Second-line nintedanib + docetaxel for patients with lung adenocarcinoma after first-line immuno-chemotherapy treatment: updated efficacy and safety results from VARGADO Cohort C

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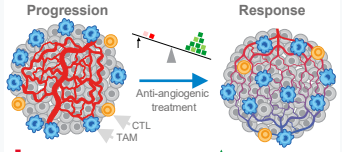
Introduction

- Recent Phase III trials in patients with advanced NSCLC found that combined 1L ICT had significant survival benefits versus CT alone[1]
- This has precipitated a major paradigm shift in treatment, bringing ICIs into 1L[1]
- For an efficacious anti-tumoural immune response, T cells must infiltrate and proliferate within the TME[2,3]
- Tumour angiogenesis has been implicated in the resistance to ICIs by modulating immune cell function and reducing immune cell access, thus promoting an immunosuppressive TME[4]
- Anti-angiogenic agents could potentially improve access of immune cells into the tumour by normalising blood vessels; tipping the balance towards an immunosupportive TME in a hypothesised 'angio-immunogenic switch'[5]

1L, first-line; CT, chemotherapy; ICIs, immune-checkpoint inhibitors; ICT, immunochemotherapy; NSCLC, non-small cell lung cancer; TME, tumour microenvironment

A hypothesised angio-immunogenic switch



Left: depiction of an immunosuppressive TME, with abnormal vasculature. *Right*: depiction of TME with normalised vasculature following anti-angiogenic treatment. Based on Fukumura et al. 2018.[5]CTL, cytotoxic T lymphocyte; TAM, tumour-associated macrophage.

- Nintedanib is an oral triple angiokinase inhibitor that targets VEGF receptors 1–3, PDGF receptors α/β and FGF receptors 1–3[6,7]
- In the LUME-Lung 1 Phase III trial, nintedanib plus docetaxel significantly improved OS and PFS versus docetaxel plus placebo in patients with adenocarcinoma of the lung following failure of 1L CT.[8] Based on these findings, the combination was approved in the EU in this setting[9]
- Only limited data are available assessing the sequence of treatments after 1L ICT[4,10]

FGF, fibroblast growth factor; OS, overall survival; PDGF, platelet-derived growth factor; PFS, progression-free survival; VEGF, vascular endothelial growth factor

Methods

- VARGADO (NCT02392455) is a prospective, non-interventional study of nintedanib plus docetaxel in routine clinical practice after 1L CT
- Between March 15, 2015 and August 2, 2021, 547 patients were enrolled in centres across Germany
- Results from Cohort B (nintedanib plus docetaxel in 3L, following 1L CT and subsequent ICI therapy) have been reported previously[11]
- Here we present updated interim safety and efficacy data from Cohort C, in patients receiving nintedanib plus docetaxel in 2L after 1L ICT (data cut-off: April 1, 2021)

2L, second-line; 3L, third-line

Patient cohorts in VARGADO

	Cohort A FPI: March 2015	Cohort B 2L ICI Amendment: May 2016	Cohort C 1L ICI + CT Amendment: Sept 2018
1L	CT	CT	CT + ICI
2L	Nintedanib + docetaxel	ICI	Nintedanib + docetaxel
3L		Nintedanib + docetaxel	

Patients with advanced adenocarcinoma NSCLC were enrolled into one of three cohorts according to previous therapy (Cohort A: 1L CT; Cohort B: 1L CT and 2L ICI; Cohort C: 1L CT + ICI) to receive nintedanib plus docetaxel as 2L or 3L. Following protocol amendments, inclusion of patients who received previous 2L ICI therapy (May 2016), and inclusion of patients who received previous 1L therapy with an ICI plus CT (September 2018) was permitted. FPI, first patient in

- Patients received docetaxel (IV, 75 mg/m^2) on Day 1 plus nintedanib (oral, 200 mg, BID) on Days 2–21 of each 21-day cycle
- Patients were followed-up for safety and efficacy (up to 24 months) after treatment initiation. 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, ORR, DCR, and safety
- The incidence and severity of AEs were reported according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03)

AEs, adverse events; BID, twice daily; DCR, disease control rate; IV, intravenous; ORR, objective response rate

Results

- 137 patients were treated
- Median duration of follow-up was 4.2 months (95% CI: 3.4–5.5)
- Overall survival data were immature and are not reported

CI, confidence interval

Key findings and conclusions

Second-line nintedanib plus docetaxel has clinically meaningful efficacy following failure of 1L ICT (median PFS: 4.8 months; ORR: 37.5%, DCR: 72.5%)

Nintedanib plus docetaxel showed efficacy regardless of the time since start of 1L treatment (<9 vs ≥9 months) and *KRAS* mutation status

Treatment was tolerable with no unexpected safety signals

Nintedanib plus docetaxel should be considered as a treatment option in patients with adenocarcinoma of the lung following failure of ICT

