A Phase I/II study of Selinexor (SEL) with Sorafenib in Patients with Relapsed and/or Refractory FLT3-mutated Acute Myeloid Leukemia (AML)

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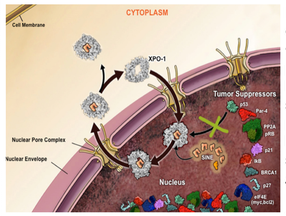
Abstract

Background: Responses to FLT3-inhibitors are usually transient due to emergence of resistance through the acquisition of kinase domain point mutations and other non-mutational mechanisms. SEL is a potent first-in-class Selective Inhibitor of Nuclear Export/SINE™ that exerted marked cell killing of human and murine FLT3-mutant AML cells, including those with ITD, D835Y, ITD+Y842C or ITD+F691L mutations by modulating the cdk inhibitor p27 and anti-apoptotic Mcl-1 (Zhang W et al, Blood 2015 126). The combination of SEL+sorafenib had synergistic pro-apoptotic effects in FLT3-mutated AML cells by suppressing phosphorylation levels of FLT3 and its downstream signaling mediators ERK/AKT, and by inducing myeloid differentiation in ITD and D835 mutated cell lines. **Methods:** We designed a phase I/II trial of SEL with sorafenib for FLT3-ITD and/or -D835 R/R AML pts. In phase I, the primary objectives were to determine the maximum tolerated dose (MTD), the recommended phase 2 dose (RP2D), and dose-limiting toxicity (DLT) of the combination. In phase II, primary objectives included the rate of complete remission (CR) + CR with incomplete count recovery (CRi) + partial response + >50% blast reduction within 3 months of therapy initiation. Secondary objectives were safety and overall survival (OS). SEL was given orally twice a week for 3-weeks on and 1-week off in 28-day cycles and sorafenib was given continuously at a dose of 400mg twice daily from cycle 1 day 1 of SEL. In phase I, SEL dose was de-escalated in "3+3" fashion starting at dose level 0 and going down if DLTs were exceeded (dose levels 0, -1, -2 = 80, 60, 40 mg, respectively). Once MTD was established, the phase II enrolled pts in 2 cohorts: prior FLT3-inhibitor failure (cohort 1) and FLT3-inhibitor naïve (cohort 2). PB or BM samples were collected at pre-dose (C1D1), 24 h (C1D2) and day 28 (C1D28) of cycle 1, and apoptosis induction was determined by measuring annexin V positivity with FACS. **Results:** Fourteen pts with a median age of 71 years (range, 24-81) were enrolled. All pts had baseline next generation sequencing for AML specific mutations (Figure 1A). The median number of prior therapies was 3 (range, 1-5) as follows: salvage (S) 1: n=1, S2: n=5, S3+: n=8. 11 (79%) pts had prior FLT3-inhibitors: 1 prior FLT3-inhibitor (n=9); 2 prior FLT3-inhibitors: n= (2). Three pts had prior SCT. Four pts were treated at dose level 0 (SEL 80mg) with DLTs in 2 (Grade (G) 3 sepsis, n=1; G3 mucositis, syncope, adrenal insufficiency, n=1). Three pts were subsequently treated at dose level -1 (SEL 60mg) with no DLTs and this was established as the MTD/RP2D. Seven pts were treated in expansion: 6 had prior FLT3-inhibitor therapy (cohort 1) and 1 had no prior FLT3-inhibitor (cohort 2). The median duration of treatment for all 14 pts was 28 days (range, 14-122) and therapy is ongoing in 1 pt. All pts are evaluable for response. Overall, 6 pts achieved CRi (2/14, (14%) CR with incomplete platelets recovery (CRp; n=2) and >50% blast reduction (n=2) as best responses, all of them had prior FLT3 inhibitor. Two pts with CRi and 1 with CRp (2 with FLT3-ITD and 1 with ITD+D835) achieved negative RT-PCR for FLT3. (Figure1B). One pt in CRi was bridged to SCT and remains alive at 1 year. The most common G 3/4 adverse events irrespective of causality were bleeding (gastrointestinal, n=4; intracranial, n=1), febrile neutropenia (n=4), pneumonia (n=3) and syncope (n=2). The reasons for discontinuing study therapy were disease progression (n=9; 64%), toxicity (n=3; 21%) and SCT (n=1; 7%). The median OS for pts on study was 3.5 months (range, 0.9-15). Translational analysis showed that SEL+sorafenib induced apoptosis in 4 of 5 tested patients, especially in the BM samples (Figure 1C) **Conclusions:** The combination of SEL and sorafenib is safe with clinical activity and apoptosis induction in R/R FLT3+ AML. The benefit was especially encouraging in pts exposed to prior FLT3 inhibitors, with a response rate of 55% (6/11; including 2 CRi and 2 CRp). The RP2D is 60 mg twice weekly of SEL and the study is accruing (NCT01607892).

