and >2N DNA content and inhibition of histone H3 phosphorylation. This translates to potent *in vivo* activity with dose-dependent tumor growth inhibition in various tumor models including HL60 human acute myelogenous leukemia, HCT-116 human colon carcinoma and H460 human. *In vivo* dose and schedule optimization studies demonstrated tumor growth inhibition without myelosuppression, a common side effect of Aurora Kinase inhibitors currently in development.
Conclusion: ACTB-1010 is a potent and selective Aurora Kinase inhibitor with reduced off target side inhibition of other kinases and eliminates unwanted side effects such as myelosuppression. The selectivity of ACTB-1010, allows optimal inhibition of Aurora kinase A and B that may be developed as a therapeutic for multiple tumor types.

138 POSTER

Combination of PI3K inhibitor BAY 80-6946 with allosteric MEK inhibitor BAY 86-9766 (RDEA119) and with erlotinib for the treatment of non-small cell lung cancer

N. Liu[1], F. Puehler[1], A. Haegebarth[1], A. Scholz[1], J. Hoffmann[2], D. Mumberg[1], K. Ziegelbauer[1]. *[1]Bayer Schering Pharma AG, GDD-TRG-Oncology, Berlin, Germany; [2]EPO-Berlin GmbH, EPO-Berlin GmbH, Berlin, Germany*

Lung cancer is the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases. We evaluated the anti-tumor activity of the combination of BAY 80-6946, a highly selective pan class I PI3K inhibitor with the allosteric MEK inhibitor, BAY 86-9766, as well as with erlotinib, in NSCLC cell lines and tumor models. A set of 40 well characterized human lung tumor cell lines were profiled with BAY 80–6946 and BAY 86-9766 in tumor cell proliferation assays. Eight NSCLC tumor cell lines representing various clinically relevant somatic mutations and different sensitivities to each agent were selected for further studies. *In vitro* combination of BAY 80-6946 (PI3K) and BAY 86-9766 (MEK) demonstrated a strong synergy resulting in lowering both the IC_{50}s (combination Index/CI: 0.12–0.59) and even more dramatically the IC_{90}s (CI: 0.07–0.34). More importantly, neither BAY 86-9766 nor BAY 80-6946 induced significant tumor cell apoptosis in the eight NSCLC cell lines tested, while the combination of the both agents led to a significant activation of caspases (3/7) in 4 out of 8 cell lines tested. Interestingly the combination of BAY 80-6946 (PI3K) with erlotinib showed a differential profile of synergy compared to the combination with BAY 86-9766 (MEK), with the strongest synergy observed in erlotinib sensitive NSCLC cell lines. *In vivo*, BAY 80-6946 (i.v.) demonstrated high to low anti-tumor efficacy (T/C: 0.13–0.69) in 11 human NSCLC xenograft tumor models (1 tumor cell line and 10 patient-derived primary tumors) in mice. Combining BAY 80-6946 (PI3K) with BAY 86-9766 (MEK) demonstrated strongest activity in KRAS mutated and erlotinib-resistant primary NSCLC xenograft tumor model, while combining BAY 80-6946 (PI3K) with erlotinib further enhanced tumor growth inhibition and prolonged the time to tumor regrowth in erlotinib active (T/C < 0.5), carboplatin- and etoposid-resistant patient-derived NSCLC models. In conclusion: (1) combination of BAY 80-6946 (PI3K) and BAY 86–9766 (MEK) is a promising approach for the treatment of NSCLC, especially for tumors with KRAS mutations; (2) BAY 80-6946 (PI3K) can further enhance the anti-tumor efficacy of erlotinib in preclinical tumor models responsive to erlotinib. Currently BAY 80-6946, a selective pan class I PI3K investigational agent is being evaluated in a phase I study in solid tumors.

139 POSTER

Inhibition of osteolysis by CSF-1R antagonist in MM.1S orthotopic multiple myeloma model

S. Palakurthi[1], S. Grondine[1], N. Gingles[2], X. Rong[1], D. Lawson[1], P. Hall[1], Y. Cao[1], K. Wu[1], C. Reimer[1]. *[1]AstraZeneca R&D, Cancer Bioscience, Boston Massachusetts, USA; [2]AstraZeneca, Translational Science, Macclesfield, United Kingdom*

Multiple myeloma (MM) is a B-cell malignancy characterized by excess abnormal plasma cells in the bone marrow (BM), myeloma bone disease (MBD), characterized by diffuse osteopenia, focal lytic lesions, bone fractures and pain causing major discomfort to the patients. In patients with MBD, bisphophonates show reduced skeletal complications when dosed by intravenous infusion but show minimal beneficial effects when dosed by oral route, indicating a paucity of oral agents that ameliorate MBD and improve the quality of life. CSF-1R signaling axis is important for bone homeostasis and CSF-1 directly contributes to osteoclastogenesis, as both mice that fail to express functional CSF-1 and the mice lacking *csf1r*, exhibit osteopetrotic phenotype due to reduction in osteoclasts. We hence reasoned that an orally available CSF-1R antagonist, may have potential beneficial effects in MBD.

