CyFi: A phase I study exploring the role of cMET pathway inhibition with ficlatuzumab (Fi) combined with high-dose cytarabine (Cy) in patients with high risk relapsed or refractory acute myeloid leukemia (AML)

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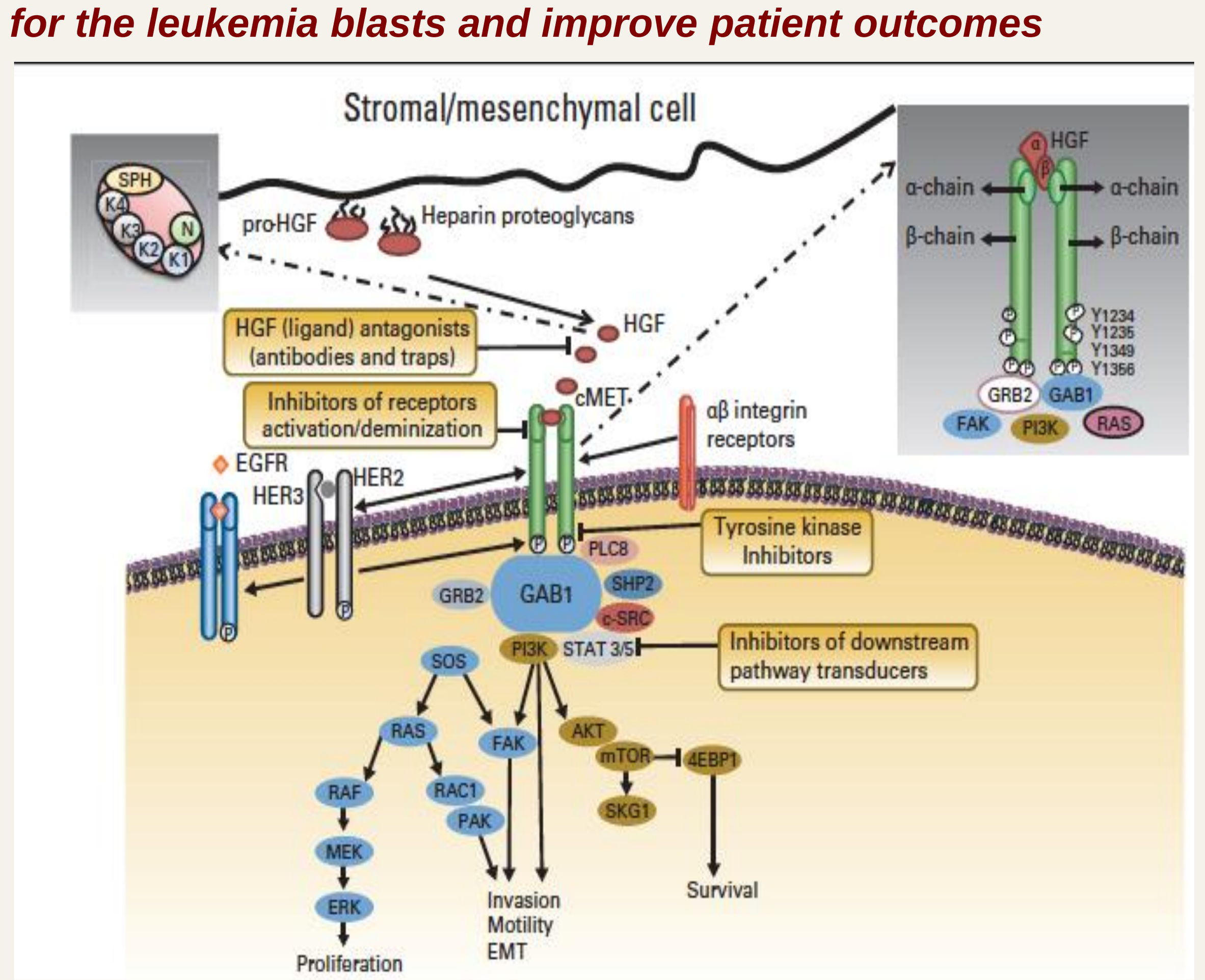
Abstract

