cetuximab (60 mg/kg, twice a week) significantly inhibited the growth of OVCAR-5 tumors with a T/C% of 48 ($p = 0.0001$). When both antibodies were combined no additional antitumor benefits were observed (T/C% = 44; $p = 0.22$ versus ME1, $p = 0.23$ versus cetuximab). No partial tumor regressions were observed with any treatment. Tumor histological analysis utilizing MECA 32 staining revealed that ME1 treatment had no effect on blood vessel density in this model ($p = 0.72$), while cetuximab significantly ($p = 0.015$) decreased blood vessel density compared to the control group. The combination of both ME1 and cetuximab showed a trend towards greater antivascular effects compared to cetuximab monotherapy, but the difference did not reach statistical significance ($p = 0.20$). These data suggest that the antivascular effects following EGFR inhibition in the OVCAR-5 model result from targeting tumor cell EGFR.
In the GEO colorectal cancer model, ME1 and cetuximab significantly inhibited tumor growth with T/C% values of 61 ($p = 0.039$) and 31 ($p < 0.0001$), respectively. The combination of ME1 and cetuximab resulted in significantly increased efficacy compared to monotherapies (T/C% = 19; $p < 0.0001$). Moreover, the combination was associated with a partial tumor regression frequency of 83%, compared to 17% with cetuximab and 25% with ME1. Histological analysis in the GEO model is pending. Nevertheless, results support the conclusion that while targeting EGFR expressed outside the tumor cell, presumably on the endothelial cells, contributes towards the antitumor effects of an EGFR targeting antibody strategy, antitumor effects are mostly related to targeting tumor cell EGFR.

537 POSTER

Detection of EGFR mutation in the sample of pleural effusion is contributive as a determinant of EGFR-TKI-therapy for the patients with lung cancer

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Background: Activating mutations in the epidermal growth factor receptor (EGFR) underlying responsiveness of non-small cell lung cancer (NSCLC) to EGFR tyrosine kinase inhibitor (TKI). Recently, EGFR mutation can be easily examined using cytological specimens.
Methods: We examined the EGFR mutation status in eight pleural effusion samples from the patients with NSCLC using peptide nucleic acid-locked nucleic acid (PNA-LNA) PCR clamp assay in our institution.
Results: Eight patients (Median age; 69 y.o. [ranging from 50−82 y.o]; man/female: 6/2; smoker/non-smoker 2/6; adeno/adenosquamous 7/1; ECOG performance status 2/3/4: 3/4/1), were enrolled. PNA-LNA PCR clamp assay detected three EGFR-mutative cases, all of which represented exon21 L858R in EGFR and the rest five showed wild type EGFR. Two of the three patients carrying L858R mutation and one patient with were treated with gefitinib. One patient with the wild type EGFR was treated with erlotinib. Consequently, all of the patients treated with EGFR-TKI revealed clinical response, and side effects were tolerable.
Conclusion: Pleural effusion is a common complication of advanced lung cancer, which is easily obtained from the patients. The results suggest that detection of the EGFR mutations by PCR from these samples is considered to be useful as a choice of application of EGFR-TKI for the advanced therapy.

538 POSTER

ARH460-16-2, targeting the CD44 cancer stem cell marker, uses multiple mechanisms to achieve its therapeutic anti-cancer effects

