# #9511

# STREAM - A randomized discontinuation, blinded, placebo-controlled phase II study of sorafenib treatment of chemonaïve patients with metastatic uveal melanoma (MUM)


Universitätsklinikum Essen

Universitätsklinikum Erlangen

CHARITÉ Comprehensive Cancer Center Universitätstumorzentrum

M. E. Scheulen[1], E. Kämpgen[4], U. Keilholz[5], L. Heinzerling[4], S. Ochsenreither[5], A. Abendroth[1], R. Hilger[1], M. Grubert[1], A. Wetter[3], N. Guberina[3], S. Bauer[1], G. Schuler[4], N. Bornfeld[2], M. Schuler[1], H. Richly[1]

Departments of [1]Medical Oncology, [2]Ophthalmology & [3]Radiology, West German Cancer Center, University Hospital Essen, Germany; [4]Department of Dermatology, University Hospital Erlangen, Germany; [5]Charité, Comprehensive Cancer Center, Berlin, Germany


## BACKGROUND

There is no approved systemic treatment for pts with MUM. The STREAM study evaluated the efficacy of the oral multikinase inhibitor sorafenib in chemonaïve pts with MUM with the primary endpoint progression-free survival (PFS) in the blinded phase.

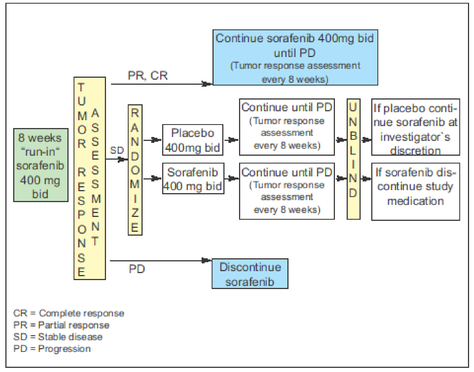


**Fig. 1.** STREAM-study design

**Table 1.** Characteristics of evaluable patients on day 56 (run-in phase) and randomized patients

| | evaluable patients on day 56 | | randomized set | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Overall | | Overall | | Placebo | | Sorafenib | |
| number of patients (n) | 117 | | 78 | | 39 | | 39 | |
| male (n) | 69 | 59% | 49 | 63% | 26 | 67% | 23 | 59% |
| female (n) | 48 | 41% | 29 | 37% | 13 | 33% | 16 | 41% |
| age (years, median, range) | 62 | 23-88 | 63.5 | 23-88 | 66* | 47-88 | 58* | 23-79 |
| **ECOG (evaluable patients, n)** | 106 | | 71 | | 35 | | 36 | |
| - ECOG 0 (n) | 85 | 80% | 56 | 79% | 27 | 77% | 29 | 81% |
| - ECOG 1 (n) | 20 | 19% | 14 | 20% | 7 | 20% | 7 | 19% |
| - ECOG 2 (n) | 1 | 1% | 1 | 1% | 1 | 3% | 0 | 0% |
| time since first diagnosis (months, median, range) | 34.0 | 1.3-431 | | | | | | |
| **localisation** | | | | | | | | |
| - liver only (n) | 65 | 56% | 38 | 49% | 18 | 46% | 20 | 51% |
| - liver & other site(s) (n) | 47 | 40% | 37 | 47% | 19 | 49% | 18 | 46% |
| - other site(s) except liver (n) | 5 | 4% | 3 | 4% | 2 | 5% | 1 | 3% |
| **number of sites** | | | | | | | | |
| - 1 site (n) | 66 | 56% | 39 | 50% | 19 | 49% | 20 | 51% |
| - 2 sites (n) | 31 | 27% | 24 | 31% | 14 | 36% | 10 | 26% |
| - ≥ 3 sites (n) | 20 | 17% | 15 | 19% | 6 | 15% | 9 | 23% |
| LDH (U/L, x ± SD) | 364 ± 289 | | 321 ± 231 | | 364 ± 279 | | 279 ± 162 | |
| S100 (µg/L, x ± SD) | 0.2 ± 0.5 | | 0.2 ± 0.6 | | 0.3 ± 0.8 | | 0.1 ± 0.1 | |
| MIA (ng/mL, x ± SD ) | 13.5 ± 15.0 | | 13.7 ± 15.4 | | 17.8 ± 18.4 ** | | 8.8 ± 9.2 ** | |

