cytotoxic drugs (carboplatin, cisplatin, gemcitabine, fluorouracil, etoposide and doxorubicin). Three cell lines (H28, MSTO211H and LO68) were screened against 1524 JHCCL compounds. SYBR(R) Green I- fluorometric assay was used to measure compound activity.
**Results:** All lines were sensitive to doxorubicin and gemcitabine except MM05 and H226, which were resistant to gemcitabine. MSTO211H was chemosensitive to carboplatin and etoposide and H226 was resistant to flurouracil.
50 drugs (9 antineoplastic, 10 antheminithic, 14 antiseptic, 5 antibiotics, 3 antidote, 3 antihistaminic, 2 antihyperlipidemic, 2 antimalarial, 3 carditonic, 2 dermatologic, 2 progestogen, and other include aesthetic, antifungal, antiparkinsonian, antiprotozoal, antipsychotic, diagnostic aid, hemostatic) have been short listed after first screening with 10uM of each drug of JHCCL. Compound activity was analysed by comparison to an arbitrary point within the dynamic range defined by assay controls (e.g. representing 50% cell death). A five-log range of final concentrations from 100 uM to 1 nM was tested and IC50 was determined. The results ranged within 0.7 uM−10 uM.
**Conclusions:** Active compounds were identified from a panel of agents with history of clinical use. The anti-mesothelioma action of several candidates active *in vitro* at levels below PPC now requires validation in vivo or in clinical settings.
**Acknowledgements:** Cancer Australia, Dust Disease Board And The Prince Charles Hospital Foundation.

## *Oral Presentations* (Mon, 26 Sep, 09:00−10:55)
## Drug Development

**1200** ORAL

### RP5237- a Novel, Selective, and Potent Inhibitor of PI3Kdelta With Therapeutic Potential in B-cell Lymphomas

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**Background:** Pan-PI3K inhibitors currently in development have been associated with adverse side-effects such as insulin resistance, thus necessitating the need to develop isoform specific inhibitors of PI3K. Because expression of PI3Kδ isoform is limited to blood cells, it serves as an ideal target against cancers associated with dysfunctional expansion of hematopoietic cells. Herein, we describe the biological and pharmacokinetic properties of RP5237, a novel and small molecule PI3Kδ inhibitor with scope to be further developed as a clinical candidate for B-cell lymphomas.
**Material & Methods:** Activity of RP5237 on individual PI3K isoforms was determined by a Homogenous Time Resolved Fluorescence assay (Millipore, Billerica, MA) with modifications. Potency of the compound on the delta isoform was further corroborated in FcεR1 induced CD63 expression studies using human whole blood and anti-IgM induced human B-cell proliferation assays. Anti-tumour efficacy of the compound was confirmed *via* cell viability and apoptosis assays besides testing for inhibition of pAkt, a downstream kinase regulating cell survival and growth. Metabolic stability of the compounds was evaluated in liver microsomes. Pharmacokinetic parameters were estimated in plasma from mice and rat.
**Results:** RP5237 demonstrated significant potency against PI3Kδ (**13.8 nM**) with several fold selectivity over the α (**>1000**), β (**>50**), and γ (**>9**) isoforms. Additionally, the compound inhibited B-cell proliferation (**32.2 nM**) and FcεR1 induced CD63 expression in human whole blood basophils (**48.9 nM**) indicating specificity towards the delta isoform. Viability assays demonstrated that the compound caused a dose-dependent inhibition in growth of B-cell mediated cancerous cell lines such asTHP-1, TOLEDO, HL-60, and Raji. Reduction in viability was accompanied by a reduction in pAKT along with a significant increase in apoptosis manifested by an induction of caspase-3 activity in the cell lines tested. Pharmacokinetic studies in mice and rat indicated good oral absorption with favourable peak plasma concentrations.
**Conclusions:** Results demonstrate the therapeutic potential of RP5237 in B-cell mediated cancers *via* the PI3Kδ pathway. *Ex vivo* studies using blood obtained from naive lymphoma patients are currently underway to determine the efficacy of the compound in different tumour sub-sects. Additionally, the compound shall be tested in mouse xenograft models of haematological malignancies.

