the result of progressive disease or an AE of underlying cancer [nintedanib, $n = 47$ (12%); placebo, $n = 47$ (12%)]. Seven deaths were due to AEs that were not associated with disease progression [nintedanib, $n = 6$ (1.6%); placebo, $n = 1$ (0.3%)]. For two patients in the nintedanib group and three in the placebo group, it was unknown whether death was related to underlying disease. One patient in the nintedanib group died of treatment-related hepatic failure, and two patients in the placebo group died due to a treatment-related AE.

AEs leading to treatment discontinuation were experienced by 55 patients treated with nintedanib (14%) and 40 patients treated with placebo (11%). The most common of these in the nintedanib group was fatigue ($n = 8$), followed by asthenia, decreased appetite, and malignant neoplasm progression (all $n = 6$); in the placebo group, the most common were increased blood bilirubin and increased AST levels (both $n = 5$).

Discussion

This study of nintedanib versus placebo in patients with refractory metastatic CRC did not meet the co-primary end point; there was no improvement in OS, and there was a statistically significant, but modest, improvement in PFS.

In our study, median OS was longer in the placebo arm than was reported in the CORRECT study with regorafenib [3] and the RECOURSE study with trifluridine/tipiracil [4]. This may be related to more treatment options, including regorafenib and trifluridine/tipiracil, being available post-study compared with the CORRECT/RECOURSE studies. Exploratory post hoc analyses of OS were conducted that censored patients at the start of subsequent therapy. In this analysis, median OS was 6.1 months (95% CI 5.6–6.6) with nintedanib compared with 5.1 months (95% CI 4.5–5.9) with placebo (HR 0.79; 95% CI 0.65–0.96) (supplementary Figure S2, available at *Annals of Oncology* online).

Improvements in PFS were modest. However, the shape of the PFS curves in this study, with a noticeable early drop-off in the control arm but a later drop-off in the investigational arm, is similar to the shape of the PFS curves in the CORRECT study [3]. A possible interpretation of these PFS data is that there is a subgroup of patients that did benefit from nintedanib treatment. However, this remains speculative at this stage; as shown in Figure 3B, the effect of nintedanib on PFS was consistent in most subgroups. Exploratory biomarker analyses are ongoing to try and identify a biologically driven subgroup that has a more pronounced benefit from nintedanib treatment. However, these analyses will be hypothesis generating only and further investigation of nintedanib in an unselected patient population is not warranted at this time.

Although there were no complete or partial responses, there was a significant improvement in disease control with nintedanib versus placebo due to patients achieving stable disease. Patient-reported outcomes confirmed that overall HRQoL was not impaired by treatment with nintedanib.

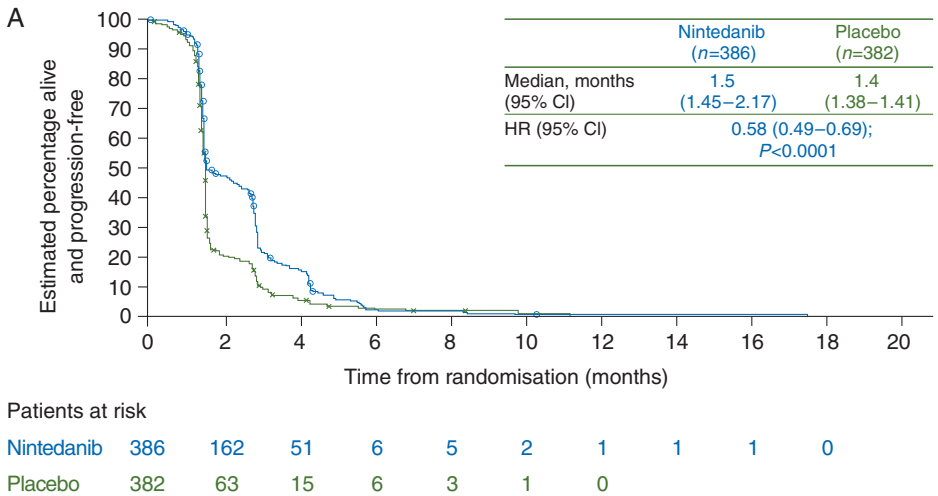

Figure 3. PFS by central review. (A) Kaplan–Meier curves for intention-to-treat population. (B) Subgroup analyses (forest plot). CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PFS, progression-free survival. *Exploratory analysis.

