Efficacy of docetaxel plus ramucirumab as palliative second-line therapy following first-line chemotherapy plus immune-checkpoint-inhibitor combination treatment in patients with non-small cell lung cancer (NSCLC) UICC stage IV

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Background: Chemotherapy plus immune-checkpoint inhibitor (CTx+ICI) therapy has become the preferred 1st line treatment in patients with metastatic NSCLC without oncogenic driven mutations. However, the optimal subsequent 2nd line treatment is not defined and several alternatives exist. The purpose of this analysis was to evaluate the efficacy of 2nd line docetaxel plus ramucirumab (D+R) initiated after failure of 1st line CTx+ICI.

Methods: Retrospective data were collected during routine care from German thoracic oncology centers. Only patients who had received at least one course of 2nd line D+R were included. ORR, PFS, OS and numbers of courses of D+R were investigated with PFS after initiation of D+R being the primary endpoint.

Results: Seventy-seven patients met the inclusion criteria. 2nd line treatment with D+R achieved an ORR and DCR of 32.5% and 62.4%, respectively. Median PFS for 2nd line therapy was 3.9 months with a DOR of 6.4 months. Median OS of 15.5 and 7.5 months were observed from the start of 1st line therapy and 2nd line treatment, respectively. No unexpected toxicities occurred. Presence of KRAS mutations was associated with significantly worse median PFS to D+R (2.8 *vs.* 4.5 months in wild-type cases; P=0.021) and was an independent predictor of inferior PFS in multivariate analysis.

Conclusions: D+R is an effective and safe 2nd line treatment after failure of 1st line CTx+ICI irrespective of NSCLC histology. However, patients with a KRAS mutation did not benefit from D+R in terms of PFS

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and will require further investigations.

Introduction

In recent years, ICI directed against PD-1 or PD-L1 have expanded the treatment options for advanced NSCLC. Initially, ICI were approved for palliative 2nd and 3rd line treatment of metastatic NSCLC in patients without druggable driver mutations (1-6). Up to 16% of NSCLC patients receiving the PD-1 inhibitor nivolumab as palliative 2nd line treatment survive for more than five years (7). ICI quickly became established in the 1st line setting. The PD-1 ICI pembrolizumab is approved in Europe as a 1st line monotherapy for patients with an immunohistochemically based tumor proportion score (TPS) for PD-L1 ≥50% or in combination with a platinum based combination chemotherapy regardless of the TPS score (8-10). Currently approved 1st line therapies also include the PD-L1 ICI atezolizumab either in combination with chemotherapy or even as a four-drug regimen in combination with the VEGF antibody bevacizumab (11,12). In addition, the PD-1 antibody nivolumab is approved in combination with the CTLA-4 ICI ipilimumab and platinum-based combination therapy (13). These ICI combination strategies have resulted in a median PFS rates of 7 to 9 months and median OS rates of 16 to 22 months. Most patients will sooner or later experience progression of their tumor disease and require 2nd line treatment. However, there is a lack of knowledge about the efficacy of drugs being considered for 2nd line therapy following CTx+ICI, since the current options were all tested and approved before the widespread use of immunotherapy. It is currently unclear to what extent the results of former trials can be extrapolated to inform the choice of 2nd line therapy after immunotherapy (14).

So far, no studies have prospectively compared different therapy strategies in 2nd line. Thus, real-world data from high-volume centers with well-defined treatment sequences could help physicians to make treatment decisions in individual NSCLC patients. Recently we could show excellent efficacy of 3rd line docetaxel plus ramucirumab (D+R) combination therapy after failure of both 1st line chemotherapy and 2nd line ICI monotherapy (15). In this retrospective analysis we now report on D+R in the palliative 2nd line treatment after progression on the current standard 1st line treatment comprising of platinum based combination chemotherapy plus ICI (CTx+ICI). We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-197).

Methods

Design and participating centers

This retrospective analysis studies the clinical effects of a palliative 2nd line treatment with D+R in patients with metastatic NSCLC directly after progression on a 1st line combination therapy with platinum based chemotherapy and an anti-PD-1 or PD-L1 ICI agent (CTx+ICI). Patients had a histologically or cytologically proven NSCLC UICC stage IV according to the eight edition of the UICC TNM classification. Patients with ICI monotherapy as 1st line therapy were excluded. Patients with a history of adjuvant chemotherapy before 1st line palliative therapy could be included, if there was an interval of more than 12 months between the adjuvant treatment and the first systemic treatment for stage IV disease. Patients with a history of palliative radiation therapy could also be enrolled into the study. NSCLC with a non-squamous histology were tested for EGFR mutations and ALK translocations and in case of a positive result excluded.

