IDH1 mutation detection in plasma circulating tumor DNA (ctDNA) and association with clinical response in patients with advanced intrahepatic cholangiocarcinoma (ICC) from the phase 3 ClarIDHy study

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BACKGROUND

- Somatic mutations of isocitrate dehydrogenase 1 (*IDH1*) result in neomorphic catalytic activity, leading to the conversion of α-ketoglutarate to D(−)-2-hydroxyglutarate (2-HG)[1]
  - Accumulation of 2-HG contributes to tumor initiation and progression through epigenetic dysregulation and a block in cellular differentiation[2–4]
- Mutations in *IDH1* are commonly found in cholangiocarcinoma (CC), with higher incidence (~13%) among intrahepatic CC (ICC) cases[5]
- The mutant IDH1 (mIDH1) inhibitor ivosidenib (IVO; AG-120) has been evaluated as monotherapy in CC across two clinical studies (phase 1 and phase 3)
- In the ongoing, global, phase 3 ClarIDHy study evaluating IVO vs placebo (PBO) in patients with nonresectable or metastatic m*IDH1*-CC (ClarIDHy, ClinicalTrials.gov NCT02989857):[6]
  - IVO demonstrated a favorable safety profile
  - Progression-free survival (PFS) for IVO was significantly improved relative to PBO, with a hazard ratio (HR) of 0.37 (95% CI 0.25, 0.54); p < 0.001
  - For IVO, 6-month and 12-month PFS rates were 32% (95% CI 23%, 42%) and 22% (95% CI 13%, 32%), respectively; no patients in the PBO group were progression free for > 6 months
- The emergence of actionable mutations in CC, including *IDH1*, highlights the relevance of molecular testing in this disease
  - Tissue-based genomic profiling remains the gold standard for personalized therapy in this indication; however, CC tumors are not easily accessible, and biopsies often yield suboptimal tumor cell content for genomic profiling[7]
- Previous work has demonstrated the feasibility of circulating tumor DNA (ctDNA) detection in patients with biliary tract cancer, including CC, and the mutational landscape of plasma appears similar to that of tissue, indicating that liquid biopsies are a reliable approach for genomic profiling at baseline as well as for disease monitoring upon treatment[8–10]
- Previous data from our group demonstrated the feasibility of m*IDH1* detection in plasma ctDNA from patients with CC enrolled in phase 1 studies of mIDH1 inhibitors, with high concordance with m*IDH1* status in tumor tissue[11]

OBJECTIVES

Baseline assessments

- To determine the concordance of m*IDH1* detection in plasma and formalin-fixed paraffin-embedded (FFPE) tumor tissue in a larger patient cohort
- To correlate plasma m*IDH1* variant allele frequency (VAF) with plasma 2-HG
- To explore the potential predictive value of m*IDH1* ctDNA levels for PFS

Longitudinal assessments

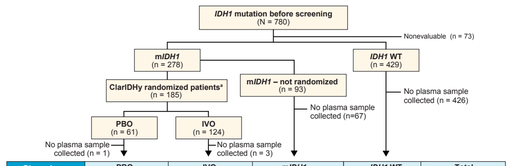
- To determine m*IDH1* ctDNA levels upon treatment with IVO or PBO
- To determine if *IDH1* mutation clearance in IVO-treated patients is associated with PFS

METHODS

- Archival FFPE tumor tissue samples were analyzed using Oncomine Focus Assay for prospective central confirmation of m*IDH1* with 2.5% sensitivity. Tumor tissue samples were collected from 0.3 months up to 7.5 years before randomization (median 3.7 months)
- Pretreatment plasma samples from all patients participating in screening were collected, and longitudinal samples from patients who were enrolled were obtained on Day (D) 1 of each treatment cycle. Blood samples were processed according to Sysmex plasma preparation instructions[12]
- BEAMing digital PCR (Sysmex) was used for the detection and quantification of five m*IDH1* alleles (R132C, R132H, R132L, R132S, and R132G) with 0.02% analytical sensitivity (0.04% for R132H)
- Baseline plasma levels of 2-HG were measured using a qualified liquid chromatography-tandem mass spectrometry method with a lower limit of quantitation of 30.0 ng/mL
- The clinical data cutoff date was 31Jan2019; for longitudinal m*IDH1* VAF analysis the biomarker data cutoff date was Mar2020

RESULTS

Figure 1. Screening plasma ctDNA sample collection flowchart and summary



Biomarkers dataset	PBO	IVO	m*IDH1*	*IDH1* WT	Total
	n = 60	n = 121	n = 26	n = 3	N = 210

*Number of patients as of the clinical data cutoff date (31Jan2019)
WT = wild type

Table 1. Concordance of m*IDH1* status in plasma and tissue

		Detection in plasma, n	
		Positive	Negative
Detection in tissue, n	Positive	192	15
	Negative	2	1