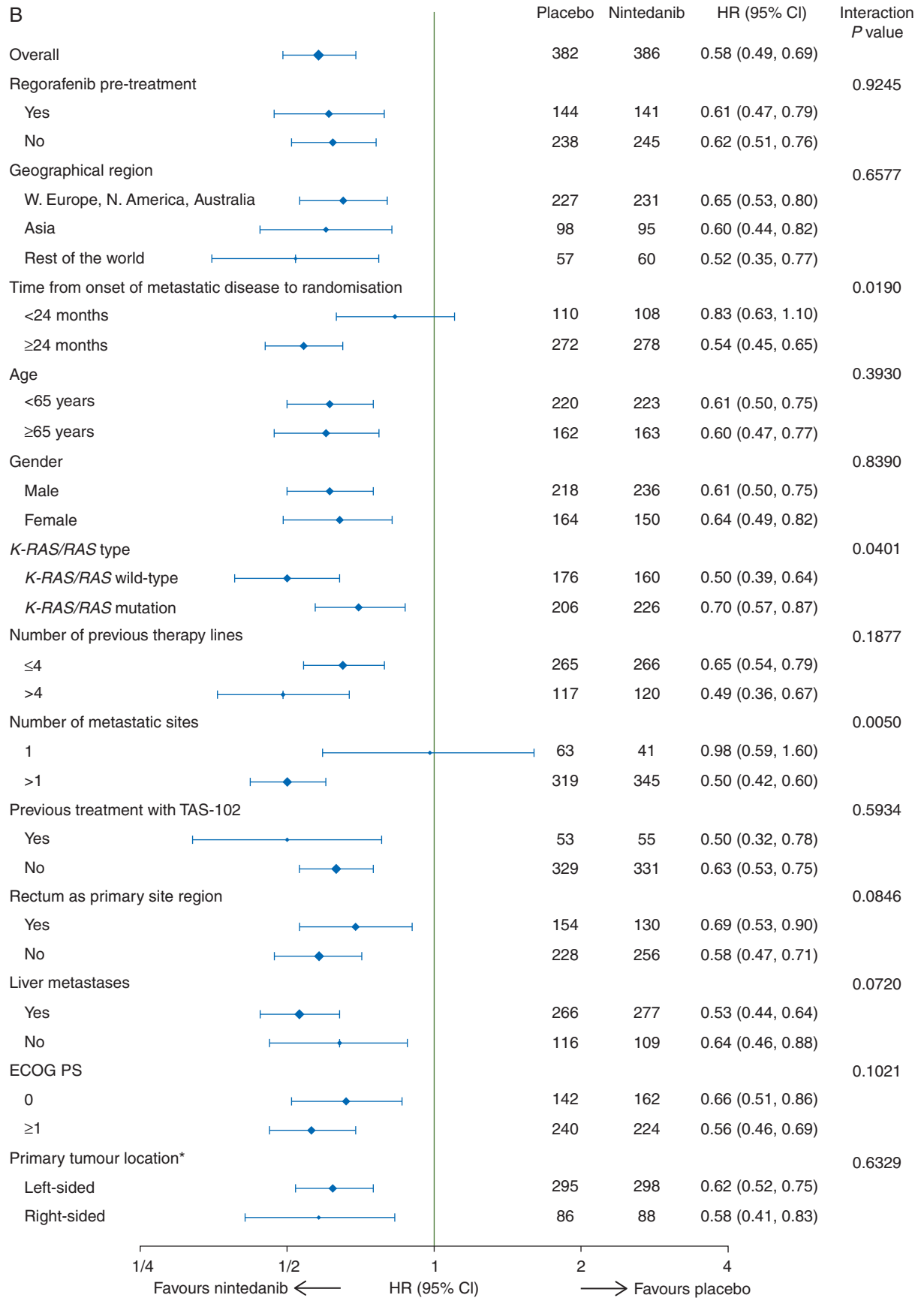

Figure 3. Continued.

