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Research Article

Effectiveness and Safety of Docetaxel in Combination with Nintedanib or Ramucirumab Following Chemoimmunotherapy in Patients with Metastatic Non-Small-Cell Lung Cancer

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Abstract

Background: The combination of docetaxel with nintedanib (D+N) or ramucirumab (D+R) is the standard of care for the second- or third-line therapy after simultaneous or sequential chemoimmunotherapy for patients with non-small cell lung cancer (NSCLC) without targetable molecular alterations. Data about the safety of docetaxel plus an antianiogenic agent after ICI treatment in the real life setting are limited. **Methods:** Retrospective data from 5 German oncology centers and practices were collected. The number of cycles, progression-free survival (PFS) and overall survival (OS), objective response rates (ORRs) and adverse events (AEs) resulting in therapy discontinuation were analyzed. **Results:** 173 patients were recruited. 115 (66.5%) patients had an adenocarcinoma, 47 (27.2%) a squamous cell carcinoma and 5 (2.9 %) a large cell neuroendocrine carcinoma. 61 patients (35.3%) received D+N and 112 patients (64.7%) D+R. To 70 patients (40.5%) docetaxel-based therapy (D+N or D+R) was administered as second-line, to 76 patients (43.9%) as third-line and to 27 patients (15.6%) as further line. ORR induced by D+N or D+R were 50% (27 patients) resp. 54% (47 patients). Dose reduction was performed in 16 (27.1%) patients with D+N and 43 (53.7%) patients with D+R. Median PFS was increased (7.6 months versus 6.3 months, p=0.002) in the D+R cohort compared to the D+N cohort in the multivariate analysis, although there was no significant difference in the univariate analysis (p=0.402). Median OS of all patients was 9.1 months. Focusing on adenocarcinoma patients (105 pts), 60 patients (52%) received D+N and 55 (48%) D+R. Median OS were 8.8 months for D+N and 6.9 months for D+R with no statistically significant difference (p=0.297). **Conclusion:** In adenocarcinoma patients the effectiveness of D+N or D+R after chemoimmunotherapy differed not significantly. Docetaxel dose was reduced more often during D+R therapy.

Introduction

Lung cancer is still the second most frequent cancer and the cancer with the highest mortality worldwide [1] and it has been historically classified as small cell lung cancer (SCLC: 15%) and non-small cell lung cancer (NSCLC: 75%), which is based on morphological features [2]. NSCLC patients have often an advanced, unresectable disease stage not amenable to curative treatment or a metastatic disease stage at their initial diagnosis [3].

Until the advent of immune checkpoint inhibitors (CPIs) in the recent treatment of the aforementioned group of NSCLC patients without oncogenic driver mutations systemic therapy was limited to chemotherapy, which was associated with poor survival times and an unfavorable toxicity profile [4]. The availability of CPIs caused a paradigm shift in the treatment landscape of NSCLC opening new perspectives for a relevant number of patients, particularly of those with comorbidities and a reduced performance status [5].

Results from phase 3 clinical studies comparing second-line treatment with docetaxel versus monoclonal antibodies targeting programmed cell death receptor 1 (PD-1) or programmed cell death receptor-ligand 1 (PD-L1) revealed marked improvements in survival with CPIs compared with standard chemotherapies and led to the approval of nivolumab, pembrolizumab and atezolizumab after platinum-based chemotherapy for the treatment of metastatic NSCLC [6-8].

Due to the success of the CPIs in previously treated NSCLC patients, their effectiveness either as single agent therapy or in combination with chemotherapy in the frontline setting was evaluated. Currently, efficacious first-line treatment options for NSCLC patients without driver alterations include several antibodies directed against CTLA-4, PD-1 and PD-L1 according to phase 3 clinical trials with atezolizumab, cemiplimab, durvalumab, nivolumab, ipilimumab, pembrolimumab and tremelimumab either as single agent therapy or as a combined chemoimmunotherapy [6,7,8]. These agents improved clinical outcomes with patients experiencing prolonged overall survival (OS) and durable responses compared with chemotherapy alone [9]. However, approximately 50% of patients receive subsequent treatment upon progression during or after first-line treatment [10].

The current treatment guidelines for metastatic NSCLC patients who experience disease progression after standard-of care first-line therapy [11,12] recommend single agent chemotherapy or a combination of docetaxel with an antiangiogenic agent such as ramucirumab and nintedanib, or single agent anti-PD-(L)1 antibodies if not previously administered [13,14]. But clinical outcomes with single-agent chemotherapy are modest. In comparison to best supportive care, treatment with docetaxel, resulted in an objective response rate (ORR) of 7.1%, time to progression of 10.6 weeks, and median OS of 7.0 months [15]. Treatment with gemcitabine, nab-paclitaxel or pemetrexed demonstrated a similar median OS of 5.1 months [16], and 8.5 months [17], and 8.3 months respectively [18]. Combination approaches with chemotherapy and antiangiogenic agents in the second-line setting have produced more favorable outcomes compared with chemotherapy alone [9].

Nintedanib is a potent, oral angiokinase inhibitor targeting the pro-angiogenic pathways mediated by vascular endothelial growth factor receptor (VEGFR) 1-3, fibroblast growth factor receptors (FGFR) 1-3, and platelet-derived growth factor receptors (PDGFR) a and ß [19]. Receptor kinases of RET, FLT3, and the Src family are also inhibited [19]. In phase 1/2 clinical trials, nintedanib showed a manageable safety profile and antitumour activity in patients with solid tumours, including NSCLC [20, 21].

Ramucirumab is a fully human immunoglobulin G1 monoclonal antibody specifically binding to the vascular endothelial growth factor (VEGF) receptor-2 extracellular domain with high affinity, preventing binding of all VEGF ligands and subsequent receptor activation [22].

In the LUME-Lung 1 study, the combination of docetaxel with nintedanib (D+N) [14] resulted in a statistically significant improvement in PFS (3.4 vs. 2.7 months), compared to docetaxel monotherapy as second-line therapy for metastatic NSCLC patients with a previous platinum-based combination chemotherapy. However, a statistically significant improvement in OS was observed only in the subgroup of patients with adenocarcinoma histology (12.6 vs. 10.3 months) but not in the total study population (10.1 vs. 9.1 months) [13, 14]. Hence, the approval of nintedanib by the EMA was restricted to NSCLC patients with adenocarcinoma histology who have undergone first-line chemotherapy.

In the phase 3 REVEL trial, the combination of docetaxel plus ramucirumab (D+R) demonstrated a significant improvement in objective response rates (ORR: 23% vs 14%), median progression-free survival (PFS: 4.5 vs 3.0 months) and overall survival (OS: 10.5 vs 9.1 months) relative to docetaxel plus placebo in patients with stage IV NSCLC whose disease had progressed during or after first-line platinum-based chemotherapy [13]. Importantly, ramucirumab plus docetaxel had a manageable safety profile and no detrimental impact on quality of life [13, 23].

Additionally, second-line treatment with ramucirumab plus docetaxel resulted in an improvement of median PFS relative to docetaxel in other studies [24, 25].

The currently recommended treatment options for patients with NSCLC whose disease progressed during or after first-line treatment were investigated before the approval of ICIs in immunotherapy-naïve patients.

Therefore, the results from these trials, including LUME-Lung 1 and REVEL, do not optimally reflect the current patient population with disease progression after ICI treatment. Randomized controlled studies investigating the efficacy and safety of docetaxel plus nintedanib or ramucirumab in the post-immunotherapy setting are lacking. Nevertheless, the efficacy and safety of docetaxel plus nintedanib or ramucirumab in patients previously treated with ICIs have been reported in recent years, mostly from retrospective observational studies and electronic health record studies [9] analyzing the efficacy and safety of D+R. Although there are some prospective, non-randomized clinical trials investigating either D+N [26, 27] or D+R [28, 29] after chemoimmunotherapy, no randomized, prospective clinical trial has so far been performed and published, since simultaneous chemoimmunotherapy has become the standard of care for first-line or combined first-/second-line standard of care for a sequential chemoimmunotherapy.

In the clinical routine, the decision whether D+N or D+R should be administered to patients with metastatic pulmonary adenocarcinoma mainly depends on the availability of the antiangiogenic agents, comorbidities of the patients (particularly comorbidities which require anticoagulation and are associated with an increased risk of bleedings) and personal experiences of the treating oncologist. However, no comparison between D+N and D+R in patients with previous chemoimmunotherapy has been performed. Although several pro- and retrospective studies have assessed the value of D+N or D+R after chemoimmunotherapy in metastatic NSCLC patients, the majority of these studies recruited Asian patients and data about dose reductions, and administration of granulocyte colony stimulating factors (GCSF) particularly in Caucasian patients, are lacking.

Materials and Methods

Study Design and Patients

Data from a total of 173 metastatic NSCLC patients, who started their first cycle of D+N or D+R from May 1, 2018 until April 30, 2024 at the Lung Cancer Center Essen-Mitte, at the MVZ Hematology and Oncology in Bottrop, Essen or Velbert, Germany or at the Medical Practice for Hematology and Oncology Bochum were retrospectively analyzed. All of the patients received the combination of docetaxel with nintedanib (D+N) or ramucirumab (D+R) as second-line or further line therapy after simultaneous or sequential chemoimmunotherapy. The clinical data collected for this analysis were age, gender, the smoking status, TNM or IASLC/Union for International Cancer Control (UICC) stages, dose reduction of chemotherapy and administration of GCSF.

All tumor sample evaluations were conducted by board-certified pathologists. All tissues were stained with hematoxylin and eosin (H&E), rabbit monoclonal immunoglobulin as a negative reagent control, and with the VENTANA PD-L1 (SP263) Assay, which is one of the recommended assays for PD-L1 diagnostics [30]. The H&E staining was performed to determine the adequacy of tumor. A tissue sample was adequate for the assay interpretation if it contained at least 100 viable tumor cells. For each staining run, prequalified human benign tonsil tissue was used as positive and negative tissue control. Tonsil tissue stained with PD-L1 was assessed for staining in lymphocytes and macrophages in germinal centers, and scattered PD-L1 staining cells among PD-L1-negative cells in paracortical regions. Tonsil tissue was also assessed for the presence of diffuse staining observed in the reticulated crypt epithelial cells with the absence of staining of superficial squamous epithelial cells. Patient-matched tissue stained for negative reagent control was evaluated for the presence and acceptability of nonspecific background staining. Once the H&E and the control slides were deemed acceptable, the PD-L1 stained slide was assessed.

