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Nintedanib plus docetaxel in lung adenocarcinoma patients following treatment with immune checkpoint inhibitors: updated efficacy and safety results of the ongoing non-interventional study VARGADO (NCT02392455)

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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]
- This approval was supported by 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)

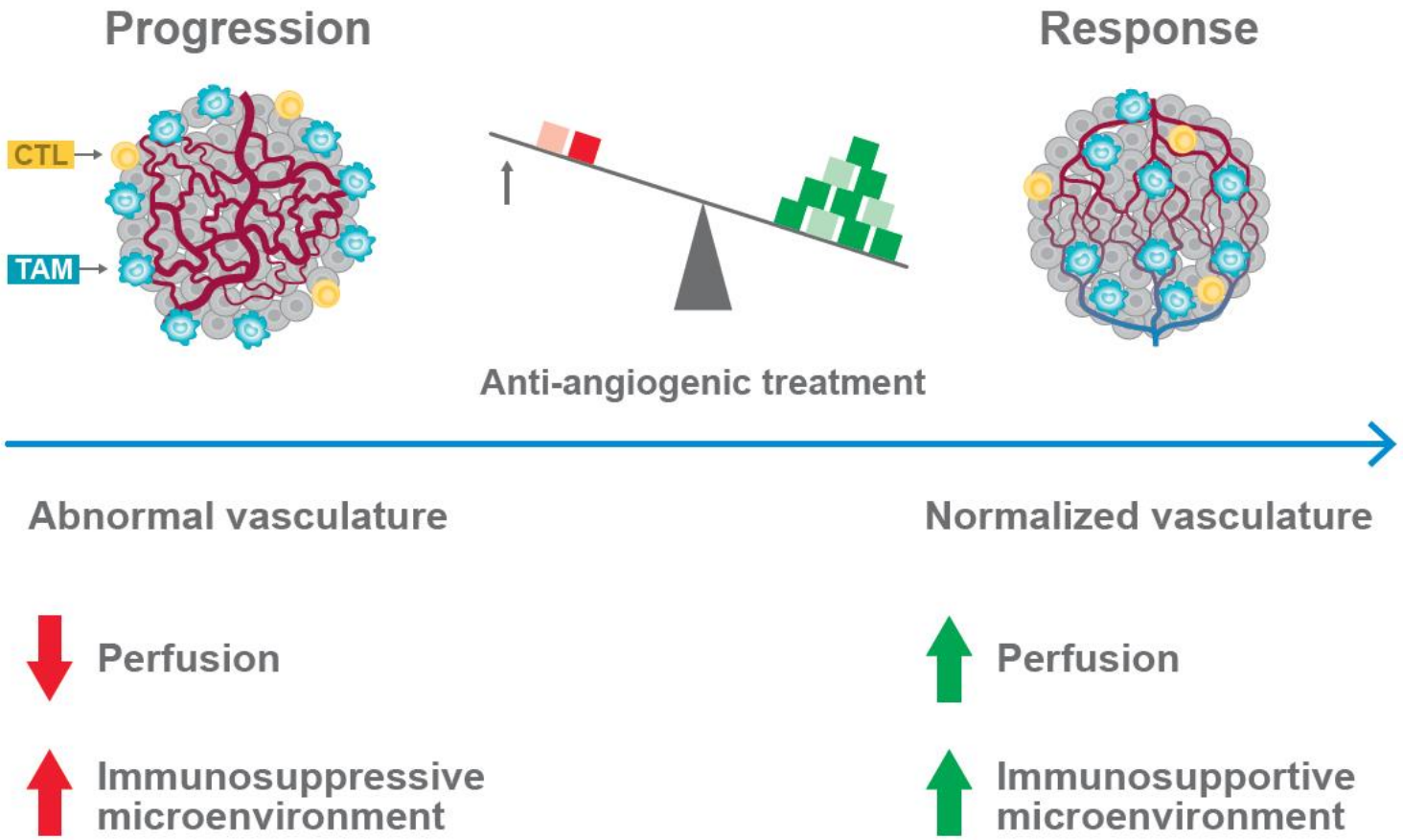
- Understanding the underlying tumor biology may help to guide the selection of the optimal treatment sequence. In addition to promoting angiogenesis, excessive VEGF can also create an immunosuppressive tumor microenvironment (TME) by modulating immune cell function and impeding migration of immune cells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

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

- Limited clinical data are available to help guide treatment decisions 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 hypothesized ‘angio-immunogenic switch’

