A Phase I Study of Selinexor in Combination with Daunorubicin and Cytarabine in Patients with Newly Diagnosed Poor-Risk Acute Myeloid Leukemia

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Background

Induction chemotherapy for older adults with poor-risk AML typically results in CR rates of 20-50%, with 5-year OS ranging from 2-15%. This illustrates the need for novel treatment strategies. Selinexor is an oral Selective Inhibitor of Nuclear Export (SINE) that has shown promising single agent activity in AML (NCT01607892). By inhibiting the primary export protein, XPO1, selinexor localizes tumor suppressor proteins to the nucleus leading to their activation. Furthermore, selinexor inhibits DNA damage repair, rationalizing its use in combination with DNA damaging agents. Preclinical data from our institution suggest selinexor synergizes with daunorubicin when used in $CD34^+$ AML cells. Here we report results from a phase I clinical trial with selinexor plus cytarabine and daunorubicin in patients with newly diagnosed, poor-risk AML.

Study Design and Endpoints

Single institution phase I clinical trial with a 3+3 design and an expansion phase at the maximal tolerated dose (MTD)/recommended phase 2 dose (RP2D).

Primary endpoint: MTD/RP2D of selinexor
Secondary endpoints:
- CR/CRi rate
- Overall survival (OS)
- Relapse free survival (RFS)
- Toxicity assessment.

Eligibility and Enrollment

- Previously untreated AML (non-M3)
- Poor-risk features (at least one of the following):
  - Karyotype
  - Mutational profile
  - Secondary AML (sAML)
  - Age ≥ 60 years

- 21 patients enrolled on study
- 21 patients evaluable for safety
- 18 patients evaluable for response

Phase of Treatment	Eval. for Response (n=18)
Induction	18 (100%)
Re-Induction	6 (33%)
Consolidation	6 (33%) – Each received 1 cycle
Maintenance	1 (6%) – Received 5 cycles
Allogeneic Stem Cell Transplant	6 (33%)

Treatment

Induction
7+3+Selinexor
- Daunorubicin 60 mg/m^2/day D1-3
- Cytarabine 100 mg/m^2/day CIVI D1-7
- Cohort 1: Selinexor 60 mg D1,3,8,10,15,17
- Cohort 2: Selinexor 80 mg D1,3,8,10,15,17

Re-induction
(if indicated)
5+2+Selinexor
- Daunorubicin 45 mg/m^2/day D1&2
- Cytarabine 100 mg/m^2//day CIVI D1-5
- Selinexor same dose as induction

Consolidation
q28 days up to 2 cycles
5+2+Selinexor
- Daunorubicin 45 mg/m^2/day D1&2
- Cytarabine 100 mg/m^2/day CIVI D1-5
- Selinexor same dose as induction D1,3,8,10

Maintenance
q21 days up to 12 mos
Selinexor
- Cohort 1: Selinexor 60 mg D1&8
- Cohort 2: Selinexor 80 mg D1&8

Demographics

	Total Enrollment (n=21)	Evaluable for Response (n=18)
Gender (M/F)	14 M/7 F (67%/33%)	12 M/6 F (67%/33%)
Median Age (years)	68 (37-77)	68 (37-77)
Age ≥60 years	18 (86%)	15 (83%)
Age ≥70 years	9 (43%)	7 (39%)
Risk Stratification	Intermediate: 2 (10%)	Intermediate: 1 (6%)
	Poor: 19 (90%)	Poor: 17 (94%)
Secondary AML	13 (62%)	11 (61%)
Prior HMA for AHD	8/13 (62%) w/ sAML	7 /11 (64%) w/ sAML
Cohort 1: selinexor 60 mg	4 (19%)	2 (11%)
Cohort 2: selinexor 80 mg	17 (81%)	16 (89%)

Results (n=18)

