A phase I/II, open-label, randomised study of nintedanib plus mFOLFOX6 versus bevacizumab plus mFOLFOX6 in first-line metastatic colorectal cancer patients

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Background: This randomised, open-label, phase I/II study evaluated the efficacy and safety of nintedanib, an oral, triple angiokinase inhibitor, combined with chemotherapy, relative to bevacizumab plus chemotherapy as first-line therapy in patients with metastatic colorectal cancer (mCRC).

Patients and methods: Patients with histologically confirmed mCRC (adenocarcinoma), an Eastern Cooperative Oncology Group performance status ≤2 and adequate organ function were included. Patients were randomised 2:1 to receive nintedanib 150 mg or 200 mg b.i.d. plus mFOLFOX6 (oxaliplatin 85 mg/m2, l-leucovorin 200 mg/m2 or d,l-leucovorin 400 mg/m2, 5-fluorouracil bolus 400 mg/m2 followed by 2400 mg/m2, every 2 weeks) or bevacizumab (5 mg/kg every 2 weeks) plus mFOLFOX6. During phase I, patients underwent a 3 + 3 dose-escalation schema to determine the maximum tolerated dose (MTD) of nintedanib in combination with mFOLFOX6. The primary end point was progression-free survival (PFS) rate at 9 months. Objective response (OR) was a secondary end point.

Results: The nintedanib recommended phase II dose was 200 mg b.i.d. plus mFOLFOX6 based on safety data from phase I (n = 12). Of 128 patients randomised in the phase II part, 126 received treatment (nintedanib plus mFOLFOX6, n = 85; bevacizumab plus mFOLFOX6, n = 41). PFS at 9 months was 62.1% with nintedanib and 70.2% with bevacizumab [difference: −8.1% (95% confidence interval −27.8 to 11.5)]. Confirmed ORs were recorded in 63.5% and 56.1% of patients in the nintedanib and bevacizumab groups, respectively. The incidence of adverse events (AEs) considered related to treatment was 98.8% with nintedanib and 97.6% with bevacizumab; the incidence of serious AEs was 37.6% with nintedanib and 53.7% with bevacizumab. The pharmacokinetics of nintedanib and the components of mFOLFOX6 were unaffected by their combination.

Conclusions: Nintedanib in combination with mFOLFOX6 showed efficacy as first-line therapy in patients with mCRC with a manageable safety profile and further studies in this population are warranted.

Key words: CRC, nintedanib, angiogenesis, VEGF, FOLFOX

introduction

Anti-angiogenic therapy with bevacizumab, a humanised anti-vascular endothelial growth factor (VEGF) monoclonal antibody, is now an established first-line treatment option for patients with advanced unresectable colorectal cancer (CRC). This strategy was validated by the observation that adding bevacizumab to standard chemotherapy significantly improved overall survival (OS) and progression-free survival (PFS) versus chemotherapy alone [1]. However, contemporary chemotherapy regimens (such as FOLFOX or FOLFIRI) plus bevacizumab confer OS of only ~20–30 months and PFS of ~10 months [2]. Therefore, there is a clear need for better treatment strategies in patients with advanced CRC.

Recent phase III trials of anti-angiogenic tyrosine kinase inhibitors (TKIs) plus standard chemotherapy have failed to
patients and methods

Eligible patients were aged ≥18 years with mCRC histologically proven as adenocarcinoma, which was not amenable to potentially curative treatment, and with ≥1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST). Prior systemic therapy for metastatic disease was not permitted. Prior surgery or systemic therapy for local disease was permitted with the exception of no previous oxaliplatin-based chemotherapy unless disease-free survival after the end of chemotherapy was ≥12 months and no previous adjuvant therapy with fluoropyrimidines unless disease-free survival after the end of chemotherapy was >6 months. Additional patient eligibility criteria are listed in the supplementary Table S1, available at Annals of Oncology online. The trial was undertaken in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the institutional review board of each participating centre. All patients provided written informed consent before participating.

study design and treatments

This was an open-label, randomised, parallel group, phase I/II, study conducted at 27 centres in five Western European countries. The study was exploratory and designed to provide insight into the efficacy and safety of nintedanib plus mFOLFOX6 in patients with CRC, with the potential for a subsequent larger-scale trial. A bevacizumab-containing treatment arm was included for clinical context; however, the study was not powered to allow a formal statistical comparison between the treatment arms.

