

A Phase I Trial of AEG35156 (XIAP Antisense) administered as a 7-day continuous intravenous infusion in patients with advanced tumours

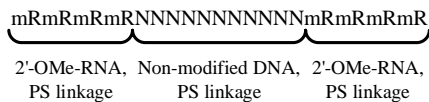
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Introduction

- The Inhibitors of Apoptosis (IAPs) are important endogenous inhibitors of caspases
- XIAP is the most potent of the IAPs and can inhibit both the intrinsic and extrinsic apoptotic pathways
- XIAP is commonly up-regulated in human cancer and high expression is associated with poor patient outcome and resistance to therapy
- Knockdown of XIAP with antisense or RNAi produces significant in vivo activity in multiple xenograft models with limited or no toxicity and sensitises tumours to chemotherapy agents and radiotherapy
- AEG35156 is an 19-mer antisense inhibitor of XIAP and uses second generation, mixed backbone, full phosphorothioate chemistry.
- This is the first administration of AEG35156 in man

Figure 1. Schematic Representation of the structure of AEG35156



Objectives

Primary

- To establish the toxicity profile, maximum tolerated dose and dose limiting toxicity of AEG35156

Secondary

- To determine the PK and PD of AEG35156
- To document possible anti-tumour activity

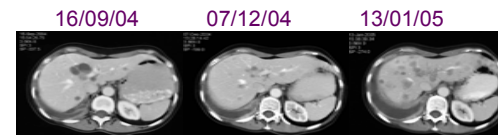
Methods

- AEG35156 is administered as a 7 day continuous IV infusion q 3 weeks for up to 6 cycles at dose levels of 48, 96, 125, and 160mg/m²/day
- Single patient cohort size until drug-related toxicity of ≥grade 2 observed. Then cohort expansion to 3-6 patients per cohort
- MTD defined as the dose level below the level at which more than 30% of the cohort developed a drug related DLT
- DLT defined by grade 3 or 4 non-haematologic toxicity, grade 4 thrombocytopenia or grade 3 thrombocytopenia for ≥7 days or associated with bleeding, grade 3 anaemia or grade 4 neutropenia, drug related death
- Toxicity assessed at least weekly and graded according to CTC version 2.0
- PK and PD sampling obtained in cycle 1 at 3, 6, 24, 72 and 168 hrs post start of infusion and at 0.5, 1, 1.5, 2, 4, 6 and 24 hrs post end of infusion. PK analyzed for plasma levels of study drug and major metabolites using CGE.
- PD assessments include mRNA knockdown of XIAP by RT-PCR in PBMCs, in circulating tumour cells (NHL patients) and in paired tumour biopsies (at predicted MTD)
- Serial serum M30/M65 cytokeratin 18 is also assessed in patients with epithelial tumours

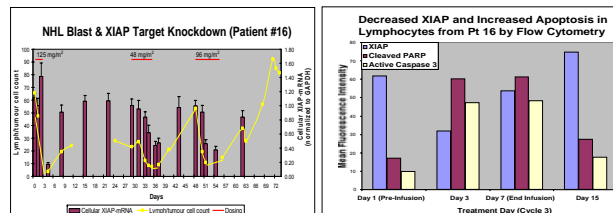
Results

Clinical:

- 19 patients with advanced refractory tumours have been treated to date
- AEG35156 is very well tolerated at doses of ≤125mg/m²/d x 7 days
- Clinically significant toxicities encountered to date have been limited to reversible, asymptomatic transaminitis, mild thrombocytopenia and occasional central line related infection
- DLT (transaminitis) occurred in 2 of 6 patients treated at 160mg/m²/day
- An expanded cohort is ongoing at 125mg/m² x 7 days as this dose levels is the likely MTD
- A 3 day schedule is also being explored
- One patient with refractory stage IV breast cancer exhibited a partial response of short duration (see below)



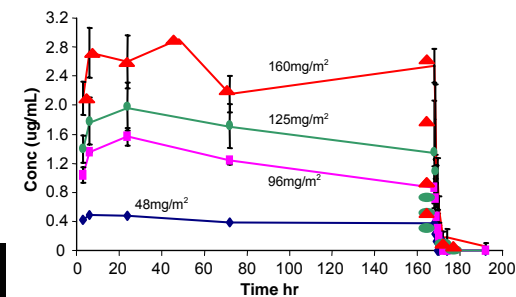
- One patient with refractory low grade NHL had repeated marked reductions in circulating lymphoma cells coincident with XIAP mRNA knockdown of up to 82% (left panel). Loss of XIAP protein, and elevated levels of active caspase 3 and PARP cleavage observed in Cycle 3 (right panel)



Results (contd)

Pharmacokinetics:

- Steady-state plasma concentrations were approximately dose-proportional and were reached rapidly (6 hrs) after start of infusion
- A rapid decrease in plasma concentrations occurred upon cessation of infusion (t_{1/2} ranged from 0.64 to 1.5 hrs)
- Significant formation of N-1, N-2 metabolites occurred accounting for approximately 30% of total oligonucleotides



Conclusions

- AEG35156 is the first inhibitor of XIAP to enter clinical development and is well tolerated at doses up to 125mg/m² x 7 days
- DLT consists of reversible, asymptomatic transaminitis at 160mg/m²/day x 7 days
- Evidence of clinical anti-tumour activity has been observed in refractory breast cancer and in refractory NHL patients
- Recruitment to the study is ongoing