The International Journal of Biological Markers, Vol. 22 no. 1 (suppl 4), 2007, pp. S77-S87

Rationale and clinical results of multi-target treatments in oncology

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ABSTRACT: During the last 10 years, the concept of targeted biological therapy for the treatment of cancer has emerged. Targeted agents entered clinical practice only recently, and the first drugs with demonstrated clinical efficacy were mainly inhibitors of the ErbB family of receptors (i.e., EGFR and HER-2), either monoclonal antibodies (MAbs) or tyrosine kinase inhibitors (TKIs). After the proof of concept for the clinical efficacy and tolerability of these selective agents, it was conceived that most tumors will depend on more than one signaling pathway for their growth and survival. As a consequence, different strategies were pursued to inhibit multiple signaling pathways or multiple steps in the same pathway, either by the development of multi-targeted agents or the combination of single targeted drugs. The recent FDA and EMEA approval of sorafenib and sunitinib, both multi-targeted TKIs, marked the coming of age of this new generation of drugs. Now a whole new wave of multi-targeted compounds is moving into clinical trials, raising in the minds of investigators important questions about the best strategies to pursue in their use and many doubts about their differences and the seeming redundancies in the pipelines of pharmaceutical companies. This review will deal with the rationale underlying the multi-targeted approach and with the available clinical experience with multi-targeted agents, especially focusing on molecules with anti-EGFR mechanisms of action. (Int J Biol Markers 2007; 22 (suppl 4): S77-87)

Key words: Targeted therapy, Tyrosine kinase inhibitors, EGFR, VEGF

INTRODUCTION

Over the last few years, the eagerly awaited targeted drugs have made their entry into clinical practice for the cure of solid tumors. Following imatinib, which yielded dramatic results in GIST, the first agents that demonstrated clinical efficacy were mainly drugs targeting the ErbB family of receptors (i.e., EGFR and HER-2), either monoclonal antibodies (MAbs) or tyrosine kinase inhibitors (TKIs). Among the MAbs, cetuximab and trastuzumab are now registered drugs, both in the US and Europe, for the treatment of advanced colon cancer and locally advanced head and neck cancer for the first one and advanced breast cancer for the second one, whereas the TKIs erlotinib and gefitinib yielded responses and survival benefit (erlotinib) in second-line treatment of NSCLC. In 2006, sorafenib and sunitinib were licensed for advanced renal cell carcinoma, both drugs sharing the common feature of being multi-targeted TKIs, thus marking the coming of age of a new generation of drugs. At present, a whole new wave of multi-targeted compounds is moving into clinical trials, raising in the minds of investigators important questions about the best strategies to pursue in their use and many doubts about their differences and the seeming redundancies in the pipelines of different pharmaceutical companies. This review will deal with the rationale underlying the multi-targeted approach and with the available clinical experience with multi-targeted agents, especially focusing on molecules with anti-EGFR mechanisms of action.

MULTI-TARGETED TYROSINE KINASE INHIBITORS: SETTING THE STRATEGY FOR TREATMENT SUCCESS

Rationale of the multi-targeted approach and open questions

Data from clinical trials with the first anti-EGFR TKIs gefitinib and erlotinib provided proof of concept for the efficacy and tolerability of anti-ErbB TKIs, but it was also clear soon that these drugs could benefit only a limited subset of patients, with response rates in the range of 9% to 18% (1). Subsequent subset analyses suggested that female, never-smoker, Asian patients with adenocarcinoma and patients with bronchioalveolar carcinoma were more responsive, achieving greater clinical benefit. This could partly be explained by the subsequent identifica-

0393-6155/S77-11$15.00/0

tion of somatic mutations in exon 18 through 21 encoding the TK domain of the EGFR and the observation of a strong correlation between the presence of mutations and response to anti-EGFR TKIs (2). Then the problem of resistance emerged, either primary or acquired, with the identification of secondary mutations such as the T790M within exon 20 (3). Interestingly, T790M primary mutations may also occur in previously untreated patients and primary transforming mutations may also be resistant to gefitinib and erlotinib; this has been recently shown by the identification of an exon 20 insertion mutant that is completely resistant to these inhibitors (4). In addition, the T790M mutation is present in some but not all patients with acquired resistance to gefitinib and erlotinib, indicating the presence of additional mechanisms of resistance such as increased receptor trafficking.

