Original Article

Nintedanib plus docetaxel after progression on first-line immunochemotherapy in patients with lung adenocarcinoma: Cohort C of the non-interventional study, VARGADO

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Background: Immune checkpoint inhibitors (ICIs) with or without chemotherapy represent first-line standard of care for patients with advanced non-small cell lung cancer (NSCLC) without targetable driver mutations. The most appropriate second-line therapy after failing immunochemotherapy remains an open question. Nintedanib, an oral triple angiokinase inhibitor that targets the vascular endothelial growth factor receptor, fibroblast growth factor receptor, and, platelet-derived growth factor receptor, in combination with docetaxel, is approved for treatment of advanced NSCLC (adenocarcinoma histology) following progression on first-line chemotherapy.

Methods: VARGADO (NCT02392455) is an ongoing, prospective, non-interventional study investigating the efficacy and safety of nintedanib plus docetaxel following first-line chemotherapy with or without ICIs in patients with locally advanced, metastatic, or locally recurrent NSCLC of adenocarcinoma histology. This analysis focuses on Cohort C, which enrolled patients who had received prior first line chemotherapy with ICIs. Patients received second-line docetaxel (75 mg/m^2) by intravenous infusion on Day 1, plus oral nintedanib (200 mg twice daily) on Days 2–21 of each 21-day cycle during routine clinical care. The primary endpoint is overall survival (OS) rate 1 year after the start of treatment with nintedanib plus docetaxel. Secondary endpoints include progression-free survival (PFS), OS, and disease control rate (DCR). Safety was also assessed.

Results: Among 137 patients treated, the median age was 63 years (range, 37–84); 57 patients (41.6%) were female, most patients had Eastern Cooperative Oncology Group performance status of 0 (28.5%) or 1 (43.1%); 118 (86.1%) had stage IV NSCLC and 27 (19.7%) had brain metastases. Most (n=120, 87.6%) patients had received pembrolizumab/pemetrexed/platinum-based chemotherapy as first-line treatment. In 80 patients with available response data, the DCR was 72.5% (complete response: 1.3%; partial response: 36.3%; stable disease: 35.0%). Median progression-free survival was 4.8 months (95% confidence interval: 3.7–6.6). OS data were immature. Grade ≥3 treatment-emergent adverse events (TEAEs), serious TEAEs,

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and TEAEs leading to treatment discontinuation were reported in 62 (45.3%), 50 (36.5%), and 40 patients (29.2%), respectively.

Conclusions: This analysis indicates that nintedanib plus docetaxel represents an effective second-line treatment option in patients with advanced adenocarcinoma NSCLC following progression on first-line immunochemotherapy. The safety profile was manageable with no unexpected signals.

Keywords: Nintedanib; docetaxel; immunochemotherapy; non-small cell lung cancer (NSCLC); adenocarcinoma

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Introduction

Until relatively recently, platinum-based chemotherapy was the established first-line treatment of choice for patients with advanced non-small cell lung cancer (NSCLC) without targetable mutations. However, Phase III studies have shown that the combination of anti PD-1/PD-L1 agents with chemotherapy significantly improves efficacy versus chemotherapy alone in this setting (1-3). These findings precipitated a major and rapid paradigm shift in the treatment of patients with NSCLC, bringing immune checkpoint inhibitors (ICIs) into the first-line, rather than a second-line setting post chemotherapy (4-6). Accordingly, the emergence of front-line immunochemotherapy regimens poses an urgent clinical question: if ICIs might not be used as second-line treatment options, how should patients be treated following the failure of ICI based first-line regimens (7,8)? In general, only limited clinical data are available assessing the optimal sequence of treatment following immunochemotherapy in the first line.

Integral to the mechanism of action of ICIs is the ability of anti-tumor T cells to infiltrate and proliferate within the tumor microenvironment (TME), thereby facilitating T cell-mediated immune destruction of tumor cells (9). As such, vascular disruption within the tumor could be an underlying factor in acquired resistance to ICIs. Vascular endothelial growth factor (VEGF)-mediated tumor angiogenesis has been implicated in the resistance to ICIs by modulating immune cell function and reducing immune cell access, thus promoting an immunosuppressive TME (10). Accordingly, agents that target VEGF signaling and other pro-angiogenic pathways could potentially improve immune cell access into the tumor by normalizing blood vessels. This could promote development of an immune-supportive TME in a hypothesized 'angio-immunogenic switch' (8).

Nintedanib is an oral triple angiokinase inhibitor that targets VEGF receptors 1–3, fibroblast growth factor (FGF) receptors 1–3, and platelet-derived growth factor (PDGF) receptors α/β (11,12). Recent preclinical data indicate that nintedanib can promote an anti-tumor immune response and potentiate the activity of ICIs in mice, possibly by inhibiting immunosuppressive cancer associated fibroblasts and by facilitating the intratumoral accumulation and activation of CD8+ T cells (13,14).

