A First-in-Human Phase 1 Study of LY3410738, a Covalent Inhibitor of Mutant IDH1 and IDH2, as Monotherapy and in Combination with Cisplatin and Gemcitabine in Advanced IDH-mutant Cholangiocarcinoma

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Background

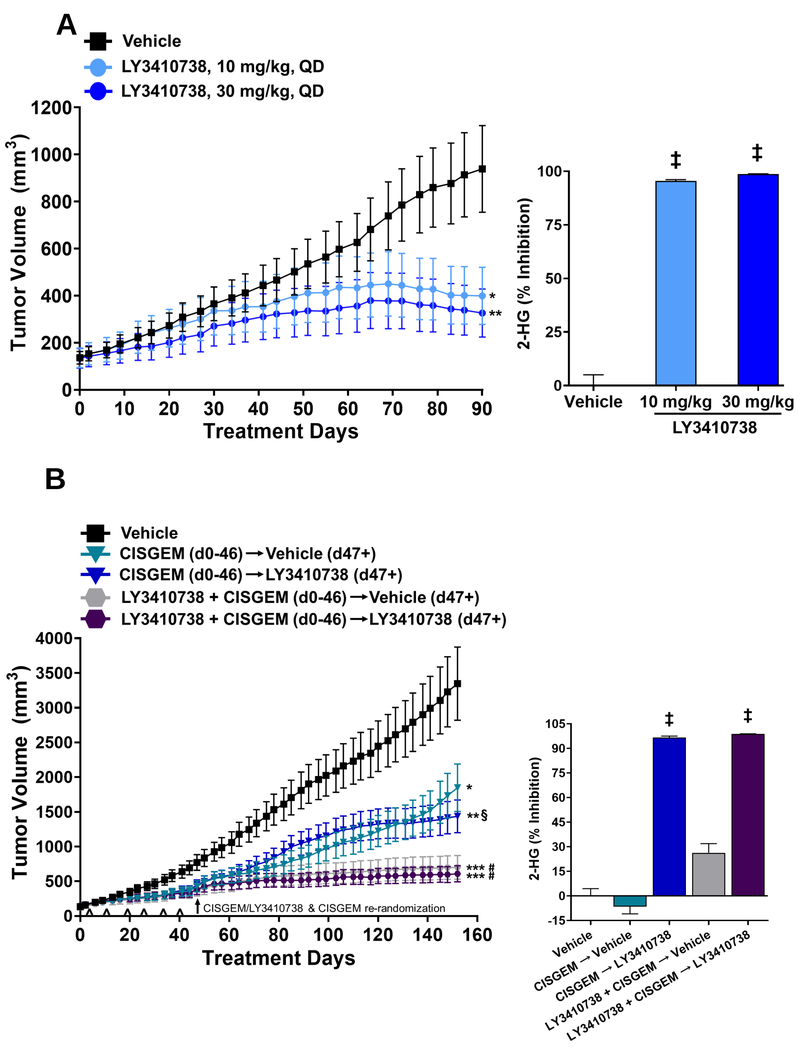
- Isocitrate dehydrogenase 1 and 2 (IDH1/2) are mutated in 15 - 20% of intrahepatic cholangiocarcinoma (CCA).[1] Cisplatin and gemcitabine (CISGEM) are the standard first line chemotherapy backbone with immune checkpoint inhibitors for advanced CCA[2-3]
- LY3410738 is an oral, potent, selective, dual inhibitor of IDH1/2 mutations (IDH1/2m)
- LY3410738 binds covalently at a novel binding site, enabling continued potency in preclinical models in the setting of second site IDH resistance mutations
- Previously we disclosed that in LY3410738 monotherapy, dose proportional increase in exposure from 25 mg - 600 mg QD was observed and majority of the patients (IDH1m R132, IDH2m R172) achieved D-2-HG inhibition at total daily dose ≥150 mg.[4] Thus, LY3410738 doses 400 mg QD and 300 mg BID were chosen in combination with CISGEM
- Here, we present translational *in vivo* findings and data from the first-in-human phase 1 study of LY3410738 as monotherapy and with CISGEM in advanced IDH1/2m CCA (NCT04521686)