While MAbs are clearly specific for their targets, these first TKIs were actually designed to be highly selective towards only one tyrosine kinase, providing a "clean" approach in order to avoid unexpected toxicities caused by inhibition of other pathways.

We know from tumor biology that, at the level of the single cell, it is unlikely that a neoplasm could be dependent on just one receptor or signaling pathway for its growth and survival; furthermore, compensatory crosstalk among receptors within a signaling network or with heterologous receptors could take place. At the level of tumor cell populations, the combination of genetic heterogeneity – arising from either genetic instability or a large number of cell replications at normal mutation rates – and selection pressure occurring during invasion and metastasis result in the generation of genetically distinct tumor cell sublines, which display characteristic signatures of protein expression. These differentially expressed proteins are suitable targets for therapeutic intervention but, depending on the predominance of the target, the treatment might result in partial response but not in definitive cure, which would require the identification of key early oncogenic mutations that should be present in all tumor cells (5). Given this important limitation, efforts have been made to develop strategies to inhibit multiple signaling pathways or multiple steps within the same pathway in order to increase the efficacy and overcome resistance to TKIs. This task can be accomplished in 2 ways: a) by combining relatively specific TKIs, or b) by using newer multi-targeted agents that inhibit more receptor tyrosine kinases at once.

In the first case, since TKIs have very different IC_{50} values for each target, one possible benefit is the possibility of obtaining exact titration of the concentration of either agent alone, reaching optimal inhibition of the involved targets (6). On the other hand, concomitant administration of 2 selective TKIs might result in drug-drug interactions, either at the level of absorption (almost all of these agents are orally administered), or at the level of drug metabolism. Biochemical and pharmacokinetic studies have shown that erlotinib acts as an inhibitor of CYP3A4 activity in vitro, whereas gefitinib is able to induce this enzyme. When these agents are administered in combination with other drugs metabolized by CYP3A4, the possibility of drug-drug interactions should be taken into account (6).

The second strategy, i.e., the use of single, multi-targeted TKIs, is a widely investigated field, with many agents having entered clinical trials (Tab. I and II). Administration of a single compound allows better compliance with treatment and avoids possible drug-drug interactions. Moreover, even though interference with multiple pathways could entail potential unexpected toxicities, the actual data from clinical trials revealed a manageable toxicity profile for most of these agents, and the dose-limiting toxicities observed in the phase I clinical trials tended to correlate with the targets inhibited. For instance, ZD6474 is an orally administered competitive inhibitor of the ATP-binding site of the VEGFR-2 tyrosine kinase and also inhibits EGFR-1 tyrosine kinase at submicromolar concentrations (see next section) (7). Accordingly, the dose-limiting toxicity in the phase I study consisted of diarrhea and rash, reflecting the inhibition of EGFR-1, and hypertension, linked to the inhibition of VEGFR-2 (8). The possible downside of the single-drug approach is that administration of a multi-targeted TKI disables exact titration of inhibition of the separate targets in each patient. The recommended dose based on phase I studies might not reflect optimal inhibition of all of the targets, which could be accomplished at plasma

TABLE I - MULTI-TARGETED TKIs ACTING THROUGH INHIBITION OF ErbB RECEPTOR FAMILY

Agent	Molecular target	TK inhibition	Development stage
AEE788	EGFR, HER-2, VEGFR-2	Reversible	Phase I
BMS-599626	EGFR, HER-2, ErbB4	Reversible	Phase I
Lapatinib (GW-572016)	EGFR, HER-2	Reversible	Phase I/II/III
BIBW-2992	EGFR, HER-2	Irreversible	Phase I
Canertinib (CI-1033)	EGFR, HER-2, ErbB3, ErbB4	Irreversible	Phase I/II
EKB-569	EGFR, HER-2	Irreversible	Phase I-II
HKI-272	EGFR, HER-2	Irreversible	Phase I, phase II (ongoing)
Vandetanib (ZD6474, Zactima)	VEGFR-2, EGFR, RET	Irreversible	Phase I/II, phase III (ongoing)

