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IDH1/2

ISAL 2019 | Inhibitors of IDH1 and IDH2 for targeted therapy in acute myeloid leukemia

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On February 25, 2019, Courtney DiNardo from The University of Texas MD Anderson Cancer Center, Houston, TX, presented at the Acute Leukemias XVII Biology and Treatment Strategies biennial symposium, in Munich, Germany on isocitrate dehydrogenase (IDH) type 1 (IDH1) and IDH type 2 (IDH2*)* inhibitors in the treatment of acute myeloid leukemia (AML). Dr. DiNardo began by discussing the biology of *IDH* mutations, moving on to discuss how these have been utilized as therapeutic targets in AML and showing the data that led to the clinical adoption of the *IDH* inhibitors enasidenib and ivosidenib. The presentation concluded with a summary of ongoing trials of these inhibitors in combination therapies.[1]

IDH mutations – biology

Whilst *IDH* mutations are not the most commonly occurring in AML, approximately 20% of patients have mutant *IDH* (*mIDH*) genes with approximately 8% affecting *IDH1* and 12% in *IDH2.* These mutations are early events, with 20% of *IDH1* and 35% of *IDH2* occurring at diagnosis. However, these can also be acquired during progression from myelodysplastic syndrome or myeloproliferative neoplasms to AML in 10–15% and 20–25% of cases, respectively.

At a cellular level, IDH1 (in the cytoplasm) and IDH2 (in the mitochondria) usually act to metabolize the reaction of isocitrate to α-ketoglutarate (α-KG). When these genes are mutated, α-KG cannot breakdown D-2-hydroxyglutarate (2-HG), an oncometabolite, causing it to accumulate and inhibit α-KG-dependent dioxygenases. This leads to impaired differentiation, epigenetic changes, and metabolic dysregulation.

Targeting *IDH1* and *IDH2*

Currently, there are two *IDH* inhibitors approved for the treatment of AML by the U.S. Food and Drug Administration (FDA). These are AG-120 (ivosidenib, TIBSOVO®) for *mIDH1* and AG-221 (enasidenib, IDHIFA®) for *mIDH2.*[2,3] Others under investigation include IDH305 for *mIDH1* and AG-881 for both *IDH1* and *IDH2* inhibition.

Bin Fan *et al.* identified that ivosidenib effectively inhibits 2-HG in patients with m*IDH1* AML with a reduction to normal plasma 2-HG levels in the majority of patients, at all doses. The study also supported once-daily oral dosing (QD).[4]

Enasidenib for *mIDH2*

In a first-in-human phase I/II study (NCT01915498), patients with advanced myeloid malignancies with *IDH2* mutations were enrolled into the dose escalation phase. Patients were given cumulative daily doses of 50–650 mg of enasidenib in continuous 28-day cycles. This identified the optimal dose of 100 mg, daily, with no maximum tolerated dose (MTD)

reached. This study then moved into the expansion phase, recruiting patients predominantly with relapsed/refractory (R/R) *mIDH2* AML.[5] The updated results from this study were presented by Dr. DiNardo and are shown in Table 1 below, in patients with R/R AML.[6]

	Enasidenib, 100 mg/day (n = 214)
Overall response rate (ORR)	83 (38.8%)
Complete remission (CR) + CR with incomplete hematologic recovery/CR with incomplete platelet recovery (CRi/CRp)	62 (29%)
Best response: CR CRi/CRp Partial remission (PR) Morphologic leukemia-free state (MLFS) Stable disease (SD) Progressive disease (PD) Not evaluable (NE)	 42 (19.6%) 20 (9.3%) 9 (4.2%) 12 (5.6%) 98 (45.8%) 19 (8.9%) 3 (1.4%)

Overall survival (OS) (n = 280)	
Median OS	8.8 months (7.7–9.6)
Median OS with CR (n = 42)	22.9 months
Median OS with non-CR response	10.6 months
Median OS with NR	5.6 months

Table 1: Efficacy of enasidenib in R/R AML

In a paper by Michael D. Amatangelo *et al.* the impact of co-occurring mutations on response to treatment with enasidenib was investigated. In this study, fewer co-occurring mutations were observed in patients achieving a response (≥PR or CR). The ORR of patients with a low mutational burden (≤ 3 co-occurring mutations) (n = 27) was 70.4% compared to 21.9% in patients with a high mutational burden (≥ 6 co-occurring mutations) (n = 32). Additionally, ***NRAS*** mutations were found to be significantly correlated with CR rates (*P = 0.0114).*[7]