Study Design

- In preclinical IDH1m CCA PDX studies, treatment was initiated following randomization when tumor volumes reached 100 - 150 mm^3. Tumor volumes and body weights were measured semiweekly
- In the phase 1 study, dose escalation utilized a 3+3 design and evaluated monotherapy in dose levels ranging from a total daily dose of 25 - 600 mg; key eligibility criteria included the presence of locally advanced or metastatic, and relapsed/ refractory (R/R) IDH1/2m CCA. Prior treatment with an IDH1 inhibitor was allowed
- Dose expansion evaluated LY3410738 (400 mg QD and 300 mg BID) in combination with CISGEM in treatment naïve advanced IDH1/2m CCA. CISGEM was planned for a total of 6-8 cycles, and treatment beyond 8 cycles may be permitted. Up to 2 cycles of CISGEM as the first-line therapy while waiting for molecular testing results were allowed
- Data cutoff date was November 1, 2022

Fig 1. *In vivo* efficacy of LY3410738

- A - LY3410738 demonstrated single agent efficacy
- B - When combined with CISGEM during the simulated chemo induction phase followed by LY3410738 maintenance treatment, superior tumor growth inhibition over CISGEM alone was observed (ΔT/C=18%)
- ≥96% 2-HG inhibition was achieved in all groups on LY3410738 at study termination



IDH1m (R132C) CCA PDX model CH-17-0800 in nude mice were used. Data are mean ± SEM. *p≤0.05, **p≤0.01, ***p≤0.001 RM ANOVA, Log 10 volume and spatial power covariance structure compared with vehicle (■); §p≤0.01, #p<0.001 compared with CISGEM → vehicle(▼). ‡p<0.001 compared with vehicle, Dunnett's Method. ^CISGEM dosing on days 5, 12, 19, 26, 33, 40.

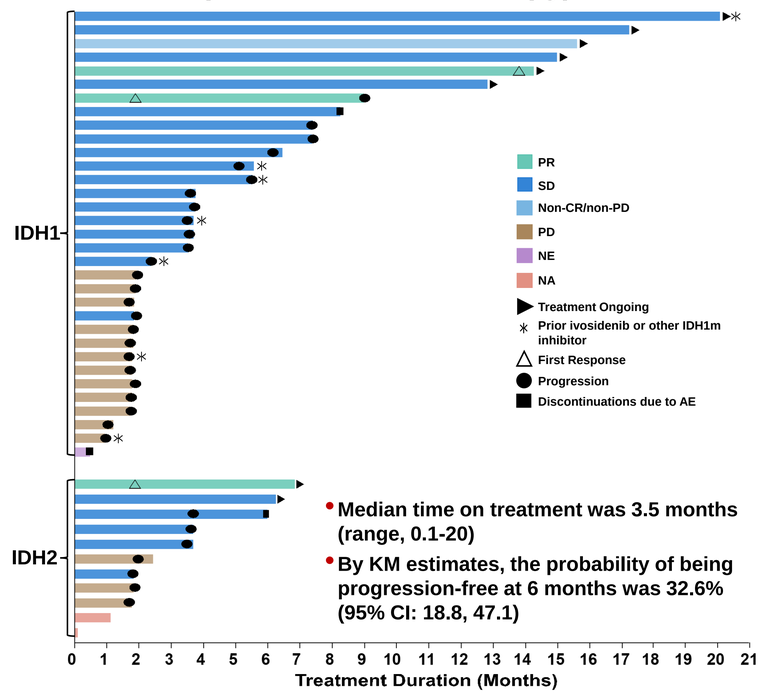
Results

Table 1. Patient and Disease Characteristics

Characteristic	Relapsed/Refractory CCA (LY3410738 monotherapy) N=45	Treatment naïve CCA (LY3410738 + CISGEM) N=13
Median age, years (range)	57 (28-78)	64 (51-77)
Sex, n (%)		
Male	19 (42)	4 (31)
Female	26 (58)	9 (69)
Race, n (%)[a]		
Asian	24 (53)	6 (46)
Caucasian	19 (42)	7 (54)
ECOG PS, n (%)		
0	21 (47)	8 (62)
1	24 (53)	5 (39)
Median number of lines of prior systemic therapy (range)	2 (1-7)	-
Prior IDH1 inhibitor therapy, n (%)	7 (16)	-
Site of origin, n (%)		
Intrahepatic	43 (96)	13 (100)
Extrahepatic	1 (2)	-
Unknown	1 (2)	-
IDH mutation status, n (%)		
IDH1 R132	33 (73)	11 (85)
IDH2 R172	12 (27)	2 (15)

[a]1 patient on LY3410738 monotherapy reported 'other' as race and 1 patient's race was unknown.