Table 2. AEs (safety population)

	Nintedanib ($n = 384$)		Placebo ($n = 381$)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	362 (94.3)	161 (41.9)	323 (84.8)	109 (28.6)
Fatigue	183 (47.7)	33 (8.6)	143 (37.5)	23 (6.0)
Diarrhea	175 (45.6)	10 (2.6)	59 (15.5)	2 (0.5)
Nausea	165 (43.0)	8 (2.1)	105 (27.6)	5 (1.3)
Vomiting	151 (39.3)	5 (1.3)	72 (18.9)	2 (0.5)
Liver-related	141 (36.7)	63 (16.4)	89 (23.4)	32 (8.4)
Increased ALT	96 (25.0)	31 (8.1)	27 (7.1)	7 (1.8)
Increased AST	96 (25.0)	30 (7.8)	50 (13.1)	15 (3.9)
Abdominal pain	95 (24.7)	11 (2.9)	89 (23.4)	5 (1.3)
Infection	82 (21.4)	23 (6.0)	57 (15.0)	12 (3.1)
Hyperbilirubinemia	42 (10.9)	12 (3.1)	31 (8.1)	15 (3.9)
Hypertension	42 (10.9)	18 (4.7)	17 (4.5)	3 (0.8)
Bleeding	37 (9.6)	1 (0.3)	38 (10.0)	6 (1.6)
Proteinuria	35 (9.1)	2 (0.5)	12 (3.1)	2 (0.5)
Mucositis	34 (8.9)	0	18 (4.7)	0
Electrolyte imbalance	33 (8.6)	10 (2.6)	26 (6.8)	13 (3.4)
Rash	32 (8.3)	1 (0.3)	28 (7.3)	0
Peripheral neuropathies	31 (8.1)	6 (1.6)	39 (10.2)	9 (2.4)
Cardiac failure	29 (7.6)	3 (0.8)	37 (9.7)	0
Increased ALKP	28 (7.3)	7 (1.8)	22 (5.8)	8 (2.1)
Anemia	28 (7.3)	8 (2.1)	30 (7.9)	13 (3.4)
Cholestasis and jaundice of hepatic origin	21 (5.5)	9 (2.3)	15 (3.9)	7 (1.8)
Hepatic failure	16 (4.2)	12 (3.1)	18 (4.7)	10 (2.6)
Renal failure	12 (3.1)	9 (2.3)	6 (1.6)	2 (0.5)
Increased GGT	10 (2.6)	9 (2.3)	3 (0.8)	2 (0.5)

AEs shown by user-defined category using US National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. User-defined AE categories represent groupings of AEs by medical concept, e.g. Standardized MedDRA Queries or tailored searches. User-defined categories for nintedanib include identified adverse drug reactions and potential risks of nintedanib, of other VEGF(R) inhibitors, of chemotherapies and of other agents used in this setting, as well as conditions of interest in the treated patient population.

AE, adverse event; ALKP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; VEGF(R), vascular endothelial growth factor (receptor).

The safety profile of nintedanib in this study was consistent with that previously reported in early-phase studies in patients with CRC [7, 10], and also consistent with previously reported studies in other cancer types [11–14]. The most frequent AEs of grade 3 or higher were liver-related AEs, mainly increased ALT and AST levels, and fatigue. Liver enzyme elevations were manageable with dose reduction and were not a frequent reason for treatment discontinuation. As expected, based on the mechanism of action of nintedanib, skin-related AEs that are commonly reported with regorafenib were not reported in the LUME-Colon 1 study.

Concerns have previously been raised regarding the feasibility of conducting controlled trials in CRC with BSC as the comparator. This trial recruited patients faster than anticipated, highlighting the need for active treatment options in this setting despite the availability of regorafenib and trifluridine/tipiracil. Nonetheless, in this last-line treatment setting, it is especially important to consider aspects of the study design that affect patients, such as frequency of assessments requiring clinic visits.

In summary, LUME-Colon 1 did not meet both co-primary end points. Results demonstrated that nintedanib did not improve OS and provided a statistically significant but modest increase in PFS in heavily pretreated patients with metastatic CRC that was refractory to all currently approved standard therapies.

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Disclosure

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