Ivosidenib for *mIDH1*

In the first-in-human phase I study (NCT02074839) of ivosidenib in patients with m*IDH1,* patients with advanced hematologic malignancies with *mIDH* were recruited for a dose escalation phase. Patients were treated with 100 mg twice daily (BID) or 300 mg, 500 mg, 800 mg or 1200 mg QD. The MTD was not reached. The optimal dose, however, was found to be 500 mg QD. An expansion cohort of patients with *mIDH1* R/R AML, untreated AML or non-AML *mIDH1* advanced hematologic malignancies were treated with this dose.[8]

Table 2 shows the results presented by Dr. DiNardo in patients with R/R AML with a median of 2 prior therapies.[1]

	Ivosidenib, 500 mg/day (n = 179)
Overall response rate (ORR) (95% CI)	75 (41.9%, 34.6–49.5)
CR + CR with partial hematologic recovery (CRh) (95% CI)	57 (31.8%, 25.1–39.2)

Best response:	
CR	43 (24.0%)
CRi/CRp	21 (11.7%)
MLFS	11 (6.1%)
SD	68 (38.0%)
PD	15 (8.4%)
Not assessed (NA)	21 (11.7%)
OS	
Median OS	9 months (7–10)
Median OS with CR/CRh	18.8 months
Median OS with non-CR/CRh responders	9 months
Median OS in non-responders	5 months

Table 2: Efficacy of ivosidenib in R/R AML

Further studies evaluating the impact of the depth of response have been conducted. These include an investigation by Daniel A. Pollea *et al*. where patients treated with ivosidenib who had deeper clearance of *IDH1*, as detected by digital polymerase chain reaction, had an improved OS. In this study, this was not statistically significant due to the small sample size [9]

Mechanisms of relapse in patients with mIDH[10]

In a study by Lynn Quek *et al*. clonal heterogeneity was examined in patients with *mIDH2* AML treated with enasidenib. At relapse, in patients who had acquired resistance to enasidenib, no second-site *IDH2* mutations were detected. However, investigators observed seven patterns of clonal evolution/selection indicating these were the main mechanisms of acquired resistance.

Additionally, by measuring 2-HG levels in sixteen patients at diagnosis and relapse, it was observed that fourteen of these remained suppressed between best response and relapse. In most patients, therefore, relapsed clones did not appear to be dependent upon *mIDH2* with enasidenib remaining on-target. In the two patients whose 2-HG levels increased, mutations in *IDH1* were observed, which, prior to treatment, were not detectable using next-generation sequencing. This indicated *IDH1* mutations were present in *mIDH2* clones with isoform switching another relapse mechanism.

Combination treatment with IDH inhibitors

Another regimen being investigated is using IDH inhibitors in combination treatments. Current studies utilizing these strategies include ivosidenib/enasidenib with azacitidine or with standard chemotherapy, such as cytarabine and daunorubicin or idarubicin.

Ivosidenib or enasidenib in combination with azacitidine (AZA):[1,11,12]

- Adult patients with newly diagnosed AML who are ineligible for chemotherapy
- Phase Ib dose-finding and expansion and phase II randomized trial design:
  - *mIDH1*: ivosidenib arm
    - Phase Ib: dose-finding phase (n = 7): ivosidenib (500 mg QD) + AZA
    - Phase Ib: expansion phase (n = 16): ivosidenib (500 mg QD) + AZA
  - *mIDH2*: enasidenib arm
    - Phase Ib: dose-finding phase (3+3)
      - Enasidenib: 100 mg QD + AZA
      - Enasidenib: 200 mg QD + AZA
    - Phase II: randomized study (n = 99)
      - Enasidenib: 100 mg QD + AZA (n = 66)
      - AZA monotherapy (n = 33)
  - AZA (administered subcutaneously): 75 mg/m^2/day x 7 days per 28 day cycle (all phases)
  - Phase Ib:
    - Primary endpoint: recommended combination dose and safety
    - Secondary endpoints: ORR, CR rate, mIDH variant allele frequency
  - Phase II:
    - Primary endpoint: ORR
    - Secondary endpoints: safety, event-free survival (EFS) and OS

Dr. DiNardo presented the results from this study, as shown in Table 3 below.

	Ivosidenib + AZA (n = 23)	Enasidenib + AZA (n = 6)
ORR	18 (78%)	4 (67%)
CR	13 (57%)	3 (50%)
CRi/CRp	3 (13%)	0 (0%)
PR	0 (0%)	0 (0%)
MLFS	2 (9%)	1 (17%)
Median time to first response	1.8 months (0.7–3.8)	-
Median time to best response	3.6 months (0.8–6.7)	-
Median duration of response	Not reached	-

Table 3: Results of phase Ib studies: the efficacy of IDH inhibitor combination treatments

The ivosidenib cohort has now been progressed into a multicenter, double-blind, placebo-controlled, randomized, phase III study investigating invosidenib *versus* placebo with AZA in previously untreated patients with AML with *IDH1* mutations (AGILE, NCT03173248). The enasidenib phase II study is still currently enrolling.

