Author's response to reviews

Title: A phase II study evaluating neo-/adjuvant EIA chemotherapy, surgical resection and radiotherapy in high-risk soft tissue sarcoma

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Author's response to reviews: see over
Dear Dr. Zips, 

thank your very much for considering our manuscript entitled 

“A phase II study evaluating neo-/adjuvant EIA chemotherapy, surgical resection and radiotherapy in high-risk soft tissue sarcoma” 

by Thomas Schmitt et al. 

for publication in BMC Cancer. We furthermore want to cordially thank the reviewers for taking their time and their valuable input. 

Imaging scans were newly reviewed. Two patients did not fulfill RECIST criteria for local progression. One patient with suspected local and distant failure underwent biopsy. Histology excluded sarcoma recurrence. One further patient had suspected pulmonary metastases. The lung nodules however improved with antimycotic/antibiotic treatment and were therefore regarded as non-metastatic lesions. Therefore, disease-free survival rates were newly calculated and changed to 68% at 2 years.

Response to Dr. Lindner:

1) The background, methods, results and discussion section were revised. The increased risk of secondary leukemias has been stressed. Further neo-adjuvant chemotherapy regimens were added and discussed.
2) The term NED was changed to complete response (CR). Though some patients had received previous, non-oncologic surgical procedures for their tumors, response evaluation was focusing on the effect of neo-adjuvant chemotherapy and all patients had measurable tumor burden at study entry.

3) The corresponding information on tumor localization was added in the abstract and results section.

4) The reference on adjuvant radiation therapy was changed.

5) This section was modified and a reference to the lower response rates observed in the more recent trials was added. Grading according to RECIST was done by an experienced radiologist at the local department of radiology. Scans were not externally reviewed.

6) The corresponding reference on the work by Issels et al. was added.

7) Target doses for trunk and extremity tumors were 15 Gy during IORT and ≥45 Gy for post-operative irradiation. Patients who did not undergo IORT received adjuvant radiotherapy with a target dose ≥60 Gy. Lower doses were applied in patients with abdominal tumors due to radiosensitive structures (e.g. intestines).

8) Angiosarcomas were excluded in the current protocol as distinct susceptibility to taxane-based regimens has been shown for metastatic disease. A corresponding reference was added.

9) Eleven patients with tumors <5 cm were included in our study. These patients had undergone inadequate previous therapy, defined as an initial, non-oncologic surgical procedure on the primary tumor, resulting in tumors ≤5 cm but still measurable tumor burden. Overall, 21 patients (42%) had been operated on before definitive surgery (excluding planned incisional biopsy to establish diagnosis) in our study. This information was added in the manuscript.

10) An influence of histological subtype, resection status or grade of histological necrosis on local recurrence free survival could not be shown.

11) Categorization of responders and non-responders was based on grade of histological necrosis after neo-adjuvant chemotherapy as assessed by Salzer-Kuntschik. Response was defined as <10% viable tumor cells. Non-responders had ≥10% viable tumor cells.

12) The rates for DFS and OS have been corrected.
13) The paragraph on PET studies in the patients and methods section has been shortened.

Response to Dr. Roberge:

1) The definite role of chemotherapy for high-risk soft tissue sarcoma remains unclear. In the absence of large, prospective, randomized, multi-center trials addressing this question the current body of literature is heterogeneous. As soft tissue sarcoma represent such a rare disease and a meaningful statistical analysis in a randomized trial would require large patient numbers, we’re not planning a comparative study at this point. Outside a clinical trial, a doxorubicin/ifosfamid-based chemotherapy can be considered for high-risk patients only on an individual basis. Possibly advantages and disadvantages have to be discussed in detail. Due to the questionable activity of etoposide and the rate of secondary leukemias reported by Issels et al., we would not recommend EIA outside a clinical trial. The manuscript was revised, adding the above mentioned information.

2) The current study was solely financed by institutional funds.

3) Local control seems to be equal for pre- and post-operative irradiation. Post-operative radiotherapy was chosen due to the lower risk of wound complications. A corresponding reference was added in the manuscript.

4) As this is not a comparative protocol, sample size was chosen to complete study accrual within 5 years with an estimated number of approx. 12 newly diagnosed soft tissue sarcoma patients fulfilling the inclusion criteria per year, presenting at our institution.

5) Eleven patients with tumors $<$5 cm were included in our study. These patients had undergone inadequate previous therapy, defined as an initial, non-oncologic surgical procedure on the primary tumor resulting in tumors $\leq$5 cm but still measurable tumor burden. Overall, 21 patients (42%) had been operated on before definitive surgery (excluding planned incisional biopsy to establish diagnosis) in our study. This information was added in the manuscript.

6) Though the Salzer-Kuntschik grading system was initially established for osteosarcoma it is now widely used for soft tissue sarcoma as well. However, cut-off levels for responders vs. non-responders differ in the literature. In the current study, tumor necrosis was graded in post-operative specimen and response to
neo-adjuvant chemotherapy was defined as <10% viable tumor cells. Treatment response in general was assessed by MRI scans and graded according to RECIST.

7) Target doses for trunk and extremity tumors were 15 Gy during IORT and ≥45 Gy for post-operative irradiation. Patients who did not undergo IORT received adjuvant radiotherapy with a target dose ≥60 Gy. Lower doses were applied in patients with abdominal tumors due to radiosensitive structures (e.g. intestines).

8) Six patients had myxoid/round cell liposarcoma histology.

9) Five patients did not proceed to definitive surgery after neo-adjuvant chemotherapy: two non-extremity patients were regarded inoperable due to technical reasons, one patient was diagnosed concomitantly with rectal cancer, one patient declined surgery for the extent of the procedure and one patient had extensive tumor progression with distant metastasis.

10) In our experience, toxicities of radiotherapy were not increased by neo-adjuvant chemotherapy. However, as this is a non-randomized study, this can not be statistically proven.

The complete manuscript was revised according to the reviewers’ comments.

Thank you very much for your attention.

Sincerely yours,

Thomas Schmitt, MD