Data were collected from 9 high-volume German centers with specialization in thoracic oncology and strong experience in chemo- and immune-oncology therapy. The centers included three university hospitals, three community-based hospitals, two private hospitals and one outpatient clinic. Patients were treated with CTx+ICI between February 2016 and May 2020 and started 2nd line D+R no later than August, 1st 2020. This allowed for a follow-up of at least five months prior to the data cut-

off of December 31, 2020. Data were recorded by each center in a standardized manner with the following data being collected for each patient: age, sex, smoking habits, tumor stage, histology, PD-L1 expression determined by immunohistochemistry, mutational status, 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, cycles for combination and monotherapy, best response, date of progression and reason for treatment stop. In addition, for 2nd line therapy the following data were documented: weight at start of therapy and side effects [according to common toxicity criteria (CTC) grades 3 and 4].

Data were anonymized before being sent to the organizing center. Inclusion and exclusion criteria were verified centrally, and data were checked for completeness and plausibility. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Paracelsus Medical University Nuremberg (IRB-2019-014). Due to the retrospective nature of the study and the strict anonymization of individual data, written informed consent was not required.

Measurement of immunohistochemical and molecular factors

PD-L1 expression was assessed with the following antibodies SP263 (6 centers), ZR3 (1 center), 22C3 (1 center) and QR001 (1 center). Tumor proportional scores (TPS) were classified into three groups (<1%, 1–49% and ≥50%). The genetic make-up of tumors was analyzed using tissue-based targeted next-generation-sequencing (NGS).

Evaluation of tumor response and efficacy of treatment

The primary endpoint was efficacy of the D+R 2nd line therapy in terms of progression-free survival (PFS). Secondary endpoints were duration of response (DOR) in patients responding to D+R as well as OS from start of 2nd line therapy. In addition, response to 1st and 2nd line treatment, time interval between both lines of treatment and the relationship between tumor response to CTx+ICI and D+R were evaluated.

Tumor responses were assessed by each center by chest computer tomography (CT) and abdominal ultrasound or other clinically appropriate abdominal imaging at least every 3 months or upon clinical deterioration. Tumor responses were evaluated according to the RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1. (16). Complete response (CR) was defined as disappearance of all target and non-target lesions. Partial response (PR) was defined as ≥30% reduction in size in target lesions or disappearance of ≥1 non-target lesions. Stable disease (SD) was defined as <30% decrease or <20% increase in size of target lesions or the persistence of ≥1 non-target lesions. Progressive disease (PD) was defined as ≥20% increase in size or the appearance of new non-target lesions and/or progression of existing non-target lesions. The ORR was defined as the best response recorded from the start of treatment until disease progression or recurrence, confirmed by repeat assessments performed no less than four weeks after the first time criteria for response had been reached. Disease control rate was defined as CR plus PR plus SD.

Overall survival was recorded from the first day of 1st line palliative treatment with CTx+ICI and from the first day of 2nd line treatment with D+R to the date of death or last follow-up. PFS was defined for 2nd line therapy as the interval from the first day of 2nd line D+R to the first sign of disease progression or death whichever occurred first. For 1st line therapy, time on treatment was defined as the interval starting from the first day on drug until the date when the progression was documented.

Statistical analysis

Descriptive data were presented as mean and 95% confidence interval, categorical variables were presented using numbers and frequencies. A tornado diagram was implemented to visualize the relative importance of cycle length in 1st and 2nd line treatment. To analyze PFS and OS data were presented as median and 95% confidence interval (CI), and times to events were determined using the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazards models were used to evaluate the influence of different patient factors. Statistical results were calculated using SPSS (version 23). A P value <0.05 was considered statistically significant.

Results

Patient population

After excluding 10 patients (5 patients with ICI

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Table 1 Patients' demographics

Parameters	N	(%)
Age		
Median age 63 years (range, 41–83)		
<65 years	41	(53.2)
≥65 years	36	(46.8)
Gender		
Male	53	(68.8)
Female	24	(31.2)
ECOG PS		
0	28	(38.4)
1	40	(54.8)
2	5	(6.8)
n.r.	4	
Stage at start of 1st line chemotherapy		
IVa	20	(26.0)
IVb	57	(74.0)
Histology		
Adenocarcinoma	55	(71.4)
Squamous cell carcinoma	16	(20.8)
NOS or other type	6	(7.8)
PDL-1 expression status		
Negative	33	(47.1)
1–49%	30	(42.9)
≥50%	7	(10.0)
n.r.	7	
Kras mutational status		
Wild-type	31	(64.6)
Mutation	17	(35.4)
n.r.	29	
BMI at start of 2nd line		
<25	44	(57.1)
≥25	33	(42.9)
Palliative radiation therapy		
No radiation	37	(48.1)

Table 1 (continued)

Table 1 (continued)

Parameters	N	(%)
One site		
Brain	10	(13.0)
Bone	7	(9.1)
Lung/mediastinum	9	(11.7)
Multiple sites	4	(5.2)
n.r.	10	(13.0)

n.r., not reported; BMI, body mass index.

