signal transduction pathways. We hypothesise that simultaneous, potent inhibition of erbB1 (EGFR), erbB2 (HER2) and erbB3 (HER3) may be more efficacious than first generation of erbB family targeted therapies such as gefitinib and lapatinib, and report here the pharmacological characterisation of AZD8931 in comparison with these agents.

Methods: A broad range of assays modelling erbB family receptor signalling in homo- and hetero-dimers included: *in vitro* evaluation of erbB kinase activity; erbB receptor phosphorylation and proliferation in cells; and *in vivo* testing in a human tumour xenograft panel, with *ex vivo* evaluation of erbB phosphorylation and downstream biomarkers in some cases.

Results: *In vitro,* AZD8931 demonstrated equipotent, reversible inhibition of erbB1, erbB2 and erbB3 phosphorylation in cells (Table). In proliferation assays, AZD8931 was significantly more potent than comparators in some SCCHN and NSCLC cell lines. AZD8931 significantly inhibited xenograft growth *in vivo* in models responsive to erbB1 inhibition alone, or erbB1 and erbB2 together and furthermore had significant effects on erbB1, erbB2 and erbB3 phosphorylation and on downstream signalling pathways, apoptosis and proliferation.

	IC_{50} (μM);95% CIR		
	AZD8931	Gefitinib#	Lapatinib
Isolated kinase			
erbB1	0.012; 1.354	0.018; 1.307	0.302; 1.119
erbB2	0.014; 2.074	0.335; 4.271	0.093; 3.012
***In vitro* phosphorylation** (tumour cell lines)			
erbB1	0.004; 1.377	0.011; 1.601	0.033; 2.913
erbB2*	0.003; 1.817	0.024; 2.827	0.009; 1.952
erbB3	0.004; 1.890	0.095; 2.180	0.013; 2.270

CIR, confidence interval ratio; *ligand dependent; #Selective erbB1 inhibitor

Conclusions: AZD8931 has a distinct pharmacological profile from gefitinib and lapatinib, inhibiting erbB1, erbB2, and erbB3 equipotently and demonstrating greater anti-tumour activity than these more selective agents in some pre-clinical models. A product with this profile may deliver broader clinical activity than more selective erbB family targeted therapies in cancers where simultaneous inhibition of erbB1−3 signaling is likely to be required for optimal clinical benefit (e.g. in combination with anti-hormonal therapy in oestrogen-dependent breast cancer).

Poster presentations (Mon, 21 Sep, 09:00−12:00)
Drug development − Phase I and Phase II

1226 POSTER

Multi-arm Phase IB study of TH-302 in combination with gemcitabine, docetaxel or pemetrexed

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Background: TH-302 is a tumor-selective 2-nitroimidazole prodrug of the DNA alkylator, bromo-isophosphoramide mustard (Br-IPM). In severe hypoxia, TH-302 is reduced and Br-IPM is released. TH-302 was designed to target tumor hypoxic regions that are not well targeted by conventional anti-tumor therapies. In a Phase I study, TH-302 showed activity as a single-agent with a maximum tolerated dose (MTD) of 575 mg/m^2 weekly and mucosal dose limiting toxicity (DLT) with the absence of significant myelosuppression.

Materials and Methods: Eligible patients (pts) for the study (NCT00743379) had ECOG ⩽1, advanced solid tumors, evaluable disease by RECIST, and acceptable hematologic, hepatic and renal function. Pts received TH-302 in combination with standard doses of gemcitabine (G), docetaxel (D) or pemetrexed (P). TH-302 was administered IV on Days 1, 8 and 15 (G only) of a 21 or 28 (G only) day cycle. A standard 3+3 pts design was used. TH-302 starting dose was 240 mg/m^2. CT scans were done every 2 cycles. The objectives of the study were to determine the MTD and DLT of TH-302 and to evaluate the safety, pharmacokinetics (PK) and preliminary efficacy of TH-302 in combination with G, D or P in advanced solid tumors.

