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Efficacy of Docetaxel Plus Ramucirumab as Palliative Third-Line Therapy Following Second-Line Immune-Checkpoint-Inhibitor Treatment in Patients With Non-Small-Cell Lung Cancer Stage IV

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ABSTRACT

BACKGROUND: Antiangiogenic agents have been shown to stimulate the immune system and cause synergistic effects with chemotherapy. Effects might be even stronger after immune-checkpoint-inhibitor (ICI) therapy. The purpose of this analysis was to evaluate the efficacy of ramucirumab plus docetaxel (R + D) as third-line treatment after failure of a first-line platinum-based chemotherapy and a second-line ICI treatment in patients with non-small-cell lung cancer (NSCLC) stage IV.

METHODS: Retrospective data were collected from 9 German thoracic oncology centers. Only patients who had received at least 1 cycle of third-line R + D were included. The numbers of cycles, objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) were investigated.

RESULTS: Sixty-seven patients met the criteria for inclusion. Third-line treatment with R + D achieved an ORR of 36% and a disease control rate (DCR) of 69%. Median PFS for third-line therapy was 6.8 months with a duration of response (DOR) of 10.2 months. A median OS of 29 months was observed from the start of first-line therapy with a median OS of 11.0 months from the start of third-line treatment. No unexpected toxicities occurred.

CONCLUSION: R + D is a highly effective and safe third-line treatment after failure of second-line programmed cell death protein 1/programmed cell death-ligand 1 (PD1/PD-L1)-derived ICI therapy irrespective of NSCLC histology. As there may be synergistic effects of second- and third-line treatments, this sequence is a very suitable option for patients not treated with first-line ICI. In addition, R + D should continue to be investigated as a second-line treatment option after failure of chemotherapy plus ICI in the palliative first–line treatment.

KEYWORDS: Lung cancer, palliative treatment, angiogenesis inhibitor, ramucirumab, immune checkpoint inhibitor

Introduction

Immunotherapy has dramatically changed the treatment of metastatic non-small-cell lung cancer (NSCLC) within a very short time and contributed to a clinically relevant improvement in prognosis. Immune checkpoint inhibitors (ICIs), namely antibodies directed against programmed cell death protein 1 (PD-1) or programmed cell death-ligand 1 (PD-L1), were approved for the second- or third-line treatment of metastatic NSCLC in patients without treatable driver mutations in 2015.[1-7] Since then, ICIs have been approved in the first-line

setting, either alone in tumors with PD-L1 ⩾ 50% expression or in combination with chemotherapy independent of the receptor status.[8-13] Some patients treated with ICIs have exceptionally long-lasting responses and survival. For instance, up to 16% of NSCLC patients treated with the PD-1 inhibitor nivolumab in second-line treatement survived 5 years.[14,15]

Therefore, it is important to establish effective third-line therapies after first-line platinum-based chemotherapy and second-line ICI therapy. Antiangiogenic agents, for example, nintedanib and ramucirumab might represent a reasonable treatment option in this situation. Ramucirumab combined with docetaxel has been shown to significantly increase overall survival (OS) in comparison to docetaxel monotherapy as second-line treatment after failure of platinum-based combination chemotherapy in all NSCLC histologies; the combination of nintedanib plus docetaxel in the same setting only in adenocarcinoma histology.[6,16]

In vivo data have suggested possible synergistic effects of ICI and antiangiogenic drugs, finding that antiangiogenic agents stimulate the immune system and, conversely, immunotherapy also has an antiangiogenic action.[17,18] Furthermore, a "chemosensitisation" effect after prior exposure to immunotherapy could be shown.[2,19,20] Unfortunately, there are no published prospective studies on the effect of third-line therapies after ICI in metastatic NSCLC to date. In this situation, real-world data from centers with well-defined treatment sequences can help physicians to make treatment decisions in individual NSCLC patients. For this reason, we retrospectively evaluated the effect of a docetaxel plus ramucirumab (R + D) combination therapy after ICI failure as second-line treatment in patients with a first-line platinum-based combination chemotherapy.

