A phase 1/2 trial investigating ivosidenib plus nivolumab and ipilimumab in patients with previously treated m*IDH1* CCA

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Robin Kate Kelley,[1] James M. Cleary,[2] Vaibhav Sahai,[3] Marina Baretti,[4] John Bridgewater,[5] Clement Daniel,[6] Camelia Gliser,[6] Ghassan K Abou-Alfa[7–9]

1. University of California, San Francisco, California, USA; 2. Dana-Farber Cancer Institute, Boston, Massachusetts, USA; 3. University of Michigan, Ann Arbor, Michigan, USA; 4. Johns Hopkins University, Baltimore, Maryland, USA; 5. University College Hospital, London, UK; 6. Servier BioInnovation, Boston, Massachusetts, USA; 7. Memorial Sloan Kettering Cancer Center, New York City, New York, USA; 8. Weill Medical College of Cornell University, New York City, New York, USA; 9. Trinity College Dublin, Dublin, Ireland.

Contact: Robin Kate Kelley, MD, katie.kelley@ucsf.edu

Background

- Cholangiocarcinomas (CCAs) are rare aggressive biliary tract cancers with few treatment options[1]
  - The isocitrate dehydrogenase-1 mutation (m*IDH1*) is found in approximately 14% of patients with intrahepatic CCA and is associated with an immunosuppressed tumor microenvironment[2,3]
- Ivosidenib (IVO), a first-in-class, oral, targeted, small-molecule inhibitor of mIDH1, is approved for the treatment of patients with previously treated locally advanced or metastatic m*IDH1* CCA[4]
- Pre-clinical studies suggest combining IVO with immune checkpoint inhibitors (ICI) may have synergistic anti-tumor activity in m*IDH1* CCA and data from several clinical studies testing PD-1 or PD-L1 inhibitors with anti-CTLA4 compare favorably with anti-PD-1 monotherapy data in patients with advanced biliary tract cancer[3,5,6]
- We developed a phase 1/2 study of IVO in combination with nivolumab (NIVO) and ipilimumab (IPI) in patients with previously treated nonresectable or metastatic m*IDH1* CCA with a Safety Lead-In (SLI) Phase and an Expansion Phase (NCT05921760)
  - Here, data from the SLI Phase are reported

Methods

SLI Phase Objectives: To evaluate the safety and tolerability of IVO in combination with NIVO 3 mg/kg IV infusion and IPI 1 mg/kg IV infusion Q3W for 4 doses followed by IVO at the recommended combination dose (RCD) and NIVO at 480 mg IV infusion Q4W and to determine the RCD of IVO

Expansion Phase Objectives: To assess the clinical activity of IVO in combination with NIVO and IPI using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) and to evaluate other efficacy endpoints, as well as the pharmacokinetics (PK) and pharmacodynamic (PD) effects of IVO when given in combination with NIVO and IPI

- This phase 1/2, multicenter, open-label study enrolled patients from the USA and UK

Key inclusion criteria:

- Age ≥18 years old
- Documented *IDH1* gene-mutated disease based on local testing procedure (R132C/L/G/H/S mutations variants tested)
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1
- Histopathological nonresectable or metastatic CCA diagnosis
- Disease progression or treatment intolerance following 1–2 prior gemcitabine or 5-fluorouracil based regimens
- At least one measurable lesion as defined by RECIST v1.1

Key exclusion criterion:

- Prior treatment with an IDH inhibitor or prior treatment with an ICI other than anti-PD-1/L1 therapies

Assessments and endpoints

Primary endpoints for

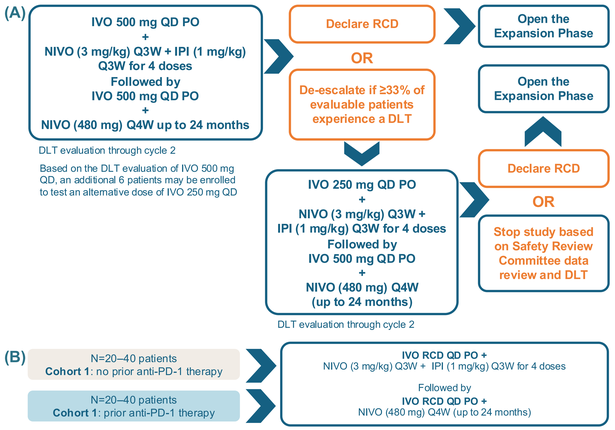
- Dose-limiting toxicities (DLTs) during the first two treatment cycles
- AEs, AESIs, and SAEs

