

Peer Review File

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Reviewers' comments	Authors' reply
<p>Reviewer A</p> <p>1) Because this is a retrospective study, patient selection is an important factor in evaluating its degree of reliability. I would like to ask the authors to show how many patients were excluded from this analysis based on which ineligibility.</p>	<p>All centers had been requested to transfer data from <u>all</u> NSCLC patients treated at their centers treated with D+R as 2nd line after CTx+ICI 1st line. This definition of the study population is given in the methods part (design and participating centers) See: pp5-6, ll 121-148.</p> <p>Certainly, we cannot definitively rule out the possibility that individual patients may have been overseen in a center and that their data not transferred. However, we had previously established a reliably functioning network with the centers, which proved very successful in a similar project evaluating D+R in third-line treatment with all these centers. (Brueckl et al., Clin Med Insights Oncol 2020). We see no evidence that a systematic error could have arisen from individual patients who might have been missing.</p> <p>The exclusion of individual patients reported by the individual centers from the final analysis is now described more precisely in the results section.: >>After excluding 10 patients (5 patients with ICI 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.<< p8, ll 203-205</p>
<p>2) The PD-L1 status and KRAS mutational analysis are a main feature of this analysis. Authors should show how they evaluated PD-L1 (22C3 or others?) and KRAS mutation (NGS based or single plex?).</p>	<p>A new section in the methods part was added to describe these measurements in more detail:</p> <p>>>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</p>

	<p>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).<< (p6, ll 156-160)</p>
<p>3) As well as efficacy, toxicity is an important aspect of the docetaxel and ramucirumab. Authors should provide at least summary of adverse events in this manuscript.</p>	<p>A summary of the toxicities is given in a new created Table 5. In addition, adverse events are reported in more detail in the results part.</p> <p>Please also see reply to comment 1 of reviewer C.</p>
Reviewer B	
<p>1) Table 1 is difficult to understand. “Median Age” is listed at “N”, and “range” is listed at “%”.</p>	<p>Sorry. N and % should be reserved for columns. Therefore, we changed this and made it more clear. In addition, number and % of patients <65 years was added. See Table 1.</p>
<p>2) This study is a research that evaluated D+R of 2nd line, but is BMI at 3rd line be a patient characteristics?</p>	<p>That was a mistake. Of course, we evaluated BMI at start of 2nd line (D+R). We corrected this. See Table 1.</p>
<p>3) Please reconfirm the grammar and spell.</p>	<p>The work was proof read by the co-author Amanda Tufman, MD, who is a native Canadian with English as her mother tongue. All changes were marked in blue.</p>
Reviewer C	
<p>The incidence of febrile neutropenia (FN) caused by D+R is over 20% without primary prophylactic G-CSF use. In the current retrospective study, authors reported grade 2-4 CTC toxicities included fatigue, dysparonychia, neutropenia, mucositis/stomatitis, and ileus.</p>	<p>There seems to be a difference in terms of occurrence of FN between NSCLC patients from Eastern Asia and Caucasian patients treated by D+R. Data from the REVEL trial showed FN rates with a CTC ≥3 of 43.8 vs 14.7% in East Asian and Non-East Asian patients, respectively (Park-K et al., Cancer Res Treat 2016). Therefore, prophylactic G-CSF and dose reductions are recommended in East-Asian patients while there is no such recommendation for patients in Germany.</p> <p>However, we asked all participating centers to check the patients’ records again for neutropenia and FN In addition, we asked all co-authors about their local standards for the use of prophylactic G-CSF and added this</p>

<p>1A) The incidence of grade 3-4 neutropenia should be shown in the study.</p> <p>1B) Grade 3-5 FN was not observed in the current retrospective study?</p> <p>1C) How many patients received primary prophylactic G-CSF treatment in total 77 patients treated with D+R?</p> <p>It is recommended that authors show the more detailed safety data of neutropenia, FN and the number of patients received primary prophylactic G-CSF treatment in the current retrospective study. That would be informative data for D+R in clinical practice.</p>	<p>information to the manuscript. With this information we hope to give some answers to your comments. Please note, that safety was not the main aspect we focused in this retrospective analysis.</p> <p>The incidence of grade 3-4 neutropenia is now shown in the text: >>Neutropenia was the most frequent side effect with CTC grades 3 and 4 documented in 7 and 5 patients, respectively.<< p9, ll237-238</p> <p>There were 3 cases of FN with CTC grades 3 and 4 in 2 and 1 cases, respectively. There was no CTC grade 5 FN. This is added in the results part: >>Febrile neutropenia was reported in 3 patients, 2 of them suffering from CTC grade 4 leading to discontinuation of the D+R treatment.<< p9, ll 239-240</p> <p>Prophylactic G-CSF treatment was not given in any of the centers. However, G-CSF was given after neutropenia CTC grades 3 or 4 for the following courses. This is added in the results part: >>Prophylactic G-CSF was not routinely administered in any of the centers. However, in patients suffering from a grade 3 or 4 neutropenia G-CSF was given for the following courses to prevent further hematologic adverse events. Alternatively, docetaxel was discontinued and ramucirumab was given as mono-therapy. << p9, ll 240-244</p> <p>In addition, a new table (Table 5) was created with numbers and % of patients suffering from side effects CTC grades ≥3.</p>
<p>2) Page 7 line 180 and Table 1; Number of median age should be integer or ended by .5.</p>	<p>Thank you, years are now integer. Changed in: p8, l205 and Table 1</p>

3a) Page 7 line 184 and Table 1; Do authors have any data about the number of KRAS G12C mutation in the study? Phase III study comparing sotorasib to docetaxel are ongoing in global, and sotorasib become a standard option of 2nd line in patients with KRAS G12C mutation. Because KRAS G12C mutation is rare fraction in Asian or Japanese population, the efficacy of D+R in patients with KRAS G12C mutation would be more informative to clinicians.

3b) If possible, it would be better to show the efficacy of D+R according to the mutation type of KRAS (ex. KRAS G12C vs. others).

4) Table 2; 4 patients were treated with platinum plus gemcitabine/ vinorelbine (please also check the spell of vinorelbine) as 1st line chemotherapy. What is the ICI combination drugs in these patients? The field of Table 2 is blank.

We got into original data again and asked all centers to provide us with the exact KRAS mutations.

These data were added in the results part:

>>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.<<
p8, ll 209-212

We have now shown the efficacy for G12C compared to other KRAS mutations and compared to wild-type KRAS. There was no difference in terms of PFS or OS between G12C and other KRAS mutations. However, the difference in terms of PFS between G12C and wild-type persisted. Due to low case numbers sufficient p values could not be calculated. A Kaplan-Meier curve was created and is presented as a **suppl. Figure 1**.

Following sentences were added in the results part:

>>There was no difference in terms of efficacy between KRAS G12C and other KRAS mutations (**suppl Figure 1**). <<
p9, ll 234-235

>>As already described for the entire cohort there was no difference in terms of PFS between KRAS G12C and other KRAS mutations for this subgroup.<<
p10, ll 279-281

You are absolutely right! Table 2 was somewhat confusing in terms of 1st line treatment. Therefore, we decided not to separate chemotherapy and ICI in different columns but to show the employed 1st line CTx+ICI regimen with decreasing numbers and %.

See **Table 2**

5) The subtitle of results section “Efficacy of D+R” should be revised as “Efficacy and safety of D+R”

The subtitle was renamed in:
>>efficacy and safety of D+R.<<
p8, 1220