Methods

Design and participating centers

This retrospective analysis documented effects of a palliative third-line treatment with R + D in patients with NSCLC stage IV directly after progression on anti-PD1 or PD-L1 ICI monotherapy. Patients had to have a histologically or cytologically proven NSCLC stage IV according to the eighth edition of the UICC TNM classification and a platinum-containing combination therapy as palliative first-line treatment with or without maintenance therapy. In order to assess third-line therapy in a relatively homogeneous cohort, we excluded patients treated with first-line chemo-immune-therapy. Patients treated with adjuvant chemotherapy more than 1 year before first-line palliative therapy were included. In addition, palliative radiation was allowed and documented. Patients harboring a nonsquamous histology must have been tested for estimated glomerular filtration rate (EGFR) mutations and ALK translocations, and those with treatable molecular alterations within these loci were excluded.

Data were collected from 9 German, high-volume centers with specialization in thoracic oncology and distinct experience in chemo- and immune-oncology therapy. The centers included 3 university hospitals, 3 community-based hospitals, 2 private hospitals, and 1 outpatient clinic. Patients were treated with palliative first-line chemotherapy between March 2013 and September 2018, and started third-line R + D no later than February 2019. This allowed for a follow-up of at least 6 months before data cutoff on August 1, 2019. Data were recorded by each center in a standardized manner using an excel template with the following data being collected for each patient: age, sex, smoking habits, tumor stage, histology, PD-L1 expression by immunohistochemistry, height and weight at diagnosis, date of NSCLC diagnosis, survival status at time point of documentation (alive or deceased), and date of last contact/death. For each treatment line, the following details of therapy were documented: date of start, number of treatment cycles, best response, date of progression, and reason for treatment stop. In addition, regarding third-line therapy, the following parameters were documented: weight at start of therapy, cycles of combination and monotherapy (either docetaxel or ramucirumab) and side effects (according to common toxicity criteria [CTC] grades 3 and 4).

Filled data sheets from every center were anonymized before transfer to the organizing center (university of Nuremberg) and compiled for further assessment and statistics. In addition, data were checked for completeness and plausibility. Patients with monochemotherapy or chemo-immuno-therapy in the first-line setting were excluded. The institutional ethics committee of the Paracelsus Medical University Nuremberg approved this analysis (IRB-2019-014). The requirement for written informed consent was waived because of the retrospective nature of the study.

Evaluation and statistics

The primary endpoint was efficacy of the R + D third-line therapy in terms of progression-free survival (PFS). Secondary endpoints were duration of response (DOR) in patients responding to R + D as well as OS from start of third-line therapy. In addition, response to first- and second-line treatment, time interval between start of second-line and start of third-line therapy and the relation between response of ICI and R + D were evaluated.

Tumor responses were evaluated by each center using performing chest computer tomography (CT) and abdominal ultrasound or other clinically relevant abdominal imaging at least every 3 months or at the time of clinical deterioration. Tumor responses were evaluated according to the RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1.[21] Responses based on target (and nontarget) lesions were defined as follows: complete response (CR), disappearance of all target (and nontarget) lesions, partial response (PR), ⩾30% reduction

Table 1. Patients' demographics.

PATIENTS' CHARACTERISTICS	N	(%)	PATIENTS' CHARACTERISTICS CONTINUED	N	(%)
Median age (range)	61.7	(43-82)	Programmed death (PD)-L1 expression status		
≥65 years	28	(42)	Negative	15	(22)
			1%-49%	17	(25)
Gender			≥50%	8	(12)
Male	46	(69)	N.R.	27	(40)
Female	21	(31)			
			BMI at diagnosis		
ECOG PS			<25	33	(49)
0	16	(24)	≥25	34	(51)
1	45	(67)			
2	2	(3)	BMI at start of third line		
N.R.	4	(6)	<25	26	(39)
			≥25	41	(61)
Stage at start of first-line chemotherapy					
IV A	24	(36)			
IV B	43	(64)	Palliative radiation therapy		
			No radiation	16	(24)
Histology			One organ	43	(64)
Adenocarinoma	39	(58)	Multiple organs	4	(6)
Squamous cell carcinoma	24	(36)	N.R.	4	(6)
Not otherwise specified or other type	4	(6)			

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; N.R., not reported.

in size (or disappearance of ≥1 nontarget lesions), stable disease (SD), <30% decrease or <20% increase in size (or the persistence of ≥1 nontarget lesions), and progressive disease (PD), ≥20% increase in size (or the appearance of new nontarget lesions and/or progression of existing nontarget lesions). The objective response rate (ORR) was defined as the proportion of patients with CR and PR recorded from the initiation of treatment until disease progression or recurrence, confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met.

