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Phase I, safety, pharmacokinetic and biomarker study of telatinib (BAY 57–9352), an oral VEGFR-2 inhibitor, in a continuous schedule in patients with advanced solid tumors

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Background: Telatinib (BAY 57–9352) is a potent inhibitor of VEGFR-2/3, PDGFR-β, and c-Kit tyrosine kinase activity.
Methods: Patients with advanced solid tumors received oral telatinib on a continuous basis, in escalating doses. One cycle was defined as 21 days of treatment. Safety, pharmacological parameters, and anti-tumor activity were assessed. To evaluate systemic mechanisms on the vascular system, flow-mediated dilatation (FMD), nitroglycerin-mediated dilatation (NMD), and pulse-wave velocity (PWV) were measured at baseline and after 5 weeks of treatment in 10 patients.
Results: Forty-seven patients (median 55 years) received oral dosing ranging from 20 mg solution once daily to 1500 mg twice daily (bid; 150 mg tablets) for a total of 215 cycles (range 1−18). The most frequent drug-related adverse events were hypertension, nausea, hoarseness, vomiting, diarrhea, anorexia, fatigue, headache, rash, and dry skin. Three patients experienced drug related toxicity leading to a dose reduction: hypertension at 600 mg bid in Cycle 2; AST/ALT increase at 600 mg bid in Cycle 2; and fatigue combined with anorexia and weight loss at 1500 mg bid at the end of Cycle 1. One patient with a hemangio-endothelioma (600 mg bid) had a clinical response and one desmoid tumor patient (900 mg bid) had a 53% reduction in tumor volume. There were no partial responses. Telatinib exposure increased with dose and exhibited moderate to high variability. At 300 mg bid, levels were reached similar to preclinical active levels (target exposure AUC of 5). Increased $VEGF_{165}$ and decreased soluble (s)VEGFR-2 levels reached a plateau at doses of 900 mg bid. Mean systolic blood pressure increased from 129.0 mmHg to 139.4 mmHg after 5 weeks of treatment (difference 10.4 mmHg; $P = 0.002$). Mean diastolic blood pressure increased from 80.9 to 87.4 mmHg (difference 6.5 mmHg; $P = 0.013$). Endothelium-dependent vasodilatation (measured by FMD) decreased from 5.6% to 3.0% ($P = 0.003$). NMD, indicating endothelium-independent vasodilatation, decreased from 12.9% to 7.7% ($P = 0.001$). Arterial stiffness (measured by PWV) increased from 9.4 m/s to 10.3 m/s ($P = 0.07$).
Conclusions: Telatinib was well tolerated and, based upon clinical and pharmacologic assessments, the recommended dose level is 900 mg bid. VEGF and sVEGFR-2 levels demonstrated a dose-dependent change. A possible hypothesis for the observed vascular effects is a reduced functional number of microvessels.

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Pharmacokinetic characterization of BIBF 1120, an orally active triple angiokinase inhibitor (VEGFR, PDGFR, FGFR) in advanced cancer patients

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Background: BIBF 1120 is a triple angiokinase inhibitor targeting VEGFR, PDGFR, FGFR kinases. Basic pharmacokinetic (PK) characteristics were investigated when BIBF 1120 was administered orally to patients with various refractory advanced malignancies.
Methods: 124 male and female patients from three Phase I studies were included into this analysis. BIBF 1120 was continuously administered once (qd) or twice (bid) daily for 28 days with or without a 7 day wash out period. PK sampling was performed on days 1–2 and at steady state of the initial treatment course.
Results: After oral administration, BIBF 1120 was absorbed with median t_{max} values between 1–4 hours. Overall, BIBF 1120 maximum plasma concentrations and exposure increased with raising single-dose administrations and at steady state (qd dosing). For bid dosing, BIBF 1120 maximum plasma concentrations and exposure were highly variable over all dose groups. This was observed for single doses and at steady state. Splitting the cummulative daily dose into two daily administrations allowed an increase in the tolerable total daily dose, thereby permitting an increased exposure to BIBF 1120. Overall, BIBF 1120 pre-dose plasma concentrations increased with increasing doses at steady state. The terminal half-life of BIBF 1120 was ranged between 7 and 19 hours. The apparent volume of distribution during the terminal phase ranged between 8000 and 25,000 L, which might indicate an extensive tissue distribution of BIBF 1120. A high apparent total body clearance between 8000 and 23,000 mL/min was determined. Steady state was reached within 9 days after the first administration.
Conclusion: BIBF 1120 exposure and maximum plasma concentration increased with increasing doses after single dose administration and at steady state. The bid treatment regimen allowed an increase in the tolerable total daily dose. The values for total body clearance and volume of distribution should be treated with caution, since the absolute bioavailability of BIBF 1120 in humans has not yet been determined.