Given that the clinical profile of bevacizumab plus mFOLFOX6 is well established, patients were randomised 2:1 to receive nintedanib (150 or 200 mg b.i.d.) or bevacizumab (5 mg/kg i.v. every other week) plus mFOLFOX6. Randomisation was carried out via a third-party interactive voice response system stratified according to key prognostic factors [Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase (LDH) levels and use of adjuvant therapy].

All patients received i.v. mFOLFOX6 in 2-week cycles (oxaliplatin, 85 mg/m² infused over 2 h, 5-fluorouracil 200 mg/m² or i.v.-leucovorin 400 mg/m² infused over 2 h, 5-fluorouracil (5-FU) bolus 400 and 2400 mg/m² continuous infusion over 46 h). Any required 5-FU and/or oxaliplatin dose reductions were made at the next cycle.

phase I part. Twelve patients were randomised and treated in accordance with a 3 + 3 dose-escalation design with two prespecified dose levels of oral nintedanib b.i.d. (150 mg followed by 200 mg) plus mFOLFOX6 to evaluate dose-limiting toxicities (DLTs). Patients who discontinued prematurely during the first two treatment cycles for any reason other than DLT were to be replaced. The dose-escalation schema (supplementary Figure S1) and definition of DLT (supplementary Table S2) are provided in the supplementary material, available at Annals of Oncology online.

phase II part. The efficacy, safety and pharmacokinetics (PK) of study treatment were assessed in the phase II part of the trial using the nintedanib maximum tolerated dose (MTD) from phase I. Patients included in the phase I part of the study were also included in phase II. The phase II part comprised the period from the end of phase I until the last patient had died, progressed, received other anticancer therapy or been lost to follow-up. Nintedanib dose reductions were allowed in the event of drug-related AEs following a protocol-defined dose reduction scheme based on AE severity and type. Reducing the bevacizumab dose due to AEs was not recommended; if indicated, bevacizumab was either permanently discontinued or temporarily suspended.

assessments

The objective of the phase I part of the study was to determine the MTD of the treatment regimen in the nintedanib arm. The MTD was defined as the highest nintedanib dose where no more than one-third of patients experienced a DLT during the first two treatment cycles. Safety and efficacy were also assessed and blood samples were collected to determine the PK of nintedanib and its metabolites, as well as oxaliplatin, and 5-FU (supplementary Table S3, available at Annals of Oncology online). Plasma concentrations of nintedanib (and metabolites) were determined by a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay.

The primary end point of the phase II part was 9-month PFS rate, defined as the proportion of patients without objective disease progression and alive 9 months after randomisation. This primary end point was chosen on the basis that this time period corresponded approximately to the median PFS for the combined bevacizumab plus mFOLFOX6 regimen [10]. A primary end point of the 9-month PFS rate also offers the practical advantage over a PFS event-driven statistical method of allowing early analysis at a fixed time point, 9 months after the last patient is recruited into the study. Efficacy and safety data from this early analysis have been presented previously in abstract form and are consistent with data presented here. Secondary end points included OS, PFS, objective response (OR), resection rate (colon or metastases) and tumour shrinkage. Tumour response was based on the response of target, non-target and new lesions according to RECIST, version 1.0, and tumour assessment. Safety was assessed by incidence and intensity of AEs graded according to Common Terminology Criteria for Adverse Events (CTCAE; version 3.0). Other safety assessments included various laboratory parameters, vital signs, electrocardiograms and physical examination. Blood samples for PK analysis of nintedanib and its metabolites were taken at various time points from all nintedanib-treated patients (supplementary Table S5, available at Annals of Oncology online).