Overall survival was recorded from the first day of first-line palliative treatment with a platinum-containing regimen to the date of death or last follow-up. Progression-free survival was defined for third-line therapy as the interval from the first day of drug to the first sign of disease progression or death whichever occurs first. For first- and second-line treatment intervals starting from the first day of drug to the first day of drug from the further therapy were reported.

Statistics

Descriptive data were presented as median and interquartile range (IQR), categorical variables were presented using numbers and frequencies. To analyze PFS and OS, times to events were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards models evaluating several patient factors were used. All data were calculated using SPSS (version 23). A *P* value < .05 was considered statistically significant.

Results

Patient population

After excluding 9 patients (8 patients with chemo-immunotherapy first line; 1 patient with monotherapy first line) 67 patients from 9 centers met the inclusion criteria for this retrospective analysis. The baseline demographics and essential tumor information are listed in Table 1. The median age was

Table 2. Drugs and drug combinations used in different lines of treatment.

FIRST-LINE THERAPY, (N=67)	N (%)	SECOND-LINE THERAPY, (N=67)	N (%)	THIRD-LINE THERAPY (N=67)	N (%)	FOURTH-LINE THERAPY, (N=17)	N (%)
Cisplatin/pemetrexed	13 (19.4)	Nivolumab	49 (73.1)	Docetaxel/ ramucirumab	67 (100)	Erlotinib	5 (29.4)
Carboplatin/gemcitabine	12 (17.9)	Pembrolizumab	7 (10.4)			Afatinib	3 (17.6)
Carboplatin/pemetrexed	12 (17.9)	Atezolizumab	9 (13.4)			Vinorelbin	3 (17.6)
Cisplatin/vinorelbine	10 (14.9)	Durvalumab	2 (2.9)			Carboplatin/gemcitabine	3 (17.6)
Platinum/pemetrexed/ bevacizumab	9 (13.4)					Carboplatin/vinorelbine	1 (5.8)
Carboplatin/(nab)paclitaxel	9 (13.4)					Carboplatin/pemetrexed	1 (5.8)
Carboplatin/vinorelbine	2 (2.9)					Gemcitabine/vinorelbine	1 (5.8)
Carboplatin based	38 (57)	PD-1 ICI	56 (84)			TKI	8 (47)
Cisplatin based	29 (43)	PD-L1 ICI	11 (16)			Combination chemotherapy	6 (35)
						Monotherapy	3 (18)

Abbreviations: ICI, immune checkpoint inhibitor; PD, progressive disease; TKI, tyrosine kinase inhibitor.

62 years (range 43-82), with 69% of the patients being male. Most patients had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 1 (71%) and 49% had a body mass index (BMI) before starting therapy of less than 25, respectively. Programmed cell death-ligand 1 immunohistochemistry expression was available for 60% with 12% having a tumor proportion score of ≥50%. Thirty-eight patients (57%) received carboplatin-based chemotherapy as first-line therapy. Second-line therapy consisted of a PD-1 or PD-L1 ICI, with nivolumab given in 73% of the cases. Third-line therapy consisted of R + D with at least one cycle of therapy had to be applied as a combination therapy. Fourth-line therapy was given in 25% with an EGFR tyrosine kinase inhibitor (TKI) in 47% of those treated patients. Details of chemotherapy regimen for first-, third-, and fourth-line and ICI therapy, for second line are presented in Table 2.

