the 17-AAG ratio. Utilizing recombinant human cytochrome P450 3A4 and 3A5 preparations, we found 17-AAG to be a substrate for both CYP3A4 and CYP3A5 with a similar rate of transformation. Therefore, we proceeded with CYP3A5 genotyping (n=13) and found 2/13 patients carried the *3 polymorphism and 0/13 patients carried the *6 polymorphism. At the time of the meeting we will update the PK analysis on the remaining patients and include CYP3A5 and NQO1 genotype correlation. (Supported by CA69912, CA15083, and RR00585)

171

Combination therapy with ZD1839 ('Iressa') and docetaxel in patients with advanced or metastatic non-small-cell lung cancer (nsclc): preliminary safety results of an open-label, pilot trial

C. Manegold[1], U. Gatzemeier[2], S. Averbuch[3], A. Fandi[4]. [1]*Thoraxklinik, Heidelberg, Germany;* [2]*Krankenhaus Großhansdorf, Großhansdorf, Germany;* [3]*AstraZeneca, Wilmington, USA;* [4]*AstraZeneca, Macclesfield, United Kingdom*

Patients (pts) with advanced non-small-cell lung cancer (NSCLC) continue to have a poor prognosis with conventional therapy. ZD1839 ('Iressa') is an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), which has antitumor activity and is generally well tolerated as monotherapy in pretreated pts with advanced NSCLC. ZD1839 has shown additive/synergistic activity with a range of chemotherapy agents in preclinical studies. In this study, we investigated the combination of ZD1839 with docetaxel, an agent established as a second-line therapy for advanced NSCLC. The primary trial objective was to assess the safety of ZD1839 (250 or 500 mg) once daily, in combination with docetaxel in pts with advanced or metastatic, untreated or pretreated NSCLC. Oral ZD1839 treatment started on day 2 of the first cycle of the standard chemotherapy regimen of docetaxel (75 mg/m^2 iv), which started on day 1. Further cycles of docetaxel were administered every 3 weeks concurrently with ZD1839 for up to 6 cycles in total. To date, 18 pts have been enrolled - median (range) age: 59 (40-73) years; M/F: 13/5; performance status 0/1: 4/14; disease stage IIIB/IV: 3/15. Adverse event (AE) data are available for 12 pts (6 pts at each ZD1839 dose level). At 250 mg/day ZD1839, no dose-limiting toxicities (DLTs) were observed. AEs considered to be ZD1839-related included G1/2 skin rash (4 pts) and G1 diarrhea (1 pt), and AEs considered to be docetaxel-related included leucopenia (G1/2, 2 pts; G3, 4 pts), neutropenia (G1, 1 pt; G3/4, 5 pts), fatigue (G2, 4 pts), mucositis/stomatitis (G1, 4 pts), and nausea (G1/2, 3 pts). In the 500 mg/day group, 2 pts had DLT: G3 diarrhea lasting over 4 days (1 pt) and G3 skin rash (1 pt). At this dose, the most common ZD1839-related AEs were diarrhea (G1/2, 3 pts; G3, 3 pts) and skin rash (G1/2, 3 pts; G3, 1 pt), and docetaxel-related AEs included leucopenia (G2, 2 pts; G3/4, 4 pts), neutropenia (G2, 1 pt; G3/4, 5 pts of whom 3 had febrile neutropenia with no proven sepsis), and mucositis/stomatitis (G1/2, 4 pts; G3, 1 pt). Pharmacokinetic data and antitumor activity will be presented. In conclusion, the combination of ZD1839 and docetaxel for the treatment of pts with advanced NSCLC did not cause any unpredictable toxicity. No DLT has been observed to date at the recommended monotherapy doses of 250 mg ZD1839 and 75 mg/m^2 docetaxel. 'Iressa' is a trademark of the AstraZeneca group of companies

172

A Phase I study of weekly BMS-214662, a novel farnesyl:protein transferase inhibitor, combined with weekly paclitaxel

H. Bailey[1], J. Thomas[1], R. Marnocha[1], K. Binger[1], J. Volkman[1], K. Tutsch[1], M. Cooper[2], D. Sonnichsen[2], S. Bai[2], G. Wilding[1]. [1]*University of Wisconsin Comprehensive Cancer Center, Medicine, Madison, USA;* [2]*Bristol-Myers Squibb, Pharmaceutical Research, Lawrenceville, USA*

BMS-214662 is a novel farnesyl:protein transferase (FPT) inhibitor (FTI) undergoing phase I and II testing. Preclinical testing has revealed potent and specific inhibition of FPT at nanomolar concentrations with growth inhibitory effects against many tumor types independent of ras status. Preclinical studies have demonstrated a significant, sequence-specific synergy between anti-microtubular agents, such as paclitaxel, and FTIs. We are conducting a phase I dose escalation study of weekly paclitaxel (80 mg/m^2 over 1 hour) and BMS-214662 (escalating doses over 1 hour) administered 30 minutes after paclitaxel. Nineteen patients, with advanced solid tumors, have been entered at 6 dose levels of BMS-214662; level 0 (80 mg/m^2/week, 3 pts), level 1 (120 mg/m^2, 3 pts), level 2 (160 mg/m^2, 3 pts), level 3 (200 mg/m^2, 4 pts), level 4 (225 mg/m^2, 3 pts), and level 5 (245 mg/m^2, 3 pts). Commonly observed toxicities have been grade 1 nausea, diarrhea and fatigue. Two of three patients at level 5 had rapid onset (day 2 of course 1) of culture positive, grade 4 febrile neutropenia, which resolved with supportive measures. Evidence of clinical response (measurable or evaluable) has been observed at multiple dose levels in patients with laryngeal, prostate, and ovarian cancer and in a patient with sarcoma. Paclitaxel pharmacokinetics have not significantly varied with increasing doses of BMS-214662. Preliminary assessment of FPT activity in peripheral mononuclear cells and BMS-214662 pharmacokinetics has observed a correlation between degree of FPT inhibition and drug concentrations. Further enrollment is ongoing with patients receiving BMS-214662 as a 24-hour infusion rather than a 1-hour infusion. In preclinical models, 24-hour infusions of BMS-214662, compared to bolus infusions, increase this compound's therapeutic index, both when used as a single agent or in combination with paclitaxel.

