4092 Phase 1 Expansion Study of FF-10832 (Liposomal Gemcitabine) Antitumor Activity in Patients with Advanced Biliary Carcinomas

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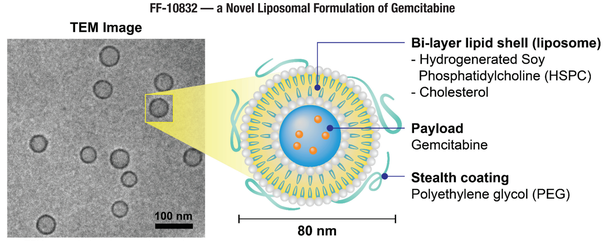
Liposomal Encapsulation Provides Stable, Consistent Delivery of Gemcitabine

FF-10832 — a Novel Liposomal Formulation of Gemcitabine

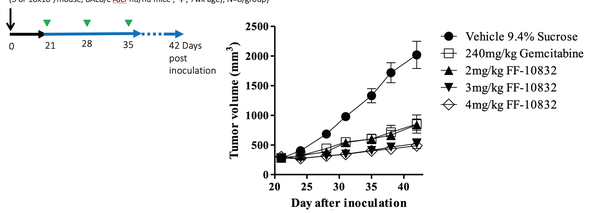


TEM: transmission electron micrograph

- The FF-10832 liposome formulation is stable for >3 years when stored at 2–8°C
- Stable liposome encapsulation increases the circulating half-life of gemcitabine (~ 30 hours) and enhances drug delivery via macrophage uptake with subsequent release and accumulation in tumor tissue

Pre-clinical Activity of FF-10832 in Biliary Carcinoma

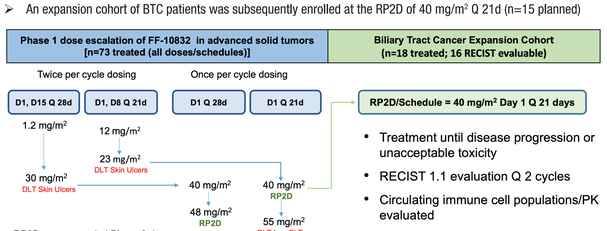
- Improved in vivo activity has been demonstrated with FF-10832 compared to gemcitabine in both gemcitabine-sensitive and resistant tumor models[1], including activity demonstrated in a human bile duct cancer model



- FF-10832 has demonstrated immune activation in the TME that is distinct from gemcitabine, with ability to enhance effects of immune checkpoint blockade[2-5]
- Marrow-sparing biodistribution has been demonstrated, contributing to a favorable safety profile[1]

Study Design: Data Are Presented For Biliary Tract Expansion (BTC) Cohort

- The first in human dose finding trial (NCT03440450)[3] demonstrated a tolerable safety profile with once per cycle dosing; anti-tumor activity was observed in heavily pre-treated patients who progressed on prior gemcitabine
- In dose finding, two gallbladder carcinoma patients were evaluable; both were treated at 40 mg/m^2 D 28d and had progressed on gemcitabine therapy; one maintained a PR for 72 weeks, one progressed after 2 cycles
- An expansion cohort of BTC patients was subsequently enrolled at the RP2D of 40 mg/m^2 Q 21d (n=15 planned)



- Treatment until disease progression or unacceptable toxicity
- RECIST 1.1 evaluation Q 2 cycles
- Circulating immune cell populations/PK evaluated

Key Entry Criteria of Biliary Tract Expansion Cohort

- ≥18 years of age with metastatic/unresectable cholangiocarcinoma or gallbladder cancer
- Progressed on gemcitabine/cisplatin or gemcitabine-based therapy
- No more than 3 prior lines of systemic therapy
- RECIST 1.1 evaluable
- ECOG status of 0 or 1; life expectancy of ≥ 3 months
- Hgb ≥9 g/dL; Plts ≥100 K/μL; ANC ≥1.5 K/μL
- Creatinine ≤1.5X ULN; bilirubin ≤2X ULN; AST/ALT ≤2.5X ULN (5X ULN with hepatic metastases); albumin >3 g/dL
- Serious cardiac condition (NYHA class III or IV) is exclusionary (QTc ≤450/470 msec for male/female)

Baseline Demographics & Prior Therapy of Treated BTC Patients

(21 consented, 18 enrolled and treated; 16 evaluable for RECIST response)

	N=18 treated
Median age, years (range)	68 (34–79)
Male/female, n	12 / 6
Biliary tract cancer type/location, n	
Cholangiocarcinoma (CCA)	17
Intrahepatic (iCCA)	10
Extrahepatic	7
Perihilar (pCCA)	6
Distal (dCCA)	1 (ampullary)
Gallbladder adenocarcinoma	1
Screening ECOG performance status, n, (0 / 1)	3 / 15
Prior therapy	
No. of prior treatment regimens, median (range)	2 (1–3)
Best response to most recent cancer therapy, n	CR (0), PR (0), SD (5), PD (9), UNK (4)
Prior gemcitabine therapy, n (%)	18 (100%)
Prior PD-1/L1 therapy , n (%)	8 (44%)
Targetable mutations / prior treatment	FGFR2 / tinengotinib (Patient 9) BRCA1 / olaparib (Patient 18) IDH1 / ivosidenib (Patient 4)