Efficacy of R + D

The median number of treatment cycles with R + D was 5 (IQR 3-9) with a median number of 4 cycles (IQR 2-4) given as a combination treatment. Number of cycles of second and third line (third line divided into combination and ramucirumab monotherapy) were plotted in patients with response to R + D (Figure 1). Twelve patients (18%) were still on treatment at the date of data cutoff. Overall, therapy with R + D led to an ORR of 36% and a disease control rate (DCR) of 69%. More patients achieved measurable response to third line as to second line with 11% having a response to both lines (Figure 2). The median PFS for third-line therapy was 6.8 months (95% confidence interval [CI] 4.6-9.0) with a DOR time of 10.2 months (95% CI 9.3-11.1). There was no difference in PFS between patients with squamous or nonsquamous tumor histology receiving R + D (Figure 3). The median OS from starting with third-line therapy was 11 months (95% CI 7.1-14.9). A median OS of 29 months (95% CI 25.4-32.8) was observed from the start of first-line palliative treatment (Figure 4A and B). None of the clinical factors documented was of significant prognostic value for response to second- or third-line therapy or OS. In particular, BMI, documented and analyzed twice before start of first-line treatment and immediately before third-line therapy was not associated with outcome. During treatment with docetaxel/ramucirumab, there was no unexpected toxicity documented. Reported common toxicitiy criteria (CTC) grade 3/4 toxicities were neutropenia, diarrhea, stomatitis, and haematothorax in 8, 7, 4, and 1 cases, respectively. However, it is likely that side effects were underreported in this cohort, as data collection was retrospective.

Outcome of first- and second-line treatment

Response to first-line chemotherapy was present in 54% of the patients with a mean time interval to second-line treatment of 9.1 months (95% CI 7.8-10.4). A median number of 4 cycles (IQR 4-6) was given during this time. The choice of cisplatin or carboplatin did not appear to affect OS. Subsequent treatment was an ICI as second line. Patients recieved a median of 8 cycles (IQR 3-9) of ICI. The overall response rate and DCR were 24% and 46%, respectively. The mean time interval from start of second-line to start of
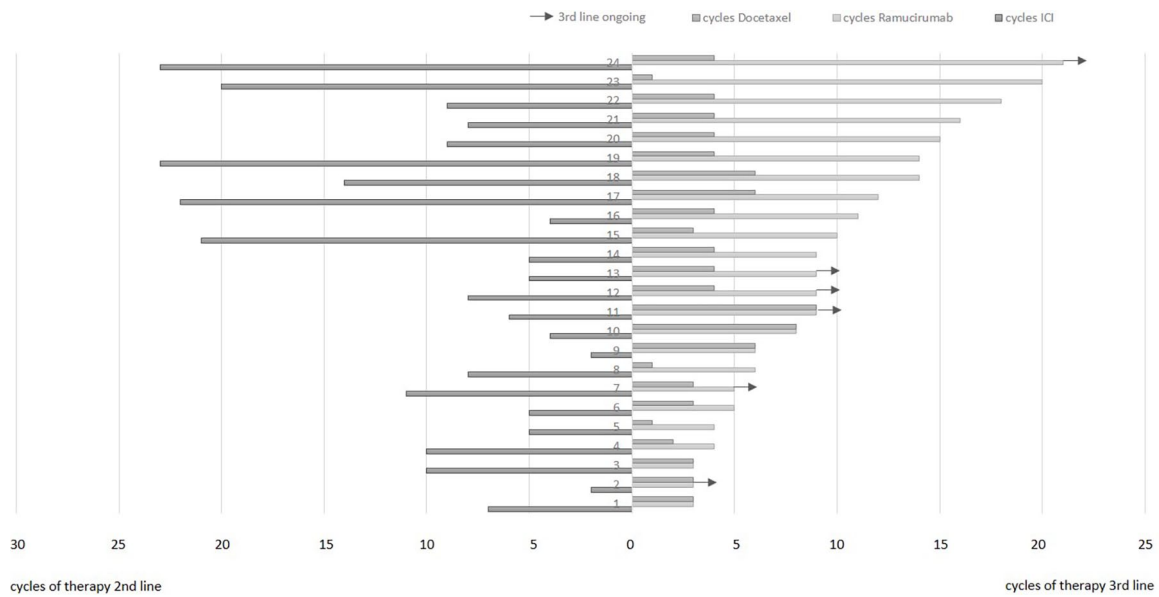
Figure 1. Treatment duration in cycles of therapy for second- and third-line therapy.
Only patients responding to third-line treatment are listed. Third-line therapy is divided into docetaxel (upper line) and ramucirumab (lower line) as combination therapy could be maintained as monotherapy. Arrow: alive and on treatment as of database lock. ICI indicate immune checkpoint inhibitor.
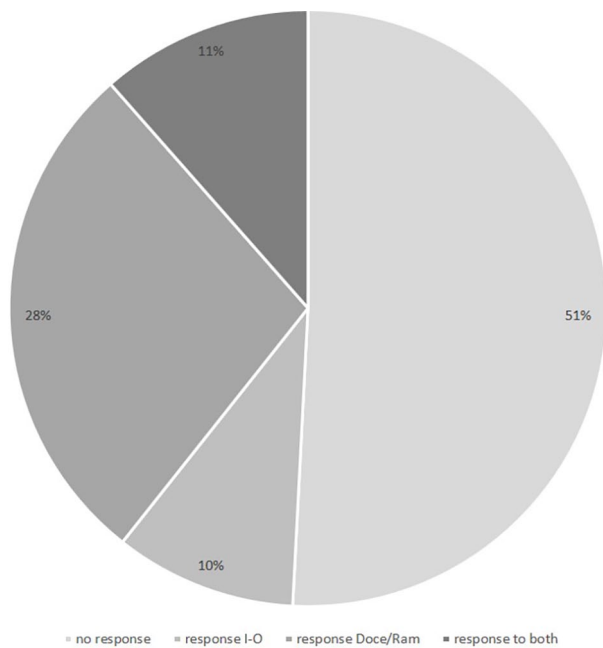