The PD-L1 Tumor Proportion Score (TPS) was calculated as the percentage of at least 100 viable tumor cells with complete or partial membrane staining and was separated into the following three groups: <1% (no expression: category 0), 1%–49% (low expression: category 1) and =50% (high expression: category 2).

Immunocyto- and -histochemistry were performed at the Practice for Pathology Essen-Mitte (Zentrum fuer Pathologie Essen-Mitte), Essen, Germany, which is accredited by the German Accreditation Body (Deutsche Akkreditierungsstelle: DAkkS). Furthermore, PD-L1-testing is certified by the Initiative for Quality Assurance in Pathology (Qualitätssicherungsinitiative in der Pathologie: QuIP) of the German Society of Pathology (Deutsche Gesellschaft für Pathologie: DGP).

Treatment and Assessment

Docetaxel (standard dosage of 75 mg/m2, d1, every three weeks or 60 mg/m2, d1, every three weeks in case of primary dose reduction) in combination with nintedanib (200 mg orally bid except on the day of docetaxel infusion) or with ramucirumab (10 mg/kg body weight, d1, every three weeks) was administered according to local standard. Radiological evaluation of response to treatment was carried out using RECIST 1.1 [31]. For progression-free survival (PFS) and overall survival (OS) analysis, patients were followed up until June, the 30th of 2024.

Statistical Analysis

The retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board of the DKG-certified Lung Cancer Center (approval on July 10, 2019 for analysis of docetaxel plus nintedanib resp. April 1, 2020 for analysis of docetaxel plus ramucirumab). Individual consent for this retrospective analysis was waived.

The statistical tests were performed using IBM SPSS Statistics (version 29), the associated figures were created using GraphPad PRISM (version 7). The Chi-square test was used to compare categorical variables (when necessary, Fisher's exact test). Students t-test was used for age, Mann Whitney U test for „pack years" and PD-L1 expression (%). Multivariate logistic regression was used to estimate associations (wald test). Models were adjusted for all variables. Kaplan-Meier methodology was used for estimation of medians, survival curves and their comparisons. Cox proportional hazard model was performed to identify prognostic factors in both the univariate analysis and the multivariate analysis (wald test).

Results

Clinicopathological Features

Detailed clinicopathological information is shown in table 1. A total of 173 patients with metastatic NSCLC receiving either D+N or D+R were identified. Due to the approval status by the EMA, docetaxel plus nintedanib was only administered to patients suffering from a non-squamous NSCLC. However, the majority of the patients suffered from an adenocarcinoma (115 patients (66.5%)). In the univariate analysis of the clinicopathological features (table 1), significant differences between patients receiving D+N or D+R regarding age, histology, PD-L1 expression at the time of first diagnosis, number of induction chemotherapy cycles, percentage of patients with dose reductions of docetaxel and the kind of the used PD-1-/PD-L1-antibody were found.

Variable	Docetaxel + Nintedanib	Docetaxel + Ramucirumab	total	p-value
Numbers	61	112	173	
Age in years				
Mean (CI: 95%)	61.9 (59.6-64.5)	66.3 (64.9-67.7)	64.8 (63.5-66.1)	**0.001**
Median (Range)	61 (38-81)	67 (49-84)	65 (38-84)	
<65	37 (60.7%)	47 (42.0%)	84 (48.6%)	**0.019**
≥65	24 (39.3%)	65 (58.0%)	89 (51.4%)	
Gender				0.125
Female	25 (41.0%)	33 (29.5%)	58 (33.5%)	
Male	36 (59.0%)	79 (70.5%)	115 (66.5%)	
Smoking status				
Unknown	2 (3.3%)	21 (18.8%)	23 (13.3%)	
Known	59 (96.7%)	91 (81.2%)	150 (86.7%)	0.672
Non-smoker	12 (20.3%)	16 (17.6%)	28 (18.7%)	
Smoker	47 (79.7%)	75 (82.4%)	122 (81.3%)	
Pack Years				
Median (Range)	36 (5-170)	42 (2-120)	40 (2-170)	0.063
Mean (CI: 95%)	40 (32-50)	46 (41-52)	44 (39-49)	
TNM stages				
T				0.581
1	8 (13.1%)	17 (15.2%)	25 (14.5%)	
2	10 (16.4%)	21 (18.8%)	31 (17.9%)	
3	13 (21.3%)	31 (27.7%)	44 (25.4%)	
4	30 (49.2%)	43 (38.4%)	73 (42.2%)	
N				0.57
0	12 (19.7%)	22 (19.6%)	34 (19.7%)	
1	13 (21.3%)	15 (13.4%)	28 (16.2%)	
2	19 (31.1%)	38 (33.9%)	57 (32.9%)	
3	17 (27.9%)	37 (33.0%)	54 (31.2%)	

M				0.107
0	16 (26.2%)	43 (38.4%)	59 (34.1%)	
1	45 (73.8%)	69 (61.6%)	114 (65.9%)	
Initial IASLC/UICC stages				0.439
I	3 (4.9%)	7 (6.3%)	10 (5.8%)	
II	3 (4.9%)	7 (6.3%)	10 (5.8%)	
III	10 (16.4%)	29 (25.9%)	39 (22.1%)	
IV	45 (73.8%)	69 (61.6%)	114 (65.9%)	
Histology				**<0.001**
ADC	60 (98.4%)	55 (49.1%)	115 (66.5%)	
SCC	0	47 (42.0%)	47 (27.2%)	
LCNEC	1 (1.6)	4 (3.6%)	5 (2.9%)	
NOS	0	3 (2.7%)	3 (1.7%)	
Others	0	3 (2.7%)	3 (1.7%)	
PD-L1 expression (TPS)				
Unknown	4 (6.6%)	9 (8.0%)	13 (7.5%)	
Known	57 (93.4%)	103 (92.0%)	160 (92.5%)	**0.005**
0%	32 (56.1%)	32 (31.1%)	64 (40.0%)	
1-49%	17 (29.8%)	40 (38.8%)	57 (35.6%)	
≥50%	8 (14.0%)	31 (30.1%)	39 (24.4%)	
Mean (CI: 95%)	15.0 (7.9-22.2)	25.9 (19.9-31.6)	22 (17.4-26.6)	**0.003**
Systemic therapy				
Induction cycles				
Median (range)	5.5 (1-24)	3 (1-26)	4 (1-26)	**0.003**
Maintenance cycles				0.478
No	37 (60.7%)	74 (66.1%)	111 (64.2%)	
Yes	24 (39.3%)	38 (33.9%)	62 (35.8%)	
Median (range)	5 (1-88)	4.5 (1-23)	5 (1-88)	0.442
Dose reduction of docetaxel				
Unknown	2 (3.3%)	32 (28.6%)	34 (19.7%)	
Known	59 (96.7%)	80 (71.4%)	139 (80.3%)	**0.003**
No	43 (72.9%)	37 (46.4%)	80 (57.6%)	
Yes (primary)	5 (8.5%)	23 (28.7%)	28 (20.1%)	
Yes (secondary)	11 (18.6%)	20 (25.0%)	31 (22.3%)	
G-CSF administration				
Unknown	4 (6.6%)	38 (33.9%)	42 (24.3%)	
Known	57 (93.4%)	74 (66.1%)	131 (75.7%)	0.421
No	31 (54.4%)	35 (47.3%)	66 (50.4%)	
Yes	26 (45.6%)	39 (52.7%)	65 (49.6%)	
PD-1-/PD-L1-antibody				**0.038**
Atezolizumab	22 (36.1%)	20 (17.9%)	42 (24.3%)	
Durvalumab	7 (11.5%)	11 (9.8%)	18 (10.4%)	

Nivolumab	11 (18.0%)	24 (21.4%)	35 (20.2%)	
Pembrolizumab	21 (34.4%)	51 (45.5%)	72 (41.6%)	
Others	0	6 (5.4%)	6 (3.5%)	
Lines of therapy				0.259
2	28 (45.9%)	42 (37.5%)	70 (40.5%)	
3	27 (44.3%)	49 (43.8%)	76 (43.9%)	
4 and further lines	6 (10.0%)	21 (18.8%)	27 (15.6%)	
Median (range)	3 (2-5)	3 (2-7)	3 (2-7)	0.173
Response status				0.079
Unknown	7(11.5%)	25(22.3%)	32(18.5%)	
Known	54 (88.5%)	87 (77.7%)	141 (81.5%)	0.369
CR	0	0	0	
PR	27 (50.0%)	47 (54.0%)	74(52.5%)	
SD	21 (38.9%)	25 (28.7%)	46(32.6%)	
PD	6 (11.1%)	15 (17.2%)	21(14.9%)	
Progression status				**0.008**
No	19 (31.1%)	59 (52.7%)	78 (45.1%)	
Yes	42 (68.9%)	53 (47.3%)	95 (54.9%)	
PFS in months				
Median (CI: 95%)	6.3 (5.0-7.5)	7.6 (6.7-8.5)	7.2 (6.3-8.1)	0.402
PFS rate				
1-year-PFS	20.5% (10.0-33.5%)	22.4% (12.2-34.5%)	21.8% (14.1-30.5%)	
Survival status				0.366
Death	46 (75.4%)	91 (81.3%)	137 (79.2%)	
Alive	15 (24.6%)	21 (18.8%)	36 (20.8%)	
OS in months				0.157
Median (CI: 95%)	9.1 (5.2-13.1)	6.9 (3.7-10.0)	7.3 (4.9-9.7)	
OFS rate				
1-year-OS	41.3% (28.5-53.6%)	33.8% (24.7-43.0%)	36.5% (29.0-46.0%)	

Table 1: Comparison of clinicopathological factors between metastatic non-small cell lung cancer patients receiving docetaxel plus nintedanib or docetaxel plus ramucirumab after chemoimmuntherapy (entire cohort). ADC: Adenocarcinoma, CR: Complete Response, IASLC: International Association for the Study of Lung Cancer, LCNEC: Large Cell Neuroendocrine carcinoma, NOS: Not Otherwise Specified carcinoma, OTH: Others, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SCC: Squamous Cell Carcinoma, SD: Stable Disease, and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

In the subgroup of adenocarcinoma patients, significant differences between patients receiving D+N or D+R regarding age, gender, PD-L1 expression at the time of first diagnosis), number of induction chemotherapy cycles, percentage of patients with reduced docetaxel doses and the chosen PD-1-/PD-L1-antibody were noted.