Recruitment and follow-up are ongoing for patients in this cohort; updated results will be presented at a later date

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Results (cont'd)

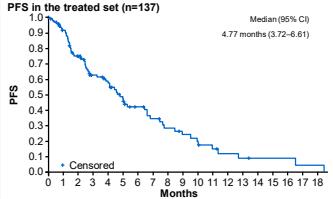
Patient and disease characteristics (n=137)

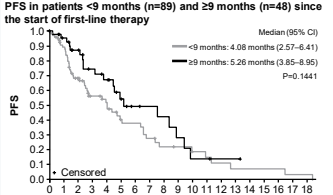
Median age, years (range)		63 (37–84)
Sex, n (%)	Female	57 (41.6)
	Male	80 (58.4)
ECOG PS, n (%)	0	39 (28.5)
	1	59 (43.1)
	≥2	20 (14.6)
	Not reported	19 (13.9)
Clinical stage at baseline, n (%)	<IV	9 (6.6)
	IV	118 (86.1)
	Not reported	10 (7.3)
Brain metastases present, n (%)		27 (19.7)
Previous first-line therapy, n (%)	Pembro/pem/platinum	120 (87.6)
	Other pembro/CT combination	7 (5.1)
	Atezolizumab/CT combination	7 (5.1)
	Nivolumab/CT combination	2 (1.5)
	Other immunotherapy	1 (0.7)
Time since the start of first-line treatment, n (%)	<9 months	89 (65.0)
	≥9 months	48 (35.0)
Best response to first-line therapy, n (%)	Complete response	0
	Partial response	37 (27.0)
	Stable disease	28 (20.4)
	Progressive disease	38 (27.7)
	Other	1 (0.7)
	Not reported	33 (24.1)
EGFR mutation status,[†] n (%)	Wild-type	111 (94.1)
	Mutated	2 (1.7)
	Not reported	5 (4.2)
KRAS mutation status,[†] n (%)	Wild-type	43 (38.7)
	Mutated	24 (21.6)
	Not reported	44 (39.6)

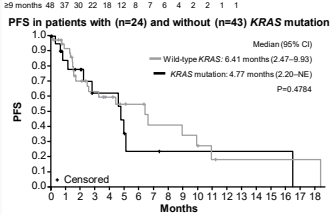
[†]% values refer to patients with initial biopsy (n=118). % values refer to patients with additional biomarker analysis (n=111). ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; pem, pemetrexed; pembro, pembrolizumab

Results (cont'd)

PFS, disease control rate and objective response rate were encouraging







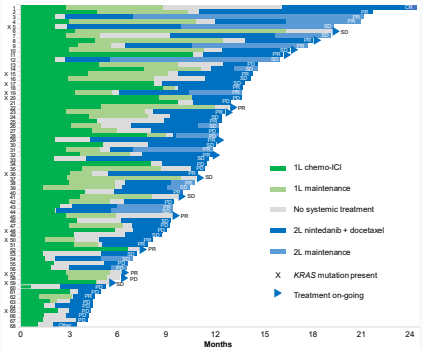
Best response (n=80 evaluable patients)

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

NE, not estimable

Results (cont'd)

Responses were observed both in patients with fast-progressing and slower-progressing disease



Swimmer plot showing overall time on treatment (1L and 2L) and best responses to nintedanib plus docetaxel. [‡]Patients included had a documented best response and had received prior treatment with 1L pembrolizumab/pemetrexed/platinum-based regimen. Other = mixed response. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

There were no new safety signals or unexpected toxicities

TEAEs by drug relationship in the treated set (n=137)

TEAE	Nintedanib-related		Docetaxel-related	
	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)
Diarrhoea	42 (30.7)	6 (4.4)	17 (12.4)	4 (2.9)
Nausea	19 (13.9)	0 (0)	23 (16.8)	0 (0)
Fatigue	12 (8.8)	0 (0)	17 (12.4)	0 (0)
Vomiting	10 (7.3)	0 (0)	8 (5.8)	0 (0)
WBC count decreased	8 (5.8)	7 (5.1)	10 (7.3)	9 (6.6)
Decreased appetite	6 (4.4)	0 (0)	8 (5.8)	0 (0)
Alopecia	4 (2.9)	0 (0)	10 (7.3)	0 (0)

Treatment-related TEAEs shown were reported in ≥5% of patients. TEAEs, treatment-emergent adverse events; WBC, white blood cell

- Grade ≥3 TEAEs/serious TEAEs were observed in 45.3%/36.5% of patients
- Nintedanib dose reductions and therapy interruptions were reported in 33.6% and 21.9% of patients, respectively
- Docetaxel dose reductions and therapy interruptions were reported in 13.1% and 16.1% of patients, respectively
- TEAEs leading to discontinuation were reported in 40 patients (29.2%)

References and acknowledgements

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