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.

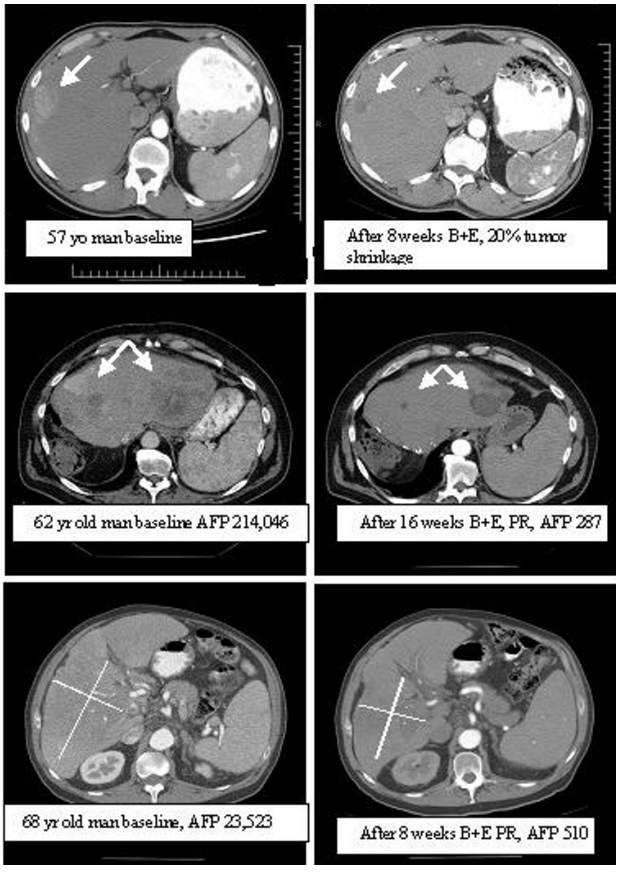


Fig. 1.

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

age was 68 (29−77), 13 (75.5%) were male, 11 (64.7%) were Caucasian, 4 had prior systemic therapy, and 6 pts had prior TACE. Of the 13 pts evaluable for response, 5 SD at 16 wks (38% PFS; 2/5 showed tumor shrinkage <20%), 3 have confirmed PRs, 2 SD at 8 weeks continuing on therapy; 2 pts SD at 8 wks but removed for toxicity; 1 PD. 3 pts not yet evaluable, 1 pt withdrew consent. 8 pts with SD showed radiographic evidence of decreased tumor vascularity (Fig. 1). One pt with 20% tumor shrinkage and improved portal vein involvement was removed from the study and underwent surgical resection. Generally B+E are well tolerated; the most common Gr 1 and 2 toxicities are folliculitis, anorexia, diarrhea, dry skin, and epistaxis. Gr3 toxicities experienced by 4 pts were TA elevation, diarrhea, fatigue, hyperkalemia, hypertension, and proteinuria. No Gr4 toxicities have been encountered.
Conclusions: The trial will continue to full accrual of 40 patients. Based on these early encouraging results and the favorable side effect profile, the combination of B+E warrants further study in HCC.

35 POSTER

A Phase I trial of a combination of the mTOR Inhibitor Everolimus (RAD001) and two schedules of the vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor Vatalanib (PTK787/ZK 222584) in patients (pts) with advanced solid tumors

G. Dy, G. Croghan, A. Furth, J. Reid, L. Hanson, M. Roos, A. Tan, A. Adjei. *Mayo Clinic, Rochester, USA*

Background: Preclinical studies demonstrate synergistic antitumor effects of mTOR inhibitors in combination with anti-angiogenesis agents.
Materials and Methods: A phase I study was performed to define the maximum tolerated dose (MTD), toxicities and clinical activity of escalating single daily doses of vatalanib in combination with RAD001, followed by determination of the MTD of twice daily doses of vatalanib in combination with RAD001 (see table), in pts with advanced cancers. A cycle length was 28 days. Once the optimal dose and schedule of the combination is defined, the study will expand to evaluate pharmacokinetics (PK), and temporal changes in functional imaging and in molecular markers of VEGF inhibition (sVEGFR, VEGF levels) and mTOR inhibition (4EBP, eIF4E, p70S6 kinase activity).
Results: 29 pts received 106 cycles of treatment through 5 dose levels. The most common toxicities were fatigue, hyperlipidemia, transaminitis, nausea, stomatitis and hypertension. NCI CTC grade3+ treatment-related toxicities (cumulative events in all cycles, CTC grade) included transaminitis (3 grade 3 ALT elevation; 1 grade 3 AST elevation), diarrhea (3 grade 3), hypercholesterolemia (1 grade 3), hypertriglyceridemia (2 grade 3), thrombosis (1 grade 3), pancreatitis (1 grade 3), and muscle spasms (1 grade 3). DLTs were grade 3 ALT elevation, muscle spasms and diarrhea. Partial responses were seen in 2 patients (chemo-refractory neuroendocrine pancreatic cancer at dose level 0, treatment-naïve clear cell renal cell cancer at dose level 3). Stable disease (4+ cycles) occurred in 8 pts. Dose level 2 (10 mg RAD001 and 1250 mg vatalanib) is the MTD for the single daily dose schedule. Dose level 4 (10 mg RAD001 and 1000 mg vatalanib) is the MTD for the twice daily dose schedule of vatalanib.

