Clinical Activity of Crizotinib In Advanced, Chemoresistant ALK+ Lymphoma Patients

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ALK fusion partners are functionally diverse but all provide an

- Compassionate use of crizotinib was authorized by our institution’s IRB under a named patient protocol.

DOSE

- An ongoing Phase 1 trial (A0B11001) evaluating crizotinib as a single agent is being conducted to investigate safety, pharmacokinetics and pharmacodynamics in patients with advanced cancer.

The trial included a dose escalation component where the maximum tolerated dose was determined to be 250 mg BID.

In the current study, crizotinib was administered at this schedule, and all other drugs with therapeutic activity (including steroids) were stopped.

SUBJECTS

All patients signed Informed Consent forms.

KEY INCLUSION CRITERIA

- ALK+ Non-Hodgkin Lymphoma diagnosis evidenced by immunohistochemistry and fluorescence in situ hybridization (FISH) using an ALK break-apart probe.

- Refractory or relapsed disease after ≥1 prior chemotherapeutic regimens; presence of measurable disease by physical examination, CT, PET-CT scan, or bone marrow aspirate (evaluated by FISH).

- <21 years of age.

- ECOG performance status 0–3.

- Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN) or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy.

- Total serum bilirubin ≤1.5 x ULN (except patients with documented Gilbert’s syndrome).

- Creatinine ≤1.5 x ULN.

- Adequate bone marrow (BM) function (unless linked to BM invasion).

- Absolute neutrophil count (ANC) ≥10000/μL; platelets ≥50 000/μL; hemoglobin ≥9.0 g/dL.

EXCLUSION CRITERIA

- Major surgery within 28 days prior first dose of crizotinib.

- Use of cytotoxic drugs in the previous 14 days, except where there was clear evidence of disease progression.

- History of uncontrolled cardiac disease including: myocardial infarct, uncontrolled arrhythmias or hypertension, clinically significant ventricular arrhythmia, unexplained syncope.

- Pregnancy or breastfeeding.

- Use of drugs or foods that are known potent CYP3A4 inhibitors, known potent CYP3A4 inducers, and/or CYP3A4 substrates with narrow therapeutic indices.

Two patients with ALK+ ALCCL were treated with crizotinib (results presented here).

One additional patient is currently on treatment (at 4 weeks) and another patient is in screening.

Patient 1

A 35-year old female diagnosed with ALCCL in September 2009.

- Received 7 cycles of CHOP-15 obtaining a partial response lasting 1 month.

- Subsequently treated with the DHAP and ICE regimens in an attempt to collect stem cells for an autologous bone marrow transplant (ABMT).

- Relapsed within 2–3 weeks after each salvage therapy.

- Pretreatment evaluation included: fever (>39°C), splenomegaly, cervical and inguinal adenopathies, positive PET and CT scans of paraaortic, iliac, and mediastinal adenopathies; BM aspirate showed 3% of cells ALK FISH+. ECOG score was 3.

- After crizotinib treatment: fever disappeared within 48 hours; by day 7 all superficial adenopathies disappeared; PET and CT scans were performed on day 28 days showed complete regression of lesions, which persists 6 months post-treatment initiation.

- Adverse events (AEs) included transient ocular flashes and grade I LFT elevation.

Results

Crizotinib 250 mg BID/day showed important therapeutic activity in two heavily pretreated ALK+ ALCCL patients; both patients obtained durable (>4 months) responses.

- Toxicity appeared minimal, with no grade 3/4 toxicity; raising the possibility for further dose escalations.

- The long-term (>6 months) assessment of these responses needs further investigation.

A Phase Ib study of crizotinib in relapsed ALK+ lymphomas will begin in 2011.

Conclusions

No relevant conflicts of interest to declare

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