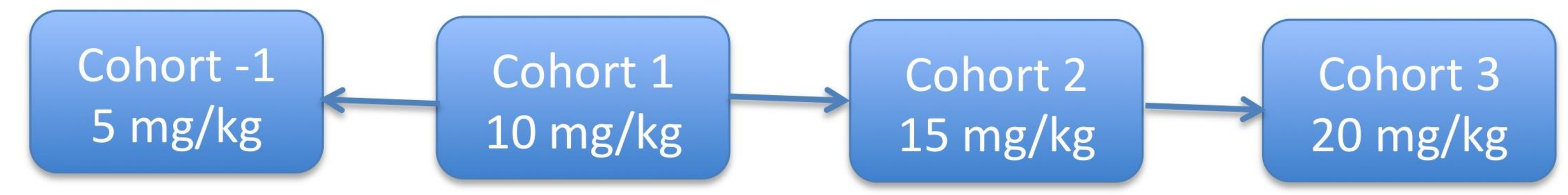
Background: Patients with AML who are refractory to induction therapy or relapse within 1 year have poor outcomes. Elevated serum hepatocyte growth factor (HGF) level is an adverse prognostic factor in AML[1,2]. Pre-clinical models have shown that myeloid blasts produce HGF in an autocrine fashion and pharmacologic blockade of the HGF/c-Met axis sensitizes blasts to cell death[3]. **Methods:** We initiated a phase I study to assess the safety and tolerability of Fi combined with Cy in patients with AML who are refractory to 7+3 or have relapsed within 1 year of induction. Fi is given in escalated dosing of 10, 15, or 20 mg/kg for 4 doses every 2 weeks, starting on day 0, and Cy at a fixed dose of 2 g/m² on days 2-7, using a 3x3 design. PBMCs, BM and serum are collected at defined time points to assess HGF levels and activation of the c-Met pathway. **Results:** Dose escalation is completed and there were no protocol-defined DLTs identified in 9 evaluable pts. All patients treated to date were refractory to induction. 4 had de novo AML; 2 had undifferentiated leukemia; 2 prior MDS; 1 prior MPN. Most frequent grade 3/4 TEAEs were febrile neutropenia (56%), LFT abnormalities (11%), and electrolyte disturbance (11%). There was 1 death (11%) from sepsis and multi-organ failure on day 23, following ANC recovery. Of the 9 evaluable patients, 4 achieved a CR (44%). Two of the 4 CRs are long lasting 11 and 12 months following allo-HCT. All patients had detectable circulating HGF levels at baseline relative to controls without AML. HGF levels increased following exposure to Fi by an average of 193%. Baseline HGF levels or change from baseline were not associated with treatment response. **Conclusions:** Ficlatuzumab can be safely combined with HiDAC in this high-risk AML population and produce durable clinical responses. Circulating HGF levels were detectable at baseline and uniformly increased with treatment suggestive of a feedback response or immune complex stabilization. Dose expansion is ongoing. Clinical trial information: NCT02109627