* p=0.0042; ** p=0.0173

## METHODS

During the initial 56d run-in period all pts received oral sorafenib 400 mg bid with concomitant monitoring by magnetic resonance imaging including diffusion weighted imaging (DWI-MRI) **(Fig. 1)**. Pts with partial remission (PR) on d56 according to RECIST 1.1 were further treated with open-label sorafenib and monitored, pts with progressive disease (PD) were taken off study, and pts with stable disease (SD) were randomly assigned to blinded sorafenib or placebo and were further monitored every 8 wks and unblinded in case of PD. Pts on sorafenib were taken off study and pts on placebo were offered sorafenib with further monitoring.

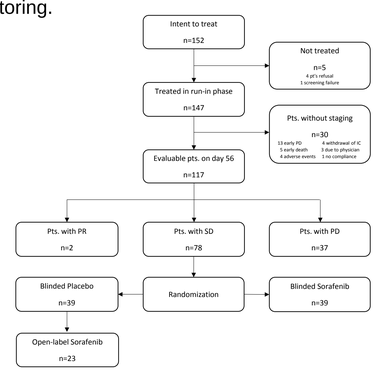


**Fig. 2.** STREAM patient flow diagram

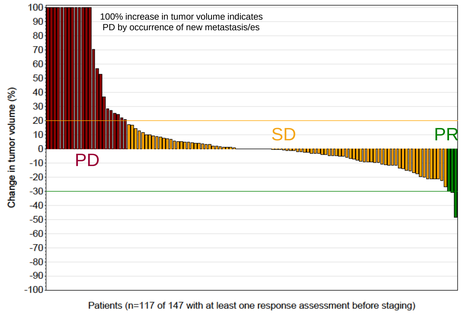


**Fig. 3.** Waterfall plot of best response of all patients evaluable after the run-in period (n=117)

## RESULTS

Altogether, 117 (79.6%) of 147 pts entering the run-in period were evaluable for response on d56. Two pts had PR (1.7%), 78 pts had SD (66.7%) and 38 pts had PD (32.5%), respectively **(Fig. 2)**. Median PFS from randomization was significantly longer with sorafenib (5.5 mths) than placebo (1.9 mths, p = 0.0079) **(Fig. 4)**. Sorafenib was readministered to 23 pts with PD under placebo (59.0%) with a median PFS of 1.9 mths (range 1.2-15.7 mths). Overall survival (OS) was not different between the sorafenib group (median 13.0 mths, range 0.9-36.2 mths) and the placebo group (median 12.2 mths, range 1.4-35.3 mths).

In the safety set of 147 pts there were 104 Treatment-Emergent Adverse Events (TEAEs) and 22 Treatment-Emergent Serious Adverse Events (TESAEs) with NCI-CTC grade 3/4 **(Table 2)** with highest incidences for rash (n=20), hypertension (n=14), hand-foot-syndrome (n=10), diarrhea (n=8) and nausea/vomiting (n=8), respectively. Intermittent dose reduction of sorafenib to 200 mg bid or discontinuation were performed, respectively. No pt died from toxicity.

The evaluation of the apparent diffusion coefficient (ADC) ratio derived from DWI-MRI in 47 pts of the run-in period showed a significant difference between pts with SD and pts with PD (p < 0.05) **(Fig. 6)**.

