Evaluation of the first-in-class antimitochondrial metabolism agent CPI-613 in hematologic malignancies

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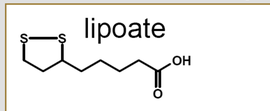
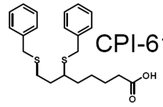
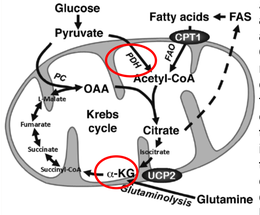
CPI-613 is a Novel Lipoate Derivative



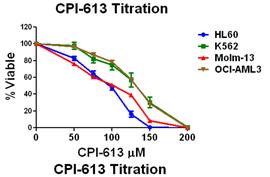


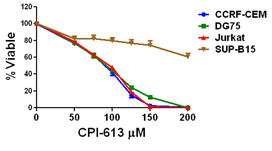


Samudio, et. al., *J Clin Invest.* 2010;120(1):142-56

Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) are aggressive malignancies. Glycolytic and mitochondrial metabolism are widely aberrant in cancer cells. Altered mitochondrial function with increased fatty acid oxidation (FAO) is associated with therapy-resistant leukemia cells and inhibition of FAO increases sensitivity to therapy. Pyruvate dehydrogenase complex (PDH) and α-Ketogluterate dehydrogenase complex (α-KG) are 2 key mitochondrial enzymes that require lipoate for their function. CPI-613 is a non-redux active lipoate derivative manufactured by Cornerstone Pharmaceuticals.

CPI-613 is Active Against AML and ALL

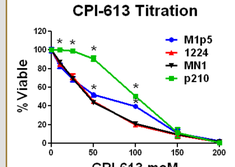


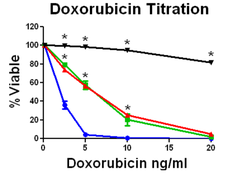


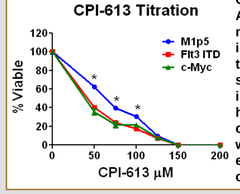
Cell line	IC50 μM
HL60	95.42 (90.2-101.0)
K562	133.3 (121.9-145.7)
Molm-13	107.3 (95.5-120.6)
OCI-AML3	133.3 (130.0-136.6)
CCRF-CEM	94.30 (86.3-103.0)
DG75	108.9 (95.7-124.0)
Jurkat	100.8 (92.3-110.1)
SUP-B15	ND
(95% Confidence interval)	

CPI-613 has activity against acute leukemia. Cells were subjected to 72 hour exposures to CPI-613 prior to viability assessment. Graphs represents combined results of 3 separate experiments carried out in triplicate. Of note, both K562 and SUP-B15 cell lines express the BCR-ABL tyrosine kinase. DG75 over-expresses c-MYC, HL60 has deleted p53 and Molm-13 expresses the Flt3 ITD.

CPI-613 is Effective Against Several Adverse Prognostic Markers

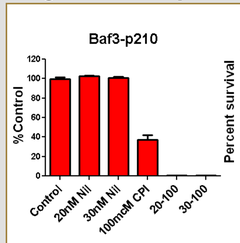


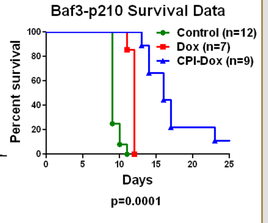




CPI-613 is Effective Against Several Adverse Prognostic Markers. A murine AML cell line (M1p5) was infected with retrovirus engineered to express the indicated gene or shRNA. Cells were exposed to the indicated amount of drug for 72 hours prior to viability assay. All concentrations done in triplicate with at least 2 independent experiments. * = p value <0.05 compared to lines below.

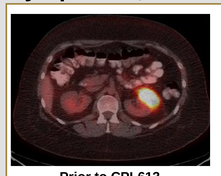
CPI-613 is Synergistic with Standard and Targeted Therapies





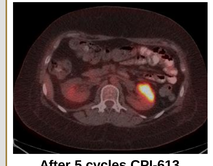
CPI-613 is synergistic with standard and targeted therapy. Left Panel: CPI-613 is synergistic with nilotinib against BCR-ABL expressing cells. Cells were incubated with the indicated drugs for 72 hours prior to viability assessment. Combinatorial index (CI) values for Baf3-p210 (Nilotinib 30 nM + CPI) was 0.059 (+/-0.002). Right Panel: CPI-613 is synergistic with doxorubicin *in vivo*. Balb/c mice were injected with Baf3-p210 cells and on day 3 treated with saline (control), Doxorubicin at 3mg/kg or CPI at 250mg/kg plus doxorubicin. Dox= Doxorubicin, CPI=CPI-613. P value shown is for Dox vs CPI-Dox.

CPI-613 has activity in Burkitt's Lymphoma, Patient #14



Prior to CPI-613

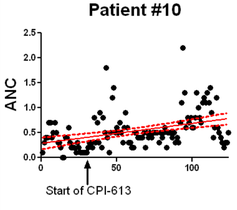
After 3 cycles CPI-613

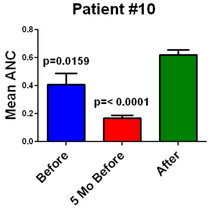


After 5 cycles CPI-613

Patient #14, 19y/o female diagnosed with Burkitt's Lymphoma 4/2010, s/p 7 cycles chemotherapy as per CALGB 10002. Relapsed 12/2010, s/p 2 cycles salvage Hyper-CVAD. Received full myeloablative, matched sibling, allogeneic peripheral blood stem cell transplant with Cytoxan-Etoposide-TBI conditioning 3/2011. Relapsed again 9/2011, enrolled on trial. Continues on therapy after 8 cycles. Shown are PET-CT fusion images demonstrating stable disease.