In the subgroup of patients who only received D+R regardless of histology, significant differences in the percentage of patients with primary metastatic disease at the time of first NSCLC diagnosis (Suppl. table 1), histology, and the type of the used PD-1-/PD-L1-antibody were recognized.

Variable	Non-SCC	SCC	total	p-value
Numbers	65	47	112	
Age in years				
Mean (CI: 95%)	66.3 (64.4-68.2)	66.4(66.1-68.8)	66.3 (64.9-67.7)	0.9
Median (Range)	66 (51-84)	67 (49-84)	67 (49-84)	
<65	29 (44.6%)	18 (38.3%)	47 (42.0%)	0.504
≥65	36 (55.4%)	29 (61.7%)	65 (58.0%)	
Gender				0.366
Female	17 (26.2%)	16 (34.0%)	33 (29.5%)	
Male	48 (73.8%)	31 (66.0%)	79 (70.5%)	
Smoking status				
Unknown	13 (20.0%)	8 (17.0%)	21 (18.8%)	
Known	52 (80.0%)	39 (83.0%)	91 (81.2%)	0.633
Non-smoker	10 (19.2%)	6 (15.4%)	16 (17.6%)	
Pack Years	42 (80.8%)	33 (84.6%)	75 (82.4%)	
Median (Range)	40 (10-120)	50 (2-120)	42 (2-120)	0.121
Mean (CI: 95%)	43 (36-51)	49 (41-59%)	46 (41-52)	
TNM stages				
T				0.93
1	11 (16.9%)	6 (12.8%)	17 (15.2%)	
2	12 (18.5%)	9 (19.1%)	21 (18.8%)	
3	17 (26.2%)	14 (29.8%)	31 (27.7%)	
4	25 (38.5%)	18 (38.3%)	43 (38.4%)	
N				0.595
0	10 (15.4%)	12 (25.5%)	22 (19.6%)	
1	9 (13.8%)	6 (12.8%)	15 (13.4%)	
2	24 (36.9%)	14 (29.8%)	38 (33.9%)	
3	22(33.8%)	15 (31.9%)	37 (33.0%)	
M				**0.019**
0	19 (29.2%)	24 (51.1%)	43 (38.4%)	
1	46 (70.8%)	23 (48.9%)	69 (61.6%)	
Initial IASLC/UICC stages				0.094
I	3 (4.6%)	4 (8.5%)	7 (6.3%)	
II	2 (3.1%)	5 (10.6%)	7 (6.3%)	
III	14 (21.5%)	15 (31.9%)	29 (25.9%)	
IV	46 (70.8%)	23 (48.9%)	69 (61.6%)	
Histology				**<0.001**
ADC	55(84.6%)	0	55(49.1)	
SCC	0	47(100%)	47(42.0%)	

LCNEC	4(6.2%)	0	4(3.6%)	
NOS	3(4.6%)	0	3(2.7%)	
Others	3(4.6%)	0	3(2.7%)	
PD-L1 expression (TPS)				
Unknown	6 (9.2%)	3 (6.4%)	9 (8.0%)	
Known	59 (90.8)	44 (93.6%)	103 (92%)	0.772
0%	20 (33.9%)	12 (27.3%)	32 (31.1%)	
1-49%	22 (37.3%)	18 (40.9%)	40 (38.8%)	
≥50%	17 (28.8%)	14 (31.8%)	31 (30.1%)	
Mean (CI: 95%)	24.1 (17.1-31.9)	28.3 (19.6-37.1)	25.9 (20.4-31.8)	0.39
Systemic Therapy				
Induction cycles				
Median (range)	3 (1-26)	3 (1-14)	3 (1-26)	0.785
Maintenance cycles				0.217
No	46 (70.8%)	28 (59.6%)	74 (66.1%)	
Yes	19 (29.2%)	19 (40.4%)	38 (33.9%)	
Median (range)	5 (1-12)	4 (1-23)	4.5 (1-23)	0.908
Dose reduction of docetaxel				
Unknown	24 (36.9%)	8 (17.0%)	32 (28.6%)	
Known	41 (63.1%)	39 (83.0%)	80 (71.4%)	0.214
No	20 (48.8%)	17 (43.6%)	37 (46.3%)	
Yes (primary)	14 (34.1%)	9 (23.1%)	23 (28.7%)	
Yes (secondary)	7 (17.1%)	13 (33.3%)	20 (25.0%)	
G-CSF administration				
Unknown	28 (43.1%)	10 (21.3%)	38 (33.9%)	
Known	37 (56.9%)	37 (78.7%)	74 (66.1%)	0.485
No	19 (51.4%)	16 (43.2%)	35 (47.3%)	
Yes	18 (48.6%)	21 (56.8%)	39 (52.7%)	
PD-1-/PD-L1-antibody				**0.031**
Atezolizumab	14 (21.5%)	6 (12.8%)	20 (17.9%)	
Durvalumab	3 (4.6%)	8 (17.0%)	11 (9.8%)	
Nivolumab	10 (15.4%)	14 (29.8%)	24 (21.4%)	
Pembrolizumab	33 (50.8%)	18 (38.3%)	51 (45.5%)	
Others	5 (7.7%)	1 (2.1%)	6 (5.4%)	
Lines of therapy				0.261
2	27 (41.5%)	15 (31.9%)	42 (37.5%)	
3	29 (44.6%)	20 (42.6%)	49 (43.8%)	
4 and further lines	9 (13.8%)	12(25.5%)	21 (18.8%)	
Median (range)	3(2-7)	3(2-5)	3(2-7)	0.149

Response status				0.821
Unknown	15 (23.1)	10 (21.3)	25 (22.3)	
Known	50 (76.9%)	37 (78.7%)	87 (77.7%)	0.418
CR	0	0	0	0
PR	24 (48.0%)	23 (62.2%)	47 (54.0%)	
SD	16 (32.0%)	9 (24.3%)	25 (28.7%)	
PD	10 (20.0%)	5 (13.5%)	15 (17.2%)	
Progression status				0.5
No	36 (55.4%)	23 (48.9%)	59 (52.7%)	
Yes	29 (44.6%)	24 (51.1%)	53 (47.3%)	
PFS in months				
Median (CI: 95%)	7.6 (6.4-8.8)	7.4 (5.9-9.0)	7.6 (6.7-8.5)	0.847
PFS rate				
1-year-PFS	26.1% (11.7-43.1%)	18.6% (6.2-36.1%)	22.4% (12.2-24.4%)	
Survival status				0.374
Death	51 (78.5%)	40 (85.1%)	91 (81.3%)	
Alive	14 (21.5%)	7 (14.9%)	21 (18.8%)	
OS in months				
Median (CI: 95%)	6.9 (4.9-8.7)	7.6 (2.9-12.3)	6.9 (3.7-10.0)	0.673
OS rate				
1-year-OS	35.1% (23.0-47.4%)	31.7% (18.7-45.6%)	33.8% (24.3-43.0%)	

Suppl. Table 1: Comparison of clinicopathological factors between metastatic non-small cell lung cancer patients receiving only docetaxel plus ramucirumab after chemoimmunotherapy (subgroup). ADC: Adenocarcinoma, CR: Complete Response, IASLC: International Association for the Study of Lung Cancer, LCNEC: Large Cell Neuroendocrine carcinoma, NOS: Not Otherwise Specified carcinoma, OTH: Others, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SCC: Squamous Cell Carcinoma, SD: Stable Disease, and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

Treatment Effectiveness

ORR was assessable in 141 patients (81.5%), but 7 patients (11.5%) with D+N and 25 patients (22.3%) with D+R discontinued therapy before radiographic assessment of response, but the difference was not statistically significant (p=0.079) Partial response (PR) occurred in 52.5%, stable disease (SD) in 32.6% and progressive disease (PD) in 14.9% of the assessable patients (table 1). There were no differences between the treatment groups (p=0.369, table 1). In the subgroup of adenocarcinoma patients, a trend towards a higher percentage of patients without a radiographic assessment of response in the D+R treated patients (25.5%) compared to the D+N treated patients (11.7%) were observed, but the ORRs between D+N and D+R did not differ (table 2, p=0.673). In the subgroup of patients treated with D+R (Suppl. table 1), ORRs did not differ significantly between non-squamous and squamous cell carcinoma patients (p=0.418).

Variable	Docetaxel + Nintedanib	Docetaxel + Ramucirumab	total	p-value
Numbers	60	55	115	
Age in years				
Mean (CI: 95%)	62.1 (59.7-64.6)	66.5 (64.4-68.5)	64.2 (62.5-65.9)	**0.007**
Median (Range)	61 (38-81)	67 (51-83)	64 (38-83)	
<65	36 (60.0%)	24 (43.6%)	60 (52.2%)	0.079
≥65	24 (40.0%)	31 (56.4%)	55 (47.8%)	
Gender				**0.036**
Female	24 (40.0%)	12 (21.8%)	36 (31.3%)	
Male	36 (60.0%)	43 (78.2%)	79 (68.7%)	
Smoking status				
Unknown	2 (3.3%)	9 (16.4%)	11 (9.6%)	
Known	58 (96.7%)	46 (83.6%)	104 (90.4%)	0.672
Non-smoker	12 (20.7%)	8 (17.4%)	20 (19.2%)	
Pack Years	46 (79.3%)	38 (82.6%)	84 (80.8%)	
Median (Range)	37 (5-170)	40 (10-120)	40 (5-170)	0.13
Mean (CI: 95%)	40 (32-51)	46 (39-54)	43 (37-50)	
TNM stages				
T				0.686
1	8 (13.3%)	10 (18.2%)	18 (15.7%)	
2	10 (16.7%)	9 (16.4%)	19 (16.5%)	
3	13 (21.7%)	15 (27.3%)	28 (24.3%)	
4	29 (48.3%)	21 (38.2%)	50 (43.5%)	
N				0.4
0	12 (20.0%)	6 (10.9%)	18 (15.7%)	
1	13 (21.7%)	9 (16.4%)	22 (19.1%)	
2	18 (30.0%)	22 (40.0%)	40 (34.8%)	
3	17 (28.3%)	18 (32.7%)	35 (30.4%)	
M				0.782
0	15 (25.0%)	15 (27.3%)	30 (26.1%)	
1	45 (75.0%)	40 (72.7%)	85 (73.9%)	
Initial IASLC/UICC stages				0.635
I	3 (5.0%)	1 (1.8%)	4 (3.5%)	
II	3 (5.0%)	2 (3.6%)	5 (4.3%)	
III	9 (15.0%)	12 (21.8%)	21 (18.3%)	
IV	45 (75.0%)	40 (72.7%)	85 (73.9%)	
PD-L1 expression (TPS)				
Unknown	4 (6.7%)	5 (9.1%)	9 (7.8%)	
Known	56 (93.3%)	55 (90.9%)	106 (92.2%)	**0.01**
0%	32 (57.1%)	15 (30.0%)	47 (44.3%)	
1-49%	16 (28.6%)	18 (36.0%)	34 (32.1%)	
≥50%	8 (14.3%)	17(34.0%)	25 (23.6%)	