monotherapy in 1st line; 3 patients with D+R in the 3rd line, 2 patients with insufficient follow-up data), 77 patients from 9 centers met the inclusion criteria. The baseline demographic data and tumor characteristics are listed in *Table 1*. The median age was 63 years (range, 41–83), and 68.8% of the patients were male. More than half of the patients had an ECOG-PS (Eastern Cooperative Oncology Group performance status) of 1 (54.8%). PD-L1 data were available for 70 patients (91%); of those 47.1%, 42.9% and 10% exhibited a tumor proportion score (TPS) of 0%, 1–49% and ≥50%, respectively. The KRAS mutational status was available from 48 tumors (68.6%); of those a KRAS mutation was detected in 17 (35.4%) of the cases. A G12C mutation was identified in 5 cases (29.4%). KRAS G12V, G12D, G12A, G12S and a codon 13 mutation were observed in 5, 3, 2,1 and 1 cases, respectively. All patients had received a platinum based combination CTx+ICI as palliative 1st line therapy with carboplatin being the backbone in 83.1%. ICI included pembrolizumab in 80.5%, atezolizumab in 13% and durvalumab (due to a clinical study) in 6.5%. In 20 patients a 3rd line therapy was initiated following D+R. 3rd line therapy consisted of combination CTx, CTx monotherapy, ICI monotherapy and a tyrosine kinase inhibitor (TKI) were given in 8, 3, 6 and 3 cases, respectively. Details of agents and combinations are reported in *Table 2*.

Efficacy and safety of D+R

The mean number of 2nd line combination treatment cycles was 6.0 (95% CI, 5.1–7.0) with a mean number of 2.1 cycles given as a ramucirumab mono therapy. Fifteen patients (19.5%) were still on treatment with D+R at

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

1st line		2nd line		3rd line therapy	
Chemotherapy + ICI (N=77)	N (%)	R+D (N=77)	N (%)	(N=20)	N (%)
Platinum + pemetrexed + pembrolizumab	50 (64.9)				
Platinum + paclitaxel/nab-paclitaxel + pembrolizumab	9 (11.7)	Docetaxel + ramucirumab	77 [100]	Chemotherapy mono	8 [40]
Platinum + paclitaxel/nab-paclitaxel + atezolizumab	8 (10.4)			Chemotherapy combination	3 [15]
Platinum + gemcitabine/vinorelbine + durvalumab + tremelimumab	3 (3.9)			ICI	6 [30]
Platinum + pemetrexed + durvalumab +tremelimumab	2 (2.6)			TKI	3 [15]
Carboplatin + paclitaxel + bevacizumab + atezolizumab	2 (2.6)				
Platinum + gemcitabine/vinorelbine + pembrolizumab	2 (2.6)				
Platinum + gemcitabine/vinorelbine + pembrolizumab	1 (1.3)				

ICI, immune-checkpoint-inhibitor; TKI, tyrosine kinase inhibitor.

data cut-off. Overall, this treatment led to an ORR of 32.5% and a DCR of 62.4%. The median PFS for 2nd line therapy was 3.9 months (95% CI, 3.1–4.6) with a DOR of 6.4 months (95% CI, 5.4–7.4) (*Table 3* and *Figure 1A*). There was no significant difference in PFS between patients with squamous or non-squamous tumor histology receiving D+R (*Table 3*, *Figure 1B*). The median OS from first dose of 2nd line therapy was 7.5 months (95% CI, 5.1–10.0). A median OS of 15.5 months (95% CI, 12.2–18.9) was observed from the start of 1st-line palliative treatment (*Figure 2*). Cox regression analyses were carried out to analyze potential prognostic effects on PFS including gender, age, stage, BMI, histology, response to 1st line treatment, PD-L1 TPS and KRAS mutational status. PD-L1 TPS and KRAS mutational status were prognostic in the univariate analysis. Only KRAS wild-type status turned out to be of independent positive prognostic value (*Figure 3A,B*, *Table 4*). There was no difference in terms of efficacy between patients with KRAS G12C and other KRAS mutations (*Figure S1*).

During D+R treatment no unexpected toxicity was documented. Neutropenia was the most frequent side effect with CTC grades 3 and 4 documented in 7 and 5 patients, respectively. Febrile neutropenia was reported in 3 patients, 2 of them suffering from CTC grade

4 leading to discontinuation of the D+R treatment. Prophylactic G-CSF was not routinely administered in any of the centers. However, in patients with grade 3 or 4 neutropenia prophylactic G-CSF was given for subsequent courses to prevent further hematologic adverse events. Alternatively, in some cases docetaxel was discontinued and ramucirumab was given as a mono-therapy. Further commonly documented grade 3-4 CTC toxicities included fatigue, dysparonychia, mucositis, stomatitis, and ileus in 5, 4, 3, 1 and 1 cases, respectively. No pulmonary toxicities, such as interstitial pneumonitis, or treatment-related deaths were observed. The adverse events associated with 2nd line therapy are listed in *Table 5*.

