60 tumor cell line panel. Similar to CA-4, compounds **1a–c** had a definite cytotoxic activity, displaying MG_MID $LogGI_{50}$ values of −6.59, −7.50 and −7.17, respectively. Docking experiments also showed that the trend of the calculated interaction energies of **1** and **2** with the colchicine binding site on tubulin, which is the target for combretastatins, is similar to that of the *in vitro* $LogGI_{50}$ values of these compounds.
Conclusions: Combretastatin-like imidazole derivatives possess vascular disrupting activity, hence representing promising chemical entities for the design of novel VDA.

29 ORAL

Embryonic stem cell vaccination prevents lung cancer

J. Eaton, R. Mitchell, B. Brewer, E. Krishnan, L. Williams, X. Gao, M. Janjua, H. Bodduluri. *University of Louisville, J. G. Brown Cancer Center, Louisville, KY, USA*

Background: The antigenic similarities between tumor cells and embryos prompted us to test the idea that vaccination with embryonic stem cells (ESC) would prevent tumorigenesis. Here, we report that, in two separate models of lung cancer, vaccination with allogeneic ESC provides protection against tumor outgrowth.
Materials and Methods: C57Bl6 mice were vaccinated s.c. (primary and boost 10 days apart) with live allogeneic ESC alone or with a combination of ESC and a source of GM-CSF (STO fibroblasts retrovirally infected with a GM-CSF retroviral expression vector).
Results: In animals subsequently challenged with transplanted (syngeneic) Lewis lung carcinoma (LLC), prior vaccination with ESC alone or ESC + STO/GM-CSF is 80–100% effective (respectively) in preventing tumor outgrowth. Prevention of tumor growth is primarily due to the activity of cytotoxic T lymphocytes because (1) splenocytes from vaccinated animals are exceptionally active in in vitro tumor cell killing (e.g., 20% kill of LLC at an effector:target ratio of 5:1) and (2) in vivo depletion of CD8+ T lymphocytes completely abrogates the anti-tumor effect of prior vaccination on the outgrowth of implanted LLC. Most importantly, this vaccination strategy prevents the development of lung tumors in a mouse model of carcinogen-initiated lung cancer (3-methylcholanthrene administration followed by repetitive dosing with butylated hydroxytoluene). While 100% of control (unvaccinated) mice developed lung tumors, 60% of ESC vaccinated and 90% of ESC + STO/GM-CSF vaccinated mice remained tumor free after 27 weeks. In over 200 mice vaccinated with ESC we found no evidence of autoimmune disease or significant decline in the numbers of adult pluripotent bone marrow stem cells.
Conclusions: Our results thus far raise the exciting possibility of developing a prophylactic vaccine capable of preventing the appearance of various types of cancers in humans, especially those with hereditary, chronological or environmental predispositions to neoplastic disease.

29LB1 Late Breaking ORAL

Final safety, pharmacokinetic and antitumor activity results of a phase I study of YM155, a novel survivin inhibitor, when administered by 168 hour continuous infusion

A.C. Mita[1], S. Antonia[2], L.D. Lewis[3], J.J. Mahany[2], N.J. Reddy[3], A. Ricart[1], E. Till[1], D. Buell[4], A.T. Keating[4], A.W. Tolcher[1]. [1]*Institute for Drug Development, CTRC, San Antonio, TX, USA;* [2]*Moffitt Cancer Center, Tampa, Fl, USA;* [3]*Dartmouth Hitchcock Medical Center, Lebanon, NH, USA;* [4]*Astellas Pharma US, Deerfield, IL, USA*

Background: Targeting the inhibitor of apoptosis proteins (IAPs) is a novel anticancer therapeutic strategy. Survivin is a key member of the IAP family, selectively expressed in most solid tumors but not expressed in most normal tissues. YM155 is an imidazole bromide derivative selected via high throughput screening, which inhibits survivin mRNA transcription and protein expression and showed potent (nM) anti-proliferative activity in a broad spectrum of preclinical models. In vivo, YM155 exhibited high distribution in tumor tissue and induced major tumor regressions (including complete remissions) in lymphoma, lung and prostate xenografts.
Material and Methods: This classical "3+3'' dose-escalation study aimed to determine the maximum tolerated dose (MTD) of 168 hour continuous IV infusion of YM155 every 3 weeks, to evaluate toxicity, characterize the pharmacokinetics and observe anti-tumor activity. Additional patients (pts) were added to fully characterize toxicities at the MTD. Pharmacokinetic sampling was performed during cycles 1 and 2.
Results: A total of 41 pts (M/F: 31/10, median age 61, range 28−78) with performance status of 0–2 were treated at 4 dose levels [1.8 mg/m^2/day (N = 8), 3.6 (6), 6.0 (2) and 4.8 (25)]. Most common tumor types were prostate (9), and colorectal (5) carcinomas and NHL (5). Dose-limiting toxicities (DLTs) were encountered at 6.0 mg/m^2/day (reversible renal tubular necrosis with grade 3 mucositis in one pt and increased serum creatinine in one pt). The MTD was established at 4.8 mg/m^2/day. Serious adverse events related to YM155 included: one grade 4 transient neutropenia, 2 grade 3 mucosal inflammations and 1 grade 3 renal tubular necrosis. Common grade 1–2 toxicities were pyrexia, arthralgia, nausea, fatigue and diarrhea. At MTD, median clearance was 45.6 L/hr with a median steady state concentration of 7.67 ng/mL and a median terminal half-life of 24 hours. Three pts with NHL (2 chemotherapy refractory intermediate grade B-cell, and 1 follicular B-cell NHL) had PRs. One of these pts had near CR and subsequently went onto BMT and is currently in remission for 14+ months. The 2 other NHL pts remain on YM155 (75 and 57 weeks respectively) with sustained PRs. Two HRPC pts exhibited PSA response and one NSCLC pt had a minor response.
Conclusion: YM 155, the first survivin inhibitor, was well tolerated at the MTD of 4.8 mg/m^2/day × 7 days and exhibited anti-tumor activity in 5 pts. Broad phase 2 evaluation is ongoing.