Mean (CI: 95%)	15.0 (7.9-22.2)	27.1 (18.8-35.3)	20.8 (15.2-26.4)	**0.008**
Systemic Therapy				
Induction cycles				
Median(range)	6 (1-24)	3 (1-14)	4 (1-24)	**0.002**
Maintenance cycles				0.296
No	37 (61.7%)	39 (70.9%)	76 (66.1%)	
Yes	23 (38.3%)	16 (29.1%)	39 (33.9%)	
Median (range)	4.5 (1-88)	4.5 (1-12)	4.5 (1-88)	0.672
Dose reduction of docetaxel				
Unknown	2 (3.3%)	22 (40.0%)	24 (20.9%)	
Known	58 (96.7%)	33 (60.0%)	91 (79.1%)	**0.003**
No	43 (74.1%)	15 (45.5%)	58 (63.7%)	
Yes (primary)	5 (8.6%)	12 (36.4%)	17 (18.7%)	
Yes (secondary)	10 (17.2%)	6 (18.2%)	16 (17.6%)	
G-CSF administration				
Unknown	4 (6.7%)	25 (45.5%)	29 (25.2%)	
Known	56 (93.3%)	30 (54.5%)	86 (74.8%)	0.752
No	30 (53.6%)	15 (50.0%)	45 (52.3%)	
Yes	26 (46.4%)	15 (50.0%)	41 (47.7%)	
PD-1-/PD-L1-antibody				**0.006**
Atezolizumab	21 (35.0)	10 (18.2)	31 (27.0)	
Durvalumab	7 (11.7)	1 (1.8)	8 (7.0)	
Nivolumab	11 (18.3)	9 (16.4)	20 (17.4)	
Pembrolizumab	21 (35.0)	31 (56.4)	52 (45.2)	
Others	0	4 (7.3)	4 (3.5)	
Lines of therapy				0.879
2	27 (45.0%)	23 (41.8%)	50 (43.5%)	
3	27 (45.0%)	25 (45.5%)	52 (45.2%)	
4 and further lines	6 (10.0%)	7 (12.7%)	13 (11.3%)	
Median (range)	3 (2-5)	3 (2-7)	3 (2-7)	0.644
Response status				0.056
Unknown	7 (11.7%)	14 (25.5%)	21 (18.3%)	
Known	53 (88.3 %)	41 (74.5%)	94 (81.7%)	0.673
CR	0	0	0	
PR	27 (50.9%)	21 (51.2%)	48 (51.1%)	
SD	20 (37.7%)	13 (31.7%)	33 (35.1%)	
PD	6 (11.3%)	7 (17.1%)	13 (13.8%)	
Progression status				**0.008**
No	19 (31.7%)	31 (56.4%)	50 (43.5%)	
Yes	41 (68.3%)	24 (43.6%)	65 (56.5%)	
PFS in months				0.721
Median (CI: 95%)	6.3 (4.7-7.9)	7.6 (6.2-9.0)	6.9 (6.0-7.7)	

PFS rate				
1-year-PFS	21.0% (10.2-34.3%)	26.1% (10.5-45.0%)	23.8% (13.6-33.9%)	
Survival status				0.522
Death	45 (75.0%)	44 (80.0%)	89 (77.4%)	
Alive	15 (25.0%)	11 (20.0%)	26 (22.6%)	
OS in months				
Median (CI: 95%)	8.8 (5.3-12.4)	6.9 (5.1-8.6)	7.2 (4.6-9.9)	0.297
OS rate				
1-year-OS	40.3% (27.4-52.8%)	34.9% (21.8-48.2%)	37.8% (28.0-47.0%)	

Table 2: Comparison of clinicopathological factors between metastatic pulmonary adenocarcinoma patients receiving docetaxel plus nintedanib or docetaxel plus ramucirumab after chemoimmunotherapy (subgroup). CR: Complete Response, IASLC: International Association for the Study of Lung Cancer, NOS: Not Otherwise Specified carcinoma, OTH: Others, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SD: Stable Disease, and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

Median PFS of the entire cohort was 7.2 months and median OS was 7.3 months (figure 1A/B). In contrast, in the subgroup of patients with D+N or D+R as second-line therapy PFS and OS were 6.8 months (95%-CI: 6.1-7.0) and 6.9 months (95%-CI: 3.4-9.7), while they were 8.7 months (95%-CI: 6.2-11.1) and 9.9 months (95%-CI: 4.9-14.8), respectively, in the subgroup of third-line patients.

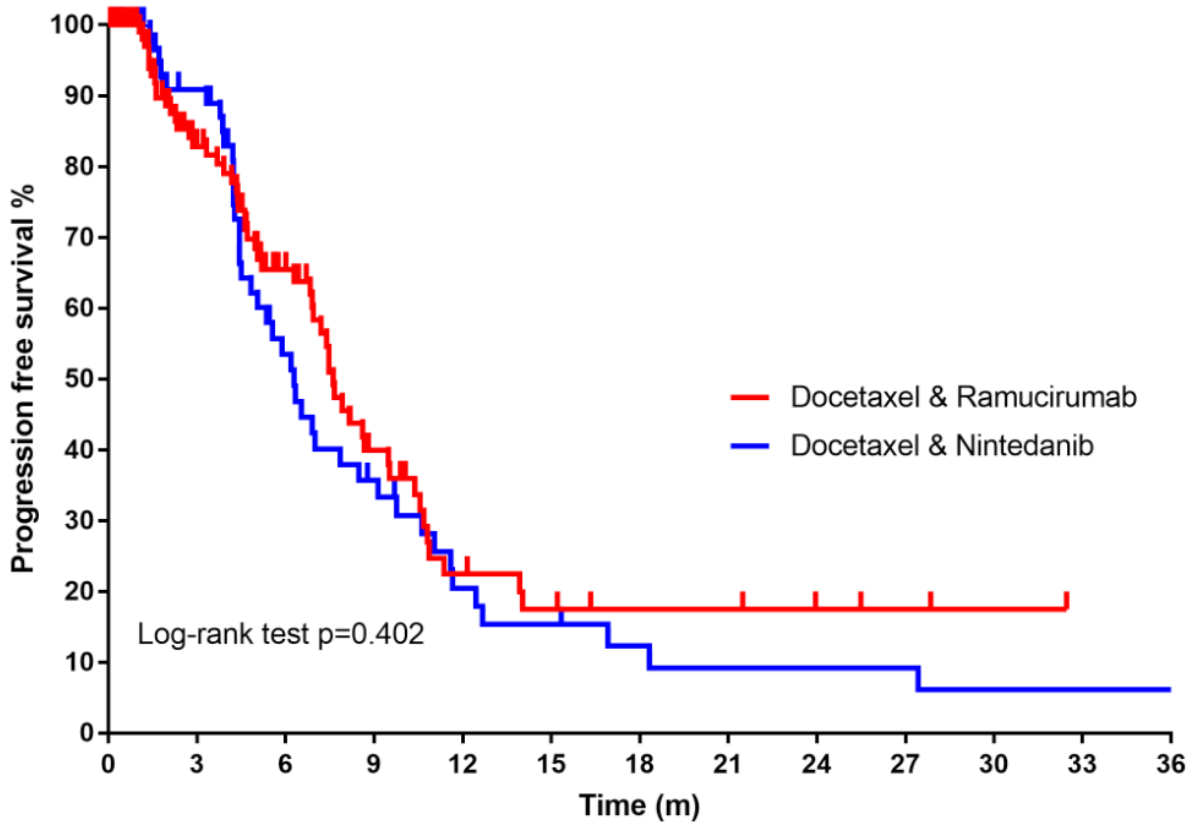


Figure 1A: Progression-free survival (PFS) of metastatic NSCLC patients receiving either docetaxel plus nintedanib or docetaxel plus ramucirumab after previous simultaneous or sequential chemoimmunotherapy.

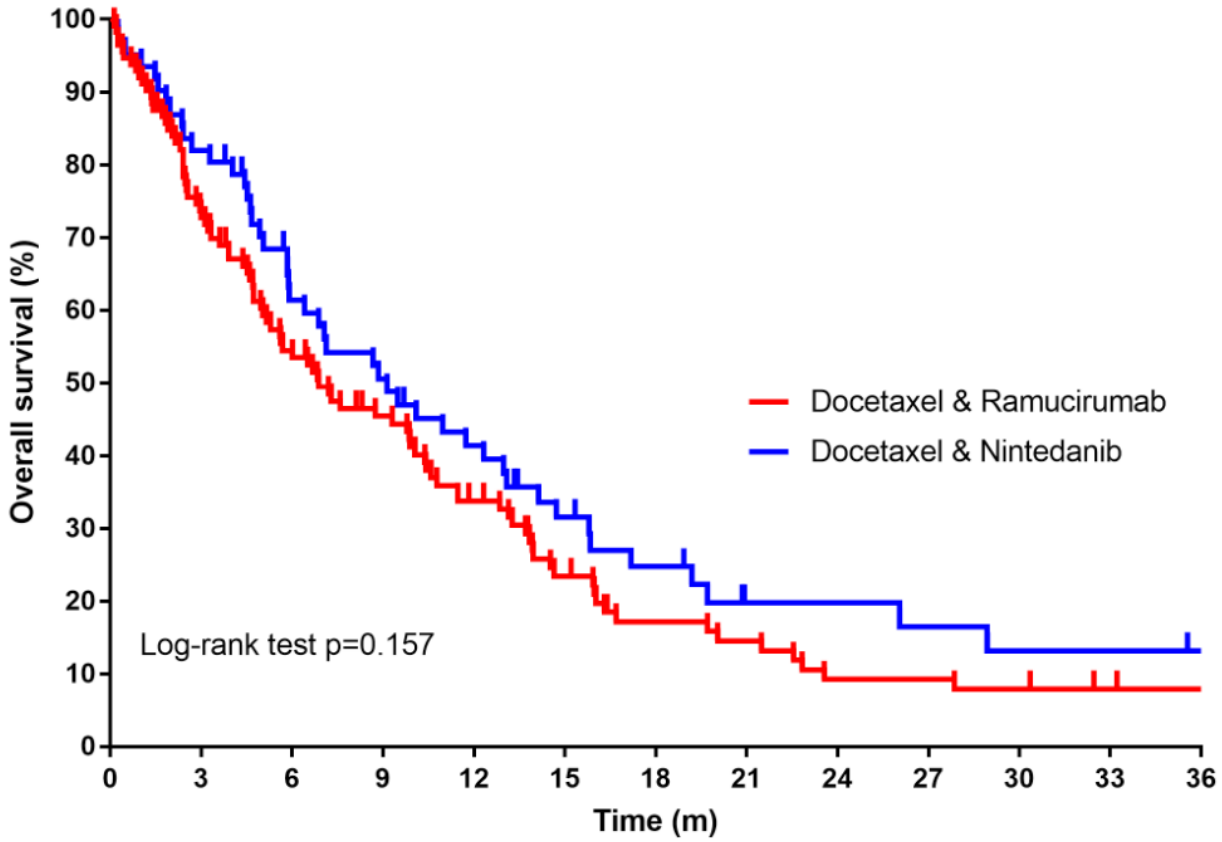


Figure 1B: Overall survival (OS) of metastatic NSCLC patients receiving either docetaxel plus nintedanib or docetaxel plus ramucirumab after previous simultaneous or sequential chemoimmunotherapy.

