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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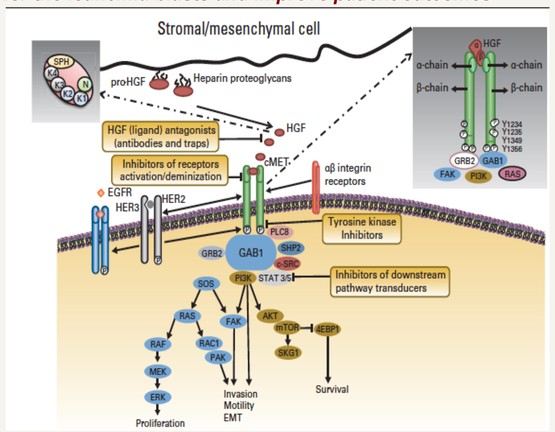
Abstract

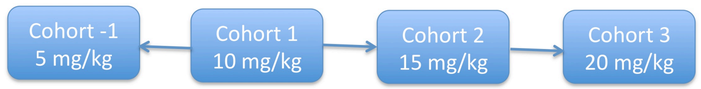
Objective: Patients with AML who are refractory to induction therapy or relapse within 1 year have poor outcomes. Elevated serum hepatocyte growth factor (HGF) level is an adverse prognostic factor. Pre-clinical models have shown that myeloid blasts produce HGF in an autocrine fashion and pharmacologic blockade of the HGF/c-Met axis sensitizes 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

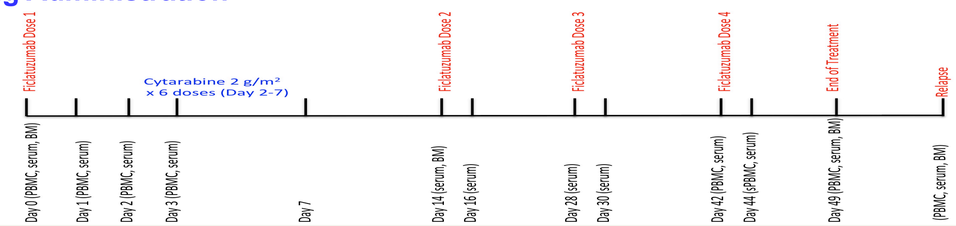
- High serum level of HGF is a poor prognostic factor in AML with respect to disease course and outcome[1, 2]
- Autocrine secretion of HGF by AML blasts fueling tumor growth[3]
- Ficlatuzumab is a fist in class monoclonal antibody against HGF
- ***Hypothesis: blocking this pathway will decrease survival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

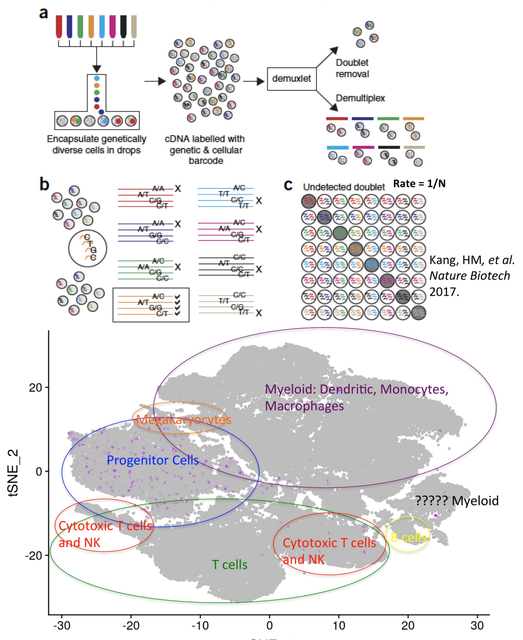
Dose Escalation

	Age	Sex	Disease	Cytogenetics/NGS	Response	MRD	Live/ Dead	Remission Duration
E1	72 yr	M	Induction Failure	7q,8q translocation	PD		Dead	
E2	60 yr	M	Induction Failure	5, 21 translocation, trisomy 6,8,10, 13,22	PD		Dead	
E3	50 yr	M	Induction Failure	Normal cytogenetics; IDH2 mutation	PD		Dead	
E4	68 yo	M	Induction Failure	Normal cytogenetics	CR	Neg	Dead	31 months
E5	59 yr	M	Induction Failure	Complex; deletion 5, Myc amplificaiton, RNX1T1	CR	Neg	Alive	38 months
E6	58 yr	F	Induction Failure	Trisomy 11; IDH2	CR	Neg	Alive	38 months
E7	43 yr	M	Induction Failure	Complex; deletion 5q, 6p, 7q, 9q, gain 5p, gain 13q34, loss 4, 13, 16, rearrangement 19q	PD		Dead	Sepsis
E8	65 yr	F	Induction Failure	Gain 1q, deletion 11q, rearrangement 19p	PD		Dead	
E9	58 yr	F	Induction Failure	Normal; NPM1, TET2	CR	Neg	Alive	38 months