Efficacy
Relapsed/Refractory Cholangiocarcinoma (LY3410738 Monotherapy)



- **Median time on treatment was 3.5 months (range, 0.1-20)**
- **By KM estimates, the probability of being progression-free at 6 months was 32.6% (95% CI: 18.8, 47.1)**

Safety

Monotherapy and combination therapy:

- **No DLT was observed and MTD not reached**
- **No dose/toxicity relationship observed**
- **No treatment-related death observed**

Table 2. TEAEs Reported in ≥10% in LY3410738 Monotherapy

All Doses and Patients (N=45)				
	Treatment-Emergent AEs, n (%)		LY3410738-Related AEs, n (%)	
Adverse Event	Any grade	Grade ≥3	Any grade	Grade ≥3
Nausea	13 (29%)	-	8 (18%)	-
Decreased appetite	12 (27%)	1 (2%)	4 (9%)	-
Vomiting	11 (24%)	-	5 (11%)	-
Pyrexia	8 (18%)	-	-	-
Anemia	6 (13%)	1 (2%)	2 (4%)	-
AST increased	6 (13%)	-	1 (2%)	-
Constipation	6 (13%)	-	-	-
Diarrhea	6 (13%)	1 (2%)	2 (4%)	-
Blood creatinine increased	5 (11%)	-	2 (4%)	-

AST, aspartate aminotransferase

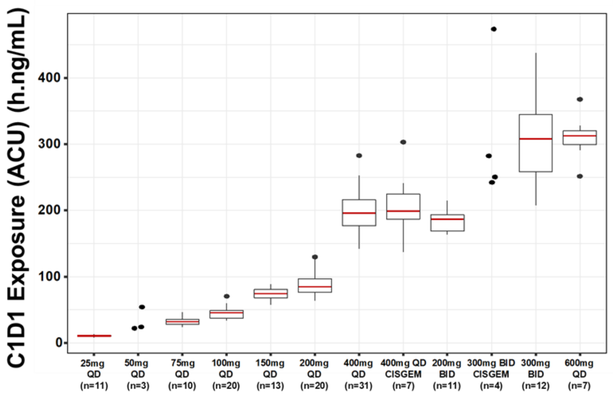
- **Monotherapy: Median duration of LY3410738 exposure was 3.5 months (range, 0.1-20)**
- **1 patient (2%) dose reduced, and 1 patient (2%) discontinued due to LY3410738-related adverse event**

Table 3. TEAEs Reported in ≥15% in LY3410738 + CISGEM

All Doses and Patients (N=13)				
	Treatment-Emergent AEs, n (%)		LY3410738-Related AEs, n (%)	
Adverse Event	Any grade	Grade ≥3	Any grade	Grade ≥3
Anemia	7 (54%)	4 (31%)	-	-
Platelet count decreased	7 (54%)	5 (39%)	-	-
Nausea	6 (46%)	1 (8%)	4 (31%)	1 (8%)
Decreased appetite	5 (39%)	-	1 (8%)	-
Neutrophil count decreased	5 (39%)	5 (39%)	1 (8%)	1 (8%)
Constipation	4 (31%)	-	-	-
Vomiting	3 (23%)	-	2 (15%)	-
Fatigue	3 (23%)	-	1 (8%)	-
COVID-19	3 (23%)	-	-	-
WBC count decreased	3 (23%)	1 (8%)	-	-
Neutropenia	3 (23%)	3 (23%)	-	-
Thrombocytopenia	3 (23%)	2 (15%)	-	-

- **Combination therapy: Median duration of LY3410738 exposure was 6 months (range, 2-9); Median number of CISGEM cycles was 6 (range, 2-11)**
- **No patient dose reduced LY3410738, or discontinued due to LY3410738-related adverse event**