In the LUME-Lung 1 Phase III trial, nintedanib plus docetaxel significantly improved overall survival (OS) and progression-free survival (PFS) versus placebo plus docetaxel in patients with recurrent, advanced NSCLC of adenocarcinoma histology following first-line chemotherapy (15). Based on these findings, the combination was approved in the European Union (EU) in this setting (16). Of note, the greatest relative benefit versus placebo was observed in patients who rapidly progressed (<9 months) on first-line chemotherapy. As LUME-Lung 1 was undertaken prior to the era of first-line ICIs, only limited data are available assessing the activity of nintedanib plus docetaxel following immunochemotherapy. Moreover, almost all studies undertaken to date have assessed nintedanib plus docetaxel in a third-line setting after successive chemotherapy and ICI monotherapy; in these studies, nintedanib plus docetaxel was associated with an unprecedentedly high response rate in this setting (36.5–58.3%), and encouraging PFS (3.2–6.4 months) (17-21). While these studies have demonstrated clinical activity of the combination, its activity following first-line immunochemotherapy is uncertain.

The ongoing VARGADO non-interventional study (NCT02392455) is investigating the efficacy and safety of nintedanib plus docetaxel following first-line chemotherapy or immunochemotherapy in patients with advanced NSCLC of adenocarcinoma histology treated in routine practice. In Cohort A, patients received the combination

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following first-line chemotherapy (17). Results of Cohort B of VARGADO, which assessed nintedanib plus docetaxel in a third-line setting after sequential chemotherapy and ICIs, have been reported previously (17,21). Here, we present interim efficacy and safety data from Cohort C, assessing the combination in a second-line setting following first-line immunochemotherapy. Despite its immaturity, the purpose of the interim analysis is to provide physicians with clinically relevant information in an area where there is currently a paucity of prospective clinical data regarding subsequent treatment options beyond first-line standard of care. We present the article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-1018/rc).

Methods

Study design and patients

VARGADO is ongoing at approximately 100 centers in Germany. Eligibility criteria included age ≥18 years, locally advanced, metastatic, or locally recurrent adenocarcinoma NSCLC and prior treatment with first-line immunochemotherapy. Exclusion criteria included contraindications for trial drugs, and treatment with more than one prior chemotherapy for NSCLC (except prior adjuvant/neoadjuvant therapy). Although patients could enroll concurrently in other non-interventional trials, simultaneous participation in other clinical trial types was not permitted.

Nintedanib and docetaxel were administered during routine clinical care according to the approved labels. Patients received docetaxel (75 mg/m^2, intravenous infusion) on Day 1, plus nintedanib (200 mg twice daily, orally) on Days 2–21 of each 21-day cycle, until disease progression or until the development of intolerable adverse effects. Data on patient characteristics (including oncological history and prior and concomitant therapies), efficacy and safety were collected by the treating physician during routine clinical visits using a standardized electronic case report form. Follow-up for safety and efficacy is for a maximum of 2 years following the start of treatment. The final follow-up for survival is planned to take place 2 years after enrollment of the last patient.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was assessed and approved by the ethics committee of the Charité Berlin (No. EA1/332/14). All patients provided signed informed consent. Participating physicians were compensated by Boehringer Ingelheim Pharma GmbH & Co. KG for documentation, monitoring, and study initiation within the range of the official German Physicians' Fee Schedule (GOÄ). For all patients enrolled in VARGADO Cohort C at cut-off (01 April 2021), baseline patient data, and efficacy and safety data were collected and analyzed.

Endpoints

The primary endpoint was the OS rate 1 year after the start of treatment with nintedanib plus docetaxel. Secondary endpoints included: disease control rate (DCR); PFS; OS; PFS and 1-year OS rate for patients for whom less than 9 months elapsed between the start of first-line treatment and start of second-line treatment [i.e., <9 months' time since the start of first-line therapy (TSFLT)]. Additionally, secondary endpoints included the duration of treatment, dose modifications, and the incidence of nintedanib-related adverse events (AEs). In prespecified sub-group analyses, efficacy outcomes according to prior therapy and the TSFLT (<9 months or ≥9 months) were also examined.

Assessments

Response to treatment was evaluated by investigators based on routine staging investigations per Response Evaluation Criteria in Solid Tumors (RECIST). DCR was calculated as the percentage of evaluable patients with a best response of complete response (CR), partial response (PR), or stable disease (SD). PFS was measured from the beginning of treatment with nintedanib plus docetaxel until the occurrence of progression or until death.

