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

EP620

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BACKGROUND

- Isocitrate 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 differentiation[4–6]
- 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 m*IDH1* or m*IDH2*, respectively

OBJECTIVES

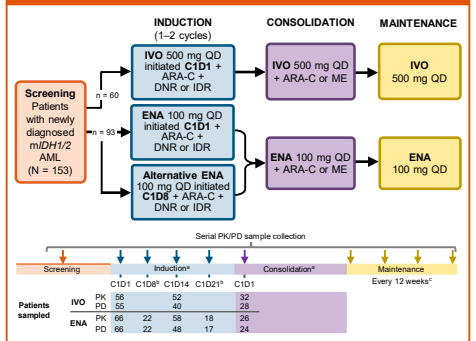
- To characterize the plasma PK profiles of IVO and ENA given in combination with intensive induction and consolidation chemotherapy for the treatment of patients with newly diagnosed AML
- To evaluate the PK/PD relationships of IVO and ENA given in combination with intensive induction and consolidation 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 m*IDH1* or m*IDH2* 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)

Figure 1. Study design and sampling schedule



[a]During induction and consolidation, sample collection occurred pre dose and at 0.5, 2, 4, 6, 8, and 24 hr post dose
[b]Sampling for alternative ENA schedule (initiated C1D8) only
[c]Pre dose sampling only
ARA-C = cytarabine; DNR = daunorubicin; IDR = idarubicin; ME = mitoxantrone with etoposide; QD = once daily

- 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 (AUC_{0-24}), 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

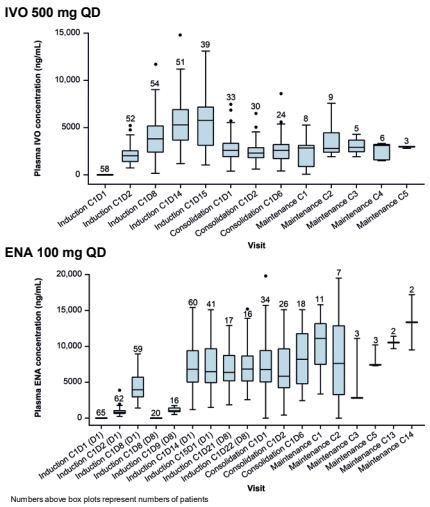
RESULTS (CONTINUED)

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

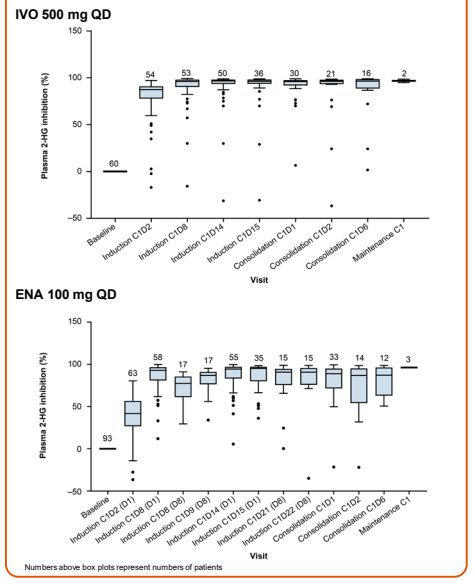
[a]PK/PD parameters for IVO at induction C1D14
[b]PK/PD parameters for combined ENA schedules at induction C1D14 and C1D21
[c]For standard ENA schedule at induction C1D14
[d]2-HG inhibition for alternative ENA schedule at C1D21 was 82.6% (CV 31.9%; n = 18)
CV = coefficient of variation; T_{max} = time 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)

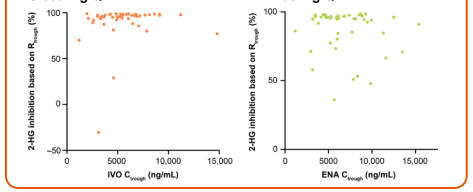
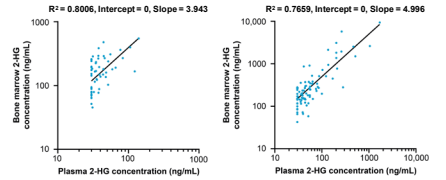


Figure 5. Comparisons of 2-HG concentrations in bone marrow and plasma after oral doses of IVO or ENA in combination with chemotherapy



[a]Excludes one outlier with unexpectedly high bone marrow 2-HG level at induction C1D14 that exceeded the baseline level

CONCLUSIONS

- **When combined with intensive induction and consolidation chemotherapy in patients with newly diagnosed m*IDH1/2* AML, IVO and ENA demonstrated PK profiles similar to those observed with their use as single agents,[10,11] 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**

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