Figure 2. Response to second and third line therapy.

third-line treatment was 7.4 months (95% CI 5.9-8.9; details are presented in Table 3). There was no significant association between PD-L1 status and time on ICI treatment. However, PD-L1 immunohistochemistry was not performed in 40% of the patients. Radiation therapy had no significant influence on first- or second-line response or outcome.

Discussion

To our knowledge, this is the largest Caucasian cohort studied so far with a specific sequence consisting of first-line platinum-based combination chemotherapy followed by ICI in second line and R + D in third line. Using data from daily practice, we were able to demonstrate that this sequence is not only feasible in clinical routine but also highly effective. R + D in this third-line setting seems to be even more effective than in second line when comparing these real-world data with data from the phase III REVEL study.[16] While this registration trial showed a median PFS of 4.5 months for this combination, our cohort showed a median PFS of 6.8 months and a DOR of 10.2 months. A similar observation has previously been demonstrated in a small retrospective analysis by Harada et al.[18] This group reported a median PFS of 5.7 months with a sequence of ICI followed by R + D in contrast to 2.3 months with R + D followed by ICI ($P = 0.020$). Our data are also in line with another small study from Japan reporting a median PFS of 5.9 months using R + D after ICI.[22] Very recently, 2 studies from Japan performed a propensity score weighted analysis of R + D after ICI treatment in NSCLC patients to investigate the effect of this sequence in comparison to a control group without PD-1/PD-L1-directed therapy.[23,24] While Kato et al described a benefit for the ICI pretreated cohort in terms of ORR, but not for outcome parameters, Tozuka et al in contrast showed a significant increase in PFS, 5.9 months versus 2.8 months (in the control group); $P = 0.03$, and a trend toward an improved OS for the ICI pretreated cohort. Further details of all mentioned R + D third-line studies are presented in Table 4.

