Poster 1372P
Abstract 2082

Efficacy and safety of nintedanib plus docetaxel in lung adenocarcinoma patients after failure of previous immune checkpoint inhibitor therapy: updated results from the ongoing non-interventional study VARGADO (NCT02392455)

Christian Grohé,[1] Wolfgang Gleiber,[2] Siegfried Haas,[3] Stefan Hammerschmidt,[4] Stefan Krüger,[5] Harald Müller-Huesmann,[6] Mathias Schulze,[7] Thomas Wehler,[8] Judith Atz,[9] Rolf Kaiser[9]

[1]Department of Pneumology, ELK, Berlin, Germany; [2]Department of Pulmonary Medicine, University Hospital, Goethe University Frankfurt, Frankfurt, Germany; [3]Clinics for Haematology, Oncology and Nephrology, Friedrich-Ebert Hospital, Neumünster, Germany; [4]Department of Internal Medicine, Klinikum Chemnitz GmbH, Chemnitz, Germany; [5]Department for Pulmonology/Allergology/Sleep Medicine and Respiratory Care, Florence Nightingale Hospital, Düsseldorf, Germany; [6]Klinik für Hämatologie und Onkologie, Bruederkrankenhaus St. Josef, Paderborn, Germany; [7]Praxis, Dr. Schulze, Zittau, Germany; [8]EVK, Evangelisches Krankenhaus Hamm, Hamm, Germany; [9]Medical Affairs, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim Am Rhein, Germany

Presented at the European Society for Medical Oncology (ESMO) Virtual Congress, 19–21 September 2020

Corresponding author email address: Christian.Grohe@pgdiakonie.de

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]
- This approval was based on data from the Phase III LUME-Lung 1 trial, in which nintedanib plus docetaxel significantly prolonged progression-free survival (PFS) versus placebo plus docetaxel in patients with NSCLC who had progressed on first-line chemotherapy; overall survival (OS) was also significantly longer in the nintedanib plus docetaxel arm in patients with adenocarcinoma histology[4]
- The treatment landscape in advanced NSCLC has undergone recent advances, including the approval of immune checkpoint inhibitors (ICIs) in combination with chemotherapy for the first-line treatment of metastatic non-squamous NSCLC without an actionable driver mutation,[5,6] but the optimal treatment sequence after progression on this therapy has not yet become clear

INTRODUCTION (CONT'D)

