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Abstract: 2275

Detection of *IDH1* mutations in plasma cell-free circulating tumor DNA (ctDNA) from patients with cholangiocarcinoma

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BACKGROUND

- Somatic mutations in the isocitrate dehydrogenase 1 gene (*IDH1*) are detected in 13–15% of cholangiocarcinoma (CC) cases overall and up to ~25% of intrahepatic CC cases.[1-3]
- The mutant IDH1 (mIDH1) enzyme has a gain-of-function activity, catalyzing the reduction of alpha-ketoglutarate to produce the oncometabolite D-2-hydroxyglutarate (2-HG),[4] which leads to epigenetic dysregulation and a block in cellular differentiation.[5-8]
- Ivosidenib (AG-120) is a first-in-class, oral, potent, reversible, targeted inhibitor of the mIDH1 protein,[9] and vorasidenib (AG-881) is an oral, potent inhibitor of both mIDH1 and mIDH2.
  - Both ivosidenib and vorasidenib have been evaluated in patients with CC in phase 1 studies (NCT02073994, NCT02481154).[10,11]
- Tissue-based genomic profiling continues to be the gold standard for personalized therapy in oncology. However, CC tumors are not easily accessible, and biopsies often yield suboptimal tumor cell content for genomic profiling.[12]
- Circulating tumor DNA (ctDNA) comprises DNA fragments released into the bloodstream by tumor cells undergoing apoptosis or necrosis; these fragments carry genetic and epigenetic alterations such as point mutations, copy number variations, and DNA methylation patterns that reflect the biology of the original tumor.[12,13]
- The evaluation of ctDNA is emerging as a promising tool not only for the genetic characterization of tumors but also for monitoring tumor dynamics in a noninvasive manner.
- Previous work has demonstrated the feasibility of ctDNA detection in patients with biliary tract cancer, including CC. The mutational landscape in 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.[14]

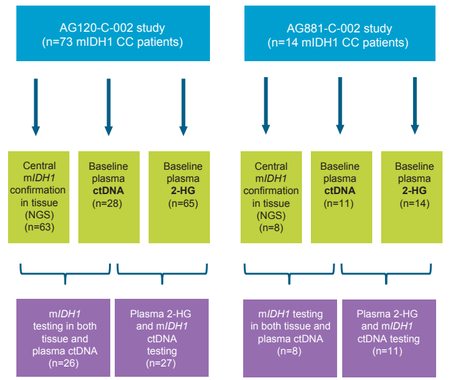
OBJECTIVES

- To examine the feasibility of detecting m*IDH1* in ctDNA from patients with m*IDH1* CC enrolled in ivosidenib and vorasidenib phase 1 studies.
- To explore the concordance of m*IDH1* detection in plasma ctDNA by digital PCR with that of tumor tissue using next-generation sequencing (NGS) assays.
- To study the association between baseline m*IDH1* variant allele frequency (VAF) from ctDNA and baseline plasma levels of 2-HG.

METHODS

- Baseline plasma samples were collected and processed according to Sysmex plasma preparation instructions.[15]
- BEAMing Digital PCR (Sysmex) was employed 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).
- Archival formalin-fixed paraffin-embedded samples or baseline fresh-frozen tumor tissues were analyzed using a FoundationOne and/or a Personalis® Accuracy and Content Enhanced (ACE) cancer research targeted panel for retrospective central confirmation of *IDH1* mutation.
- 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 and correlated with m*IDH1* VAF from plasma ctDNA.

Figure 1. Data availability for analysis



Analyses performed using samples pooled from both studies

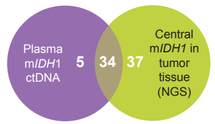
RESULTS

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

- m*IDH1* ctDNA was detected in 34 of 39 patients who had plasma collected (87.2%), demonstrating the feasibility of m*IDH1* detection in plasma from patients with CC.
- Detection of m*IDH1* in plasma ctDNA was concordant with *IDH1* mutation status in tissue in 31 of 34 patients (91.2%), including 30 double positive and one double negative (**Table 1**, **Figure 2**).
  - Concordance: 91.2% (31/34); positive-positive, negative-negative
  - Discordance: 8.8% (3/34), all three detected from tissue (NGS) but not plasma.
- Additional details for patients with discordant m*IDH1* detection between plasma ctDNA and tissue can be found in **Table 2**. Failure to detect m*IDH1* in ctDNA cannot be explained by low m*IDH1* VAF in tissue or low tumor burden at baseline.

