

Case Report

Nintedanib plus Docetaxel after Immune Checkpoint Inhibitor Failure in Patients with Advanced Non-Small-Cell Lung Cancer: A Case Series

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Keywords

Adenocarcinoma · Chemo-immunotherapy · Lung tumor · Non-small-cell lung cancer · Targeted therapy

Abstract

Advances in the treatment of non-small-cell lung cancers (NSCLCs) lacking an actionable driver mutation have included the approval of immunotherapies, such as monotherapy or in combination with chemotherapy. However, limited evidence exists to guide clinical decision-making after progression with immunotherapy. The vascular endothelial growth factor (VEGF) signaling pathway promotes tumor angiogenesis and the development of an immunosuppressive tumor microenvironment (TME). Anti-VEGF treatment is postulated to favor an immunosupportive TME through an “angio-immunogenic switch.” Nintedanib, an anti-VEGF receptor treatment, is approved in the EU and other countries, in combination with docetaxel for the treatment of locally advanced, metastatic, or locally recurrent adenocarcinoma NSCLC after failure of first-line chemotherapy. We present a case series from 5 patients treated with nintedanib plus docetaxel, after chemotherapy and immunotherapy, during routine clinical practice in Austria and Hungary. Four patients were treated with nintedanib plus docetaxel as a second- or third-line treatment after chemotherapy and immunotherapy, and a fifth patient received immunotherapy before and after nintedanib plus docetaxel. Although these patients would typically have a poor prognosis, each achieved a partial response with nintedanib plus docetaxel, with response duration from 8 months to over 30 months. Adverse events were

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manageable. The fifth patient case shows that nintedanib does not preclude later-line immunotherapy or chemotherapy, supporting the angio-immunogenic switch hypothesis. Overall, the case studies indicate that nintedanib plus docetaxel is an effective and well tolerated treatment, after sequential or combined chemo-immunotherapy for advanced NSCLC, and is compatible with a rechallenge with immunotherapy.

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Published by S. Karger AG, Basel

Introduction

Recent advances in advanced non-small-cell lung cancer (NSCLC) have included the approval of immunotherapies [1]. For patients without actionable driver mutations, ESMO recommends first-line treatment with immune checkpoint inhibitors such as monotherapy or in combination with chemotherapy, depending on programmed cell death protein 1 expression levels [1]. Although limited clinical evidence exists to optimize treatment selection after progression on immunotherapy, the tumor biology may guide treatment selection. The vascular endothelial growth factor (VEGF) signaling pathway promotes oncogenesis through the development of new blood vessels and supports tumor survival by fostering an immunosuppressive tumor microenvironment (TME) [2]. Excessive VEGF signaling can also modulate immune cell function and hinder immune entry, which may contribute to immunotherapy resistance. Tumors that are extensively reliant on VEGF pathways may therefore be sensitive to antiangiogenic treatment. The angio-immunogenic switch theory hypothesizes that inhibition of VEGF and other pro-angiogenic factors, such as platelet-derived growth factor and fibroblast growth factor, could renormalize blood vessels and improve immune cell access to the TME [2, 3].

Nintedanib is an oral, triple angiokinase inhibitor targeting VEGF receptors 1–3, platelet-derived growth factor receptors α and β , fibroblast growth factor receptors 1–3, and RET [4]. It is approved in the EU and other countries, in combination with docetaxel for the treatment of locally advanced, metastatic, or locally recurrent adenocarcinoma NSCLC after progression on first-line chemotherapy. ESMO recommends nintedanib plus docetaxel as a potential option after first-line chemotherapy in advanced NSCLC lacking an actionable driver mutation [1].