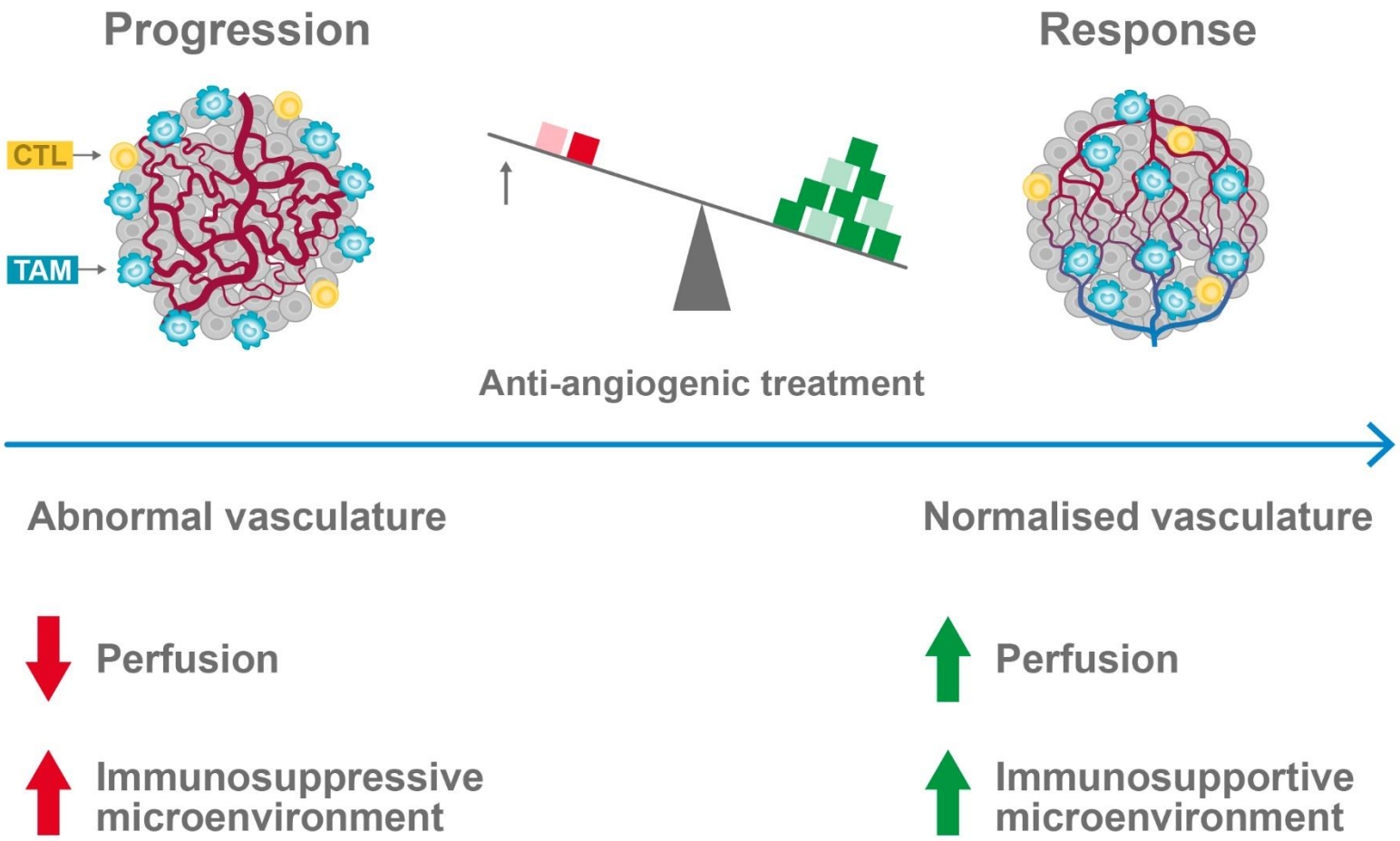
- Understanding the underlying tumour biology may help to guide the selection of the optimal treatment sequence. In addition to promoting angiogenesis, excessive VEGF can also create an immunosuppressive tumour microenvironment (TME) by modulating immune cell function and impeding migration of immune cells into the tumour.[7,8] These mechanisms are likely to contribute to ICI resistance and, conversely, could prime the tumour for anti-angiogenic therapy

- An anti-angiogenic treatment strategy involving inhibition of VEGF, as well as PDGF and FGF, could potentially support vessel normalisation and improve access of immune cells to the tumour, tipping the balance towards an immunosupportive TME in an 'angio-immunogenic switch' (**Figure 1**)

- Limited clinical data are available to help guide physicians when selecting the most appropriate treatment after progression on ICI therapy[9–12]

- Here, we present updated data from a cohort of patients who received nintedanib plus docetaxel after chemotherapy and ICI therapy, as part of the non-interventional, prospective VARGADO study[13]

Figure 1. A hypothesised ‘angio-immunogenic switch’

