Addition of nintedanib or placebo to neoadjuvant gemcitabine and cisplatin in locally advanced muscle-invasive bladder cancer (NEOBLADE): a double-blind, randomised, phase 2 trial

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Summary

Background Recurrence is common after neoadjuvant chemotherapy and radical treatment for muscle-invasive bladder cancer. We investigated the effect of adding nintedanib to neoadjuvant chemotherapy on response and survival in muscle-invasive bladder cancer.

Methods NEOBLADE was a parallel-arm, double-blind, randomised, placebo-controlled, phase 2 trial of neoadjuvant gemcitabine and cisplatin chemotherapy with nintedanib or placebo in locally advanced muscle-invasive bladder cancer. Patients aged 18 years or older, with an Eastern Cooperative Oncology Group performance status of 0–1, were recruited from 15 hospitals in the UK. Patients were randomly assigned (1:1) to nintedanib or placebo using permuted blocks with random block sizes of two or four, stratified by centre and glomerular filtration rate. Treatments were allocated using an interactive web-based system, and patients and investigators were masked to treatment allocation throughout the study. Patients received oral nintedanib (150 mg or 200 mg twice daily for 12 weeks) or placebo, in addition to usual neoadjuvant chemotherapy with intravenous gemcitabine 1000 mg/m² on days 1 and 8 and intravenous cisplatin 70 mg/m² on day 1 of a 3-weekly cycle. The primary endpoint was pathological complete response rate, assessed at cystectomy or at day 8 of cyclde 3 (plus or minus 7 days) if cystectomy did not occur. Primary analyses were done in the intention-to-treat population. The trial is registered with EudraCT, 2012-004895-01, and ISRCTN, 56349930, and has completed planned recruitment.

Findings Between Dec 4, 2014, and Sept 3, 2018, 120 patients were recruited and were randomly allocated to receive nintedanib (n=57) or placebo (n=63). The median follow-up for the study was 33·5 months (IQR 14·0–44·0). Pathological complete response in the intention-to-treat population was reached in 21 (37%) of 57 patients in the nintedanib group and 20 (32%) of 63 in the placebo group (odds ratio [OR] 1·25, 70% CI 0·84–1·87; p=0·28). Grade 3 or worse toxicities were observed in 53 (93%) of 57 participants who received nintedanib and 50 (79%) of 63 patients in the placebo group (OR 1·65, 95% CI 0·74–3·65; p=0·24). The most common grade 3 or worse adverse events were thromboembolic events (17 [30%] of 57 patients in the nintedanib group *vs* 13 [21%] of 63 patients in the placebo group [OR 1·63, 95% CI 0·71–3·76; p=0·29]) and decreased neutrophil count (22 [39%] in the nintedanib group *vs* seven [11%] in the placebo group [5·03, 1·95–13·00; p=0·0006]). 45 treatment-related serious adverse events occurred in the nintedanib group and 43 occurred in the placebo group. One treatment-related death occurred in the placebo group, which was due to myocardial infarction.

Interpretation The addition of nintedanib to chemotherapy was safe but did not improve the rate of pathological complete response in muscle-invasive bladder cancer.

Funding Boehringer Ingelheim.

Introduction

Guidelines recommend cisplatin-based neoadjuvant chemotherapy followed by either radical cystectomy and pelvic lymph node dissection, or organ-preserving chemoradiotherapy as the standard management of muscle-invasive bladder cancer.[1] Cisplatin-based neoadjuvant chemotherapy is the recommended standard of care based on level 1 evidence from randomised clinical trials and meta-analyses showing an absolute 5-year overall survival benefit of 5% and a 14% reduction in the risk of death.[2–4] Despite the proven efficacy of neoadjuvant chemotherapy, the disease course is associated with high rates of recurrence and metastatic disease. Hence, a clear opportunity exists to increase the cure rate by optimising cisplatin-based chemotherapy.

Research in context

Evidence before this study

The standard of care for localised muscle-invasive carcinoma (stage T2–4, N0, M0) is cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy and pelvic lymph node dissection, or with organ-preserving chemoradiotherapy. The addition of cisplatin-based neoadjuvant chemotherapy offers an overall survival benefit of 5% and a 14% reduction in the risk of death. However, the disease course is associated with a high rate of recurrence and metastatic disease. Hence, there is a need to optimise cisplatin-based chemotherapy. We searched PubMed for articles published between Jan 1, 1990, and Dec 31, 2012, without language restrictions, using the terms "neoadjuvant chemotherapy", "NAC", "muscle invasive bladder cancer", "MIBC", "nintedanib", "tyrosine kinase inhibitors", and "TKI". The search identified no previous data on the combination of nintedanib and chemotherapy in muscle-invasive bladder cancer.

Added value of this study

Nintedanib is a multikinase inhibitor of the receptor tyrosine kinases PDGF-R, FGFR-1, and VEGFR-2. To our knowledge, this is the first randomised trial to show that intensification of neoadjuvant chemotherapy with the addition of multikinase inhibitors can be safely delivered. The trial did not meet its primary endpoint of pathological complete response.

Implications of all the available evidence

The study did not meet its primary endpoint of improvement in pathological complete response. Therefore, cisplatin-based neoadjuvant chemotherapy remains the standard of care for the treatment of muscle-invasive bladder cancer.