The approval of nintedanib plus docetaxel was based on the phase III LUME-Lung 1 trial [5]. In this randomized trial of patients with stage IIIB/IV recurrent NSCLC that had progressed after first-line chemotherapy, progression-free survival (PFS) was significantly improved with nintedanib plus docetaxel, compared with placebo plus docetaxel (median 3.4 vs. 2.7 months). Patients with adenocarcinoma NSCLC on nintedanib plus docetaxel had a significantly improved overall survival (OS) compared with patients on placebo plus docetaxel (median 12.6 vs. 10.3 months) [5]. OS was also greater with nintedanib plus docetaxel in patients with adenocarcinoma histology who progressed within 9 months after starting first-line treatment (median 10.9 vs. 7.9 months). Median OS in the full study population was 10.1 months for nintedanib plus docetaxel versus 9.1 months for placebo plus docetaxel [5]. An exploratory sub-analysis indicated that the OS benefits were independent of age or prior therapy [6]. The difference in median OS with nintedanib plus docetaxel compared with placebo plus docetaxel was larger in European patients (13.4 vs. 8.7 months) than the overall adenocarcinoma study population (12.6 vs. 10.3 months) [6]. Based on the LUME-Lung 1 trial, the recommended dosing is nintedanib (200 mg) twice daily plus docetaxel (75 mg/m²) once every 3 weeks [5]. Although weekly docetaxel dosing is not currently approved in advanced NSCLC, similar efficacy and improved tolerability have been reported [7].

Limited data are available for nintedanib after chemo-immunotherapy, but data are emerging from noninterventional studies. Clinical case studies complement prospective, real-world studies by providing detailed insight into treatment outcomes across the entire treatment continuum and identifying clinical interactions that may be worthy of further exploration. In this case series, we discuss 5 patients treated during routine clinical practice in Austria and Hungary, who received second-line or third-line nintedanib plus docetaxel after either combined or sequential immunotherapy and chemotherapy (Table 1).

Case Series

Patient 1: Second-Line Nintedanib after Combination Chemo-Immunotherapy

A 57-year old Caucasian female was diagnosed with stage IV adenocarcinoma NSCLC (T2a N3 M1a disease), without mutations in *EGFR*, *ALK*, *ROS1*, *MET*, or *BRAF* and a PD-L1 expression of <1%. A magnetic resonance imaging scan confirmed the absence of brain metastases at diagnosis. She was a current smoker with a chronic cough and has hypertension and type 2 diabetes mellitus. First-line treatment consisted of pembrolizumab (200 mg intravenous [IV]; every 3 weeks) plus four cycles of carboplatin (AUC 5 mg/mL/min IV; every 3 weeks) and pemetrexed (500 mg/m² IV; every 3 weeks), followed by maintenance pemetrexed and pembrolizumab. She achieved partial response (PR), with duration of response of 15 months. First-line treatment was continued for 8 months, and tumor progression occurred 4 months after discontinuation. Adverse events (AEs) during first-line treatment included interstitial nephritis, which was suspected to be related to immunotherapy and creatinine elevation, both of which normalized following treatment discontinuation. Second-line treatment consisted of nintedanib (200 mg oral; twice daily) in combination with docetaxel (25 mg/m² IV; weekly for six cycles) based on clinical guidelines. Docetaxel was discontinued after 4 months due to fatigue, grade 2 anemia, grade 2 leukopenia, and the patient's decision to discontinue. Nintedanib was continued as maintenance therapy and treatment was ongoing at the data cutoff (October 2020), at which point the patient had received >32 months of nintedanib treatment. The best response was PR, which lasted for >30 months. Overall, the time between initial diagnosis and data cutoff was >47 months.