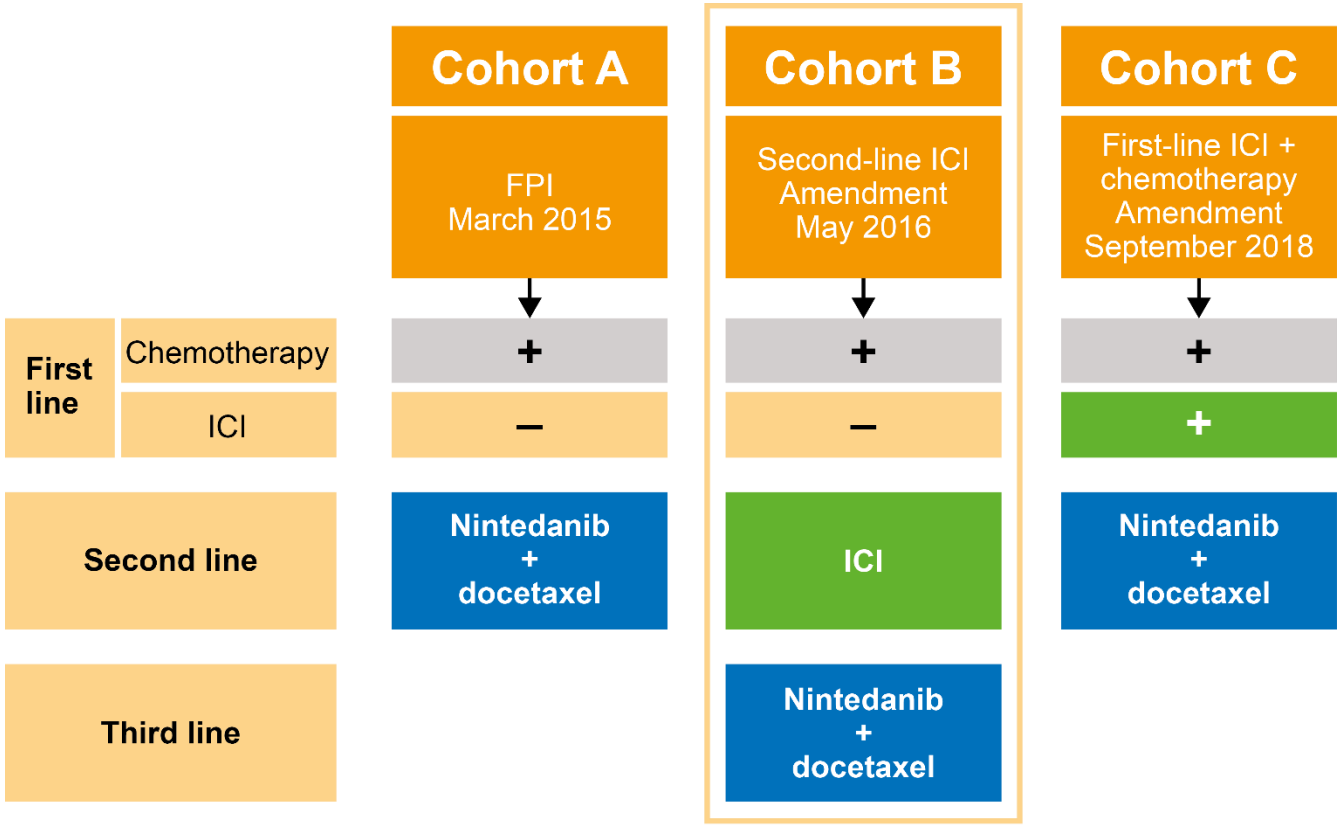


Modified from Fukumura D, et al. Nat Rev Clin Oncol 2018;15:325–40.
CTL, cytotoxic T lymphocyte; TAM, tumor-associated macrophage.

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 March 15, 2015 and April 1, 2020, 429 patients have been enrolled in centers across Germany
- We present an updated interim analysis of Cohort B (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

- Baseline characteristics for the 57 patients included in this analysis are shown in **Table 1**

Efficacy

- At the time of this interim analysis (data cut-off: December 2, 2019), median duration of follow-up was 6.6 months for patients treated with nintedanib plus docetaxel
- Twenty-eight PFS events had occurred (10 patients had disease progression and 18 patients died). For the PFS analysis, 19 patients were censored and data were not yet available for 10 patients
- For the analysis of OS from the start of first-line therapy, 21 patients had died, 33 patients were censored and data were not yet available for three patients
- For the analysis of OS from the start of third-line therapy, 22 patients had died, 33 patients were censored and data were not yet available for two patients
- PFS and OS data are shown in **Table 2** and in **Figure 3** and **Figure 4**, respectively