Table 1. Treatment data

Dose level	RAD001 (mg, daily)	Vatalanib (mg)	No. pts (No. replaced)	No. cycles	No. DLTs
0*	5	1000 QD	3 (3)	32	0
1	10	1000 QD	3	14	0
2	10	1250 QD	6	21	1
3	10	750 BID	6 (1)	26	1
4	10	1000 BID	5 (2)	13	1

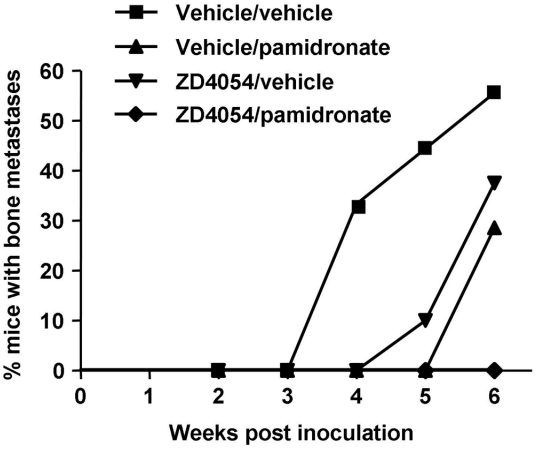
Conclusions: The combination of RAD001 and vatalanib is effective and well-tolerated. We recommend the twice-daily schedule of vatalanib in combination with RAD001 for future evaluation in phase II studies, based on a higher dose intensity and tolerability. Results of PK and pharmacodynamic studies in the expanded cohort will be presented.

36 POSTER

The combination of a specific endothelin A receptor antagonist ZD4054 and submaximal bisphosphonate pamidronate prevents bone metastasis

E.D. Williams[1], E.W. Thompson[2], D. Sreedharan[2], N. Brooks[3]. *[1]Bernard O'Brien Institute of Microsurgery, Prostate Cancer Metastasis Laboratory, Fitzroy, Australia; [2]University of Melbourne, Department of Surgery (St Vincent's Hospital), Melbourne, Australia; [3]AstraZeneca, Alderley Park, Macclesfield, United Kingdom*

Bone metastases cause significant morbidity for people with cancer due to bone pain, fractures, and nerve compression. Bone metastases are most commonly osteolytic, but some tumour types, most notably prostate cancer, typically form osteoblastic metastases. Nevertheless, many overtly osteolytic metastases have an osteoblastic component, which has been attributed to the ability of bone-synthesising osteoblasts to increase osteoclast function (as osteoblasts are the main regulators of osteoclasts). Tumour secreted endothelin-1 is thought to be a key factor stimulating the osteoblastic phenotype. Clinically approved bisphosphonates prevent bone resorption by osteoclastic mechanisms and reduce the release of bone growth factors, resulting in fewer skeletal-related events.
We have investigated the interaction between the specific endothelin A receptor antagonist ZD4054 and the bisphosphonate pamidronate on the formation of mixed osteoblastic/osteolytic metastases following systemic inoculation of the metastasis-selected B1 subline of the TSU-Pr1 human bladder carcinoma cell line.
Male SCID mice (n = 7–10/group) were randomly allocated to 4 experimental arms: (i) vehicle (oral gavage, daily)/vehicle (s.c., twice weekly), (ii) vehicle/pamidronate (4 mg/kg s.c., twice weekly), (iii) ZD4054 (25 mg/kg, oral gavage, daily)/vehicle, and (iv) ZD4054/pamidronate. Treatment was initiated the day prior to intracardiac inoculation of TSU-Pr1-B1 cells. Mice were X-rayed weekly, and tissues collected for histological analysis and measurement of human DNA at the conclusion of the experiment (6 weeks following inoculation of tumour cells). Treatment with either ZD4054 or pamidronate significantly delayed the formation of bone metastases. In the mice receiving both agents, no bone metastases were detected using high resolution X-ray.
Endothelin A receptors are found both on osteoblasts and on many types of tumour cells, including the majority of invasive bladder carcinomas. Bisphosphonates act on bone cells (predominantly osteoclasts) rather than tumor cells. These data suggest that combined therapy targeting tumour cells and the bone environment by a combination of anti-osteoblastic and anti-osteolytic treatments may provide maximal inhibition of bone metastasis.



37 POSTER

VEGFRs inhibitor E7080 inhibits lymph node metastasis of human breast carcinoma, by preventing murine lymphatic endothelial cells from lymphangiogenesis

M. Junji[1], A. Tsuruoka[1], K. Morimoto[2], T. Uenaka[1], Y. Yamamoto[1], T. Watanabe[3], M. Okada[2], S. Abe[1], T. Wakabayashi[1], M. Asada[1]. *[1]Discovery Research Laboratories II, Eisai Co., Ltd., Ibaraki, Japan; [2]KAN Research Institute, Kyoto, Japan; [3]New Product Development, Clinical Research Center, Eisai Co., Ltd., Tokyo, Japan*

The spread of tumor cells into regional lymph nodes through the lymphatic system correlates with poor prognosis in breast, lung and