Mutational status of tumors (e.g., the presence of *EGFR* or *KRAS* mutations) was assessed according to routine procedures of participating centers. Frequency and severity of AEs was also recorded. The severity of AEs was classified per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Whether AEs were related to the study drug was assessed by the treating investigator.

Statistical analyses

All analyses were descriptive. All patients who received at least one dose of nintedanib were included in the analysis (treated set). Based on the 1-year survival rate of 53% in

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LUME Lung 1 (15), it was calculated that 700 patients across the three cohorts in VARGADO (A–C) would provide a sufficient sample size for evaluation of the primary endpoint [95% confidence interval (CI) for 1-year OS rate: 49.2–56.6%]. PFS was analyzed using the Kaplan–Meier method. The analysis was performed with SAS® software.

Results

Patient demographics and clinical characteristics

Between October 2018 and 01 April 2021, 137 patients were enrolled in Cohort C [41.6% female; median age: 63 years (range, 37–84); *Table 1*]. The majority of patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (n=39, 28.5%) or 1 (n=59, 43.1%), and 118 (86.1%) had stage IV NSCLC. Brain metastases were reported in 27 (19.7%) patients. Most (n=120, 87.6%) patients had received pembrolizumab/pemetrexed/platinum-based chemotherapy as first-line therapy and seven (5.1%) had received another pembrolizumab/chemotherapy combination. Combination therapy including atezolizumab or nivolumab had been received by seven (5.1%) and two (1.5%) patients, respectively.

Median time on first-line immunochemotherapy was 5.5 months (95% CI: 4.7–6.3). Overall, 89 (65.0%) and 48 (35.0%) patients had TSFLT <9 months or ≥9 months, respectively. Of 118 patients who underwent a tumor biopsy prior to treatment, mutations in *EGFR* or *KRAS* were detected in two (1.7%) and 24 (21.6%) patients, respectively. No *EML4-ALK* translocations were reported. PD-L1 status was reported in 79 patients (negative: 48.1%; ≥1%: 10.1%; 1–49%: 6.3%; <50%: 19.0%; ≥50%: 16.5%).

Efficacy

Among 80 evaluable patients, the DCR was 72.5% and the objective response rate (ORR) was 37.5% (CR: n=1, 1.3%; PR: n=29, 36.3%. *Table 2*). SD was observed in 28 (35.0%) patients. ORR (36.5% and 39.3%) and DCR (69.2% and 78.6%) were generally similar in patients with TSFLT <9 months or ≥9 months, respectively (Table S1). The DCR was 76.9% and 69.6% for patients with mutant (n=24) or wild-type *KRAS* (n=43), respectively.

Overall treatment duration and best response in evaluable patients who had received prior treatment with first-line pembrolizumab/pemetrexed/platinum-based regimens (n=68) are shown in *Figure 1*. Responses were observed both in patients with fast progressing disease on first-line immunochemotherapy, as well as those with slower-progressing disease.

At the time of this interim analysis, the median duration of follow-up was 4.2 months (95% CI: 3.4–5.5). In the treated set (n=137), median PFS was 4.8 months (95% CI: 3.7–6.6; *Figure 2A*). The median PFS was 4.1 months (95% CI: 2.6–6.4) and 5.3 months (95% CI: 3.9–9.0) in patients with TSFLT <9 months (n=89) and ≥9 months (n=48), respectively (*Figure 2B*). PFS events were recorded for 70 (51.1%) patients, and 67 (48.9%) patients were censored. Median PFS was 4.8 months (95% CI: 2.2–not estimable) and 6.4 months (95% CI: 2.5–9.9) for patients with and without *KRAS* mutations, respectively (P=0.4784, Figure S1). OS data were immature and are not reported.

Safety

In the treated set (n=137), treatment-emergent adverse events (TEAEs) of any grade and of grade ≥3 were reported in 106 (77.4%) and 62 (45.3%) of patients, respectively. Serious TEAEs were reported in 50 patients (36.5%). The most common any-grade TEAEs were diarrhea (n=44, 32.1%), nausea (n=28, 20.4%) and fatigue (n=18, 13.1%) (*Table 3*). The most common grade ≥3 TEAEs were white blood cell count decreased (n=9, 6.6%), diarrhea and neutrophil count decrease (n=6, 4.4% each).

Treatment-related AEs (TRAEs) were reported in 78 (56.9%) patients. Serious TRAEs were reported in 16 (11.7%) patients. The most common nintedanib-related TRAEs of any grade were diarrhea (n=42, 30.7%), nausea (n=19, 13.9%) and fatigue (n=12, 8.8%); the most common TRAEs of grade ≥3 were white blood cell count decreased (n=7, 5.1%), diarrhea (n=6, 4.4%), gamma glutamyl transferase increase and hypertension (n=3, 2.2% each). The most common docetaxel-related TRAEs of any grade were nausea (n=23, 16.8%), diarrhea (n=17, 12.4%), and fatigue (n=17, 12.4%); the most common TRAE of grade ≥3 was white blood cell count decrease (n=9, 6.6%).