Table 1. Baseline characteristics (N=57)

Median age, years (range)		61 (45–80)
Sex, n (%)	Male	32 (56)
	Female	25 (44)
ECOG PS, n (%)	0	13 (23)
	1	28 (49)
	2	2 (4)
	3	1 (2)
	Missing	13 (23)
Tumor stage at baseline, n (%)	I–III	9 (16)
	IV	34 (60)
	Unknown	13 (23)
	Missing	1 (2)
Current or former smokers, n (%)		46 (81)
Presence of brain metastases, n (%)		12 (21)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 1. Baseline characteristics (N=57) (cont'd)

Previous first-line therapy, n (%)*	Pemetrexed	36 (63)
	Cisplatin	29 (51)
	Carboplatin	33 (58)
	Bevacizumab	14 (25)
	Vinorelbine	13 (23)
	Paclitaxel	8 (14)
	Docetaxel	1 (2)
Previous second-line therapy, n (%)	Nivolumab	35 (61)
	Pembrolizumab	14 (25)
	Atezolizumab	7 (12)
	Other	1 (2)
Best response to second-line ICI therapy, n (%)**	Complete response	0
	Partial response	5/32 (16)
	Stable disease	6/32 (19)
	Progressive disease	21/32 (66)
	Not yet documented	25

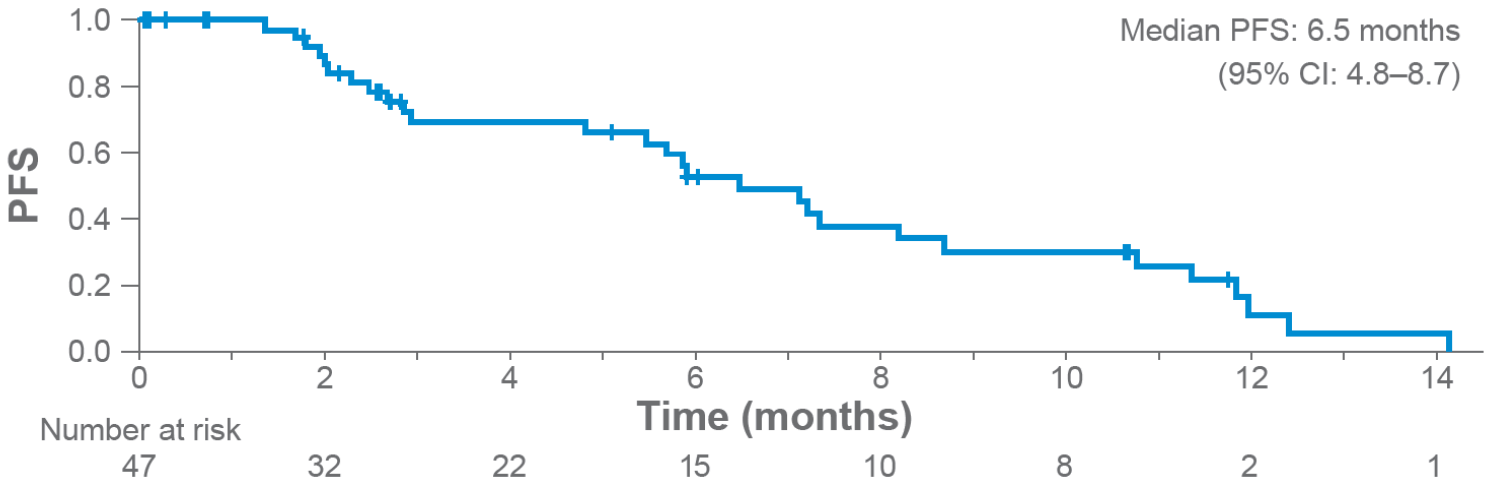
*Previous first-line therapy includes combination regimens; **Percentage based on patients with a documented response at the time of analysis.
ICI, immune checkpoint inhibitor.