Ivosidenib and enasidenib with standard chemotherapy:[1,13]

- Patients with AML who are fit for intensive chemotherapy at the time of diagnosis
- Open-label, multicenter, phase I study (NCT02632708)
- Ivosidenib or enasidenib with cytarabine (ARA-C) and daunorubicin (DNR) or idarubicin (IDR)
  - ARA-C dose: 200 mg/m^2/day x 7 days
  - DNR dose: 60 mg/m^2/day x 3 days
  - IDR dose: 12 mg/m^2/day x 3 days
- Induction (1–2 cycles):

- *mIDH1:* ivosidenib (500 mg) + ARA-C + DNR or IDR
- *mIDH2:* enasidenib (100 mg) + ARA-C + DNR or IDR

- Consolidation after CR/CRi/CRp (≤4 cycles):
  - *mIDH1:* ivosidenib (500 mg) + ARA-C
  - *mIDH2:* enasidenib (100 mg) + ARA-C
- Maintenance*:* after CR/CRi/CRp (up to 2 years from day 1 of induction)
  - *mIDH1:* ivosidenib (500 mg) daily
  - *mIDH2:* enasidenib (100 mg) daily

All data given as ivosidenib versus enasidenib

- Patient characteristics:
  - Patient numbers: 60 *vs* 93
  - Median age: 62.5 (24–76) *vs* 63 (27–77) years
  - *De novo* AML: 42 (70%) *vs* 59 (63%)
  - Poor cytogenetics: 20 (33%) *vs* 29 (31%)
  - Co-occurring mutations:
    - *mIDH1: DNMT3A, NPM1, ASXL1* and *BCOR*
    - *mIDH2* group: *DNMT3A, SRSF2, ASXL1* and *RUNX1*

Dr. DiNardo presented the results from this study, as shown in Table 4 below.

	Ivosidenib + chemotherapy (n = 49)	Enasidenib + chemotherapy (n = 89)

CR + CRi/CRp	39 (80%)	64 (72%)
CR	35 (71%)	50 (56%)
CRi/CRp	4 (8%)	14 (16%)
MLFS	3 (6%)	11 (12%)
PT	1 (2%)	1 (1%)
Treatment failure	6 (12%)	13 (15%)
Measurable residual disease (MRD)-negative (CR/CRi/CRp best response group)	15 (88%) (n = 17)	9 (45%) (n = 20)
Median follow-up (months)	9.4	11.2
Estimated 12-month OS after induction day 1 (%)	79	75
Median OS (months)	Not estimable	Not estimable

Table 4: Results of phase I study of induction + ivosidenib or enasidenib. Data cut-off 01 Aug 2018.

Future Studies

A phase III study, HOVON 150/ AMLSG 29-18, stratifying patients by *mIDH* status aims to recruit approximately a thousand patients with AML who are eligible for intensive chemotherapy at the end of 2018. The study will determine the efficacy of enasidenib or ivosidenib with chemotherapy *versus* placebo treatment. The induction treatment is two cycles of 7+3 and enasidenib (*mIDH2)* or ivosidenib (*mIDH1) versus* 7+3 and placebo. This is followed by consolidation chemotherapy (1 or 3 cycles) and allo- or auto-hematopoeitic stem cell transplant (HSCT). The maintenance phase will be enasidenib (*mIDH2)* or ivosidenib (*mIDH1) versus* placebo.[14]

A phase Ib/II study investigating the combination of ivosidenib and venetoclax with and without AZA. The primary endpoints of the study will be safety, tolerability, MTD and recommended phase II dose of ivosidenib + venetoclax +/- AZA. Ivosidenib (500 mg QD) will be administered continuously from day 15 with the venetoclax dose as per protocol, on days 1–14 per 28-day cycle and AZA (75 mg/m^2 on days 1–7) as per protocol. In the phase I cohort, dosing will be:

- Starting dose (0): 400 mg venetoclax + ivosidenib

- Target dose (+1): 800 mg venetoclax + ivosidenib
- Target dose (+2): 400 mg venetoclax + ivosidenib + AZA

Conclusion

Patients with *IDH1* or *IDH2* mutant R/R AML can be treated with the oral agents, ivosidenib, and enasidenib, which are safe and effective as single-agent therapy. However, it is expected that combining these with other regimens, such as 7+3 and AZA, will improve responses and durability. Studies combining these with targeted therapies, such as FLT3i, will also be undertaken, or are ongoing, to investigate any additional benefit.

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