Addition of Crenolanib to Induction Chemotherapy Overcomes the Poor Prognostic Impact of Co-Occurring Driver Mutations in Patients with Newly Diagnosed FLT3-Mutated AML

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Abstract

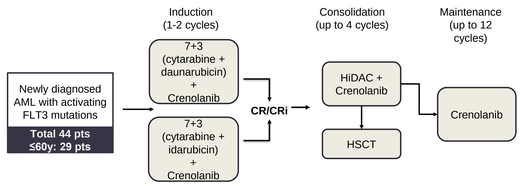
Background: Patients with AML harboring FLT3 mutations have poor clinical outcomes. Furthermore, FLT3 mutations frequently co-occur with other driver mutations, such as NPM1 with DNMT3A, WT1, and RUNX1, that are associated with poor prognosis. Crenolanib is a highly potent and specific type-I FLT3 inhibitor, which has shown promising safety and efficacy in combination with chemotherapy. Here we report the outcomes of newly diagnosed FLT3 mutated AML patients treated with crenolanib and intensive 7 + 3 based chemotherapy (NCT02283177) by baseline genomic profile.

Methods: Patients were treated on clinical trial with 7+3 induction chemotherapy combined with crenolanib, consolidation with high-dose cytarabine (HiDAC) combined with crenolanib, and/or allo-HCT followed by crenolanib maintenance. Of 44 pts enrolled and treated, 36 had sequencing performed at baseline. The median survival follow-up for these patients was 20.7 months with data cut off July 25, 2018. A post hoc analysis was performed to assess the impact of genomic profile on patient outcomes using published data from the German-Austrian AML Study Group as ahistorical control.

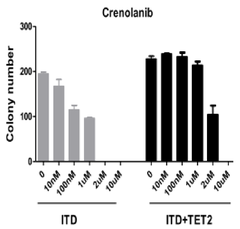
Results: Concurrent FLT3-ITD, NPM1, and DNMT3A mutations ("triple mutant") were present in 9 pts. These patients demonstrated improved OS with crenolanib treatment compared with historical controls. Similarly, patients with FLT3-ITD and WT1 mutations (n = 6) showed dramatically improved outcomes, with no deaths occurring by 18 months. Patients with FLT3 (ITD or TKD) and RUNX1 mutations (n = 10) also had improved OS.

Conclusions: This analysis suggests that adding a potent pan-FLT3 inhibitor can overcome the poor prognostic implication of adverse mutations co-occurring with mutated FLT3. These data support the combination of crenolanib with chemotherapy to improve the overall outcome of FLT3mutated AML with diverse mutational profiles. Hence, a randomized trial has been initiated of standard chemotherapy combined with either crenolanib or midostaurin in newly diagnosed patients with FLT3-mutant AML (NCT03258931).

Study Design



Mutations Occurring in the Background of FLT3 Mutations Can Lead to Resistance to FLT3 TKIs

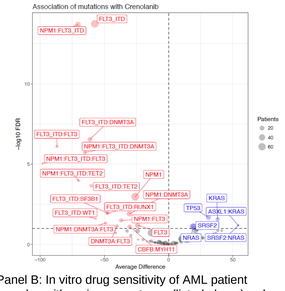


Panel A: TET2 mutations with FLT3 mutations lead to less crenolanib sensitivity *in vitro*. Colony formation assay with mouse stem cells expressing FLT3-ITD with or without TET2 mutation grown with increasing concentrations of crenolanib *Zhang et al. 2017 AACR Annual Meeting.*

Mutations in FLT3 are the most frequent molecular abnormality in AML (1). Patients with FLT3 mutant AML have poor clinical outcomes, which additionally makes targeting FLT3 an attractive target in AML. Crenolanib is a type I FLT3 tyrosine kinase inhibitor (TKI) that has been shown to have activity against both FLT3 internal tandem duplications (ITD) and tyrosine kinase domain (TFD) mutations. Preclinical studies with crenolanib have shown that some mutations, such as TET2 can contribute to resistance to crenolanib. Furthermore, co-occurring mutations frequently contribute to both resistance to TKIs or relapse.

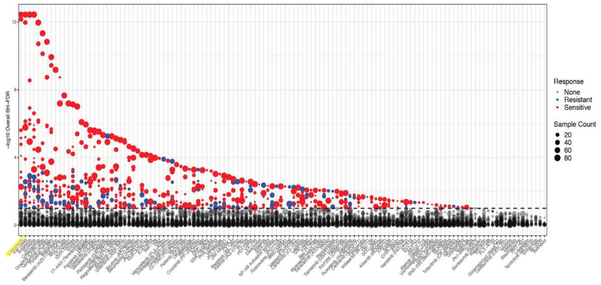
NPM1:DNMT3A:FLT3-ITD is the most frequent three gene mutational co-occurrence (6%) seen in AML(1). This genotype is associated with a particularly poor prognosis, worse than would be seen by simply adding the effects of each gene together.

