Supplementary appendix

Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed or refractory *IDH1*-mutated AML

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Methods for translational analyses

Peripheral blood samples for exploratory pharmacodynamic assessments including 2-HG, a biomarker of the on-target activity of olutasidenib, were collected at baseline and subsequently during each 28-day treatment cycle. Bone marrow aspirate and peripheral blood samples for exploratory assessments of cancer-associated mutations and/or genetic alterations were collected during screening. Cancer-associated mutation analysis was then performed on bone marrow aspirate or biopsy samples collected for response during treatment with olutasidenib. Peripheral blood samples for mutation analysis were collected at screening and at each timepoint that a bone marrow aspirate or biopsy was obtained.

DNA for mutational analyses was extracted from peripheral whole blood and plasma collected in PAXGene® tubes. Droplet Digital polymerase chain reaction was used to quantify IDH1 mutant allele frequencies. IDH1 variant allele frequency (VAF) data were based on >20,000 droplets with a limit of sensitivity of 0.1%. IDH1 mutation clearance was defined as VAF <1%. Co-mutations were assessed using next generation sequencing. Target enrichment was conducted using the HaloPlex® target enrichment system (Agilent®; Santa Clara, CA) followed by Illumina® sequencing using a 74-genes custom myeloid panel, with a coverage of >100× achieved across the panel.

Parameters recorded at baseline included 2-HG concentration, IDH1 VAF, IDH1 R132 mutation subtype, and the co-mutational profile. Exploratory analyses were conducted, including assessment of clinical response according to baseline mutational profile and VAF clearance.

Supplemental Table 1: Patients with TEAEs of differentiation syndrome

Patients with TEAEs of differentiation syndrome	**Olutasidenib 150 mg BID (N = 153)**
Patients with any TEAE of DS, n (%)	22 (14)
Median time to TEAE of DS, days (range)	17.5 (1-561)
Median time to resolution of TEAE of DS, days (range)	13.0 (0-56)
Patients with any grade 3/4 TEAE of DS, n (%)	13 (8)
Patients with any serious TEAE of DS, n (%)	14 (9)
Patients with any TEAE of DS leading to dose modification, n (%)	12 (8)
Patients with dose hold, n (%)	11 (7)
Patients with dose reduction, n (%)	2 (1)
Patients discontinued treatment, n (%)	3 (2)
Patients with any TEAE of DS leading to death, n (%)	1 (1)

AE = adverse event; BID = twice daily; DS = differentiation syndrome; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Supplemental Table 2: Summary of shifts in liver function parameters from baseline to highest reported grade

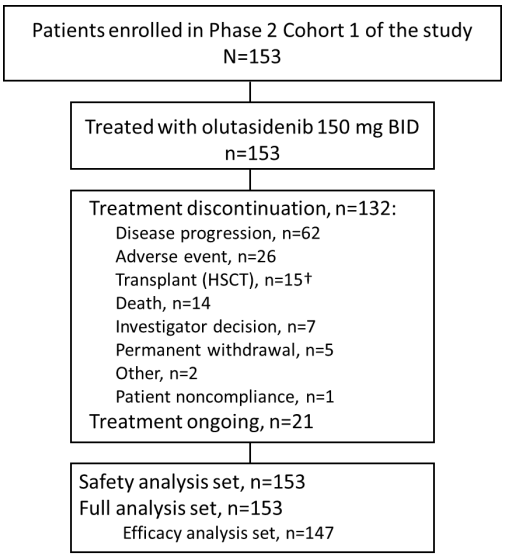
	Olutasidenib 150 mg BID (N=153) Highest reported grade of liver function parameter		
Parameter	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Aspartate aminotransferase increased	70 (46)	13 (9)	2 (1)
Alanine aminotransferase increased	70 (46)	17 (11)	3 (2)
Alkaline phosphatase increased	64 (42)	11 (7)	0
Bilirubin increased	40 (26)	3 (2)	0

BID = twice daily.

