completed the 1st treatment course have received additional courses; none have discontinued therapy due to progressive disease.
**Conclusions:** Outpatient therapy with rIL-21 plus sorafenib is well tolerated with appropriate dose modification and associated with anti-tumor activity as a 2nd or 3rd-line therapy for mRCC. Updated results from all available subjects in Phase 2, including 6 months of follow-up for the first 15 subjects, will be available at the meeting.

**205** POSTER

**A phase II study of oral enzastaurin HCl in patients with metastatic colorectal cancer**

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**Background:** About 50% of all colorectal cancer (CRC) patients (pts) ultimately die of metastatic disease signifying a need for improved treatment. Enzastaurin, a protein kinase C-β/AKT inhibitor with antiangiogenic and proapoptotic properties, has shown activity in hematological and solid tumors. We evaluated enzastaurin monotherapy using a Phase 2 Window study in chemonaive pts with asymptomatic metastatic CRC (mCRC) for whom standard chemotherapy could be safely delayed. The main objective of this single-arm, open-label study was to estimate the 6-month progression-free survival (PFS); secondary objectives included evaluation of safety and efficacy, time-to-event measures, and carcinoembryonic antigen (CEA) levels.
**Materials and Methods:** Patients with asymptomatic mCRC with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 with at least one measurable lesion received a 400 mg TID loading dose of enzastaurin on Day 1 of Cycle 1, followed by 500 mg once daily for the remaining cycle (1 cycle = 28 days), and all subsequent cycles. Patients were considered eligible only if they were not candidates for chemotherapy-induced tumor reduction that could potentially lead to total tumor resection. Plasma samples for pharmacokinetic characterization were collected on Day 2, Cycle 1 (day after loading dose); Day 1, Cycle 2; and Day 1, Cycle 3 (both steady-state).
**Results:** A total of 28 pts (16 male, 12 female; median age 69 yrs) enrolled and received treatment. Six (21%, 95% CI = 13−44%) pts reached a 6 month PFS. No pt had a clinical response, 12 (43%) achieved stable disease. Overall survival was censored at 82%. The survival rate at 20 months = 77% (CI 47%-92%) and median PFS was 2 months (95% CI = 1.8–4.5 months). Correlation between CEA level changes and enzastaurin activity was not apparent. Four of 28 pts received the planned 6 cycles of therapy. Of the 2 discontinuations, one (cerebral hemorrhage leading to death) was possibly related to study drug. There were 4 dose omissions but no dose reductions. Eight pts had Grade (Gr) 3 toxicities and 1 pt had a Gr 4 upper respiratory infection. The Gr 3 toxicities included nausea, transaminase elevation (possibly related to study drug), edema, etc, but no prevalence of any specific toxicity was evident. Alterations in QTc intervals observed on electrocardiogram assessments were not deemed medically significant even when conducted at Cmax level. Slit-lamp exams did not indicate cateractogenesis or changes in existing cataracts with enzastaurin treatment. Pharmacokinetics of enzastaurin and its active metabolite in mCRC pts were comparable to those seen in previous studies in other tumor types.
**Conclusions:** Enzastaurin is well tolerated but exhibits modest activity as monotherapy in chemonaive pts with mCRC. Further studies of enzastaurin in combination with other agents in mCRC are warranted.

**206** POSTER

**Phase II study of sunitinib in patients (pts) with progressive metastatic adenoid cystic carcinoma (ACC)**

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**Background:** A high level of c-kit expression, usually of wild-type, has been identified in >90% of ACC. However, imatinib has been found to be inactive in that population likely because its activity is dependent on specific c-kit mutations (Hotte et al, J Clin Oncol 2005). VEGF overexpression has been correlated with worse clinical outcome in ACC (Zhang et al, Clin Cancer Res 2005). Sunitinib, which inhibits multiple receptor tyrosine kinases including VEGFR and unmutated c-kit, is of interest for evaluation in ACC.
**Methods:** This is a two-stage, single-arm phase II clinical trial of sunitinib in adult pts with unresectable or metastatic ACC measurable by RECIST criteria, progressive disease is not mandatory at study entry. All patients were treated with a starting dose of sunitinib 37.5 mg PO on a daily and continuous schedule, in 4-week cycles. The primary endpoint is objective response rate, assessed radiologically every 8 wks. One or more objective responses must be observed out of 12 pts in the first stage for the study to enrol to a total of 37 pts.
**Results:** Since February 2007, 12 pts, including 8 males, with a median age of 61 (range, 50−70) were entered onto stage 1. Nine pts had no prior systemic treatments and 11 had prior radiation. Pts had a median of 5 target sites (range, 2−9) and lung lesions were most common. A total of 56 cycles and a median of 5 cycles (range, 2−8) have been administered. All pts but one had a best response of SD and 2 pts remain on study. No PR observed; PFS was nine months (mo) (95%CI 7.3 – NR) and 6-month progression free rate was 91%. Median time to failure was 7.3 mo (95%CI 6.6 mo – NR). This compares favourably to other phase 2 trials conducted by our group (Table). Four pts came off study because of toxicity. The most frequent adverse events (AE) of all grades and at least possibly related to sunitinib were (# of pts): fatigue (9), lymphopenia (9), mucositis (8), leucopenia (7), dyspepsia (7), hypophosphatemia (7), diarrhea (6), neutropenia (6), hand foot syndrome (6). Grade 3 AE of possible attribution were infrequently encountered (# of pts) and most common were: lymphopenia (4), fatigue (4) and neutropenia (3).
**Conclusions:** Sunitinb is associated with the expected toxicities but is reasonably well tolerated and may favourably affect rate of progression of disease. Decision regarding proceeding to second stage is pending.

