Second-line nintedanib + docetaxel for patients with lung adenocarcinoma after failure on first-line immune checkpoint inhibitor combination therapy: initial efficacy and safety results from VARGADO Cohort C

Abstract 9033

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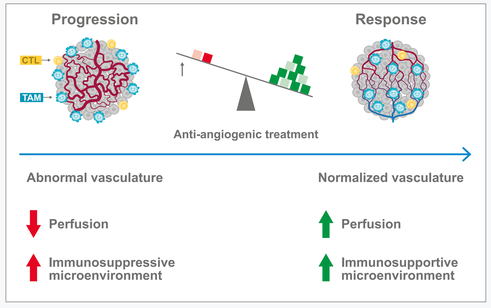
INTRODUCTION

- Treatment of advanced non-small cell lung cancer (NSCLC) has undergone significant changes, with immune checkpoint inhibitors (ICIs) alone, or in combination with chemotherapy, now the first-line standard of care for metastatic non-squamous NSCLC lacking an actionable driver mutation[1]
- For patients progressing on ICIs, only limited data are available on the efficacy of subsequent treatment sequences[2–8]
- Understanding the underlying tumor biology may help to guide treatment selection
- Excessive vascular endothelial growth factor (VEGF) can promote angiogenesis and create an immunosuppressive tumor microenvironment (TME) by modulating immune cell function and reducing immune cell access,[7,9,10] which likely contributes to ICI resistance and may potentially prime the tumor for anti-angiogenic therapy
- An anti-angiogenic treatment strategy involving inhibition of VEGF, platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF), could support vessel normalization and improve immune cell access to the tumor, favoring the restoration of an immunosupportive TME in an 'angio-immunogenic switch' (**Figure 1**)

Figure 1. A hypothesized 'angio-immunogenic switch'



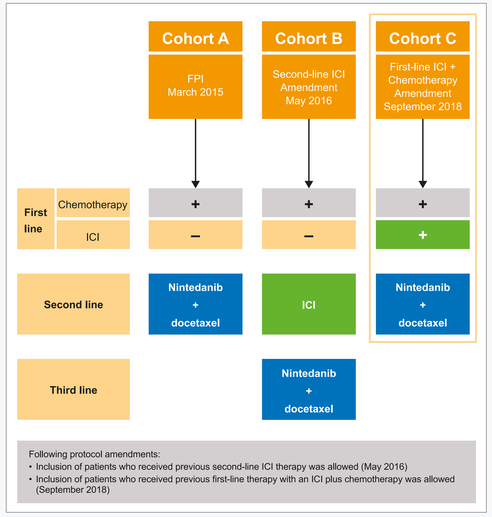
Modified from Fukumura D, et al. 2018.[9]
CTL, cytotoxic T lymphocyte; TAM, tumor-associated macrophage.

- Nintedanib is an oral, triple angiokinase inhibitor that targets VEGF receptors 1–3, PDGF receptors α/β, FGF receptors 1–3, and RET[11,12]
- In the Phase III LUME-Lung 1 trial of patients with NSCLC who had progressed on first-line chemotherapy, nintedanib plus docetaxel significantly prolonged both progression-free survival (PFS) compared with placebo plus docetaxel, and overall survival (OS), in patients with adenocarcinoma NSCLC[13]
- This combination is approved in the European Union and other countries for the treatment of locally advanced, metastatic or locally recurrent adenocarcinoma NSCLC after first-line chemotherapy[14]
- The VARGADO study is being undertaken to assess the clinical utility of nintedanib plus docetaxel in a real-world setting, including patient cohorts who have progressed after prior chemotherapy and ICI therapy, to help inform clinical decision-making in the current ICI era[15]
- Here, we present the first analysis from Cohort C, the cohort of patients who received second-line nintedanib plus docetaxel after progression on first-line chemo-immunotherapy (chemo-ICI) treatment, as part of the non-interventional VARGADO study[15]