Dose reduction or interruption of nintedanib was reported in 46 (33.6%) and 30 (21.9%) patients, respectively. Nintedanib-related TRAEs leading to dose reduction affecting more than one patient were diarrhea (n=11, 8.0%), nausea (n=6, 4.4%), vomiting (n=3, 2.2%), and fatigue (n=2, 1.5%). Dose reduction or interruption of docetaxel was reported in 18 (13.1%) and 22 (16.1%) patients, respectively. Docetaxel-related TRAEs leading to dose reduction affecting more than one patient were

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Table 1 Patient characteristics at baseline

Characteristic	Items	Treated set (n=137)
Age	Median age, years [range]	63 [37–84]
	Age <70 years, n (%)	112 (81.8)
	Age ≥70 years, n (%)	25 (18.2)
Sex, n (%)	Female	57 (41.6)
	Male	80 (58.4)
ECOG PS, n (%)	0	39 (28.5)
	1	59 (43.1)
	2	18 (13.1)
	3	2 (1.5)
	Not reported	19 (13.9)
Clinical stage at baseline, n (%)	<IV	9 (6.6)
	IV	118 (86.1)
Brain metastases, n (%)	Yes	27 (19.7)
	No	110 (80.3)
Previous first-line therapy, n (%)	Pembrolizumab/pemetrexed/platinum[†]	120 (87.6)
	Other pembrolizumab/CT combination	7 (5.1)
	Atezolizumab/CT combination	7 (5.1)
	Nivolumab/CT combination	2 (1.5)
	Other immunotherapy	1 (0.7)
Best response to first-line therapy, n (%)	CR	0
	PR	37 (27.0)
	SD	28 (20.4)
	PD	38 (27.7)
	Other	1 (0.7)
	Not reported	33 (24.1)
EGFR status[‡], n (%)	Wild-type	111 (94.1)
	Mutated	2 (1.7)
	Not reported	5 (4.2)
EML4-ALK translocation[§], n (%)	Wild-type	97 (87.4)
	Mutated	0
	Not reported	14 (12.6)
KRAS mutation[§], n (%)	Wild-type	43 (38.7)
	Mutated	24 (21.6)
	Not reported	44 (39.6)

[†], pembrolizumab/pemetrexed/carboplatin, n=93 (67.9%); pembrolizumab/pemetrexed/cisplatin, n=25 (18.2%); pembrolizumab/pemetrexed/cisplatin + carboplatin, n=2 (1.5%). [‡], % values refer to patients with initial biopsy (n=118). [§], % values refer to patients with additional biomarker analysis (n=111). CR, complete response; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD, progressive disease; PR, partial response; SD, stable disease.

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Table 2 Best response to treatment with nintedanib plus docetaxel following failure of firstline immunochemotherapy

Response	Evaluable patients (n=80)*
Objective response rate, n (%)	30 (37.5)
Complete response	1 (1.3)
Partial response	29 (36.3)
Stable disease, n (%)	28 (35.0)
Disease-control rate, n (%)	58 (72.5)
Progressive disease, n (%)	22 (27.5)

*, data are for patients in the treated set who had a documented best response to nintedanib plus docetaxel.

white blood cell count decrease, anemia (n=3, 2.2% each), peripheral sensory neuropathy, diarrhea, and fatigue (n=2, 1.5% each).

TRAEs leading to discontinuations of the trial drug were reported in 24 (17.5%) patients. Fatal TEAEs were reported in 13 (9.5%) patients. These were pneumonia (n=3, 2.2%), febrile neutropenia, death, cardiac failure, fatigue, general physical health deterioration, anorectal infection, sepsis, cerebrovascular accident, seizure, and dyspnea (n=1, 0.7% each). The cases of febrile neutropenia and sepsis were deemed treatment related.

Discussion

This interim analysis of VARGADO represents the first prospective real-world evidence of the efficacy of second-line nintedanib plus docetaxel following immunochemotherapy in patients with NSCLC, and is the largest study of any approved second-line regimen in this treatment sequence. Meaningful efficacy was observed, with promising DCR and ORR, and treatment was tolerable with no unexpected safety signals.