Table 1

| | lapatinib (mo) | imatinib (mo) | sunitinib (mo) |
|---|---|---|---|
| Median TTP | 3.5 (31-NA) | 2.3 (1.8-NA) | 9 (7.3-NA) |
| 3-mo PFS | 70% (53−93%) | 37% (19−74%) | – |
| 6-mo PFS | 35% (19−64%) | 20% (6−62%) | 91% (75–100%) |

**207** POSTER

**Phase II study of gefitinib in combination with cisplatin and concurrent radiotherapy in patients with stage III/IV squamous cell head and neck cancer and to analyse the effect of gefitinib on tumour gene expression**

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**Background:** Gefitinib has shown modest activity in squamous cell head and neck cancer (SCHNC) and is synergistic with radiation and cisplatin in exerting anti-tumour effects. This study aims to determine the feasibility and toxicity of adding gefitinib to cisplatin and concurrent radiotherapy in patients with locally advanced SCHNC.
**Methods:** Patients with accessible primary tumour site for repeat biopsies and who have stage III/IV unresectable SCHNC or who were deemed unsuitable for curative resection were eligible. Baseline biopsy of the tumour at the primary site was done and the patient was started on gefitinib at 500 mg/day as induction for 3 weeks. Two weeks after the start of gefitinib, a second tumour biopsy was done. A repeat CT/MR of the head/neck was done after the induction phase for response evaluation. Radiotherapy of 70 Gy in standard fractionation was started after induction phase with cisplatin at 80 mg/m$^2$ given on weeks 1, 4 and 7 of the radiation concurrently. Gefitinib was maintained at 500 mg/day during the radiotherapy phase and continued for 4 months as consolidation upon completion of radiotherapy. A repeat CT/MR was done 8 weeks after completion of radiation for evaluation and 3−4 monthly thereafter for the first 2 years. The paired tumour samples were analysed for changes in gene expression after gefitinib using the Affymetrix Gene Chip Human Genome U133 set.
**Results:** 31 patients were recruited; one patient declined further treatment after 1 week of induction gefitinib. Patient characteristics are as follows: median age 55 yrs (44−77), male 77%, eversmoker 68%. Tumour characteristics: oral cavity 36%, oropharynx 45%, others 19%; T1−2 19%, T3−4 81%, N0−1 32%, N2−3 68%. Three pts responded during induction phase (10%) with 2 complete responses (CR); at the first evaluation after completion of chemoradiotherapy, 74% had a major response (PR/CR). The 2-yr progression-free (PFS) and overall survival rate (OS) was 45%

and 61% respectively. The treatment schedule was generally well tolerated with oropharyngeal mucositis as the main toxicity: 65% grade 2 and 29% grade 3. Grade 3 neutropenia occurred in 3 patients (10%). One patient died of acute myocardial infarction during the treatment. Relative dose intensities of gefitinib was good at a median of 95% (49–100); 13 patients (42%) completed the intended gefitinib dose. Eleven patients were not able to receive the 3rd cycle of cisplatin due mainly to mucositis. There were 14 paired tumour samples suitable for gene expression analysis. Analysis is still ongoing and will be presented at the meeting.
**Conclusion:** The combination of gefitinib and cisplatin with concurrent radiotherapy is feasible and well accepted by patients with stage III/IV SCHNC with 2-yr PFS and OS which are encouraging.