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Microvessel density (a measure of tumour angiogenesis) and high serum VEGF concentrations appear to be associated with worse clinical outcomes in urothelial carcinoma.[5,6] Thus, a potential strategy is to combine VEGF receptor-targeting tyrosine kinase inhibitors with neoadjuvant chemotherapy.[7,8] Any such strategy should not compromise the dose or schedule of the neoadjuvant chemotherapy itself, which has been a limitation in previous combination studies due to toxicity.[9,10] To that end, nintedanib has emerged as a potential candidate with a favourable efficacy and toxicity profile, rendering it suitable for combination with neoadjuvant chemotherapy.

Nintedanib is an orally available, potent, small molecule inhibitor that targets tyrosine kinases PDGFR, FGFR-1, and VEGFR-2. Nintedanib in combination with other cytotoxic agents has shown activity in lung cancer.[11–13] Lung cancer and bladder cancer share common risk factors such as smoking, have a high tumour mutational burden, and share similar chemotherapy regimens. Therefore, nintedanib was tested to assess outcomes in muscle-invasive bladder cancer in combination with gemcitabine and cisplatin.

The primary objective of this study was to assess the effects of adding nintedanib to neoadjuvant gemcitabine and cisplatin on pathological complete response in patients with muscle-invasive bladder cancer.

Methods

Study design and participants

NEOBLADE was an investigator-initiated, parallel-arm, double-blind, randomised, phase 2 placebo-controlled trial of neoadjuvant gemcitabine and cisplatin chemotherapy with nintedanib or placebo in locally advanced muscle-invasive bladder cancer, and was done at 15 UK hospitals (appendix p 13).

Patients aged 18 years or older with histologically proven muscle-invasive urothelial cancers and those with urothelial cancers with a minor component of variant histology were included. Other inclusion criteria were localised muscle-invasive carcinoma (stage T2–T4, N0, M0) by CT assessment, an Eastern Cooperative Oncology Group performance status of 0–1, adequate haematological and hepatic function, and a glomerular filtration rate (GFR) of more than 60 mL/min (assessed by either EDTA clearance, 24-h urine collection, or the Cockcroft-Gault calculation[14]). Based on results of a dose-finding run-in substudy, eligibility criteria for GFR were expanded to include rates higher than 40 mL/min. The dose-finding study ran in parallel. It was completed, and then, following amendment, inclusion criteria for GFR were expanded after 92 patients in the phase 2 trial were already recruited. 11 patients with GFR between 40 mL/min and 60 mL/min were recruited after the amendment. The full eligibility criteria are available in the protocol (appendix).

All patients provided written, informed consent after receiving all relevant information before trial entry. The trial protocol was evaluated by an independent research ethics committee and underwent site-specific assessment by completing the site-specific information forms within the Integrated Research Application System, with the primary site (Clatterbridge Cancer Center, Bebington, UK) receiving ethical approval.

The NEOBLADE protocol was amended seven times (version 1 on Feb 6, 2013, version 2 on Dec 11, 2013, version 3 on Feb 6, 2015, version 4 on July 23, 2015, version 5 on March 29, 2016, version 6 on April 7, 2017, and version 7 on Jan 12, 2018). Full details of all protocol amendments are provided within the protocol (appendix).

Randomisation and masking

Randomisation lists were generated using permuted blocks with random block sizes of two and four. Lists were generated by a statistician at the Liverpool Clinical Trials Centre (Liverpool, UK) before randomisation of the first patients, including stratification by centre and GFR

See Online for appendix

(40–60 mL/min *vs* >60 mL/min). Allocation of treatments was performed using an interactive web-based system. Both the patient and investigator remained masked to the treatment allocation throughout the course of the study, and the treatments were identical in appearance. The trial statistician received the full unblinding information at the point of preparing the final statistical analysis report.

Procedures

Patients with GFR higher than 60 mL/min received 1000 mg/m² intravenous gemcitabine on days 1 and 8 and intravenous cisplatin 70 mg/m² on day 1 of a 3-weekly cycle. Patients with GFR of 40–60 mL/min received split-dose intravenous cisplatin 35 mg/m² on days 1 and 8 (split over two doses on days 1 and 8). The total number of cycles was four. Patients also received oral nintedanib 200 mg or matching placebo twice daily (150 mg for patients with GFR of 40–60 mL/min) for 12 weeks continuously. The administration of granulocyte colony-stimulating factors was permitted according to local protocol. Before any administration of study treatment, haematology, biochemistry, and coagulation parameters were evaluated, and a clinical assessment was performed. Dose modifications of medicinal products were allowed by the study protocol. Nintedanib doses were permitted to be reduced to 150 mg, 100 mg, or 50 mg (or to 100 mg or 50 mg for patients with GFR 40–60 mL/min). Both gemcitabine and cisplatin were permitted to be reduced to 75% and 50% of their planned dose.

Radical cystectomy and lymphadenectomy were performed as per UK practice, to include removal of the bladder, adjacent organs, and pelvic lymph nodes.[15,16] As an alternative to radical cystectomy, organ preservation treatments, including radiotherapy alone or chemoradiotherapy, were also permitted as possible radical treatment options in line with UK national clinical guidelines.[17] Radical radiotherapy doses of 55 Gy in 20 fractions or 64 Gy in 32 fractions were permitted, as was the use of a concomitant radiosensitiser. The decision about the radical treatment modality was based on multidisciplinary team discussion and patient preference. Data were collected through study-specific case report forms and stored at the Liverpool Clinical Trials Centre. After completion of radical treatment, patients were followed up at 3, 6, and 12 months, and annually for up to 5 years.

