SU11248 and ZD6474 are metabolized by CYP3A4. Thus, a cocktail of single targeted TKI has an increased risk of drug-drug interaction.
**Toxicity:** Targeting multiple kinases with a single agent comes at a cost (eg SU11248 adverse-event profile), and optimizing such multitargeted molecules in terms of toxicity is challenging. Combination of cytotoxic agents leads usually to the addition of common toxicities (i.e. neutropenia), such assumption cannot be made for TKI, especially if they inhibit different pathways. In that regard the preclinical evaluation of single targeted TKI combinations is an important prerequisite. Combination of selective tyrosine kinase inhibitors has the advantage of the possibility to titrate the dose of either agent to optimize target inhibition.
**Efficacy:** EGFR TKI lead to response rates in NSCLC of only 9–18%. In contrast, imatinib achieves cytogenetic response rates of 60% and complete haematological responses in 95% of CML patients. It also leads to 50% objective remissions in GIST, plus an additional 40% long lasting absence of progression. SU11248 leads to an impressive response rate in renal cell cancer of 37 to 40%.
**Resistance:** The use of cocktail therapies to prevent or delay the appearance of resistant kinase variants, analogous to the use of drug cocktail for the treatment of tuberculosis or HIV infections, is of importance.
**Pragmatic issues:** When combining TKI, pharmaceutical companies will prefer to combine agents from their own development pipeline, rather than using agents from competitors. From a regulatory point of view developing a combination of agents will be challenging.

**33** INVITED

**Combination of tyrosine kinase inhibitors, or monoclonal antibodies, with radiotherapy and chemotherapy**

M.J. Ratain. *University of Chicago, Medicine, Chicago, USA*

Systemic therapy of cancer has included drug combinations for more than 40 years, stimulated in part by the success in treating tuberculosis with multiple drugs. The vast majority of advances in the treatment of cancer have resulted from the use of combination therapy, although our recent successes with kinase inhibitors have focused on the use of these agents as monotherapy. Although there have been notable successes in combining newer agents with chemotherapy (e.g., bevacizumab), there have also been some very high profile failures (e.g., gefitinib). Thus, it is important to identify a contextual framework for successful development of these newer agents with established treatment regimens. Generally, combinations are developed because of a hypothesis (not necessarily supported by any data) that a particular kinase inhibitor improves the therapeutic index of a particular chemotherapy agent. The development of most combinations begins with preclinical studies. It is important to emphasize that in vivo studies (e.g., xenografts) are more relevant to the aforementioned hypothesis than in vitro studies, as the former allows for an assessment of modulation of toxicity. Assuming that the preclinical studies support clinical development, the next major challenge is the clinical development plan. Although phase I studies of such combinations are routinely performed today, such studies are probably not necessary for all combinations. The most important issue to be assessed (should a phase I be performed) is whether the kinase inhibitor enhances the toxicity of the chemotherapeutic. Most phase I combination studies performed to date have not adequately addressed this specific question. The phase II challenge is even more daunting, and the specific plan depends on whether the kinase inhibitor has demonstrable single-agent activity in the disease of interest. As a general rule, the most important principle for phase II studies of such combinations is randomization, which allows formal comparison of the combination to monotherapy. The initiation of phase III trials based primarily on single-arm phase II data (compared to historical controls) is unlikely to be a good use of patient and monetary resources. Specific examples to support the need for randomized phase II trials of combinations will be discussed.

## Wednesday 8 November

# Poster Sessions

# Angiogenesis and metastasis inhibitors

**34** POSTER

**A phase II study of the combination of bevacizumab and erlotinib in patients with patients with unresectable hepatocellular carcinoma**

M. Thomas[1], M. Iwasaki[1], K. Higginbotham[1], R. Lozano[2], K. Glover[1], J. Abbruzzese[1]. *[1]University of Texas of M.D. Anderson Cancer Center, Gastrointestinal Medical Oncology, Houston, USA; [2]University of Texas M. D. Anderson Cancer Center, Department of Pharmacy, Houston, USA*

**Purpose:** HCC is the 5th most common solid tumor worldwide and the incidence is rising in western countries. >75% of patients (pts) are ineligible for liver transplant, resection, or ablation, and existing chemotherapy does not prolong pt survival and can have significant toxicity in pts with hepatic dysfunction. HCC are highly vascular tumors, and based on the prevalence of vascular endothelial growth factor (VEGF) and epidermal growth factor receptors (EGFR) in HCC, we are conducting a Phase II, single-arm, open-label trial of bevacizumab (B) and erlotinib (E) in pts with HCC.
**Patients and Methods**: Eligibility criteria include biopsy-proven unresectable HCC, Child-Pugh class A or B cirrhosis, bilirubin $\leqslant$2.0 mg/dL, transaminases (TA) $\leqslant 5\times$ULN, Plts $\geqslant$ 60,000 K/UL and ECOG PS $\leqslant$ 2. Prior allowed therapies are surgery, external radiotherapy, ablation, chemoembolization (TACE) and one systemic therapy. Pts receive B 10 mg/kg q14 days plus E 150 mg orally daily. Early stopping rules were included for lack of efficacy.

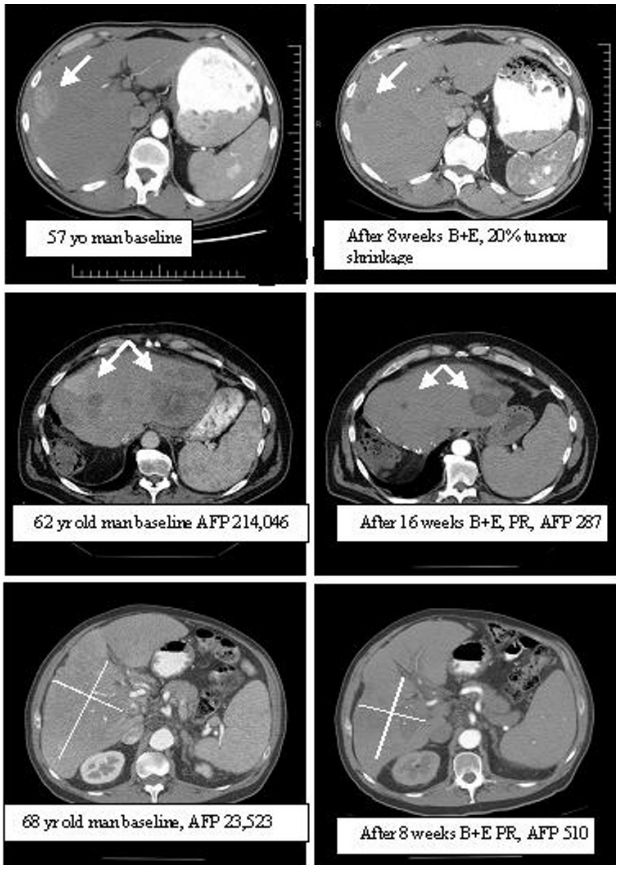


Fig. 1.

**Results:** The primary endpoint is the percent of pts alive and progression free (PFS) after 16 wks of therapy based on median PFS of 16 wks in pts treated with doxorubicin in published studies. Response is evaluated by RECIST criteria. 17 pts have been enrolled. This interim report focuses on evidence of anticancer activity of B+E in HCC pts. For all pts, the median