**208** POSTER

**A phase II study of sunitinib, an oral multi-targeted tyrosine kinase inhibitor, in patients with unresectable, locally advanced or metastatic cervical carcinoma: IND184**

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**Background:** Sunitinib malate (SU11248) is an oral, multi-targeted tyrosine kinase inhibitor targeting VEGFR, PDGFR, KIT and FLT3. Patients with advanced or metastatic cervix cancer have a poor prognosis and have low response rates to conventional chemotherapy. In preclinical and clinical models VEGFR and c-kit, amongst other receptor tyrosine kinases, have been implicated in the development and progression of cervical cancer.
**Methods:** The aim of this multi-centre 2-stage design phase II study was to assess the activity of sunitinib in patients (pts) with locally advanced or metastatic cancer of the cervix. Eligibility criteria included: squamous cell, adenosquamous or adenocarcinoma histology, ECOG PFS 0−1. Prior neoadjuvant, adjuvant or concurrent chemoradiation and up to 1 prior line of chemotherapy for metastatic disease were allowed. Primary endpoint was objective response, secondary endpoints included duration of response, time to progression and tolerability. Pts received sunitinib 50 mg/day for 4 wks followed by 2 wks off treatment in 6-wk cycles. Tumor response was assessed by RECIST criteria every cycle. One response out of the first 18 patients had to be observed to proceed to the second stage of accrual.
**Results:** 19 pts enrolled, 15 with prior chemoradiation, median age 44 (range 28−78) yrs received a total of 55 cycles of treatment (median 2; range 1 to 6). 15 pts have had stable disease and 4 progressive disease: 2 pts remain on treatment. The most common drug related adverse events any grade (% of patients) were diarrhea (74%), fatigue (74%), nausea (58%), hypertension (47%), taste alteration (53%) and hypopigmentation (58%). Grade 3/4 lymphopenia was seen in 8 pts with grade 3/4 anemia in 4. Thyroid stimulating hormone was elevated in 9 pts. 6 pts have developed fistula on study (3 possibly drug related): 5 had received prior chemoradiation and the remaining pt adjuvant radiation alone following surgery. 1 pt died on study (symptomatic progression, hemorrhage/fistula). Three serious unexpected and possibly drug related adverse events have been seen (1 pt with dyspnea and fall in LVEF, 1 pt with pulmonary infiltrates and 1 pt with PV hemorrhage). 7 pts required dose reduction, there were 114 missed doses (58 drug related) in 10 pts.
**Conclusions:** Sunitinib has insufficient activity in cervix cancer to warrant further investigation. The higher than expected rate of fistula formation in this population is of concern. The study has closed to accrual.

**209** POSTER

**An open-label, multicenter, phase 1/2 study of AT-101 in combination with docetaxel and prednisone in men with hormone refractory prostate cancer**

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**Background:** Antiapoptotic Bcl-2 family proteins are overexpressed in hormone refractory prostate cancer (HRPC) and contribute to resistance to therapy. The oral, pan-Bcl-2 (Bcl-2, Bcl-XL, Bcl-W, Mcl-1) inhibitor AT-101 is active as a single agent in men with HRPC and in combination with docetaxel in in vitro and in vivo prostate cancer tumor models. In this Phase 1/2 study, men at least 18 years of age with chemotherapy-naive HRPC were treated with docetaxel 75 mg/m$^2$ q3 weeks, prednisone 5 mg/b.i.d. on days 1−21, and AT-101 at 40 mg/b.i.d. on days 1−3 of each cycle.
**Material and Methods:** The primary objectives of this study were to assess PSA response (Bubley criteria) and toxicities to treatment (NCI CTCAE v. 3.0). Secondary objectives include time to PSA response, duration of PSA response, time to PSA progression, and objective tumor responses (RECIST).
**Results:** This analysis includes 20/37 subjects who received >3 months of treatment. Subject characteristics: median age 69.5 (55−84), median baseline PSA was 174 ng/ml with all subjects having a PSA level >20 ng/mL; 40% had a Gleason score of 8−10; 85% progressed following >2 prior hormonal therapies; 75% had bone metastases; 65% had visceral disease; and all subjects treated had evidence of PSA progression at study entry. Preliminary results showed that 70% (14/20) of subjects achieved a partial response (>50% PSA decline), 80% (16/20) had at least a 30% decrease in PSA level, and 5% (1/20) were refractory to therapy based on PSA measurements. PSA response data is presented graphically in the Waterfall plot. The median time to response was 42.5 days. Of the subjects with measurable disease 54% (6/11) had a PR per RECIST. Six subjects are still on therapy and, thus far, 30% (6/20) of subjects have received >10 cycles of therapy. Mature data regarding duration of response and time to progression are not yet available. Safety data was available on 15 subjects. The majority of AEs were Grade 1/2 (60%/29%); 6% were Grade 3 and 2% were Grade 4. The most common AEs experienced included fatigue (9/15), diarrhea (6/15), nausea (5/15), taste alteration (5/15), constipation (4/15), alopecia (4/15), dehydration (3/15), vomiting (3/15), abdominal pain (3/15), hypomagnesemia (3/15), and edema (3/15).
**Conclusions:** Preliminary data suggests that oral AT-101 when given in combination with docetaxel and prednisone is well tolerated and shows preliminary evidence of efficacy in subjects with HRPC.