Patient were monitored by laboratory tests and imaging (a schedule of tests done at each visit is provided in the protocol in the appendix). Radiological assessment of patients was performed via CT scans at baseline, after cycle 3, and at 6 and 12 months of follow-up. Response assessment was not centrally reviewed. Blood samples were obtained for laboratory monitoring at baseline, before each cycle, at the end of treatment, and subsequently every 3 months as part of patient follow-up. Evaluation of adverse events was done at all study visits up to 28 days beyond the end of study treatment, according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Patients could be removed from the study treatment due to withdrawal of consent, unacceptable toxicity, serious violation of the study protocol, clinical rationale unrelated to the trial, or any change in the patient's condition that justified discontinuation of treatment (further details are in the protocol).

Outcomes

The primary endpoint was pathological complete response rate. For patients undergoing cystectomy, pathological complete response was defined as the complete absence of carcinoma in the resected bladder. For patients who did not undergo cystectomy, including those who underwent bladder preservation, pathological complete response was defined as the complete absence of visible or histological disease after three cycles of neoadjuvant chemotherapy, assessed via cystoscopic biopsy mandated on day 8 of cycle three (plus or minus 7 days). All patients underwent CT scan after three cycles of neoadjuvant treatment to exclude extravesical disease progression or recurrence using Response Evaluation Criteria in Solid Tumors version 1.1 criteria.

Secondary endpoints were progression-free survival, measured as the time from randomisation until disease progression or death by any cause, and toxicity.

Statistical analysis

We estimated that the primary endpoint of pathological complete response rate in the control group would be 35%.[3,18] The study was designed to detect a clinically relevant difference, which was considered to be an absolute increase of 20% (ie, to 55%), equivalent to an odds ratio (OR) of 2·27. Using a single-stage Jung's design[19] for randomised phase 2 trials with a one-sided type 1 error rate of 0·15 and a power of 78%, 92 patients were required, with a final sample size of 120 to allow for patient attrition.

The primary analysis of pathological complete response was performed in the intention-to-treat population. A separate analysis was reported in the modified intention-to-treat population, which was defined as evaluable patients for pathological complete response based on cystectomy samples or tumour biopsy for organ preservation patients, as specified in the protocol. Patients were defined as unevaluable if a response category was unable to be defined. Analyses were done using logistic regression, including stratification factors as main effects in the model. Results of the primary outcome are presented as OR and associated two-sided 70% CI, consistent with the one-sided 0·15 α level included in the study design. A one-sided p value of less than 0·15 was used to determine statistical significance for the primary outcome. Prespecified sensitivity analyses were done, adjusting for prognostic covariates (age, sex, baseline GFR status, and centre) and allowing for treatment interactions by

participating centre. Pathological complete response in patients undergoing cystectomy was performed as a post-hoc analysis.

Overall survival, measured as the time from randomisation until death by any cause, was excluded from the planned analysis of the phase 2 trial to permit potential inclusion of these patients in a future phase 3 extension if the phase 2 were positive. Overall survival is, therefore, presented here as a post-hoc analysis. Landmark post-hoc progression-free survival analyses were performed at 12, 24, and 60 months. Time-to-event outcomes (progression-free survival and overall survival) are expressed as Kaplan-Meier estimates, with efficacy measured using hazard ratios (HRs) obtained from Cox proportional hazards modelling. The assumption of proportional hazards was assessed via inspection of Schoenfeld residuals. A test against a χ^2 distribution was performed to assess non-proportionality. Progression-free survival and overall survival results are presented alongside two-sided 95% CIs. Progression-free survival and overall survival post-hoc analyses were performed among evaluable patients for pathological complete response.

A post-hoc analysis of complete tumour response rate was done to accommodate patients undergoing organ preservation when tumour biopsy was not available. This was recommended by the trial steering committee and was endorsed by the independent data monitoring committee on March 27, 2017. Complete tumour response rate is a composite of pathological complete response (exclusively based on pathological complete response for patients who underwent cystectomy) and cystoscopic biopsy, radiographic complete response, or both (for patients who did not undergo cystectomy). The number of patients with a complete tumour response in each treatment group was compared using ORs with 95% CIs.

Comparisons of adverse events were prespecified in the study protocol. Results for toxicities are presented in terms of ORs with 95% CIs, comparing the number of patients to have grade 3 or worse adverse events in the intention-to-treat population. A post-hoc analysis was performed on treatment delays and reductions and presented as ORs with 95% CIs to compare the treatment groups.

All analyses were performed using SAS (version 9.4). The trial is registered with EudraCT, 2012-004895-01, and ISRCTN, 56349930.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

196 patients were screened for eligibility between Dec 4, 2014, and Sept 3, 2018, of whom 120 were recruited and randomly assigned to receive nintedanib (n=57) or placebo (n=63). The study stopped recruitment because the planned sample size had been reached. 102 (85%) of 120 patients received potentially curative treatment; 49 (86%) of 57 patients in the nintedanib group received radical curative treatment (26 had cystectomy within 90 days and 23 opted for organ preservation), and 53 (84%) of 63 patients in the placebo group received potentially curative treatment (36 had cystectomy and 17 opted for organ preservation; figure 1). No difference in safety signals was found between groups in terms of perioperative complications or delays in surgery (data not shown).