statistical analysis

Enrolment was planned for 12–18 patients into the phase I part of the study and 120 patients in the phase II part. Details of the sample size calculation are provided in supplementary Table S4, available at Annals of Oncology online. Safety and efficacy were analysed for the treated set (all patients who
received at least one dose of study drug). All analyses were descriptive and exploratory in nature. No formal statistical testing was planned and statistical analyses were carried out only to provide a statistical framework from which to view the results and plan further studies. For the primary efficacy end point, asymptotic 95% confidence interval (CI) using Peto’s variance estimate in each group and difference between the groups were calculated. OS was also evaluated using the Kaplan–Meier (KM) method. The main analysis (described here) was planned to take place once follow-up had concluded (a minimum of 12 months after the last patient had entered the trial).

**results**

**patient characteristics**

Between June 2009 and May 2010, 136 patients were enrolled, 128 were randomised and 126 received treatment (supplementary Figure S2, available at Annals of Oncology online). Patient demographics and baseline characteristics were well balanced between the treatment groups (Table 1).

**MTD determination**

In total, 12 patients were included in the MTD set: three received 150 mg b.i.d. and nine 200 mg b.i.d. nintedanib plus mFOLFOX6. Demographic and baseline characteristics for the MTD set were similar to all patients in the trial. DLTs were reported for one patient in the 150 mg b.i.d. nintedanib cohort (grade 3 maculo-papular rash) and two in the 200 mg b.i.d. nintedanib cohort (grade 2 diarrhoea leading to drug interruption for >14 days, and grade 3 hepatotoxicity, respectively). All patients with DLTs recovered fully following treatment interruption and appropriate therapy. Hence, the MTD for nintedanib in combination with mFOLFOX6 was 200 mg b.i.d. and this dose was used in the phase II part.

**efficacy**

The primary end point, PFS rate at 9 months, was 62.1% (95% CI 50.2–73.9) in the nintedanib group and 70.2% (95% CI 54.5–85.8) in the bevacizumab group [difference: −8.1% (95% CI −27.8 to 11.5); Figure 1A]. For nintedanib, the primary end point was consistent across patient subgroups while the effect of bevacizumab was more variable (supplementary Figure S3, available at Annals of Oncology online). Median PFS was 10.5 months (95% CI 9.4–12.4) in the nintedanib group and 15.4 months (95% CI 9.6–18.9) in the bevacizumab group.

The proportion of censored patients who discontinued the study without progressive disease was higher in the bevacizumab versus nintedanib treatment arm [n = 16 (39%) versus n = 23 (27%); supplementary Figure S2, available at Annals of Oncology online]. Therefore, a post hoc sensitivity analysis of PFS was undertaken in which all censored patients in both treatment arms were assumed to have had an event at the date of

<table>
<thead>
<tr>
<th>Table 1. Patient demographics and baseline characteristics</th>
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<tr>
<td>Nintedanib + mFOLFOX6 (N = 85)</td>
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<tr>
<td>Age (years), median (range)</td>
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<td>Male, n (%)</td>
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<tr>
<td>ECOG score, n (%)</td>
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<td>0</td>
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<tr>
<td>1</td>
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<td>2</td>
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<tr>
<td>Number of target lesions, median (range)</td>
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<td>Primary site, n (%)</td>
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<td>Colon</td>
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<td>Rectum</td>
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<td>Differentiation grade, n (%)</td>
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<tr>
<td>Well</td>
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<tr>
<td>Moderate</td>
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<tr>
<td>Poorly</td>
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<tr>
<td>Not specified/assessed</td>
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<tr>
<td>Metastatic sites, n (%)</td>
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<tr>
<td>Lung</td>
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<td>Liver</td>
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<td>Pleura</td>
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<td>Bone</td>
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<td>Distant lymph nodes</td>
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<td>Other</td>
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<td>Prior surgerya</td>
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<td>Adjuvant</td>
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<td>Neoadjuvant/adjuvant</td>
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</table>

