Efficacy and safety of nintedanib and docetaxel in lung adenocarcinoma patients following treatment with immune checkpoint inhibitors: first interim results of the ongoing non-interventional VARGADO study (NCT02392455)

55P
Abstract 389

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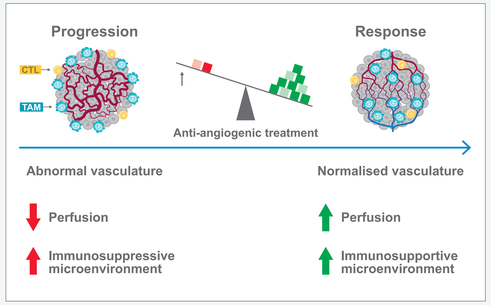
INTRODUCTION

- Nintedanib is an oral, triple angiokinase inhibitor targeting vascular endothelial growth factor (VEGF) receptors 1–3, platelet-derived growth factor (PDGF) receptors α/β, and fibroblast growth factor (FGF) receptors 1–3,[1] as well as RET[2]
- Nintedanib is approved in the EU and other countries in combination with docetaxel for the treatment of patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma histology after first-line chemotherapy[3]
- Approval was based on data from the Phase III LUME-Lung 1 trial, in which nintedanib plus docetaxel was associated with a clinically meaningful extension in overall survival (OS) compared with placebo plus docetaxel in patients with adenocarcinoma NSCLC who had progressed after first-line chemotherapy[4]
- Following the introduction of second-line immune checkpoint inhibitors (ICIs), the treatment landscape in non-targetable advanced NSCLC is continuing to advance with their use in the first-line setting[5]
- With this growing number of treatment options, it is becoming increasingly important in clinical practice to establish the optimal treatment after ICI ± chemotherapy. So far, none of the available treatments have been investigated in patients who have progressed on ICIs
- An immunosuppressive tumour microenvironment (TME) is closely linked with hypoxia-induced, VEGF-promoted angiogenesis and upregulation of immunosuppressive cells.[6] It is possible that the abnormal vasculature resulting from tumour angiogenesis contributes to or underlies some tumours' resistance to ICIs. This same mechanism would also prime the tumour for anti-angiogenic therapy
- We hypothesise that an anti-angiogenic treatment strategy involving inhibition of VEGF, as well as PDGF and FGF, tips the balance towards an immunosupportive TME: an 'Angio-Immunogenic Switch' **(Figure 1)**

Figure 1. 'Angio-Immunogenic Switch'



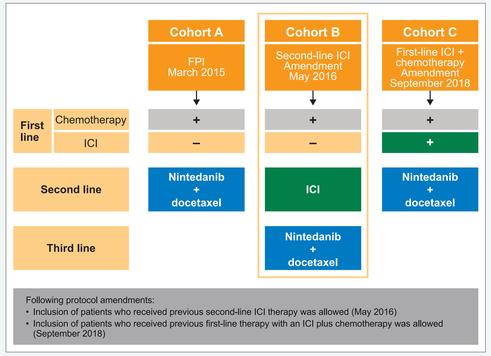
Modified from Fukumura D, et al. Nat Rev Clin Oncol 2018;15:325–40.
CTL, cytotoxic T lymphocyte; TAM, tumour-associated macrophage.

- One small dataset has been published on the efficacy of nintedanib plus docetaxel in patients with advanced lung adenocarcinoma who have previously been treated with ICIs: a retrospective analysis of patients in Spanish sites who participated in the nintedanib named patient use programme[7]
- In this dataset, 11 patients received nintedanib plus docetaxel after chemotherapy and ICI therapy. Treatment with nintedanib plus docetaxel was associated with an objective response rate (ORR) of 36%, a disease control rate (DCR) of 82% and a median progression-free survival (PFS) of 3.2 months[7]
- Here we present data from a larger cohort of patients who received nintedanib plus docetaxel after chemotherapy and ICI therapy in the non-interventional, prospective VARGADO study

STUDY DESIGN AND PATIENT POPULATION

- VARGADO is a prospective, non-interventional study of nintedanib plus docetaxel after first-line chemotherapy in the routine clinical treatment of patients with locally advanced, metastatic or locally recurrent adenocarcinoma NSCLC[§]
- Three patient cohorts in VARGADO are being evaluated (**Figure 2**)
- Between 15 March 2015 and 1 November 2018, 311 patients have been enrolled at 100 study sites across Germany
- We present the first interim analysis of Cohort B (N=22)

Figure 2. Patient cohorts in VARGADO



FPI, first patient in; ICI, immune checkpoint inhibitor.

