Novel AKT inhibitor afuresertib shows favorable safety, pharmacokinetics, and clinical activity in Multiple Myeloma: Phase 1 study results

SUPPLEMENTAL MATERIAL

Methods

Patients and methods

Patients

Additional key inclusion criteria were as follows: Eastern Cooperative Oncology Group (ECOG) status 0-2; fasting serum glucose < 126 mg/dL (< 7 mmol/L); absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L; hemoglobin ≥ 8 g/dL; platelets ≥ 50 x 10^9/L without transfusion in the past 7 days; prothrombin time (PT), international normalized ration (INR) and partial thromboplastin time (PTT) ≤ 1.1x upper limit of normal (ULN); total bilirubin < 1.5x ULN; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3x ULN; creatinine clearance (24-hour urine or calculated) ≥ 50 mL/min; and left ventricular ejection fraction (LVEF) ≥ 50%.

Adherence to hematologic inclusion criteria was not required for patients with acute leukemia. Key exclusion criteria included chemo-, radio-, or immunotherapy within 21 days prior to the first dose of study medication, and previously diagnosed diabetes mellitus (type 1 or 2) due to the potential risk of inducing hyperglycemia with AKT inhibitor. Systemic corticosteroids were allowed up to 7 days prior to the first dose (topical and inhaled steroids were allowed while on study). Patients with a history of previous treatment with a small-molecule AKT inhibitor, PI3K inhibitor, or mTOR inhibitor were excluded (perifosine was allowed). A list of concomitant drugs that were prohibited or cautionary due to concerns about potential drug-drug interactions
was provided in the protocol. More detailed information on prior treatment was collected retrospectively for patients with MM, and was not a part of the initial database.

Study Design and Treatment Administration

Study drug was administered once daily continuously (assessments were done every 21 days, ie, 21-day cycles) until disease progression, intolerable toxicity, consent withdrawal, or occurrence of inter-current illness that prevented further administration. All patients were instructed to take the study medication on an empty stomach with approximately 200 mL of water after fasting for at least 1 hour, and to fast for 2 hours after dosing. The starting dose was 25 mg/d. Part 1 (dose escalation) started with an accelerated dose titration design, which transitioned to a traditional 3+3 dose-escalation approach once predefined criteria were met. Each cohort in Part 1 consisted of Cycle 0 (single dose), which after 72 hours was followed by continued repeat dose (Cycle 1 and beyond). Once the MTD was defined in Part 1, Part 2 (expansion cohort) enrolled patients at the MTD. Specific dose modification guidelines were included in the protocol. If necessary, dose reductions occurred in increments of 25 mg. DLTs were defined as occurring during the first cycle (21 days repeat dosing) of therapy and fulfilling one of the following criteria: (1) any Grade 3 (G3) or greater nonhematologic toxicity (excluding alopecia, electrolyte disturbances responding to correction within 24 hours, diarrhea, vomiting, and nausea responding to standard treatment); (2) any Grade 4 (G4) or greater hematologic toxicity; (3) treatment delay of 14 days or greater due to unresolved toxicity; (4) G3 or greater hyperglycemia only if observed after the overnight fasting period immediately prior to afuresertib dose, or any G4 hyperglycemia (fasting, or in fed state of at least 2 hours’ duration); (5) ketoacidosis in the presence of G3 hyperglycemia; or (6) liver chemistry abnormalities including ALT ≥ 8x ULN, ALT ≥ 5x ULN for more than 2
weeks, ALT ≥ 3x ULN, and presence of either bilirubin ≥ 2x ULN without evidence of biliary obstruction or INR > 1.5, ALT ≥ 3x ULN, with the appearance or worsening of eosinophilia.

Safety Assessments

Safety and tolerability were assessed according to the adult Common Terminology Criteria for Adverse Events (CTCAEv.3.0) based on symptom evaluation and laboratory abnormalities. Patients were assessed for safety weekly during the first cycle of therapy and every 21 days in subsequent cycles. Safety assessments included collection of adverse events, interim medical history and physical examinations, ECOG performance status, vital signs, weight, laboratory parameters of glucose, clinical chemistry, hematology, and coagulation. In addition, 12-lead electrocardiogram (ECG) and evaluation of LVEF were performed at intervals mandated by the protocol.