Outcome of 1st line treatment

A response to 1st line therapy was observed in 50.7% of patients. The mean time on 1st line treatment was 5.8 months (95% CI, 5.0–6.6). After an average of 4 cycles of platinum-based CTX+ICI, 37.8% received a maintenance therapy with CT+ICI and 41% received ICI monotherapy (*Table 3*). There were no significant differences in OS between the different platinum agents. Regarding PD-L1 TPS and duration of treatment with ICI there was a trend toward longer duration of therapy in patients with a high expression (≥50%). The

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Table 3 Efficacy data in different lines of treatment

Parameters	1st line CTx+ICI	2nd line R+D	3rd line
	N=77	N=77	N=20
Number of cycles; mean (95% CI)	9.0 (7.4–10.6)	6.0 (5.1–7.0)	–
Of those			
Maintenance CTx+ICI	2.0 (1.2–2.8)	2.1 (1.3–3.0)	
Maintenance ICI mono	3.5 (2.0–5.0)		
Ramucirumab mono	–		
ORR; N (%)			
CR	3 (3.9)		
PR	36 (46.8)	25 (32.5)	2 (2.6)
SD	23 (29.9)	23 (29.9)	4 (5.2)
PD	15 (19.5)	23 (29.9)	8 (10.4)
n.r.	–	6 (7.8)	6 (7.8)
			2nd line ongoing 15 (19.5); no further therapy 42 (54.5)
DOR; median (95% CI)	8.7 (6.3–11.0)	6.4 (5.4–7.4)	–
PFS; median (95% CI) (months)	5.8 (5.0–6.6)	3.9 (3.1–4.6)	–
PFS according to subgroups			
Histology			
Adenocarcinoma	6.0 (5.0–7.0)	3.9 (3.0–4.8)	–
Squamous cell carcinoma	5.6 (5.0–6.2)	4.4 (2.3–6.4)	–
PD-L1			
TPS <1%	4.8 (3.7–6.0)	3.5 (2.6–4.5)	–
TPS 1–49%	6.0 (5.6–6.4)	5.1 (3.1–7.1)	–
TPS ≥50%	7.2 (7.1–7.3)	12.3 (2.5–22.0)	–
KRAS			
Wild-type	6.0 (4.8–7.2)	4.5 (2.6–6.4)	–
Mutated	4.8 (3.2–6.3)	2.8 (1.7–3.9)	–
OS from line of thx; median (95%CI) (months)	15.5 (12.2–18.9)	7.5 (5.1–10.0)	3.4 (2.6–4.2)

TPS, tumor proportional score on immunohistochemistry; DOR, duration of response.

median time interval from end of 1st line to start of 2nd line treatment was 23 days (95% CI, 19.6–26.4). There was no statistically significant effect of this interval on the efficacy of 2nd line D+R. Radiation therapy had no significant effect on 1st or 2nd line response or outcome. However, BMI appeared to be of prognostic value in terms of OS. From the start of 1st line median OS was 21.4 months in patients with initial BMI ≥25 and 13.8 months in patients with BMI <25

(P=0.018). BMI did not affect clinical response or PFS in either treatment line.

Subgroup analysis of patients treated with platinum + pemetrexed + pembrolizumab in the 1st line