Secondary endpoints for

- Plasma concentrations and PK parameters
- Plasma 2-HG concentration

- Objective radiographic response was assessed per RECIST v1.1 by the investigator every 6 weeks for the first two assessments, and then every 8 weeks
- Secondary endpoints assessed the PK and PD effects of IVO when given in combination with NIVO and IPI

Figure 1. Study design overview – (A) Safety Lead-In Phase and (B) Expansion Phase



Results

- The SLI Phase enrolled 7 female patients, all with iCCA (**Table 1**); all 7 developed immune-mediated adverse events (IMAEs), including intolerable rashes arising within a median of 12 days (10–41 days) of study treatment initiation; 3/7 (42.9%) developed immune-mediated pyrexia (**Table 2**)
- All 4 patients in the IVO 500 mg cohort developed IMAEs, including rashes, diarrhea and pyrexia, leading to dose de-escalation in IVO to 250 mg QD (**Table 2**)
  - All 3 patients enrolled in the IVO 250 mg cohort developed IMAEs
- All events of immune-mediated rash required dose modifications and included 3 nonserious and 3 serious grade 3 events, with 1 DLT in the IVO 250 mg cohort
- The most commonly reported non-IMAEs related to any of the study drugs were dyspnea, nausea and fatigue occurring in 3 (42.9%) patients each (**Table 3**)
- Based on IMAE frequency, onset, and outcome, and in the absence of documented radiographic responses (overall best response: 3 patients with stable disease and 4 patients with progressive disease), further recruitment was stopped after completion of the SLI cohort

Table 1. Baseline characteristics

Characteristic, n (%)[a]	IVO + NIVO (3 mg/kg) + IPI (1 mg/kg)		
	IVO (500 mg) (N=4)	IVO (250 mg) (N=3)	Overall (N=7)
Age, mean (SD), years	60.8 (20.61)	49.3 (15.37)	55.9 (18.12)
Female sex	4 (100.0)	3 (100.0)	7 (100.0)
Race: Asian/White	1 (25.0)/3 (75.0)	0/3 (100.0)	1 (14.3)/6 (85.7)
IDH1 mutation			
R132C	2 (50.0)	3 (100.0)	5 (71.4)
R132L	2 (50.0)	0	2 (28.6)
ECOG PS 0/1	0/4 (100.0)	2 (66.7)/1 (33.3)	2 (28.6)/5 (71.4)
Prior ICI treatment: Yes/No	4(100.0)/0	1 (33.3)/2 (66.7)	5(71.4)/2(28.6)

[a]All characteristics shown as n (%) aside from age.

Results, cont.

Table 2. Immune-mediated adverse events

Preferred term	IVO + NIVO (3 mg/kg) + IPI (1 mg/kg)					
IMAE, n (%)	IVO (500 mg) (N=4)		IVO (250 mg) (N=3)		Overall (N=7)	
Any IMAE[a]	G1/G2 0	G3/G4 4 (100)	G1/G2 0	G3/G4 3 (100)	G1/G2 0	G3/G4 7 (100)
Dermatitis	1 (25.0)	3 (75.0)	0	3 (100.0)	1 (14.3)	6 (85.7)
Pyrexia	2 (50.0)	0	1 (33.3)	0	3 (42.9)	0
Diarrhea	2 (50.0)	0	0	1 (33.3)	2 (28.6)	1 (14.3)
Pruritus	2 (50.0)	1 (25.0)	0	0	2 (28.6)	1 (14.3)
Fatigue	1 (25.0)	0	1 (33.3)	0	2 (28.6)	0
Cough	0	0	1 (33.3)	0	1 (14.3)	0
Burning sensation	0	0	1 (33.3)	0	1 (14.3)	0
Hepatitis	0	1 (25.0)	0	0	0	1 (14.3)
Lung disease	0	0	1 (33.3)	0	1 (14.3)	0

[a]If a patient experienced multiple occurrences of the same AE, only the event with the highest grade was considered.

Table 3. Treatment-emergent related adverse events[a] in ≥2 patients (overall)

Preferred term	IVO + NIVO (3 mg/kg) + IPI (1 mg/kg)		
AE, n (%)	IVO (500 mg) (N=4)	IVO (250 mg) (N=3)	Overall (N=7)
Any AE	4 (100)	3 (100)	7 (100)
Any grade ≥3	4 (100)	3 (100)	7 (100)
Dyspnea	2 (50.0)	1 (33.3)	3 (42.9)
Nausea	2 (50.0)	1 (33.3)	3 (42.9)
Fatigue	3 (75.0)	0	3 (42.9)
Diarrhea	2 (50.0)	0	2 (28.6)
Cough	1 (25.0)	1 (33.3)	2 (28.6)
Decreased appetite	2 (50.0)	0	2 (28.6)
Dizziness	1 (25.0)	1 (33.3)	2 (28.6)
Dry mouth	2 (50.0)	0	2 (28.6)
Taste disorder	2 (50.0)	0	2 (28.6)

[a]Not including IMAEs.