**1201** ORAL

### Early Studies of the Safety, Pharmacokinetics (PK), Pharmacodynamics (PD), and Anti-tumour Activity of the Humanized Monoclonal Antibody (huMAb) Anti-EGFL7 (MEGF0444A) Alone and in Combination With Bevacizumab (Bev) With and Without Paclitaxel (Pac) in Patients (pts) With Advanced Cancer

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**Background:** Epidermal growth factor-like domain 7 (EGFL7) is a vascular-restricted, tumour-enriched, extracellular matrix protein that forms perivascular tracks and promotes endothelial cell adhesion and survival. Anti-EGFL7 (MEGF0444A) is a huMAb that inhibits the activity of EGFL7 and reduces vascular density and perfusion in murine tumour models. Anti-EGFL7 as a single agent (SA) has limited anti-tumour activity, but it significantly enhances the anti-tumour activity of anti-VEGF in multiple murine tumour models.
**Materials and Methods:** A standard 3+3 dose escalation was used to study safety, PK, PD, and anti-tumour activity of MEGF0444A in 2 serial Phase I trials. In a Phase Ia study, 30 pts were treated with SA MEGF0444A in 21-day cycles at doses ranging from 0.3 to 15 mg/kg. In a subsequent 2-arm Phase Ib study, 40 pts were enrolled. In Arm A, MEGF0444A was given at doses of 2, 5, or 10 mg/kg along with Bev at 10 mg/kg on Days 1 and 15 of each 28-day cycle; in Arm B, pts additionally received Pac (90 mg/m$^2$) on Days 1, 8, and 15 of each cycle. PD biomarkers including circulating progenitor cells (CPCs) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) were assessed.
**Results:** In the Phase Ia trial, the highest planned dose of 15 mg/kg was reached without dose-limiting toxicities. MEGF0444A was well tolerated with no attributed Grade ⩾3 serious adverse events (AEs). There were no responses. In the Phase Ib study, the combination of MEGF0444A and Bev with or without Pac did not appear to exacerbate Bev-related AEs. Five partial and 2 minor responses were observed in multiple tumour types in the Phase Ib trial. In both studies, MEGF0444A had linear PK typical of an IgG1 huMAb. Enumeration of CPCs showed a decrease in a subset of pts within 15 days of MEGF0444A therapy. DCE-MRI results were suggestive of anti-angiogenic activity in select pts. Five mg/kg q2weeks (w) was chosen as the recommended Phase II dose.
**Conclusions:** MEGF0444A has favorable PK and is well tolerated as a SA and in combination with Bev and Bev/Pac. Changes in CPC levels and DCE-MRI parameters are consistent with MEGF0444A anti-angiogenic and anti-vascular activity. Study data support a Phase II dose of 5 mg/kg q2w (equivalent to a flat dose of 400 mg q2w or 600 mg q3w). Phase II trials of MEGF0444A with chemotherapy/Bev are planned.

**1202** ORAL

### A Phase I Study of the Potent AKT Inhibitor MK-2206 in Combination With Carboplatin and Paclitaxel, Docetaxel or Erlotinib in Patients With Advanced Solid Tumours

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**Background:** MK-2206 is a novel allosteric inhibitor of all 3 isoforms of AKT, which are targets implicated in malignant progression and resistance to anti-cancer therapies. *In vitro*, MK2206 demonstrated synergistic or additive anti-cancer effects when combined with C+P, D and E.
**Material and Methods:** Pts with advanced solid tumours, ECOG PS ⩽1 were recruited to a 3-arm phase I study of MK2206 QOD (days 1, 3, 5, 7) or Q3W with carboplatin (C) (AUC6) and paclitaxel (P) (200 mg/m$^2$) (Arm 1), or docetaxel (D) (60 & 75 mg/m$^2$) (Arm 2) or QOD (alternate days continuous) and QW with erlotinib (E) (100 and 150 mg) OD (Arm 3). The primary objectives were to determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) of MK2206 in combination with C+P, D or E. Secondary objectives were to determine preliminary activity

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 $1.25\times10^7$ cells per injection, $2.5\times10^7$ cells per injection, or $5.0\times10^7$ 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