Patients with primary dose reduction of docetaxel (p=0.010), with stable disease (p=0.034) or progressive disease (p<0.001) as response and with a previous pembrolizumab therapy (p=0.014) resulted in a worse PFS (table 3) in the multivariate analysis. Median PFS was increased (7.6 months versus 6.3 months, p=0.002) in the D+R cohort compared to the D+N cohort, although there was no significant difference in the univariate analysis (p=0.402). Furthermore, a younger age (<65 years, p<0.001) and a higher number of induction therapy cycles (=3, p=0.047) led to an OS prolongation (table 4) in the multivariate analysis. But stable disease (p=0.002) or progressive disease as response (p<0.001) or an unknown response status resulted in a worse OS (table 4) in the multivariate analysis.

Variable	Median PFS in months	Hazard Ratio (CI 95%)	p-value
	7.2		
Antiangiogenic agent			
Ramucirumab	7.6	1 (ref.)	
Nintedanib	6.3	2.28 (1.35-3.84)	**0.002**
Age			
<65	7.6	1(ref.)	
≥65	6.8	1.21(0.74-1.99)	0.444
Gender			
Female	6.3	1 (ref.)	

Male	7.6	0.81(0.50-1.33)	0.411
Smoking status			
Non-smoker	5.9	1 (ref.)	
Smoker	7.2	0.90 (0.46-1.75)	0.748
Unknown	8.6	1.62 (0.64-4.10)	0.304
IASLC Stadium			
I-II	8.6	1 (ref.)	
III-IV	7.2	1.32 (0.62-2.77)	0.47
Histology			
Non-SCC	6.9	1 (ref.)	
SCC	7.5	0.88 (0.49-1.58)	0.663
PD-L1 expression (TPS)			
0%	7.4	1 (ref.)	
1-49%	7	1.24 (0.66-2.32)	0.506
≥ 50%	7.2	1.49 (0.66-3.37)	0.336
Unknown	6.5	1.36 (0.50-3.74)	0.548
Systemic therapy			
Induction cycles			
1-4	5.5	1 (ref.)	
>4	9.5	0.61 (0.35-1.04)	0.071
Maintenance cycles			
No	6.9	1 (ref.)	
Yes	7.6	1.12 (0.64-1.94)	0.695
Dose reduction of docetaxel			
No	6.8	1 (ref.)	
Yes (primary)	5.3	2.49(1.24-4.99)	**0.01**
Yes (secondary)	7.6	1.14 (0.62-2.10)	0.673
Unknown	7.6	-	-
G-CSF administration			
No	6.9	1 (ref.)	
Yes	6.9	0.62 (0.66-2.06)	0.06
Unknown	8.1	-	-
PD-1-/PD-L1 antibody			
Atezolizumab	6.8	1 (ref.)	
Durvalumab	10.5	0.90 (0.34-2.39)	0.84
Nivolumab	10.6	0.76 (0.38-1.53)	0.445
Pembrolizumab	6.2	2.08 (1.16-3.73)	**0.014**
Others	3.7	1.63 (0.48-5.49)	0.431
Lines of therapy			

<3	6.8	1 (ref.)	
≥3	7.9	0.76 (0.46-1.27)	0.303
Response status			
PR	7.9	1 (ref.)	
SD	7.6	1.73 (1.04-2.89)	**0.034**
PD	1.8	85.3 (4.78-20.3)	**<0.001**
NA	10.5	3.79 (1.09-13.2)	0.036

Table 3: Multivariate logistic regression analysis by choosing progression-free survival (PFS) as the terminal point variable. IASLC: International Association for the Study of Lung Cancer, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SD: Stable Disease and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

Variable	**Median OS in months**	**Hazard Ratio (CI 95%)**	**p-value**
	7.3		
Antiangiogenic agent			
Ramucirumab	6.9	1 (ref.)	
Nintedanib	9.1	1.23 (0.73-2.08)	0.433
Age			
<65	10.8	1 (ref.)	
≥65	5.9	2.24 (1.54-3.28)	**<0.001**
Gender			
Female	7.2	1 (ref.)	
Male	8.7	0.77 (0.53-1.14)	0.2
Smoking status			
Non-smoker	5.9	1 (ref.)	
Smoker	8.7	0.96 (0.53-1.74)	0.899
Unknown	6.5	0.78 (0.36-1.69)	0.525
IASLC Stadium			
I-II	8.8	1 (ref.)	
III-IV	7.2	1.03 (0.55-1.93)	0.917
Histology			
Non-SCC	7.3	1 (ref.)	
SCC	7.6	1.10 (0.73-1.65)	0.639
PD-L1 expression (TPS)			
0%	9.9	1 (ref.)	
1-49%	7.6	0.92 (0.56-1.51)	0.739
≥ 50%	6.9	0.83 (0.48-1.42)	0.499
Unknown	9.5	1.72 (0.79-3.74)	0.171
Systemic therapy			
Induction cycles			
1-4	4.6	1 (ref.)	

>4	13.8	0.72 (0.48-1.09)	0.119
Maintenance cycles			
No	5.1	1 (ref.)	
Yes	11.5	0.70 (0.46-1.09)	0.115
Dose reduction of docetaxel			
No	6	1 (ref.)	
Yes (primary)	7.2	1.19 (0.74-1.92)	0.475
Yes (secondary)	10.8	0.84 (0.50-1.40)	0.497
Unknown	9.5	-	-
G-CSF administration			
No	8.7	1 (ref.)	
Yes	6.8	0.89 (0.57-1.40)	0.617
Unknown	9.5	0.69 (0.29-1.68)	0.417
PD-1-/PD-L1 antibody			
Atezolizumab	8.7	1(ref.)	
Durvalumab	5.6	1.10 (0.54-2.23)	0.79
Nivolumab	13.8	0.72 (0.39-1.32)	0.284
Pembrolizumab	5.9	1.07 (0.68-1.67)	0.77
Others	2.3	1.80 (0.66-4.89)	0.248
Lines of therapy			
<3	6.9	1 (ref.)	
≥3	8.8	0.68 (0.47-0.99)	**0.047**
Response status			
PR	11	1 (ref.)	
SD	13	1.02 (0.65-1.59)	**0.002**
PD	3.6	5.01 (2.82-8.90)	**<0.001**
NA	1.4	10.8 (6.22-18.7)	**<0.001**

Table 4: Multivariate logistic regression analysis by choosing overall survival (OS) as the terminal point variable. IASLC: International Association for the Study of Lung Cancer, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SD: Stable Disease and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

In the subgroup of patients with pulmonary adenocarcinoma, median PFS was 6.9 months and median OS was 7.2 months (figure 2A/B). Results of the multivariate analysis for PFS/OS are shown in tables 5/6. Similarly to the entire cohort, patients with primary dose reduction of docetaxel (p=0.007), with stable disease (p=0.002) or progressive disease (p<0.001) as response resulted in a worse PFS (table 5) in the multivariate analysis. Median PFS was only numerically higher (7.6 months versus 6.3 months, p=0.111) in the D+R cohort compared to the D+N cohort.