Furthermore, there are data from studies combining bevacizumab or nintedanib, other antiangiogenic drugs, directed against vascular endothelial growth factor (VEGF) alone (bevacizumab) or VEGF, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF; nintedanib), with paclitaxel or docetaxel in third line after second-line ICI. Bilger et al[25] recently presented retrospective data from the AVATAX trial
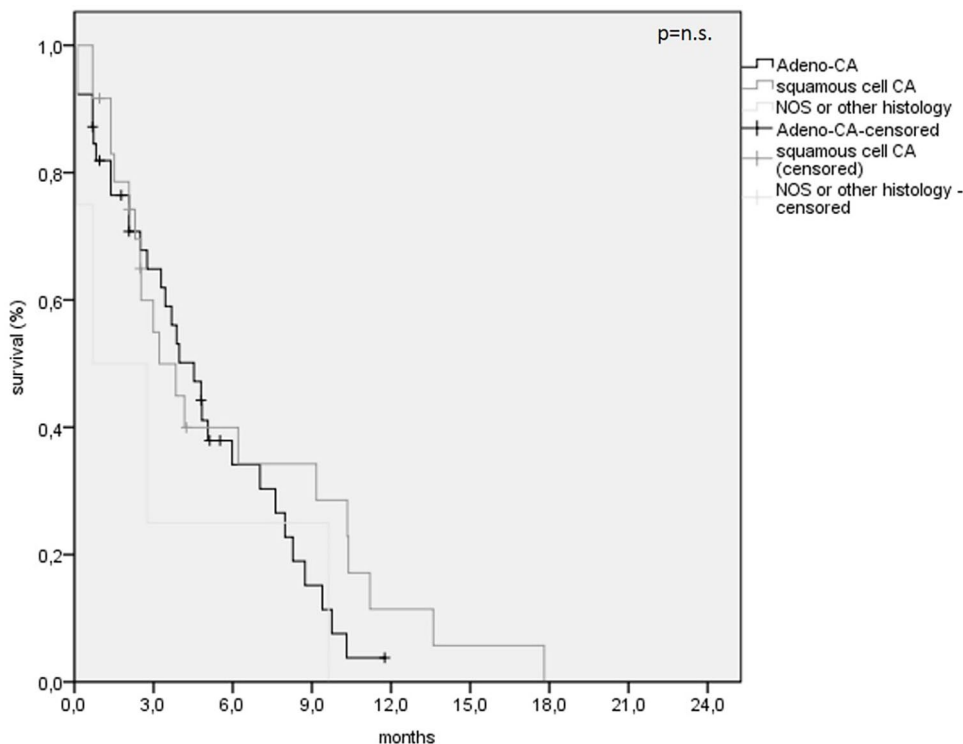
Figure 3. Kaplan-Meier curve for PFS.
There was no significant difference for different NSCLC histologies. n.s. indicates nonsignificant; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; CA, carcinoma.
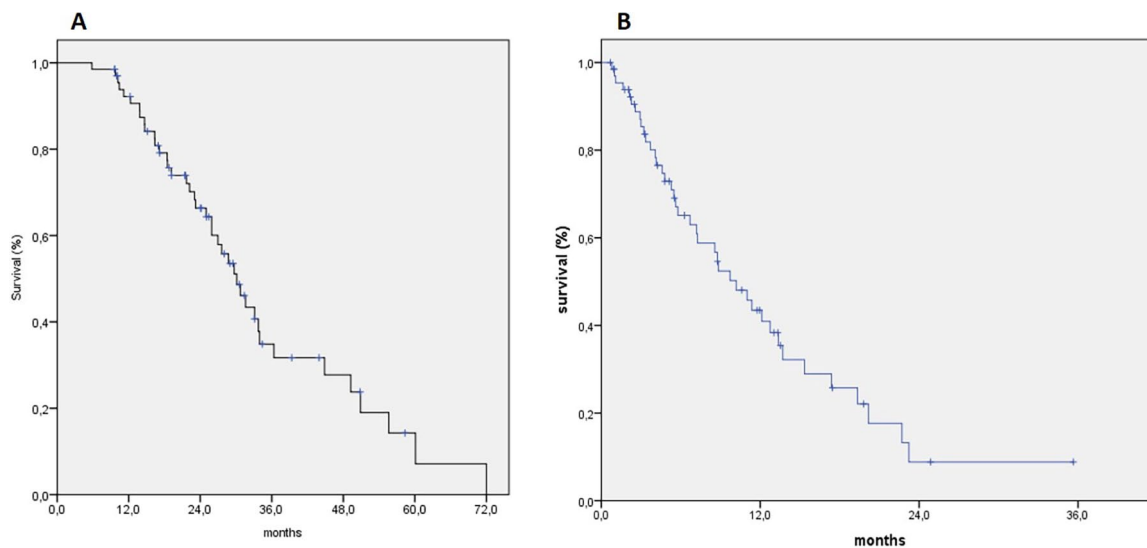