Patient 2: Second-Line Nintedanib after Combination Chemo-Immunotherapy

A 69-year old Caucasian female was diagnosed with stage IV (T4 N3 M1a) adenocarcinoma NSCLC. Mutation testing performed with RNA/DNA next-generation sequencing revealed an activating *KRAS* G12D mutation on exon 2, without mutations in *EGFR*, *ALK*, *ROS1*, *MET*, or *BRAF*. The tumor was negative for PD-L1 expression. The patient was a current smoker, with exposure of 50 pack-years, and had stage 2 (moderate) chronic obstructive pulmonary disease. She received first-line pembrolizumab (200 mg IV; every 3 weeks) plus four cycles of carboplatin (AUC 5 mg/mL/min IV; every 3 weeks) and pemetrexed (500 mg/m² IV; every 3 weeks), followed by pembrolizumab plus pemetrexed maintenance therapy. Stable disease (SD) was achieved after two cycles with a response duration of 3 months, and the treatment was well tolerated with no reported AEs. Upon relapse, second-line treatment with nintedanib (200 mg oral; twice daily) plus docetaxel (25 mg/m² IV; weekly) was initiated. Nintedanib was continued as maintenance therapy after docetaxel discontinuation (docetaxel was discontinued due to anemia and neutropenia, which were both of Grade 2 severity, and the patient's preference), and was ongoing at the time of data collection (October 2020). The total duration of nintedanib treatment was >6.4 months. Best response was PR, which lasted for >7 months. The time between initial diagnosis and data cutoff was >10.4 months.

Table 1. Patient characteristics and treatments

Patient characteristics	Second-line nintedanib plus docetaxel			Third-line nintedanib plus docetaxel	
	patient 1	patient 2	patient 3	patient 4	patient 5
Sex	Female	Female	Female	Male	Female
Race/ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Age at initial diagnosis, years	57	69	56	44	49
Disease stage at initial diagnosis	Stage IV (T2a N3 M1a)	Stage IV (T4 N3 M1a)	Stage IV (T2 N2 M1)	Stage IIIB [†] (T4 N2 M0)	Stage IV (T4 N3 M1a)
Mutation status	<i>EGFR</i> -wt, <i>ALK</i> -wt, <i>ROS1</i> -wt, <i>MET</i> -wt, and <i>BRAF</i> -wt; PD-L1 expression <1%	<i>EGFR</i> -wt, <i>ALK</i> -wt, <i>ROS1</i> -wt, <i>MET</i> -wt, and <i>BRAF</i> -wt; <i>KRAS</i> G12D mutant [‡] ; PD-L1 expression negative	<i>EGFR</i> -wt, <i>ALK</i> -wt, and <i>ROS1</i> -wt; <i>BRAF</i> -V600-negative; PD-L1 expression negative	<i>EGFR</i> -wt, <i>ALK</i> -wt, <i>ROS1</i> -wt, and <i>BRAF</i> -wt; <i>KRAS</i> -mutant; PD-L1 expression negative	<i>EGFR</i> -wt, <i>ALK</i> -wt, <i>ROS1</i> -wt, <i>BRAF</i> -wt, and <i>KRAS</i> -mutant; PD-L1 expression negative
Smoking status (exposure)	Current smoker	Current smoker (50 pack-years)	Ex-smoker (23 pack-years)	Ex-smoker (37 pack-years)	Current smoker (10 pack-years)
Comorbidities	Hypertension and type 2 diabetes mellitus	COPD (stage 2)	Arterial hypertension and COPD (stage 2)	–	–
Treatment summary and outcomes					
First-line treatment	Pembrolizumab + carboplatin + pemetrexed	Pembrolizumab + carboplatin + pemetrexed	Pembrolizumab + carboplatin + pemetrexed	Pemetrexed + carboplatin	Paclitaxel + carboplatin + atezolizumab
1L BOR	PR	SD	PR	SD	PR
1L DoR, months	15	3	5.3	1	6
Second-line treatment	Nintedanib + docetaxel	Nintedanib + docetaxel	Nintedanib + docetaxel	Nivolumab	Cisplatin + pemetrexed [§]
2L BOR	PR	PR	PR	PR	PR
2L DoR, months	>30*	>7*	4.2*	1.4	5

Table 1 (continued)

	Second-line nintedanib plus docetaxel		Third-line nintedanib plus docetaxel	
	patient 1	patient 2	patient 3	patient 4
Third-line treatment	-	-	-	Nintedanib plus docetaxel
3L BOR	-	-	-	PR
3L DoR, months	-	-	-	11*
Fourth-line treatment	-	-	-	Nivolumab
4L BOR	-	-	-	SD
4L DoR, months	-	-	-	4
Fifth-line treatment	-	-	-	Pemetrexed
5L BOR	-	-	-	SD
5L DoR, months	-	-	-	4.7†

BOR, best overall response; COPD, chronic obstructive pulmonary disease; DoR, duration of response; N, node; M, metastasis; PD-L1, programmed death ligand 1; SD, stable disease; T, tumor; wt, wild-type.