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CD44 is expressed on the cancer stem cells of breast, colon, prostate, head and neck, pancreatic cancer and AML where it is thought to play key roles in tumor maintenance, cell survival, adhesion, migration and invasion. The murine, chimeric, and humanized versions of a highly effective anti-CD44 anti-cancer antibody (ARH460-16-2) have similar binding, apogenic and anti-tumor properties. A murine monoclonal antibody was generated using the ARIUS' FunctionFIRST™ platform and demonstrated potent anti-tumor efficacy and a significant increase in survival time in models of human breast, liver, prostate and pancreatic cancer and AML. A dose-ranging toxicology study was carried out in cynomolgus monkeys with the chimeric form of the antibody and revealed no demonstrable dose limiting toxicity. Based on these results a humanized version of the antibody was generated for clinical testing. The mechanism by which ARH460-16-2 exhibits anti-tumor activity was studied. ARH460-16-2 directly inhibited tumor cell adhesion to hyaluronic acid (HA)-coated surfaces. Blocking of the binding of MB-231 breast cancer cells to HA-coated surfaces is consistent with the role of CD44 in promoting adhesion and may have important physiological effects and include blocking of motility and/or migration of tumor cells, and induction of apoptosis. ARH460-16-2 induced apoptosis in several cancer cell lines and suppressed phosphorylation of the Tie-1 receptor tyrosine kinase in breast cancer cells. CD44 is involved in cell survival in different cell types through distinct mechanisms, and induction of early apoptosis events by ARH460-16-2, as assessed by Annexin-V staining, in MB-231, MB-468 and in HUVEC cells, indicate that the antibody has an apogenic effect. The apogenic effect of ARH460-16-2 in HUVEC cells and decreased Tie-1 phosphorylation in MB-231 cells is consistent with the anti-neoangiogenic effect of CD44 deficiency in the tumors of tumor-bearing CD44 knockout animals. ARH460-16-2 may also recruit effector cells to enhance tumor ADCC. In vitro assays showed that the antibody failed to induce complement activation; however, in ADCC assays there was evidence of increased lysis of target cells. These results show that ARH460-16-2 can affect tumor growth by multiple mechanisms, and further studies to characterize the impact of the antibody on cell signaling pathways are ongoing. Humanized ARH460-16-2 is currently in development for treatment of solid and hematological cancers.

539 POSTER

Translational pharmacokinetic (PK), pharmacodynamic (PD) modeling and simulation analysis of MetMAb

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Background: MetMAb is a recombinant humanized, monoclonal, monovalent (one armed) anti Met antibody with potential as a novel targeted therapy for cancer. The goal of this analysis was to predict a minimally effective MetMAb dose regimen for objective response using cynomolgus monkey PK and KP4 xenograft mice anti tumor efficacy data.
Materials and Methods: Human MetMAb serum concentrations were predicted using species invariant time transformations of cynomolgus monkey data (0.5, 3, 10, and 30 mg/kg MetMAb), and nonlinear mixed effects modeling of composite individual animal data. A separate mixed effects PK/PD model describing anti-tumor efficacy in KP4 xenograft mice was also developed from single and time dose-fractionated multiple dose regimens of MetMAb (0.825–120 mg/kg). The predicted human PK model was subsequently imposed on the established MetMAb exposure/anti-tumor activity relationship for clinical simulations of expected tumor responses at various treatment dose regimens. The exposure/target predictor of clinical treatment success, i.e. 'progression-free objective response defined as = 20% increase in tumor mass, was identified by classification and regression tree analysis. Additionally, simulated tumor responses were analyzed by Cox proportional hazards tests.
Results: A population PK/PD model, comprised of a two-compartment nonlinear PK model with direct KP4 tumor growth inhibition, was developed for MetMAb. The probability of attainment of 'progression-free objective response' was achieved at an AUC/tumoristatic concentration ratio = 16 in an individual patient as determined from analysis of projected clinical MetMAb exposure/anti-tumor activity simulations. Progression-free time to event analyses of simulated MetMAb tumor responses, compared with an identified standard of care, showed that the dose regimens of = 12.5 mg/kg once weekly (Q1W) and = 20.0 mg/kg once every 3 weeks (Q3W) increased treatment success (hazard ratio = 0.75) and achievement of the MetMAb exposure/target.
Conclusions: MetMAb dose regimens demonstrating a target stable disease treatment outcome of = 20% increase in tumor mass were determined via modeling and simulation methodologies which utilized efficacy data from KP4 xenograft mice and PK data from monkeys. Dose regimens of = 12.5 mg/kg Q1W and = 20.0 mg/kg Q3W are projected to result in a significant improvement in progression free disease (hazard ratio = 0.75) over an identified standard of care.