- Nintedanib and docetaxel were administered according to the approved label
- Patients were followed up for safety and efficacy for up to 24 months after the start of treatment. Patient data were collected during routine clinic visits
- All patients provided signed informed consent
- The primary endpoint is OS rate 1 year after the start of treatment with nintedanib plus docetaxel. Secondary endpoints include PFS, OS, ORR and DCR
- Incidence and severity of adverse events (AEs) are being reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

RESULTS

Patient characteristics

- Baseline characteristics for the 22 patients included in this analysis are shown in **Table 1**

Table 1. Baseline characteristics (N=22)

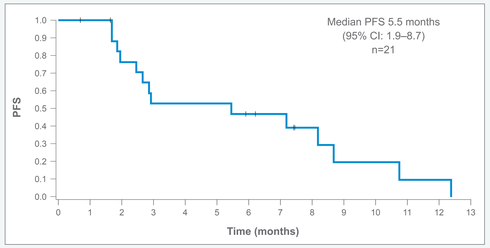
Median age, years (range)		58 (45–76)
Sex, % (n)	Male	68 (15)
ECOG PS, % (n)	0	18 (4)
	1	55 (12)
	2	9 (2)
	3	5 (1)
	Missing	14 (3)
Tumour stage at baseline, % (n)	IV	55 (12)
	<IV	18 (4)
	Unknown	14 (3)
	Missing	14 (3)
Brain metastases, % (n)	Yes	18 (4)
Previous first-line therapy,* % (n)	Pemetrexed	68 (15)
	Carboplatin	55 (12)
	Cisplatin	55 (12)
	Bevacizumab	27 (6)
	Vinorelbine	18 (4)
	Paclitaxel	9 (2)
	Docetaxel	5 (1)
Previous second-line therapy, % (n)	Nivolumab	77 (17)
	Pembrolizumab	23 (5)
Best response to second-line therapy, % (n)	ORR	23 (3/13[§])
	SD	15 (2/13)
	PD	62 (8/13)
	Not documented, n	9

*Multiple concurrent first-line therapies possible; [§]Of which one was a CR.
CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; PD, progressive disease; SD, stable disease.

Efficacy

- At the time of this interim analysis (data cut-off: 1 August 2018), median duration of follow-up was 6.0 months (95% confidence interval [CI]: 3.5–8.8)
- 14 PFS events had occurred (10 patients had disease progression and four patients died). Seven patients were censored and data were not yet available for one patient
- Median PFS was 5.5 months (95% CI: 1.9–8.7; **Figure 3**)

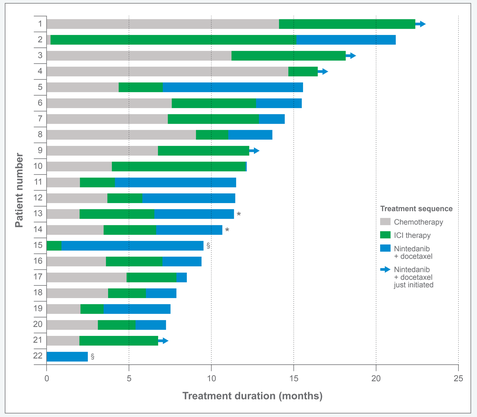
Figure 3. PFS by investigator assessment (n=21)



Data cut-off: 1 August 2018.
CI, confidence interval; PFS, progression-free survival.

- Treatment duration by treatment for each patient is shown in **Figure 4**

Figure 4. Swimmer plot showing treatment duration by treatment for each patient



*Single-agent nintedanib treatment ongoing; [§]Previous therapies not documented.
Data cut-off: 1 August 2018. ICI, immune checkpoint inhibitor.

- OS data are not yet mature and are not reported here
- ORR data and DCR data (**Table 2**) were available for 12 patients at the time of analysis
- Seven patients (32%) had at least one nintedanib dose reduction and five patients (23%) had at least one docetaxel dose reduction

Table 2. Best response to nintedanib plus docetaxel (n=12)

ORR, % (n)	58 (7)
PR, % (n)	58 (7)
SD, % (n)	25 (3)
DCR, % (n)	83 (10)

DCR, disease control rate; ORR, objective response rate; PR, partial response; SD, stable disease.

Safety

- Safety was evaluated in all 22 patients
- 21 (95%) patients had AEs; 11 (50%) had serious AEs
- The most common nintedanib-related AEs of any grade were diarrhoea (36%), stomatitis (27%), decreased white blood cell count (14%) and nausea (14%)
- The most common Grade ≥3 nintedanib-related AEs were stomatitis (14%), decreased white blood cell count (14%) and febrile neutropenia (9%)
- The most common docetaxel-related AEs of any grade were diarrhoea (27%), stomatitis (27%), decreased white blood cell count (23%) and nausea (18%)
- The most common Grade ≥3 docetaxel-related AEs were decreased white blood cell count (18%), stomatitis (14%), and nausea, decreased neutrophil count and febrile neutropenia (each 9%)

CONCLUSIONS

- These data, while from a small patient cohort, provide a second independent indication that patients who progress on previous ICI therapy may benefit from treatment with nintedanib plus docetaxel
- We propose that the rational sequencing of anti-angiogenic therapy after ICIs may be a promising approach to treatment in this patient population that warrants further investigation
- Further research into a potential 'Angio-Immunogenic Switch' may facilitate patient selection and optimal treatment sequencing in future
- Collection of additional clinical data in this area is ongoing, with patient recruitment in the VARGADO study being extended

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