The patient population was characterized by a relatively short median duration of first-line treatment of 5.5 months, (95% CI: 4.7–6.3), with an ORR of 35.6%, lower than reported in first-line Phase III trials of immunochemotherapy (median PFS of 6.7–8.8 months; ORRs of 38.2–47.6%) (1,2,22). Most patients had short TSFLT (<6 months: 39.4%; <9 months: 65.0%), 14.6% had an ECOG PS ≥2, median age was 63 years and 42% were female. In contrast, LUME-Lung 1 excluded patients with ECOG PS ≥2 and among adenocarcinoma patients, median age was 58.5 years, and 37% were female (23). It would appear, therefore, that the enrolled population represented one with highly advanced, more rapidly progressing disease compared with contemporary trials in this setting. Given this observation, efficacy was encouraging: the median PFS with second-line nintedanib plus docetaxel was 4.8 months, and the DCR and ORR were 72.5% and 37.5%, respectively. Interestingly, in this cohort, the ORR of 37.5% with second-line nintedanib plus docetaxel was higher than that previously achieved in the same population with first-line immunochemotherapy (27.0%).

In LUME Lung 1, second-line nintedanib plus docetaxel conferred a median PFS of 4 months, median OS of 12.6 months, DCR of 60.2% and ORR of 4.7% (independently assessed) in patients with lung adenocarcinoma following chemotherapy (15). Of note, in LUME-Lung 1, the relative efficacy of nintedanib plus docetaxel versus docetaxel alone appeared to be higher in patients with TSFLT <9 months (median PFS of 3.6 *vs.* 1.5 months) than in patients with TSFLT ≥9 months (median PFS of 4.2 *vs.* 4.5 months) (15,23). In the current study, meaningful efficacy was observed regardless of TSFLT. In patients with TSFLT <9 months, DCR was 69.2% and median PFS was 4.1 months, and in patients with TSFLT ≥9 months, DCR was 78.6% and median PFS was 5.3 months. The observation that nintedanib plus docetaxel demonstrated a PFS benefit even numerically higher than in LUME Lung 1 and a high DCR in patients with <9 months TSFLT in this study provides further proof of principle that the combination will benefit patients who progress rapidly on first-line treatment, be it chemotherapy or immunochemotherapy (15).

At present, approved second-line treatment options (other than ICIs) include nintedanib or ramucirumab (an anti-VEGFR2 antibody), in combination with docetaxel; docetaxel monotherapy; pemetrexed and erlotinib (24). Few data exist assessing these options after immunochemotherapy. A recent smaller retrospective cohort study assessed second-line ramucirumab plus docetaxel following immunochemotherapy in 77 patients with stage IV NSCLC (adenocarcinoma: n=55; squamous cell carcinoma: n=16: other: n=6); median OS was 7.5 months, and ORR and DCR were 32.5% and 62.4%, respectively. In patients with adenocarcinoma, median PFS was 3.9 months (25). In contrast to the VARGADO study, which is ongoing at over 100 centers in Germany, the ramucirumab study was restricted to nine high-volume German oncology centers with specialist expertise in the use of immunochemotherapy for thoracic cancers. Therefore, it is likely that VARGADO is more representative of 'real-world' clinical practice across

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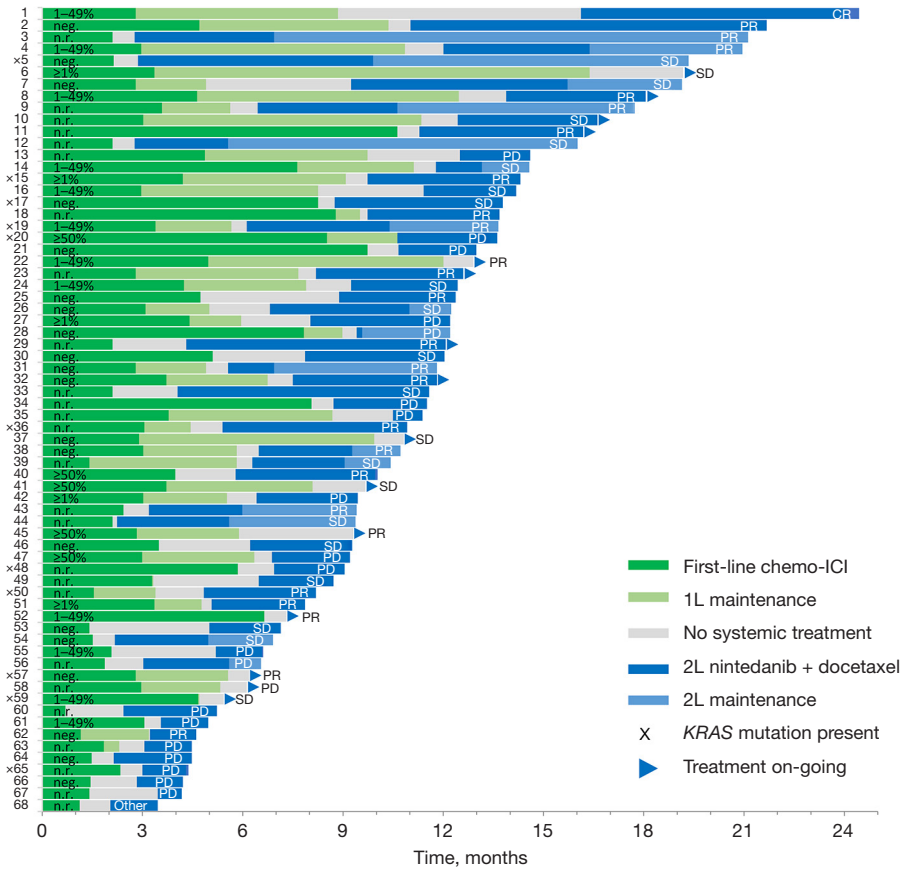

