tumors. Vascular endothelial growth factor (VEGF) induces vascular permeability and plays a major role in vasculogenesis, angiogenesis, and endothelial integrity and survival. Besides VEGF-, other proangiogenic factors such as platelet derived- (PDGF), and fibroblast growth factor (FGF) with their receptors compose critical cellular pathways controlling lung cancer vascularization, growth and progression. BIBF 1120 is an oral potent triple angiokinase inhibitor targeting VEGFR, PDGFR, FGFR kinases.

Methods: In this double blind multi-centre trial, patients with an ECOG score of 0-2 with locally advanced or metastatic (stage IIIB/IV) relapsed NSCLC after failure of first or second line chemotherapy were randomly assigned to daily treatment with 2x250 mg or 2x150 mg of BIBF 1120 until progression. In the event of dose limiting toxicity, a single dose reduction to open label treatment with 2x150 or 2x100 mg of BIBF 1120 was allowed. Patients with stable brain metastases or squamous cell carcinoma were not excluded. The primary endpoints were progression free survival (PFS) and objective tumour response according to RECIST (determined every 6 weeks).

Results: A total of 74 patients were enrolled and 73 patients treated with BIBF 1120 (61% males, median age: 64 years, range 36-80). The most common histology was adenocarcinoma (55%), followed by squamous cell carcinoma (23%). The median PFS of all patients (n= 73) was 1.6 months without significant difference between both treatment arms. The stable disease rate was 48%. One confirmed partial response was observed.

Patients with an ECOG performance status of 0 or 1 (n= 57) had a median PFS of 2.9 months and a three- and five months PFS rate of 46% and 31%, without any difference between both treatment arms. The stable disease rate in this group of patients was 59% and the median overall survival was 144 days.

Patients treated with 2x250 mg per day had more CTCAE Grade 3 and 4 toxicities as compared to patients treated with 2x150 mg (27% versus 2.8%, p=0.006, two-sided Fisher-test). The most frequent adverse events irrespective of relatedness observed in 73 patients were of CTCAE Grade 1 or 2 and included nausea (41%), diarrhoea (41%), vomiting (33%), fatigue (29%), and abdominal pain (22%). Grade 3 and 4 toxicities included nausea (8%), diarrhoea (7%), vomiting (4%), abdominal pain (4%) and AST and/or ALT elevations (5.4%) which were fully reversible.

Conclusions: These results suggest that continuous treatment with BIBF 1120 is safe and well tolerated, and showed promising efficacy in ECOG 0-1 patients. A considerably high rate of disease control could be observed in this study.

B1-04 **Novel Therapeutics I, Tue, 13:45 - 15:30**

DN-101-004: a multicenter, open label, dose ranging study of DN-101 (ASENTAR™) and docetaxel in patients with stage IIIB or IV non-small cell lung cancer (NSCLC) after platinum-based chemotherapy

West, Howard[1] Reyno, Leonard[2] Lee, Stella[2] Fehrenbacher, Louis[3] Cohn, Allen L.[4] Hopkins, Judith O.[5] Irwin, David H.[6] Smith, David A.[7] Boyd, Thomas E.[8] Olsen, Mark R.[9]

[1] Swedish Cancer Institute, Seattle, WA, USA [2] Novacea, Inc., South San Francisco, CA, USA [3] Kaiser Permanente Medical Center, Vallejo, CA, USA [4] Rocky Mountain Cancer Center, Denver, CO, USA [5] Piedmont Hematology/Oncology Association, Winston-Salem, NC, USA [6] Alta Bates Comprehensive Cancer Center, Berkeley, CA, USA [7] Northwest Cancer Specialists, Vancouver, WA, USA [8] Yakima Valley Memorial Hospital/North Star Lodge Cancer Center, Yakima, WA, USA [9] Oklahoma Cancer Care Associates, Tulsa, OK, USA

Background: DN-101 is a high dose oral formulation of calcitriol, the most potent ligand of vitamin D receptor. Calcitriol has various antineoplastic effects on malignant cells and increases activity of cytotoxic agents, including taxanes. DN-101 in combination with docetaxel increased survival in a phase 2 study in androgen-independent prostate cancer and ASCENT 2, a phase 3 confirmatory study is underway. The objective of the study was to determine the maximum tolerated dose, response rate (ORR), progression-free survival (PFS), and overall survival (OS) of DN-101 in combination with docetaxel in advanced NSCLC patients (pts).

Methods: Eligible pts had Stage IIIB or IV NSCLC that progressed on or after platinum-based chemotherapy, ECOG ≤ 1, and measurable disease by RECIST criteria. DN-101 was administered on day 1 in doses of 45 (n=5), 75 (n=4), 135 (n=3), or 180 μg (n=53) in the q21d group, or 180 μg on day 1, followed by 45 (n=5), 90 (n=4), or 180 μg (n=12) on days 8 and 15 in the q7d group. Docetaxel (75 mg/m^2 BSA) was given on day 2 q21d for all pts.