Figure 4. Kaplan-Meier curves for OS: (A) OS from start of first line therapy and (B) OS from start of third line therapy.
OS indicates overall survival.

combining bevacizumab and paclitaxel. Patients receiving the combination in third-line treatment received an ORR of 42% and a PFS of 6.2 months. In addition, there are some published data with nintedanib combinations. While Corral et al showed a median PFS of 3.2 months in 11 patients, Grohe et al very recently published preliminary data from 35 NSCLC patients receiving third-line nintedanib plus docetaxel combination after second-line ICI and reported a median PFS of 7.2 months[2,26] (Table 4). These data for third-line therapy with nintedanib plus docetaxel after second-line ICI are again better

than the results of second-line treatment with nintedanib plus docetaxel in the pivotal trial of this combination with a median PFS of 3.4 months.[6] This superior effect of an antiangiogenic chemotherapy combination in third line versus second line is thought to result from a synergistic interaction with the ICI treatment in second line after progress to the first-line platinum-based chemotherapy.

Antiangiogenic drugs seem to stimulate the immune system and, in turn, ICI agents might have antiangiogenic effects.[27] Although these synergistic interactions are still not understood

Table 3. Efficacy data in different lines of treatment.

	FIRST LINE N=67	SECOND LINE N=67	THIRD LINE N=67	FOURTH LINE N=17
Number of cycles; median (IQR)	4 (4-6)	8 (4-13)	5 (3-9)	
			4 (2-4) as combination	
RR; N (%)				
CR	1 (2)			1 (6)
PR	35 (52)	16 (24)	24 (36)	2 (12)
SD	16 (24)	15 (22)	22 (33)	3 (18)
PD	14 (21)	36 (54)	15 (22)	6 (36)
N.R.	1 (2)		6 (9)	5 (29)
Time to next therapy; mean (95% CI)	9.1 (7.8-10.4)	7.4 (5.9-8.9)		–
PFS; median (95% CI)	N.D.	N.D.	6.8 (4.6-9.0)	–
DOR; median (95% CI)	N.D.	N.D.	10.2 (9.3-11.1)	
OS from, months; median (95% CI)	29.0 (25.4-32.8)	20.0 (15.1-24.9)	11.0 (7.1-14.9)	–

Abbreviations: CI, confidence interval; CR, control rate; DOR, duration of response; IQR, interquartile range; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RR, response rate; SD, stable disease.

Table 4. First chemotherapy/second ICI/third R + D or nintedanib + D strategies reported in the literature (selection of cases from the published studies treated by this sequence).

AUTHORS	DOCETAXEL/NINTEDANIB		DOCETAXEL/RAMUCIRUMAB				
	CORRAL ET AL[2]	GROHE ET AL[26]	KATO ET AL[23]	HARADA ET AL[18]	YOSHIMURA ET AL[22]	TOZUKA ET AL[24]	THIS STUDY
N	11	25	77	18	40	25	67
Histology (%)							
Adenocarcinoma	100	100	79	72	N.R.	88	56
Squamous cell carcinoma	–	–	16	28	N.R.	4	36
Others			5			8	
RR/DCR (%)							
Second line	18/45	21/35	14/N.R.	N.R.	N.R.	N.R.	24/46
Third line	36/82	45/80	20/68	38/83	21/71	N.R.	36/69
PFS third line (mos)	3.2	7.2	4.6	5.7	5.9	5.9	6.8
mOS (mos)							
From start of first line	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	29
From start of second line	12.4	N.R.	N.R.	N.R.	N.R.	20	20
From start of third line	7.7	N.R.	12	13.8	12.2	N.R.	11

Abbreviations: DCR, disease control rate; ICI, immune checkpoint inhibitor; N.R., not reported; OS, overall survival; PFS, progression-free survival; RR, response rate.