Rationale

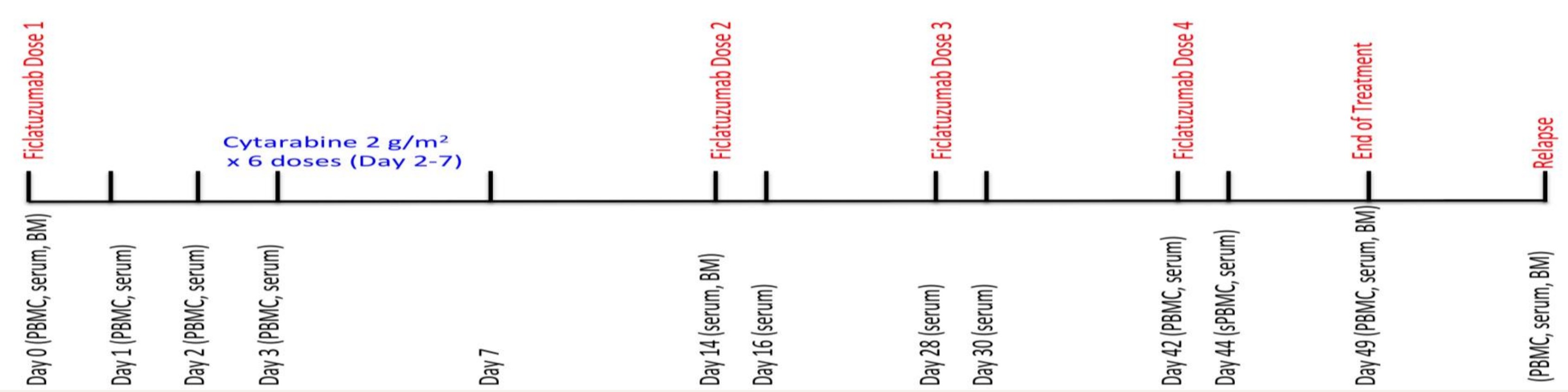
- High serum level of HGF is a poor prognostic factor in AML with respect to disease course and outcome[1, 2]
- Autocrine secretion of HGF by AML blasts fueling tumor growth[3]
- Ficlatuzumab is a first in class monoclonal antibody against HGF
- ***Hypothesis: blocking this pathway will decrease survival signal for the leukemia blasts and improve patient outcomes***



Study Design



Drug Administration



Inclusion Criteria

1) 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
2) Histologically confirmed AML
3) No more than 2 cycles of prior therapy, one must be an anthracycline + cytarabine combination
4) Ejection fraction >=40%, adequate organ function
5) Ability to sign consent and comply with treatment

Exclusion Criteria

1) APML
2) More than 2 cycles of prior induction
3) Prior cytarabine in excess of 2 g/m²/day
4) Prior grade 4 toxicity to cytarabine, anti-c-Met or anti-VEGF directed therapy
5) Transplant (allo or auto) < 90 days of study entry or active immunosuppressive therapy
6) Uncontrolled infection, active second malignancy, active HIV, hep B, C
7) Pregnancy

