The clinical course of five patients after accidental overexposure of radiotherapy is presented. On February 27th 2001 in Bia3ystok Oncology Center (BOC) five patients treated by radiotherapy for breast cancer were accidentally overexposed. All patients developed necrotic ulcerations involving chest wall structures, and were qualified to surgical treatment. Three patients were operated in HCC and two at IC. The patients has been locally cured and followed up two years after operation. Surgical excision of necrotic tissues with reconstruction by well vascularised tissues is an effective mode of treatment of postradiation injures. The use of greater omentum flap is an optimal solution for this purpose.

Translational Research

Oral presentations (Tue, 1 Nov, 9.15–11.15)
Translational research

1448 ORAL

Molecular pharmacodynamic (MPD) phase I study with serial tumor and skin biopsies of the oral mTOR inhibitor Everolimus (E, RAD001) at different doses and schedules in patients (pts) with advanced solid tumors

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Background: E is an orally active derivative of rapamycin with antiproliferative effect shown in several human tumor models, *in vitro* and *in vivo*. E inhibits mTOR, a serine/threonine protein kinase downstream of PI3K and AKT, involved in the regulation of cell growth, proliferation and survival. In preclinical models, the administration of E is associated with reduction in downstream phosphorylated(p)-S6 (p-S6) and p-4EBP1, and increased upstream AKT phosphorylation (p-AKT). This study explores safety, drug levels and MPD changes in serial tumor and skin biopsies at different doses and schedules of E to help to define the recommended dose for further development.
Methods: Pts were treated in successive cohorts of E: weekly (WK) 20, 50 and 70 mg or daily (D) 5 and 10 mg. Dose escalation depended on dose limiting toxicity (DLT) rate during the first 4 weeks of treatment. Pre- and on-treatment steady-state (week 4 or 5: 24hr post-dose and, for the WK schedule, 5 days post-dose) tumor and skin biopsies were obtained from each pt. Biopsies were evaluated by immunohistochemistry for total and p-S6, p-4EBP1, p-eIF4G, p-AKT and Ki67 expression.
Results: 55 pts were treated with 6–8 fully evaluable pts in each cohort. Grade 3 DLT in 5 pts included stomatitis (1 pt at 10 mg/d, 2 at 70 mg/wk), neutropenia and hyperglycemia (1 pt each at 70 mg/wk). There was one partial response (colon cancer) and 4 stabilizations of >4 months (renal cell, melanoma, breast cancer in 2 pts). MPD studies demonstrated a dose and schedule-dependent inhibition of the mTOR pathway in tumor and skin after E treatment. In the D schedule, p-S6 and p-eIF4G were highly inhibited at 5 mg and completely inhibited at 10 mg, whereas p-AKT was upregulated in some patients in both cohorts. In the WK schedule p-S6 inhibition was complete and sustained at all levels, p-eIF4G only at doses *50 mg, whereas p-AKT was upregulated although unsustained, at doses *50 mg. No MPD distinction was evident between pts with clinical benefit and those without. Preliminary PK/MPD modeling shows a moderate correlation between trough concentration in blood and certain MPD effects in the D schedule.
Conclusions: This phase I study shows that E, at the doses and schedules studied, results in similar mTOR signaling inhibition in tumor and skin. Based on the safety and MPD findings, a dosage of 10 mg/d can be recommended for further phase II-III studies with E as a single agent.

1449 ORAL

A phase I/II trial to assess tolerability and efficacy of RAD-001 with gefitinib in patients with glioblastoma multiforme and castrate metastatic prostate cancer