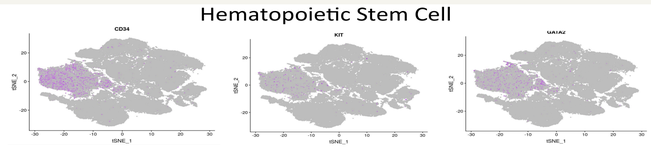
Dose Expansion

ID	Age	Sex	Disease	Cytogenetics/NGS	Response	MRD	Live/ Dead	Remission Duration
E10	55 y	F	Induction Failure	Inversion 3, monosomy 7	NE		Dead	Fungal PNA
E11	46 yr	M	Induction Failure	Normal cytogenetics; FLT3-TKD, WNT	CR	+	Alive	23 months
E12	61 yr	F	Induction Failure	Complex; p53	CR	+	???	10 months
E13	30 yr	M	Induction Failure	Normal, RUNX1, TET2	CR	+	Alive	20 months
E14	22 yr	M	Induction Failure	1, 11 translocation , trisomy 8, 21, IDH2, BCOR 3, WNT1, TET2	CR	Neg	Alive	23 month
E15	27 yr	F	Induction Failure	Trisomy 8, FLT3, WNT1, TET2	PD		Alive	60 days
E16	61 yr	F	Induction Failure	Complex	PD		Dead	21 months
E17	74 yr	F	Induction Failure	Inv 3, MECOM rearrangement, ASXL1, SRSF2, JAK2, SMC1A	CR	Neg	Alive	6 months
E18	25 yr	M	Induction Failure	Monosomy 7, GATA2 germline, WNT1	PD		Alive	

Multiplex Single Cell RNA Sequencing Using Naturally Occurring SNPs

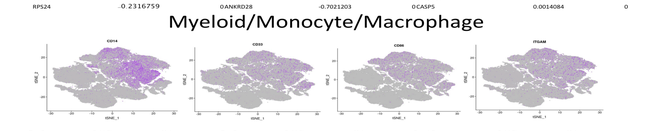


Hematopoietic Stem Cell



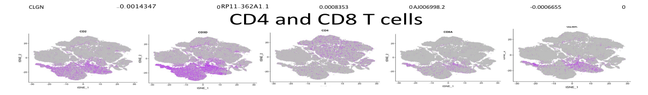
Day 0	Fold Change	p Value	Day 2	Fold Change	p Value	Count Recovery	Fold Change	p Value
AP003774.6	0.0031582		0SERPINB2	0.0031315		0RND3	-0.0067734	0
XIST	0.3350302		0FAM20A	0.0027173		0SERPINB2	-0.0038875	0
MT-CO3	0.3171092		0RPS26	1.1852629		0GFRA2	-0.0030557	0
MT1H	-0.0017517		0XIST	0.3561925		0RAPH1	-0.0024303	0
B2M	0.4470136		0DAAM2	-0.0021396		0KLF5	-0.002296	0
GPER1	0.0014196		0HLA-DRB5	0.425918		0PPARG	-0.0021583	0
HLA-A	0.745947		0NAV3	0.0019395		0CLEC5A	-0.0019833	0
HLA-B	0.6596891		0B2M	0.5306837		0SRGAP1	-0.0025309	0
TPT1	-0.2939997		0OLFM1	0.001803		0ADAMDEC1	-0.002203	0
LILRA4	-0.001392		0HLA-B	0.8220292		0CLEC4C	-0.0015463	0
HLA-C	0.6772145		0HLA-C	0.8470608		0MYCL	0.0035397	0
MT-CO2	0.2433264		0XIST	-0.7831421		0TPRG1-AS1	0.0014685	0
CASP5	0.0012567		0ALDH1A1	0.221535		0S100A12	0.4134502	0
SPIC	-0.0012026		0HOXB-AS3	0.0963839		0S100A8	0.9511515	0
RPS4Y1	-0.6441469		0PTPRC	0.6454036		0ADAMTS2	-0.0023596	0
HOXB-AS3	0.0859479		0HOPX	-0.7689151		0SLC2A14	0.0015695	0
SLC6A12	0.001191		0NAP1L1	-0.5611778		0DNAAF1	-0.0013112	0
IFI6	0.538357		0CA6	0.0015209		0BMP2	-0.0012761	0
RPS26	0.6140755		0COTL1	0.5035022		0ZFP36L1	0.3700183	0
RPS24	-0.2316759		0ANKRD28	-0.7021203		0CASP5	0.0014084	0

