KRAS, mutations. The frequency of EML4-ALK fusion transcripts is around 5% or less in Caucasians patients. Crizotinib (PF-02341066) is an ALK and MET inhibitor that has demonstrated outstanding activity in monotherapy in patients with EML4-ALK translocations: 57% objective response in 82 patients with a median duration of treatment of 5,7 months and a predicted 67% PFS rate at 6 months.
Many other abnormalities linked to tyrosine kinase receptors could be used for selection of specific therapy such as amplification or activation mutation of HER2, HER3, HER4, FGFR1, FGFR2, KDR .... However correlation of presence of such abnormalities and clinical response are still not firmly documented, although some interesting case reports have been documented. Table 1 provides a summary of specific alterations and their potential corresponding drug. DNA repair markers are also potential predictors of chemotherapy bases therapies (ERCC1, MSH2, BRCA1, PARP).

Table 1

Molecular alteration	Potential Drugs
EGFR mutation	Erlotinib, gefitinib New pan-HER inhibitors
EML4-ALK translocation	Crizotinib
HER2 mutation or amplification	Trastuzumab Lapatinib
PI3K mutation or amplification	GDC-0941 XL-147 XL-765 PX-866 BEZ-235 BKM120
MET amplification	XL184 ARQ917
RAS and RAF mutations	Sorafenib AZD6244; GSK1120212; AS703026

Thursday, 18 November 2010

Poster Sessions

Animal models

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Multi-modality in vivo imaging of bone metabolism and tumor growth in a mouse model of bone metastasis

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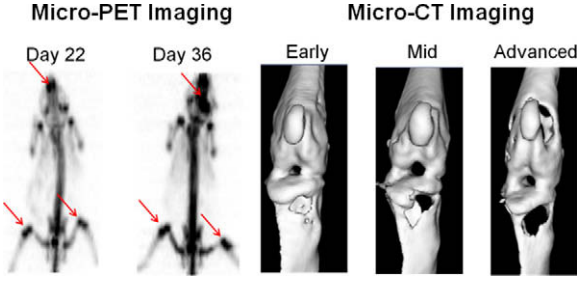
Background: The ability to visualize and quantify early stages of bone involvement in mouse models of bone metastasis would provide a platform for development of new agents targeted at inhibition or treatment of bone metastases. While micro-CT imaging provides a qualitative assessment of bone erosion and bioluminescence imaging using luciferase expressing tumor lines enables monitoring of tumor burden, there is a need to track bone lesion progression as well.
Materials and Methods: Optical imaging using biphosphonate fluorescent probes and 18F-NaF PET imaging both provide readouts for hydroxyapatite (HA) activity, a key feature of bone metastasis. Female nu/nu mice underwent intracardiac inoculation with MDA-MB-231-luc-D3H2LN human mammary adenocarcinoma cells (10^5 cells in 100 µl). On Day 14, all mice were imaged using bioluminescence and enrolled on study based on incidence of luciferase signals at bone sites. Subsequent bioluminescence imaging was used to monitor growth of bone metastases. Micro-CT (see figure: right panel) was used to assess the extent of corresponding bone lesions. 18F-NaF PET imaging (45 min uptake) (see figure: left panel), and fluorescence imaging (24 h after Osteosense 750 administration) were used to characterize HA activity.
Results: Both 18F-NaF PET imaging and fluorescent imaging using Osteosense highlighted localized bone signals that were associated with bioluminescent tumor signals and micro-CT visualized bone lesions from approximately Day 17. Bioluminescence imaging showed the greatest sensitivity to disease progression in both the mandible and hindlimb bones. The PET and fluorescence imaging approaches showed bone involvement (presumably through HA), indicating osteoblastic activity.
Conclusion: The combination of PET, fluorescent imaging of bone remodeling mechanism coupled with bioluminescent imaging of tumor growth and microCT imaging of bone anatomy, enables quantitative, non-invasive means for characterizing bone metastasis. Importantly, the use of complimentary imaging methods can provide assessment of novel therapeutics against both metastatic tumor growth and bone lesion progression.



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Effects of isoflurane anesthesia on bioluminescence measurements: impact on pharmacological assessment of anti-tumor activity of chemical entities

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Bioluminescence imaging (BLI) has been used for several years in oncology research to quantify tumor growth. In order to allow immobilization during data acquisition, animals are usually anesthetized by isoflurane gas inhalation. However, anesthesia leads to modifications of many physiological parameters, and particularly decreases in heart rate, blood pressure and blood flow, leading to decrease of substrate availability. Thus, it can be postulated that anesthesia will impair bioluminescence read outs. This may in turn profoundly affect interpretation of compound activity based on BLI.
We have investigated the difference in BLI measurements performed in conscious and anesthetized animals using subcutaneous xenografts (HCT116 colorectal and U87MG glioblastoma) and orthotopic (U87MG cells injected directly in the brain) models. Moreover, functional tumor vessel mapping and hypoxia stage were obtained using casting technology and HypoxyProbe™, respectively. Anti-tumor activity of 5-fluorouracil and temozolomide were assessed in the HCT116 xenograft and U87MG orthotopic models, respectively.
Our results have clearly demonstrated that in all tested tumor models, tumor growth and efficacy of different compounds were not affected by the regular anesthesia procedure used for bi-weekly BLI assessments. We found a good correlation between caliper and BLI over a wide range of tumor size in conscious mice. When BLI was measured in anesthetized mice, signal intensity dropped significantly up to 70%, impairing the assessment of the antitumor efficacy of 5-FU. A clear correlation to functional tumor vessel density was evidenced.
In the U87MG tumors cells implanted intracranialy, we could clearly follow tumor growth over time using BLI readouts. Isoflurane did not impair BLI measurements or the efficacy profile of temozolomide.
In conclusion, we can say that BLI measurements in conscious tumor bearing mice offers a better alternative for resolving pharmacologic queries without the confounding effects of anesthesia. Obviously, more extended studies over a wide range of tumor types will be needed to reinforce these conclusions. Moreover, a more quantitative approach to assess vessel density and distribution in the casts using micro-CT technologies would be pivotal.

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Establishment of patient-tumor derived xenograft models for testing anticancer agents

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Human xenograft tumor models established by transplantation of human tumor cell lines into immunodifficient mice have been routinely used for preclinical test of anticancer agents. But such tumor models have a relatively low transplantability, limited number of cell lines available for certain tumor types, and limited correlation with clinical findings. Recently, we have developed patient-tumor derived xenograft tumor models by transplanting human fresh tumor tissues into nude mice, and which have been used for test of clinically used anticancer drugs as positive