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Background: This trial tested the hypothesis that simultaneous inhibition of both the EGFR and mTOR pathways will have antitumor efficacy in patients with PTEN deficient tumors, specifically advanced prostate cancer (PC) and glioblastoma multiforme (GBM). RAD-001 (RAD) is an orally available inhibitor of mTOR, a serine-threonine kinase located downstream of Akt that regulates cellular growth. Animal models have shown that markers for RAD activity include p70 S6 kinase, and that FDG-PET uptake intensity may reflect mTOR inhibition. While previous data suggest that EGFR inhibition alone will be ineffective in patients with PTEN deficient tumors, combination therapy with mTOR and EGFR inhibitors may be synergistic.
Methods: Patients with progressive castrate metastatic PC or GBM were eligible. Phase I was designed to determine safety and pharmacokinetics (PK) of an escalating dose of RAD (30/ 50/ 70 mg po weekly) and a fixed dose of gefitinib (250 mg po qd). A 3-week lead-in period allowed for toxicity and PK assessment of each drug alone. Patients initiated combination therapy at week 4. Immunohistochemical (IHC) staining of markers for drug activity was performed. Phase II evaluated the efficacy of the combination. PET scans and p70 S6 kinase assays were evaluated pre- and post-therapy in both phases.
Results: 12 patients (2 GBM, 10 PC) were treated in phase I, 6 patients at the highest dose level. No dose-limiting toxicities were observed. Grade 3 or 4 events possibly related to treatment were limited to grade 3 lymphopenia (25%). No patient had a PSA decline of $\geqslant$50% and no patient showed an objective radiographic response. PET scans showed decreased FDG uptake in some patients. PK parameters (tmax, Cmax and AUC) estimated by non-compartmental analyses suggested no clinically relevant PK interaction between RAD and gefitinib. Results from phase I suggested a phase II dose of RAD of 70 mg weekly with gefitinib 250 mg qd. Phase II accrual is ongoing with 16 patients (7 GBM, 9 PC) treated. An insufficient number of phase II outcomes are available to assess activity.
Conclusions: Combination therapy with RAD 70 mg weekly and gefitinib 250 mg daily appears to be safe. Antitumor activity with the drug combination on this schedule was not observed in the phase I portion of the study. A decrease in SUV FDG-PET imaging may correlate with RAD activity. IHC staining of tumor biopsies are pending.
Support: Novartis Pharmaceuticals, AstraZeneca Pharmaceuticals

1450 ORAL

Clinical synergism from combinatorial VEGF signal transduction inhibition in patients with advanced solid tumors – early results from a phase I study of sorafenib (BAY 43–9006) and bevacizumab

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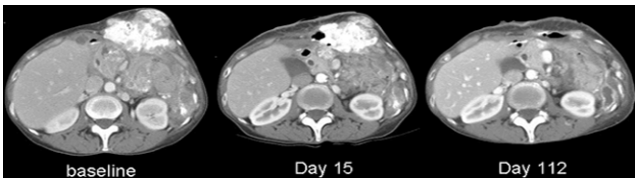
Background: A number of signal transduction inhibitors (STIs) have come to clinical trials and have yielded mixed results. The majority of these agents appear to be cytostatic despite cytoxicity in preclinical models. We hypothesized that the combination a VEGF inhibitor and a tyrosine kinase inhibitor with activity against VEGFR2 will produce supra-additive effects in patients.
Methods: We have opened a phase I study of sorafenib (BAY) and bevacizumab (BEV) for patients with refractory solid tumors. This study is designed to both determine the maximum tolerated dose and a biologically effective dose of this combination. All patients have initiated treatment with BAY 200 mg bid. BEV was given at 5 mg/kg every 2 weeks at dose level (DL) 1; at DL2, 10 mg/kg was administered every 2 weeks. These are doses below those used in phase II clinical studies. Dose reductions were applied for drug-related toxicity. A 6-week delay was required between DL1 and DL2.
Results: Twelve patients have been enrolled since the trial opened in December 2004: 7 ovarian cancers (EOC), 2 renal cell carcinoma (RCCA), 2 melanoma, and 1 colon cancer. A synergy between the two agents was observed in both toxicity and clinical response. No grade 4 toxicities have been observed. Dose limiting toxicities have been seen at DL2 including hypertension, hand–foot syndrome, fatigue, diarrhea, elevated lipase, proteinuria, and thrombocytopenia. Other observed toxicities have been grade 1 and 2 and include neuropathy, rhinorrhea, weight loss, and anorexia. The maximum tolerated dose for continuously administered BAY with q2week BEV was determined to be 200 mg bid + 5 mg/kg, respectively. A cytotoxic clinical effect was seen in both dose levels with partial responses (5+ mos.; 3+ mos. – figure) in 2 of 7 heavily pretreated chemo-refractory ovarian cancer patients. Nine of the remaining patients have stable disease to minor tumor shrinkage. All 12 patients treated have experienced clinical benefit and disproportionately greater toxicity than would be predicted based on individual agent activity.
Conclusions: A clinical synergy was observed with the administration of BAY-BEV. This synergy is reflected in both anti-tumor effect and toxicity. We are proceeding to examine the individual contributions of the agents using sequential biopsies with proteomic analysis, biological imaging including PET and DCE-MRI, and pharmacokinetic/pharmacogenomics analysis.



