Background: Responses to FLT3-inhibitors are usually transient due to emergence of resistance through the acquisition of non-mutational mechanisms. SEL is a potent first-in-class Selective Inhibitor of Nuclear export (SINE) that exerts marked cell killing of human and murine FLT3-mutant AML cells, including those with FLT3-ITD, -D835 or -ITD+D835. SEL has been shown to overcome FLT3-driven resistance mechanisms, such as FLT3-mediated nuclear export of eIF4E, preventing translation of the translation initiation factor, important for oncogene-driven protein synthesis. In this study, we examined the antileukemic activity of the combination of SEL and sorafenib in patients with relapsed and/or refractory FLT3-mutant AML (AML).

Methods: A Phase I/II study of Selinexor (SEL) with Sorafenib in Patients with Relapsed and/or Refractory FLT3-mutant Acute Myeloid Leukemia (AML) was conducted with the hypothesis that the combination of SEL and sorafenib had synergistic pro-apoptotic effects in FLT3-mutant AML cells. The combination of SEL and sorafenib had synergistic pro-apoptotic effects in FLT3-mutant AML cells by decreasing Akt phosphorylation levels of levels of phospho-AKT, inducing ERK/AKT, and by inducing myeloid differentiation in ITD- and D835-mutated cell lines. We designed a phase I/II trial of SEL with sorafenib for patients with FLT3-mutant R/R AML, which included dose escalation, dose expansion, and a parallel group clinical trial. The reasons for discontinuing study therapy were disease progression (n=9; 64%), non-hematologic toxicity (n=3; 20%), and patient withdrawal (n=2; 13%). Seven pts were treated in expansion: 6 had prior therapies was 3 (range, 1-5) as follows: salvage (S) 1: n=1, S2: n=5, S3+: n=8. 11 pts were evaluable for response. The median OS for all pts was 3.5 months (range, 0.9-18). The median OS for all pts was 3.5 months (range, 0.9-18).

Results:
- Phase I (3+3 design): 10 patients (71%) had 1 or more mutations in addition to FLT3.
- Six pts achieved 2/14, (2 with FLT3-ITD and 1 with ITD+D835) achieved negative RT-PCR for FLT3.
- Overall, 6 pts achieved CRi (2/14, 14%) + PR rate within 3 months therapy initiation.
- Secondary objectives were safety and overall survival (OS). SEL was given at indicated dose levels (1-8) and sorafenib at 400 mg twice daily.
- The combination of SEL and sorafenib had synergistic pro-apoptotic effects in FLT3-mutant AML cells by decreasing Akt phosphorylation levels of levels of phospho-AKT, inducing ERK/AKT, and by inducing myeloid differentiation in ITD- and D835-mutated cell lines. We designed a phase I/II trial of SEL with sorafenib for patients with FLT3-mutant R/R AML, which included dose escalation, dose expansion, and a parallel group clinical trial. The reasons for discontinuing study therapy were disease progression (n=9; 64%), non-hematologic toxicity (n=3; 20%), and patient withdrawal (n=2; 13%). Seven pts were treated in expansion: 6 had prior therapies was 3 (range, 1-5) as follows: salvage (S) 1: n=1, S2: n=5, S3+: n=8. 11 pts were evaluable for response. The median OS for all pts was 3.5 months (range, 0.9-18).

Conclusions:
- The combination of SEL and sorafenib is safe with clinical activity early 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 Pr).
- The RP2D is 60 mg twice weekly of SEL and the median OS for all pts was 3.5 months (range, 0.9-18).