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**

J. Baselga[1], H. Burris[2], I. Judson[3], K. Hazell[4], F. Rojo[1], S. Jones[2], L. Vidal[3], N. Shand[4], T. Macarulla[1], J. Tabernero[1]. *[1]Vall d'Hebron University Hospital, Medical Oncology, Barcelona, Spain; [2]Sarah Cannon Cancer Center, Medical Oncology, Nashville, USA; [3]Royal Marsden Hospital, Medical Oncology, London, United Kingdom; [4]Novartis, Oncology, Basel, Switzerland*

**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**

D.R. Shaffer, L. Abrey, K. Beekman, M. Morris, C. Eicher, W.K. Kelly, S. Slovin, D. Solit, N. Rosen, H.I. Scher. *Memorial Sloan-Kettering Cancer Center, Medicine, New York, USA*

**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**

E. Posadas[1,2], V. Kwitkowski[1], M. Liel[2], H. Kotz[1], L. Minasian[1], G. Sarosy[1], N. Harold[1], S. Fioravanti[1], E. Kohn[1,2]. *[1]National Cancer Institute, Medical Oncology Clinical Reserach Unit, Bethesda, MD, USA; [2]National Cancer Institute, Laboratory of Pathology, Bethesda, MD, USA*

**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.