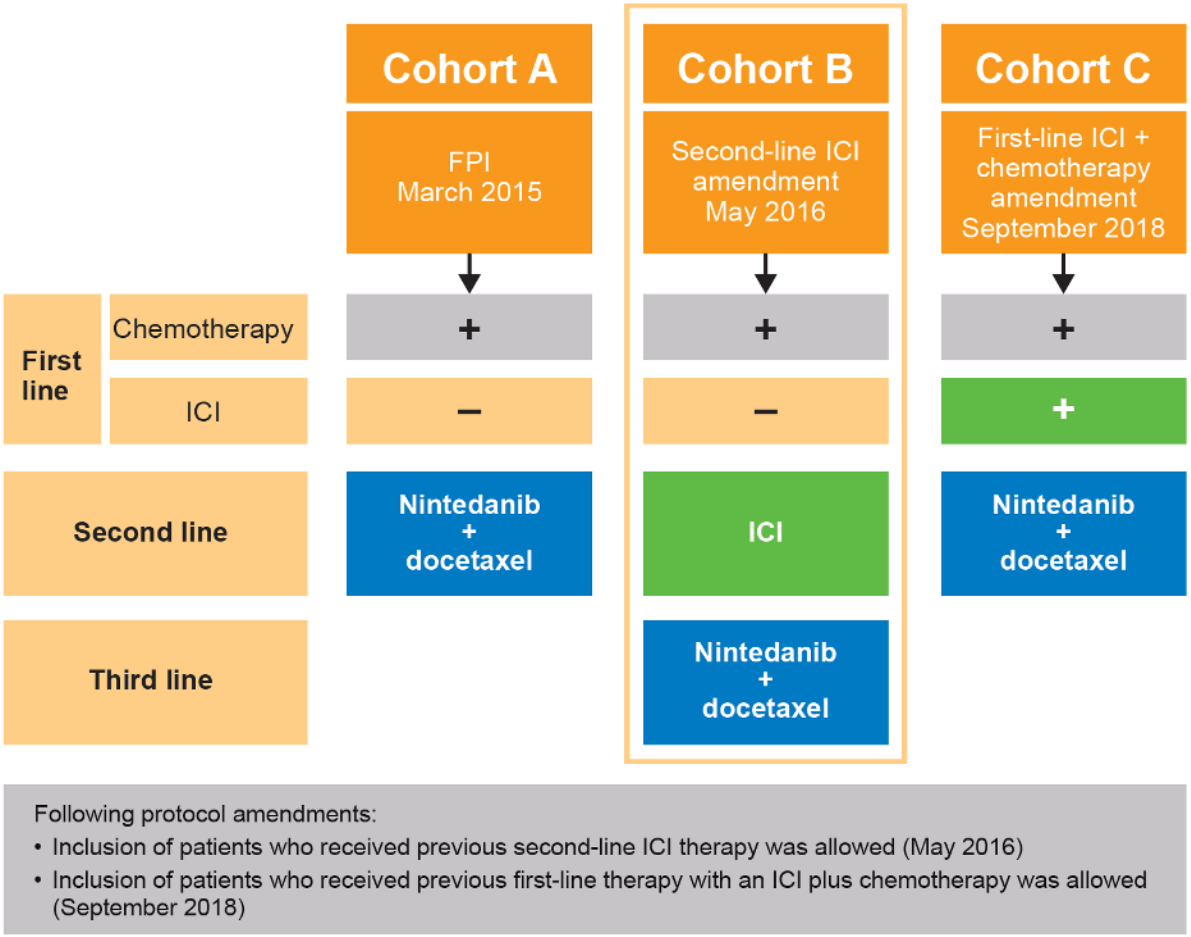


Modified from Fukumura D, et al. Nat Rev Clin Oncol 2018;15:325–40.
CTL, cytotoxic T lymphocyte; TAM, tumour-associated macrophage.

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[13]
- Three patient cohorts in VARGADO are being evaluated (**Figure 2**)
- Between 15 March 2015 and 1 August 2019, 456 patients have been enrolled in centres across Germany
- We present an updated interim analysis of Cohort B (N=65), and an initial analysis of patient characteristics in Cohort C (N=57)
- 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 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 OS rate 1 year after the start of treatment with nintedanib plus docetaxel. Secondary endpoints include PFS, OS, objective response rate, disease control rate 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

Figure 2. Patient cohorts in VARGADO



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

RESULTS

Patient characteristics

- Clinical characteristics and previous treatments for patients in Cohort B and Cohort C are shown in **Table 1** and **Table 2**

- Efficacy data are not yet mature for patients in Cohort C who are undergoing treatment or being followed up

Table 1. Clinical characteristics for patients in Cohort B and Cohort C

		Cohort B (N=65)	Cohort C (N=57)
Median age, years (range)		60 (41–80)	63 (46–80)
Sex, n (%)	Male	34 (52)	30 (53)
	Female	31 (48)	27 (47)
ECOG PS, n (%)	0	17 (26)	18 (32)
	1	30 (46)	23 (40)
	2	4 (6)	9 (16)
	3	1 (2)	2 (4)
	Missing	13 (20)	5 (9)
Tumour stage at baseline, n (%)	I–III	9 (14)	6 (11)
	IV	40 (62)	42 (74)
	Unknown	14 (22)	5 (9)
	Missing	2 (3)	4 (7)
Smoking status, n (%)	Current or former smokers	52 (80)	47 (82)
	Non-smokers	3 (5)	7 (12)
	Not applicable	10 (15)	3 (5)
Presence of brain metastases, n (%)	Yes	15 (23)	11 (19)
	No	50 (77)	46 (81)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Previous treatments for patients in Cohort B and Cohort C