STUDY DESIGN AND PATIENT POPULATION

- VARGADO (NCT02392455) is an ongoing 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[15]
- Three patient cohorts are being evaluated (**Figure 2**)
- Between March 15, 2015 and April 6, 2021, 528 patients were enrolled in centers across Germany
- We present an initial analysis of Cohort C (n=100) (data cut-off: December 1, 2020)

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 received 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
- Patients were followed for up for safety and efficacy for up to 24 months after the start of treatment. Patient data were collected during routine clinic visits
- The primary endpoint is the OS rate at 12 months after the start of treatment with nintedanib plus docetaxel. Secondary endpoints include PFS, OS, objective response rate (ORR), disease control rate (DCR) and safety
- Incidence and severity of adverse events (AEs) were reported according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

RESULTS

Patient characteristics

- This initial analysis includes the first 100 patients from Cohort C (second-line nintedanib plus docetaxel after failure of first-line chemo-ICI therapy)
- Clinical characteristics and previous treatments for patients in Cohort C are shown in **Tables 1** and **2**

Table 1. Clinical characteristics for patients in Cohort C (n=100)

Median age, years (range)		63 (43–84)
Sex, n (%)	Male	58 (58)
	Female	42 (42)
ECOG PS, n (%)	0	32 (32)
	1	39 (39)
	2	15 (15)
	3	2 (2)
	Not reported	12 (12)
Clinical stage at diagnosis, n (%)	≤III	20 (20)
	IV	75 (75)
	Not reported	5 (5)
Current or former smokers, n (%)		75 (75)
Presence of brain metastases, n (%)		17 (17)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Previous treatments for patients in Cohort C (n=100)

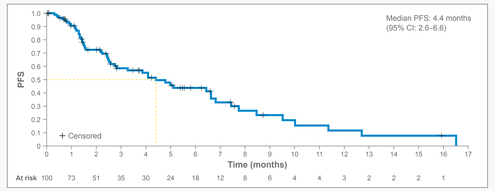
Previous first-line therapy, n (%)*	Pembro/pem/platinum	89 (89)
	Pembro/pem/carboplatin	68 (68)
	Pembro/pem/cisplatin	21 (21)
	Other pembro/chemo combination	6 (6)
	Atezo/pac/platinum	3 (3)
	Atezo/pac/carboplatin	1 (1)
	Atezo/pac/carboplatin/bevacizumab	2 (2)
	Nivolumab + chemotherapy	1 (1)
	Other	1 (1)
Best response to first-line therapy, n (%)†	Complete response	0 (0)
	Partial response	27 (27)
	Stable disease	18 (18)
	Progressive disease	27 (27)
	Other	2 (2)
Time since start of first-line treatment	<9 months	66 (66)
	≥9 months	34 (34)

*Percentage values refer to all patients (N=100); †Percentage based on patients with a documented response at the time of analysis.
Atezo, atezolizumab; pac, paclitaxel; pem; pemetrexed; pembro, pembrolizumab.

Efficacy

- We present initial efficacy data for patients in Cohort C (n=100) who received nintedanib plus docetaxel after first-line chemo-ICI
- At the time of this initial analysis (data cut-off: December 1, 2020), the median duration of follow-up was 5.3 months for patients treated with nintedanib plus docetaxel
- Fifty-one PFS events (disease progression or death) had occurred. For the PFS analysis, 49 patients had been censored
- Median PFS was 4.4 months (95% confidence interval [CI]: 2.6–6.6; n=100) (**Figure 3**)
- OS data are not yet mature and are not reported here

Figure 3. PFS from the start of second-line nintedanib plus docetaxel after failure of chemo-ICI (n=100)



CI, confidence interval; PFS, progression-free survival.

