cellular reliance on PI3K signaling. These data are consistent with the hypothesis that mesenchymal-like cells rely more heavily on the PI3K-Akt survival pathway, and that dual inhibition of the MAPK and PI3K signaling networks may drive cellular dependence on Akt-mediated survival signals. Mesenchymal-like cancer cells are further characterized by increased cellular motility which has been linked to the metastatic potential of these cells. OXA-01 inhibited migration of mesenchymal-like cells and inhibited OTC2-mediated regulation of the F-actin cytoskeleton.
Conclusions: These observations suggest that erlotinib may sensitize mesenchymal-like cancer cells to mTOR inhibition. The combination of erlotinib and OXA-01 may be an effective strategy to target heterogeneous tumors, and may inhibit the metastatic potential of mesenchymal tumor cells.

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Dose-finding study of pegylated liposomal doxorubicin (PLD) and the mTOR inhibitor RAD001 (R) in patients (pts) with advanced solid tumors

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Background: R is an orally available mTOR protein kinase inhibitor derivative of rapamycin that has direct effects on tumor cell growth combined with an antiangiogenic mechanism. R enhances the cytotoxicity of cisplatin, paclitaxel, gemcitabine and doxorubicin in preclinical studies.PLD is a pegylated liposomal formulation of doxorubicin with a better tolerability and reduced cardiologic and GI toxicities and alopecia. Aim of the present study is to assess the feasibility of combining R and PLD.
Materials and Methods: A phase Ib study is ongoing in pts with advanced solid tumors. Treatment consists of R given daily continuously at the starting dose of 2.5 mg daily and PLD given at 40 mg/m^2 on day 1 q28 days (1 cycle). The dose of R is escalated according to 3 + 3 cohort design depending on the observed toxicity. Treatment is planned until disease progression or unacceptable toxicity. The dose limiting toxicity (DLT) is assessed on pre-defined criteria during cycle 1. The plasma disposition of PLD is analyzed when given concomitantly (cycle 1) or 48 hrs before R (cycle 2). Tumor response is evaluated every 2 cycles by modified RECIST.
Results: 12 pts were recruited from 2 centers over 6 months, 6 pts in Cohort 1, and 3 in Cohorts 2 and 3, respectively. Median age was 51 (range 27−68 years), ECOG PS was 0−1, the main tumor type was ovarian ca. Preliminary safety data related to cycle 1 are available in the first 9 pts: no DLTs were observed in Cohort 1 (R 2.5 mg/day) but 3 of 6 pts temporarily required R discontinuation due to G2 mucositis (respectively for 5, 8 and 10 days). The administration of R was therefore changed from continuous to intermittent for 21 days q28. Also in Cohort 2 (R 5 mg/day) no DLT were observed and Cohort 3 (7.5 mg/day) is ongoing. The most frequent grade 1−2 treatment related toxicities observed during cycle 1 were: mucositis (78%), skin toxicity (33%), fatigue (22%). No >G1 hematological toxicity was reported. A confirmed partial response was observed in 1 pt with ovarian ca. in Cohort 1. The disposition of D was studied in 6 pts at cycles 1 and 2: total plasma exposure to PLD was unaffected by R.
Conclusions: Preliminary results suggest that the combination of R and PLD is feasible but that a discontinuation interval of R administration is needed to keep an adequate daily dose. No major pharmacokinetic interference of R on PLD disposition was observed.

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The serine 2481-autophosphorylated form of mTOR directly binds the mitotic apparatus to control breast cancer cell proliferation: A new role of mTOR as mitotic checkpoint in cell cycle progression