	Cohort B (N=65)		Cohort C (N=57)	
Previous first-line therapy, n (%)*	Pemetrexed	43 (66)	Pembro/pem/platinum	54 (95)
	Carboplatin	39 (60)	Pembro/pem/carboplatin	41 (72)
	Cisplatin	31 (48)	Pembro/pem/cisplatin	13 (23)
	Bevacizumab	13 (20)	Other pembro/chemo combination	2 (4)
	Vinorelbine	13 (20)	Nivo/chemo combination	1 (2)
	Paclitaxel	10 (15)		
	Other	2 (3)		
Previous second-line therapy, n (%)	Nivolumab	37 (57)	Not applicable	
	Pembrolizumab	16 (25)		
	Atezolizumab	11 (17)		
	Other	1 (2)		
	Best response to second-line ICI therapy, n (%)**		Best response to first-line ICI + chemotherapy, n (%)**	
Complete response	0		0	
Partial response	6/36 (17)		16/43 (37)	
Stable disease	6/36 (17)		10/43 (23)	
Progressive disease	23/36 (64)		17/43 (40)	
Other	1/36 (3)		0	
Not yet documented	29		14	

*Previous first-line therapy includes combination regimens; **Percentage based on patients with a documented response at the time of analysis. Chemo, chemotherapy; ICI, immune checkpoint inhibitor; nivo, nivolumab; pem, pemetrexed; pembro, pembrolizumab; platinum, platinum-based chemotherapy

RESULTS (CONT'D)

Efficacy

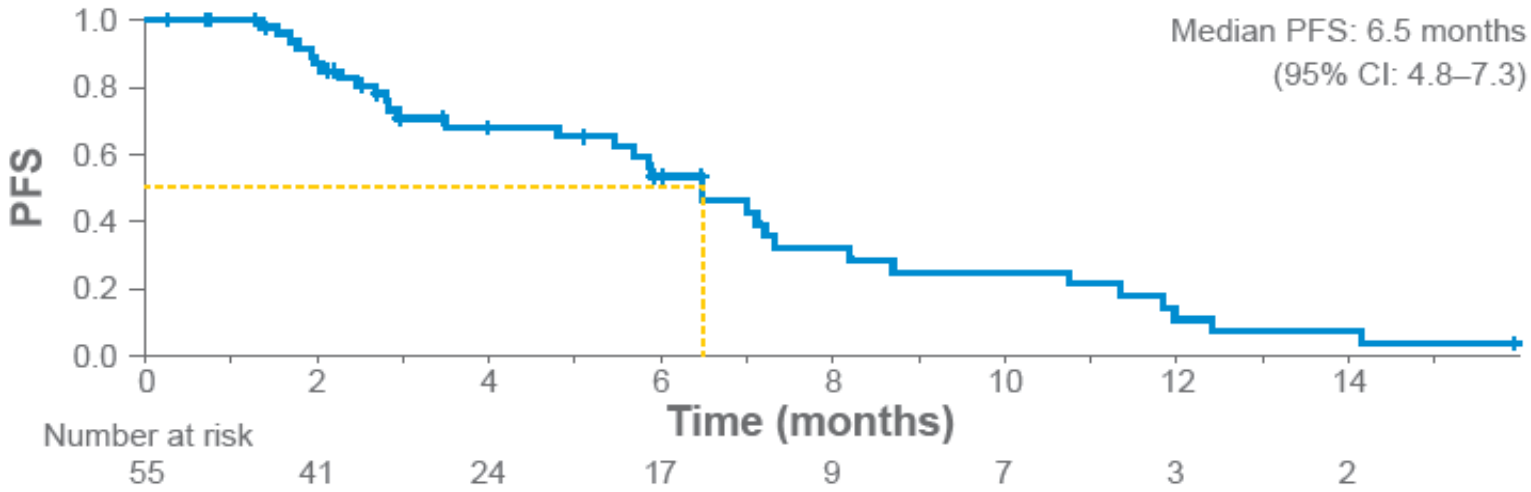
- We present efficacy data for patients in Cohort B (N=65) who received nintedanib plus docetaxel after prior chemotherapy and ICI therapy
- At the time of this interim analysis (data cut-off: 1 April 2020), median duration of follow-up was 7.0 months for patients treated with nintedanib plus docetaxel
- Thirty-three PFS events had occurred (12 patients had disease progression and 21 patients had died). For the PFS analysis, 22 patients were censored and data were not yet available for 10 patients
- For the analysis of OS from the start of first-line therapy, 24 patients had died, 37 patients were censored and data were not yet available for four patients
- For the analysis of OS from the start of third-line therapy, 25 patients had died, 37 patients were censored and data were not yet available for three patients
- PFS and OS data are shown in **Table 3** and in **Figure 3** and **Figure 4**, respectively