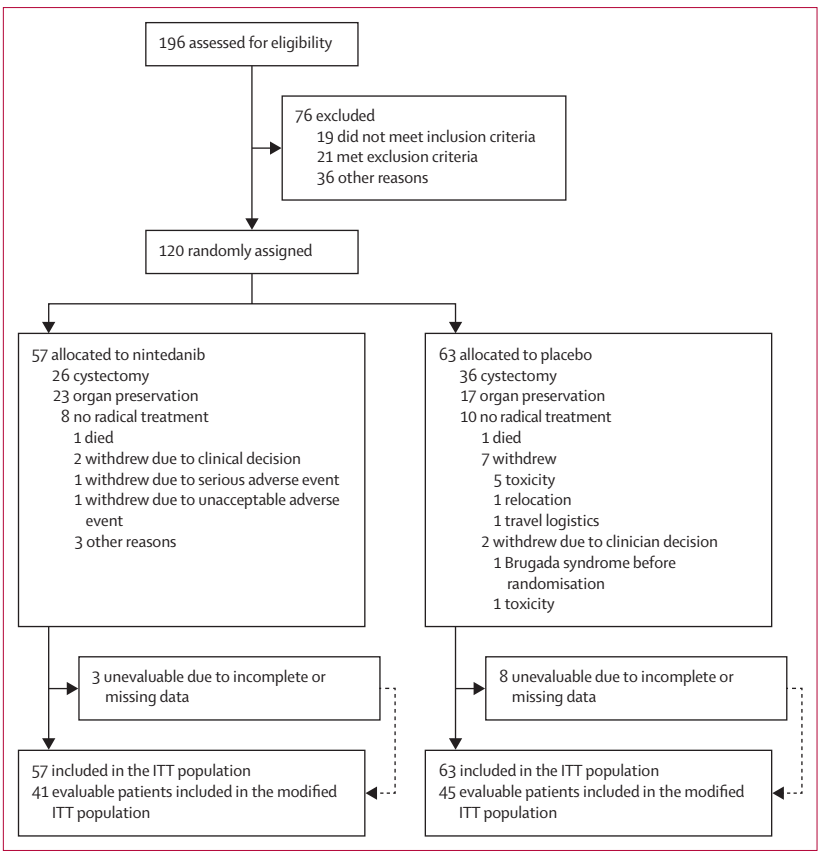

Figure 1: **Trial profile**
ITT=intention-to-treat.

The median follow-up for the study was 33·5 months (IQR 14·0–44·0). Patients had a median age of 68·5 years (62·0–75·0); 94 (78%) of 120 patients were men and 73 (61%) had T2 disease (table 1).

All 120 patients who were randomly allocated to a group were included in the intention-to-treat population. 86 evaluable patients with available tissue for assessment of pathological response either at cystectomy or cystoscopy were included in the modified intention-to-treat population. Pathological complete response rate by intention-to-treat was 21 (37%) of 57 in the nintedanib group and 20 (32%) of 63 in the placebo group (OR 1·25, 70% CI 0·84–1·87; p=0·28). Pathological complete response rate in evaluable patients in the modified intention-to-treat population was 21 (51%) of 41 in the

	Placebo (n=63)	Nintedanib (n=57)
Sex		
Female	11 (17%)	15 (26%)
Male	52 (83%)	42 (74%)
Age, years	70·0 (62·0–75·0)	67·0 (62·0–75·0)
Glomerular filtration rate, mL/min	84·0 (69·0–103·0)	89·0 (73·0–112·0)
Serum creatinine, µmol/L	82·0 (71·0–102·0)	78·0 (70·0–89·0)
ECOG performance status		
0	48 (76%)	50 (88%)
1	15 (24%)	7 (12%)
Histological T stage		
T2	38 (60%)	35 (61%)
T3a	4 (6%)	4 (7%)
T3b	12 (19%)	13 (23%)
T4	2 (3%)	2 (4%)
T4a	3 (5%)	3 (5%)
Missing	4 (6%)	0
Tumour differentiation		
Moderately differentiated	16 (25%)	5 (9%)
Poorly differentiated	44 (70%)	50 (88%)
Undifferentiated	1 (2%)	0
Could not be assessed	1 (2%)	2 (4%)
Missing	1 (2%)	0
Smoking status		
Current smoker	12 (19%)	11 (19%)
Ex-smoker	35 (56%)	30 (53%)
Never smoked	15 (24%)	13 (23%)
Missing	1 (2%)	3 (5%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Patient baseline characteristics**

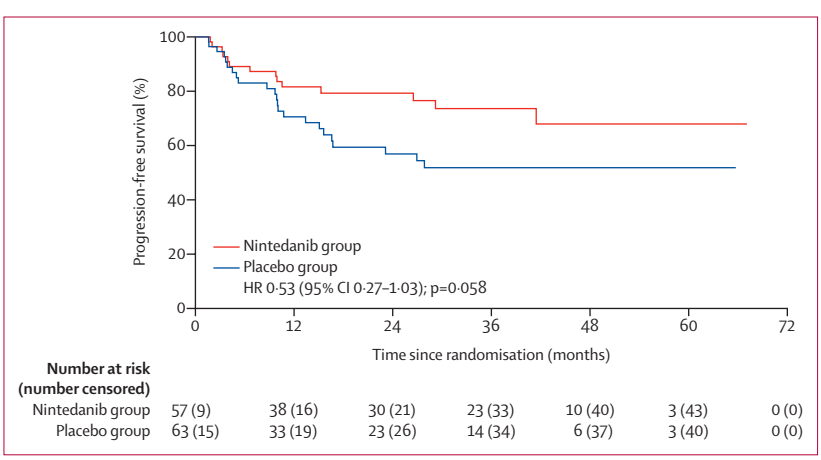

Figure 2: **Progression-free survival**
HR=hazard ratio.

nintedanib group and 20 (44%) of 45 in the placebo group (1·31, 0·84–2·06; p=0·74). Prespecified sensitivity analyses for the primary endpoint adjusting for prognostic covariates are shown in the appendix (pp 2–3). The post-hoc complete tumour response rate was 22 (38%) of 57 in the nintedanib group and 25 (39%) of 63 in the placebo group (OR 0·96, 95% CI 0·46–1·99; p=0·45). Similarly, in a post-hoc analysis of 62 patients who underwent cystectomy, 12 (47%) of 26 in the nintedanib group and 17 (46%) of 36 in the placebo group had a pathological complete response (OR 1·00, 95% CI 0·31–2·96; p=0·94).

