Limited clinical data are available to help guide treatment decisions after progression of non-small cell lung cancer (NSCLC) of adenocarcinoma histology after first-line chemotherapy for the first-line treatment of metastatic non-squamous NSCLC without including the approval of immune checkpoint inhibitors (ICIs) in combination with chemotherapy; overall survival (OS) was also significantly longer in the nintedanib plus docetaxel group compared with chemotherapy alone. 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.1 But the optimal treatment sequence after progression is not yet determined.

Nintedanib is approved in the EU and other countries in combination with docetaxel and is one of the few agents that target multiple pathways involved in tumor angiogenesis, invasion, and immune cell function and impeding migration of immune cells into the tumor.2 Optimal treatment sequence. In addition to promoting angiogenesis, excessive VEGF signaling promotes immune cell infiltration and immune suppression in the tumor microenvironment.

"Figure 1" is an 'angio-immunogenic switch' (3). Widespread abnormal vasculature is associated with a decreased neovascularization potential of tumor cells and a coordinated immune response.3,4 With nintedanib plus docetaxel, vascular normalization may be accompanied by an ‘angio-immunogenic switch’ (Figure 1).

**Study Design and Patient Population**

- **VARGADO (NCT02392455)** is an ongoing, prospective, non-interventional study of nintedanib plus docetaxel after first-line chemotherapy in the local clinical treatment of patients with locally advanced, metastatic or locally recurrent adenocarcinoma of the lung (NSCLC).
- Three patient cohorts in VARGADO are being evaluated (Figure 2).
- Between March 15, 2015 and April 1, 2020, 69 patients have been enrolled in various countries across Germany.
- We present an updated interim analysis of Cohort B (N=51).

**Figure 2. Patient cohorts in VARGADO**

**RESULTS**

- Treatment duration and best response to nintedanib plus docetaxel for each patient with a documented response are shown in Figure 3.
- At the time of analysis, best overall response data were available for 42 patients who received nintedanib plus docetaxel after failure of ICI therapy (N=15).

**Table 1. Baseline characteristics (N=51)**

**Table 3. Best response to nintedanib plus docetaxel after failure of ICI therapy (N=42)**

**Table 4. Treatment-related AEs reported in ≥10% of patients (N=42)**

**Abbreviations:** ALK = anaplastic lymphoma kinase; B = bosutinib; CAR-T = chimeric antigen receptor T-cell; CR = complete response; CRR = clinical response rate; CRP = C-reactive protein; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; dd-LVS = delayed distant visceral spread; F = gemcitabine; FGF = fibroblast growth factor; ICI = immune checkpoint inhibitor; IR = immune-related; LVS = local visceral spread; M = maintenance; MCB = microvascular density; Neut = neutrophils; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed death-ligand 1; PR = partial response; PT = pembrolizumab; QOL = quality of life; SD = stable disease; TKI = tyrosine kinase inhibitor; VARGADO = 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).

**CONCLUSIONS**

- This updated analysis of the VARGADO study continues to demonstrate the antitumoral clinical benefit and manageable safety profile of nintedanib plus docetaxel after failure of ICI therapy in patients with metastatic non-squamous NSCLC.
- The clinical benefit was consistent across multiple outcomes: PFS, OS, response rate and disease control rate.
- These data are consistent with the CI-pretreated subgroup analysis of the LUME-BioNIS study which shows that previous data from the nintedanib-naïve patient population remain relevant.
- Rational sequencing of an antiangiogenic agent after ICI therapy may be a promising treatment approach in this patient population that warrants further investigation.

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- The authors were responsible for the study design, conduct and analysis of this study and had access to all data.
- The authors were responsible for the writing of this document and all authors had an opportunity to review and give final approval of the version to be submitted.
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