*aIncludes resection of primary tumour and metastases. ECOG, Eastern Cooperative Oncology Group.
In this analysis, median PFS was 8.5 months (95% CI 7.1–9.9) in the nintedanib group and 9.3 months (95% CI 6.5–10.6) in the bevacizumab group (Figure 1B).

Secondary efficacy end points in the nintedanib and bevacizumab groups are summarised in Table 2. The incidence of a confirmed OR was 63.5% versus 56.1% in the nintedanib versus bevacizumab groups, respectively; while the median duration of confirmed OR was 8.2 versus 12.4 months. KM estimates for median OS could not be calculated because of an insufficient number of deaths (supplementary Figure S4, available at Annals of Oncology online). The frequencies of resection were 15.3% in the nintedanib group and 22.0% in the bevacizumab group.

Figure 1. Kaplan–Meier curves for (A) progression-free survival. (Progression-free survival according to investigator by RECIST version 1.0 (from target, non-target and new lesion responses in CRF) with clinical disease assessment.) and (B) a post hoc sensitivity analysis of progression-free survival with alternative censoring rules. (All censored patients in both treatment arms were assumed to have had an event at the date of censoring.) CI, confidence interval; CRF, case report form; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours.
bevacizumab group, primarily due to an increased incidence of nausea, asthenia, neutropenia, vomiting, decreased appetite and constipation (Table 3). Gastrointestinal and haematological events occurred more frequently with nintedanib versus bevacizumab. The incidence of patients with at least one AE considered related to study medication was 98.8% in the nintedanib group and 97.6% in the bevacizumab group. The most common grade ≥3 AEs were neutropenia, diarrhoea, neurotoxicity, paraesthesia and asthenia. The overall incidence of serious AEs (SAEs) was 37.6% for the nintedanib group and 53.7% for the bevacizumab group. The most common SAEs (nintedanib versus bevacizumab) were pyrexia (5.9% versus 0%), pulmonary embolism (4.7% versus 0%), diarrhoea (3.5% versus 7.3%), intestinal obstruction (3.5% versus 7.3%) and abdominal pain (2.4% versus 4.9%). Incidences of AEs leading to permanent discontinuation of randomised treatment (with or without discontinuation of mFOLFOX6) were 27.1% in the nintedanib group and 31.7% in the bevacizumab group.

Among AEs of special interest associated with VEGF inhibitor therapy (Table 3), the incidence of patients with bleeding was 25.9% in the nintedanib group but higher at 41.5% in the bevacizumab group, primarily due to an increased incidence of epistaxis with bevacizumab. Analysis of other AEs of special interest did not reveal any excess clinical risk in the nintedanib group (see Table 3).

Five patients died during the on-treatment period (two nintedanib patients; three bevacizumab patients). AEs leading to death were sepsis, intestinal perforation, hepatic failure and renal failure (all in one nintedanib patient); aggravated condition (one nintedanib patient); intestinal perforation, intestinal obstruction and general deterioration of physical health (reported for one bevacizumab patient each).

AEs of increased liver enzymes were more frequent in the nintedanib group versus the bevacizumab group for ALT (5.9% versus 2.4%), AST (4.7% versus 2.4%) and GGT (5.9% versus 4.9%), but were reversible during treatment. Hyperbilirubinaemia occurred in one patient in the nintedanib group and in no patients in the bevacizumab group. There were no clinically noteworthy changes in vital signs.