*Treatment ongoing at the time of data cutoff (October 2020).

†Determined by RNA and DNA next-generation sequencing.

#The patient progressed after diagnosis and was reevaluated as having stage IV NSCLC.

§Second-line systemic treatment was preceded by radiotherapy.

††Treatment ongoing at the time of data cutoff (January 2021).

Patient 3: Second-Line Nintedanib after Combination Chemo-Immunotherapy

A 56-year old female was diagnosed with stage IV (T2 N2 M1) adenocarcinoma NSCLC, without mutations in *EGFR*, *ALK*, *ROS1*, or *BRAF*, and negative PD-L1 expression. She previously smoked (prior exposure of 23 pack-years). Comorbidities included arterial hypertension and stage 2 chronic obstructive pulmonary disease. First-line treatment consisted of pembrolizumab (200 mg IV; every 3 weeks) plus four cycles of carboplatin (AUC 5 mg/mL/min IV; every 3 weeks) and pemetrexed (500 mg/m² IV; every 3 weeks), followed by maintenance pemetrexed and pembrolizumab. The patient achieved PR with duration of response of 5.3 months. During treatment, she experienced grade 3 nephritis, which was managed by discontinuing chemotherapy, interrupting pembrolizumab treatment, and administering concomitant corticosteroids. Tumor progression occurred 5 months later, and second-line treatment with nintedanib (200 mg oral; twice daily) plus docetaxel (75 mg/m² IV; every 3 weeks) was initiated. The patient received six cycles of docetaxel before planned discontinuation. Nintedanib was continued as maintenance therapy and was ongoing at the time of data collection (October 2020). The total duration of nintedanib treatment was >6.6 months. The patient achieved PR, which lasted >4.2 months. The total time between diagnosis and the data cutoff date was >16.3 months.