Background

- Responses to FLT3-inhibitors are usually transient due to emergence of resistance through the acquisition of kinase domain point mutations and other non-mutational mechanisms.
- SEL is a potent first-in-class oral Selective Inhibitor of Nuclear Export/SINE™ that inactivates exportin-1-mediated nuclear export of eIF4E, preventing translation of the eIF4E-bound mRNAs on ribosomes and reducing the oncogenic and growth-promoting proteins AKT, PI3K, mTOR, FOXO, STAT5, BCL2, BCL-x(L), implicated in non-mutational resistance to FLT3-inhibitors.
- SEL exerts marked cell killing of human and murine FLT3-mutant AML cells, including those with ITD, D835Y, ITD+Y842C or ITD+F691L mutations by modulating the cdk inhibitor p27 and anti-apoptotic Mcl-1 .

SINE™ + Sorafenib: Rationale



In preclinical studies, the combination of SEL +sorafenib had synergistic pro-apoptotic effects in FLT3-mutated AML cells by suppressing phosphorylation levels of FLT3 and its downstream signaling mediators ERK/AKT, and by inducing myeloid differentiation in ITD and D835 mutated cell lines.

Objectives

Primary

- In phase I→ To determine the maximum tolerated dose (MTD), the recommended phase 2 dose (RP2D), and dose-limiting toxicity (DLT) of the combination.
- In phase II→ To determine the rate of complete remission (CR) + CR with incomplete count recovery (CRi) + partial response (PR) + >50% blast reduction (HI-B) within 3 months of therapy initiation.

Secondary

- Phase I→ To determine the CR + CRi + PR rate within 3 months
- To determine the safety of the combination
- To estimate overall survival (OS), event-free survival (EFS) and the duration of response (DOR) to the combination.

Exploratory

- Quantitative changes of FLT3-ITD and -D835 allelic burden with time in patients treated with the combination.

Key Eligibility Criteria

- Age ≥18 years at the time of enrollment
- Relapsed/refractory *de novo* or secondary AML
- Confirmed FLT3-ITD and/or FLT3-D835 mutations
- Patients must have failed therapy with up to two prior salvage regimens (SCT or stem cell therapy in remission is not be considered a salvage regimen)
- Patients may have failed prior FLT3-inhibitor (cohort 1) or are FLT3-inhibitor naïve (cohort 2)

- ECOG performance status 0-2
- Adequate hepatic function (serum total bilirubin </= 2.0 x ULN) (or </= 3.0 x ULN if due to leukemia), alanine aminotransferase and/or aspartate transaminase </= 3.0 x ULN (or </= 5.0 x ULN if deemed to be elevated due to leukemia)
- Adequate renal function (creatinine </=2.0 mg/dL).
- Cardiac ejection fraction ≥ 40% by ECHO or MUGA.

Treatment Plan

- Phase I/II, single-institution, open-label, non-randomized, parallel group clinical trial.

Phase I

- Includes FLT3-ITD and -D835 mutated patients who may have been previously exposed to one or more FLT3-inhibitors.
- The DLT assessment period will be performed only during Cycle 1 (Day 1- 28) of Phase I.

Phase II→ two cohorts

- Cohort 1: FLT3-ITD/D835 mutated R/R AML (up to salvage 2) who have previously been exposed to at least one prior FLT3 inhibitor.
- Cohort 2: FLT3-ITD and -D835 mutated R/R AML (up to salvage 2) with NO prior exposure to any FLT3-inhibitors.
- MTD and RP2D findings of the combination used the standard "3+3" design.
- If >/=2/6 patients experience DLT at dose level -2, the study will be revised to consider additional lower dose levels.

Table 1. Patient Characteristics

Characteristics (N=14)	N (%) / Median [range]
Age (years)	71 [24 – 81]
Diagnosis	
De novo AML	12 (86)
Secondary AML	2 (14)
Median prior therapies	3 [1 – 5]
Salvage	
1	1 (7)
2	5 (36)
3 and beyond	8 (57)
Prior FLT3 inhibitors	11 (79)
Prior SCT	3 (21)
Cytogenetics	
Diploid	7 (50)
Poor*	5 (36)
Miscellaneous	2 (14)
FLT3 mutation	
ITD alone	5 (36)
D835/D836 alone	2 (14)
ITD+D835	7 (50)
Other mutations**	
DNMT3A	5 (36)
IDH	5 (36)
RUNX1	4 (29)
RAS	4 (29)
NPM1	3 (21)
TET2	3 (21)
WT1	3 (21)
TP53	2 (14)

*Poor cytogenetics includes complex, -5/5q- and -7/7q-
**10 patients (71%) had 1 or more mutations in addition to FLT3.