There was no formal evidence of non-proportionality for either progression-free survival or overall survival (appendix p 14). Post-hoc landmark progression-free survival was 82% (95% CI 71–92) in the nintedanib group and 71% (58–83) in the placebo group at 12 months, 79% (68–90) in the nintedanib group and 57% (43–71) in the placebo group at 24 months, and 68% (52–84) in the nintedanib group and 52% (37–66) in the placebo group at 60 months. 14 (25%) of 57 patients in the nintedanib group and 23 (37%) of 63 patients in the placebo group experienced a progression-free survival event. Median progression-free survival was not reached in either group at the time of analysis (not reached [95% CI not reached to not reached] in the nintedanib group *vs* not reached [17 to not reached] in the placebo group; HR 0·53, 95% CI 0·27–1·03; p=0·058; figure 2). In a post-hoc analysis of progression-free survival among the 86 patients who were evaluable for pathological complete response, the HR was 0·40 (95% CI 0·18–0·89; p=0·024; appendix p 15).

Overall survival was an exploratory post-hoc endpoint; however, in view of the progression-free survival results and the decision not to proceed directly into a phase 3 study, it is reported here. Ten (18%) of 57 patients in the nintedanib group and 19 (30%) of 63 patients in the placebo group died. Overall survival was 96% (95% CI 91–100) in the nintedanib group and 81% (70–92) in the placebo group at 12 months, 89% (80–98) in the nintedanib group and 69% (56–83) in the placebo group at 24 months, and 60% (30–89) in the nintedanib group and 49% (30–68) in the placebo group at 60 months. Median overall survival was 50·6 months (95% CI 33·5 to not reached) in the placebo group and was not reached (54·5 to not reached) in the nintedanib group at the time of analysis (HR 0·45, 95% CI 0·21–0·98; p=0·038; figure 3). In a post-hoc analysis of overall survival among the 86 patients who were evaluable for pathological complete response, the HR was 0·35 (95% CI 0·13–0·89; p=0·028; appendix p 17). Full details of all observed deaths are included in the appendix (p 10).

Toxicity is reported in table 2 as grade 1 or 2 adverse events occurring in at least 10% of patients and grade 3 or worse adverse events occurring in at least 2% of patients across treatment groups. All adverse events by treatment group are reported in the appendix (p 5). All grade 3 or worse toxicities are also presented in the appendix (pp 6–9). Grade 3 or worse toxicities were observed in 53 (93%) of 57 participants in the nintedanib group and 50 (79%) of 63 patients in the placebo group (OR 1·65,

95% CI 0·74–3·65; p=0·24). The most common grade 3 or worse adverse events were thromboembolic events (17 [30%] of 57 patients in the nintedanib group *vs* 13 [21%] of 63 patients in the placebo group [OR 1·63, 95% CI 0·71–3·76; p=0·29]), decreased neutrophil count (22 [39%] in the nintedanib group *vs* seven [11%] in the placebo group [5·03, 1·95–13·00; p=0·0006]), and hypertension (nine [16%] in the nintedanib group *vs* four [6%] in the placebo group [2·77, 0·80–9·54; p=0·14]). 45 treatment-related serious adverse events occurred in the nintedanib group and 43 occurred in the placebo group (appendix pp 11–12). One treatment-related death occurred in the placebo group, which was due to myocardial infarction.

In post-hoc analysis of treatment delivery, there were 295 cycles of gemcitabine delivered, with 60 (20%) delays and 67 (23%) reductions. A greater number of dose reductions of gemcitabine were made in the nintedanib group (42 [31%] of 136) compared with the placebo group (25 [16%] of 159; OR 2·39, 95% CI 1·37–4·20; p<0·0001]. No differences were found between treatment groups in terms of treatment delays (data not shown). Regarding cisplatin, there were 332 cycles with 36 (11%) delays and 46 (14%) reductions, with no differences between treatment groups (data not shown). There were 313 cycles of nintedanib or placebo with 47 (15%) delays and 45 (14%) reductions, with no differences between treatment groups. 28 patients (15 [26%] of 57 in the nintedanib group and 13 [21%] of 63 in the placebo group) withdrew from the study due to toxicity (appendix p 4).

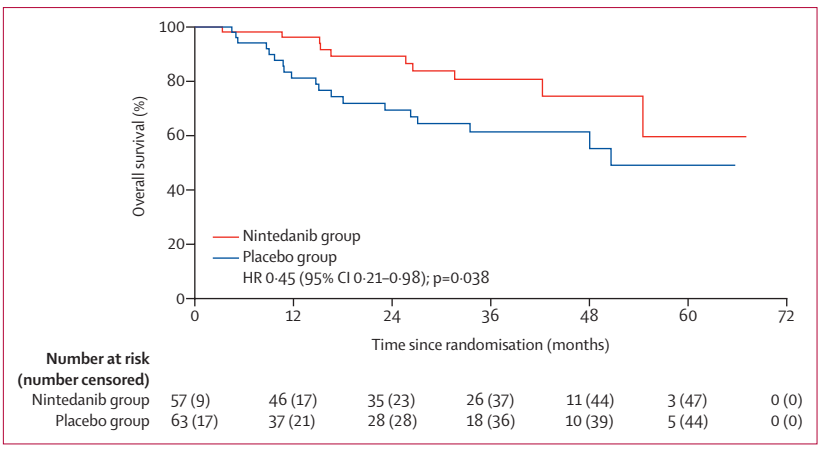

Figure 3: **Overall survival (post-hoc analysis)**
HR=hazard ratio.

