

Pharmacokinetic/pharmacodynamic evaluation of ivosidenib or enasidenib combined with intensive induction and consolidation chemotherapy in patients with newly diagnosed IDH1/2-mutant AML

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BACKGROUND

- Isoictrate dehydrogenase 1 and 2 (IDH1/2) are critical metabolic enzymes
- Somatic IDH1/2 mutations occur in multiple solid and hematologic tumors, including ~20% of cases of acute myeloid leukemia (AML)¹
- Mutant IDH1/2 (mIDH1/2) proteins possess novel enzymatic activity, catalyzing the reduction of α-ketoglutarate to produce the oncometabolite, D-2-hydroxyglutarate (2-HG),^{2,3} which drives multiple oncogenic processes, including impaired cellular differentiation⁴⁻⁶
- Ivosidenib (IVO) and enasidenib (ENA) are first-in-class, oral, potent, reversible, and selective inhibitors of the mIDH1 and mIDH2 enzymes, respectively
 - Both IVO and ENA have been shown to lower 2-HG concentrations and restore cellular differentiation^{7,8}
 - IVO is approved in the US for the treatment of AML with a susceptible IDH1 mutation as detected by an FDA-approved test in adults with newly diagnosed AML who are ≥ 75 years of age or who have comorbidities that preclude the use of intensive induction chemotherapy, and in adults with relapsed or refractory AML
 - ENA is approved in the US for the treatment of relapsed or refractory AML with a susceptible IDH2 mutation as detected by an FDA-approved test in adult patients
- Here we report pharmacokinetic/pharmacodynamic (PK/PD) data from a phase 1 trial of either IVO or ENA combined with intensive induction and consolidation chemotherapy in patients with newly diagnosed AML and mIDH1 or mIDH2, respectively

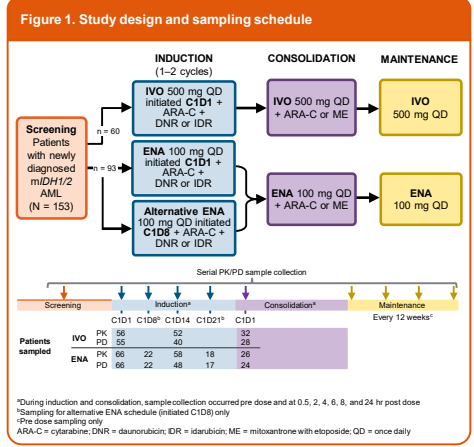
OBJECTIVES

- To characterize the plasma PK profiles of IVO and ENA given in combination with intensive induction and consolidation chemotherapy for the treatment of patients with newly diagnosed AML
- To evaluate the PK/PD relationships of IVO and ENA given in combination with intensive induction and consolidation chemotherapy for the treatment of patients with newly diagnosed AML

METHODS

- This was a multicenter, open-label, phase 1 study enrolling patients ≥ 18 years of age with newly diagnosed mIDH1 or mIDH2 AML (ClinicalTrials.gov NCT02632708)
- Schedules for drug administration and sampling for PK/PD assessments are outlined in **Figure 1**
 - Blood samples for full PK/PD analysis were collected on induction Cycle (C) 1 Day (D) 1 and C1D14, and consolidation C1D1
 - An alternative ENA schedule was assessed, in which blood samples were collected on induction C1D8 and C1D21, and consolidation C1D1
 - Pre dose PK/PD samples were collected during the maintenance phase

METHODS (CONTINUED)



- Plasma concentrations of IVO and ENA were measured using a validated liquid chromatography-tandem mass spectrometry method
- Plasma and bone marrow concentrations of 2-HG were measured using qualified liquid chromatography-tandem mass spectrometry methods
- PK/PD analyses were performed using a validated version of Phoenix[®] WinNonlin[®] 7.0