TABLE II - MULTI-TARGETED TKIs INHIBITING PATHWAYS OTHER THAN THE ErbB RECEPTOR FAMILY

Agent	Molecular target	Development stage
AMG 706	VEGFR, PDGFR, c-kit, Ret	Phase I, phase II (ongoing)
Axitinib (AG-013736)	VEGFR-2, VEGFR-3, PDGFR-β	Phase II (RCC)
AZD2171	VEGFR-1,-2,-3, PDGFR-β, c-kit	Phase I
BIBF 1120	VEGF, PDGF, FGFR, src family of tyrosine kinases (Src, LcK, Lyn)	Phase I
Imatinib (STI-571)	c-Abl, PDGFR-β, c-kit	Licensed for GIST (CML), orphan drug request for DFSP
Sorafenib (BAY43-9006)	c-Raf-1, B-Raf, VEGFR, PDGFR	Licensed for advanced RCC, phase II/III (melanoma, HCC, NSCLC)
Sunitinib (SU11248)	PDGFR, VEGFR, KIT, FLT-3	Licensed for advanced RCC and imatinib-resistant/intolerant GIST
Vatalanib (PTK787/ZK 222584)	VEGFR, PDGFR, c-kit	Phase II/III (colorectal carcinoma)

DFSP = dermatofibrosarcoma protuberans

concentrations yielding intolerable toxicity. For example, in the first phase II study on once-daily oral administration of ZD6474 to patients with previously treated metastatic breast cancer, the starting dose was 100 mg, which was increased to 300 mg in the absence of grade 3-4 QTc prolongation at the 100 mg dose (9). Diarrhea was the most commonly reported side effect with 4.5% of the patients at the 100 mg dose level and 37.5% at the 300 mg dose level experiencing ≥ grade 2 diarrhea. Rash was reported by 26% of the patients but no grade 3 or 4 rash occurred. Interestingly, hypertension requiring treatment was not reported, while the steady-state ZD6474 plasma concentrations for individual patients exceeded the projected IC_{50} for inhibition of VEGF-stimulated human umbilical vascular endothelial cell (HUVEC) proliferation in 90% of patients treated at 100 mg and in 100% of patients treated at 300 mg. In contrast, only one patient treated at 100 mg achieved a steady-state concentration above the projected IC_{50} for inhibition of EGFR-stimulated HUVEC proliferation, while 60% of the patients did so at 300 mg. However, these IC_{50} values are based on in vitro inhibition of VEGF- and EGF-stimulated HUVEC proliferation and do not reflect the heterogeneity of the tumor. Although most of the patients achieved plasma concentrations above the IC_{50} for VEGF inhibition, the lack of effects on blood pressure combined with the lack of effect on tumor perfusion studied with DCE-MRI in this phase II study suggests insufficient inhibition of VEGF during treatment with ZD6474. The absence of high-grade rash suggests suboptimal inhibition of EGFR as well (9). In addition, no antitumor activity was observed in this patient population.

Finally, a critical question ahead for multi-targeted therapy including anti-EGFR agents is whether newer molecules in early clinical development will be superior or complementary to the currently available anti-EGFR drugs, since the field of EGFR inhibitors is becoming increasingly crowded. An important discriminating feature in choosing different TKIs could be the presence of a reversible or irreversible mechanism of action (Tab. I). It was demonstrated that, in patients with acquired or primary resistant mutations to gefitinib and erlotinib, the irreversible EGFR inhibitors EKB-569, HKI-272 and CI-1033 (canertinib) were active in blocking receptor signaling and inhibiting growth at low concentrations (10). Specifically, HKI-272 showed in vitro capacity to circumvent not only the resistance conferred by T790M mutation, but also T790M-independent resistance mechanisms correlated with altered receptor trafficking (11). These observations encourage the use of irreversible anti-EGFR TKIs, even though, at this time, we cannot rule out that this class of agents may be less active against gefitinib- or erlotinib-sensitive mutations.