In a recent report of the functional genomic landscape of AML, mutations that are associated with sensitivity or resistance to various drugs, crenolanib was one of the drugs studied in this large preclinical report. As seen in Panel B, crenolanib is able to kill a variety of AML patient samples with varied genomic landscapes, including the triple mutation, RUNX1 (3).

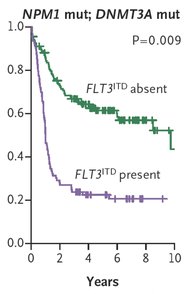


Panel B: In vitro drug sensitivity of AML patient samples with various genotypes (listed above) red are sensitive to crenolanib and blue are resistant to crenolanib. *Tyner et al. 2018 Nature.*

Crenolanib Has Excellent *in vitro* Cytotoxic Activity Against Primary AML Blasts



Panel C: Crenolanib can kill primary AML cells with a multitude of mutations in addition to mutations in FLT3. In vitro drug sensitivity of AML patient samples tested against a panel of small molecules. Each dot represents a particular mutation, or set of mutations; the color of the circle corresponds to the response of primary cells response to that drug, and the size of the dot corresponds to how many samples with that mutation responded in that fashion. *Tyner et al. 2018 Nature.*



Among the inhibitors studied by Tyner et al, crenolanib can kill patient samples that have mutant FLT3 and with additional varying mutations (Panel C above). Mutations, such as NPM1 with DNMT3A, WT1, or RUNX1 have been reported to associated with poor prognosis. Papaemmanuil et al., showed that driver mutation can be used to accurately classify large sets of AML, and also if these classifications were used with clinical data that trends in changes between the groups can easily be seen (Panel D).
To investigate the ability of crenolanib to clear FLT3 mutant clones with varied co-occurring mutations, we did a retrospective analysis of ARO-006.

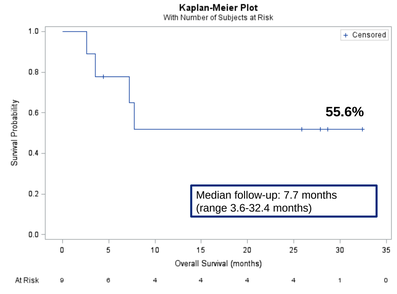
Panel D: Kaplan-Meier curves for overall survival according to the presence or absence of FLT3-ITD in the background of mutations in both DNTM3A and NPM1. *Papaemmanuil et al. 2016 N Engl J Med.*

Favorable Results With Chemo Plus Crenolanib in AML Patients With DNMT3A, FLT3, and NPM1 Mutations

- 9 patients were enrolled that had FLT3-ITD, NPM1, and DNMT3A mutations
  - These triple mutant AML historically have a very poor prognosis (30% survival at 2 years)

Age/Sex	FLT3 Type	Other Mutations	Overall Response	Status
47/M	ITD	DNMT3A, NPM1, RUNX1	CR	Alive in remission
59/F	ITD	DNMT3A, NPM1	CR	Alive in remission
47/F	ITD	DNMT3A, NPM1	CRi	Alive in remission
44/F	ITD	DNMT3A, NPM1	CR	Alive in remission
61/M	ITD	DNMT3A, NPM1	CR	Alive in remission
59/F	ITD	DNMT3A, NPM1	CR	Died (relapsed)
74/F	ITD	DNMT3A, NPM1, TET2	CR	Died (relapsed)
57/M	ITD	DNMT3A, NPM1	CR	Died (relapsed)
59/F	ITD	DNMT3A, NPM1	RD	Died (refractory)

8 of the 9 patients achieved a CR, 5 of the 9 remain alive

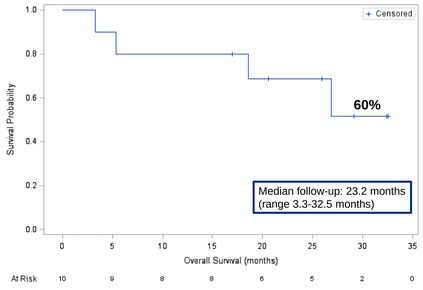


Favorable Results With Chemo Plus Crenolanib in AML Patients With FLT3 and RUNX1 Mutations