Screening m*IDH1* detection in plasma is highly concordant with mutations in tumor tissue

- The plasma ctDNA sample collection flowchart is shown in **Figure 1**
- Detection of m*IDH1* in plasma ctDNA was concordant with *IDH1* mutation status in tissue in 193 of 210 patients (92%) (**Table 1**)
  - 15 of 210 patients (7.1%) showed m*IDH1* detection in tissue but not in plasma
    - Tissue m*IDH1* VAF: median (range) 15.3% (3.8–37.0%)
    - Plasma m*IDH1* VAF: median (range) below detection limit (below detection limit, cutoff 0.02–0.04%)
  - 2 of 210 patients (0.95%) were deemed negative for m*IDH1* in tissue but showed detection in plasma
    - Tissue m*IDH1* VAF: 1.5% and 0.6% (tissue assay cutoff, 2.5%)
    - Plasma m*IDH1* VAF: 0.093% and 6.89% (plasma assay cutoff, 0.02–0.04%)
- The m*IDH1* allele detected was concordant, across all samples, with m*IDH1* detection in both tissue and plasma
- m*IDH1*-R132 allele distribution was similar between concordant and nonconcordant prescreening samples (**Table 2**)

Table 2. Similar m*IDH1*-R132 allele distribution in prescreening samples

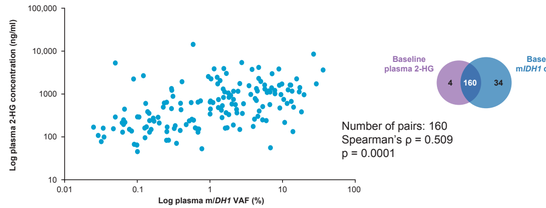
Allele	Concordant samples,* n (%)	Nonconcordant samples, n (%)
R132C	135 (70.3)	13 (76.5)
R132L	29 (15.1)	3 (17.6)
R132G	22 (11.5)	1 (5.9)
R132H	2 (1)	0
R132S	4 (2.1)	0
Total	**192**	**17**

*Only m*IDH1* positive samples included

Baseline circulating m*IDH1* VAF correlates with plasma 2-HG levels

- Spearman's rank correlation analysis demonstrated a moderate correlation between plasma m*IDH1* VAF and plasma 2-HG (**Figure 2**)
  - This correlation was maintained when samples were separated by treatment arm:
    - IVO, Spearman's ρ = 0.57; p < 0.0001 (n = 105)
    - PBO, Spearman's ρ = 0.36; p = 0.006 (n = 55)

Figure 2. Correlation between baseline plasma m*IDH1* VAF and plasma 2-HG levels



*Patients without baseline m*IDH1* detection in plasma were excluded from this analysis (n = 16). 15 out of 16 were m*IDH1* positive in tissue

Lower levels of baseline m*IDH1* ctDNA are associated with longer PFS in IVO-treated patients

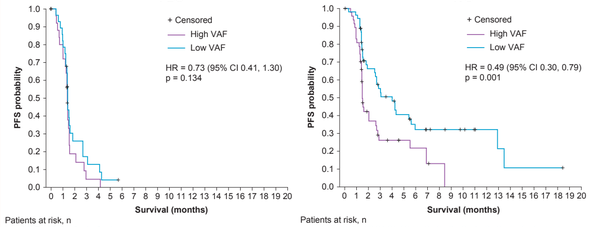
- Higher levels of baseline plasma m*IDH1* ctDNA were associated with shorter PFS in patients treated with IVO (**Table 3**, **Figure 3**)
  - No differences were found in the PBO control arm
  - Patients without baseline plasma m*IDH1* detection were excluded from this analysis (PBO, n = 2; IVO, n = 13) (**Figure 1**)
  - m*IDH1* VAF low vs high category was determined by calculating the median plasma VAF across all prescreening samples with m*IDH1* detection (n = 194)
    - VAF categories were defined as follows: low VAF, < 1.533; high VAF, ≥ 1.533
  - At screening, median VAF was similar in the PBO and IVO arms: 1.53 (n = 58) vs 1.41 (n = 108), respectively (p = 0.554)

Table 3. Median PFS in patients with low and high baseline plasma m*IDH1* VAF levels

	PBO		IVO	
	Low VAF n = 27	High VAF n = 29	Low VAF n = 49	High VAF n = 56
Median PFS (95% CI)	1.4 (1.3, 1.6)	1.4 (1.2, 1.6)	4.0 (2.5, 5.6)	1.5 (1.4, 2.6)
HR (95% CI)		0.73 (0.41, 1.30)		0.49 (0.30, 0.79)
p-value		0.134		0.001

m*IDH1* VAF category was determined by calculating the median plasma VAF across all prescreening samples (n = 194). VAF categories were defined as follows: low VAF, < 1.533; high VAF, ≥ 1.533