RESULTS

- IVO and ENA were rapidly absorbed, with median peak plasma concentrations at 4 hr following single and multiple doses (**Table 1**)
 - Exposure at steady state was higher than after a single dose, with mean estimated accumulation ratios (Racc) calculated as induction C1D14 / induction C1D1) of 2.4 and 8.3 using the area under the plasma concentration-time curve from time 0 to 24 hr (AUC₀₋₂₄), and 1.7 and 6.3 using the maximum observed plasma concentration (C_{max}) for IVO and ENA, respectively, following 14 days of QD dosing
- On the basis of trough concentrations (C_{trough}) across treatment cycles, PK steady state was achieved within 14 days of continuous dosing for both IVO and ENA (**Figure 2**)
 - For IVO, mean C_{trough} decreased upon reaching consolidation therapy, and the lower plasma levels compared with induction therapy remained constant throughout the maintenance phase
 - For ENA, steady state was maintained upon reaching consolidation; there were insufficient data available during the maintenance phase (n ≤ 3) to determine any meaningful trends

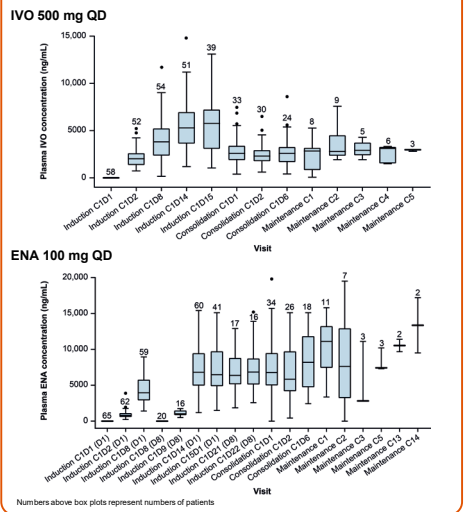
RESULTS (CONTINUED)

Table 1. Summary of PK/PD parameters after multiple doses of IVO or ENA in combination with induction chemotherapy

	IVO N = 50 ^a	ENA N = 75 ^b
C _{max} mean (CV%), ng / mL	7650 (40.5) n = 50	8200 (40.4) n = 75
T _{max} median (min, max), hr	3.92 (0.52, 22.75) n = 50	4.18 (0, 23.75) n = 75
AUC ₀₋₂₄ , mean (CV%), hr·ng / mL	137,000 (44.6) n = 44	161,000 (40.4) n = 55
Racc AUC ₀₋₂₄	2.4 n = 38	8.3 ^c n = 38
Racc C _{max}	1.7 n = 49	6.3 ^c n = 53
2-HG inhibition, % (CV%)	90.4 (23.0) n = 49	84.2 (27.9) ^{c,d} n = 51

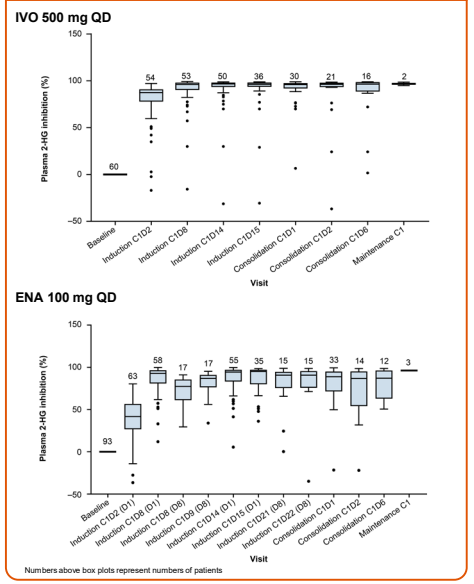
^aPK/PD parameters for IVO at induction C1D14
^bPK/PD parameters for combined ENA schedules at induction C1D14 and C1D21
^cFor standard ENA schedule at induction C1D14
^d2-HG inhibition for alternative ENA schedule at C1D21 was 82.6% (CV 31.9%; n = 18)
 CV = coefficient of variation; T_{max} = time at maximum observed plasma concentration

Figure 2. Plasma concentrations over time of IVO or ENA in combination with chemotherapy



- Plasma 2-HG concentrations were elevated at baseline and decreased after both single and multiple doses of the IVO or ENA combination regimens (**Figure 3**)
 - After multiple doses, mean trough plasma 2-HG concentrations decreased to within the range observed in healthy volunteers (up to 99% inhibition),⁹ and 2-HG inhibition was maintained throughout continued IVO or ENA dosing
- Mean trough bone marrow 2-HG concentrations also decreased (up to 99% inhibition) after multiple doses of the IVO or ENA combination regimens