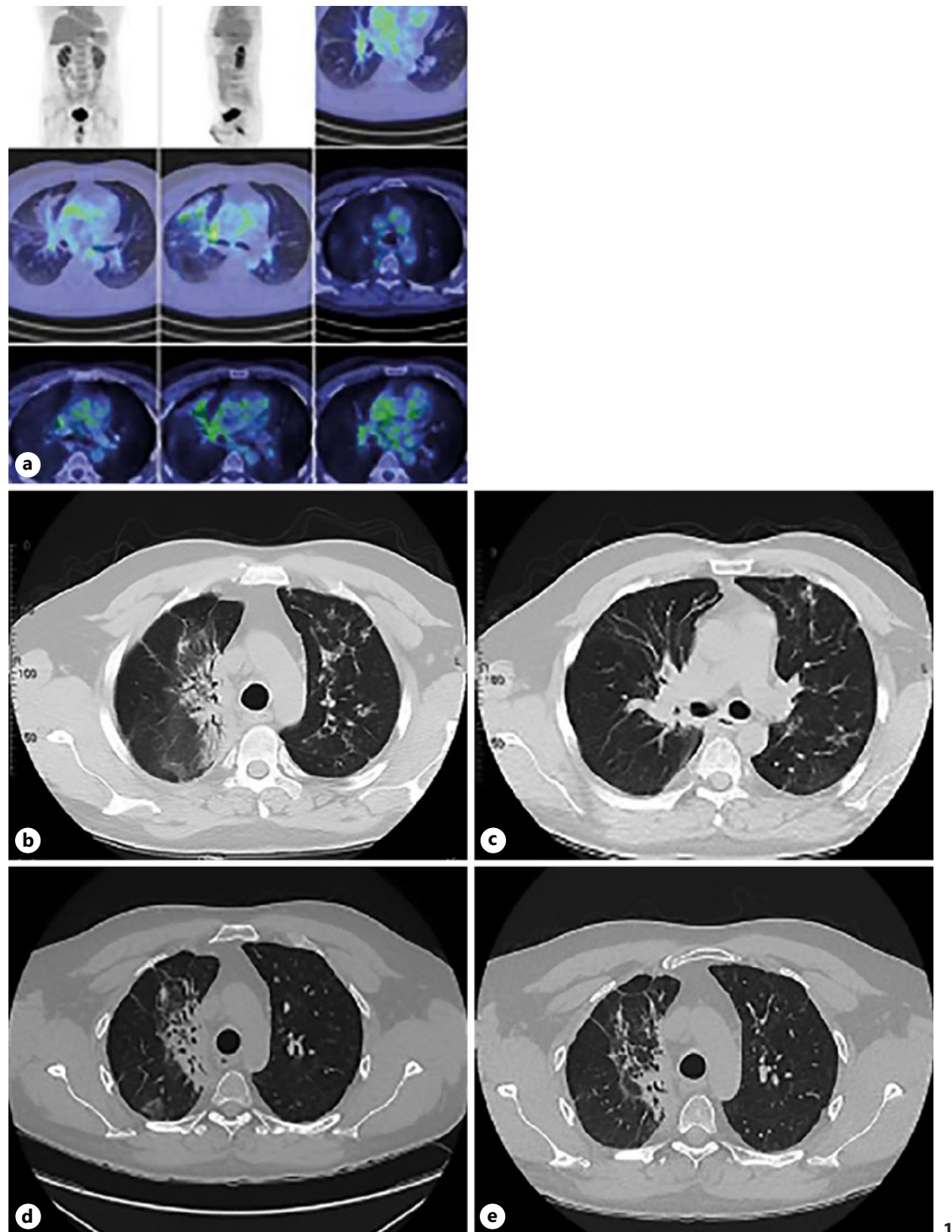
Patient 4: Third-Line Nintedanib plus Docetaxel after Sequential Chemo-Immunotherapy

A 43-year old male was diagnosed with stage IIIB (T4 N2 M0) adenocarcinoma NSCLC (shown in Fig. 1a). Molecular testing revealed a *KRAS* mutation without mutations in *EGFR*, *ALK*, *ROS1*, or *BRAF* and negative PD-L1 expression. The patient was an ex-smoker (prior exposure of 37 pack-years) and had previously undergone a semicastration. The patient started first-line pemetrexed (800 mg IV) plus carboplatin (640 mg IV) for four cycles and achieved SD for 1 month. He experienced grade I anemia and nausea (managed with ondansetron), which were not treatment limiting. After tumor progression, he started second-line nivolumab (240 mg IV; biweekly for 10 cycles) and achieved PR for 6 weeks. Nivolumab was stopped due to progressive disease and symptomatic brain metastases. The patient was reevaluated as having stage IV disease and underwent a metastasectomy. He subsequently received third-line nintedanib (200 mg oral; twice daily) plus docetaxel (75 mg/m²; every 3 weeks for six cycles). Nintedanib was continued as maintenance therapy after planned docetaxel discontinuation. When nintedanib was initiated, chest scans were taken, which revealed dystelectasis and atelectasis, with evidence of regression during nintedanib treatment (shown in Fig. 1b–d). After 10 cycles, the dose of nintedanib was reduced to 100