in details, the inhibition of dendritic cell maturation, the reduction of T-cell tumor infiltration, and the promotion of inhibitory cells in the tumor microenvironment (TME) seem to be the most relevant mechanisms of VEGF-mediated immunosuppression.[18,27] Antiangiogenic agents might not only antagonize these VEGF-driven effects but also affect tumor blood

vessels by reducing their size and length in the tumor and promoting vessel maturation leading to a better drug penetration of chemotherapy and ICI substances.[28-30] By improving the perfusion and oxygenation in the TME, the tumor infiltration by immune cells may be increased.[29,31] Moreover, as the ICI agent nivolumab binds to the PD-1 receptor for up to 2 months after the last infusion of the drug, synergistic effects with subsequent cytotoxic and antiangiogenic treatments seem likely and might have led to the striking effects of the third-line treatment of our study.[32]

With this in mind, it might be even more effective to combine the 2 therapeutic principles simultaneously. In a preclinical model of lung cancer, a PD-L1 antibody in combination with a vascular endothelial growth factor receptor 2 (VEGFR-2) antibody has been demonstrated to downregulate the expression of PD-1 and PD-L1, increase tumor-infiltrating leucocytes (TILs), and inhibit tumor growth by reducing regulatory T-cells.[29] There are also some clinical data which corroborate these in-vitro effects. Herbst et al[33] very recently published data from a phase Ia/b trial combining pembrolizumab and ramucirumab in second line and demonstrated a striking 12-month PFS of 43% for the NSCLC subcohort. There are also supporting data from ImPower 150, a phase-III trial combining 2 chemotherapeutical compounds (carboplatin and paclitaxel), anti-PD-L1-derived ICI therapy (atezolizumab) and anti-VEGF-derived antiangiogenesis (bevacicumab) in first line for metastatic NSCLC.[10] In direct comparison to chemotherapy plus antiangiogensis, the addition of atezolizumab significantly increased mPFS and mOS by 1.5 and 4.8 months, respectively.

Some potential limitations of our study must be addressed. This was a retrospective study, and some underreporting of potential side effects may have occurred. Since severe side effects are usually well documented during clinical routine, underreporting may have mostly affected the documentation of those side effects not explicitly documented in routine care. Furthermore, there may have been some unreported selection bias, since patients who have been considered unfit for third-line therapy were not included. As only patients who survived first- and second-line treatment were included, the reported median OS of 29 months from start of first-line treatment is bolstered by approximately 18 months of survival during early treatment lines. In this study patient's response to treatment was evaluated by criteria used during routine care in the participating centers and not in a predefined standardized way by independent investigators. Thus, some variability between the centers may be assumed, which may affect PFS but not OS data.

In addition, as there were no patients treated with docetaxel monotherapy in third line after progress to ICI second line, the additional effect from ramucirumab could not be assessed in this cohort. In a small retrospective study, Park et al[19] reported about 38 patients treated with a taxane-based monochemotherapy after ICI receiving an ORR of 47.4%. However, in this trial, there was no significant difference in terms of mPFS with

3.8 and 3.5 months with NSCLC patients treated by salvage chemotherapy after ICI or last chemotherapy before ICI, respectively.

Today ICI monotherapy with atezolizumab or pembrolizumab in patients with PD-L1 high expressing tumors or chemotherapy in combination with ICI regardless of PD-L1 status has become standard first-line palliative treatment for patients without a targetable driver mutation.[6,8-13] Therefore, the treatment sequence studied in our cohort with R + D in third line, though very effective, will not be part of future clinical standards. Nevertheless, our findings give a sound basis to study R + D in second-line after a combination of chemotherapy and ICI or other simultaneous or sequential combinations of ICI and antiangiogenic therapies.

Overall, our results showed excellent clinical effects of R + D as third-line treatment after second-line ICI therapy for metastatic NSCLC. The response rate of this third-line therapy was even higher than for second-line ICI, irrespective of how long immune therapy was given. Our data add further support for a synergistic interaction of ICI and antiangiogenic agents and should stimulate further prospective trials exploring simultaneous and sequential use of ICI and antiangiogenic therapies.

Authors' Note

Part of this paper had been presented as a scientific poster at the German Cancer Congress in Berlin, Germany, on February 22, 2020.

Author Contributions

All authors made substantial contributions to conception, data aquisition and design. Data analysis was done by BU, WMB, EL. WMB, JHF and EL gave final approval of the version to be submitted and any revised version.

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