and correlate this to PIK3CA or pTEN mutations, and the pharmacokinetic (PK) profile of MK2206 when administered with either agent.
Results: 72 pt (36 M; median age 58 y; ECOG PS 0/1: 21/46) were treated. In Arm 1, 45, 60 and 90 mg QOD, and 90, 135 and 200 mg Q3W were tested. DLTs were rash (QOD and Q3W) and febrile neutropenia (FN) (QOD). In Arm 2 QOD, 3 DLTs of FN were observed in 3 of 5 patients at 45 mg QOD and D 75 mg/m^2. This schedule was abandoned in favor of a Q3W schedule with 60 mg/m^2 D; 3 dose levels were tested − 90, 135 and 200 mg − with 1 DLT of tinnitus at 200 mg. In Arm 3, 45 mg QOD daily or 135 mg QW of MK2206 was tested with 100 and 150 mg of E with DLTs of mucositis (QOD) and rash (QOD and QW). Grade 3&4 events included: anemia (n = 1), FN (n = 4), hyperglycemia (n = 1), leukopenia (n = 8), neutropenia (n = 15), rash (n = 8), thrombocytopenia (n = 1). There was no evidence of PK interaction between MK2206 and C, P, D or E. In Arm 1, Q3W, there was 1 complete response (squamous cell cancer [SCC] orbit) and 1 partial response (PR; SCC head and neck); and in QOD, 2 PRs (endometrial and neuroendocrine prostate cancer). A total of 6 pt demonstrated stable disease lasting >6 months. PI3K mutation was observed in 1 patient with SD.
Conclusions: Based on tolerability, PK and preliminary evidence of activity, the MTD and recommended schedule of MK-2206 with C (AUC 6) + P (200 mg/m^2) was 135 mg Q3W; with D (60 mg/m^2), 200 mg Q3W; and with E (150 mg OD), 135 mg QW.

Arm	Schedule	Dose (MK2206)	*n*	DLT
1. C, AUC6; P 200 mg/m^2	QOD	45	6	1
		60	9	3
	Q3W	90	5	1
		135	5	1
		200	6	2
2. D*	QOD(75 mg/m^2)*	45	5	3
	Q3W (60 mg/m^2)*	90	3	0
		135	4	0
		200	4	1
3. E†	QOD(100 mg)†	45	9	2
	(150 mg)†	45	4	2
	QW (100 mg)†	135	6	0
	(150 mg)†	135	6	1

1203 ORAL

Long-term Survival in a Phase II Study of Belagenpumatucel-L (TGF-β Antisense Modified Tumour Cell Vaccine) in Non-small Cell Lung Cancer (NSCLC)

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Background: Belagenpumatucel-L (Lucanix®), a therapeutic vaccine comprised of 4 TGF-β2 antisense gene-modified allogeneic NSCLC cell lines, was tested in a phase II trial.
Material and Methods: Seventy-five subjects (2 stage II, 12 stage IIIA, 15 stage IIIB, and 46 stage IV) were enrolled. Subjects were randomized into three dose cohorts of 1.25×10^7 cells per injection, 2.5×10^7 cells per injection, or 5.0×10^7 cells per injection and received an intradermal injection monthly for up to 16 injections.
Results: Median survival for all subjects was 14.5 months and five-year survival was 20%. Stages IIIB/IV subjects enrolled into cohorts 2 and 3 had a median survival of 15.9 months and a five-year survival of 18%. For subjects with stable disease or better following frontline chemotherapy, median survival was 44.4 months and five-year survival was 50%. For subjects who progressed following frontline chemotherapy, median survival was 14.1 months and five-year survival was 9.1%. We performed a number of assays of cellular (ELISPOT and cytoplasmic cytokine expression) and humoral (antibody ELISA) immunity on subjects in the trial and correlated these data with overall survival. Subjects who demonstrated an increase in both cellular and humoral immune reactivity following treatment had a significant survival advantage over subjects who showed an increase in only one measure of immunity with a median survival of 32.5 months vs. 11.6 months (p = 0.015). Based on these data, we have instituted an international, randomized, pivotal Phase III trial to evaluate the efficacy of belagenpumatucel-L in a maintenance setting in stage III/IV NSCLC patients who have stable disease or better following frontline chemotherapy. The trial is designed to enroll 506 patients and is powered to measure a 3.5 month survival difference. There are two planned interim analyses. To date, over 227 subjects have been enrolled in 49 clinical sites in 8 countries.
Conclusions: Confirmation of the phase II data in a randomized, phase III setting would provide an important improvement for the treatment of non-small cell lung cancer.

