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

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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

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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

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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,