173

Final results of a phase I study of the Raf-1 kinase inhibitor bay 43-9006 in patients with advanced refractory solid tumours

H. Hirte[1], M. Moore[2], S. Hotte[1], A. Oza[2], L. Siu[2], H. Harris[1], M. MacLean[2], O. Petrenciuc[3], W. Fiander[3], C. Lathia[4]. [1]*Hamilton Regional Cancer Centre, Medical Oncology, Hamilton, Canada;* [2]*Princess Margaret Hospital, Medical Oncology, Toronto, Canada;* [3]*Bayer Inc., Etobicoke, Canada;* [4]*Bayer Inc., Westhaven, USA*

Introduction: Raf-1 is a protein kinase that exerts its effects downstream of Ras in the mitogen-activated protein kinase pathway and is thus likely to be crucial in the development of a malignant phenotype. BAY 43-9006 is a selective inhibitor of Raf-1 and the first compound of its class to enter clinical trials. Final results of a phase I study designed to determine the maximal tolerated dose (MTD), toxicity profile, pharmacokinetics and antitumour activity of BAY 43-9006 in patients(pts) with refractory solid tumors are presented.
Patients and methods: BAY 43-9006 was administered orally in escalating doses to eligible pts during the first 28 days of a 35-day cycle. 37 pts were entered in 8 cohorts (50mg twice weekly - 3 pts, 50mg every other day - 6 pts, 50mg daily - 4 pts, 100mg daily - 4 pts, 100mg BID - 3 pts, 200mg BID - 6 pts, 400mg BID - 3 pts, 600mg BID - 7 pts). PS 0-2, median age 52 (range, 33-70), 46% male. Primary tumor types: ovary/abdominopelvic (13 pts), colon (14 pts), pancreas (3 pts), renal (2pts), other (5 pts). Cohort 7 has recently been expanded by 5 pts (CRC - 4, ovary - 1).
Results: MTD has been reached. A total of 101 cycles have been given and 28 pts are off study (adverse event (AE) - 6, progression or death - 21, other - 1). Most drug-related AEs were mild (grade 1-2) and consisted of dermatologic (31), dyspepsia (7), flatulence (8), diarrhea (7), nausea (5), anorexia (5), fatigue (9), pain (5), neurological (6), alopecia (3), insomnia (2). Grade 3 biochemical abnormalities included hyponatremia (10), ALP (8), lymphocytes (8), bilirubin (5), AST/ALT (5), others (8). In cohort 8, one pt had grade 3 hand-foot syndrome (HFS). This cohort was expanded by 4 pts, with 2 pts getting HFS. Analysis of D1 PK samples resulted in Cmax values of 0.60 $\pm$ 0.20, 0.66 $\pm$ 0.37, 0.49 $\pm$ 0.24, 0.86 $\pm$ 0.32, and 1.28 $\pm$ 0.19 mg/L, AUC (0-24) values of 8.72 $\pm$ 2.52, 10.97 $\pm$ 6.61, 7.0 $\pm$ 2.9, 10.7 $\pm$ 4.4 and 18.7 $\pm$ 6.8 hr mg/L, and a terminal half-life of 27.7 $\pm$ 4.3, 27.9 $\pm$ 6.2, 21.5 $\pm$ 1.7, 24.8 $\pm$ 1.4 and 38.6 $\pm$ 6.5 hours for cohorts 1 to 5. To date, 3 pts have had tumour shrinkage of at least 20%.
Conclusions: DLT has been reached at 600mg BID. Future phase II studies are planned and should use the RPTD of 400mg BID.

174

A Phase I trial assessing the pharmacokinetics and tolerability of ZD1839 ('Iressa') in hepatically impaired patients with solid tumours

A. Harris[1], C. Twelves[2], J. White[2], M. Verrill[3], J. Carmichael[4], J. Farebrother[5], R. Smith[5], A. Laight[5]. [1]*Cancer Research UK Oxford Cancer Centre, Medical Oncology Unit, Oxford, UK;* [2]*Beatson Oncology Centre, Glasgow, UK;* [3]*Northern Centre for Cancer Treatment, Newcastle-upon-Tyne, UK;* [4]*City Hospital, Nottingham, UK;* [5]*AstraZeneca, Macclesfield, UK*

ZD1839 ('Iressa'), an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), has shown antitumour activity and good tolerability in patients (pts) with a range of tumours. Hepatic dysfunction as a result of liver metastases is common in pts with solid tumours;