Table 2. 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=47)	6.5	4.8–8.7
OS from the start of first-line therapy (n=54)	34.5	25.5–37.5
OS from the start of third-line therapy (n=55)	12.4	11.4–14.1

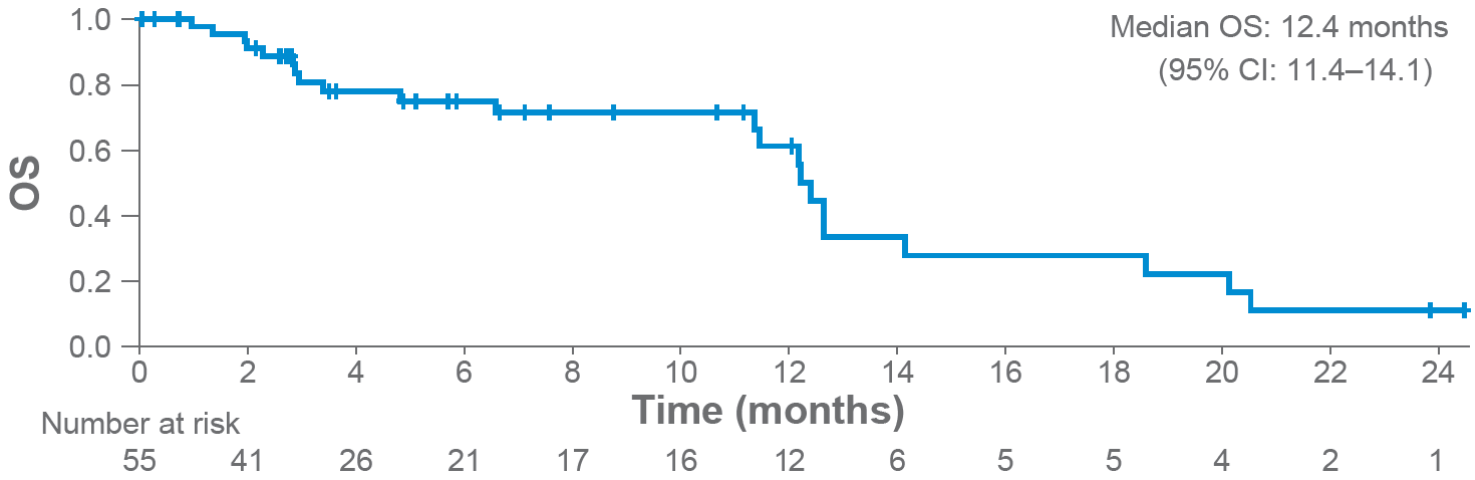
CI, confidence interval; ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival.

Figure 3. PFS from the start of third-line nintedanib plus docetaxel after failure of ICI therapy (n=47)



CI, confidence interval; ICI, immune checkpoint inhibitor; PFS, progression-free survival.

Figure 4. OS from the start of third-line nintedanib plus docetaxel after failure of ICI therapy (n=55)