Table 3. PFS and OS for third-line nintedanib plus docetaxel after failure of ICI therapy

	Median, months	95% CI
PFS from the start of third-line therapy (n=55)	6.5	4.8–7.3
OS from the start of first-line therapy (n=61)	34.5	25.5–37.5
OS from the start of third-line therapy (n=62)	12.2	11.4–14.1

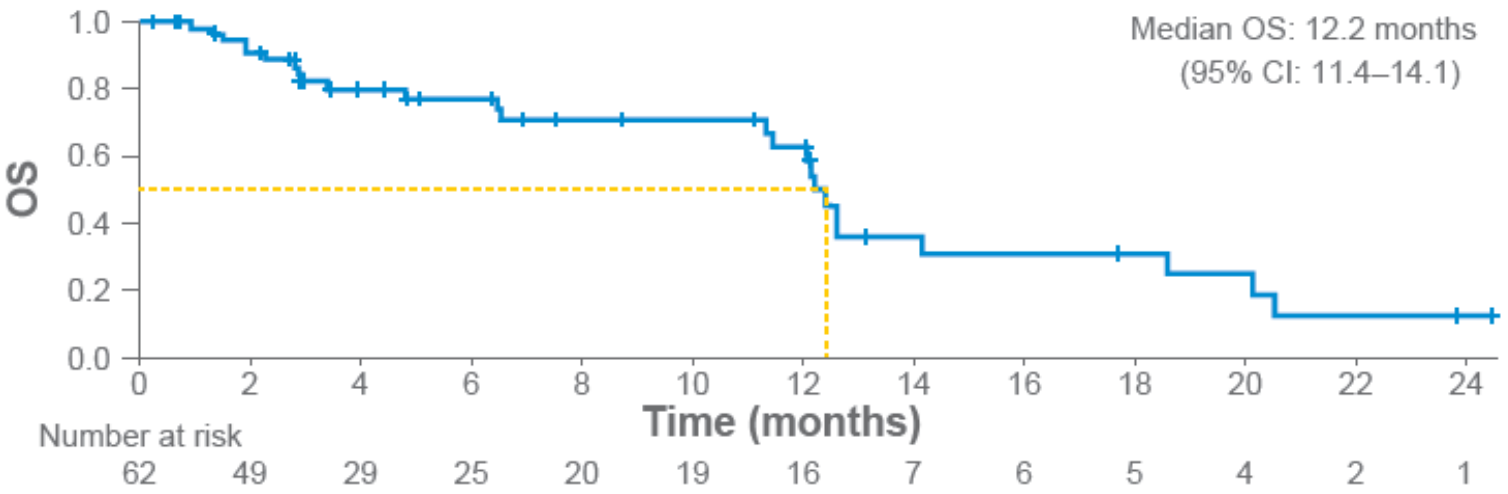
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Figure 3. PFS from the start of third-line nintedanib plus docetaxel after failure of ICI therapy (n=55)*



*10 patients who had died or experienced disease progression were excluded from the treated set because of a missing date for disease progression or death.
CI, confidence interval; PFS, progression-free survival.

Figure 4. OS from the start of third-line nintedanib plus docetaxel after failure of ICI therapy (n=62)*