Pharmacokinetics/pharmacodynamics

- IVO plasma exposures after multiple dose administration of IVO at 500 mg QD or 250 mg QD in the PK analysis set (N=7) were largely comparable to previously observed exposures in CCA participants from phase 1 and phase 3 studies assessing IVO alone[7,8]
- 4/7 (57.1%) of patients had elevated baseline plasma 2-HG; mean 2-HG inhibition was 89.4% (CV: 3.30%) after 1 cycle of IVO in all 4 patients
- NIVO/IPI anti-drug antibody (ADA) testing at baseline and on treatment did not identify any confirmed positive ADAs, although these analyses were limited by the small sample size
- Due to the limited number of evaluable baseline (n=4) and paired (n=2) biopsies, RNA/DNA analyses were inconclusive

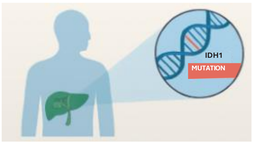
Conclusions

- **While no new safety signals were specifically identified for IVO during this study, IMAEs, including immune-mediated rashes, were observed in 100% of patients; consequently, the decision was made to stop the study after completion of the SLI cohort**
- **Further studies to optimize mIDH1 inhibition in CCA are ongoing, including IVO plus durvalumab + gemcitabine/cisplatin in front-line CCA (NCT06501625)**

Table and Figure abbreviations: AE, adverse event; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; G, grade; iCCA, intrahepatic cholangiocarcinoma; ICI, immune checkpoint inhibitors; IDH1, isocitrate dehydrogenase-1; IMAE, immune-mediated adverse events; IPI, ipilimumab IVO, ivosidenib; n, number of patients; NIVO, nivolumab; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PO, per os; Q3W, every 3 weeks; Q4W, every 4 weeks; QD, once daily; RCD, recommended combination dose; SD, standard deviation.

Patient summary

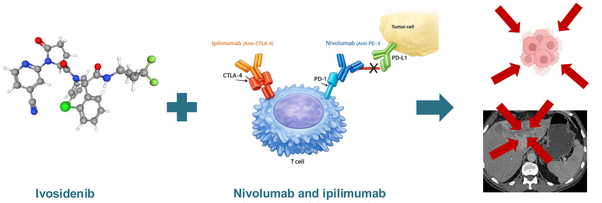
Background and rationale



- Ivosidenib (IVO) is an oral small-molecule inhibitor currently approved for patients with previously treated cholangiocarcinoma (CCA) harboring a mutation in the *IDH1* gene (m*IDH1*)
- Preclinical data suggest that combining IDH1 inhibition with other drugs known as immune checkpoint inhibitors could shrink the tumor more than if they were given separately
- Therefore, researchers initiated a study to evaluate the combination of IVO with two immune checkpoint inhibitors, ipilimumab (IPI) and nivolumab (NIVO)

Study methodology

- The multicenter, open-label trial enrolled patients with unresectable or metastatic m*IDH1* CCA who had progressed on or were intolerant to one or two prior lines of therapy
- The primary focus of this initial phase was to assess safety and dose-limiting toxicities (DLTs)



Ivosidenib (mIDH1 inhibitor) | Nivolumab and ipilimumab (immune cell activators) | Tumor shrinkage

Results

The study enrolled 7 patients across two dose cohorts:

- Cohort 1 (IVO 500 mg): Four patients received the standard IVO dose alongside IPI and NIVO. All 4 developed side effects related to the immune system, especially intolerable rashes
- Cohort 2 (IVO 250 mg): Due to the initial toxicity, the IVO dose was reduced. However, all 3 patients in this cohort also developed IMAEs, including intolerable rashes
- Across both cohorts, 100% of patients experienced side effects related to the immune system. These complications required dose modifications, and one DLT was reported in Cohort 2

Conclusions

- **No new side effects were discovered for ivosidenib when used in this specific triple-combination, specifically, the frequency and severity of side effects related to the immune system, including rashes**
- **However, researchers decided to end the study after completion of the Safety Lead-In cohort due to these side effects**
- **Research continues into other drug combinations, such as ivosidenib with other types of immune cell activator drugs and chemotherapy (NCT06501625), to further optimize outcomes for patients with m*IDH1* CCA**

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