CyFi: Results from a phase Ib expansion cohort of ficlatuzumab (Fi) combined with high-dose cytarabine (Cy) in patients with high risk relapsed or refractory acute myeloid leukemia (AML)

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Abstract

Objective: Patients with AML who are refractory to induction therapy or relapse within 1 year have poor outcomes. Elevated serum hepatocyte growth factor (HGF) level is an adverse prognostic factor. Pre-clinical models have shown that myeloid blasts produce HGF in an autocrine fashion and pharmacologic blockade of the HGF/c-Met axis sensitized blasts to cell death. We initiated a Phase Ib study with dose expansion cohort study to assess the safety and tolerability of the anti-HGF antibody ficlatuzumab with cytarabine in AML patients who are refractory to 7+3 or have relapsed within 1 year of induction.

Methodology: The 3 x 3 design was used for the Phase I with an expansion cohort of an additional 13 patients accrued and treated at the MTD. Ficlatuzumab was administered in escalated dosing of 10, 15, or 20 mg/Kg for 4 doses every 2 weeks starting on day 1. 20 mg/Kg dose was used for the expansion cohort. Cytarabine was administered at a fixed dose of 2 g/m2 on days 2-7. PBMCs were collected at defined time points. Differential expression from multiplexed single cell RNA sequencing (scRNAseq) was used to assess biomarkers predictive of response.

Results: Of the total 18 patients accrued thus far, 16 are evaluable. 5 had progressive disease, and 11 responded, all complete responses. Most frequent grade 3/4 TEAEs were febrile neutropenia, LFT abnormalities, and electrolyte disturbance. There was 1 death from sepsis and multi-organ failure on day 23, following ANC recovery, from the disease, and 1 patient who withdrew from the study due to grade 4 gastrointestinal bleed, likely ficlatuzumab related, both prior to response assessment. scRNA sequencing identified a TNF alpha and IFN gamma inflammatory signature that correlates with response to ficlatuzumab at count recovery.

Conclusion: Cytarabine and ficlatuzumab is a safe combination with promising efficacy in high risk relapsed and refractory AML. This combination is warranted in further Phase II studies. scRNAseq may be used to identify biomarkers of response.

Clinical trial information: NCT02109627

Rationale

• High serum level of HGF is a poor prognostic factor in AML with respect to disease course and outcome1,2
• Autocrine secretion of HGF by AML blasts fueling tumor growth3
• Ficlatuzumab is a first in class monoclonal antibody against HGF
• Hypothesis: blocking this pathway will decrease survival signal for the leukemia blasts and improve patient outcomes

Study Design

Drug Administration

Inclusion Criteria

- Relapsed or refractory AML
- Within 12 months after first CR
- Persistence of disease on BMBx 28 days after first induction
- Hypercellular marrow >20% cellularity and >10% blasts at least 14 days after induction

Exclusion Criteria

- APML
- More than 2 cycles of prior induction
- Persistence of disease on BMBx 28 days after first induction
- Prior cytarabine in excess of 2 g/m2/day
- Prior grade 4 toxicity to cytarabine
- Hypercellular marrow >20% cellularity and >10% blasts at least 14 days after induction
- Anti-c-Met or anti-VEGF directed therapy
- Transplant (allo or auto) < 90 days of study entry
- Uncontrolled infection, active malignancy, active HIV, hib, B, C
- Pregnancy

Patient Characteristics and Response

Table: Patient Characteristics and Response

Conclusions and Future Directions

1. Ficlatuzumab may be safely combined with high-dose cytarabine
2. No dose limiting toxicities were identified at 20 mg/kg of ficlatuzumab
3. ORR is 50% in this high risk population
4. Randomized phase II is planned
5. Single cell RNA sequencing can be used to identify biomarkers of response

References


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