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

(Ktrans) and the initial area under gadolinium concentration (IAUGC) were evaluated 24 hours before and 2 hours after dosing in 25 patients (DLs: 80–275) by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI).
Results: Overall, 42 patients (PS 0/1: 18/24; M/F: 33/9) with a median age of 61 years (range 23 to 76) received a total of 101 cycles (range 1 to 7). Prior treatment lines ranged from 1 to 7 (median 3). No DLT occurred and MTD has not yet been reached. Related toxicities were grade 1 chills in 18 patients (53%) over 34 cycles (42%). Nine patients (26%) had grade 2 toxicities. Cmax and AUC increased with dose ($p = 0.0006$ and $p = 0.001$, respectively). Levels of sR2 peaked higher than those of sR1 (7.9 v 3.6 ng/mL; p<.0001). Changes in sRs however did not differ across DLs ($p = 0.49$ for sR1 and $p = 0.43$ for sR2), suggesting a plateau in shedding kinetics. By DCE-MRI, median values pre- and post-first cycle were 0.15 and 0.09 min-1 for Ktrans and 10.4 and 7.2 mM/L/sec for IAUGC, respectively ($p = 0.02$ for both). Twenty patients (80%) showed dose-unrelated reductions in tumour vascularity. In these patients, Ktrans significantly decreased from 0.19 to 0.07 min-1 ($p < 0.0001$), with a median change of −62% (range −24 to −91), whereas IAUGC declined from 14.6 to 5.4 mM/L/sec ($p < 0.0001$), with a median reduction of −54% (range −3 to −97). These decreases correlated inversely with high baseline values of Ktrans ($r = -0.91$, $p < 0.0001$) and IAUGC ($r = -0.51$, $p = 0.02$). Additional dose escalations are ongoing.
Conclusion: NGR-hTNF can be safely escalated at doses higher than MTD and induces low shedding of receptors and early antivascular effects.

1206 ORAL

Smaller, Faster Phase III Trials − New Approach for Assessing Targeted Agents?

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Background: Traditional clinical trial designs strive to definitively establish the superiority of an experimental treatment, which results in risk adverse criteria and large sample sizes. Increasingly, common cancers are recognized to consist of small subsets with a specific aberration for targeted therapy, making large trials infeasible. We performed simulations studies to compare the performance of different trial design strategies to determine over a 15 year research horizon.
Methods: We simulated a series of two-treatment superiority trials over 15 years using different trial design parameters. Trial parameters examined included: number of positive trials to establish superiority (1 versus 2), α-level (from 0.025 to 0.50), and number of trials over 15 years (thus trial sample size, SS). Different disease scenarios (median survivals), accrual rates, and distributions of treatment effect were studied. Metrics used included: gain in survival rate (Hazard Ratio, HR, year 15 versus year 0) and risk of an overall effect of harm ($HR > 1$).
Results: For all scenarios, overall gains were greater using the criterion of 1 positive trial (versus 2) and as α increased from 0.025 to 0.50. Gains increased substantially as α increased from 0.025 to 0.20, but plateaued for values beyond 0.20. Important gains in survival were achieved with SSs smaller than required under traditional criteria. Reducing the SS and increasing α increased the mean gain but also the likelihood of having a poorer survival rate at year 15, but the chance was <7% in all scenarios with α lower or equal to 0.20. Results were consistent under different assumed distributions for treatment effect. The greatest gains were achieved in disease scenarios with smallest expected median survival.
Below is an example of results: median survival 1 year, accrual rate 100/year, historical scenario (mean HR 0.95).

Decision criterion		Optimal strategy		Performance	
No. of positive trials	0.025	No. of trials	SS	Mean HR (at 15 year)	Risk of HR > 1
1	0.025	7	114	0.59	0.5%
1	0.05	8	88	0.55	1%
1	0.10	10	50	0.50	3%
1	0.20	10	50	0.42	3%
2	0.025	5	200	0.69	<0.1%
2	0.05	7	114	0.65	<0.1%
2	0.10	8	88	0.60	0.5%
2	0.20	9	66	0.53	1%

Conclusions: A traditional trial design strategy yields smaller expected gains over a 15 year horizon compared to strategies using larger α and smaller SSs. As patient populations become more specific (and thus smaller), the current risk adverse trial design strategy may slow long term progress and deserves reexamination.

Poster Presentations (Mon, 26 Sep, 14:00−16:30)
Drug Development

1207 POSTER

Phase I Dose-Finding Study for Pazopanib (P) and Paclitaxel (T) in Combination in the First-line Setting in Patients (pts) With Advanced Solid Tumours

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Background: This open-label Phase I study (VEG111109, NCT00866528, sponsored by GSK) investigated the safety and pharmacokinetics (PK), of P, an oral multikinase angiogenesis inhibitor, in combination with T in pts with advanced solid tumours. A secondary objective was to describe clinical activity. Results from the dose-escalation phase of the study are reported; 6 additional pts are currently being enrolled in an expansion cohort at the recommended Phase II dose.
Material and Methods: A 3+3 design was used for dose-escalation. T (3h infusion q3W x6 cycle) started at 135 mg/m^2 due to an anticipated PK interaction with P (once daily po from Cycle 1, Day 2 [C1D2]). PK samples were obtained C1D1 (T alone) and C2D1 (T+P) from pre-dose to 24h post-dose to determine area-under-curve (AUC) and max concentration (Cmax).
Results: The dose-escalation phase of the study enrolled 24 pts (median age 58 years [31−80], 13M/11F, ECOG PS 0−1) with previously untreated advanced solid tumours (14 metastatic melanoma/10 advanced NSCLC); 22 pts received T+P (median cycles 5; P up to 274 days). The most frequent AEs were: hypertension (95%), alopecia (86%), fatigue (73%), nausea (64%), diarrhea (55%), hair color change (50%), and myalgia (50%); 94% AEs were G1/2, 5% G3, and 1% G4. DLTs were seen in 3 pts; 1 pt in Cohort 1 resulting from a possible drug-drug interaction with a concurrent medication and 2 pts in Cohort 2, thereby exceeding the MTD. No DLTs were observed in Cohort 3 or 4; however 2/6 subjects in Cohort 4 had reduced dose T in C2 due to C1 neutropenia. Cohort 3 was a better tolerated dose level than Cohort 4. Median T AUC increased in the presence of P by approximately 25−30% at each dose level tested.

T mg/m^2/ P mg	N	T PK, median ratio C2:C1		No. of subj by worst	DLT
		AUC(0-inf)	Cmax	Grade AE G3/G4	
135/800	6	1.23, n = 5	1.25, n = 5	2/2	1 G4 ALT
175/800	4	1.30, n = 2	1.14, n = 3	3/1	1 G3 rash 1 G3 ALT+G2 rash
150/800	6	1.33, n = 6	1.31, n = 6	4/0	
175/400	6	1.28, n = 4	1.23, n = 4	2/1	

T+P was active at each dose level; of the 20 pts evaluable for response, 10 (4 NSCLC, 6 melanoma) had confirmed PRs and 6 (3 NSCLC, 3 melanoma) had SD $\geqslant$12 weeks.
Conclusions: The 150 mg/m^2 T/800 mg P dose level was selected as the recommended Phase II dose. Due to PK interaction, T exposure at this dose level is approximately equal to exposure after 200 mg/m^2 T alone. T+P demonstrated promising anti-tumour activity in both NSCLC and melanoma.