Figure 3. Plasma 2-HG inhibition over time pre dose and after multiple oral doses of IVO or ENA in combination with chemotherapy



- Exploratory analyses of the relationship between plasma IVO/ENA PK parameters and inhibition of plasma 2-HG at induction C1D14 are shown in **Figure 4**
 - For overall plasma IVO C_{trough} values observed, plasma 2-HG percent inhibition based on the observed response value at the end of a dosing interval (R_{trough}) was mostly within the range of 95–100%
 - For overall plasma ENA C_{trough} values observed, plasma 2-HG percent inhibition (R_{trough}) was within the range of 60–100%

- Exploratory analyses of visit-matched plasma and bone marrow samples showed that overall, 2-HG concentrations in bone marrow correlated with those in plasma following multiple daily doses of IVO or ENA in combination with induction and consolidation chemotherapy (**Figure 5**)

Figure 4. Comparisons of 2-HG inhibition vs C_{trough} for IVO or ENA in combination with chemotherapy (induction C1D14)

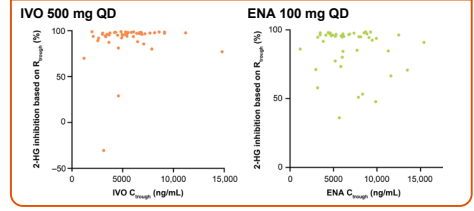
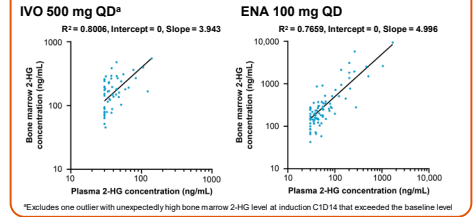


Figure 5. Comparisons of 2-HG concentrations in bone marrow and plasma after oral doses of IVO or ENA in combination with chemotherapy



CONCLUSIONS

- When combined with intensive induction and consolidation chemotherapy in patients with newly diagnosed mIDH1/2 AML, IVO and ENA demonstrated PK profiles similar to those observed with their use as single agents,^{9,11} with high plasma exposures relative to those needed for target inhibition
 - PK/PD profiles of IVO and ENA were also similar to those estimated in previous studies,^{10,11} and appeared to be similar across the combination cohorts
- Plasma concentrations of 2-HG were reduced to within the range found in healthy volunteers, as observed in studies of these inhibitors given as single agents
 - In spite of the modest decrease in IVO pre dose concentrations following the completion of induction therapy, mean trough plasma 2-HG concentrations remained within the range observed in healthy volunteers

Acknowledgments We would like to thank the patients taking part in this study. We thank Michelle Jia and Kha Le for their contributions to this work. **Disclosures** This study was funded by Agios Pharmaceuticals, Inc. in collaboration with Bristol-Myers Squibb. YC, FY, CA, SN, MC, MH, and HY: Agios – employee and stockholder. LH and BF: Agios – employee and stockholder at time of this study. Editorial assistance was provided by David Pertab, PhD, Excel Medical Affairs, Glasgow, UK, and supported by Agios. **References** 1. Medeiros BC et al. *Nature* 2017;31:272–81. 2. Dang L et al. *Nature* 2009;462:739–44. 3. Ward PS et al. *Cancer Cell* 2010;17:225–34. 4. Lu C et al. *Nature* 2012;483:474–8. 5. Saha SK et al. *Nature* 2014;513:110–4. 6. Xu W et al. *Cancer Cell* 2011;19:17–30. 7. DiNardo CD et al. *N Engl J Med* 2018;378:2386–98. 8. Amalangelo MD et al. *Blood* 2017;130:732–41. 9. Fan B et al. *Invest New Drugs* 2020;38:433–44. 10. Fan B et al. *Cancer Chemother Pharmacol* 2020;85:959–68. 11. Stein EM et al. *Blood* 2017;130:722–31.