Results: A total of 86 pts were treated. No unexpected toxicities were reported with DN-101. Grade (G3/4) toxicities and fatal adverse events (AEs) were consistent with the reported toxicity of docetaxel alone. Stomatitis (0% in q7d, 9% in q21d) and G3/4 asthenia and fatigue (5% in q7d, 14% in q21d) were less frequent on DN-101 compared to published reports on docetaxel. No pt on DN-101 q21d developed hypercalcemia while 2 pt on DN-101 q7d (180 μg cohort) developed G3/4 hypercalcemia. Three fatal AEs included 2 on DN-101 q21d (1 lung infiltration, 1 pneumonitis) and 1 on DN-101 q7d (intestinal perforation). The ORR was 5.9% (CI 0.1%, 28.7%) and 6.6% (1.8%, 15.9%), median PFS 14.1 (6.0, 20.0) and 11.6 (8.4, 17.4) weeks, median OS 8.8 (7.1, NA) and 6.9 (5.5, 9.7) months, and 1 year survival rate 40% (15.2%, 64.8%) and 31% (18.9%, 42.2%) for the q7d and q21d group, respectively.

Conclusion: DN-101 in combination with docetaxel is well-tolerated in advanced NSCLC. The observation of improved PFS, OS, and 1 year survival rate with weekly DN 101 supports further investigation, as does the appearance of ameliorated docetaxel-induced toxicity when combined with DN-101.

B1-05 **Novel Therapeutics I, Tue, 13:45 - 15:30**

Activity of MAGE-A3 cancer immunotherapeutic as adjuvant therapy in stage IB/II non-small cell lung cancer (NSCLC): final results of a multi-center, double-blind, randomized, placebo-controlled phase II study

Vansteenkiste, Johan[1] Zielinksi, Marcin[2] Linder, Albert[3] Dahabre, Jubrail[4] Esteban, Emilio[5] Malinowski, Wojciech[6] Jassem, Jacek[7] Passlick, Bernward[8] Lehmann, Frédéric[9] Brichard, Vincent G.[9]

[1] Respiratory Oncology Unit (Pneumology) - Univ. Hosp. Leuven, Leuven, Belgium [2] Szpital Chorub Pluc, Zakopane, Poland [3] LungenKlinik, Hemer, Germany [4] Medical Centre, Athens, Greece [5] Hospital Central de Asturias, Oviedo, Spain [6] Szpital Kopernika, Tuszin, Poland [7] Klinika Onkologii Radiotherapii, Gdansk, Poland [8] University Klinik, Freiburg, Germany [9] GlaxoSmithKline Biologicals, Rixensart, Belgium

Background: NSCLC is associated with poor outcome: even after complete surgical resection, about half of the patients with stage IB or II NSCLC relapse and die within 5 years. Cisplatin-based adjuvant che-

motherapy improves overall survival but at the expense of substantial toxicity. The MAGE-A3 gene is expressed specifically in tumor cells with no expression in normal cells. Pilot studies evaluating the MAGE-A3 cancer immunotherapeutic (i.e. MAGE-A3 recombinant protein combined with a potent GSK proprietary immunological adjuvant) showed a good tolerability and long-lasting clinical objective responses in metastatic melanoma. Because MAGE-A3 is significantly expressed in NSCLC (35% in stages IB or II), post-operative immunization with the MAGE-A3 cancer immunotherapeutic may be a tumor-specific, well tolerated, and effective adjuvant therapy.

Methods: Patients with completely resected, MAGE-A3 (+), pathological stage IB or II NSCLC were randomly assigned to postoperative intramuscular administrations of MAGE-A3 or placebo (2:1), with 5 administrations at 3-week intervals, followed by 8 administrations every 3 months. Stratification factors included stage (IB vs. II), histology (squamous carcinoma vs. other), and lymph-node procedure (minimal lymph-node sampling vs. radical mediastinal lymphadenectomy). The primary endpoint was disease-free interval; secondary endpoints were safety, disease-free survival, and overall survival. This Phase II study (study ID249553/004/NCT00290355) was designed to detect a clinically relevant hazard ratio with a 10% one-sided α.

Results: 1089 tumor samples were examined, of which 363 expressed the MAGE-A3 gene. 182 patients (122 stage IB, 60 stage II) from 59 centers in 14 European countries were randomized over 2 years. The patient characteristics are the following: Median age 63 (45-81); 87% male; 65% squamous cell carcinoma; 65% systematic radical mediastinal lymphadenectomy. After a median follow-up of 28 months, 67 recurrences were observed. Group comparisons of disease-free interval, disease-free survival, and overall survival gave respectively a hazard ratio of 0.74 (95% CI 0.44-1.20, p=0.107), 0.73 (95% CI 0.45-1.16, p = 0.093) and 0.66 (95% CI 0.36-1.20, p = 0.088) in favor of the MAGE-A3 group. Overall, treatment was well tolerated. Subset analysis suggests that systematic radical mediastinal lymphadenectomy may have a positive effect on survival.