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VLA-4 integrin regulates prometastatic gene signatures in microenvironmentally-inducible melanoma cell subpopulations

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Experimental B16F10 melanoma (B16M) metastasizes to the liver and other organs through an oxidative stress-inducible VLA-4 integrin-mediated mechanism. However, the exact molecular mediators and regulatory factors that determine the process remain unclear. In the present work we studied the transcriptional profiles of active and inactive VLA-4-expressing melanoma cell subpopulations in order to determine the transcriptional signature associated to VLA-4-dependent melanoma metastases.
B16M cell subpopulations were separated through their adhesion to immobilized recombinant VCAM-1 (iVCAM-1) substrate and further assessed through ELISA quantification of secreted VEGF and in vivo quantification of their metastatic potential. 44K oligo-DNA microarray hybridizations allowed the identification, analysis and Gene Ontology classification of subpopulation-specific transcriptomes. Transcription level differences for selected genes were confirmed by means of real time PCR.
Active VLA-4 cells adhered very efficiently to iVCAM, secreted high levels of VEGF and produced a high number of large-size metastases. In contrast, the larger number of melanoma cells had inactive VLA-4 and therefore did not adhere to iVCAM, secreted low levels of VEGF and produced low metastasis number. Addition of 100 ng/ml soluble VCAM-1 and 10 μM hydrogen peroxide (H_2O_2) to inactive VLA-4 subset increased their tumor cell adhesion to iVCAM and increased their metastatic potential. Transcriptome analysis showed a subpopulation-specific signature of 178 differentially expressed genes (cutoff 1.8-fold, $p < 0.01$) in active VLA-4 cells compared to the inactive VLA-4 cells. Active VLA-4 cells showed overexpression of genes related to cell adhesion, death and metabolism, while inactive VLA-4 cells were characterized by proliferation and cell growth genes. Different transcriptional levels of genes with signaling functions indicated that these subpopulations had distinct signal response pathways. Transcriptional changes induced by sVCAM-H_2O_2-induced oxidative stress treatment differ between both subpopulations, with 113 and 308 treatment-induced genes in the active VLA-4 cells and inactive VLA-4 cell subsets, respectively. According to the functionality of the affected genes, there was an activation of cell death mechanisms in both cell subpopulations, and also a proadhesive effect induced by the treatment, specially in inactive VLA-4 cells. More specifically, Inactive VLA-4 cells showed an increased metabolism and signaling pathways while active VLA-4 cells responded through increased proliferation and cell growth mechanisms. Moreover, pretreatment with a synthetic VLA-4 inhibitor prevented transcriptional changes induced by sVCAM-H_2O_2 in both B16M cell subpopulations. In active VLA-4 cells, the synthetic compound prevented activation of 85% genes and inhibition of 87% genes. While in the inactive VLA-4 cell subpopulation, it prevented 96% of the genes from being activated and only 20% of the genes from being inhibited by the oxidative stress treatment. This approach overcame the dilution effect of analyzing the global B16M cell population, indicating the prometastatic cooperation of cell subpopulations, molecular interactions and environmental conditions.
This VLA-4-mediated prometastatic molecular mechanisms offers novel gene targets for the development of multiparametric diagnostic and therapeutic strategies.