Final Results from a Phase I Trial Combining Selinexor with High-dose Cytarabine (HiDAC) and Mitoxantrone (Mito) for Remission Induction in Acute Myeloid Leukemia (AML)

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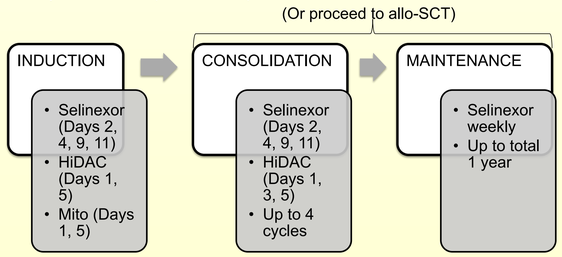
Background

Selinexor, an exportin 1 (CRM1/XPO1) inhibitor, has demonstrated anti-leukemic effects as a single agent and in combination with anthracyclines and DNA damaging agents. HiDAC/Mito is an effective induction regimen for patients with relapsed/refractory (R/R) AML and has a reported overall response rate (ORR) of 55% at our institution. We hypothesized that adding Selinexor to HiDAC/Mito would be feasible and have synergistic anti-leukemic effects. Early results of the trial were previously reported (Wang et al., J Hematol Oncol, 2018), and here we present more mature data on survival and relapse.

Study Design & Schema

We performed a phase 1 dose escalation trial with cohort expansion in a 3+3 design (NCT02573363).

The primary endpoint was to determine the maximum tolerated dose (MTD). Secondary endpoints were to determine ORR, toxicities, relapse free survival (RFS), overall survival (OS), and allogeneic stem cell transplantation (allo-SCT) success rate.



- Selinexor dose levels: 60mg (~35mg/m^2), 80mg (~50mg/m^2)
- Selinexor was given orally on days 2, 4, 9, and 11 during the induction phase.
- HiDAC (1.5 to 3 g/m^2 depending on age, IV over 3 hours) followed immediately by Mito (20 to 30 mg/m^2 IV over 1 hour) was administered on day 1 and 5.
- Patients who entered remission proceeded to SCT or consolidation chemotherapy.
- Dose limiting toxicities (DLT) were only evaluated during dose escalation and defined as any grade 3 or greater non-hematologic toxicity, except transient (<48 hours) nausea/vomiting or liver function abnormalities, or by persistent bone marrow aplasia >56days in the absence of disease.

Eligibility Criteria

Total 28 patients enrolled
(10/2015-10/2017)
Inclusion criteria:
- Newly diagnosed or R/R
- LVEF >50%
- ECOG ≤2
- Renal and hepatic function (CrCl >30cc/min, total bilirubin ≤2mg/dl, AST/ALT <3x ULN, PT/PTT< 2x ULN)

Exclusion criteria:
- Investigational agent within 2 weeks
- CNS involvement
- Significant co-morbidities

Demographics

Patient Characteristics	Number (%)
Total patients enrolled	28
Selinexor 60 mg	3
Selinexor 80 mg	25
# Female	18 (64)
Median age	61 (range 37-76)
Initial AML diagnosis	
De novo	15 (54)
Secondary	12 (43)
Therapy-related	1 (3)
Disease state on enrollment	
Newly diagnosed	15 (54)
R/R	13 (46)
Median lines of treatment (R/R only)	1 (range 1-3)
ELN risk (2010 criteria)	
Favorable	6 (21)
Intermediate I/II	14 (50)
Adverse	8 (29)
Mutation status	
FLT3-ITD	3 (11)
FLT3-TKD	2 (7)
CEBPA	3 (11)
NPM1	7 (25)

Results

Most Common Adverse Events (AE)	Grade 1/2 (%)	Grade 3/4 (%)
Febrile neutropenia	0	21 (75)
Diarrhea	9 (32)	0
Electrolyte disturbance	8 (29)	1 (4)
Bacteremia	0	9 (32)
Anorexia	8 (29)	0
Nausea/vomiting	7 (25)	1 (4)
Fatigue	7 (25)	0
Acute kidney injury	6 (21)	1 (4)
Cardiac toxicity*	5 (18)	3 (11)

**Not thought to be related to selinexor*

- No DLTs were observed in dose escalation.
- Myelosuppression was universal.
- Median time to count recovery (ANC >1.0 x 10^9/L, plt >100 x 10^9/L) for CR patients was 46 days.
- One death from hemorrhagic stroke prior to completing induction.