Conclusions: The final analysis of this randomized Phase II study shows a positive signal for clinical activity of MAGE-A3 cancer immunotherapeutic as adjuvant treatment in completely resected Stage IB or II NSCLC. The relative improvement in disease-free interval and disease-free survival is 27%. This treatment is well tolerated. Further Phase III evaluation in early NSCLC is planned for 2007.

B1-06 **Novel Therapeutics I, Tue, 13:45 - 15:30**

Multicenter, randomized study of Docetaxel versus Docetaxel plus Oblimersen in patients previously treated for non-small cell lung cancer (NSCLC)

Herbst, Roy S.[1] Ansari, Rafat H.[2] Gorbunova, V[3] Manikhas, G[4] Saleh, Mansoor N.[5] Boyd, Thomas E.[6] Azzoli, Christopher G.[7] Robert, Francisco[8] Itri, Loretta M.[9] Chapman, Robert[10]

[1] The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA [2] Northern Indiana Cancer, Research Consortium, South Bend, IN, USA [3] NN Blokhin Cancer Research Center RAMS, Moscow, Russia [4] St Petersburg Municipal Oncological Dispensary, St. Petersburg, Russia [5] Georgia Cancer Specialists, Atlanta, GA, USA [6] Yakima Valley Memorial Hospital, Yakima, WA, USA [7] Memorial Sloan-Kettering Cancer Center, New York, NY, USA [8] University of Alabama Comprehensive, Cancer Center, Birmingham, AL, USA [9] Genta Incorporated, Berkeley Heights, NJ, USA [10] Henry Ford Health System, Detroit, MI, USA

Background: Bcl-2 protein is a fundamental cause of tumor cell accumulation and resistance to anticancer therapy. Oblimersen (Genasense®), a Bcl-2 antisense oligonucleotide, selectively targets *bcl*-2 RNA for degradation by RNase H and thus decreases Bcl-2 protein production. Oblimersen enhances the activity of anticancer agents (including docetaxel) in animal models, including NSCLC. Findings in clinical studies conducted in patients with various solid tumors and hematologic malignancies support this effect.

Methods: A multicenter, randomized study of docetaxel versus docetaxel plus oblimersen was conducted in patients with NSCLC who had received not more than 1 prior exposure to cytotoxic chemotherapy and had relapsed after or were refractory to that therapy. Patients were ≥ 18 years of age and had measurable disease (Stage IIIB or IV) not previously irradiated, ECOG performance status ≤ 2, adequate organ function, and a life expectancy ≥ 12 weeks. Key exclusion criteria were untreated or symptomatic brain metastases, peripheral neuropathy ≥ Grade 2, and prior radiation therapy to ≥ 25% of the bone marrow. Patients were stratified based on 3 factors (response to prior chemotherapy, ECOG performance status [0 or 1 versus 2], and prior paclitaxel treatment [yes versus no]) and then centrally randomized at a 1:1 ratio. Patients received docetaxel 75 mg/m^2 on Day 1 by IV infusion or oblimersen 7 mg/kg/d on Days 1 to 7 by continuous IV infusion plus docetaxel 75 mg/m^2 on Day 5 of each 21-day cycle for up to 8 cycles. Patients were assessed for response prior to Cycles 3, 5, and 7, at completion of treatment, and up to 18 months after randomization. Endpoints include time to progression, survival at 6 and 12 months post randomization, response rate (complete and partial), response duration, and safety.

Results: Of 298 patients randomized, 287 initiated treatment. Among all patients randomized, the median age was 63 years, and 61% of patients were male. A total of 86% of patients had Stage IV disease; 94% had metastatic disease; and 91% had an ECOG performance status of 0 or 1. Prior radiotherapy was reported for 39% of patients and prior paclitaxel therapy for 48%. Grade 4 neutropenia of 23% among all treated patients compared favorably with that historically reported with docetaxel alone.

Conclusions: The database will be unblinded in Quarter 2, 2007, and results presented.

B1-07 **Novel Therapeutics I, Tue, 13:45 - 15:30**

Decreased neurocognitive progression with Motexafin Gadolinium (MGd) plus Whole Brain Radiation Therapy (WBRT) in non-small cell lung cancer (NSCLC) patients with brain metastases: pooled analysis of two randomized phase 3 trials

Mehta, Minesh[1] Leibenhaut, Mark[2] Suh, John[3] Meyers, Christine[4] Renschler, Markus F.[5] Smith, Jennifer[5] Phan, See C.[5]

[1] University of Wisconsin, Medical School, Madison, WI, USA [2] Sutter Cancer Center Radiation Oncology Center, Sacramento, CA, USA [3] Cleveland Clinic Foundation, Cleveland, OH, USA [4] M.D. Anderson Cancer Center, Houston, TX, USA [5] Pharmacyclics, Sunnyvale, CA, USA

Background: In two randomized studies, MGd when combined with WBRT prolonged time to progression of neurologic endpoints in NSCLC patients (pts) with brain metastases (BM). Neurocognitive testing, which has been shown to correlate with clinical outcome in brain tumor patients, was performed in both studies. The purpose of this analysis was to pool the neurocognitive data from both trials.