We established and validated a mouse MM model by intravenous injection of luciferase tagged MM.1S cells in to SCID mice. The MM model presents with the characteristic features of bone marrow infiltration and progressive MBD, leading to hind limb paralysis caused due to vertebral bone destruction. At the early signs of BM infiltration, the mice were randomized into various treatment groups and monitored for tumor load, as measured by either IVIS imaging or MM markers expression such as, CD138 in the bone marrow or serum IgG levels. Progression of MBD was evaluated either by trabecular volume measurement in the femero tibial joint by microCT method or by measurement of TRAP5b, serum bone resorption marker levels. In this study, CSF-1R antagonist was treated by po route at a well tolerated dose, shown to inhibit CSF-1R in vivo as demonstrated by its ability to decrease the expression of F4/80 macrophage marker. We report here that CSF-1R antagonist caused significant increase in bone density as measured by trabecular volume and reduction of osteolytic lesions in the femero tibial joint, there by, leading to decreased incidence and time of onset of hind limb paralysis with overall improvement in the mobility of mice. This was consistent with the ability of CSF-1R antagonist to cause inhibition of serum TRAP5b levels. However, CSF-1R antagonist treatment had negligible effects on tumor growth per se, showed minimal effects on mean overall survival of mice, indicating that CSF-1R- signaling axis does not have a direct role in either the survival of myeloma cells or their infiltration in to the BM. We conclude that targeting CSF-1R by a small molecule inhibitor reversed osteoclastic activity, ameliorated MBD, with negligible antimyeloma effects in an in vivo disseminated orthotopic MM model. The data from this report supports setting the stage for testing CSF-1R inhibitors in human MM clinical trials in combination either with current standards of care or novel agents under investigation − potentially offering an alternative to bisphosphonates with an oral route dosing option.

140 POSTER

Combination of PI3K inhibitor BAY 80-6946 and allosteric MEK inhibitor BAY 86-9766 (RDEA119), a promising approach for the treatment of colorectal cancers

N. Liu[1], A. Haegebarth[1], F. Puehler[1], A. Scholz[1], J. Hoffmann[2], R. Dubowy[3], H. Krissel[4], S. Wilhelm[5], D. Mumberg[1], K. Ziegelbauer[1]. *[1]Bayer Schering Pharma AG, GDD-TRG-Oncology, Berlin, Germany; [2]EPO-Berlin GmbH, EPO-Berlin GmbH, Berlin, Germany; [3]Bayer HealthCare Pharmaceuticals, Global Clinical Pharmacology, Montville NJ, USA; [4]Bayer Schering Pharma AG, Global Clinical Development, Berlin, Germany; [5]Bayer HealthCare Pharmaceuticals, GMA Oncology, Montville NJ, USA*

Despite the introduction of new chemotherapeutic and targeted agents, the prognosis for patients with metastatic CRC (mCRC) remains poor. Particularly, patients with mutant KRAS tumors have limited treatment options after failure of standard chemotherapy. We report our preclinical studies on the combination of a highly selective pan class I PI3K inhibitor, BAY 80-6946 and an allosteric MEK inhibitor, BAY 86-9766 (RDEA119) in CRC models. A set of 32 well characterized CRC tumor cell lines were profiled with BAY 80-6946 (PI3K) and BAY 86-9766 (MEK). Seven cell lines with various clinic-relevant genetic alterations were selected for further studies. Interestingly, combining BAY 86-9766 (MEK) and BAY 80-6946 (PI3K) inhibitors demonstrated a significant synergy not only in lowering cellular IC_{50}s (CI: 0.21–0.90), but also more dramatically in decreasing the concentration needed to reach complete tumor growth inhibition (CI at IC_{90}: 0.02–0.18) in the CRC cell lines with either KRAS or BRAF mutations. Neither BAY 86-9766 (MEK) nor BAY 80-6946 (PI3K) were able to induce apoptosis in Colo205 ($BRAF^{mut}$) and HCT116 ($KRAS^{mut}$ and $PIK3CA^{mut}$) tumor cells whereas the combination of these two compounds led to the activation of caspase 3/7 with CI<0.2. *In vivo* profiling of BAY 86–9766 (MEK) in 18 different patient-derived CRC xenografts demonstrated strong to moderate efficacy with a median treatment/control (T/C) value of 0.13 (0.05–0.46). Three CRC tumor models with differential sensitivities to BAY 86-9766 (MEK) were further evaluated in the combination studies with BAY 80-6946 (PI3K). BAY 86-9766 was dosed at 25 (MTD) and 12.5 mg/kg, po, QD with two dosing regimens for BAY 80-6946 (i.v., Q2D and weekly), respectively. The combination of MEK (p.o.) and PI3K (i.v.) at both dosing schedules significantly enhanced anti-tumor efficacy in all 3 patient-derived CRC xenograft models and 4 CRC tumor cell line derived xenograft models. In addition, an increase in number of animals with tumor shrinkage (PRs) was observed in HCT116 ($KRAS^{mut}$ and $PIK3CA^{mut}$) xenograft model and complete tumor growth inhibition was also observed in two cetuximab-resistant patient derived primary CRC models (carrying KRAS and PIK3CA mutations, respectively). In conclusion these promising preclinical data suggest that future clinical trials are warranted to examine the efficacy of BAY 80-6946 (PI3K) in combination with BAY 86-9766 (MEK) in mCRC patients, especially those with mutant KRAS tumors.