Dual targeting of EGFR and VEGFR through tyrosine kinase inhibitors

Newer multi-targeted TKIs can act through inhibition of multiple steps in the same pathway (as in the case of anti-EGFR/ErbB2 molecules, see Tab. I) or by prohibiting activation of different signaling pathways. Among the latter group of compounds, the most investigated approach so far has been dual EGFR/VEGFR inhibition, whose rationale will be discussed in this section.

Although they signal by separated mechanisms, EGFR and VEGF share common downstream pathways and several preclinical studies have provided evidence for direct or indirect angiogenic effects of EGFR signaling (12). In vitro studies demonstrated that human microvascular endothelial cells (HMVECs) do express EGFR, and that stimulation with EGF or TGF-alpha induces tube formation. Moreover, treatment with gefitinib, an EGFR TKI, inhibited EGF-induced migration and tube formation (13, 14). This was not observed for HUVECs, which do not express EGFR and do not migrate in the presence of EGF or TGF-alpha, suggesting that these ligands may not have a direct angiogenic effect. However, in the same cells cocultured with A431 cells, which express high levels of EGFR, EGF enhanced the migration of HUVECs. Under EGF stimulation A431 actually produced VEGF and IL-8, both positive regulators of angiogenesis that stimulate endothelial cell growth through paracrine mechanisms, accounting for an indirect effect of EGFR signaling on angiogenesis (13). It was also shown that EGF stimulation of glioma cells consistently increased the production of VEGF by these cells. The conditioned medium of the stimulated glioma cells induced activation of HUVECs, which could be inhibited by an anti-VEGF antibody (15). Given these important interactions between the two, it was not surprising to find that the inhibition of EGFR activation using monolconal antibodies or small-molecule TKIs confirmed the involvement of EGFR in tumor-induced angiogenesis. As for TKIs, gefitinib treatment of various cancer cell lines caused a dose- and time-dependent decrease in VEGF and bFGF production in vitro (16). Moreover, in head and neck squamous cell carcinoma, gefitinib also inhibited the expression of cyclooxygenease-2, which is considered to be involved in tumor-induced angiogenesis (17). In vivo studies with xenograft models have also been used to evaluate the effect of EGFR inhibitors on angiogenesis and metastasis formation, a process tightly dependent on new vessel formation. In these models, the antiangiogenic effects of anti-EGFR treatments were measured by assessing the apoptosis of tumor-associated endothelial cells and by microvessel density (MVD) in tumor specimens. Pancreatic carcinoma xenografts showed decreased expression of VEGF and IL-8 after several weeks of treatment with either cetuximab or PKI 166 (a TKI of EGFR), which was accompanied by decreased EGFR activation. The reduction in VEGF and IL-8 expression was associated with a decrease in MVD and an increase in endothelial cell apoptosis (18, 19). In a different cancer model, i.e., colon carcinoma, therapy with either cetuximab or gefitinib resulted in a decrease in VEGF, bFGF and TGF-alpha expression and a reduction in MVD (20).