Fig. 1. Patient 4 – PET/CT images of the thorax taken during treatment. **a** PET/CT (June 2018) An irregularly shaped, inhomogenous 28 × 31 mm density expanding behind the superior vena cava, compressing the right main bronchus with a bundle toward the pleura in the right upper pole. Ventrally in S3, an approx. 54 mm atelectasis and in the S3-S6 border toward lateral, an approx. 30 mm bundled area with dystelectasis. From the rise of the right mainstem bronchus at the trachea level, a 13-mm mildly active lymph node. **b** Chest CT (October 2019) Left side: a 3.1-cm wide area connecting with the hilus and the pleura; a dystelectasis is seen in the lower lobe. Right side: in the parahilar region, centrally in the upper lobe dys- and atelectasis area is seen which could be followed up in the height of the hilus. A new 3.5-cm nodule can be seen in the left lower lobe. **c** Chest CT (February 2020) Right side: 35 × 75 mm atelectasis near the hilus. Left side: dystelectasis in the upper- and middle-third. The lesions and the extent of the atelectasis have decreased. **d** Chest CT (June 2020) The previously detected area with dystelectasis is in regression, and only a small bundle is seen. The lesion on the right side is also in regression. The decreased transparency distally from the lesion has almost ceased. No abnormally enlarged lymph nodes were detected in the mediastinal area. **e** Chest CT (September 2020) Status of the left lung is unchanged. Suspected metastatic lesions have not appeared. The lesion in the right side of the mediastinum has decreased from 72 × 43 mm to 67 × 36 mm. CT, computerized tomography; PET, positron emission tomography.

(For figure see next page.)

mg due to diarrhea, and this dose was well tolerated (Eastern Cooperative Oncology Group [ECOG] performance status grade 0). The patient achieved a PR with nintedanib, which lasted 11 months. Nintedanib maintenance treatment was ongoing at the time of data collection (October 2020), with a total treatment duration of >11.8 months. The total time since initial diagnosis was >31 months.



Patient 5: Third-Line Systemic Treatment with Nintedanib after Chemo-Immunotherapy Followed by Chemotherapy

A 49-year old Caucasian female presented with stage IV adenocarcinoma NSCLC (T4 N3 M1a) and was ECOG performance status grade 0. Mutation testing revealed a *KRAS* mutation without mutations in *EGFR*, *ALK*, *ROS1*, or *BRAF* and negative PD-L1 expression. She was a current smoker (exposure of 10 pack-years). First-line treatment consisted of atezolizumab (1,200 mg IV; every 3 weeks) plus four cycles of carboplatin (AUC 6 mg/mL/min IV) and paclitaxel (200 mg/m² IV), followed by four maintenance cycles of atezolizumab. The patient experienced grade 3 alopecia and grade 2 nausea (managed effectively with antiemetics). Her best response was PR, which was maintained for 6 months until progression. Subsequent radiotherapy was well tolerated, resulting in a mixed radiologic response, and a PR that was maintained for 16 months. The patient relapsed and received second-line systemic treatment with cisplatin (75 mg/m² IV) plus pemetrexed (500 mg/m² IV) every 3 weeks, followed by maintenance pemetrexed. Best response was PR, sustained for 5 months. After tumor progression, she received third-line nintedanib (200 mg oral; twice daily), initially in combination with docetaxel (75 mg/m² IV; for five cycles) and then as maintenance following docetaxel discontinuation due to neutropenia. Best response with third-line systemic treatment was PR, sustained for 8 months. On tumor progression, fourth-line systemic treatment with nivolumab (480 mg IV; every 4 weeks) was initiated. The patient achieved SD but relapsed after 4 months. Fifth-line systemic treatment with pemetrexed (500 mg/m² IV) was then initiated, which the patient was still taking at the time of data collection (November 2020), with a best response of SD. Overall, the total time between initial diagnosis and data cutoff (including all lines of treatment) was >56 months.