Response Rates

	All Patients (n=18)	Age ≥60 (n=15)	Age ≥70 (n=7)	sAML (n=11)	sAML w/ Prior HMA (n=7)
ORR (CR+CRi)	10 (56%)	9 (60%)	3 (43%)	4 (36%)	1 (14%)
CR	8 (44%)	7 (47%)	3 (43%)	3 (27%)	1 (14%)
CRi	2 (12%)	2 (13%)	0 (0%)	1 (9%)	0 (0%)
Treatment Failure	8 (44%)	6 (40%)	4 (57%)	7 (64%)	6 (86%)

All Patients	n=18
Median f/u time	6.7 months
Remain alive	10 (56%)
Median OS	Not Reached
Event occurred	12 (66%)
Median EFS	3.5 months
Est. 12 month OS	42%

Responders	n=10
Median age (years)	68 (58-77)
Age ≥70	3 (30%)
Poor Risk	9 (90%)
Secondary AML	4 (40%)
Prior HMA for AHD	1 (10%)
2nd Induction Needed	1 (10%)

Response Rate in Patients Treated at RP2D (n=16)	
ORR (CR+CRi)	8 (50%)
CR	6 (37.5%)
CRi	2 (12.5%)
Treatment Failure	8 (50%)

	All Patients (n=18)	CR/CRi	Relapse
Complex Karyotype	7 (39%)	3/8 (43%)	1/3 (33%)
Monosomal Karyotype	6 (33%)	2/6 (33%)	0/2 (0%)
Chromosome 5/7 abnormalities	8 (44%)	3/8 (38%)	2/3 (67%)
p53 mutation	7 (39%)	3/7 (43%)	0/3 (0%)
Splicing mutations	5 (28%)	3/5 (60%)	1/3 (33%)
FLT3-ITD mutations	2 (11%)	1/2 (50%)	1/1 (100%)
MLL Rearrangement	5 (28%)	3/5 (60%)	2/3 (67%)

Responders	n=10
Median f/u time	8.5 months
Remain alive	8 (80%)
Remain in CR	6 (60%)
Est 12 month RFS	45%
Went to allo. HCT	5 (1 planned) (60%)

Patients s/p HCT	n=5
Median f/u time	5.1 months
Remain alive	5 (100%)
Remain in CR	5 (100%)

Median Time to Recovery (days)	
Hospital Days (n=19)	37 (24-82)
Plts >50,000 (n=10)	35 (25-77)
ANC > 500 (n=10)	26 (18-45)
Response (n=10)	42 (31-77)

Toxicity Assessment (n=21)

Treatment Emergent Adverse Events in Induction ≥10% (n=21)

	Grade 1/2	Grade 3/4
Febrile Neutropenia	0	16 (76%)
Diarrhea	11 (52%)	6 (29%)
Hyponatremia	11 (52%)	7 (32%)
Sepsis	0	4 (19%)
Nausea	15 (71%)	0
Rash	3 (14%)	0
Hypotension	9 (43%)	0

Treatment Emergent Adverse Events in Consolidation ≥20% (n=6)

	Grade 1/2	Grade 3/4
Dyspnea	1 (17%)	1 (17%)
Headache	1 (17%)	1 (17%)
Nausea	5 (83%)	0

60 Day Mortality (n=21)	1 (4.8%)*

Treatment Emergent Adverse Events in Maintenance (n=1)

	Grade 1/2	Grade 3/4
Fatigue	0	1
Anorexia	1	0
Blurred vision	1	0
Constipation	1	0
Weakness	1	0

*1 pt died on day 24 of induction due to acute renal failure caused by antibiotics. Never had a response assessment.

Conclusion

- The MTD of selinexor was not reached
- The RP2D of selinexor was 80 mg twice weekly which was safely administered with daunorubicin and cytarabine as induction for patients with poor-risk AML, including older adults
- Most prominent AEs were febrile neutropenia, diarrhea and hyponatremia
- Count recovery is similar to 7+3 alone
- Response rates are encouraging compared to historical data
- Many older adults proceeded to transplant
- 7+3 plus selinexor warrants further investigation with direct comparison to 7+3