

enroll in a phase I dose-escalation study (standard 3+3 design) of SASP in combination with CDDP and pemetrexed (PEM) as first-line treatment. Patients receive SASP daily as well as CDDP (75 mg/m<sup>2</sup>) and PEM (500 mg/m<sup>2</sup>) on day 1 of a 21-day cycle. The primary end point is the percentage of patients who experience dose-limiting toxicity (DLT) between administration of the first dose of SASP (day 1) and day 21.

**Results:** From April 2015 to January 2016, 15 patients were enrolled in the study (mean age, 64 years; age range, 42–74 years; male/female ratio, 10/5; ECOG performance status 0/1 ratio, 6/9). Immunohistochemical staining of tumor biopsy specimens revealed that the proportion of CD44v-positive cells was >10% in 9 patients before SASP treatment. No DLT was observed in the first three patients treated at SASP dose level 1 (500 mg TID) or those treated at dose level 2 (1000 mg TID). At dose level 3 (1500 mg TID), two of three patients experienced a DLT (anorexia of grade 3). We enrolled additional patients at dose level 2 and two of the total of five patients treated at this dose level experienced DLTs (hypotension or pneumonitis, each of grade 3). To confirm the safety of dose level 1, we enrolled additional patients at this dose level and one of the total of six patients treated at this dose level experienced DLTs (AST and ALT elevation, each of grade 3). Exposure of SASP following oral administration varied markedly among individuals according to *ABCG2* and *NAT2* genotypes as previously reported.

**Conclusion:** SASP 500 mg TID was the recommended dose when administered with CDDP plus PEM.

**Keywords:** Cancer stem cell, non-small cell lung cancer, chemotherapy, Salazosulapyridine

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### P3.02c-002

#### Mannosylated Poly (Propylene Imine) Dendrimer Mediated Lung Delivery of Anticancer Bioactive



*Topic: Targeted Therapy*

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**Background:** Tumors originating in lung tissues or in the bronchi invade adjacent tissue and cause infiltration beyond the lung. Lung macrophages express mannose-specific endocytosis receptor that might binds or internalize mannose terminated dendrimer. Therefore, it is hypothesized that incorporation of anticancer drug into

mannose anchored dendrimer will transport the drug effectively to the tumor cells via receptor mediated endocytosis. Dendrimer are easy to synthesis and better stability, Nanoscopic size range, High drug loading propensity, Dose reduction possible, Number of free surface groups available for further conjugation. The project aimed to investigate the targeting potential of mannose conjugated Poly Propyl Imine (PPI) dendrimer having potent anticancer drug, Gemcitabine in lung cancer cells. The dendrimers were conjugated so as to enhance the therapeutic potential and reduce adverse effect of anticancer drug.

**Methods:** The 5.0 generation dendrimers were synthesized and were characterized by FTIR and Nuclear Magnetic Resonance (NMR). The PPI dendrimers prepared were then conjugated with mannose and drug was loaded. The shape and size were characterized by Transmission Electron Microscopy (TEM), drug loading efficiency, In-vitro drug release and stability studies. The ex-vivo studies constituted Hemolytic toxicity study and Cell cytotoxic study by MTT Cytotoxicity Assay on A-549 (Lung adenocarcinoma epithelial) cell line. The *in-vivo* studies were performed on albino rats and Pharmacokinetic parameters were studied, also Biodistribution Studies were done to access gemcitabine level attained in different organs.

**Results:** Thus Mannosylated PPI dendrimers showed high gemcitabine loading, sustained release and excellent biocompatibility as evident by low hemolytic toxicity. MTT assay suggested high cytotoxicity of GmCH-MPPI against A549 cancer cell lines. The presence of ligand on dendrimer molecule, elevated receptor mediated binding or internalization in AM. The developed ligand conjugated dendritic system targeted higher concentration of GmCH to lung than the free drug.

**Conclusion:** Thus, we concluded that GmCH loaded mannosylated PPI dendritic system could have higher potential to target anticancer drug to lungs for effective chemotherapy of lung tumor.