Results

- Median duration of treatment: 28 days (range, 14-122)
- All pts evaluable for response.
- 6/14 (42%) pts responded: CRi in 2 (14%) CRp in 2 (14%), and >50% blast reduction in 2 (14%) as best responses, all 6 had prior FLT3 inhibitor.
- Two pts with CRi (one with ITD only and one with ITD+D835) and 1 with CRp (with ITD only) achieved negative RT-PCR for FLT3.
- One pt in CRi was bridged to SCT and remains alive at 1+ year.
- The median OS for all pts was 3.5 months (range, 0.9-18).

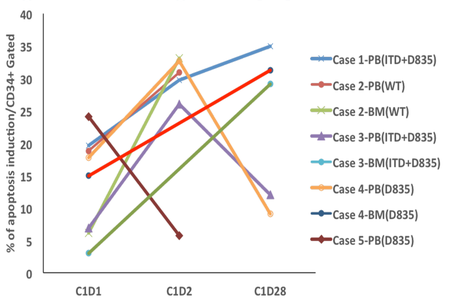
Table 2. Characteristics of Responders

Pt	Age	Prior therapies	Karyotype	FLT3 Status	Other Mutations	Cohort	Dose Level (SEL)	Best Response
1	81	Aza+ Sorafenib, Anti-CD25	Diploid	ITD	IDH2/ TP53/ RUNX1/	Dose level 0	80 mg	CRp Negative FLT3 by PCR
2	24	7+3, MEC, quizartinib, IA +crenolanib	Diploid	ITD/ D835	NRAS/ TET2/ IDH1	Dose level 0	80 mg	CRi Negative FLT3 by PCR
3	78	Aza, aza+ sorafenib	Diploid	ITD/ D835	DNMT3A/ RUNX1	Dose level -1	60 mg	HI-B
4	38	7+3+Sorafenib, G-CLAC, Aza +Crenolanib, SCT	Miscella-neous	ITD	RUNX1	Expansion 1 (prior FLT3-inhibitor)	60 mg	CRi Positive FLT3 by PCR
5	50	7+3, MEC, MUD SCT, Dac +Sorafenib	Miscella-neous	ITD/ D835	WT1	Expansion 1 (prior FLT3-inhibitor)	60 mg	HI-B
6	63	7+3, CLIA +Sorafenib	t(6;9)	ITD	HRAS/ WT1	Expansion 1 (prior FLT3-inhibitor)	60 mg	CRp FLT3 negative by PCR

Table 3. Treatment-Emergent Adverse Events

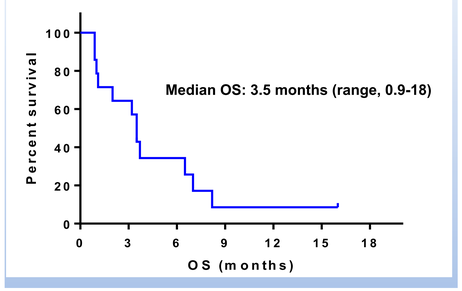
Adverse Event	Grade 1-2	Grade 3-4
Fatigue	5 (36)	9 (64)
Nausea/Vomiting	6 (43)	1 (7)
Anorexia	7 (50)	5 (36)
Diarrhea	7 (50)	1 (7)
Weight loss	6 (43)	0
Weakness	4 (29)	2 (14)
Confusion	2 (14)	1 (7)
Chest pain	4 (29)	0
Febrile neutropenia	1 (7)	2 (14)
Infections, other	1 (7)	4 (29)
Bleeding	2 (14)	2 (14)
Hyponatremia	4 (29)	4 (29)
Acute kidney injury	3 (21)	1 (7)
Adrenal Insufficiency	1 (7)	0
Hyperbilirubinemia	2 (14)	0

Fig 1. Percentage of Apoptosis Induction



Peripheral blood and bone marrow samples were obtained at indicated time points from R/R AML patients who received SEL+sorafenib therapy after written informed consent. White blood cells were purified by processing the samples with red blood cell lysis buffer. The percentage of apoptosis induction was determined via FACS by measuring annexin V positivity after gating the CD34 positive population.

Fig 2. Overall Survival



Conclusions

- The combination of SEL and sorafenib is safe with clinical activity with early apoptosis induction in R/R FLT3+ AML.
- The benefit was especially encouraging in pts exposed to prior FLT3 inhibitors, with a response rate in this population of 55% (6/11; including 2 CRi and 2 CRp).
- The RP2D is 60 mg twice weekly of SEL and the study is accruing (NCT01607892).

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