Nearly two-thirds of the patients (N=50; 64.9%) had been treated with CTx+ICI consisting of platinum + pemetrexed
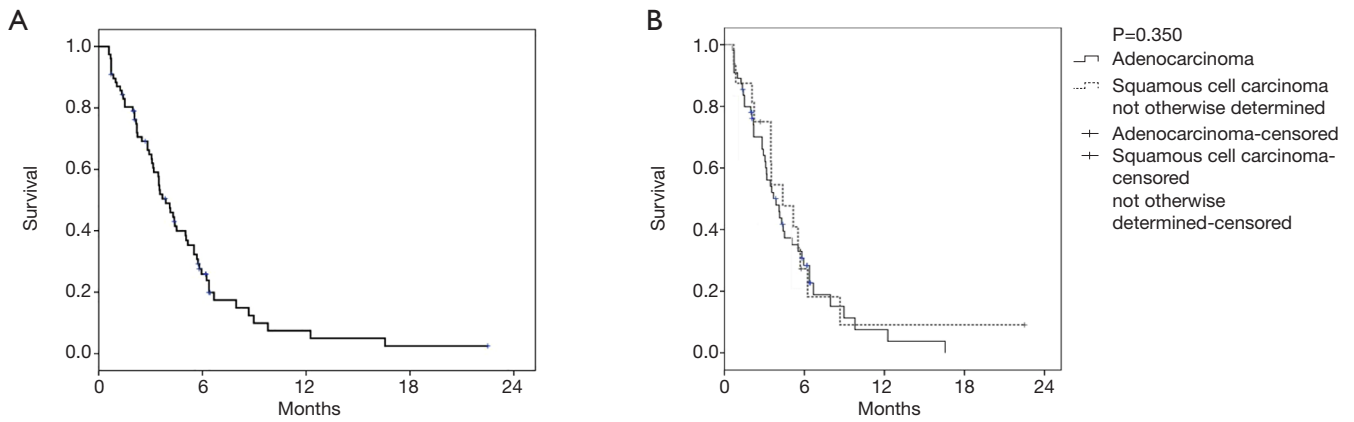
Figure 1 Kaplan-Meier curve for PFS. (A) PFS Kaplan Meier curves of the whole collective, (B) PFS due to different histologies, ADC, adeno carcinoma; SCC, squamous cell carcinoma.
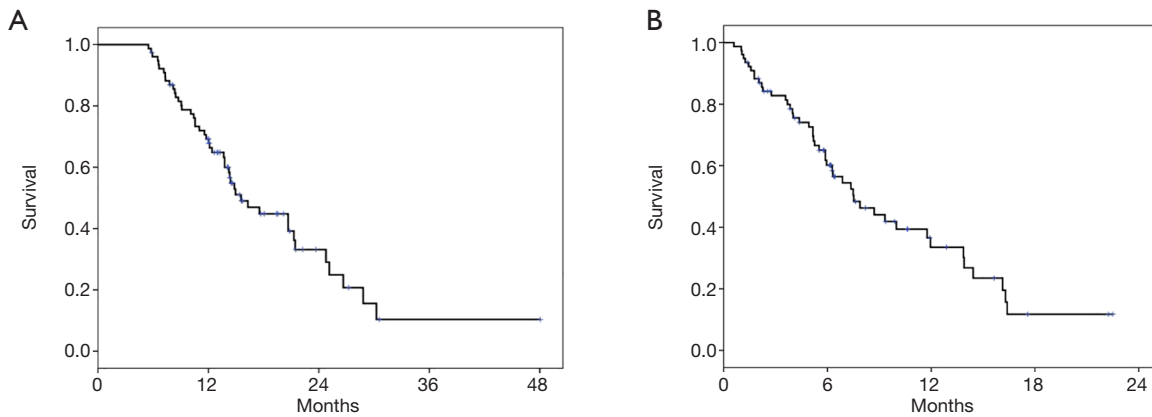

Figure 2 Kaplan-Meier curves for OS due to start of (A) 1st line and (B) 2nd line treatment, respectively.
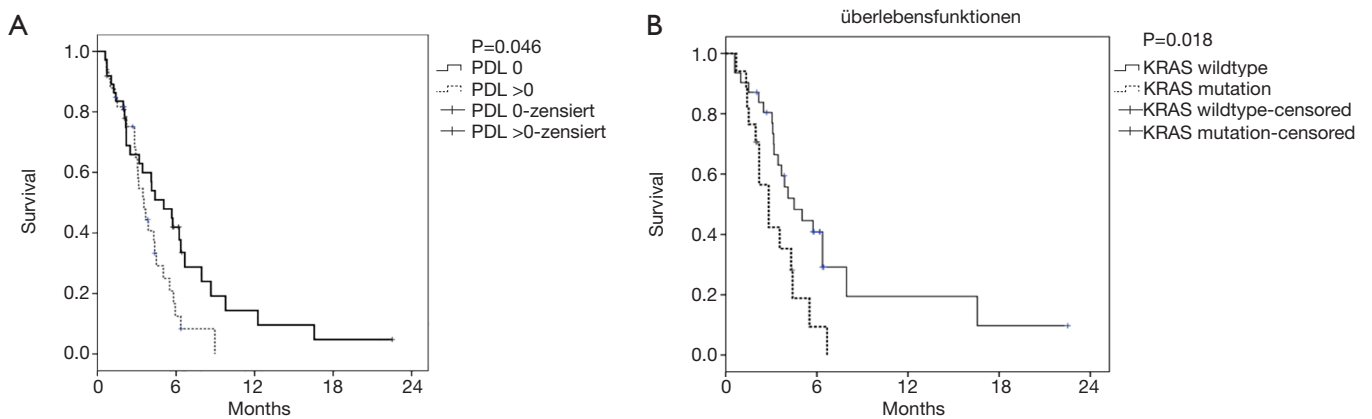

Figure 3 Kaplan-Meier curves for molecular subgroups. PFS. (A) PFS due to PD-L1 TPS scores; (B) PFS due to KRAS mutational status. mut, KRAS mutated; wt, KRAS wild-type.