Fig 2. Pharmacokinetics[a]



Red line – 50th percentile
Lower/upper hinges – 25th/75th percentiles
Whiskers - 1.5* IQR
Dots – outlying points beyond end of whiskers

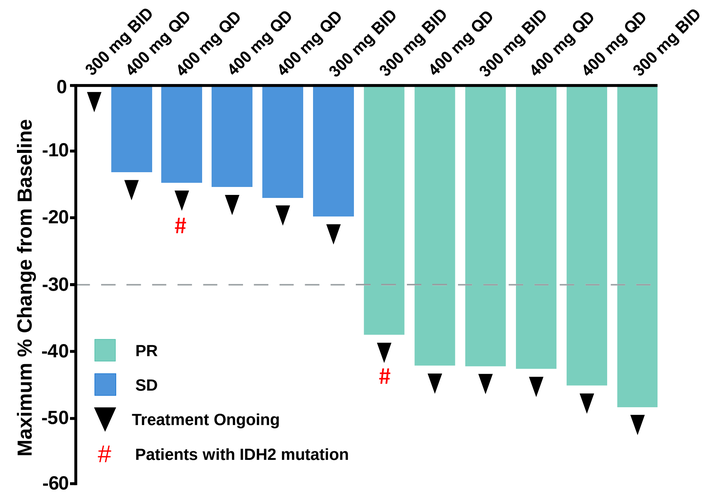
[a]Data generated from LOXO-IDH-20001 (AML) and LOXO-IDH-20002 (solid tumors) studies

- **Rapid absorption and short half-life (1.5 – 3 h). No accumulation with repeat dosing**
- **PK/PD profiles of the combination therapy were consistent with LY3410738 monotherapy[4]**

Best Overall Response[a]	IDH1 CCA (n=33)	IDH2 CCA (n=11)	Total (n=44)[d]
ORR[b], %	6%	9%	7%
PR, n (%)	2 (6%)[c]	1 (9%)	3 (7%)
SD, n (%)	17 (52%)	5 (46%)	22 (50%)
mPFS, months (95% CI)	3.6 (1.9, 6.1)	3.6 (1.7, NE)	3.6 (1.9, 5.1)
Median follow-up, months (95% CI)	13.8 (11.2, NE)	5.5 (0.03, NE)	13.8 (11.2, 15.4)

[a]Response was investigator-assessed per RECIST v1.1 in efficacy evaluable patients who are those who had at least 1 post-baseline response assessment or had discontinued treatment before the first post-baseline response assessment. [b]ORR includes best response of CR+PR. [c]1 patient had unconfirmed PR which was confirmed after the data cutoff date. [d]1 IDH2 R/R CCA patient was not efficacy evaluable because the patient enrolled 5 days before the data cutoff date (October 27, 2022). This patient is not included in the swimmer plot.

Treatment naïve Cholangiocarcinoma (LY3410738 + CISGEM)



Best Overall Response[a]	LY3410738 + CISGEM (N=13)[c]
ORR[b], %	46%
PR, n (%)	6 (46%)[d]
SD, n (%)	6 (46%)
mPFS, months (95% CI)	NE (5.9, NE)
Median follow-up, months (95% CI)	4.1 (1.9, 7.8)

[a]Response was investigator-assessed per RECIST v1.1 in efficacy evaluable patients who are those who had at least 1 post-baseline response assessment or had discontinued treatment before the first post-baseline response assessment. [b]ORR includes best response of CR+PR. [c]1 patient had SD within 39 days of C1D1, which was not deemed to be BOR of SD and excluded from the above waterfall plot and table. SD was confirmed after the data cutoff date. [d]3 patients had unconfirmed PR which were confirmed after the data cutoff date

Conclusions

- LY3410738 in combination with CISGEM demonstrated a favorable safety profile and preliminary efficacy in treatment naïve locally advanced or metastatic IDH1/2m CCA
- RP2D evaluation is ongoing
- A separate cohort is evaluating LY3410738 in combination with durvalumab

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Presenter Information

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ESMO-GI Annual Meeting; Barcelona, Spain; June 28 – July 1, 2023

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