Discussion

This case series builds on the evidence supporting antiangiogenic agents such as nintedanib in adenocarcinoma NSCLC after progression on chemo-immunotherapy. The treatment outcomes support the hypothesis that inhibiting excessive VEGF signaling with nintedanib may revert the TME to an immunosupportive state [2]. The 5 patients presented in the above case studies received nintedanib plus docetaxel after chemo-immunotherapy, and each achieved a PR, with a response duration ranging from >4.2 months to >30 months (shown in Fig. 2). Each patient had a total time on treatment of over 10 months, and for case presentation 5, the total time on treatment was >56 months (including chemo-immunotherapy, radiotherapy, nintedanib plus docetaxel and two subsequent systemic treatments). These outcomes are clinically relevant because they were achieved in patients with stage IV adenocarcinoma NSCLC, who would otherwise have been expected to have a continued poor prognosis. The combination was well tolerated and AEs, which included diarrhea (case presentation 4) and neutropenia (case presentation 5), and were managed by reducing the dose of nintedanib and discontinuing docetaxel respectively. After docetaxel discontinuation, nintedanib can be continued as maintenance therapy where disease control has been achieved. There is ongoing interest in ascertaining whether the tolerability of docetaxel is improved with once weekly dosing. Patient cases 1 and 2 indicate that treatment regimens with once weekly docetaxel are effective and well tolerated, without eliciting some of the myelosuppressive AEs that have been observed in clinical trials with the more intensive three weekly dosing [5].

This case series provides further real-world evidence that nintedanib plus docetaxel is an effective and well-tolerated treatment option after progression on chemo-immunotherapy that was given either in combination or sequentially. The outcomes in patient case 5

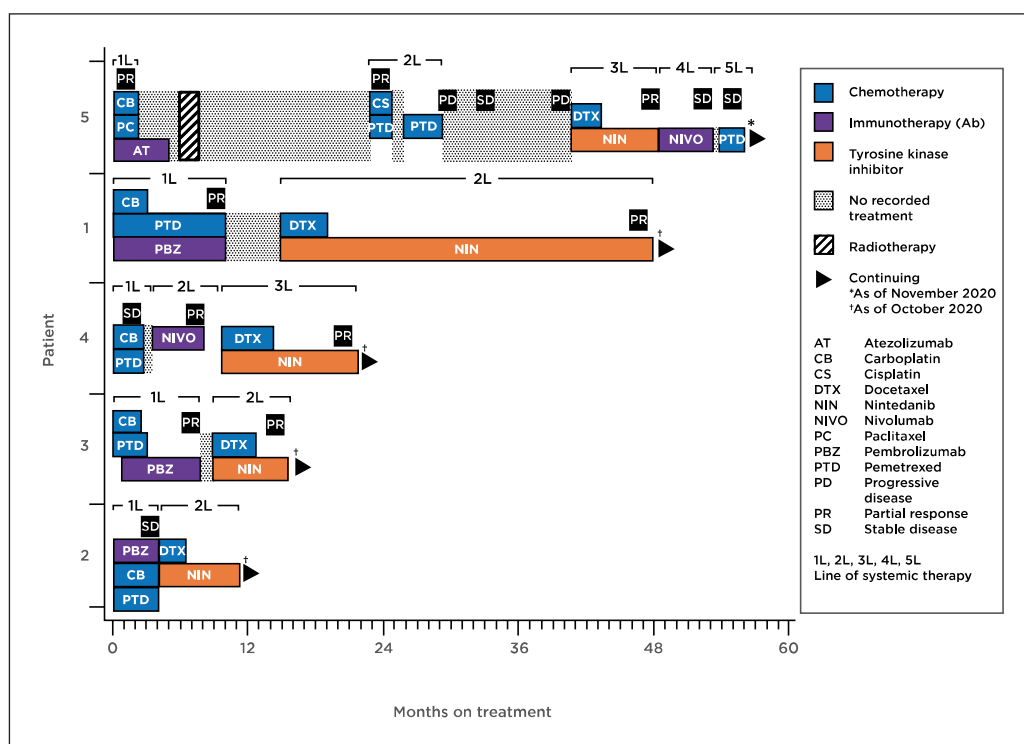


Fig. 2. Swimmer plot of treatment durations and best treatment responses for presented cases.