Discussion

The addition of nintedanib to neoadjuvant chemotherapy (gemcitabine plus cisplatin) within the context of this double-blind, placebo-controlled trial did not show a significant improvement in the primary outcome of pathological complete response when compared with the chemotherapy alone in the treatment of muscle-invasive bladder cancer. Additionally, no significant improvement was found in the secondary endpoint of progression-free survival between the two groups. A post-hoc analysis of overall survival at a median follow-up of 33·5 months showed a survival benefit of adding nintedanib to neoadjuvant chemotherapy; however, the study was not powered for this analysis, and this result should therefore be interpreted with caution.

Unlike in studies of sunitinib and sorafenib,[9,10] this combination of nintedanib with chemotherapy was found to be well tolerated. The overall venous thromboembolism rate was higher in the NEOBLADE study population with muscle-invasive bladder cancer compared with patients with metastatic disease in the CALGB study;[20] however in both studies, the rates were not increased by VEGF inhibition.

Angiogenesis inhibition has been previously tested in the advanced bladder cancer setting and showed promising results with bevacizumab in phase 2 trials,[21,22] but failed to show an overall survival benefit in a phase 3 trial.[20] Similarly, ramucirumab showed promising improvement in progression-free survival in advanced metastatic bladder cancer in a phase 3 setting,[23] but did not show improvement in overall survival.[24] Hence, the benefit of angiogenesis inhibition has not been validated in the advanced bladder cancer setting. These results suggest that there could be a role for angiogenesis inhibition earlier in the disease pathway treating localised bladder cancer. Additionally, the pluripotent activity of nintedanib that includes FGFR inhibition and anti-angiogenic effects could have an effect on the tumour microenvironment that translates into improved overall survival in bladder cancer.

The overall survival benefit seen in a post-hoc analysis in this study did not seem to be driven by the patients' choice of curative treatment modality; 36 patients in the placebo group had cystectomy and 17 opted for organ preservation (53 of 63 patients had a curative treatment modality), compared with 26 patients who opted for cystectomy and 23 patients who chose organ preservation in the nintedanib group (49 of 57 patients had a curative treatment modality). These data suggests that improvement in the post-hoc endpoint of overall survival might have been driven by nintedanib rather than by the choice of radical treatment. Of note, the study was initially designed as a standalone phase 2 trial with overall survival as a secondary outcome. Upon adaptation to a seamless phase 2–3 trial, overall survival was removed to preserve for later evaluation. Because the study was effectively halted at the phase 2 stage, we have reported overall survival alongside the other study outcomes. In this context, overall survival is best considered an exploratory outcome.

The overall survival benefit seen in a post-hoc analysis with no effect on the pathological complete response rate at cystectomy might be explained by effects on the tumour microenvironment leading to removal of immunosuppressive checks on the tumour without direct tumour cytotoxicity. Data from a 2021 study[25] suggest that