Table 4 Univariate and multivariate analysis of different parameters of the whole cohort regarding PFS due to D+R treatment

Parameters	N	mPFS	95% CI	Univariate analysis			Multivariate analysis		
				HR	95% CI	P value	HR	95% CI	P value
Gender									
Male	53	3.7	2.6–4.7						
Female	24	5.0	1.7–8.3	0.682	0.392–1.186	0.175	–		
Age (years)									
<65	41	4.5	2.8–6.2						
≥65	36	3.5	3.0–4.0	1.545	0.910–2.598	0.101	–		
Stage									
IV A	20	5.0	2.6–7.5						
IV B	57	3.5	2.9–4.1	1.617	0.909–2.875	0.102	–		
BMI (kg/m^2)									
<25	44	3.7	1.9–5.6						
≥25	33	4.3	2.1–6.5	0.702	0.417–1.179	0.181	–		
Histology									
AC	55	3.9	2.8–4.9						
SCC	16	4.4	2.3–6.4						
NOS	6	2.5	0–5.5	1.064	0.850–1.318	0.568	–		
Response 1st line									
Response	39	4.5	2.8–4.1						
No response	38	3.5	3.3–5.7	0.786	0.427–1.310	0.356	–		
PD-L1 (TPS score)									
<1	33	3.5	2.8–4.3						
≥1	37	5.1	2.9–7.3	0.569	0.325–0.997	0.049	0.546	0.260–1.148	0.110
KRAS									
Wild-type	31	4.5	2.6–6.4						
Mutation	17	2.8	1.7–3.9	2.293	1.130–4.652	0.021	2.229	1.077–4.605	0.030

+ pembrolizumab in 1st line therapy. All of these patients had a non-squamous tumor and in 84% the mutational status had been established. Thus, these patients represent a large, homogeneous, and well-characterized subgroup and were therefore analyzed in more detail in a subsequent post-hoc analysis. A tornado-plot representing the number of cycles in 1st and 2nd line treatment is given in *Figure 4*.

The platinum backbone was carboplatin and cisplatin in 78% and 22%, respectively, with no differences in duration of treatment in 1st line or 2nd line. PD-L1 TPS was 0%, 1–49%

and ≥50% in 48%, 46% and 6% of the tumors, respectively, with no differences in outcomes. 2nd line treatment with D+R resulted in an ORR of 34% and a DCR of 68%, with a DOR of 6.4 months (95% CI, 5.6–7.2 months). The mPFS for D+R was 3.9 months (2.7–5.1 months) and the mOS from the start of 1st and 2nd line was 16.3 and 8.7 months, respectively. The KRAS status of the tumor was reported for 42 patients and a KRAS mutation was detected in 16 cases (38.1%) (*Figure 4*). KRAS mutations were significantly associated with poor median PFS for D+R in contrast to the

wild type status (2.8 *vs.* 5.0 months; P=0.023). As described for the entire cohort, there was no difference between KRAS G12C and other KRAS mutations when comparing PFS in this subgroup. The duration of treatment in 1st line or

overall survival (either from the start of 1st line or 2nd line) were not significantly affected by a KRAS mutation. Other clinical parameters including age, gender, BMI, histology (adeno-carcinoma or NOS), as well as response to 1st line and length of ICI maintenance therapy were not associated with significantly different effects on efficacy parameters for D+R treatment.

Table 5 Hematological and non-hematological side effects of D+R therapy

Adverse events	CTC grade ≥3*, N (%)
Neutropenia	12 (15.6)
Febrile neutropenia	3 (3.9)
Fatigue	5 (6.5)
Dysparonychia	4 (5.2)
Mucositis	3 (3.9)
Stomatitis	1 (1.3)
Ileus	1 (1.3)

*, there were no toxicities CTC grade 5.