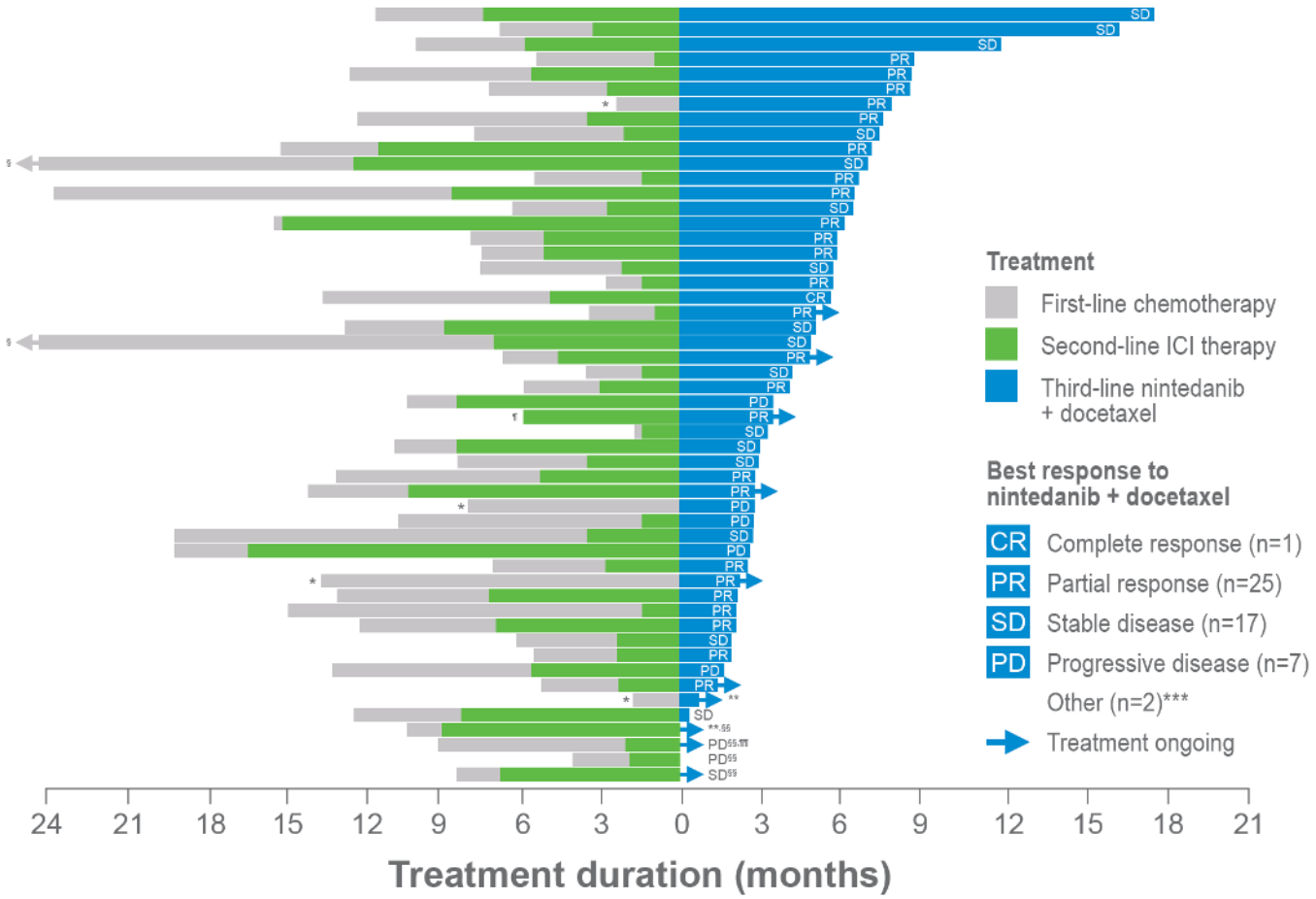
*Three patients who had died were excluded from the treated set because of a missing date of death.
CI, confidence interval; OS, overall survival.

RESULTS (CONT'D)

Efficacy (cont'd)

- Treatment duration and best response to nintedanib plus docetaxel for each patient with a documented response are shown in **Figure 5**
- At the time of analysis, best overall response data were available for 52 patients who received third-line nintedanib plus docetaxel after failure of ICI therapy (**Table 4**)

Figure 5. Swimmer plot showing treatment duration for each patient with a documented response to third-line nintedanib plus docetaxel (n=52)



*Time on ICI therapy not yet documented; §Total time on first- and second-line treatment >24 months; ¶Time on chemotherapy not yet documented; five chemotherapy cycles documented; **Clinically documented response that was not clearly attributable to any category; §§Time on nintedanib plus docetaxel not yet documented; ¶¶Clinically documented response; ***Clinically documented response that was not clearly attributable to any category.

Data are for patients in the treated set who had a documented response.

Table 4. Best response to third-line nintedanib plus docetaxel after failure of ICI therapy (n=52)*

Objective response rate, n (%)	26 (50)
Complete response, n (%)	1 (2)
Partial response, n (%)	25 (48)
Stable disease, n (%)	17 (33)
Disease control rate, n (%)	43 (83)
Progressive disease, n (%)	7 (13)
Other, n (%)**	2 (4)

*Data are for patients in the treated set who had a documented response; **Clinically documented response that was not clearly attributable to any category.
ICI, immune checkpoint inhibitor.