Figure 3. Association between baseline m*IDH1* ctDNA and PFS



Patients at risk, n
Low VAF 29 24 6 4 3 1
High VAF 27 20 4 1 1

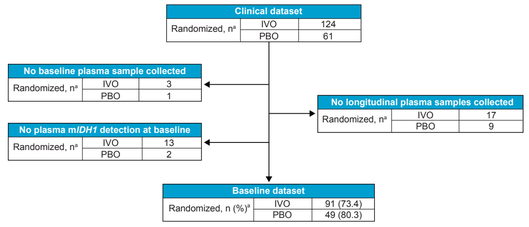
Patients at risk, n
Low VAF 56 52 30 24 21 16 11 9 8 7 6 4 3 2 1 1 1 1 1
High VAF 49 39 16 9 8 6 5 3 2

Patients without baseline plasma m*IDH1* detection were excluded from this analysis (2 PBO-treated patients and 13 IVO-treated patients)

m*IDH1* clearance was observed in a subset of IVO-treated patients

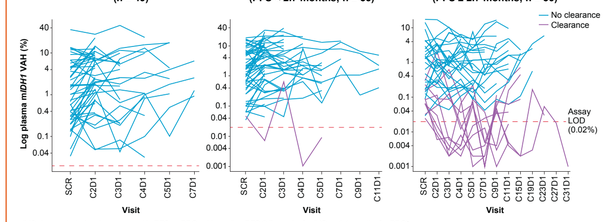
- The sample collection flowchart for longitudinal assessments is shown in **Figure 4**
- m*IDH1* clearance in plasma was found in IVO-treated but not in PBO-treated patients
  - m*IDH1* clearance was defined as m*IDH1* VAF below the assay's sensitivity for at least one on-treatment timepoint
- In IVO-treated patients, m*IDH1* clearance in plasma was found in 10 of 36 (27.8%) patients with PFS ≥ 2.7 months and 1 of 55 (1.8%) patients with PFS <2.7 months (**Figure 5**, **Table 4**)
  - IVO demonstrated an improvement in PFS vs PBO, with a median PFS of 2.7 months vs 1.4 months for IVO and PBO, respectively[6]
- Mutation clearance was achieved at Cycle (C) 3 D1 or earlier in seven of eleven (63.6%) patients
  - Early clearance might predict a favorable outcome
- Plasma m*IDH1* clearance in IVO-treated patients was associated with longer PFS (**Figure 6**)
  - In patients with clearance, median PFS was 12.9 months
  - In patients without clearance, median PFS was 2.6 months

Figure 4. ClarIDHy longitudinal plasma ctDNA sample collection flowchart and dataset summary



*As of clinical data cutoff date (31Jan2019)

Figure 5. m*IDH1* clearance in plasma in a subset of IVO-treated patients

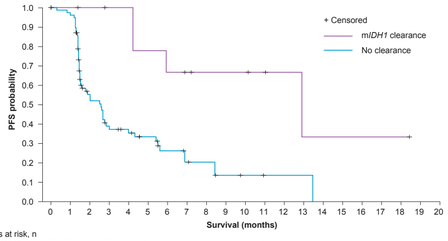


IVO demonstrated an improvement in PFS vs PBO, with median PFS 2.7 months for IVO vs 1.4 months for PBO[6]
15 of 55 patients with PFS < 2.7 months were censored, including the patient experiencing mutation clearance
LOD = limit of detection; SCR = screening

Table 4. Summary of m*IDH1* clearance in plasma

	PBO	IVO	
	All	PFS < 2.7 months	PFS ≥ 2.7 months
Patients with clearance, n / N (%)	0 / 49 (0%)	1 / 55 (1.8%)	10 / 36 (27.8%)

Figure 6. Association between m*IDH1* clearance in plasma and PFS in IVO-treated patients



Patients at risk, n
No clearance 80 75 34 23 20 15 10 7 6 3 2 1 1 1
mIDH1 clearance 11 11 10 9 9 7 6 5 4 4 4 3 2 1 1 1 1 1 1 1

Only IVO-treated patients were considered for this analysis, as none of the PBO-treated patients showed m*IDH1* clearance
This analysis should be interpreted with caution owing to the limited number of patients with mutation clearance observed

CONCLUSIONS

- **The results obtained from the ClarIDHy study reinforce the feasibility of m*IDH1*-R132 detection in plasma ctDNA from patients with ICC, showing a 92% concordance rate with detection in tumor tissue**
- **These data support the viability of using liquid biopsy for selecting patients in settings where tissue exhaustion can limit use of conventional methods**
- **Higher baseline plasma m*IDH1* levels were associated with shorter PFS in patients treated with IVO; no differences were found in the PBO control arm**
- **m*IDH1* clearance in plasma was observed in a subset of IVO-treated patients and was associated with longer PFS**

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Disclosures
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