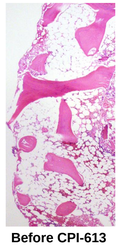
CPI-613 has Activity in MDS, Patient #10



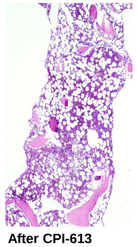


Patient #10, an 82 y/o female with high risk MDS, RAEB-2. Failed both decitabine and azacytidine. Shown above are the absolute neutrophil counts (ANC) before and after the start of CPI-613. Repeat bone marrow after four cycles showed RAEB-1. During the 2 years prior to enrolment admitted 7 times for neutropenic fever, none after starting CPI-613. She completed 7 cycles of therapy. Left panel: All absolute neutrophil count (ANC) values. Start of therapy indicated. P value for slope not equal to zero was 0.0179. Right panel: Average of all ANC values preceding (before) or the last 5 months prior to enrollment. P values are 2 tailed student's T test compared to After.

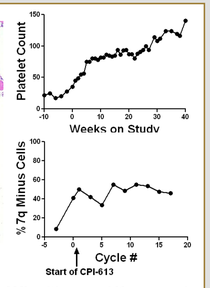
CPI-613 has Activity in AML, Patient #4



Before CPI-613

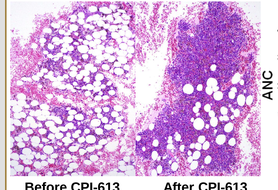


After CPI-613



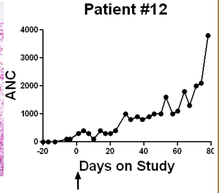
Patient #4, a 49 y/o male diagnosed with AML with normal Karyotype in 2004. After standard therapy achieved CR1. Relapsed in 2008, received a HDAC based regimen and achieved CR2. Underwent autologous BMT in 2010 while in CR2. Delayed count recovery, red cell and platelet transfusion dependent. Three months post transplant found to have 8.5% cells with 7q-. Marrow 6 months post transplant showing 41% cells with 7q-, remained transfusion dependent. Patient has been transfusion independent since starting CPI-613 and now is in CR3. He has been on continuous CPI-613 therapy for the last 18 months with no signs of toxicity.

CPI-613 has Activity in AML, Patient #12



Before CPI-613

After CPI-613



Patient #12, 66 y/o female with refractory AML. She received induction therapy with 7+3, 1st salvage attempt with cytoxan-etoposide, next salvage with high dose cytarabine-mitoxantrone-L-spar, then decitabine and finally azacytidine before starting on CPI-613. Pre-trial bone marrow biopsy showed hypocellular marrow with 9% blasts and 22% immature monocytes. After 2 cycles repeat biopsy shows hypercellular marrow with no evidence of disease. She was removed from study to undergo reduced intensity conditioned allogeneic stem cell transplant. Shown top left marrow clot section before and after 2 cycles CPI613, top right absolute neutrophil count (ANC).

CPI-613 Clinical Activity Summary

Patient #	Diagnosis	Dose mg/m²	Best response	More than 1 cycle?
1	NHL	420	NA	No
2	AML	420	PD	No
3	Myeloma	840	PD	No
4	AML	840 ->2100	CR	Yes (18 cycles)
5	Hodgkin's	840	PD	No
6	AML	1386	PD	No
7	Myeloma	1386	SD	Yes (3 cycles)
8	Myeloma	1386	SD	Yes (4 cycles)
9	AML	1386	PD	No
10	MDS (REAB-2)	2100	SD	Yes (7 cycles)
11	MDS (RA)	2100	SD	Yes (6 cycles)
12	AML	2100	MLFS	Yes (2 cycles)
13	AML	2940	NA	No
14	Burkitt's	2940	SD	Yes (8 cycles)
15	AML	2940	PD	No
16	AML	2940	PD	No
17	Myeloma	3000 over 1hr	PD	No
18	NHL	3000 over 1hr	NA	No
19	MDS (RAEB-1)	3000 over 1hr	NA	No

NA=not assessable, SD=Stable Disease, CR=Complete Remission, MLFS= Morphologically Leukemia Free State, PD=Progressive Disease

Conclusions

CPI-613 is a first in class non-redox active lipoate derivative currently under study in the laboratory and in phase I clinical trial for patients with relapsed or refractory hematological malignancies. To date we have shown:

- ❑ CPI-613 is active in vitro against multiple acute leukemia cell lines with IC50 values in the μM range.
- ❑CPI-613 has increased activity against cells expressing high levels of c-Myc, the Flt3 ITD or knocking down p53. Expression of BCR-ABL appears to confer resistance.
- ❑ CPI-613 displays strong synergy with tyrosine kinase inhibitors.
- ❑ CPI-613 displays synergy with doxorubicin *in vivo*.
- ❑CPI-613 has activity in multiple hematologic malignancies. Of the nine evaluable patients with a diagnosis of AML or MDS one achieved a CR, one a morphologic leukemia free state and two had stable disease for an overall response rate of 44%.
- ❑CPI-613 has activity in an aggressive relapsed Burkitt's Lymphoma with stable disease after 8 cycles.
- ❑DLT is acute renal failure that was reversible in two patients with a third opting for hospice.

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