Besides the synergy of EGFR/VEGF dual targeting as a result of the interactions between the 2 pathways, another important advantage of this approach is related to the possibility of overcoming resistance to anti-EGFR therapy. In cancer cells, altered control of angiogenesis could be a mechanism responsible for resistance to EGFR inhibitors in vivo, as has been shown in preclinical models with anti-EGFR blocking monoclonal antibodies and TKIs. Ciardiello et al (21) confirmed that VEGF expression was elevated in EGFR inhibitor–resistant colon cancer models, with data demonstrating that acquired resistance to EGFR antagonists might arise from enhanced VEGF expression rather than loss of the expression or functional alteration of EGFR signaling. In this study, prolonged administration of either cetuximab or gefitinib to athymic mice bearing human GEO colon cancer xenografts led to the development of resistant colon cancer cell lines that showed 5- to 10-fold increases in VEGF expression. In addition to the increase in VEGF expression, resistant tumors also exhibited expression of both cyclooxygenase-2 and activated MAPK, 2 upstream mediators of VEGF induction. In contrast to prolonged treatment with EGFR inhibitors, prolonged treatment with ZD6474, a dual TKI effective against both EGFR and VEGFR-2, did not result in the development of resistant tumors. Interestingly, sequential ZD6474 treatment of GEO tumor xenografts following cetuximab or gefitinib resulted in blockage of tumor growth, in contrast to retreatment with either selective anti-EGFR agent (21). Clinical proof of concept for this could come from a recent trial with lapatinib, a dual EGFR/Her2 reversible inhibitor, where treatment with this molecule resulted in responses in breast cancer patients resistant to trastuzumab, a MAb directed to HER-2, a different member of the ErbB family of receptors (22). Taken together, these data support the idea that a strategy based on the combination of antiangiogenic therapy and EGFR inhibition, such as with newer dual-targeting TKIs, may minimize resistance and result in greater clinical benefit.

CLINICAL EXPERIENCE WITH MULTI-TARGETED AGENTS

Multi-targeted inhibitors acting through inhibition of the ErbB family of receptors

Canertinib (CI-1033)

CI-1033 is a 4-anilinoquinazoline that acts via covalent binding to the ATP-binding site of the tyrosine kinase domains of all of the ErbB receptors (ErbB1/EGFR, ErbB2, ErbB3 and ErbB4), resulting in irreversible inhibition of these receptors. Oral administration of CI-1033 was well tolerated and the most common side effects reported in phase I studies were gastrointestinal toxicity, anorexia, rash and asthenia (23-25). In a phase II study including 105 patients with ovarian cancer who failed prior platinum-based therapy, 2 oral doses of CI-1033 were evaluated: 50 mg and 200 mg administered daily for 21 days

in a 28-day cycle. In this trial canertinib did not show significant therapeutic activity and no responses were reported; the 1-year survival rates were similar in the 2 dose level groups (37.7% and 38.5%, respectively). The percentages of serious adverse events were higher in patients receiving the 200 mg dose (26).

Lapatinib (GW572016)

Lapatinib is an orally active, reversible inhibitor of EGFR and ErbB2 tyrosine kinases. In phase I trials lapatinib was well tolerated in healthy volunteers and cancer patients (27, 28). The most common toxicity reported included rash, headache and gastrointestinal side effects (nausea, vomiting, diarrhea). In a pilot study on breast cancer patients, lapatinib exhibited biological and clinical activity, with evidence of increased tumor cell apoptosis in the specimens of patients showing tumor regression (29). In phase II trials lapatinib showed antitumoral activity in various tumor types, with a manageable toxicity profile (30-33). Recently, in a phase III study on ErbB2-positive advanced or metastatic breast cancer patients refractory to anthracyclines, taxanes and trastuzumab, lapatinib plus capecitabine showed a significant advantage over capecitabine monotherapy in terms of median time to progression (TTP) (8.4 vs 4.4 months) (22). The overall response rates were 22% and 14% for the combination arm vs capecitabine monotherapy (p=0.09). On the basis of the preliminary results, the therapeutic role of lapatinib for the treatment of brain metastases is currentlly under evaluation (34). Lapatinib was also compared to hormone therapy in a phase III study including patients with advanced renal carcinoma who expressed EGFR and/or ErbB2 by immunohistochemistry and failed prior cytokine therapy. Patients receiving lapatinib and with overexpression of EGFR had longer TTP (15.1 weeks vs 10.9 weeks; HR=0.76; p=0.06) and overall survival (OS) (46 vs 37.9 weeks; HR=0.69; p=0.02). However, in the overall study population this benefit was not observed, with similar TTP and OS (35).

