SELECTIVE INHIBITOR OF AURORA B/C
PHASE 1 COMPLETED

OVERVIEW
- Phase 2 ready potent and selective inhibitor of Aurora B/C kinases.
- Extremely long enzyme residence time offers potential clinical advantage.
- Two-site Phase 1 trial in solid tumours completed.

BACKGROUND AND RATIONALE
Uncontrolled cell proliferation is a hallmark of cancer and, due to their rapid cell division, cancer cells are hyper-sensitive to drugs which interfere with mitosis. Targeting proteins that are involved in mitosis, such as Aurora kinases, is an attractive therapeutic strategy with the potential to provide similar efficacy to conventional cytotoxic agents but with fewer side effects.

The Aurora family of kinases plays key roles in multiple steps of mitosis. Aurora B is a chromosome passenger protein required for phosphorylation of histone H3, correct chromosome orientation in prometaphase and spindle checkpoint (SAC) function. Hence, cells deficient in Aurora B exhibit chromosome malorientations but, due to SAC failure, continue to progress through anaphase and exit mitosis. Polyploid cells result, and subsequent highly disordered cell divisions ultimately lead to cell death.

It has also been recently demonstrated that Aurora B phosphorylates the tumour suppressor p53 at three sites, leading to enhanced degradation of p53 through ubiquitination (1). Inhibitors of Aurora B have been shown to elevate p53 levels in tumour xenografts and increase p53 target gene expression. This provides additional mechanisms by which inhibitors of Aurora B may interfere with tumour growth, such as by increasing the p53 up-regulated modulator of apoptosis (PUMA) and CDK inhibitor p21. Hence, Aurora B inhibitors may be particularly suited to treating cancer cells having functional p53.

Over-expression of Aurora kinases has been demonstrated in a range of malignancies, suggesting that such tumours could respond therapeutically to inhibitors (reviewed in 2). In particular Aurora B over-expression has been demonstrated to correlate with poor overall survival in metastatic colorectal cancer and glioblastoma patients, and with progression of thyroid anaplastic carcinoma. High levels are also found in haematological neoplasms.
PRE-CLINICAL DATA

GSK1070916 is a highly selective reversible Aurora B and C inhibitor derived from refinement of a lead 7-azaindole series (3) which potently inhibits Aurora B and Aurora C with IC50 values of 3.5 and 6.5 nM, respectively (4). The compound is >250-fold selective versus Aurora A and inhibits only four other targets tested with an IC50 of <100nM (Flt1, Flt4, Tie2, SIK, FGFR1).

In vitro, GSK1070916 inhibits the proliferation of cancer cell lines with a median IC50 of 8 nM and induces polyploidy and apoptosis in a dose dependent manner, consistent with Aurora B inhibition (5). Pre-clinical in vivo xenograft studies have demonstrated dose-dependent efficacy in several models (solid and haematological); Figure 1.

**Figure 1.** Evaluation of GSK1070916 (“17k”) against advanced HL-60 (acute monocytic human leukaemia) in nude mice.

A distinguishing feature of GSK1070916 compared to other Aurora B inhibitors under clinical development is that GSK1070916 has an extremely long residence time, with an inhibitor dissociation half-life of >480 min from the Aurora B-INCENP complex (cf approx 15-25 min for other inhibitors tested) (4). The slow dissociation rate of the enzyme-inhibitor complex may prove advantageous in the clinic by allowing prolonged inhibition of Aurora B even after the drug has been cleared from systemic circulation (6,7).

CLINICAL DATA

A number of Aurora inhibitors have progressed into Phase 1 and Phase 2 clinical trials, establishing some evidence of efficacy and therapeutic window. Most clinical efficacy has been observed in leukaemias with some activity also noted in solid tumour populations such as lung, ovarian, renal, colorectal, breast and pancreatic cancers.

Cancer Research UK has recently completed a first-in-man Phase 1 clinical study in adults with solid tumours with GSK1070916, led by Professors Chris Twelves (St James’s Hospital, Leeds) and Ian McNeish (Barts Cancer Institute, London) (8; summarised in Table 1).

- Two centres, 36 patients in 11 cohorts, including 23 patients treated at MTD.
- Linear and dose proportionate PK observed and evidence of on-target PD effect demonstrated by decreased phosphohistone H3 staining in tumour biopsy.
- Generally well tolerated with few non-proliferative toxicities; negligible cardiotoxicity.
- 58% patients showed a best response of stable disease, in some cases maintained over up to 10 treatment cycles.
- PR in platinum resistant ovarian cancer maintained for the duration of the study (11 cycles; 33 weeks).

**Table 1.** Best tumour responses to GSK1070916; *one patient was not evaluated due to a tumour size at cycle 2 that could not be measured.

COMMERCIAL OPPORTUNITY

CRT is seeking a licensing partner to invest in the continued clinical development of GSK1070916. Further information is available under CDA including the Investigator’s Brochure, Clinical Study Report and detailed information regarding potential Phase 2 clinical study design.

REFERENCES


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