Supplemental Table 3: Number of baseline co-mutations by response category (N=120)

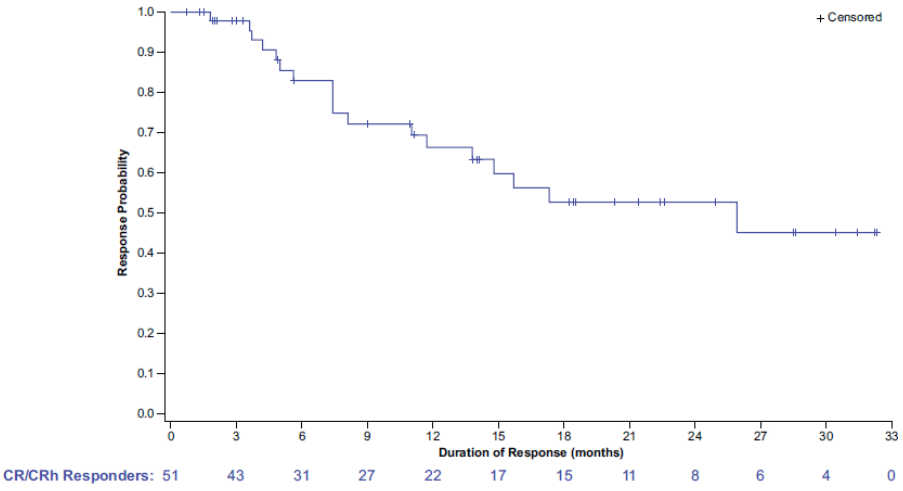
Number of co-mutations	**CR/CRh responders N=40 n (%)**	**Other responders N=16 n (%)**	**Non-responders N=64 n (%)**
0	7 (17.5)	3 (18.8)	8 (12.5)
1 to 3	29 (72.5)	9 (56.3)	32 (50.0)
4 to 10	4 (10.0)	4 (25.0)	24 (37.5)

CR: complete remission; CRh = complete remission with partial hematologic recovery.



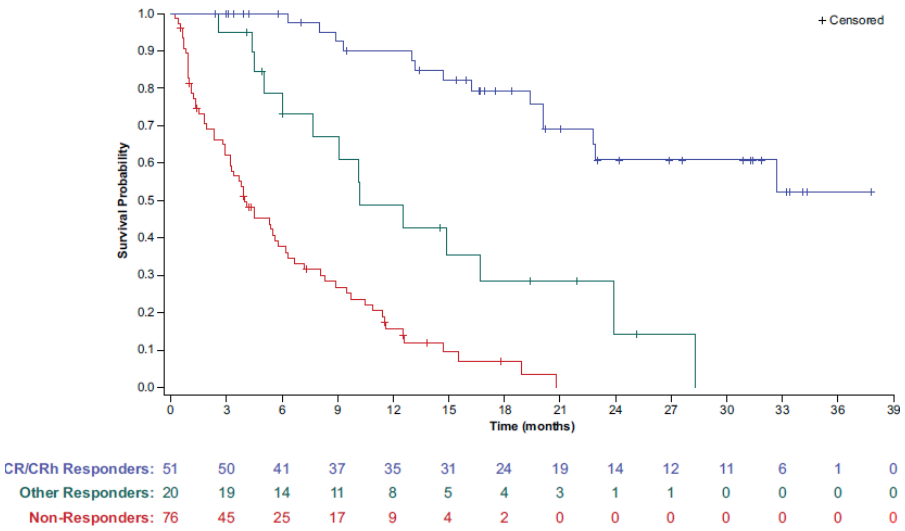
Supplemental Figure 1: CONSORT diagram. †Fifteen patients discontinued olutasidenib to receive hematopoietic stem cell transplantation (HSCT). In total, 16 patients underwent HSCT; one patient who discontinued olutasidenib due to a grade 3 AE of bone marrow hypoplasia subsequently underwent transplantation.

BID = twice daily. HSCT = hematopoietic stem-cell transplantation.



Supplemental Figure 2: Sensitivity analysis for duration of CR/CRh in the efficacy evaluable analysis set. Patients who discontinued treatment due to HSCT were censored at the date of HSCT. Median duration of CR+CRh was 25.9 months (95% CI, 11.7-NE) (n=51).

CR = complete remission; CRh = CR with partial hematologic recovery; HSCT = hematopoietic stem-cell transplantation.



Supplemental Figure 3: Sensitivity analysis for overall survival by best overall response for the efficacy evaluable analysis set. Patients who discontinued treatment due to HSCT were censored at the date of HSCT. Median overall survival was not reached (95% CI, 22.8-NE) in patients with CR/CRh (n=51); 10.2 months (95% CI, 6.0-23.9) in other responders (n=20); and 4.0 months (95% CI, 3.2-5.8) in non-responders (n=76). Other responders are patients with CRi, PR, or MLFS. Non-responders are patients in response assessment categories other than CR/CRh, CRi, PR, and MLFS.

CR = complete remission; CRh = CR with partial hematologic recovery; CRi = CR with incomplete recovery; HSCT = hematopoietic stem-cell transplantation; MLFS = morphologic leukemia-free state; PR = partial remission.