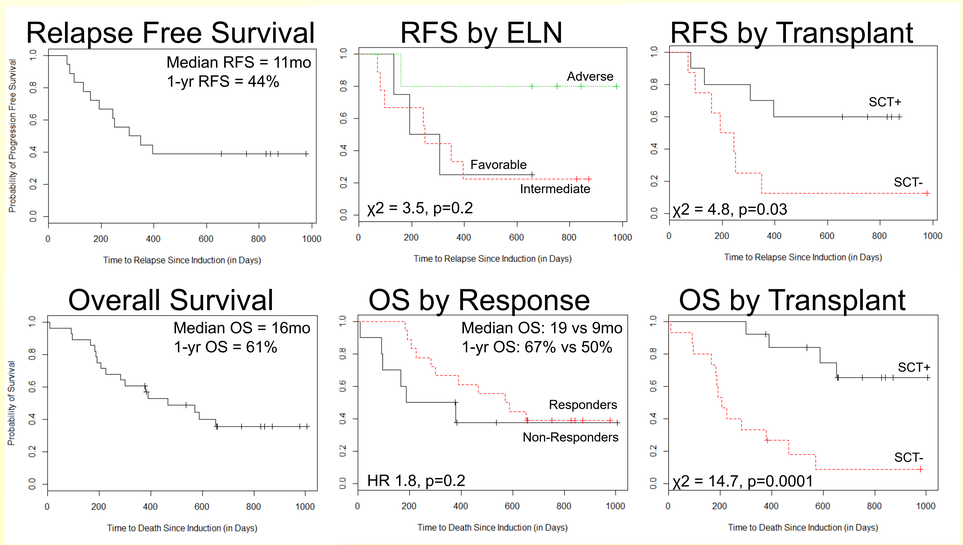
Reported Serious Adverse Events (n=12)	Grade
Cerebellar toxicity*	3
Urosepsis	3
Cellulitis	3
Bacteremia	3
Endocarditis	3
Hemorrhagic stroke*	5
Nausea/Vomiting	3
Subdural hematoma*	2
Cardiac arrest (TdP)*	4
Acute renal failure*	3
Mucor sinusitis	4
Abn electrolytes (hypoK, hypoNa)	4

**Not thought to be related to selinexor*

	ORR (CR/CRi/PR)	CR	CRi	PR	TF
All Patients (n=28)	**18 (64%)**	**13 (46%)**	**4 (14%)**	**1 (4%)**	**10 (36%)**
Disease state					
Newly diagnosed	13 (87%)	9	3	1	2
R/R	5 (38%)	4	1	0	8
Age					
>60	9 (60%)	6	3	0	6
≤60	9 (69%)	7	1	1	4
ELN risk					
Favorable	4 (67%)	4	0	0	2
Intermediate 1/2	9 (64%)	6	3	0	5
Adverse	5 (63%)	3	1	1	3
Dose level					
60mg	1 (33%)	1	0	0	2
80mg	17 (68%)	12	4	1	8

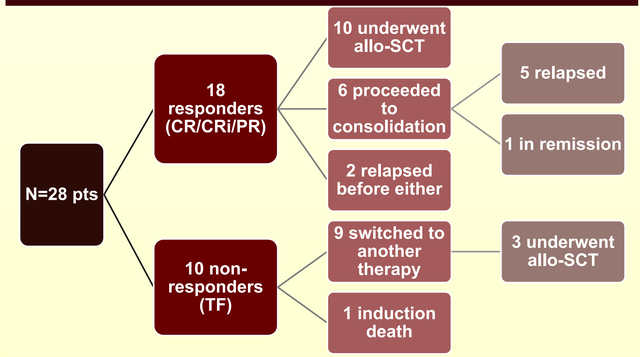
Complete remission (CR), CR with incomplete count recovery (CRi), partial remission (PR), treatment failure (TF)

Survival Data



- 11/28 (40%) patients are alive with a median observation period of 13 months (range 8 days to 34 months).
- One CR patient completed consolidation and maintenance without allo-SCT and remains in remission 33 months later.

Outcomes



Conclusions

- Selinexor plus HiDAC/Mito is feasible and tolerable. The R2PD of Selinexor is 80mg (50 mg/m^2/day).
- Most common AEs are febrile neutropenia, diarrhea, electrolyte disturbances, bacteremia, and anorexia.
- This regimen yields an ORR of 64%.
- This regimen serves as a good bridge to transplant, allowing 56% of responders to undergo allo-SCT.
- Patients with adverse risk by ELN responded at comparable rates. We recommend focusing further studies in this high-risk group.

Disclosures: AW, HW, AA, LG, MT, SK, JC, KP have no relevant financial relationships to disclose. RA: Ariad/Takeda, Novartis, Pfizer, BMS. OO: Abbvie, Pfizer, Celgene, CTI/Baxalta, Dava, Incyte, Jazz, Oncotherapy Science, Agios, NS Pharma, Janssen, Astex, Gilead. MB: United, Seattle Genetics, Celgene, Juneau, Novartis. EC: Merck. WS: Jazz. HL: BMS.