**pharmacokinetics**

During phase I, concomitant administration of 200 mg b.i.d. nintedanib for 15 days did not change the PKs of oxaliplatin or 5-FU (supplementary Table S6, available at *Annals of Oncology* online). Concomitant administration of mFOLFOX6 did not change the PKs of nintedanib and its metabolites BIBF 1202 and BIBF 1202-glucuronide (supplementary Table S7, available at *Annals of Oncology* online). During phase II, trough plasma concentrations of nintedanib and its metabolites remained stable over the treatment period.

**discussion**

This phase I/II study determined that the MTD of nintedanib in combination with mFOLFOX6 was 200 mg b.i.d. and demonstrated clinical efficacy and an acceptable safety profile for this combination in patients with mCRC.

There was no significant difference in the primary end point of PFS rate at 9 months between the arms, although the median PFS favoured bevacizumab over nintedanib. However, all analyses undertaken in this trial were descriptive and exploratory by nature and the study was not powered to determine a statistical difference between treatments. The median PFS of 15.4 months with bevacizumab plus mFOLFOX6 in this study is high in comparison with previous reports of 10.3 months for this regimen in a large-scale (*N* = 1422) phase III study [12] and values of 11.0, 12.6 and 15.9 months in smaller studies [13–15]. The high median PFS with bevacizumab plus mFOLFOX6 in this study is high in comparison with previous reports of 10.3 months for this regimen in a large-scale (*N* = 1422) phase III study [12] and values of 11.0, 12.6 and 15.9 months in smaller studies [13–15]. The high median PFS with bevacizumab in this study may be due to the higher proportion of patients who discontinued the study without progressive disease and were censored from the analysis, as well as the relatively high number of patients who underwent tumour resection. Indeed, *post hoc* sensitivity analyses indicated that PFS was impacted by an imbalance in censoring between treatment arms for patients who discontinued (possibly due to the unblinded study design). Consequently, the robustness of conclusions relating to PFS from this study is limited.

Notwithstanding the obvious pitfalls of inter-trial comparisons, the median PFS observed with nintedanib plus mFOLFOX6 in this study of an unselected mCRC patient population are comparable with data for EGFR inhibitors cetuximab and panitumumab plus FOLFOX in RAS wild-type mCRC patients [16, 17].

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**Table 2. Secondary efficacy end points**

<table>
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<tr>
<th></th>
<th>Nintedanib + mFOLFOX6 (N = 85)</th>
<th>Bevacizumab + mFOLFOX6 (N = 41)</th>
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<tbody>
<tr>
<td>Objective response, n (%)</td>
<td>54 (63.5)</td>
<td>23 (56.1)</td>
</tr>
<tr>
<td>Complete response</td>
<td>7 (8.2)</td>
<td>4 (9.8)</td>
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<tr>
<td>Partial response</td>
<td>47 (55.3)</td>
<td>19 (46.3)</td>
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<tr>
<td>Stable disease</td>
<td>23 (27.1)</td>
<td>15 (36.6)</td>
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<tr>
<td>Progressive disease</td>
<td>6 (7.1)</td>
<td>1 (2.4)</td>
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<tr>
<td>Non-evaluable</td>
<td>2 (2.4)</td>
<td>2 (4.9)</td>
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<tr>
<td>Median duration of response, months (95% CI)</td>
<td>8.2 (6.9–9.9)</td>
<td>12.4 (7.4–16.0)</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not reached</td>
<td>Not reached</td>
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<tr>
<td>Median PFS, months (95% CI)</td>
<td>10.5 (9.4–12.4)</td>
<td>15.4 (9.6–18.9)</td>
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<tr>
<td>Resection rate, n (%)</td>
<td>13 (15.3)</td>
<td>9 (22.0)</td>
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<tr>
<td>R0 resection</td>
<td>6 (7.1)</td>
<td>7 (17.1)</td>
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<tr>
<td>R1 resection</td>
<td>3 (3.5)</td>
<td>1 (2.4)</td>
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<tr>
<td>R2 resection</td>
<td>2 (2.4)</td>
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<tr>
<td>Unknown</td>
<td>2 (2.4)</td>
<td>1 (2.4)</td>
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*Details of the study protocol rules on intra-study surgery are provided in supplementary Table S5, available at *Annals of Oncology* online. CI, confidence interval; OS, overall survival; PFS, progression-free survival.*
The AE profile of nintedanib plus mFOLFOX6 was consistent with previous findings for nintedanib. Fewer patients discontinued treatment due to an AE or SAE with nintedanib versus bevacizumab. The nintedanib group reported fewer incidences of bleeding, hypertension, rash and thromboembolic events versus the bevacizumab group, although the proportion of patients with an SAE of pulmonary embolism was higher with nintedanib versus bevacizumab. Additionally, there were low incidences of cardiac failure and gastrointestinal perforation reported with nintedanib. The incidence of hand–foot syndrome was lower in the nintedanib versus the bevacizumab arm. Evidence indicates that bevacizumab augments the risk of hand–foot syndrome associated with 5-FU-based regimens, although the mechanistic basis of this effect is unclear [10, 18]. Markedly low rates of hand–foot syndrome have also been observed with nintedanib monotherapy versus sunitinib monotherapy in patients with advanced renal cell carcinoma [19], and in large-scale phase III studies of nintedanib plus docetaxel [20] or plus pemetrexed [21] in patients with non-small-cell lung cancer. PK parameters for nintedanib and mFOLFOX6 components were essentially unaffected by co-administration.