Discussion

The combination of chemotherapy plus ICI (CTx+ICI) has become the standard palliative 1st line treatment for driver negative metastatic NSCLC with more than four phase III trials demonstrating superiority of efficacy endpoints compared to chemotherapy alone (9-11,13). However, progression remains the leading clinical problem and there is an urgent medical need for efficacious 2nd line strategies to overcome resistance. As none of the pivotal trials had a predefined 2nd line therapy, no prospective data are
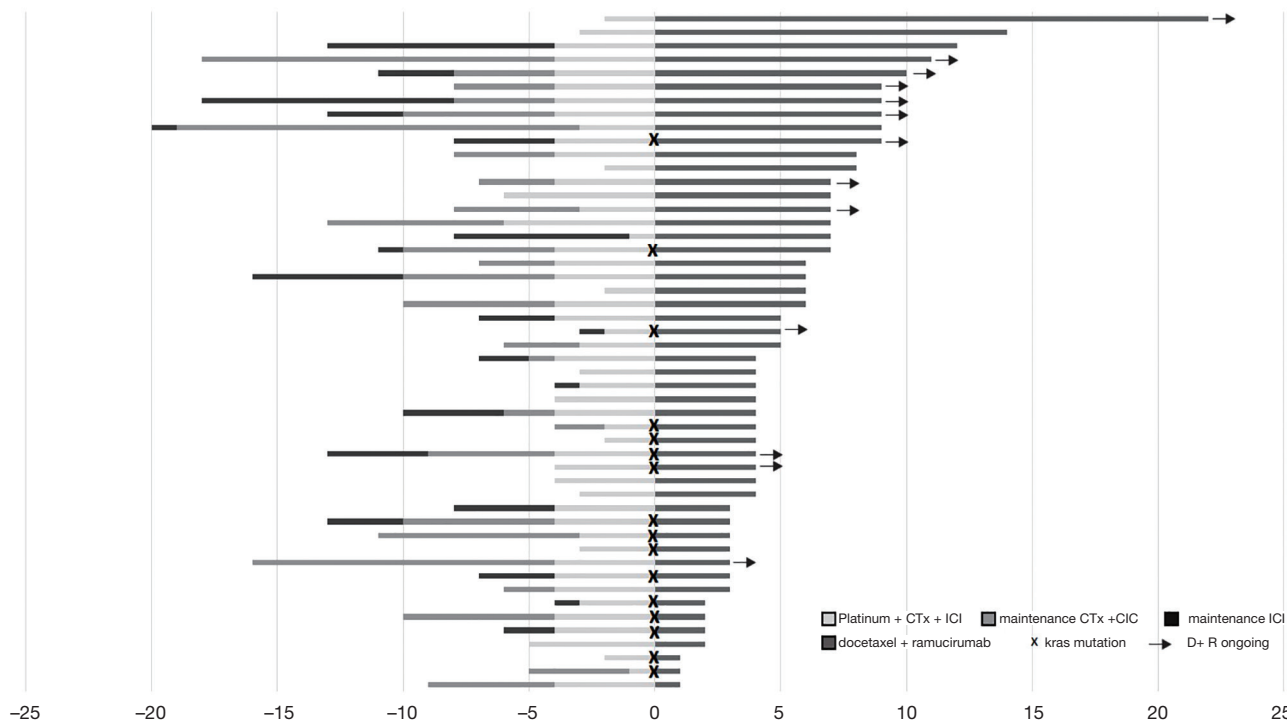

Figure 4 Treatment duration in cycles of therapy for 1st and 2nd line treatment in the subgroup of patients treated by platinum + pemetrexed + pembrolizumab 1st line (N=50). 1st line treatment left side is divided into platinum based CTx+ICI, maintenance therapy with CTx+ICI and maintenance therapy with ICI monotherapy. D+R treatment is presented at the right side. Arrows define patients with D+R ongoing, X defines patients with an underlying KRAS mutation.

available for specific treatment sequences. Second line phase III trials evaluating docetaxel with an anti-angiogenetic substance, e.g., nintedanib (D+N) or ramucirumab (D+R) have each shown superiority to the comparator docetaxel monotherapy and led to approval of both combinations (17,18). However, those trials were designed in the era before ICI were used in 1st line treatment. For D+N a prospective German non-interventional trial (VARGADO) is underway and will provide insights to the efficacy of this sequence (19).

No prospective studies have been published to date for D+R in this sequence. Thus, retrospective clinical data may provide at least some evidence for this therapeutic sequence. To the best of our knowledge, this cohort is the largest studied so far with a specific sequence of 1st line CTX+ICI followed by D+R in 2nd line. We showed that this sequence is feasible and effective in clinical routine. These results are consistent with the prospective data of the REVEL study on D+R from the pre-ICI era and our efficacy and safety data are highly comparable with response rates being even higher (17). As long as no other trial data are available for 2nd line therapy after CTx+ICI, our data provide a solid basis for the use of D+R in 2nd line after CTx+ICI in all histologies.

Nearly two-thirds of the patients in this study received platinum plus pemetrexed plus pembrolizumab in the 1st line setting. These patients represent a large, homogeneous and well-characterized subgroup, allowing for further in-depth analyses. The data for clinical efficacy and safety were very favorable in this subgroup, although OS and PFS remained slightly inferior to the corresponding arm of the Keynote 189 trial, while response rates were comparable (8,9). Patients in our analysis were treated in daily clinical practice and so were older and had more co-morbidities than those in the Keynote 189 trial. In addition, there may have been a negative selection bias in our patient population, since patients with exceptionally good response to 1st line CTx+ICI may not have yet required 2nd line treatment. Furthermore, there were less tumors with a PD-L1 TPS of ≥50% in our cohort than in the phase III trial with 6% versus 32%, respectively.