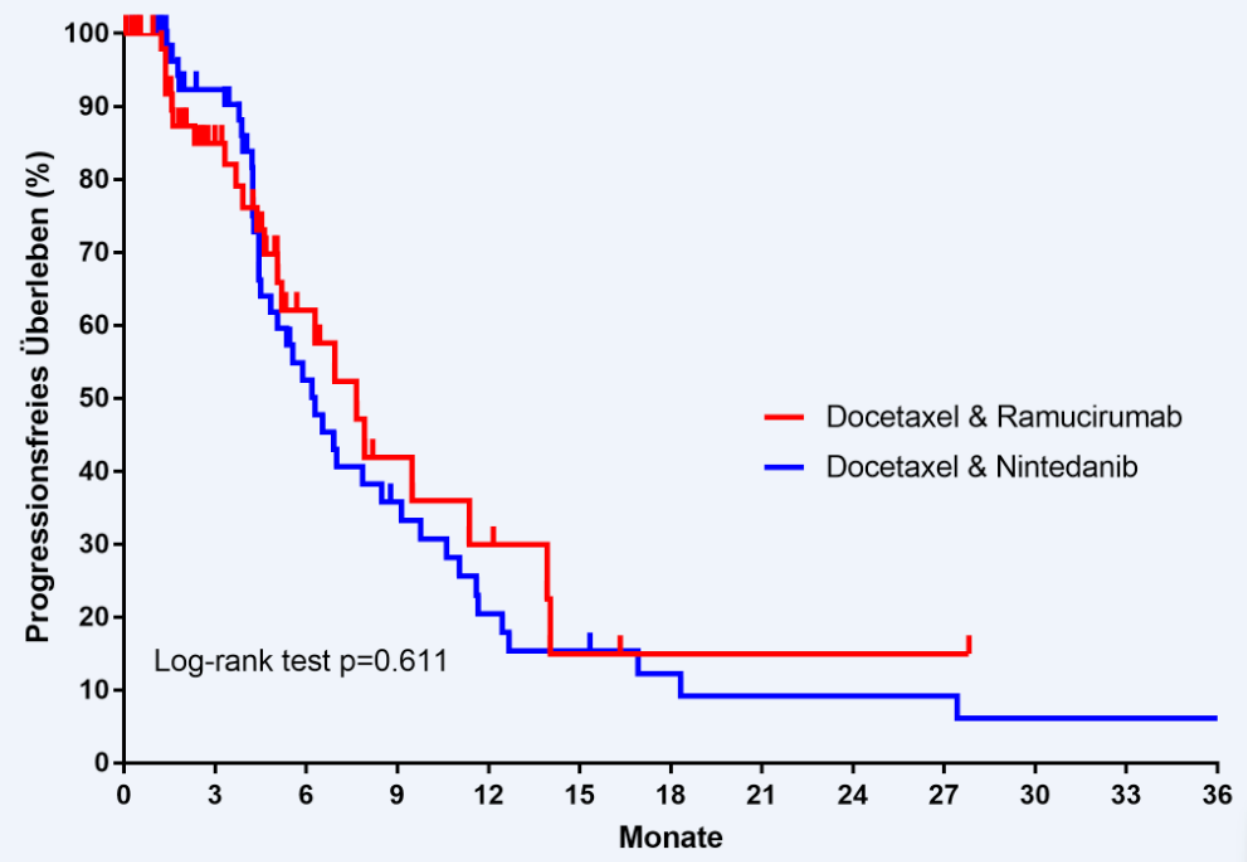


Figure 2A: Progression-free survival (PFS) of metastatic pulmonary adenocarcinoma patients receiving either docetaxel plus nintedanib or docetaxel plus ramucirumab after previous simultaneous or sequential chemoimmunotherapy.

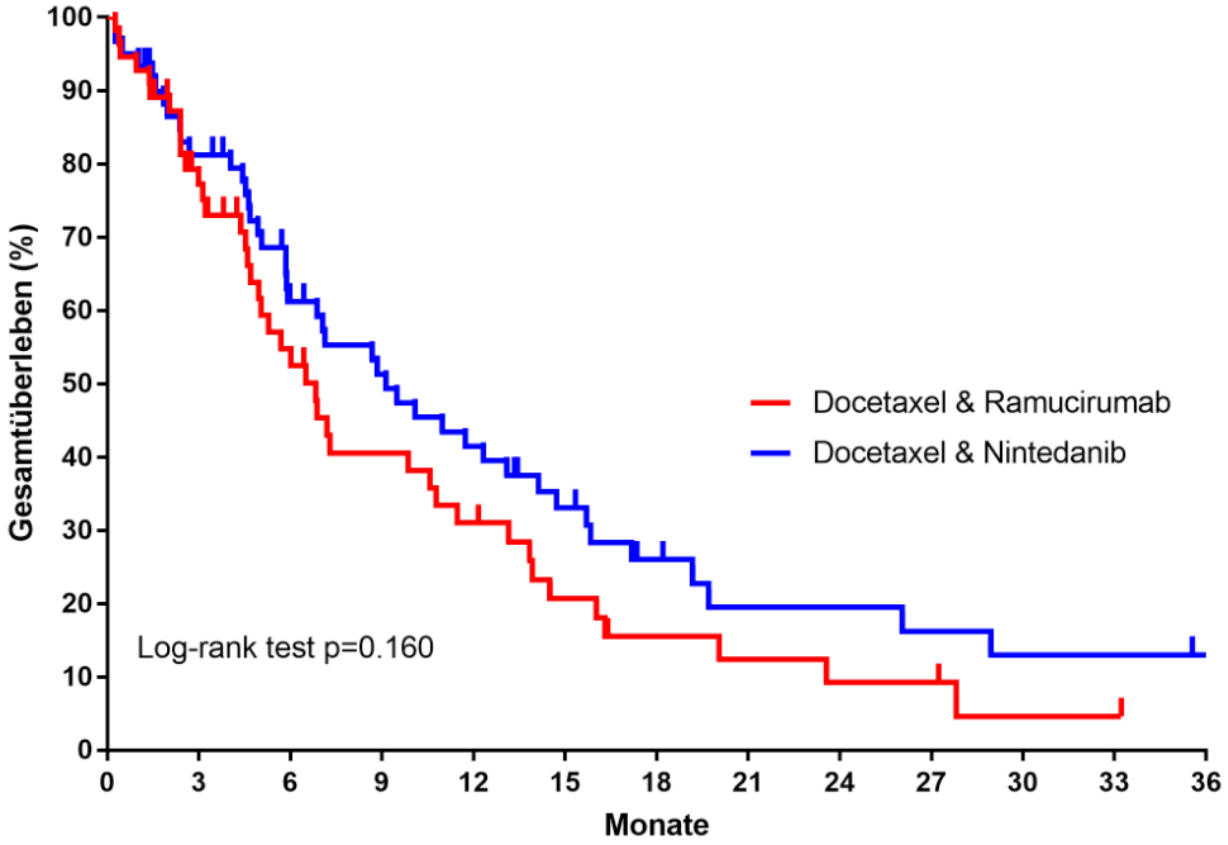


Figure 2B: Overall survival (OS) of metastatic pulmonary adenocarcinoma patients receiving either docetaxel plus nintedanib or docetaxel plus ramucirumab after previous simultaneous or sequential chemoimmunotherapy.

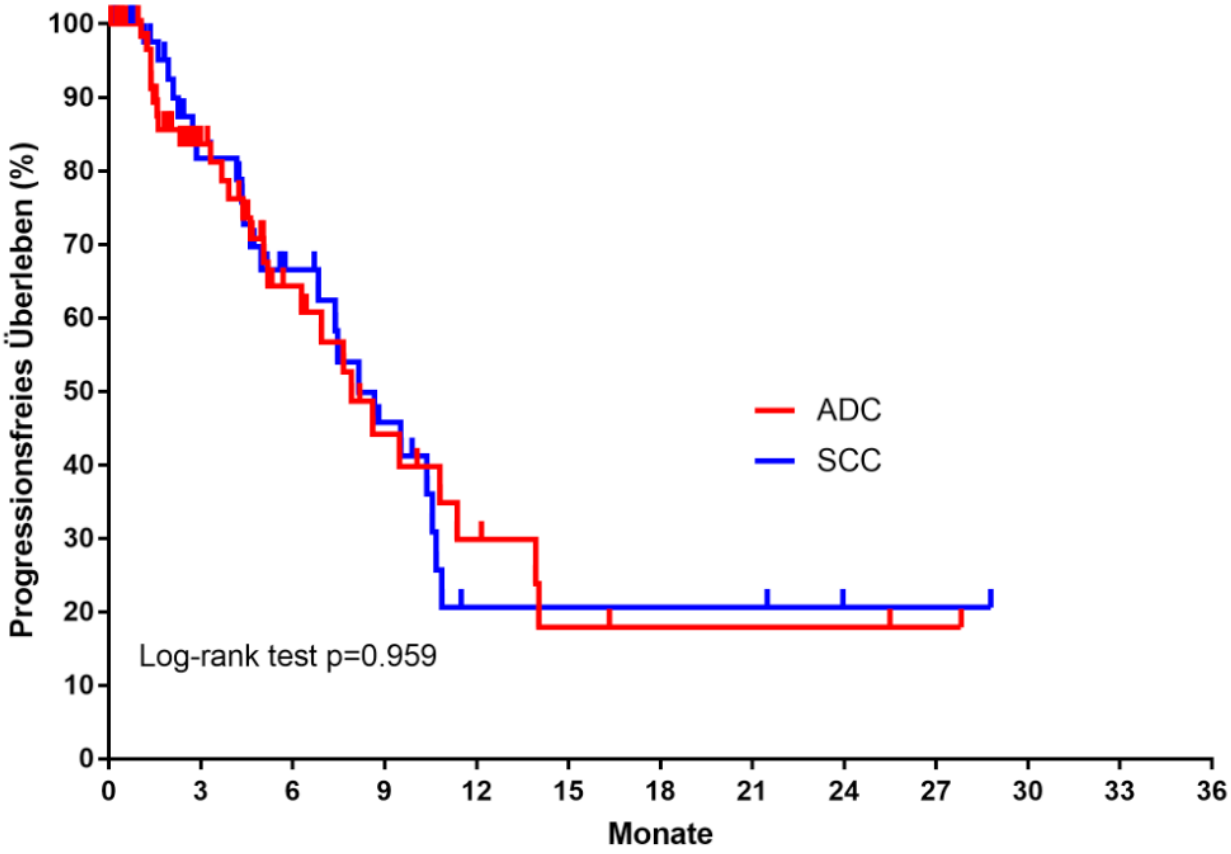
Variable	Median PFS in months	Hazard Ratio (CI 95%)	p-value
	6.9		
Antiangiogenic agent			
Ramucirumab	7.6	1 (ref.)	
Nintedanib	6.3	1.74 (0.88-3.44)	0.111
Age			
<65	7	1 (ref.)	
≥65	6.2	1.20 (0.60-2.43)	0.604
Gender			
Female	6.3	1 (ref.)	
Male	7	0.91 (0.43-1.91)	0.795
Smoking status			
Non-smoker	5.9	1 (ref.)	
Smoker	6.9	1.17 (0.53-2.58)	0.7
Unknown	5.1	3.23 (0.83-12.5)	0.09
IASLC Stadium			

I-II	12.7	1 (ref.)	
III-IV	6.9	1.63 (0.54-4.98)	0.387
PD-L1 expression (TPS)			
0%	6.3	1 (ref.)	
1-49%	7	1.45 (0.69-3.04)	0.328
≥ 50%	6.9	1.06 (0.39-2.84)	0.912
Unknown	6.5	2.05 (0.62-6.84)	0.241
Systemic therapy			
Induction cycles			
1-4	5.5	1 (ref.)	
>4	7.9	0.75 (0.38-1.49)	0.414
Maintenance cycles			
No	5.2	1 (ref.)	
Yes	7	0.96 (0.46-2.03)	0.922
Dose reduction of docetaxel			
No	7	1 (ref.)	
Yes (primary)	4.4	3.24 (1.38-7.64)	**0.007**
Yes (secondary)	7.9	1.24 (0.58-2.64)	0.574
Unknown	6.9	-	-
G-CSF administration			
No	6.9	1 (ref.)	
Yes	4.8	0.64 (0.34-1.21)	0.17
Unknown	7.6	-	-
PD-1-/PD-L1 antibody			
Atezolizumab	7.8	1 (ref.)	
Durvalumab	6.9	1.45 (0.69-3.04)	0.328
Nivolumab	13.9	1.06 (0.39-2.84)	0.912
Pembrolizumab	5.2	2.05 (0.62-6.84)	0.241
Others	9.5	0.76 (0.36-1.62)	0.482
Lines of therapy			
<3	6.9	1 (ref.)	
≥3	6.5	0.75 (0.38-1.49)	0.42
Response status			
PR	7.9	1 (ref.)	
SD	7.2	2.95 (1.51-5.75)	**0.002**
PD	1.6	208 (43-1022)	**<0.001**
NA	-	-	-