Figure 1 Time on first- and second-line treatment, and best response. Swimmer plot showing duration of therapy and best response. Patients included had a documented best response and had received prior treatment with 1L pembrolizumab/pemetrexed/platinum-based regimens. % values indicate PD-L1 expression level. Other: mixed response. 1L, first-line; 2L, second-line; CR, complete response; ICI, immune checkpoint inhibitor; neg., negative; n.r., not reported; PD, progressive disease; PR, partial response; SD, stable disease.

Germany. Moreover, the prospective and standardized nature of data collection in VARGADO C may result in more consistent safety and efficacy data reporting than might be observed in a retrospective trial. Further, the longer run-time of VARGADO may allow a greater understanding of the pattern of progression and relapse in advanced NSCLC, which may inform the design of future studies.

In the ramucirumab study, the presence of *KRAS* mutations appeared to negatively impact efficacy (25). In contrast, in the current study, PFS and DCR with nintedanib plus docetaxel were similar irrespective of *KRAS* mutation status. Emerging $KRAS^{G12C}$ inhibitors, such as sotorasib, may represent a second-line treatment option in the ~11% of NSCLC patients with this mutation, especially given the association of $KRAS^{G12C}$ with high PD-L1 expression (26). Our data suggest that nintedanib plus docetaxel could be an option in patients with *KRAS* mutations, particularly in tumors with mutations other than $KRAS^{G12C}$, which remain an area of unmet need. However, the activity of nintedanib plus docetaxel against specific *KRAS* mutation subtypes in this study was not reported and more data are required.

There are scant published safety data for nintedanib with docetaxel in the second line, following immunochemotherapy. Here, nintedanib plus docetaxel was generally tolerable, with no unexpected toxicities or new safety signals reported; 33.6% of patients required a dose reduction of nintedanib, 17.5% of patients discontinued due to TRAEs and 11.7% of patients had serious TRAEs. In LUME-Lung 1, frequently reported AEs included gastrointestinal disorders, such as diarrhea and liver enzyme elevations (15). A similar

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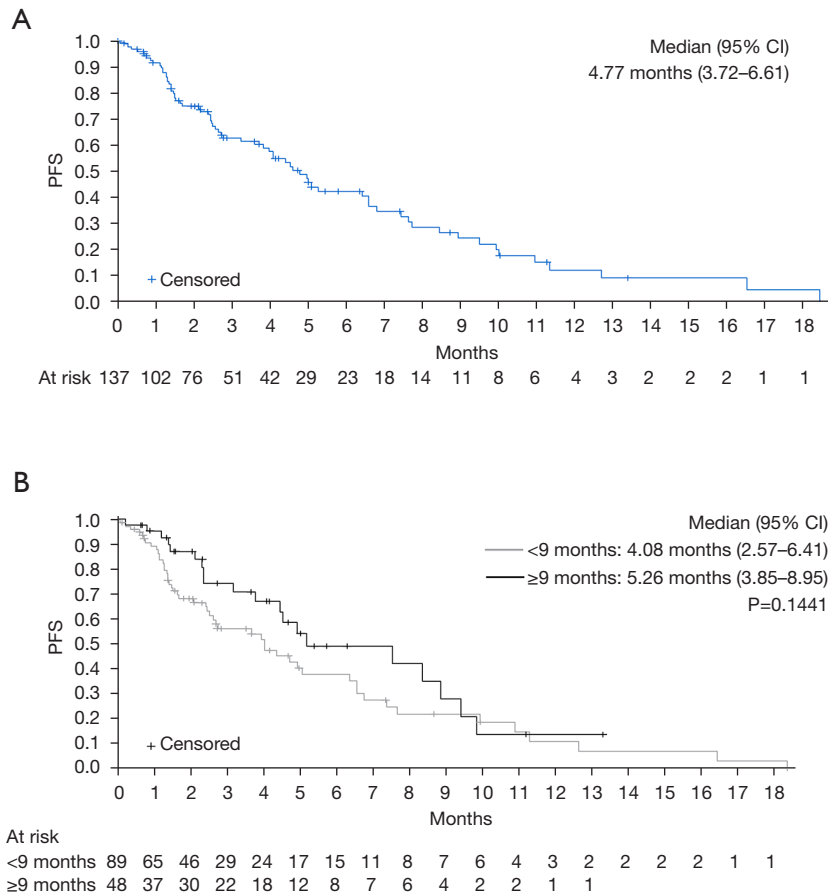