We and others recently reported excellent PFS and OS data for D+R given in 3rd line immediately after ICI monotherapy (15,20-24). We have hypothesized that anti-angiogenic agents not only act directly through VEGF-mediated effects but also produce synergistic effects with chemotherapeutic agents and ICI agents for instance by contributing to better drug penetration through their action on tumor vessels (15,25-27). Unfortunately, no clear

evidence of such a synergistic effect could be observed in our analyses of the D+R second line cohort. Especially, no superior efficacy could be proven in patients with an objective response to 1st line therapy. However, there was at least a trend toward longer PFS with D+R in patients with moderate (1–49%) and high (>50%) PD-L1 TPS scores versus tumors negative for PD-L1. Knowing that ICI bind to the PD-1 receptor up to two months after the last infusion of the drug, this could be a hint for the synergistic effect described above at least in PD-L1 high expressing tumors (28).

Most patients in the platinum plus pemetrexed plus pembrolizumab sub-cohort had available KRAS mutation data. In line with results from the KEYNOTE-189 trial, KRAS status had no impact on 1st-line therapy (29). However, a positive KRAS status was significantly associated with worse median PFS in 2nd-line D+R and was also an independent predictor of worse PFS in multivariate Cox regression analysis. To date, there is little evidence on the role of KRAS status in D+R therapy (30). Although KRAS mutations might increase the expression of VEGF, VEGFR1 and VEGFR2 in various tumors including NSCLC, the underlying mechanisms is still unclear (31-33). *In vitro* data of ramucirumab showed inferior tumor regression in a KRAS mutated xenograft tumor (NCI-H2122) which could be significantly increased by the combination of ramucirumab with a pan-RAF inhibitor (34). In addition, a KRAS mutation was a significantly negative predictor for response and time on treatment when bevacizumab, a VEGF antibody, was given in combination with carboplatin and docetaxel in NSCLC (35). These observations support our findings. Nevertheless, the significance of KRAS status in this situation has not yet been conclusively determined, and KRAS status should be analyzed systematically in future studies investigating antiangiogenic combination therapies after Ctx+ICI (36).

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 mainly affected the documentation of those side effects not immediately apparent in routine care. Furthermore, there may have been some negative selection bias since patients with limited effect of 1st line treatment may have been over-represented in our cohort. Accordingly, there remains some uncertainty whether D+R is an effective 2nd line therapy for patients

with a particularly good response to CTx+ICI 1st line therapy. In this study, patient response to treatment was assessed by criteria used during routine care at participating centers and was not collected in a predefined, standardized manner by independent investigators. Therefore, some variability between centers may be present for PFS, but this would not have affected survival data. KRAS mutation status was not reported for about one third of the patients. However, of those 20.4% presented with a squamous cell carcinoma. We do not have evidence that there was a systematic error in this regard, so the patients with unknown KRAS status should be a representative sample from the overall cohort.

Overall, our results clearly demonstrate a superb OS and PFS from 2nd line D+R therapy after 1st-line therapy with CTx+ICI for metastatic NSCLC of all histologies. This effect was even slightly more pronounced in a large subgroup treated with platinum plus pemetrexed plus pembrolizumab in 1st line. Some early evidence was found that patients with a KRAS mutation may have significantly less response to D+R after CTx+ICI. Further systematic studies are needed to identify robust criteria for patient selection for 2nd line therapy with D+R after CTs+ICI.

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Footnote

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Ethical Statement: The authors are accountable for all aspects

of the work ensuing that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Paracelsus Medical University Nuremberg (IRB-2019-014). Individual consent for this retrospective analysis was waived.

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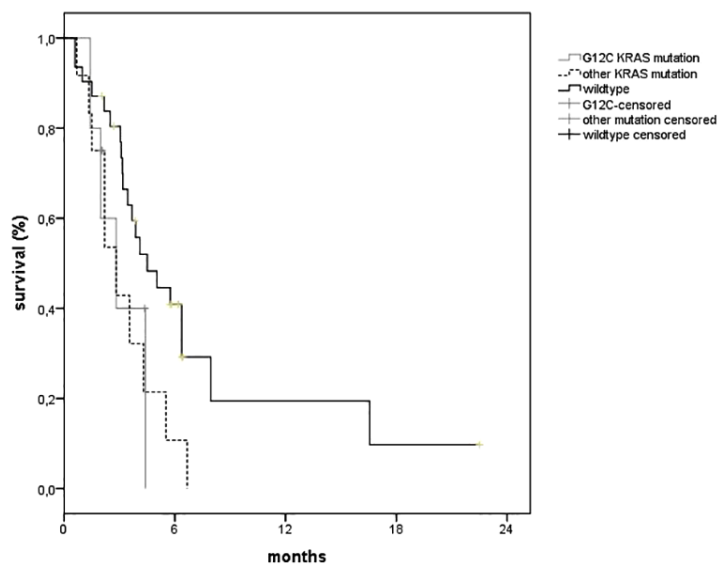
Figure S1 Kaplan-Meier curve for PFS due to KRAS status (wild-type versus G12C versus other KRAS mutations).