Patient Characteristics and Response

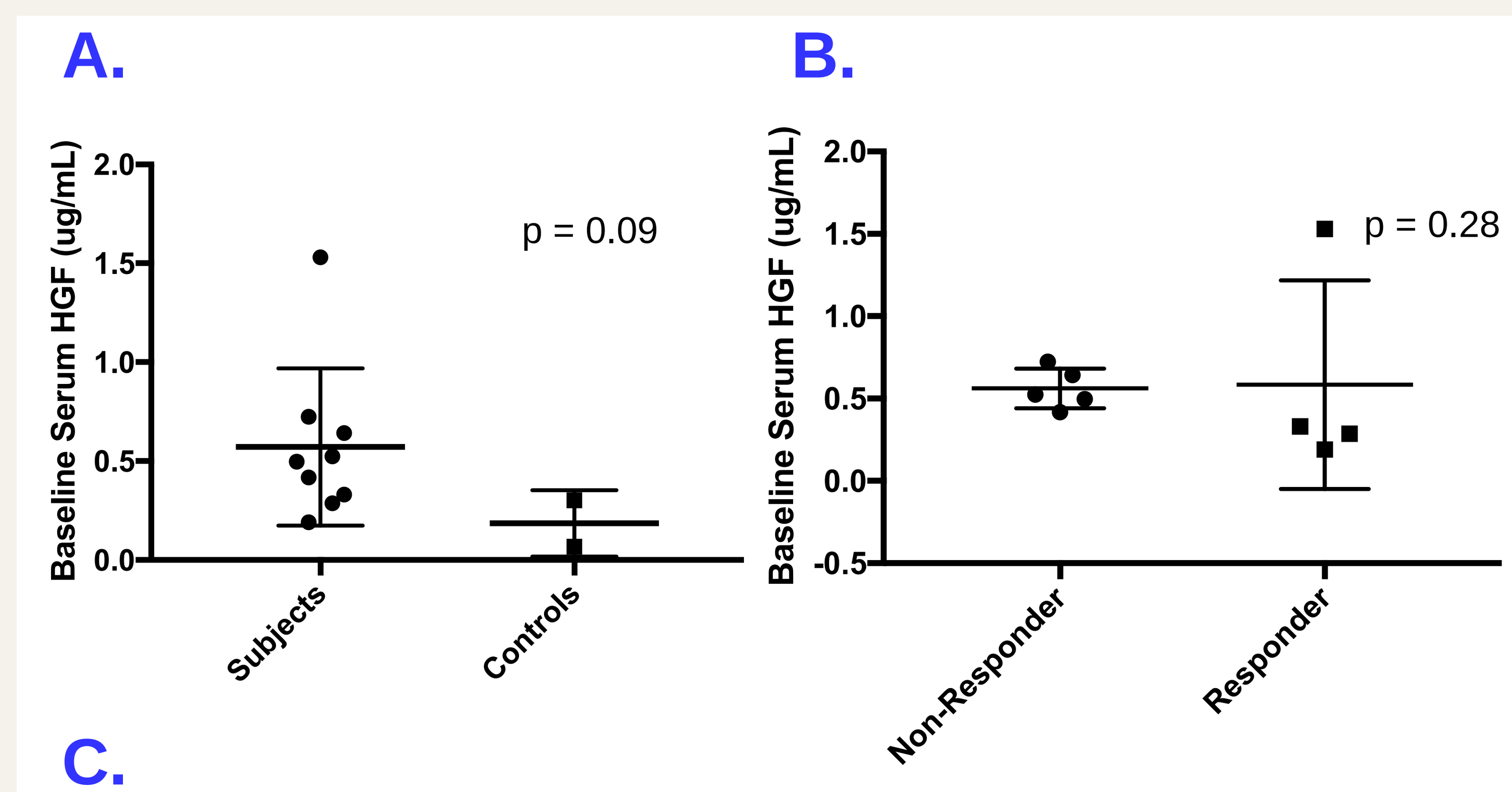
Patient	Cytogenetics/FISH	Genetics	Diagnosis	Prior Induction	Status at Study Entry	Cy-Fi Response	Disease Status
72yo M	Normal		CMML-> AML	5-Aza 7+3	refractory	PD	
61yo M	Complex 48,XY,t(5;21)(p14;q22),+6,+8,+10[8]/51,idem,+13,+22[5]/46,XY[7]		Undifferentiated Leukemia	7+3 5+2	refractory	PD	
51yo M	Normal	IDH2	AML	ADE	refractory	PD	
58yo M	Normal	NPM1	AML	7+3	refractory	CR	S/P AlloHCT CR ongoing at 17 mos
62yo M	Complex (MRC)	MYC amp RUNX1	AML-MRC	7+3	refractory	CR	S/P AlloHCT CR ongoing at 16 mos
66yo F	+11 MLL 11q23	IDH2	AML	7+3	refractory	CR	S/P HiDAC x 3 Relapsed at 9 months
45yo M	Complex 45,XY,-4,i(5)(p10),del(6)(p23),del(7)(q11.2q36),del(9)(q13q22),add(11)(p11.2),-13,-16,add(19)(q13.3),+1~5mar[cp4]/46,XY[26]		T-MN	5-Aza 7+3	refractory	PD	
67yo F	Complex 1q gain, 11q del, 19 p		Erythroid AML	XRT 7+3	refractory	Unkown	*
60yo F	Normal		AML	7+3	refractory	CR	On HiDAC Ongoing at 3 months

