Abstract  Purpose: Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that are believed to be involved in primary and metastatic tumor growth by degrading the basement membrane and changing the extracellular matrix to facilitate invasion of malignant cells and angiogenesis. Overexpression of MMPs has been documented in various solid tumors. BAY12-9566 is a selective inhibitor of MMPs, in particular MMP-2, -3, and -9. The purpose of this trial was to define the maximum tolerated dose (MTD), dose-limiting toxicities (DLT), safety profile, pharmacokinetics and pharmacodynamics of orally administered BAY12-9566 in patients with incurable solid tumors.  Methods: The starting dose of BAY12-9566 for this single institution, outpatient phase I study was 100 mg/day orally. Patients were allowed to receive drug for up to 12 months. A total of 27 patients with various solid malignancies including colorectal, breast, lung, cervical and ovarian cancers were enrolled at doses from 100 to 1600 mg/day. Patients were evaluated weekly on treatment.

Relevant radiologic examination was performed every 8 weeks to document and follow sites of measurable or evaluable disease. Results: Toxicities from BAY12-9566 included liver injury test abnormalities, anemia, shoulder and back pain, thrombocytopenia, mild nausea and fatigue, diarrhea, rash and deep vein thrombosis. No toxicity greater than grade III was observed. As doses were increased from 100 to 400 to 1600 mg/day, even in divided doses, less than proportional increases in AUC were observed. At the highest dose level of 1600 mg/day, the day 29 AUC (3778.00 mg·h/l) remained similar to the day 29 AUC (3312.60 mg·h/l) at the dose level of 1200 mg/day. No responses were seen, but 14 patients remained on study with stable disease for 4 to 26 months. Conclusions: BAY12-9566 was well tolerated at doses as high as 800 mg orally twice daily. Although mild alterations in liver injury tests, platelet count and hematocrit were noted, these were not dose-limiting. The drug was well absorbed. However, the absence of proportional increases in AUC with doses greater than 800 mg and the achievement ofCss in the range associated with biologic activity in preclinical models led to the selection of 800 mg twice daily for further evaluation in phase III trials.

Keywords Matrix metalloproteinase inhibitor · Advanced solid tumors

Introduction

Matrix metalloproteinases (MMPs) are a family of at least 16 different zinc- and calcium-containing proteolytic enzymes that play an important role in maintaining tissue homeostasis within the extracellular matrix. Although the members of this family share a highly conserved catalytic domain and a specific sequence in the prodomain, they differ in substrate specificity, inhibitor binding and matrix binding [4]. MMPs are believed to be
involved in primary and metastatic tumor growth by degrading the basement membrane and changing the extracellular matrix to facilitate invasion of malignant cells and angiogenesis. Overexpression of MMPs has been documented in various tumors, including breast, colon, gastric, head and neck, prostate and lung cancer [9]. Matrix metalloproteinase inhibitors (MMPIs) targeted against MMPs have been identified using several approaches for synthesizing and screening agents. BAY12-9566 is one of a series of MMPIs selected for inhibition of MMP-2, -3, and -9 with inhibitory constants of 11, 134 and 301 nmol/l.

In a B16.F10 murine melanoma model, growth of tumors implanted in mice was inhibited by a maximum of 50% when a 14-day course of oral twice-daily 100 mg/kg BAY12-9566 was administered [3]. When tumor cells were injected into the tail vein of B16.F10 mice 24 h before implantation, there was a 58% inhibition in the total number of metastases at the 100 mg/kg oral dose [7].

SCID mice with HCT 116 colon tumor fragments implanted in the cecum were treated with BAY12-9566 on day 5 at doses from 25 to 200 mg/kg [6]. There was inhibition of primary tumor growth of 35% at a dose of 100 mg/kg as well as a 50% reduction in the overall incidence of distant metastases. The size of the metastatic tumors was also smaller. In the H-23 human lung cancer xenograft model, BAY12-9566 was given with cisplatin. There was an increase in complete responses of established tumors with BAY12-9566 in combination with cisplatin compared to cisplatin alone.

In addition to promising preclinical data, a total 124 healthy volunteers have completed phase 1 studies with relatively little toxicity [2]. Pharmacokinetic analysis revealed a plasma half-life of 90–100 h, with protein binding of > 99.9% [10]. Kinetics were determined to be linear up to the 100 mg dose level. Based on these data and on the safety record in human volunteers, 100 mg/day was determined to be the starting dose in this trial.