Other ErbB1/ErbB2 multi-targeted TKIs in clinical development

BIBW 2992, HKI-272 and EKB 569 are highly potent irreversible dual ErbB1 and ErbB2 receptor TKIs in early clinical development. Adverse events commonly reported from phase I trials were diarrhea, skin rash, pruritus, mucositis, asthenia, anorexia, nausea, and vomiting (36-41). Interestingly, in preclinical models irreversible ErbB TKIs proved to be effective in overcoming gefitinib resistance of cultured cells that contained sensitizing and resistance-associated EGFR mutations, warranting further studies in cancer patients with acquired resistance to EGFR inhibitors (11, 42). BMS-599626 differs from the other agents in that it induces reversible inhibition of HER-1, HER-2 and HER-4 tyrosine kinases (43, 44).

Multi-targeted inhibitors with activity against ErbB and VEGF receptors

Vandetanib (ZD6474, Zactima)

ZD6474 is a once-daily oral agent targeting the key signaling pathways of VEGF, EGF and RET receptor tyrosine kinases. In phase I evaluation, ZD6474 was well tolerated at daily doses of 100-300 mg/day and commonly reported adverse events were diarrhea, rash, fatigue and asymptomatic QTc prolongation (8). Most clinical data in phase II studies are available in NSCLC.

Adding ZD6474 to carboplatin/paclitaxel in first-line chemotherapy was safe and did not significantly increase treatment toxicity (45). In a phase II randomized study performed by Heymach et al, patients with locally advanced or metastatic NSCLC after failure of first-line platinum-based chemotherapy were randomized to receive either docetaxel plus ZD6474 at a dose of 100 of 300 mg, or docetaxel alone. Median PFS was longer in patients receiving combination therapy (19 vs 17 vs 12 weeks, respectively) (46). Recently, a double-blind phase II randomized trial compared ZD6474 300 mg with gefitinib 250 mg in 168 previously treated patients with advanced NSCLC. Preliminary data showed a significantly longer PFS duration with ZD6474 than with gefitinib (11.9 vs 8.1 weeks, respectively; p=0.011) (47). These positive results were not confirmed in breast cancer: in 44 patients refractory to anthracycline/taxane, ZD6474 at a dose of either 100 mg or 300 mg did not show clinical activity (9). ZD6474 displayed promising evidence of activity in patients with hereditary medullary thyroid carcinoma; in a phase II trial with 15 evaluable patients, 3 had partial responses and 10 stable disease (48).

Other ErbB/VEGFR multi-targeted TKIs in clinical development

AEE788 is an orally active, small-molecule, multi-targeted TKI affecting several tyrosine kinases including EGFR, HER-2 and VEGFR-2. In phase I studies the most commonly reported toxicities were diarrhea, asthenia, anorexia, rash, nausea and vomiting. However, AEE788 was generally well tolerated and most of the adverse events were generally mild or moderate (49-51). Dose-limiting toxicities were observed at the 500 mg to 550 mg dose levels. Enrolment in clinical trials is continuing. XL647 is an orally bioavailable small molecule with inhibitory effects on EGFR, ErbB2, VEGFR2/KDR and EphB4. In a phase I study XL647 showed a satisfactory toxicity profile. The maximum tolerated dose was established at 4.68 mg/kg orally administered for 5 consecutive days every 2 weeks. Further examination is ongoing (52).