Figure 2 Kaplan-Meier plots of progression-free survival (treated set). Kaplan-Meier plots of progression-free survival in all patients (A), and in all patients with time since the start of first-line treatment of <9 months or ≥9 months (B). CI, confidence interval; PFS, progression-free survival.

Table 3 Summary of treatment-emergent and drug-related treatment-emergent adverse events

TEAE affecting more than 5% of patients	Nintedanib-related		Docetaxel-related		Total	
	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)
Diarrhea	42 (30.7)	6 (4.4)	17 (12.4)	4 (2.9)	44 (32.1)	6 (4.4)
Nausea	19 (13.9)	0	23 (16.8)	0	28 (20.4)	0
Fatigue	12 (8.8)	0	17 (12.4)	0	18 (13.1)	0
Vomiting	10 (7.3)	0	8 (5.8)	0	12 (8.8)	0
Alopecia	4 (2.9)	0	10 (7.3)	0	11 (8.0)	0
White blood cell count decrease	8 (5.8)	7 (5.1)	10 (7.3)	9 (6.6)	10 (7.3)	9 (6.6)
Decreased appetite	6 (4.4)	0	8 (5.8)	0	8 (5.8)	0

TEAE, treatment-emergent adverse event.

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profile was observed in this study. In patients receiving ramucirumab with docetaxel in the second line, the most common grade ≥3 side effects were neutropenia, fatigue and paronychia (15.6%, 6.5%, and 5.2%, respectively), and no treatment-related deaths were observed (25). The frequency of dose reductions of nintedanib due to toxicity was higher than observed in LUME-Lung 1, presumably reflecting differences in the baseline characteristics of patients, e.g., ECOG PS.

The data presented herein are preliminary, with a median follow-up of 4.2 months, and more mature data are required. In particular, OS data, a key outcome in the second-line setting, are eagerly anticipated. Nevertheless, given the paucity of prospective randomized trials assessing second-line treatment options after immunochemotherapy, and the urgent unmet medical need in this setting, these interim non-interventional data are of interest. Also, as the study recruited patients in the immediate aftermath of KEYNOTE 189 (1), the population was highly homogenous in terms of the first-line treatment received, with ~90% of patients receiving pembrolizumab plus chemotherapy. However, the study has several limitations. These include the non-interventional study design, as it may limit completeness of data collection, the absence of formal hypothesis testing of comparators and incomplete biomarker data, with PD-L1 status missing for 58 patients. However, the large sample size offers meaningful insight into the clinical effectiveness of the combination treatment in this setting after immunochemotherapy; recruitment is ongoing.

With the advent of first-line immunochemotherapy and the potential of nintedanib plus docetaxel as a second-line treatment option, patient outcomes may be improved by early consideration of the sequence of subsequent treatments. VARGADO is the first trial to systematically investigate the use of nintedanib plus docetaxel in the treatment sequence following immunochemotherapy or sequential chemotherapy and immunotherapy and investigates the possibility that antiangiogenic therapy might have a potentiating effect in this setting. Based on preclinical data, it has been hypothesized that antiangiogenic agents may have a synergistic effect with ICIs by normalizing tumor vasculature, thus restoring an immunosupportive TME (a so-called 'angio-immunogenic switch') (8). This may help explain why the activity of nintedanib plus docetaxel after immunochemotherapy in the current study appeared to be better than observed following chemotherapy alone in the LUME-Lung 1 study.