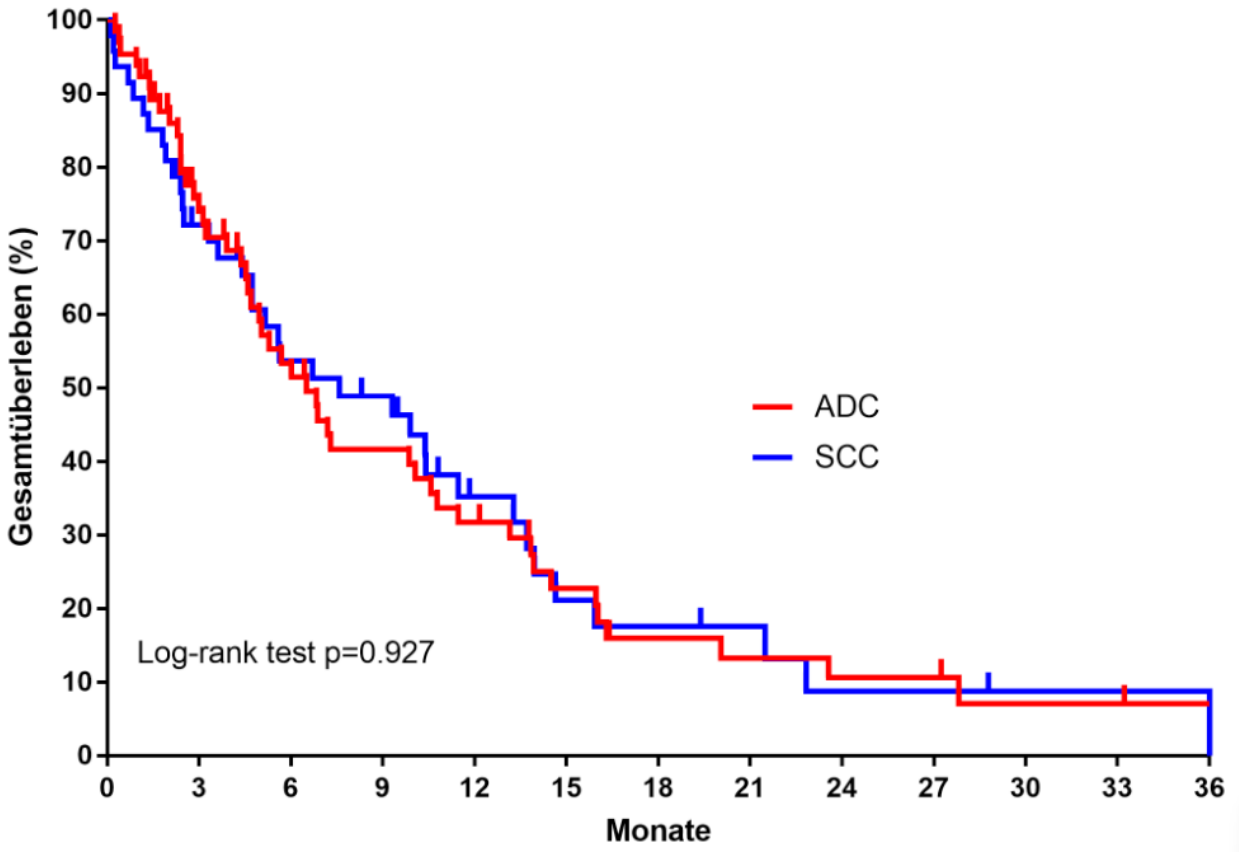
Table 5: Multivariate logistic regression analysis by choosing progression-free survival (PFS) as the terminal point variable in the subgroup of patients with pulmonary adenocarcinoma. IASLC: International Association for the Study of Lung Cancer, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SD: Stable Disease and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

Furthermore, a higher age (=65 years, p<0.001), an unknown smoking status (p=0.043) and progressive disease as response (p<0.001) or an unknown response (p<0.001) status led to a reduced OS (table 6) in the multivariate analysis.

In the subgroup of patients receiving only D+R, median PFS of NSCLC patients with a pulmonary squamous cell carcinoma was 7.4 months and median OS 7.6 months (Suppl. figure 1A/B), while it was 7.6 months and 6.8 months for non-squamous cell carcinoma patients. However, there were significant differences between the treatment groups (suppl. table 2 and 3) in the multivariate analysis. A higher number of induction cycles were associated with a prolonged PFS (>4, p=0.014), whereas progressive disease during treatment wit D+R worsened PFS (p<0.001). OS was reduced in elderly patients (= 65 years, p=0.001) and in patients with either progressive disease (p<0.001) or an unknown response status (p<0.001), but it was improved in patients with the PD-1-inhibitor nivolumab (p=0.030).



Suppl. Figure 1A: Progression-free survival (PFS) of metastatic NSCLC patients who received only docetaxel plus ramucirumab after previous simultaneous or sequential chemoimmunotherapy.



Suppl. Figure 1B: Overall survival (OS) of metastatic NSCLC patients who received only docetaxel plus ramucirumab after previous simultaneous or sequential chemoimmunotherapy.

Variable	Median OS in months	Hazard Ratio (CI 95%)	p-value
	7.2		
Antiangiogenic agent			
Ramucirumab	6.9	1 (ref.)	
Nintedanib	8.8	1.18 (1.60-2.31)	0.628
Age			
<65	12.3	1 (ref.)	
≥65	5.9	2.38 (1.50-3.79)	**<0.001**
Gender			
Female	8.7	1 (ref.)	
Male	6.9	1.04 (0.59-1.82)	0.888
Smoking status			
Non-smoker	11.3	1 (ref.)	
Smoker	7.2	1.18 (0.63-2.22)	0.604
Unknown	10.8	0.33 (0.11-0.96)	**0.043**

IASLC Stadium			
I-II	9.1	1 (ref.)	
III-IV	7.1	0.89 (0.34-2.34)	0.817
PD-L1 expression (TPS)			
0%	7.3	1 (ref.)	
1-49%	8.7	0.74 (0.40-1.39)	0.353
≥ 50%	6.9	0.56 (0.28-1.12)	0.103
Unknown	9.5	2.14 (0.82-5.53)	0.118
Systemic therapy			
Induction cycles			
1-4	4.6	1 (ref.)	
>4	13.8	0.75 (0.43-1.30)	0.3
Maintenance cycles			
No	5.3	1 (ref.)	
Yes	12.3	0.91 (0.51-1.64)	0.758
Dose reduction of docetaxel			
No	6.9	1 (ref.)	
Yes (primary)	5.7	1.62 (0.86-3.05)	0.134
Yes (secondary)	10.8	0.67 (0.33-1.38)	0.28
Unknown	13.1	0.66 (0.32-1.35)	0.255
G-CSF administration			
No	8.6	1 (ref.)	
Yes	6.8	0.67 (0.37-1.21)	0.185
Unknown	12.8	0.37 (0.11-1.19)	0.096
PD-1-/PD-L1 antibody			
Atezolizumab	10.8	1(ref.)	
Durvalumab	5	1.67 (0.68-4.08)	0.259
Nivolumab	16.3	0.48 (0.22-1.01)	0.055
Pembrolizumab	5.8	1.19 (0.69-2.05)	0.521
Others	5.3	1.15 (0.34-3.93)	0.82
Lines of therapy			
<3	6.9	1 (ref.)	
≥3	9.5	0.92 (0.52-1.63)	0.78
Response status			
PR	12.3	1 (ref.)	

SD	10.6	1.12 (0.65-1.93)	0.667
PD	4.7	4.84 (2.30-10.2)	**<0.001**
NA	1.6	21.6 (9.29-50.3)	**<0.001**

Table 6: Multivariate logistic regression analysis by choosing overall survival (OS) as the terminal point variable in the subgroup of patients with pulmonary adenocarcinoma. IASLC: International Association for the Study of Lung Cancer, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SD: Stable Disease and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

Variable	**Median PFS in months**	**Hazard Ratio (CI 95%)**	**p-value**
n	7.6		
Histology			
Non-squamous carcinoma	7.6	1 (ref.)	
Squamous cell carcinoma	7.4	1.08 (0.52-2.25)	0.831
Age			
<65	7.4	1 (ref.)	
≥65	7.6	0.81 (0.36-1.86)	0.626
Gender			
Female	6.3	1 (ref.)	
Male	8.6	0.71 (0.36-1.39)	0.317
Smoking status			
Non-smoker	6.8	1 (ref.)	
Smoker	7.6	0.86 (0.27-2.72)	0.794
Unknown	8.6	1.37 (0.40-4.88)	0.618
IASLC Stadium			
I-II	8.6	1 (ref.)	
III-IV	7.6	1.13 (0.38-3.38)	0.829
PD-L1 expression (TPS)			
0%	7.6	1 (ref.)	
1-49%	9.5	0.96 (0.43-2.16)	0.923
≥ 50%	7.2	2.14 (0.84-5.43)	0.109
Unknown	8.6	2.09 (0.50-8.81)	0.313
Systemic therapy			
Induction cycles			
1-4	6.3	1 (ref.)	
>4	10.7	0.44 (0.23-0.85)	**0.014**
Maintenance cycles			
No	7.4	1 (ref.)	
Yes	8.6	1.21 (0.59-2.46)	0.606
Dose reduction of docetaxel			
No	6.8	1 (ref.)	