RESULTS (CONT'D)

Safety

- Safety was evaluated in all 65 patients treated with nintedanib plus docetaxel
- Sixty (92%) patients had AEs, with 45 (69%) experiencing treatment-related AEs according to investigator assessment
- The most common treatment-related AEs are shown in **Table 5**
- Grade ≥3 treatment-emergent AEs occurred in 36 (55%) patients; serious treatment-emergent AEs occurred in 34 (52%) patients
- Twenty-one (32%) patients had at least one nintedanib dose reduction and 11 (17%) patients had at least one docetaxel dose reduction
- Treatment-emergent AEs led to discontinuation of study treatment in 22 (34%) patients

Table 5. Treatment-related AEs reported in ≥10% of patients (N=65)*

	Nintedanib related		Docetaxel related	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Diarrhoea	24 (37)	1 (2)	17 (26)	0
Nausea	8 (12)	1 (2)	10 (15)	2 (3)
Decreased white blood cell count	7 (11)	6 (9)	13 (20)	11 (17)
Stomatitis	7 (11)	3 (5)	6 (9)	3 (5)
Fatigue	4 (6)	0	9 (14)	1 (2)

*Data are for the treated set (all treated patients).
AE, adverse event.

CONCLUSIONS

- This updated analysis of the VARGADO study continues to demonstrate the encouraging clinical benefit and manageable safety profile of nintedanib plus docetaxel in patients who progressed on previous chemotherapy and ICI therapy
- The clinical benefit was consistent across multiple outcomes: PFS, OS, response rate and disease control rate
- These data are consistent with the ICI-pretreated subgroup analysis of the LUME-BioNIS study14 and provide further evidence that can inform clinical decision making and treatment sequencing in the changing therapeutic landscape for NSCLC
- Follow-up of patients in Cohort C is ongoing, and efficacy and safety results will be presented at a future meeting

REFERENCES

1. Hilberg F, et al. Cancer Res 2008;68:4774–82.
2. Hilberg F, et al. J Pharmacol Exp Ther 2018;364:494–503.
3. Vargatef® Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/vargatefepar-product-information_en.pdf (Accessed: 12 August 2020).
4. Reck M, et al. Lancet Oncol 2014;15:143–55.
5. Planchard D, et al. Ann Oncol 2018;29(Suppl. 4):iv192–iv237.
6. European Society for Medical Oncology Clinical Practice Living Guidelines – Metastatic Non-small-cell Lung Cancer. https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer (Accessed: 12 August 2020).
7. Fukumura D, et al. Nat Rev Clin Oncol 2018;15:325–40.
8. van der Woude LL, et al. Trends Cancer 2017;3:797–808.
9. Molife C, et al. Future Oncol 2019;15:2915–31.
10. Corral J, et al. Clin Transl Oncol 2019;21:1270–9.
11. Harada D, et al. Anticancer Res 2019;39:4987–93.
12. Shiono K, et al. Thorac Cancer 2019;10:775–81.
13. Grohé C, et al. Future Oncol 2019;15:2699–706.
14. Reck M, et al. Lung Cancer 2020 (In Press).

ACKNOWLEDGEMENTS

Disclosures: The authors were fully responsible for all content and editorial decisions, were involved in all stages of poster development and have approved the final version. CG and WG received personal fees from Boehringer Ingelheim for membership of advisory boards; HM-H received consulting fees and honoraria from Boehringer Ingelheim; SK and MS have no conflicts of interest to declare; SiH's institution received research funding from Boehringer Ingelheim and Pfizer Pharma GmbH, and travel support from Pharma Mar, Novartis, Ipsen; StH received honoraria for advice, talks and clinical trial participation from Boehringer Ingelheim, Roche, MSD, BMS and Pfizer; TW received honoraria for advice and talks from Boehringer Ingelheim, Roche, Lilly, Novartis, MSD, BMS, AstraZeneca, Pfizer and Takeda; JA and RK are employees of Boehringer Ingelheim. This study was sponsored by Boehringer Ingelheim. During the preparation of this poster, medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Syneos Health, UK. Current affiliation for Rolf Kaiser: Boehringer Ingelheim (Schweiz) GmbH, Switzerland.

Corresponding author: Christian Grohé (Christian.Grohe@pgdiakonie.de).