Discussion

Among the various AKT substrates, GSK3-α and -β are likely the key contributors to AKT inhibitor-induced hyperglycemia, as acute hyperglycemia in mice with an ATP-competitive inhibitor was shown to be potentially due to hepatic glycogenolysis and/or gluconeogenesis.\(^1\) The role of GSK3-α and GSK3-β, including phosphorylation at Ser 21/9 (GSK3-α/β) in glucose homeostasis, has been well documented.\(^2\)\(^-\)\(^3\) Several kinases, including AKT, protein kinase A (PKA), various protein kinase C (PKC) isoforms, p70S6K, and p90Rsk can phosphorylate GSK3-α/β at Ser 21/9.\(^4\)\(^-\)\(^5\) Thus, concomitant inhibition of AKT and some of these other kinases may be related to the magnitude of hyperglycemia. Our preliminary studies combining a
selective AKT kinase inhibitor and a pan-PKC inhibitor showed significantly more hyperglycemia than either single agent in mice (data not shown). In contrast to the broad kinase activity of some of the ATP-competitive AKT kinase inhibitors (eg, GSK690693, AZD5363), afuresertib is > 100-fold selective for AKT1 over various PKC isoforms, p70S6K and p90Rsk.6–8 The improved kinase selectivity coupled with differences in PK properties may explain the relatively low incidence/magnitude of hyperglycemia with afuresertib.

Perifosine is an alkylophospholipid signal transduction modulator with effects on multiple pathways, and is often referred to as an AKT inhibitor.9 Perifosine has been tested in MM for safety and efficacy in combination with lenalidomide10 and with bortezomib.11 Data from a small, single-arm, Phase 1/2 study reporting 22% PR or better with a duration of response of 6.9 months provided the rationale for a large randomized Phase 3 trial of perifosine in combination with bortezomib and dexamethasone.11 However, for reasons that are presently unclear, the data safety monitoring board (DSMB) recommended stopping the trial prematurely following a pre-planned interim analysis of safety and efficacy.12 Irrespective of this, we believe several factors provide a strong rationale for further evaluation of afuresertib in MM. First, the AKT pathway activation remains crucial for MM cell proliferation and disease expansion.13,14 Second, afuresertib is a very potent and highly specific inhibitor of AKT, while inhibition of AKT was only one of the postulated mechanisms of action for perifosine.15,16 Third, and most importantly, is the demonstration of single-agent activity for afuresertib in such a heavily pretreated MM population. With the recent confirmation that MM represents a polyclonal disease,17 combination treatment approaches are more likely to be effective than any available monotherapy. Consistent with this paradigm, we generated preclinical data with afuresertib that demonstrated strong
synergy when afuresertib was combined with proteasome inhibition in vitro against a panel of 10 genetically heterogeneous MM cell lines (unpublished data). More importantly, synergy was observed at concentrations that are clinically achievable. Based on these data, a Phase 1b trial evaluating afuresertib in combination with bortezomib and dexamethasone has been initiated in patients with relapsed MM.

REFERENCES


**Figures**

**Supplemental Figure 1. FDG-PET response in a patient with MM** (A) Extensive, widespread, metabolically active disease (July 2010 at screening). (B) Very good but incomplete response to treatment with afuresertib (November 2011, after 15 months of treatment). Fifty-seven-year-old male originally diagnosed with IgA kappa myeloma in 1999. At the time of study entry, he had progressive disease after having received four prior lines of therapy including autologous stem cell transplantation, lenalidomide, thalidomide, and bortezomib. He achieved a PR after one cycle of afuresertib that was maintained for 26 months. PET scan at study entry demonstrated widespread metabolically active disease throughout the skeleton. Repeat imaging 14 months later confirmed significant improvement with the widespread FDG-avid disease being significantly less intense. FDG-PET, 18-fluoro-deoxyglucose positron emission tomography; PR, partial response.
Supplemental Figure 1. FDG-PET response in a patient with MM

A

B