1451 ORAL

The Pan-HER inhibitor BMS-599626: biological effects, pharmacokinetic profile, and early clinical evaluation of a phase I trial

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Background: BMS-599626 is an orally bioavailable inhibitor of HER1 (EGFR), HER2 (ErbB2) and to a lesser extent HER4.
Methods: This is a phase I dose escalation study of BMS-599626 administered by daily oral dosing. Patients: ⩾18 yrs with metastatic solid tumors, refractory to standard therapies and whose tumors expressed HER1 or HER2 by IHC (FISH for breast). A large translational ancillary study included skin biopsies, optional tumor sampling (both baseline and Day 8) and analysis of biomarkers of HER1 and HER2. Dosing was initiated at 100 mg/d and escalated in subsequent cohorts based on a modified Fibonacci scheme.
Clinical results: Between May 2004 and April 2005, 19 patients have been treated (8M/11F), median age 50 (range 35–79). 18 patients harboured HER1-positive and 9 patients HER2-positive tumors. A total of 48 cycles have been given, and 6/19 patients are still on study. BMS-599626 doses in mg/d (no. pts/cohort) were: 100 (3), 200 (3), 320 (3), 480 (3), and 660 (6). Adverse events at least possibly related to BMS-599626 included anemia (1), aptyalism (1), diarrhea (6), abdominal pain upper (1), nausea (1), vomiting (1), anorexia (3), hirsutism (1), constipation (2), asthenia (3), mucositis (1), rhinitis (1), muscle cramp (1), dyspnea (1), hyperhydrosis (1), dermatitis acneiform (3), dry skin (2), pruritus (1) and rash (4). During dosing escalation, mild to moderate toxicity was observed up to 480 mg/d. Dose-limiting toxicities (DLT) were observed in 3 of 6 patients at 660 mg/d. One patient experienced grade (G) 3 QTc interval prolongation, the 2 other patients reported hepatic toxicities with G3 or G4 ALAT increased (2), G3 ASAT increased (2) and G3 alkaline phosphatase increased (1). Because the maximum tolerated dose (MTD) was exceeded, a new dose cohort of 600 mg/d is currently enrolling.
Biological and pharmacokinetic results: Preliminary immunohistochemistry data on skin (34 samples) and fresh tumor biopsies (2 samples) suggest that Ki67, a marker of cell proliferation, is a viable pharmacodynamic marker of the study. During treatment with BMS-599626, Ki-67 decreased in 15 of 17 paired skin samples. Evaluation of pAKT, pERK, pSTAT3, and p27 is currently being performed and will be correlated with Ki-67. Plasma pharmacokinetics (PK) data for doses up to 480 mg indicate that BMS-599626 was rapidly absorbed, with a mean T max between 3 and 4 hours (range 0.5–24) and T half of approximately 20 hours. PK on day 8 and day 29 revealed similar findings, suggesting no significant accumulation in exposure over time.
Conclusions: To date, 19 patients have been treated with BMS-599626 in the study and the MTD has been exceeded at 660 mg. Proof of concept of the biological effect of the pan-HER inhibitor has been achieved through modulation of Ki-67 in paired skin-biopsies and through induction of skin rash. Additional clinical, pharmacological and translational data will be presented.