There is interest in treatment approaches that aim to overcome resistance to immunotherapy, e.g., the combination of anti-PD-1/PD-L1 therapy with alternative immune checkpoint targets (27) or re-challenge with immunotherapy in later lines (28). Ongoing early-phase clinical studies are assessing the possible synergistic effect of combining antiangiogenic agents with ICIs in previously treated patients. Regimens being investigated include nintedanib with nivolumab alone (NCT04046614) or with nivolumab plus ipilimumab (NCT03377023). Ramucirumab is also under investigation in combination with nivolumab (NCT03527108), atezolizumab (NCT03689855), and platinum-based chemotherapy (NCT03904108). An ongoing phase II sub-study of the Lung-MAP master protocol umbrella trial (Lung-MAP S1800A; NCT03971474) is assessing the combination of pembrolizumab plus ramucirumab versus standard of care (investigator's choice: docetaxel plus ramucirumab or docetaxel, gemcitabine, and pemetrexed) in patients with NSCLC who progressed on prior platinum-based doublet chemotherapy and prior ICI therapy (administered sequentially or in combination). In preliminary findings, pembrolizumab plus ramucirumab significantly improved OS versus standard of care [median 14.5 *vs.* 11.6 months; HR 0.69 (80% CI: 0.51–0.92)]. Of note, OS benefit appeared to be restricted to patients with squamous or mixed histology [HR 0.43 (80% CI: 0.28–0.65)] rather than in patients with non-squamous histology [HR 0.95 (80% CI: 0.67–1.35)]. Also, OS benefit was greater in patients who had received sequential [HR 0.45 (80% CI: 0.30–0.68)] rather than combined [HR 0.84 (80% CI: 0.58–1.21)] chemotherapy and immunotherapy. PFS and ORR did not differ between arms (29). In contrast to Lung-MAP S1800A, VARGADO C assessed a more homogenous population of patients who all had adenocarcinoma and received combined chemotherapy and immunotherapy as first-line treatment.

This interim analysis of VARGADO Cohort C provides real-world data to support clinical decision-making and treatment sequencing after first-line immunochemotherapy in patients with lung adenocarcinoma. Further investigation of the combination of nintedanib with docetaxel as second-line treatment following chemotherapy plus ICI therapy is warranted. VARGADO is ongoing; further data analyses with more patients are planned. In particular, given the existence of multiple first-line immunochemotherapy options, future analyses of potential second-line regimens, including nintedanib plus docetaxel, should consider activity

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in patient subgroups according to type of previous therapy, time to treatment failure and analysis of biomarkers, such as *TTF1* (30) (thyroid transcription factor 1) negativity, that may predict the efficacy of first-line treatment. Design of future trials should account for these considerations.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was assessed and approved by the ethics committee of the Charité Berlin (No. EA1/332/14). All patients provided signed informed consent.

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Supplementary

Table S1 Best response associated with second-line nintedanib plus docetaxel, grouped by time from start of first-line therapy until start of second-line therapy (<9 months or ≥9 months)

Response	<9 months (n=52)	≥9 months (n=28)	Total (n=80)
Objective response rate, n (%)	19 (36.5)	11 (39.3)	30 (37.5)
Complete response	0	1 (3.6)	1 (1.3)
Partial response	19 (36.5)	10 (35.7)	29 (36.3)
Stable disease, n (%)	17 (32.7)	11 (39.3)	28 (35.0)
Disease control rate, n (%)	36 (69.2)	22 (78.6)	58 (72.5)
Progressive disease, n (%)	16 (30.8)	6 (21.4)	22 (27.5)

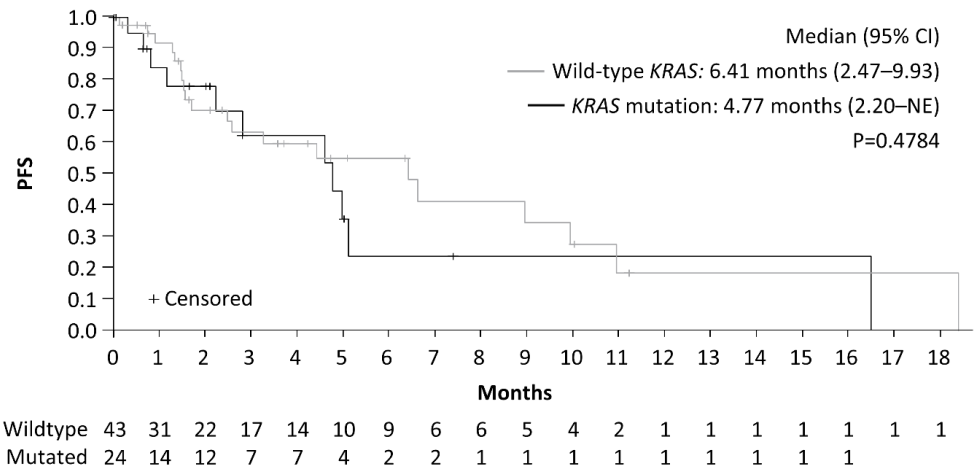

Figure S1 Kaplan–Meier plot of progression-free survival of patients with wild type or mutant *KRAS* (initial biopsy). CI, confidence interval; NE, not estimable; PFS, progression-free survival.

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