	Nintedanib (n=57)				Placebo (n=63)				OR of grade 3 or worse events (95% CI)	p value
	Grade 1 or 2*	Grade 3†	Grade 4†	Grade 5†	Grade 1 or 2*	Grade 3†	Grade 4†	Grade 5†		
Any event	57 (100%)	41 (72%)	12 (21%)	0	60 (95%)	38 (60%)	11 (17%)	1 (2%)	1·65 (0·74–3·65)	0·24
Fatigue	45 (79%)	3 (5%)	0	0	43 (68%)	1 (2%)	0	0	3·44 (0·35–34·09)	0·35
Nausea	38 (67%)	2 (4%)	0	0	34 (54%)	3 (5%)	0	0	0·73 (0·12–4·52)	>0·99
Constipation	31 (54%)	0	0	0	25 (40%)	0	0	0	NA	NA
Diarrhoea	30 (53%)	0	0	0	20 (32%)	1 (2%)	0	0	NA	>0·99
Neutrophil count decreased	0	14 (25%)	8 (14%)	0	9 (14%)	5 (8%)	2 (3%)	0	5·03 (1·95–13·00)	0·0006
Hypertension	9 (16%)	9 (16%)	0	0	11 (17%)	4 (6%)	0	0	2·77 (0·80–9·54)	0·14
Thromboembolic event	1 (2%)	16 (28%)	1 (2%)	0	1 (2%)	12 (19%)	1 (2%)	0	1·63 (0·71–3·76)	0·29
Vomiting	19 (33%)	1 (2%)	0	0	7 (11%)	4 (6%)	0	0	0·26 (0·03–2·43)	0·37
Anaemia	9 (16%)	2 (4%)	0	0	16 (25%)	1 (2%)	0	0	2·25 (0·20–25·55)	0·60
Dysgeusia	14 (25%)	0	0	0	13 (21%)	0	0	0	NA	NA
Anorexia	17 (30%)	0	0	0	9 (14%)	0	0	0	NA	NA
Alanine aminotransferase increased	7 (12%)	4 (7%)	0	0	13 (21%)	0	0	0	NA	0·048
Tinnitus	16 (28%)	0	0	0	8 (13%)	0	0	0	NA	NA
Alopecia	11 (19%)	0	0	0	10 (16%)	0	0	0	NA	NA
Anaemia	8 (14%)	1 (2%)	0	0	10 (16%)	1 (2%)	0	0	1·11 (0·07–18·12)	>0·99
Dizziness	8 (14%)	0	0	0	12 (19%)	0	0	0	NA	NA
γ-glutamyl transferase increased	7 (12%)	1 (2%)	0	0	8 (13%)	1 (2%)	1 (2%)	0	0·54 (0·05–6·17)	>0·99
Platelet count decreased	6 (11%)	1 (2%)	1 (2%)	0	8 (13%)	1 (2%)	1 (2%)	0	1·11 (0·15–8·14)	>0·99
Abdominal pain	8 (14%)	1 (2%)	0	0	8 (13%)	0	0	0	NA	0·48
Neutropenia	3 (5%)	5 (9%)	3 (5%)	0	2 (3%)	3 (5%)	1 (2%)	0	2·41 (0·68–8·48)	0·23
Urinary tract infection	8 (14%)	0	0	0	6 (10%)	1 (2%)	0	0	NA	>0·99
White blood cell decreased	6 (11%)	3 (5%)	0	0	6 (10%)	1 (2%)	0	0	3·44 (0·35–34·09)	0·35
Dyspepsia	7 (12%)	0	0	0	8 (13%)	0	0	0	NA	NA
Headache	6 (11%)	0	0	0	9 (14%)	0	0	0	NA	NA
Hiccups	9 (16%)	0	0	0	5 (8%)	0	0	0	NA	NA
Insomnia	5 (9%)	0	0	0	9 (14%)	0	0	0	NA	NA
Hypomagnesemia	7 (12%)	0	0	0	5 (8%)	0	1 (2%)	0	NA	>0·99
Raised urea	4 (7%)	0	0	0	7 (11%)	1 (2%)	0	0	NA	>0·99
Cough	8 (14%)	0	0	0	2 (3%)	0	0	0	NA	NA
Febrile neutropenia	1 (2%)	2 (4%)	2 (4%)	0	0	3 (5%)	2 (3%)	0	0·88 (0·22–3·43)	>0·99
Hyponatraemia	3 (5%)	4 (7%)	0	0	1 (2%)	0	2 (3%)	0	2·30 (0·41–13·07)	0·42
Low white blood cell count	3 (5%)	2 (4%)	0	0	2 (3%)	2 (3%)	0	0	1·11 (0·15–8·14)	>0·99
Acute kidney injury	0	1 (2%)	0	0	1 (2%)	4 (6%)	0	0	0·26 (0·03–2·43)	0·37
Dehydration	2 (4%)	2 (4%)	0	0	1 (2%)	1 (2%)	0	0	2·25 (0·20–25·55)	0·60
Hypotension	0	1 (2%)	0	0	1 (2%)	3 (5%)	0	0	0·36 (0·04–3·53)	0·62
Hyperglycaemia	0	2 (4%)	0	0	0	1 (2%)	0	0	2·25 (0·20–25·55)	0·60
Renal and urinary disorders	0	1 (2%)	0	0	0	2 (3%)	0	0	0·54 (0·05–6·17)	>0·99
Skin and subcutaneous tissue disorders	0	2 (4%)	0	0	1 (2%)	0	0	0	NA	0·22
Skin infection	0	2 (4%)	0	0	0	1 (2%)	0	0	2·25 (0·20–25·55)	0·60
Myocardial infarction	0	0	0	0	0	1 (2%)	0	1 (2%)	NA	0·50

OR=odds ratio. NA=not applicable. *Occurring in at least 10% of patients. †Occurring in at least 2% of patients.

Table 2: **Adverse events**

nintedanib might target cancer-associated fibroblast development; this theory requires further study.

The results of the NEOBLADE trial add to the debate about the optimal endpoints in neoadjuvant bladder cancer trials. Although pathological complete response was selected as a primary endpoint in view of previous data supporting its surrogacy for overall survival and relapse-free survival after neoadjuvant chemotherapy,[26] it is unknown whether this holds true for combination treatments including tyrosine kinase inhibitors or immunotherapy. Furthermore, organ preservation was allowed in this study and the association between pT0 on

post-neoadjuvant chemotherapy cystoscopic biopsy and survival is poorly defined. Some patients refused the per-protocol cystoscopic biopsy and were unable to be included in the primary efficacy endpoint analysis for this study, which is a notable weakness. Hence, from the experience of the NEOBLADE study, we would avoid the use of pathological complete response as the primary endpoint in future novel combination neoadjuvant studies that permit radical radiotherapy and would instead focus on overall survival and relapse-free survival outcomes.

We acknowledge limitations to our study. This was an efficacy-seeking, randomised, phase 2 study with a relatively small sample size. Pathological complete response was chosen as the primary endpoint, which is obtained rapidly, but is not validated in the setting. With hindsight, more established endpoints such as progression-free survival and overall survival would have been preferable. Additionally, in patients opting for bladder preservation, the absence of evaluable tissue in some patients resulted in the incomplete assessment of the primary endpoint of pathological complete response.

In conclusion, the combination of standard-of-care chemotherapy and nintedanib can be safely administered in the neoadjuvant setting, but did not improve pathological complete response, and progression-free survival was also not significantly different between groups. A post-hoc analysis suggested an improvement in overall survival in the experimental group, which could merit further investigation in the neoadjuvant setting.