Yes (primary)	7.4	1.23 (0.53-2.84)	0.632
Yes (secondary)	7.9	0.70 (0.30-1.66)	0.418
Unknown	7.6	1.42 (0.67-2.98)	0.357
G-CSF administration			
No	7.4	1 (ref.)	
Yes	8.6	0.67 (0.30-1.47)	0.321
Unknown	7.6	0.21 (0.02-1.98)	0.175
PD-1-/PD-L1 antibody			
Atezolizumab	6.8	1 (ref.)	
Durvalumab	10.7	0.78 (0.14-4.46)	0.781
Nivolumab	10.9	1.25 (0.35-4.49)	0.735
Pembrolizumab	6.9	1.81 (0.67-4.90)	0.245
Others	3.7	1.37 (0.29-6.40)	0.685
Lines of therapy			
<3	6.8	1 (ref.)	
≥3	8.1	0.60 (0.32-1.10)	0.097
Response status			
PR	7.9	1 (ref.)	
SD	9.5	0.89 (0.43-1.85)	0.767
PD	1.9	45.8 (12.8-163)	**<0.001**
NA	10.5	2.21	0.16

Suppl. Table 2: Multivariate logistic regression analysis by choosing progression-free survival (PFS) as the terminal point variable in the subgroup of patients who received only docetaxel plus ramucirumab. IASLC: International Association for the Study of Lung Cancer, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SD: Stable Disease and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

Variable	Median OS in months	Hazard Ratio (CI 95%)	p-value
n	6.9		
Histology			
Non-squamous carcinoma	6.8	1 (ref.)	
Squamous cell carcinoma	7.6	1.14 (0.73-1.79)	0.553
Age			
<65	10.4	1 (ref.)	
≥65	5.7	2.23 (1.36-3.65)	**0.001**
Gender			
Female	6.7	1 (ref.)	
Male	8.7	0.82 (0.50-1.35)	0.433
Smoking status			
Non-smoker	3.6	1 (ref.)	
Smoker	7.2	0.77 (0.36-1.64)	0.492

Unknown	7.6	0.64 (0.25-1.58)	0.33
IASLC Stadium			
I-II	6.9	1 (ref.)	
III-IV	7.2	0.78 (0.36-1.69)	0.537
PD-L1 expression (TPS)			
0%	9.9	1 (ref.)	
1-49%	6.8	1.02 (0.54-1.89)	0.961
≥ 50%	6.9	0.91 (0.44-1.88)	0.799
Unknown	6.5	2.08 (0.80-5.39)	0.132
Systemic therapy			
Induction cycles			
1-4	4.7	1 (ref.)	
>4	13.7	1.28 (0.68-2.40)	0.436
Maintenance cycles			
No	4.5	1 (ref.)	
Yes	11.4	0.62 (0.33-1.09)	0.093
Dose reduction of docetaxel			
No	5	1 (ref.)	
Yes (primary)	7.3	1.16 (0.64-2.11)	0.63
Yes (secondary)	9.8	0.76 (0.37-1.53)	0.441
Unknown	9.3	0.52 (0.29-0.91)	0.021
G-CSF administration			
No	9.8	1 (ref.)	
Yes	6.7	1.29 (0.70-2.39)	0.407
Unknown	8.7	2.03(0.59-6.98)	0.26
PD-1-/PD-L1 antibody			
Atezolizumab	6	1 (ref.)	
Durvalumab	5.6	0.52 (0.17-1.60)	0.257
Nivolumab	13.8	0.39 (0.16-0.91)	**0.03**
Pembrolizumab	6.9	0.77 (0.40-1.52)	0.457
Others	2.3	1.18 (0.41-3.45)	0.757
Lines of therapy			
<3	5.6	1 (ref.)	
≥3	9.3	0.68 (0.41-1.08)	0.101
Response status			
PR	10.8	1 (ref.)	

SD	13.9	0.86 (0.46-1.62)	0.645
PD	3.6	5.89 (2.79-12.4)	**<0.001**
NA	1.4	7.58 (3.89-14.8)	**<0.001**

Suppl. Table 3: Multivariate logistic regression analysis by choosing overall survival (OS) as the terminal point variable in the subgroup of patients who received only docetaxel plus ramucirumab. IASLC: International Association for the Study of Lung Cancer, PD: Progressive Disease, PD-L1: Programmed Death receptor Ligand 1, PR: Partial Response, SD: Stable Disease and UICC: Union for International Cancer Control, TPS: Tumor Proportion Score.

Treatment Toxicity

In the entire cohort of patients receiving docetaxel, about half of them received GCSF to avoid a clinically relevant decrease in neutrophil count and febrile neutropenia. However, 42.4% of the patients still needed dose reductions of the chemotherapy. A significantly higher percentage of patients treated with D+R had their docetaxel dose reduced (53.7%) compared to patients receiving D+N (27.1%, p=0.003). Similarly, the percentage of adenocarcinoma patients requiring dose reductions of docetaxel differed significantly between D+R and D+N (54.6% vs. 25.8%, p=0.003). Due to the assessment of the treating oncologist, the dose of docetaxel was reduced before the first administration in 5 patients (8.5% of all D+N patients with reduced chemotherapy dose), compared to 23 patients (28.7%) with D+R.

Discussion

To the best of our knowledge, this retrospective study is the first comparison of D+N and D+R in metastatic NSCLC patients after failure of either simultaneous or sequential chemoimmunotherapy. D+N has been approved by the EMA only for pulmonary adenocarcinoma patients, therefore subgroup analysis for pulmonary adenocarcinoma patients was performed.

Regarding the effectiveness of the combinations D+N and D+R, in the comparable subgroup of pulmonary adenocarcinoma patients no significant differences regarding ORR, PFS and OS were found. Compared to the pivotal trials leading to approval of D+N [13] or D+R [14] as second-line treatment after first-line chemotherapy, we observed a higher percentage of responding patients. In the LUME-Lung 1 study, confirmed ORRs in the total cohort and in the subgroup of adenocarcinoma patients were 4.4 % and 4.7%. In the REVEL-study, ORR were 22.5% in the entire cohort and 21.5% in the subgroup of patients with a non-squamous NSCLC. Our results in terms of PR, SD and PD might be biased by the relatively high number of patients discontinuing therapy before the first radiographic evaluation of response, similar to a systemic literature review of prospective and retrospective real world studies evaluating the efficacy of D+R after chemoimmunotherapy [9] Although a significant higher number of patients with docetaxel and ramucirumab received a less dose-intensive chemotherapy regimen, no significant differences in ORRs between D+N and D+R were seen. Due to the clinical assessment of the treating oncologist, the dose of docetaxel was reduced before the first administration in 5 patients (8.5% of all D+N patients with reduced chemotherapy dose), compared to 23 patients (28.7% of all D+R patients with reduced chemotherapy dose) with D+R. It might be speculated that if a higher percentage of Caucasian patients had been treated with the standard dosage of docetaxel (75 mg/m2), results might have been better compared to D+N. In the REVEL study, primary dose reduction of docetaxel to 60 mg/m2 in east Asian patients was allowed, which should be kept in mind, if a comparison between our retrospective study and the REVEL-study is performed.

In the above-mentioned systematic literature review [9], percentages of dose reductions of docetaxel were not reported in accordance with the majority of the assessed pro- and retrospective studies. Only one study reported that in seven out of twenty patients who received D+R as third-line therapy after platinum-based chemotherapy and single-agent nivolumab as second-line treatment, the dose of docetaxel was reduced because of toxicity [32]. In a recently published retrospective investigation of D+N after chemoimmunotherapy, thirteen out of 96 patients (13.5%) required a dose reduction of docetaxel, mainly due to neutropenia and peripheral neuropathy [29]. In the German prospective VARGADO study, the dose reduction of docetaxel was reported in seventeen out of 80 patients (21%) in cohort B (first-line chemotherapy, second-line CPI and third-line D+N) [26] and in eighteen out of 137 (13.1%) patients in cohort C (first-line CPI plus chemotherapy, second-line D+N) [27], respectively.

About half of the patients, regardless of the administered combination (D+N or D+R) received GCSF after the infusion of docetaxel. In a small retrospective study evaluating the benefit of prophylactic PEG-GCSF immediately after infusion of docetaxel and ramucirumab in previously treated NSCLC patients (median of two previous regimens) 29 out of 33 patients did not develop febrile neutropenia, but febrile neutropenia was observed in two of the four patients to whom GCSF were not administered [33]. It might be speculated that stricter endorsement of prophylactic GCSF might have prevented dose reductions of docetaxel,

particularly in patients with D+R therapy.

A higher percentage of patients without any radiographic treatment evaluation after the first cycle of D+N (7 patients (11.5%)) or D+R (25 patients (22.3%)) until their death was found more often in the last mentioned subgroup. This difference might explain why the median PFS and OS times overlap in the entire cohort of patients, particularly in the subgroup of patients treated with D+R. However, OS times are quite similar and they are not biased by lacking radiographic diagnostics.

We found differences in PD-L1 expression levels in the univariate between the subgroups with D+N and D+R therapy, which did neither influence PFS nor OS in the multivariate analysis. However, the PD-L1- expression was measured in pretreatment specimens and during chemoimmunotherapy significant changes might have occurred.

To summarize, combinations of an antiangiogenic agent such as nintedanib or ramucirumab with docetaxel in metastatic NSCLC patients after previous chemoimmunotherapy show rather similar effectiveness in the, to the best of our knowledge, so far largest cohort of metastatic NSCLC patients who received docetaxel plus an antiangiogenic agent after chemoimmunotherapy. Importantly, the optimum docetaxel dosage to reach the highest clinical benefit without putting the patients at an unacceptable high risk of neutropenia leading to early treatment discontinuation in this setting is an unsolved issue.

Statement of Ethics

This retrospective study protocol was reviewed and approved by the institutional review board of the DKG-certified Lung Cancer Center on on July 10, 2019 for analysis of docetaxel plus nintedanib resp. on April 1, 2020 for analysis of docetaxel plus ramucirumab. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the World Medical Association Declaration of Helsinki (as revised in 2013). The need for informed consent of the patients was waived by the above mentioned board.

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Author Contributions

FK and DCC contributed to conception and design of the study.

FK, LG, GN, PBC, AN, WL, HN, CVH, MS and DCC contributed to the acquisition of the data.

FK, AT and DCC contributed to the analysis and interpretation of data.

FK, AT and DCC wrote first draft of the manuscript.

FK, AT, LG, GN, PBC, AN, WL, HN, CVH, MS and DCC contributed to the revision of the manuscript.

All the authors made substantial contributions to this work and approved it for publication.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest Statement: Daniel C. Christoph reports consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, and payment for expert testimony from, and participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Ipsen, Janssen, Merck Sharpe & Dohme, Novartis, Novocure, Pfizer, Roche, Sanofi, and Takeda; and support for attending meetings and/or travel from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Ipsen, Janssen, Chugai, Merck Sharpe & Dohme, Novartis, Pfizer, Roche, Sanofi, and Takeda.

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