- 10 patients were enrolled that had FLT3-ITD and RUNX1 mutations
  - RUNX1 mutant AML historically have a poor prognosis
    - Median OS was 1.5 years

Age/Sex	FLT3 Type	Other Mutations	Cytogenetics	Overall Response	Status
47/M	ITD	DNMT3A, RUNX1, NPM1	Trisomy 8	CR	Alive in remission
59/M	D835V, D835E	RUNX1, DNMT3A, NRAS, BCOR, U2AF1	+13	CR	Alive (relapsed)
68/F	D835Y	RUNX1, DNMT3A, TET2, SF3B1	Normal	CR	Alive (relapsed)
34/F	ITD	RUNX1, TYK2	+8, +13	CR	Alive in remission
23/F	ITD	RUNX1, DNMT3A	Normal	CR	Alive in remission
19/M	ITD	RUNX1	Near tetraploid, 2x i(17)(q10)	RD	Alive (refractory)
66/F	ITD	RUNX1, WT1, ETV6, NUP98-PRRX2 fusion	Normal	CR	Died (relapsed)
68/M	ITD	RUNX1, DNMT3A, IDH1, SF3B1, BCORL1	der(7), t(7;11)(q33;q13)	CR	Died (relapsed)
75/M	D835V	RUNX1, ASXL1, U2AF1, MUTYH	+8, +13	RD	Died (refractory)
65/F	ITD	RUNX1, IDH1, SRSF2, STAG2, BCOR, NRAS	+8, +13	RD	Died (refractory)

7 of the 10 patients achieved a CR, 6 remain alive

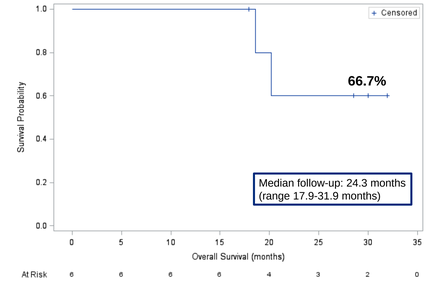


Favorable Results With Chemo Plus Crenolanib in AML Patients With FLT3 and WT1 Mutations

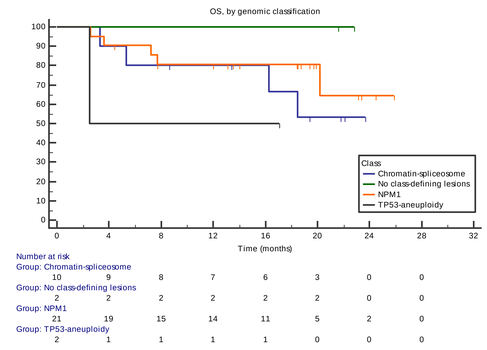
- 6 patients were enrolled that had FLT3-ITD and WT1 mutations
  - WT1 mutant AML historically have a poor prognosis (median survival at 1 year)

Age/Sex	FLT3 Type	Mutations	Cytogenetics	Overall Response	Status
22/F	ITD	WT1, NPM1, TCL1A	Normal	CR	Alive in remission
24/M	ITD	WT1, NUP98 loss (exons 13-20)	Normal	CR	Alive in remission
54/M	ITD	WT1, TET2	Normal	CRi	Alive in remission
68/M	ITD	WT1, NPM1	t(3;18)(q26;21), del(6q), der(3)	CR	Alive in remission
61/F	ITD, I836del, D593H	WT1, NPM1	Normal	CR	Died (relapsed)
66/F	ITD	WT1, RUNX1, ETV6, NUP98-PRRX2 fusion	Normal	CR	Died (relapsed)

6 of the 6 patients achieved a CR, 4 remain alive



Crenolanib in AML Patients can Overcome Poor Prognostic Mutations



- OS curves were created based on risk factors: TP53 mutation or deletion, mutations in the chromatin spliceosome, NPM1 mutations, or patients with no classifying lesions. The definition of these risk factors come from (1).

This analysis suggests that adding a potent pan-FLT3 inhibitor can overcome the poor prognostic implication of adverse mutations co-occurring with mutated FLT3. These data support the combination of crenolanib with chemotherapy to improve the overall outcome of FLT3mutated AML with diverse mutational profiles.

- This is a small study with limited patient numbers of the mutations looked at; however, this shows that in combination with chemotherapy crenolanib can potentially improve efficacy.
- As reported by Tyner et al., our data suggests that crenolanib can clear FLT3 mutant clones in the face of co-occurring mutations that could otherwise produce resistance or cause relapse.
- If these data are confirmed in Phase III study, this could broaden the patient population that can benefit from crenolanib.

References

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