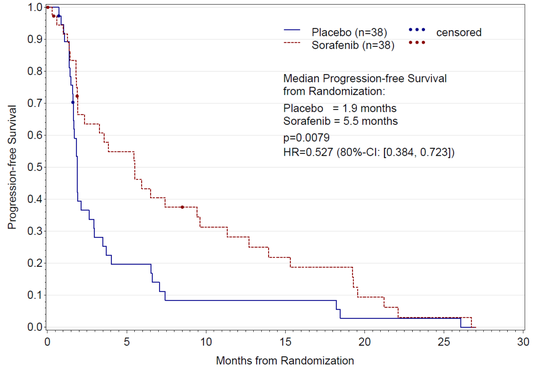


**Fig. 4.** Kaplan-Meier plot of PFS of all randomized patients (n=78) (blinded phase)

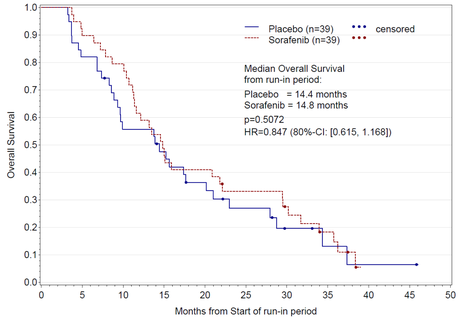


**Fig. 5.** Kaplan-Meier plot of OS of all randomized patients starting with the run-in period (n=78)

## CONCLUSIONS

- **The primary endpoint of STREAM was reached.**
- **Sorafenib is clinically active and tolerable in first-line treatment of pts with MUM with an increase of median PFS from 1.9 mths for placebo to 5.5 mths for sorafenib (p = 0.0079).**
- **The median OS of 14.8 mths compares favorably with previous findings in pts with MUM..**
- **Besides morphological MRI features, ADC ratio may be used as an additional functional response criterion.**

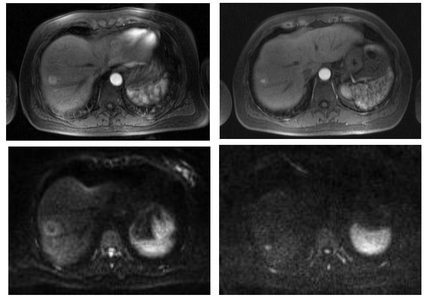

**Fig. 6.** Highlighting tumor regression of uveal melanoma metastasis under Sorafenib therapy on magentic resonance imaging **(a)** upper left: **d0** liver metastasis prior therapy **(b)** upper right: **d56** shrinking liver metastasis; **(c)** lower left: **d0** Vivid diffusion restriction prior therapy; **(d)** lower right: **d56** apparent decrease of diffusion restriction. The evaluation of the apparent diffusion coefficient (ADC) ratio derived from DWI-MRI of the run-in period showed a significant difference between patients with stable and patients with progressive disease (p<0.05).

**Table 2.** TEAEs and TESAEs with NCI-CTC grade 3/4 in the safety set of 147 pts

| | TEAEs | | TESAEs | |
|---|---|---|---|---|
| Skin and subcutaneous tissue disorders | 35 | 24% | 5 | 3% |
| Gastrointestinal disorders | 13 | 9% | 5 | 3% |
| General disorders | 7 | 5% | 3 | 2% |
| Vascular disorders | 13 | 9% | 2 | 1% |
| Nervous system disorders | 3 | 2% | 2 | 1% |
| Laboratory investigations | 16 | 11% | 2 | 1% |
| Infections | 4 | 3% | 1 | 1% |
| Neoplasms | 1 | 1% | 1 | 1% |
| Immune system disorders | 1 | 1% | 1 | 1% |
| Hepatobiliary | 2 | 1% | 0 | 0% |
| Metabolism and nutrition disorders | 6 | 4% | 0 | 0% |
| Musculoskeletal and connective tissue | 1 | 1% | 0 | 0% |
| Blood and lymphatic | 2 | 1% | 0 | 0% |

## REFERENCES


Mourinaux, F. et al. (2016) Sorafenib in metastatic uveal melanoma: efficacy, toxicity and health-related quality of life in a multicentre phase II study. Br J Cancer *115*:20-24

Di Marco, V. et al. (2013) Sorafenib: from literature to clinical practice. Ann Oncol *24 Supp2*:ii30-ii37


## ACKNOWLEDGEMENTS


We thank all patients and their families for participation in the trial and the study teams at the 3 centers for their deidcated work.

This Investigator Initiated Trial (IIT) was supported by a grant from Bayer Vital GmbH, Leverkusen, Germany. Medical monitoring and evaluation were performed by ClinAssess GmbH, Leverkusen, Germany.