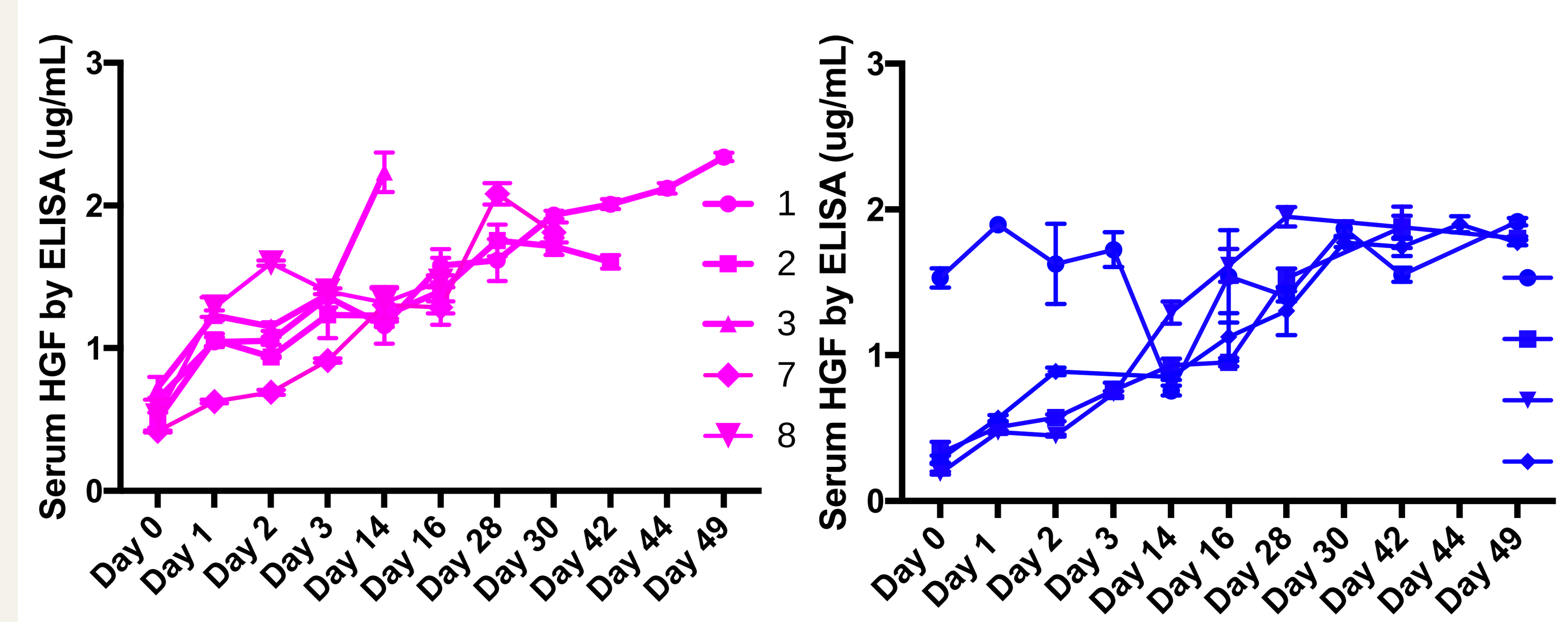
PD: persistent disease
CR: Complete remission

**** Death due to sepsis, resp distress and multi-organ failure prior to assessment of response***

Toxicities

Toxicity	%	Grade 3 above
Febrile Neutropenia	5/9 = 56%	5
Sepsis	2/9 = 22%	1
Respiratory Distress	2/9 = 22%	1
Ventricular Tachycardia	2/9 = 22%	2
LFT Elevation	1/9 = 11%	0
Hypokalemia	1/9 = 11%	1
Multi-organ Failure	1/9 = 11%	1





A. Normal controls have lower baseline serum HGF.
B. No statistically significant difference in baseline HGF between responders and non-responders.
C. Serum HGF assayed by ELISA over the course of treatment stratified by responders (blue) versus non-responders (pink).

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. Although not powered for efficacy, this combination appears to be active in this high risk population
4. Dose expansion at 20 mg/kg of ficlatuzumab is ongoing
5. Cy-TOF and single cell RNA sequencing are being performed to assess effects on signaling and gene expression throughout the treatment course

References

1. Verstovsek S, *et al. Leukemia* 2001
2. Kim, JG, *et al. Leukemia Lymphoma* 2005
3. Kentsis, A, *et al. Nature Medicine* 2012

Acknowledgments

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