Pha-739358: a pan-aurora kinase inhibitor

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PHA-739358 is a small molecule 3-aminopyrazole derivative with low nanomolar activity against all aurora kinases (AKs). It also inhibits other cancer relevant tyrosine kinases such as wild type and mutated ABL, RET, TRK-A and FGFRs.[1,2]

PHA-739358 shows a dominant aurora kinase B inhibition-related cellular phenotype and induces a p53 status dependent endoreduplication. The compound has antitumor activity in spontaneous, transgenic and xenograft models of solid and hematologic tumors with occasional cures. It is active in a broad range of BCR-ABL positive and negative cell lines, including T315I BCR-ABL mutants. A decreased phosphorylation of histone H3 under PHA-739358 treatment has been described as a pharmacodynamic biomarker of aurora kinase B inhibition in human skin at safe doses. Similarly the reduced CRKL phosphorylation documents the activity via BCR-ABL inhibition.[1,3]

In the completed phase I studies in solid tumors the pharmacokinetics were linear and dose and time independent after IV administration, with extensive tissue distribution and low to moderate plasma clearance. Disease stabilization has been reported in 28 out of 80 assessed patients, lasting more than 6 months in seven patients. One ovarian cancer patient had a 27% reduction of target lesions, and one SCLC patient presented a PR at high dose with G-CSF. Several phase I and II studies are investigating AK inhibition and other cross reactivities in hematological malignancies.

A multicenter phase II study of PHA-739358 is being conducted in patients with chronic myeloid leukemia (CML) relapsing on imatinib or other targeting therapies. Twelve CML patients (2 in chronic phase, 2 in accelerated phase, 8 in blast phase) have received doses from 250 to 400 mg/m^2/day by a once-weekly 6-hour infusion at UCLA Medical Center.[3]

Patients initially were treated for 3 consecutive weeks every 4 weeks. Dose escalation was permitted in some instances for suboptimal response. BCR-ABL mutation analysis was performed at baseline.

Two patients, both with with T315I mutated BCR-ABL, achieved a complete hematologic response (CHR) at 330 mg/m^2. One of these patients treated in blast phase achieved a complete cytogenetic response (CCyR) and a complete molecular response after 3 months. The CCyR persisted for 6 months, and a MCyR persisted for an additional 8 months on treatment. The second patient

who achieved a CHR initiated therapy in chronic phase. A minor cytogenetic response was achieved after 3 cycles of therapy, and a minimal cytogenetic response persisted after more than 12 months of treatment. All patients with advanced disease demonstrated reductions of peripheral blood blasts following drug infusion, but most experienced a "kinetic failure" with blast counts rebounding before the next scheduled infusion. Updated response data will be provided on the most recently enrolled patients.

The study drug has been well tolerated at all doses administered. Treatment-related grade 3-4 neutropenia has been observed, as expected. Non-hematologic toxicities attributed to study drug included one infusion-related reaction requiring acetaminophen, benadryl and hydrocortisone premedication. In addition, one patient had two episodes of asymptomatic grade 3 hyperbilirubinemia. PHA-739358 pharmacokinetics were in good agreement with those observed in other phase I/II studies. Pharmacodynamic analyses demonstrated treatment-associated decreases of CRKL phosphorylation in 10 out of 11 evaluable patients.

Objective clinical responses to PHA-739358 have been observed in two CML patients with T315I mutations of BCR-ABL, with an acceptable tolerability and safety profile. Additional doses and schedules of PHA-739358 are being investigated in patients with advanced phase CML.

References

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