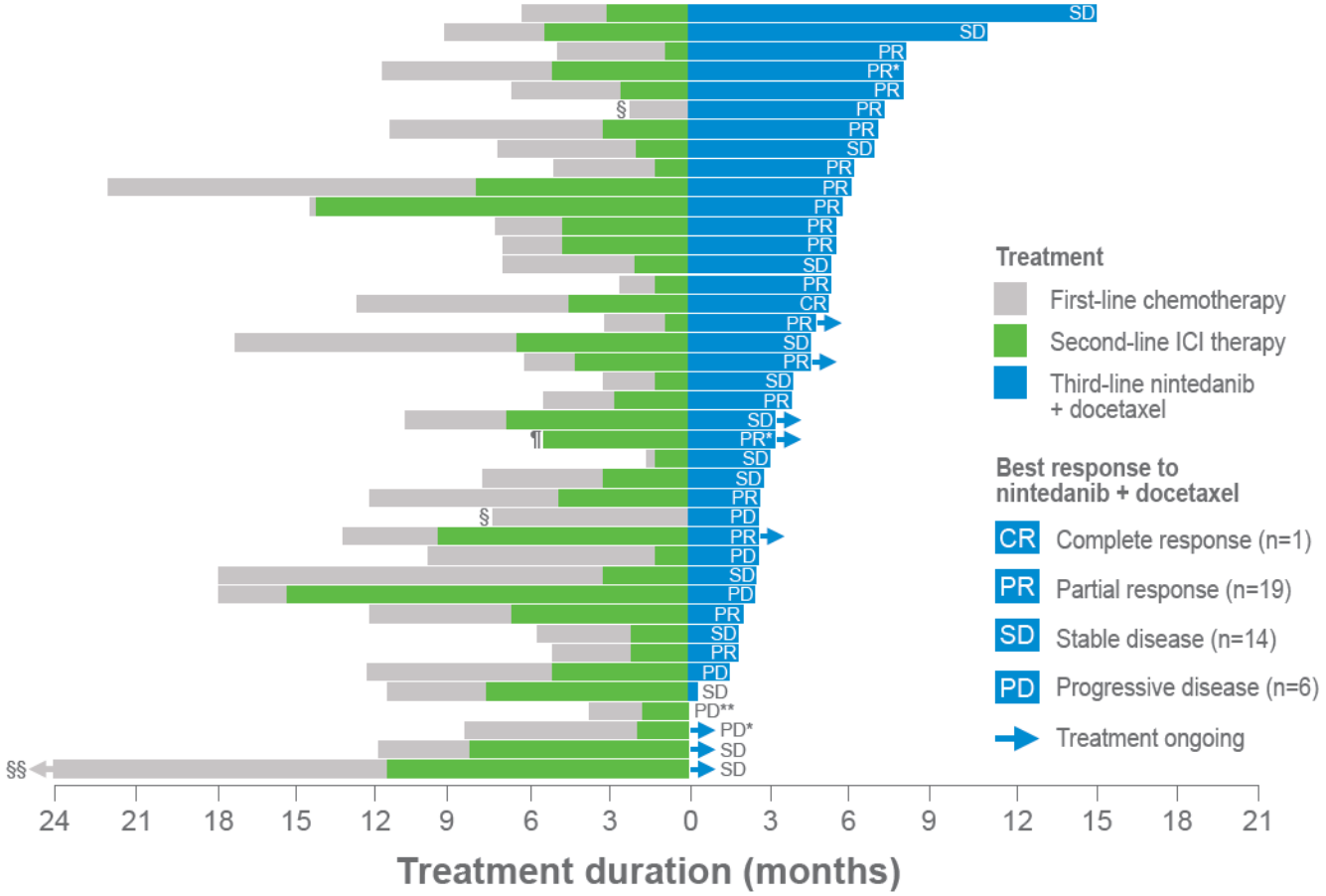
CI, confidence interval; ICI, immune checkpoint inhibitor; OS, overall survival.

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 40 patients who received third-line nintedanib plus docetaxel after failure of ICI therapy (**Table 3**)

Figure 5. Swimmer plot showing treatment duration for each patient with a documented response to nintedanib plus docetaxel (n=40)



*Clinically documented response; §Time on ICI therapy not yet documented; ¶Time on chemotherapy not yet documented; five chemotherapy cycles documented; **Time on nintedanib plus docetaxel not yet documented; §§Patient received first-line chemotherapy for 17.8 months (total time on first- and second-line treatment >24 months).
ICI, immune checkpoint inhibitor.

Table 3. Best response to third-line nintedanib plus docetaxel after failure of ICI therapy (n=40)

Objective response rate, n (%)	20 (50)
Complete response, n (%)	1 (3)
Partial response, n (%)	19 (48)
Stable disease, n (%)	14 (35)
Disease control rate, n (%)	34 (85)
Progressive disease, n (%)	6 (15)

ICI, immune checkpoint inhibitor.

RESULTS (CONT'D)

Safety

- Safety was evaluated in all 57 patients treated with nintedanib plus docetaxel
- Fifty (88%) patients had AEs, with 37 (65%) experiencing treatment-related AEs according to investigator assessment
- The most common treatment-related AEs are shown in **Table 4**
- Grade ≥3 treatment-emergent AEs occurred in 30 (53%) patients; serious treatment-emergent AEs occurred in 30 (53%) patients
- Fifteen (26%) patients had at least one nintedanib dose reduction and 11 (19%) patients had at least one docetaxel dose reduction
- Treatment-emergent AEs led to discontinuation of study treatment in 17 (30%) patients

Table 4. Treatment-related AEs reported in ≥10% of patients (N=57)

	Nintedanib related		Docetaxel related	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Diarrhea	21 (37)	1 (2)	15 (26)	0
Stomatitis	7 (12)	3 (5)	7 (12)	3 (5)
Decreased white blood cell count	6 (11)	5 (9)	11 (19)	9 (16)
Nausea	4 (7)	1 (2)	7 (12)	2 (4)
Fatigue	1 (2)	0	6 (11)	1 (2)

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 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 study[14] and with previous data from the nintedanib named patient use program[10]
- Rational sequencing of an anti-angiogenic agent after ICI therapy may be a promising treatment approach in this patient population that warrants further investigation

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/vargatef-epar-product-information_en.pdf (Accessed: April 16, 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: April 16, 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. Ann Oncol 2019;30(Suppl. 11): Abstract 180.

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