**Keywords:** Dendrimer, Lungs, Gemcitabine

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### P3.02c-003

#### TAX-TORC: The Novel Combination of Weekly Paclitaxel and the Dual mTORC1/2 Inhibitor AZD2014 for the Treatment of Squamous NSCLC



*Topic: Targeted Therapy*

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**Background:** The dual mTORC1/2 inhibitor AZD2014 has multiple effects on cell growth, apoptosis, angiogenesis and metabolism in cancer cells. AZD2014 increases the efficacy of paclitaxel in preclinical models, including patient derived xenografts. These data and clinical responses in the dose escalation arm of the TAX-TORC study led to an expansion cohort of 40 patients with squamous non-small cell lung cancer (sqNSCLC).

**Methods:** Patients, of ECOG performance status 0-1, with sqNSCLC who had received at least one line of platinum-based chemotherapy were eligible for the study. Paclitaxel was dosed once weekly at 80mg/m<sup>2</sup>, 6 weeks out of 7. AZD2014 was dosed BD, 3 days per week starting with the paclitaxel dosing. The cohort was started at 50mg AZD2014 BD.

**Results:** Thirty-two patients have been treated, 24 male/8 female with median age 68 years. The median number of previous treatments was 1 with 6/32 (19%) having received a prior taxane (docetaxel or paclitaxel). Analysis of data from the first 17 patients, by the safety review committee, showed that fatigue, skin rash and diarrhea were the most common toxicities in 59%, 47% and 41% patients respectively. The majority of toxicities were CTCAE grades 1 or 2 (112/123, 91%) and reversible with AZD2014 interruption or reduction. However, there were 9 grade 3 and 4 toxicities and 2 incidences of grade 5 respiratory infection. There were 2/17 (12%) responses though patients often stopped early due to toxicity. Following the safety review, the

dose of AZD2014 was reduced to 25mg BD which is a pharmacodynamically active dose associated with fewer toxicities. Fifteen additional patients have subsequently been treated at this lower dose. Their most common toxicities were anemia, alopecia and fatigue in 47%, 47% and 40% patients respectively. There have been no grade 5 events and only 8/78 (10%) grade 3 or 4 toxicities. The response rate in this cohort is 5/15 (33%) and recruitment is ongoing. Archival samples and circulating free DNA at baseline are being assessed with targeted next generation sequencing to explore putative predictive biomarkers for response and resistance.

**Conclusion:** We have established a tolerable dose and schedule for the combination of weekly paclitaxel and AZD2014. The promising response rate of 33% in previously treated sqNSCLC patients warrants further investigation. The study is supported by AstraZeneca, Cancer Research UK, Experimental Cancer Medicine Centre and NIHR Biomedical Research Centre Initiatives.

**Keywords:** squamous, paclitaxel, Phase 1, mTORC

P3.02c-004

**SBI0206965, a Novel Inhibitor of Ulk1, Suppresses Non-Small Cell Lung Cancer Cell Growth via Modulating Both Autophagy and Apoptosis Pathways**



*Topic: Targeted Therapy*

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**Background:** Autophagy is a catabolic process that regulates the lysosomal turnover of damaged proteins and organelles in order to maintain cellular homeostasis. Dysregulation of autophagy is often observed in lung cancer. Kinase inhibitors have proved successful in the clinic. The fact that uncoordinated (Unc) 51-like kinase (Ulk1) is the only conserved serine/threonine kinase in the autophagy cascade makes it a very attractive target for therapeutic development. Up-regulation of Ulk1 has been shown to promote cell survival of several cancer cell lines. Moreover, overexpression of Ulk1 has been shown to be negatively correlated with the prognosis of several types of human cancer. However, the role of Ulk1 in NSCLC is largely unknown.

**Methods:** We evaluated Ulk1 expression levels in human normal lung epithelial cell line BEAS-2B and five NSCLC cell lines, A549, H460, H1299, H292 and HCC827. We analyzed the correlation between Ulk1 expression levels