Wednesday 8 November 16:30–18:15

PLENARY SESSION 3

Antibody versus small molecule inhibitors of receptor tyrosine kinases

30 INVITED

Combination of monoclonal antibodies and Tyrosine Kinase Inhibitors with the same target

J. Baselga. *Spain*

Abstract not received.

31 INVITED

Combination of monoclonal antibodies against RTKs

S. Kelsey. *Genentech BioOncology, BioOncology, South San Francisco, CA, USA*

Monoclonal antibodies directed against receptor tyrosine kinases or their ligands have the attribute of being relatively specific for the intended target, which may be construed as an advantage or a disadvantage depending on the context in which they are being used. The target specificity may often be associated with a preferential toxicity profile; on the other hand the inability to target more than one kinase may result in differential efficacy. The favorable tolerability of monoclonal antibodies combined with their discrete specificity has both required and enabled preclinical and clinical studies of antibody combinations. Antibodies to many RTKs and their ligands have either entered or are soon to enter clinical development; most notably antibodies to HER2, EGFR (HER1), VEGF and KDR, PDGFR, HGF and MET, as well as antibodies directed against other cellular targets which might act synergistically with RTK inhibition, such as CD20 and death receptors DR4 and DR5. This presentation will review the preclinical rationale and overview some of the key clinical efficacy data obtained to date with combinations of therapeutic monoclonal antibodies in oncology. In addition, some of the perceived limitations to combination therapy with monoclonal antibody therapy will be discussed.

32 INVITED

Multitargeted molecules versus combined Tyrosine Kinase Inhibitors

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The present abstract aims at proving a theoretical framework for discussing the specific advantages and disadvantages of multi-targeted agents as compared to the combination of single targeted drugs. Key-points that need to be addressed are: structural and chemical issues, metabolism, toxicity, efficacy, resistance and pragmatic issues.
Structural and chemical issues: Most tyrosine kinase inhibitors (TKI) have a propensity to hit multiple targets. Imatinib was initially described as a selective agent, albeit it inhibits in fact at least 3 TKs (BCR-ABL, KIT and PDGFR). Dasatinib binds to 74 of 148 kinases recently screened at 10 micromolar.
Metabolism: Drug interaction between different TKI can be related to their absorption and/or metabolism. Several TKI can inhibit PGP pumps involved in drug absorption and elimination. Sorafenib, valatinib, erlotinib, gefitinib,

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

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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.

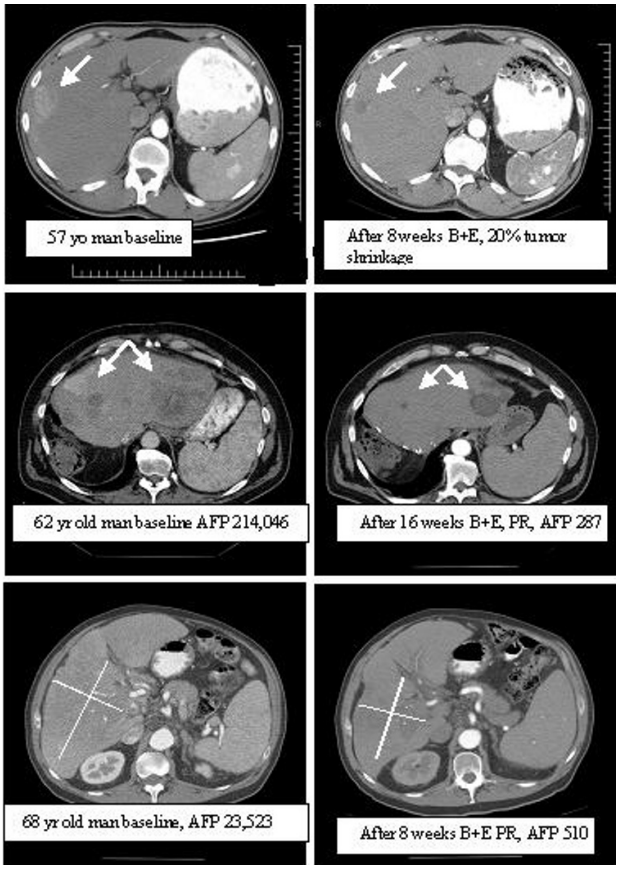

Fig. 1.

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