Author’s response to reviews

Title: LICC: L-BLP25 in patients with colorectal carcinoma after curative resection of hepatic metastases - a randomized, placebo-controlled, multicenter, multinational, double blinded phase II trial

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To the reviewer,

Thank you for the positive evaluation of our manuscript. It is a pleasure to answer your question.

In line with our previous letter, we now introduced the required information into our manuscript.

Page 11, lines 18-29

According to the German S3 guideline, adjuvant chemotherapy after R0 resection of liver metastases can be considered, whereas neo-adjuvant
chemotherapy prior to resection of liver metastases can be considered in reasonable exceptional cases (9). In contrast, R0 resectable metastases limited to the liver should be resected. In summary, the recommendation for neoadjuvant/adjuvant chemotherapy is currently not strong in Germany. As the majority of centres is located in Germany we decided to comply with the German guidelines, knowing that peri-operative chemotherapy is considered standard of care in some other countries.

Participating centres confirmed the acceptance of the protocol containing a placebo arm. The standard treatment of care after resection of liver metastases in the participating centres is to watch and wait. As a consequence, the study offers a potentially effective verum treatment to two thirds of participating patients, which would not receive any treatment otherwise.

Page 13, lines 10-15

We also decided to accept patients treated in a neo-adjuvant manner, if the neoadjuvant therapy has lasted 12 weeks or less. This became necessary, as some patients have been treated in a neo-adjuvant setting, but are presented for the study evaluation only post surgery. As a short chemotherapy seems not interfere with the postoperative immune system capacity, we agreed to include those patients in order to optimize accrual.

In addition, reference 9 has been update to the current version of the S3 guideline.

With kind regards,

Yours Sincerely

Christoph Schimanski and Ines Gockel, M.D.