1204 ORAL

A Phase Ib Open-label Study to Assess Continuous Oral Treatment With Afatinib (BIBW 2992) in Combination With Two Chemotherapy Regimens − Cisplatin Plus Paclitaxel, and Cisplatin Plus 5-fluorouracil in Patients, With Advanced Solid Tumours

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Background: Afatinib (BIBW 2992) is an oral, irreversible ErbB-family blocker with preclinical activity as monotherapy or combined with chemotherapy (CT). In this Phase Ib dose-escalation study, afatinib was combined with cisplatin and paclitaxel (A) or cisplatin and 5FU (B) in patients (pts) with advanced solid tumours to determine safety, pharmacokinetics (PK) and preliminary efficacy.
Material and Methods: This study followed a 3+3 design; the primary objective was to assess the maximum tolerated dose (MTD) for each regimen. In regimen A, pts received i.v. paclitaxel (175 mg/m^2) followed by cisplatin (50 mg/m^2 first dose cohort, 75 mg/m^2 thereafter) on Day 1, q3 weeks and oral afatinib (dose escalation: 20, 30, 40, 50 mg) on Days 3−21 in Cycle 1, and Days 1−21 thereafter. In regimen B, pts received i.v. cisplatin (75–100 mg/m^2) on Day 1 followed by 5FU (750–1000 mg/m^2) on Days 1−4 and oral afatinib (dose escalation: 20, 30, 40 mg) on Days 5−21 in Cycle 1, and Days 1−21 thereafter. CT was given for a maximum of 6 cycles; afatinib was continued as monotherapy in cases of disease control (CR+PR+SD).
Results: 47 pts (28 male) received treatment (26 pts in A; 21 pts in B). The MTD was afatinib 20 mg with paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2 and afatinib 30 mg with cisplatin 75 or 100 mg/m^2 and 5FU 750 mg/m^2, following dose-limiting toxicities (DLTs) in 5 and 4 pts in Cycle 1 across all doses of afatinib in each regimen, respectively. DLTs were asthenia, febrile neutropenia, mucosal inflammation, renal failure, liver enzyme elevations and increased blood lactate dehydrogenase (A), and decreased appetite, diarrhea, fatigue, mucosal inflammation, stomatitis, and thrombocytopenia (B). Most frequent drug-related adverse events (AEs) were diarrhea (88.5% of pts), nausea (73.1%), fatigue (53.8%) in regimen A, and nausea (85.7%), decreased appetite (76.2%), diarrhea (76.2%), fatigue (71.4%), and vomiting (61.9%) in regimen B. Disease control was observed in 54% and 29% of pts in A and B, respectively, for a median (95% CI) duration of 212 (141–273) and 112 (85–221) days, respectively. No clinically relevant PK interactions were observed between the CT agents and afatinib.
Conclusions: The MTD of afatinib was 20 mg combined with cisplatin plus paclitaxel and 30 mg with cisplatin plus 5FU. Preemptive, vigorous management of side-effects (especially diarrhea) is important to maintain adequate safety and tolerability with these combinations.

1205 ORAL

Phase I and Pharmacodynamic Study of High-dose NGR-hTNF in Patients With Refractory Solid Tumours

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Background: NGR-hTNF consists of tumour necrosis factor fused with the peptide NGR, which is able to bind selectively to CD13 overexpressed on tumour blood vessels. Maximum tolerated dose (MTD) of NGR-hTNF was previously established at 45 μg/m^2 when given as 1-h infusion every 3 weeks (q3w), with dose limiting toxicity (DLT) being grade 3 acute infusion reactions. We aimed at testing further dose escalations by prolonging the infusion time (2-h) and using a mild premedication (paracetamol).
Methods: 4 patients were enrolled at each of 11 dose levels (DLs: 60–300 μg/m^2 q3w). DLT was defined as any related grade 3−4 toxicity. Pharmacokinetics and pharmacodynamics, including the assessment of soluble TNF receptors (sR1-sR2), were tested in 33 patients (DLs: 60–250). To assess the effect on tumour vascularity, the volume transfer coefficient