Contributors

SAH was responsible for conceptualisation, funding acquisition, investigation, methodology, resources, the original draft, and writing, review, and editing. RJ contributed to data curation, formal analysis, and manuscript preparation, and accessed and verified the data. MG contributed to data curation and formal analysis, and accessed and verified the data. MQ contributed to the original draft and writing, review, and editing. JFL, AE, SJC, RAH, NV, AJB, JW, NDJ, OP, MV-V, RA, MDL, JWFC, TP, and RJJ contributed to writing, review, and editing. IBR contributed to the original draft, writing, review, and editing, and methodology. All authors had full access to all the data in the study and had full responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Individual participant data that underlie the results reported in this Article, after de-identification, will be available 9–36 months after publication to investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose, for individual participant data meta-analysis. Proposals may be submitted up to 36 months after publication. After 36 months, the data will be available in the University of Liverpool's data warehouse, but without investigator support other than deposited metadata. The study protocol is available in the appendix.

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References

1 James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012; **366:** 1477–88.

2 Vale CL. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol* 2005; **48:** 202–05.

3 Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003; **349:** 859–66.

4 Yin M, Joshi M, Meijer RP, et al. Neoadjuvant chemotherapy for muscle-invasive bladder cancer: a systematic review and two-step meta-analysis. *Oncologist* 2016; **21:** 708–15.

5 Bernardini S, Fauconnet S, Chabannes E, Henry PC, Adessi G, Bittard H. Serum levels of vascular endothelial growth factor as a prognostic factor in bladder cancer. *J Urol* 2001; **166:** 1275–79.

6 Bochner BH, Cote RJ, Weidner N, et al. Angiogenesis in bladder cancer: relationship between microvessel density and tumor prognosis. *J Natl Cancer Inst* 1995; **87:** 1603–12.

7 Pruthi RS, Nielsen M, Heathcote S, et al. A phase II trial of neoadjuvant erlotinib in patients with muscle-invasive bladder cancer undergoing radical cystectomy: clinical and pathological results. *BJU Int* 2010; **106:** 349–54.

8 Roskoski R Jr. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. *Pharmacol Res* 2020; **151:** 104567.

9 Galsky MD, Hahn NM, Powles T, et al. Gemcitabine, cisplatin, and sunitinib for metastatic urothelial carcinoma and as preoperative therapy for muscle-invasive bladder cancer. *Clin Genitourin Cancer* 2013; **11:** 175–81.

10 Necchi A, Lo Vullo S, Raggi D, et al. Neoadjuvant sorafenib, gemcitabine, and cisplatin administration preceding cystectomy in patients with muscle-invasive urothelial bladder carcinoma: an open-label, single-arm, single-center, phase 2 study. *Urol Oncol* 2018; **36:** 8.e1–e8.

11 Forster M, Hackshaw A, De Pas T, et al. A phase I study of nintedanib combined with cisplatin/gemcitabine as first-line therapy for advanced squamous non-small cell lung cancer (LUME-Lung 3). *Lung Cancer* 2018; **120:** 27–33.

12 Hanna NH, Kaiser R, Sullivan RN, et al. Nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with relapsed or refractory, advanced non-small cell lung cancer (LUME-Lung 2): a randomized, double-blind, phase III trial. *Lung Cancer* 2016; **102:** 65–73.

13 Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol* 2014; **15:** 143–55.

14 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron J* 1976; **16:** 31–41.

15 Catto JWF, Gordon K, Collinson M, et al. Radical cystectomy against intravesical BCG for high-risk high-grade nonmuscle invasive bladder cancer: results from the randomized controlled BRAVO-feasibility study. *J Clin Oncol* 2021; **39:** 202–14.

16 Jefferies ER, Cresswell J, McGrath JS, et al. Open radical cystectomy in England: the current standard of care—an analysis of the British Association of Urological Surgeons (BAUS) cystectomy audit and Hospital Episodes Statistics (HES) data. *BJU Int* 2018; **121:** 880–85.

17 National Institute for Health and Care Excellence. Bladder cancer: diagnosis and management. Feb 25, 2015. https://www.nice.org.uk/guidance/ng2/resources/bladder-cancer-diagnosis-and-management-pdf-51036766405 (accessed Oct 10, 2021).

18 Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol* 2011; **29:** 2171–77.

19 Jung SH. Randomized phase II trials with a prospective control. *Stat Med* 2008; **27:** 568–83.

20 Rosenberg JE, Ballman KA, Halabi S, et al. Randomized phase III trial of gemcitabine and cisplatin with bevacizumab or placebo in patients with advanced urothelial carcinoma: results of CALGB 90601 (Alliance). *J Clin Oncol* 2021; **39:** 2486–96.

21 Balar AV, Apolo AB, Ostrovnaya I, et al. Phase II study of gemcitabine, carboplatin, and bevacizumab in patients with advanced unresectable or metastatic urothelial cancer. *J Clin Oncol* 2013; **31:** 724–30.

22 Hahn NM, Stadler WM, Zon RT, et al. Phase II trial of cisplatin, gemcitabine, and bevacizumab as first-line therapy for metastatic urothelial carcinoma: Hoosier Oncology Group GU 04-75. *J Clin Oncol* 2011; **29:** 1525–30.

23 Petrylak DP, de Wit R, Chi KN, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. *Lancet* 2017; **390:** 2266–77.

24 Petrylak DP, de Wit R, Chi KN, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): overall survival and updated results of a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2020; **21:** 105–20.

25 Kato R, Haratani K, Hayashi H, et al. Nintedanib promotes antitumour immunity and shows antitumour activity in combination with PD-1 blockade in mice: potential role of cancer-associated fibroblasts. *Br J Cancer* 2021; **124:** 914–24.

26 Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Vavassori I, Barni S. Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. *Eur Urol* 2014; **65:** 350–57.