Results: 35 pts have been enrolled at TH-302 doses of 240–480 mg/m^2, 11 with G, 11 with D and 13 with P. Median age: 60. ECOG 0/1 in 21/14 pts. Primary tumor: NSCLC (7), ovary (3), colorectal (3), carcinoid (3), other (19). Pts received 1−11+ cycles (median 3+). 17 pts have discontinued for progressive disease (7), clinical deterioration (5), pt decision (2), adverse event (AE; 1), investigator decision (2). One DLT has occurred in each arm (all grade 3): AST elevation at 240 mg/m^2 with G, febrile neutropenia at 240 mg/m^2 with D and oral candidiasis at 480 mg/m^2 with P. Common AEs were skin or mucosal toxicity, nausea, fatigue and vomiting and were mostly grades 1 and 2. Grade 3/4 neutropenia, lymphopenia or thrombocytopenia has occurred in 38, 47 and 18% of pts. TH-302 and Br-IPM PK are not altered by G, D or P. Six of 29 (21%) evaluable pts had a partial response (PR) and 4 are confirmed (1 each with G and D, 2 with P). 24 (83%) pts had a best response of either PR or stable disease (G: 8 of 10, D: 7 of 9, P: 9 of 10). All arms are now dosing at 480 mg/m^2.

Conclusions: TH-302 can be administered safely in combination with full dose G, D or P but may increase the hematologic toxicity of these agents. Encouraging anti-tumor activity was observed.

1227 POSTER

A phase 1, dose-escalation study of BIIB022 (anti-IGF-1R monoclonal antibody) in patients with relapsed or refractory solid tumours

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Background: Antibodies to insulin like growth factor 1 receptor (IGF-1R) have been shown to inhibit tumour cell survival and proliferation pathways as well as tumour cell motility and invasion. BIIB022 is a fully human, non-glycosylated IgG4 monoclonal antibody that binds specifically to IGF-1R thereby blocking the binding of IGF1 and IGF2 ligands.

Material and Methods: This is a Phase I dose-escalation study to evaluate the safety amd toxicity of escalating doses of BIIB022 (1.5−30 mg/kg) administered by IV infusion every 3 weeks (q3 wk) in patients (pts) with advanced solid tumours. Preliminary anti-tumour effects, PK, immunogenicity, FDG-PET imaging, and tissue and blood biomarkers are also being evaluated.

Results: 15 pts (M/F 10/5) have been treated with BIIB022 at doses of 1.5−20 mg/kg.

The median age is 58 yrs (range 40−75) and all had an ECOG performance status ⩽1.

Fourteen pts (93%) experienced at least 1 adverse event (AE). The most common drug-related AEs were headache and gastrointestinal events in 7 (47%) and 6 pts (40%) respectively. Two pts treated at 10 mg/kg experienced Grade 3 events of hypertension and diarrhoea considered possibly related to BIIB022. One pt treated at 20 mg/kg experienced a cardiac dose-limiting toxicity consisting of widespread EKG T wave inversion, and transient apical hypokinesis with secondary grade 3 QTc prolongation consistent with ischaemia/infarction. No Grade 4 AEs were observed. One pt treated at 10 mg/kg had a transient Grade 2 elevation of blood glucose normalising within 7 days. Neither thrombocytopenia nor elevations in fructosamine or hemoglobin A1c values have been seen. The $t_{1/2}$ appears to increase with increasing BIIB022 dose (4.7 days [1.5 mg/kg] – 11.3 days [20 mg/kg]). C_{max} and AUC are dose dependent. IGF1-R downregulation on blood granulocytes occurred within 2 hours of BIIB022 treatment at all doses evaluated with persistent downregulation for the entire 3 week dosing cycle. One pt achieved an FDG PET response, and 6 pts received 3 or more cycles of treatment before progression.

Conclusions: Preliminary results suggest that BIIB022 is tolerated at doses up to 20 mg/kg q3 wk without the metabolic effects noted with other IGF-1R antibodies. Enrollment is continuing with expansion of the 20 mg/kg cohort and a detailed evaluation of safety, anti-tumor activity, PK, and potential biomarkers of activity.