Thus far, results with anti-angiogenic TKIs have been disappointing in mCRC [3]. Possible explanations include excessive toxicity, other pharmacodynamic interactions between TKIs and

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<th>Table 3. Adverse events reported in ≥10% of patients at any grade in either treatment arm and of special interest* (all grades and grades ≥3)</th>
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<tbody>
<tr>
<td>Adverse events</td>
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<tr>
<td>General adverse events</td>
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<tr>
<td>Diarrhoea</td>
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<tr>
<td>Nausea</td>
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<td>Asthenia</td>
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<td>Vomiting</td>
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<td>Paraesthesia</td>
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<td>Decreased appetite</td>
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<td>Fatigue</td>
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<td>Abdominal pain</td>
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<td>Mucosal inflammation</td>
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<td>Neurotoxicity</td>
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<td>Thrombocytopenia</td>
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<td>Anaemia</td>
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<td>Adverse events of special interest*</td>
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<td>Cutaneous serious skin reactions</td>
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<td>Rash</td>
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<td>Venous thromboembolism</td>
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<td>Hand–foot syndrome</td>
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<td>Specific liver-related investigationsb</td>
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<tr>
<td>Gastrointestinal perforationc</td>
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<td>Arterial thromboembolism</td>
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*Based on adverse events with bevacizumab or mFOLFOX6 or commonly associated with VEGF inhibition.

bGroup term includes alanine aminotransferase increased, aspartate aminotransferase increased, hyperbilirubinaemia, hypertransaminasaemia, transaminases increased and jaundice.

cExcludes patients with fistulae or intra-abdominal abscesses in the absence of perforation.
chemotherapy and compensatory angiogenesis. Future research should target multiple pathways to overcome signalling redundancy and drug resistance, and/or identify predictive biomarkers to help optimise treatment strategies. Nintedanib’s multiple angiogenic targets, including VEGFR-1–3, PDGFR-α/-β and FGFR-1–3 [7], may potentially overcome compensatory angiogenic pathways. The results of this study also demonstrate a lack of pharmacokinetic interactions with nintedanib and mFOLFOX6 chemotherapy and a manageable safety profile. Further evaluation of nintedanib in mCRC is therefore warranted. A large-scale phase III, randomised, placebo-controlled study has since been initiated to evaluate nintedanib plus best supporting care for patients with mCRC after failure of standard chemotherapy and biological agents (NCT02149108; Study 1199.52).

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disclosure

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references


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