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Background: The widely accepted role of mTOR is primarily to sense and integrate nutrient and growth factor signals to regulate protein synthesis. Although mTOR is also recognized as a regulator of cell cycle progression and cell proliferation, the molecular mechanisms by which mTOR might mediate these events have been poorly defined. We here sought to analyze whether changes in the sub-cellular compartmentalization of mTOR and of its autophosphorylated form (*i.e.* mTOR^{Ser2481}) occur after acquisition of auto-resistance to the anti-HER2 antibody trastuzumab (Tzb) in breast cancer (BC) cells.
Materials and Methods: Two pools of Tzb-conditioned SKBR3 BC cells optimally growing in the presence of >100 ug/ml Tzb (SKBR3/TzbR POOL1 and POOL2) were obtained by continuously culturing HER2-dependent SKBR3 cells in the presence of high-doses of Tzb for more than 12 months. Changes in the sub-cellular compartmentalization of mTOR/mTOR^{Ser2481} were monitored using a high-resolution, automated confocal imaging system (BD Pathway™ Bioimager).
Results: A homogenous cytoplasmic/perinuclear distribution of total mTOR was observed in Tzb-sensitive BC cells. Perinuclear expression was somewhat increased in a dotted-manner in Tzb-resistant pools. Surprisingly, mTOR^{Ser2481} was found to be massively accumulated within nuclear dots displaying dynamic expression during the M phase. mTOR^{Ser2481} dots showed a close association near and between separating chromosomes and also decorating the contractile ring in BC cells undergoing cytokinesis. In the case of BC cells at the anaphase stage of mitosis, eye-catching mTOR^{Ser2481} dots could be seen symmetrically splitting in the region of the mitotic spindle. The number of immunopositive condensations of mTORSer^{2481} directly related with the percentage of mitotic cells in the absence of Tzb treatment (2-fold higher in Tzb-resistant BC cells). Moreover, the rate of mTOR^{Ser2481}-immunolabeled dividing cells was significantly decreased in Tzb-treated SKBR3 parental cells whereas it remained unaltered in Tzb-treated SKBR3/TzbR POOLs.
Conclusions: mTOR-dependent regulation of the rate of cell cycle progression has been considered a secondary consequence of the mTOR's primary function (*i.e.* to make cycle progression dependent on a sufficient level of cell growth). We now propose that mTOR^{Ser2481} is a novel mitotic checkpoint that directly controls BC cell proliferation through its previously unrecognized capacity to bind the mitotic apparatus.

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Phase II study of MTOR-inhibitor RAD001 and erlotinib for advanced, gemcitabine-refractory pancreatic cancer

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Background: PI3-kinase/Akt pathway is constitutively activated in pancreatic cancer. The sensitivity of pancreatic cancer cell lines to erlotinib may be dependent on inhibition of this pathway. RAD001 selectively inhibits mTOR, a key protein kinase that is activated via the PI3-kinase pathway. Erlotinib and the mTOR inhibitor rapamycin produced a synergistic anti-tumor effect in preclinical studies. Prior phase I study identified both a weekly and daily phase II RAD001 dose when administered with daily erlotinib.
Methods: Forty adult patients with previously treated stage IV pancreatic adenocarcinoma, ECOG PS 0−1 with adequate hematologic, hepatic and renal parameters and measurable disease will be enrolled. Each cycle lasts 28 days and consists of RAD001 30 mg weekly and erlotinib 150 mg once daily. Staging radiological studies are performed every 8 weeks. Pre-treatment tumor biopsy samples are assessed for PTEN, total and activated Erk, Akt, and mTOR expression. Primary study endpoint: 6-month survival. Secondary: Progression-free survival and correlation of biomarkers with outcome.
Results: 13 patients have been enrolled; 10 males, all received prior gemcitabine. A median of one cycle has been administered (range 1−2). There was one grade 5 toxicity, possibly related. Grade 3 toxicities: diarrhea (n = 1), cholangitis (n = 3), fatigue (n = 1). Grade 2 toxicities: pneumonia (n = 2), dehydration (n = 2), nausea (n = 2), mucositis (n = 2), rash (n = 2). Progressive disease occurred in 3, CA 19−9 improvement (<50%) in one. There were 4 hospitalizations, 3 for cholangitis and sepsis. Cholangitis occurred in presence of biliary stents; these patients are now receiving prophylactic quinolones. Interim analysis will be conducted after enrolling 16 patients.
Conclusions: The immunosuppressive properties of RAD001 may predispose patients with biliary stents to cholangitis. These patients can be considered for antibiotic prophylaxis. Updated clinical and correlative data will be presented at meeting.

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Vorinostat significantly enhances the antitumor activity of temsirolimus in renal cancer

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Background: Mammalian target of rapamycin (mTOR) is a critical kinase that is involved in the regulation of protein translation, nutrient uptake and autophagy. mTOR is frequently activated in cancer due to constitutive