- At the time of analysis, best overall response data were available for 59 patients who received second-line nintedanib plus docetaxel after failure of chemo-ICI therapy (**Table 3**)
  - The ORR was 22/59 (37.3%)
  - The DCR was 40/59 (67.8%)

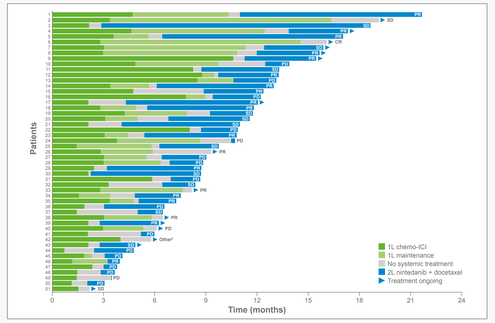
Table 3. Best response to second-line nintedanib plus docetaxel (n=59)*

Objective response rate, n (%)	22 (37.3)
Complete response, n (%)	1 (1.7)
Partial response, n (%)	21 (35.6)
Stable disease, n (%)	18 (30.5)
Disease control rate, n (%)	40 (67.8)
Progressive disease, n (%)	18 (30.5)

*One patient had a clinically documented response that was not clearly attributable to any category ('other' i.e. minimal remission).
Data are for patients in the treated set who had a documented response.

- The overall time on treatment (including first-line and second-line treatment) and best responses to nintedanib plus docetaxel (for patients with a documented response who received prior treatment with first-line pembrolizumab/pemetrexed/platinum-based regimens) are shown in **Figure 4**

Figure 4. Swimmer plot showing overall time on treatment and best responses (n=51)*



*Data are for patients in the treated set who received prior treatment with first-line pembrolizumab/pemetrexed/platinum-based regimens and had a documented response to nintedanib plus docetaxel. *Minimal remission.
1L, first-line; 2L, second-line; CR, complete response; ICI, immune checkpoint inhibitor; PD, progressive disease; PR, partial response; SD, stable disease.

Safety

- Safety was evaluated in all 100 patients treated with nintedanib plus docetaxel in Cohort C
- Seventy-eight (78%) patients had treatment-emergent AEs (TEAEs), with 55 (55%) experiencing drug-related AEs according to investigator assessment
- The most common drug-related AEs are shown in **Table 4**
- Grade ≥3 TEAEs occurred in 47 (47%) patients; serious TEAEs occurred in 37 (37%) patients
- Thirty-one (31%) patients had at least one nintedanib dose reduction, and 16 (16%) patients had at least one docetaxel dose reduction
- Investigator-defined drug-related TEAEs led to study-drug discontinuation in 16 (16%) patients
- There were no new safety signals or unexpected toxicities

Table 4. TEAE by drug relationship reported in ≥5% of patients (n=100)*

	Nintedanib related		Docetaxel related	
	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)
Diarrhea	29 (29)	4 (4)	12 (12)	3 (3)
Nausea	13 (13)	0 (0)	17 (17)	0 (0)
Fatigue	12 (12)	0 (0)	15 (15)	0 (0)
Vomiting	6 (6)	0 (0)	5 (5)	0 (0)
WBC decreased	6 (6)	5 (5)	8 (8)	7 (7)
Decreased appetite	4 (4)	0 (0)	6 (6)	0 (0)
Alopecia	4 (4)	0 (0)	8 (8)	0 (0)

*Data are for the treated set (all treated patients).
TEAE, treatment-emergent adverse event; WBC, white blood cell count.

CONCLUSIONS

- Evaluating the best therapeutic sequence is key to understanding the underlying mechanism of resistance to ICIs, and to improve the long-term treatment of advanced NSCLC patients, but there is a lack of data to guide clinical decision-making post-ICI
- The initial data from VARGADO Cohort C provide the first evidence that second-line nintedanib plus docetaxel has clinically meaningful efficacy, and a manageable safety profile following progression on first-line chemo-ICI
- An 'angio-immunogenic switch' may be the mechanism underlying the efficacy of nintedanib plus docetaxel as anti-angiogenic therapy in this setting
- The results provide further evidence that can inform clinical decision-making and treatment sequencing by demonstrating the benefit of nintedanib as the triple angiokinase inhibitor after first-line chemo-ICI in the treatment of advanced adenocarcinoma NSCLC
- Recruitment and follow-up are ongoing for patients in this Cohort, and updated results will be presented at future congresses

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