This multicenter study aimed to evaluate the efficacy and safety of neoadjuvant combination therapy with vemurafenib and cobimetinib (=cohort 1) on the one hand and of neoadjuvant triple therapy with vemurafenib, cobimetinib and atezolizumab (=cohort 2) on the other hand. Patients with malignant melanoma positive for the $BRAF^{V600}$ mutation and with limited numbers of metastases and few organ systems involved were enrolled.
The purpose of any neoadjuvant treatment is the increase of patients with completely resectable cancer due to tumor shrinkage. As a further consequence of tumor reduction, surgery after neoadjuvant treatment also can decrease adverse events associated with resection.

Recruitment period into cohort 1 was twice extended, first by 12 months and afterwards by additional 24 months. With amendment 4 recruitment into cohort 1 was stopped. Enrolled patients had a documented follow-up period of 0 – 57 months before premature study termination.

Recruitment period into cohort 2 was once prolonged by 12 months up to Q3 2020. However, because no new patients were screened for more than 6 months the clinical trial was prematurely terminated in MAY 2020. For both enrolled patients, study therapy as well as end of study were terminated prematurely due to premature end of complete clinical trial. No follow-up was documented for these patients.

Between 22 JAN 2015 and 16 OCT 2017, a total of 52 patients were screened for enrollment into cohort 1 by a total of seven German and French sites. Seven patients could not be registered due to violation of inclusion or exclusion criteria; thus 45 patients were enrolled into cohort 1. The protocol amendment introducing triple therapy as study treatment led to stop of recruitment into cohort 1.
After registration, but before receiving study treatment, one patient was discovered to have violated an inclusion criterion. Therefore, SAF/TS-set of cohort 1 consisted of 44 patients.

Regrading cohort 2, two patients were screened in OCT 2019 by one German site. Both patients were registered and received triple study therapy and were included in the analysis as SAF/TS-set. Since no further patients were screened for more than 6 months, the study was prematurely terminated in MAY 2020.

Primary endpoint of this current study was the percentage of patients who became resectable due to tumor reduction under neoadjuvant study treatment and who were R0 resected.

44 patients of cohort 1 were evaluable for efficacy and safety analysis. Of these, 16 patients (36.4%) could be resected within 18 weeks of treatment with combination therapy, with 14 patients (31.8%) and 1 patient each (2.3%) achieving complete metastectomy (R0-resection) and R1-2 or Rx, respectively.

The other 28 patients (63.6%) were assessed as unresectable at time point 18 weeks and received vemurafenib / cobimetinib combination therapy further on.
Analysis for possible biomarkers in patients of cohort 1 which might have an impact on resectebility did not yield statistically significant results for any of the tested parameters (tumor marker S100b, LDH, CRP).

Median PFS time after date of resection was calculated for the 14 patients who achieved R0 resection and amounted to 16.4. Median OS time for these patients was not reached at time of premature study termination; mean OS time was 29.4 months.

Analysis of PFS rates showed an improvement of all resected patients compared to all unresected patients at 6 months, with rates of 94% and 82% for resected and unresected patients, respectively. However, at 12 months, PFS rates were 69% and 75% for patients with and without surgery. The better results of the unresected patients for the later time point may be related to the fact, that these patients received continuous treatment with vemurafenib and

cobimetinib until progressive disease whereas R0-resected patients had to stop combination treatment.
Even though patients with R1-2 resection should be treated further on, too, these few patients may not be significant to improve the result of the resected patients.

Considering all patients of cohort 1, best overall objective response was CR/PR and SD/PD for 93.2% and 4.6% of patients. Median PFS from date of study treatment amounted to 24.9 months. As seen for subgroup of resected patients with complete metastectomy, median OS for all patients of cohort 1 was also not reached during study period; mean OS for patients of cohort 1 amounted to 37.2 months.

Regarding cohort 2, one of the two patients who received triple therapy achieved a complete metastectomy, for the other patient no surgery information was documented. Due to small number of enrolled patients and premature end of complete study no efficacy analyses were performed for cohort 2. Therefore, conclusions on efficacy of triple therapy as neoadjuvant treatment cannot be drawn.

Safety data of patients receiving neoadjuvant combination or triple therapy were in line with the product information of the study. No unexpected safety issues were reported.

In conclusion, results of this study show that neoadjuvant therapy with vemurafenib + cobimetinib was well tolerated and could lead to >30% of previously hardly resectable patients achieving complete metastectomy. However, further research is necessary to determine e.g. the best duration of neoadjuvant treatment and the best combination of drugs.