demonstrate that nintedanib does not preclude subsequent immunotherapy or chemotherapy. The 4-month duration of SD achieved with fourth-line nivolumab, after nintedanib plus docetaxel, is suggestive of an angio-immunogenic switch, although the lack of confirmative histopathological or biomarker data is acknowledged. The efficacy of antiangiogenic agents in combination with docetaxel, shown in these cases, is supported by clinical studies of nintedanib plus docetaxel in patients with NSCLC who progressed on chemo-immunotherapy. The latest analysis of 65 patients from the ongoing, prospective, noninterventional VARGADO study associated third-line nintedanib plus docetaxel with a median PFS of 6.5 months and a median OS of 12.2 months [3]. The LUME-BioNIS subgroup analysis of 67 patients who received nintedanib plus docetaxel after chemo-immunotherapy (57 of them in third-/later-line) reported a median OS of 8.8 months [8]. A nintedanib compassionate use program of 11 patients reported a median PFS of 3.2 months [9]. Although these studies were single-arm, observational studies with low patient numbers, there were no unexpected safety signals [3, 8, 9], and the results support the use of nintedanib plus docetaxel in this setting. Clinical trials are investigating the effectiveness of nintedanib in other combinations in NSCLC, including in combination with nivolumab after previous systemic therapy (NCT04046614) and in combination with nivolumab and ipilimumab, following previous treatment with chemotherapy, immunotherapy, or targeted therapy (NCT03377023).

Other antiangiogenic agents, such as ramucirumab, have also shown efficacy in NSCLC after first-line chemotherapy or immunotherapy. The response to ramucirumab in NSCLC was enhanced when it was given sequentially with immunotherapy [10] or immediately after nivolumab [11], and it has efficacy in combination with docetaxel after second-line immunotherapy in stage IV NSCLC [12]. There is evidence for a synergistic effect between antiangiogenics and immunotherapies in NSCLC. The angio-immunogenic switch describes the theoretical potential for antiangiogenic agents to enhance the effectiveness of immunotherapies

by normalizing the tumor vasculature and facilitating their delivery to the TME [13]. The promising outcomes reported in clinical studies, including the IMpower150 and the 533MO, suggest antiangiogenic treatments can augment clinical outcomes with immunotherapies when they are given in combination or sequentially [14, 15].

Conclusion

In summary, treatment guidelines recommend the use of first-line immunotherapies, as monotherapy or in combination with chemotherapy, in patients with advanced NSCLC lacking an actionable driver mutation. However, limited clinical data exist to inform treatment decisions after progression on immunotherapy. This case series provides complementary real-world evidence that nintedanib plus docetaxel is an effective and well-tolerated treatment, in appropriate patients with adenocarcinoma NSCLC, after combined or sequential treatment with chemotherapy and immunotherapy, and may also optimize outcomes with subsequent immunotherapy through an angio-immunogenic switch.

Acknowledgments

The authors wish to thank the patients who agreed to participate in this study and their carers. Viktor Sebek (an employee of the sponsor, Boehringer Ingelheim, RCV GmbH & Co KG, Vienna, Austria) provided feedback on the design of this study. Ross Jarratt (Syneos Health Ltd., UK) provided medical writing assistance during the preparation of this manuscript.

Statement of Ethics

Written informed consent was obtained from all patients for publication of the details of their medical case details and any accompanying images. A full ethics approval was not deemed necessary because this manuscript describes clinical cases experienced in routine clinical practice, rather than a clinical study.

Conflict of Interest Statement

M.J.H. received speaker honoraria from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, and Roche and has had consulting or advisory roles with Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Novartis, and Roche. R.K. received speaker fees/honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Roche. N.B. received consultancy fees/honoraria from Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Roche, and Takeda. H.Z. is an employee of Boehringer Ingelheim. R.W. has no conflicts of interest.

Funding Sources

Financial support for manuscript preparation (provided by Syneos Health Ltd., UK) was provided by Boehringer Ingelheim RCV GmbH & Co KG.

Author Contributions

All the authors were involved in data collection, analysis, and interpretation. All the authors were involved during preparation of the manuscript and provided final approval of the manuscript content prior to journal submission.

Data Availability Statement

The data that support the findings of this publication are documented in the patients' medical records and are not openly available.

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