Multi-targeted inhibitors with activity against VEGFR and other tyrosine kinases

Axitinib (AG-013736)

Axitinib is an oral multi-targeted TKI with inhibitory effects against VEGFR-2, VEGFR-3 and PDGFR-β. Phase I studies identified a maximum tolerated dose of 5 mg twice daily (53, 54). Rini and colleagues evaluated axitinib in a phase II trial including 52 patients with advanced renal cell carcinoma (RCC) refractory to one prior cytokine-based therapy. Partial response was reported in 24 patients (46%) and stable disease in a further 40%. Median time to progression was not reached after 12 to 18 months' follow-up in all patients. Most common serious adverse events (grade 3-4) were diarrhea (8%), hypertension (15%) and fatigue (8%) (55). Recently axitinib has been evaluated in 32 patients with advanced thyroid cancer, including papillary, follicular, medullary and anaplastic histology refractory to or not suitable candidates for iodine. Although response assessments are still ongoing, partial response was achieved in 3 patients (56).

Vatalanib (PTK787/ZK 222584)

Vatalanib is a small-molecule, orally active TKI of all known VEGF receptors, platelet-derived growth factor receptor (PDGFR) tyrosine kinases and the c-kit protein tyrosine kinase. In phase I studies the most common side effects reported were fatigue, hypertension, nausea, vomiting, light-headedness and transaminase elevation (57-59). The dose identified for further examination was 1250 mg daily. In phase II studies vatalanib showed clinical activity in several solid tumors (60-62). Phase III trials did not yield conclusive results in patients affected by metastatic colon-rectal carcinoma (mCRC). In fact, the CONFIRM-1 study including 1168 patients with mCRC demonstrated no beneficial effect of adding vatalanib (1250 mg once a day) to chemotherapy (FOLFOX-4) in first-line treatment (63). Adverse events attributable to PTK/ZK were generally reversible and similar to those of other antiangiogenic agents. In the phase III placebo-controlled CONFIRM-2 study that enrolled 855 patients with mCRC, the addition of valatinib to the same chemotherapy regimen (FOLFOX-4) in second-line treatment resulted in a longer PFS than with chemotherapy alone (5.5 months vs 4.1 months; HR: 0.83; p=0.026). Response rates were similar in the 2 arms (18.5% in the PTK/ZK arm vs 17.5% in the placebo arm) and no survival advantage was reported (OS was 12.1 months in the PTK/ZK arm and 11.8 months in the placebo arm. HR: 0.94; p=0.511) (64). Recently, a meta-analysis of these 2 studies was performed, based on the preliminary results from CONFIRM trials that showed a greater clinical benefit and improvement of PFS in patients with high LDH levels. This analysis confirmed that the effect of vatalanib in improving PFS is strong in the patient population with high LDH (HR 0.65; p<0.001) compared with the overall population (HR 0.85; p=0.005), although further evaluation is planned to confirm this (65).

Sorafenib (Bay 43-9006, Nexavar)

Sorafenib is an oral inhibitor targeting multiple kinases including Raf, VEGFR-2, VEGFR-3, and PDGFR-β. In a phase I study sorafenib showed activity in various tumor types and a manageable toxicity profile, both in monotherapy and in association with chemotherapy (66-68). Dose-limiting toxicity consisted of diarrhea, fatigue, hypertension, skin rash and hematological toxicity. A dose of 400 mg twice daily was identified as recommended for phase II evaluation. In this setting sorafenib showed antitumoral effect in patients with various types of solid tumors, especially RCC (69-72). In a large phase II randomized discontinuation trial including 202 patients with metastatic RCC, sorafenib showed clinical efficacy and was well tolerated. During the run-in period, 73 patients had tumor shrinkage of >25% and median overall PFS was 29 weeks for the overall population. No patients died from sorafenib-induced toxicity (73). A subsequent phase III study including 769 patients with advanced or metastatic cytokine-refractory RCC demonstrated the antitumoral activity of sorafenib in this population and significant clinical benefit (74). Indeed, median PFS was 24 weeks in the sorafenib arm versus 12 weeks in the placebo arm (HR=0.44; p<0.00001). Common side effects were diarrhea (33%), rash (34%), hand-foot skin reactions (27%), fatigue (26%) and hypertension (11%). Updated results reported recently showed a survival advantage compared to placebo (median OS 19.3 vs 15.9 months, respectively; HR=0.77; p=0.015) (75). Based on these results sorafenib was approved by the FDA for the treatment of advanced or metastatic RCC refractory to cytokine therapy. The feasibility of combination therapy with interferon-alpha (IFN-α) is now under evaluation in phase II trials, as is a direct comparison between these 2 agents in patients with RCC (76-78). Because of the positive results in phase II studies, ongoing phase III studies are evaluating the role of sorafenib in treatment of HCC, melanoma and NSCLC.