The objectives of this trial were: (1) to define the maximum tolerated dose (MTD) or to achieve the steady-state plasma concentration (Css) of BAY12-9566 in the range associated with biologic activity in preclinical models, (2) to determine the dose-limiting toxicity (DLT), if any, (3) to assess the safety profile, (4) to determine the pharmacokinetics of BAY12-9566 when administered orally on a daily schedule to patients with advanced incurable solid tumors, and (5) to observe any evidence of antitumor activity.

### Materials and methods

#### Eligibility

All patients who were enrolled in this trial were more than 18 years of age, with an ECOG performance status of ≤ 2, and had a histologically or cytopathologically documented solid tumor that was refractory to conventional treatment. Life expectancy was required to be at least 12 weeks and patients were required to be capable of and willing to give written informed consent. Laboratory requirements included the following hematology and chemistry parameters: absolute neutrophil count (ANC) > 1500/µl, platelets > 100,000/µl PT/PTT within normal limits, bilirubin < 1.5 mg/dl, ALT, AST, and alkaline phosphatase less than twice the upper limit of normal, and creatinine < 1.5 mg/dl.

Patients who had had major surgery within the past 14 days, had received large field radiation therapy or chemotherapy within 28 days, or had received mitomycin or nitrosoureas within the past 42 days were excluded from the study. Concurrent chemotherapy, radiation therapy, or immunotherapy were not allowed to be administered while on study. Any patients with brain or meningeal metastases, active infections or other severe psychological or social problems preventing full compliance were not eligible. Patients with a history of gastrointestinal disorder or gastric and small bowel resections that could result in incomplete absorption of the study medication, a history of major cardiovascular events, such as myocardial infarction or stroke in the past 3 months, as well as patients taking oral anticoagulants were excluded from the trial. Patients were required to practice adequate birth control; women were excluded if they were either pregnant or breast-feeding. Patients with hypersensitivity to BAY12-9566 or similar compounds, a significant history of drug allergies to multiple medications, or having taken investigational drugs in the past 30 days were not eligible to enroll.

Approval was granted by the Institutional Review Board and all patients signed informed consents prior to initiation of treatment.

### Treatment

BAY12-9566 was supplied by Bayer Corporation, Pharmaceutical Division, (West Haven, Ct).

The initial oral daily dose of BAY12-9566 was 100 mg. At each dose level, patients received a single oral dose of study medication between 7 and 10 a.m. on day 1. A small breakfast was allowed prior to the first dose. The first dose was witnessed by either the investigator or the study nurse to ensure patient compliance. For the following 3 days, patients received twice-daily dosing to more rapidly achieve steady-state blood levels. On day 5, patients reverted to once-daily dosing. The study was initiated with 28 days of therapy followed by 2-week treatment breaks. After the first six patients were observed, patients received continuing daily doses.

### Study design

DLT was defined as one of the following toxicities that were possibly or probably related to the study medication: (1) any toxicity greater than grade 3, (2) symptomatic grade 2 toxicity that required holding or reducing a dose, (3) any grade 2 biochemical toxicity which persisted for more than 7 days, (4) other toxicities of concern to the investigator/sponsor. MTD was defined as the dose level at which the dose-limiting toxic events occurred in two patients. The NCI Common Toxicity Criteria were used to determine grade of toxicity.

Groups of at least three patients were treated and evaluated at each dose level. The dose escalation paradigm was as follows. (1) If no DLT was observed in the three patients who were treated for 28 days, then the next cohort of patients were treated at the next dose level. Dose escalation proceeded as follows: 100 mg daily, 400 mg daily, 400 mg twice daily, 400 mg four times daily, and 800 mg twice daily. (2) If one DLT occurred within the first 28 days of treatment, then the next three patients were enrolled at the same dose level. If only one of the six patients at this dose level experienced DLT, then dose escalation continued. If two or more of the six patients experienced DLT, then this dose was declared the MTD. (3) If two DLTs occurred within the first 28 days of treatment, then three more patients were enrolled at the same dose level and this dose was declared the MTD.