Myeloid/Monocyte/Macrophage



Day 0	Fold Change	p Value	Day 2	Fold Change	p Value	Count Recovery	Fold Change	p Value
RND3	-0.0063961		0LINC01133	-0.0029938		0HIST1H2BB	0.0020327	0
C8orf56	-0.0044384		0GYPB	-0.0023224		0MT1H	0.0018403	0
ELN	-0.0030667		0ST3GAL6	-0.0020015		0POU4F1	0.0012155	0
CDH2	-0.0032783		0MACROD2	-0.0012955		0RP11.761E20.1	0.0013305	0
LINC01133	0.0027478		0LYZ	1.041712		0DIXDC1	-0.0016425	0
CSRP2	-0.0020399		0HLA-DRB1	-1.0058795		0ACE	0.0014125	0
BHLHE41	-0.0025378		0CDH2	0.0016269		0CRYGD	0.001469	0
SHD	-0.0022533		0HLA-DRB5	0.8675899		0SHD	0.0015895	0
RHAG	0.0022554		0KIAA0895	0.0011415		0HDC	0.0010138	0
RP11.77P16.4	-0.0017014		0LINC00883	0.0017793		0LINC01133	0.0014873	0
LBX2	-0.0016419		0RNF165	-0.0010714		0EFCC1	0.0009589	0
DNASE1L3	-0.0019314		0IL12A-AS1	0.0010151		0CPNE7	-0.0007631	0
PTRF	0.0017128		0MYH10	-0.0010758		0HLA-DRB5	0.810184	0
KLHL23	-0.0019516		0SCT	0.0010416		0RP11.484K9.4	0.0007115	0
DPYSL3	-0.0017739		0LINC00890	0.0009397		0ADAMTS1	0.0006778	0
AC004540.4	-0.0014753		0SLC16A9	-0.0009007		0LINC00890	-0.0006993	0
STXBP6	0.0015563		0RP526	0.7560408		0MT-CO2	-0.200933	0
AC021860.1	-0.003491		0HLA-DPA1	-0.9058257		0MREG	0.0007894	0
RP11.333A23.4	-0.0014723		0LGALS1	0.6720738		0PKHD1L1	0.0006463	0
CLGN	-0.0014347		0RP11.362A1.1	0.0008353		0AJ006998.2	-0.0006655	0

CD4 and CD8 T cells



Day 0	Fold Change	p Value	Day 2	Fold Change	p Value	Count Recovery	Fold Change	p Value
NLRC4	0.0039622		0RHAG	-0.0025843		0DPYSL3	-0.0025503	0
RP11.597D13.9	0.0033001		0KCNMA1	-0.003306		0MYOSC	-0.0025065	0
HOXA7	-0.0071398		0PZRY6	-0.0049013		0MMP2	-0.0041974	0
CALML4	0.0038685		0MYL4	-0.0026201		0SPIB	-0.002607	0
CCL3L3	-0.0031483		0KLF1	-0.003296		0SLC22A4	-0.0021484	0
HOXB6	-0.0082788		0HBXE1	-0.0028354		0PDE4H	-0.0017416	0
CTA_384D8.34	0.0060338		0SPTA1	-0.0021672		0NOV	-0.0024223	0
HOXB5	-0.0037625		0DLC1	-0.0020496		0RP11.761E20.1	-0.0018918	0
IL27	0.0019133		0FCER2	-0.003634		0HTR7	-0.0014357	0
ADAMDEC1	-0.001761		0APOB3774.6	-0.0034106		0SPP1	-0.0014854	0
MRVI1	0.0016991		0HBA2	-0.0048803		0SPRED2	-0.0015702	0
C2	0.0040211		0GYPB	-0.0020805		0ARHGAP23	-0.0015847	0
DNASE1L3	-0.0017786		0MOBC1	-0.0047237		0BMP2	-0.0013583	0
SLC37A2	0.003542		0TSPAN7	-0.0020953		0MOBC1	-0.0019372	0
AC011899.9	0.0021958		0C2	-0.0046351		0IL12A-AS1	-0.0013694	0
HOXA6	-0.0028207		0CACNA2D3	0.0019021		0GFRA2	-0.0018081	0
SYT17	-0.0014148		0RP11.598F7.3	-0.0024558		0MMP17	-0.0020382	0
SLIT1C4	-0.0022977		0SLC6A10	-0.0017732		0RP526	1.2416629	0
LYVE1	-0.0012056		0CAMP	-0.0015305		0ORZW3	-0.001255	0
GPER1	0.0017018		0SELENBP1	-0.0014231		0SLC22A16	-0.0026282	0

PD

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**
2. **Randomized phase II is planned**
4. **Single cell RNA sequencing can be used to identify biomarkers of response**

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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