Sunitinib (SU 11248, Sutent)

Sunitinib is a potent oral inhibitor of VEGFR-1, VEGFR-2, KIT (stem-cell factor [SCF] receptor), PDGFR-α, PDGFR-β and fetal liver tyrosine kinase receptor 3 (FLT3). In phase I trials sunitinib showed manageable toxicity and the most common side effects reported were fatigue, hypertension, sore mouth, and skin, gastrointestinal and hematological toxicity (79, 80). Among the side effects, an increased incidence of hypothyroidism was reported,

although the mechanism of toxicity is still unknown (81). Sunitinib demonstrated antitumoral activity in patients affected by NSCLC, neuroendocrine tumors and other tumor types, although most data are available for patients affected by GIST and RCC (82, 83). Two phase II clinical trials evaluated the activity of sunitinib (50 mg daily administered for 4 weeks followed by 2 weeks off) in patients with RCC after failure of previous immunotherapy (84, 85). In the first study of Motzer et al (n=63), 40% of partial responses were reported and TTP was 8.7 months (84). In addition, 27% of patients demonstrated stable disease lasting more than 3 months. The most commonly reported adverse event was fatigue (grade 3 in 11% of patients). Therapeutic activity was confirmed by a further study conducted in the same patient population (85). Partial response was obtained in 36 of 106 patients (34%) and the median PFS was 8.3 months. Recently, Motzer et al compared IFN-α with sunitinib as first-line therapy in metastatic RCC. Sutininib showed a statistically significant higher response rate (24.8% vs 4.9%) and PFS (47.3 vs 24.9 weeks) than IFN-α (86). Preliminary experience showed therapeutic efficacy of sunitinib in imatinib-resistant GIST (87, 88). In a phase III study conducted by Demetri et al, 312 patients were randomized in a 2:1 ratio to receive sunitinib (n=207) or placebo (n=105); the trial was unblinded early because a planned interim analysis showed a significantly better outcome in the sunitinib arm (89). The median time to tumor progression was significantly longer in the sunitinib group than in the placebo group (27.3 vs 6.4 weeks, respectively; HR 0.33; $p<0.0001$). The confirmed objective response rate was 7% in the sunitinib group versus 0% in the placebo group ($p=0.006$). The survival benefit could be underestimated as a result of the cross-over of patients receiving placebo. On the basis of these clinical results, sunitinib was approved by the FDA for the treatment of advanced RCC refractory to cytokine therapy and of imatinib-resistant or imatinib-intolerant GIST.

Other multi-targeted TKIs in clinical development

BIBF 1120 is an oral inhibitor of VEGF, PDGF, and FGF receptor kinases. It also inhibits members of the src family of tyrosine kinases (Src, LcK, Lyn). In phase I studies BIBF 1120 was well tolerated in patients with advanced solid malignancies. The most common toxicities were nausea, vomiting, diarrhea, abdominal pain, fatigue, and asymptomatic, reversible liver enzyme elevations. The maximum tolerated and recommended dose for further phase II studies was found to be 250 mg administered twice daily (90, 91). AMG 706 is an oral small-molecule multi-kinase inhibitor with both antiangiogenic and direct antitumor activity that selectively targets VEGF, PDGF, and Kit receptors. In phase I trials AMG 706 showed a manageable toxicity profile and displayed promising antitumoral activity (92). AZD2171, a potent oral inhibitor of the tyrosine kinase activity of all VEGFR subtypes, in now under evaluation in various tumor types.

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Received: December 5, 2006
Accepted: December 19, 2006