1452 ORAL

The multitargeted kinase inhibitor sunitinib malate (SU11248): soluble protein biomarkers of pharmacodynamic activity in patients with metastatic renal cell cancer

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Background: Metastatic renal cell carcinoma (RCC) is a disease both highly resistant to systemic therapy and with a vascular phenotype. In a phase II study of patients with RCC, significant clinical responses have been observed with sunitinib malate (a multitargeted tyrosine kinase inhibitor which specifically blocks VEGFR, PDGFR, KIT, RET and FLT3, and has antiangiogenic and antitumour activity). To characterise potential biomarkers of sunitinib pharmacological activity, plasma levels of 4 soluble proteins identified as candidate biomarkers (VEGF, soluble VEGFR-2 [sVEGFR-2], placenta growth factor [PlGF], and soluble KIT [sKIT]) were analysed serially.
Materials and methods: The RCC patients (n = 63) received sunitinib 50 mg/day for 28 days followed by a 14-day period without treatment in each cycle. Plasma samples for biomarker analysis were obtained pre-dose on Days 1 and 28. The biomarkers were measured via validated ELISAs.
Results: At the end of the first cycle, levels of VEGF and PlGF increased >3-fold (relative to baseline) in 24/54 and 22/55 cases, respectively, and levels of sVEGFR-2 decreased ⩾30% in 50/55 cases and ⩾20% in all cases (mean changes were all $P < 0.001$). For each of these markers, levels tended to return to near baseline at the end of the 14-day period without treatment, and some dependence of changes in levels on drug exposure (as measured by trough plasma levels) was suggested. Mean levels of sKIT also decreased over the course of the study ($P < 0.001$); a cyclical pattern was not observed for this marker, and no strong correlation with drug exposure was apparent. When mean marker level changes were correlated with tumour response, larger proportional changes in VEGF and sVEGFR-2 levels were observed in patients exhibiting objective responses compared with those exhibiting stable disease or rapid progression.
Conclusions: Results indicate that a panel of circulating proteins has utility as biomarkers of pharmacological (VEGF, sVEGFR-2 and PlGF) and clinical activity (VEGF and sVEGFR-2) of sunitinib in RCC.

1453 ORAL

SB-497115, a novel, oral platelet growth factor, increases platelet counts in healthy subjects

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Introduction: The major risk of chemotherapy-induced thrombocytopenia (CIT) is hemorrhage secondary to decreased platelet counts. Furthermore, the presence of significant thrombocytopenia can limit the benefits of chemotherapy by preventing appropriate administration of drugs at optimal doses and schedules. SB-497115 is novel, since it represents the first in a class of orally bioavailable, small molecule thrombopoietin receptor agonists that induce differentiation and proliferation of megakaryocytes and have been shown to increase platelet counts in preclinical and clinical studies.
Methods: In a randomized, single blind, placebo-controlled, parallel group, phase I study in 72 healthy male subjects, SB-497115 was administered as oral capsules once daily for 1 day and, after a 1 week washout, for 10 days at doses of 5 to 75 mg.
Results: SB-497115 was shown to be orally bioavailable in humans with a pharmacokinetic profile suitable for a once daily oral medication. When administered at oral doses of 30 mg to 75 mg for 10 days a dose dependent increase in the platelet count was observed, the maximum platelet count was observed on days 14 to 16 following initiation of dosing. At the 75 mg dose, SB-497115 increased the mean platelet count by 117,000/μL, with a maximum increase of 163,000/μL in one subject. SB-497115 was well tolerated in the study, the most common adverse event (AE) was headache. There were no serious AEs, no significant changes in laboratory or cardiovascular safety parameters and there was no observed relationship between the incidence or severity of adverse events and dose. Most AEs were mild in intensity and self-limiting. Platelet function was not affected by SB-497115, when administered at up to 75 mg for 10 days, as measured by platelet activation and aggregation.
Conclusion: On the basis of this safety, pharmacokinetic and pharmacodynamic data the oral platelet growth factor, SB-497115, is being tested in studies involving cancer patients receiving thrombocytopenic chemotherapies.