Figure 2. Summary of baseline m*IDH1* detection in plasma versus tissue

Data availability



		Detection in plasma (no. of samples)	
		Positive	Negative
Detection in tissue (no. of samples)	Positive	30	3
	Negative	0	1

Table 1. Distribution of m*IDH1*-R132 alleles in tissue and plasma

IDH1 mutant allele	Tissue n=34	Plasma n=34
R132C	29	26
R132H	1	1
R132L	3	3
R132S	0	0
R132G	0	0
None detected	1	4

Summary of m*IDH1* allele frequency in patients who had both plasma ctDNA and central NGS tissue testing

Table 2. Patients with discordant m*IDH1* detection between plasma ctDNA and tissue

Subject no.	Study	Plasma m*IDH1* VAF, %	Central *IDH1* mutation	Central m*IDH1* VAF in tissue, %	Tissue biopsy location	Stage	Distant metastasis[a]	Measurable baseline disease[b], mm
1	AG120-C-002	None detected	R132C	13.6	Primary	II	No	64
2	AG120-C-002	None detected	R132C	26.6	Metastasis	IV	Yes	19
3	AG881-C-002	None detected	R132C	21.9	Primary	IV	No	108

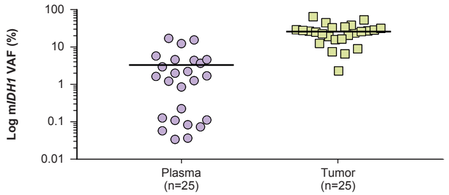
[a]Presence of distant metastases was determined by sponsor review of RECIST data
[b]Sum of longest diameters of the target lesions

Baseline m*IDH1* VAF in plasma is lower than in matching tumor tissue

- A total of 25 patients with fresh baseline tumor tissue and matching plasma samples collected immediately before treatment were analyzed. The interval between tissue and blood collection was <30 days.
- Archival tumor tissue samples and plasma ctDNA samples without m*IDH1* detection were excluded from this analysis.
- No significant correlation was found between baseline plasma m*IDH1* VAF and tumor m*IDH1* VAF (Spearman's ρ=0.23; p=0.268) (**Figure 3**).

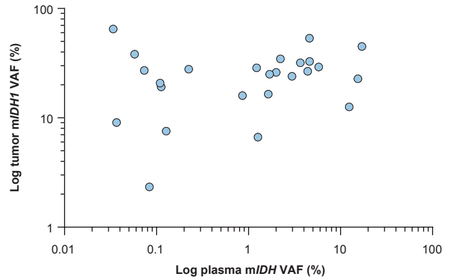
Figure 3. Baseline m*IDH1* VAF in plasma ctDNA and tumor tissue

Baseline tumor and plasma ctDNA m*IDH1* VAF



	Plasma ctDNA	Tumor tissue
Count	25	25
Median (range)	1.64 (0.03–17.13)	26.0 (2.30–65.00)
Mean (SD)	3.32 (4.79)	25.90 (14.43)

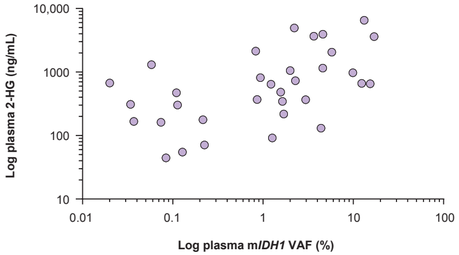
Baseline tumor and plasma ctDNA m*IDH1* VAF correlation



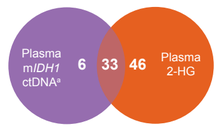
Association of baseline circulating m*IDH1* VAF with plasma 2-HG levels

- A total of 33 patients with positive m*IDH1* detection in ctDNA had matching plasma samples for 2-HG analysis.
- Spearman's rank correlation analysis demonstrated a significant correlation between both circulating biomarkers (Spearman's ρ=0.52; p=0.0016) (**Figure 4**).

Figure 4. Correlation of circulating m*IDH1* VAF levels with baseline plasma 2-HG



Data availability



[a]Plasma samples with no m*IDH1* detection in ctDNA were excluded from this analysis

CONCLUSIONS

- Our results demonstrate the feasibility of detecting m*IDH1*-R132 in plasma from patients with CC, with a 91.2% concordance rate with detection in tumor tissue.
- These results provide a rationale for exploring liquid biopsy-based testing methods when the feasibility of repeated biopsies or sample exhaustion limits the ability to detect actionable mutations through tissue-based NGS panels, which can be a major challenge for trial participation.

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Disclosures

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