An exploratory study investigating the metabolic activity and local cytokine profile in melanoma patients treated with pazopanib and paclitaxel


BACKGROUND
There is a medical need for new drugs in BRAF wildtype metastatic melanoma patients. Pazopanib is a multi-target tyrosine kinase inhibitor (TKI) with anti-tumour and anti-angiogenic activity.

OBJECTIVES
The primary aim of the study was to investigate the metabolic response to pazopanib monotherapy and pazopanib plus paclitaxel therapy in BRAF wildtype melanoma patients. Secondary endpoints were the early cytokine and chemokine profile and the histological findings.

METHODS
Orally given pazopanib (400 mg twice a day) was administered from day 1 to 10 and from day 14 to day 70. An intravenous infusion with paclitaxel (150mg/m^2 body surface) was administered on days 14, 35 and 56. Metabolic response evaluation was performed before treatment, after treatment with pazopanib (day 10) and after treatment with pazopanib and paclitaxel (day 70). Skin biopsy of metastasis tissue for chemokine and cytokine expression analysis, histology and immunohistochemistry (CD68, CD163) evaluation and blood samples were taken at the same time points.

RESULTS
2 patients failed screening, 17 were dosed. Out of 67 adverse events, 9 (13%) were grade 3 or 4. Five of 14 evaluable patients had a partial metabolic response at day 10 under pazopanib monotherapy. Response rate at day 70 under combined pazopanib-paclitaxel treatment was 0%.
Immunohistochemistry revealed an increase of M2-like macrophages in non-responders compared to responders. We observed a significant upregulation of 5 cytokines in responding (CXCL1, CXCL2, CXCL13, CCL22 and SPP1) versus non-responding lesions. Overall, the median progression-free survival was 70 days (range of 5 to 331 days), which did not significantly differ between responders (148 days) and non-responders (70 days; p=0.17).
CONCLUSION
In this patient population pazopanib efficacy was limited. Response is associated with low M2-like macrophage density and increased expression of several chemokines. This article is protected by copyright. All rights reserved.