Dose Intensity & Safety (n=18 treated)

- Median dose intensity was 90.6% (62.5–100%); median cycles received was 3.5 (1–28)
- The 2 patients still on study for 9.2 months (12 cycles) and 23.3 months (28 cycles) required dose reduction to 23 mg/m^2 by cycle 3 and cycle 21, respectively, due to fatigue
- 3 patients had dose interruption due to infusion related reactions at cycle 1; all dosing was completed
- Collectively, the most common related AEs were gastrointestinal (↓ appetite, nausea and vomiting)
- Treatment-related pyrexia was observed in ~40% of patients (1 grade 3); grade 1 pyrexia SARs (n=2) were accompanied by abdominal pain and prompted hospitalization for fever work-up 1–2 days after dosing; these findings may be associated with delayed infusion reactions
- Fatigue and muscular weakness were observed in ~30% of patients; 3 patients experienced Grade 3 muscular weakness, one that required a dose reduction at cycle 5 (Patient 14)
- Minimal hematologic toxicity was observed; no neutropenia was observed
- No grade 4 toxicity was observed

Treatment-related AEs in ≥3 Patients

	n=18 treated, n (%)*	
	All	Grade 3**
Decreased appetite	8 (44.4)	
Nausea	7 (38.9)	
Pyrexia	7 (38.9)	1 (5.6)
Fatigue	6 (33.3)	1 (5.6)
Vomiting	6 (33.3)	
Headache	5 (27.8)	
Muscular weakness	5 (27.8)	3 (16.7)
Thrombocytopenia	5 (27.8)	2 (11.1)
Dehydration	4 (22.2)	
Anemia	3 (16.7)	2 (11.1)
Back pain	3 (16.7)	
Chills	3 (16.7)	
Influenza like illness	3 (16.7)	
Infusion related reaction	3 (16.7)	

*Number of unique patients experiencing at least one occurrence

**Other grade 3 events included musculoskeletal pain and back pain (n=1), hyperbilirubinemia (n=1), hypernatremia (n=1)

Anti-tumor Activity: RECIST Response

Two partial responses (PRs) were observed (ORR, 12.5%):

69 yo M with gallbladder adenocarcinoma (Patient 14)

- Prior therapy (BOR): "NUC-gemcitabine+cisplatin;" cisplatin DC'd at cycle 9 (SD); capecitabine + XRT (SD)
- PR at cycle 2, continued through cycle 10 (greatest ↓ -55%)
- PD after 12 cycles (new lesions); continued PR in target lesions

69 yo M with perihilar CCA (Patient 15)

- Prior therapy (BOR): gemcitabine+cisplatin (SD); gemcitabine+cisplatin+durvalumab [DC'd, neuropathy (platinum), psoriasis (durvalumab)]
- PR at cycle 2, CR of target lesions (non-target lesions, nonCR/nonPD); off study at cycle 3, patient decision to pursue hospice

Best Response (n=16)*	n
CR	0
PR	2
SD	9
PD	4
Not evaluable	1

*2 of 18 treated patients discontinued prior to first RECIST 1.1 evaluation

Prolonged Stable Disease in 4 Patients

Prolonged disease control (> 6 cycles) was observed in 4 of 18 patients

2 patients remain on study:

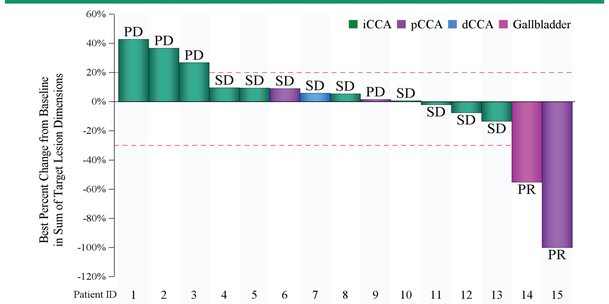
63 yo F with intrahepatic CCA (Patient 13 on study >23 months)

- Dx: 12/2019; path stage IV (5/2021); Prior therapy: gemcitabine+Nab-paclitaxel+cisplatin; gemcitabine+capecitabine; ILT2 antibody trial (BOR:SD); Y90
- Maintaining SD 23.3 months (28 cycles) on study; dose was reduced at cycle 12 (30 mg/m^2) and cycle 21 (23 mg/m^2) due to fatigue; treatment schedule to be shifted to Q 4 weeks for next cycles

79 yo M with intrahepatic CCA (Patient 12 on study >9 months)

- Dx: 12/2021, clinical stage II, mets to liver; Prior therapy: cisplatin+gemcitabine; cisplatin+gemcitabine+durvaluma b; durvalumab maintenance (BOR: SD)
- Maintaining SD 9.2 months (12 cycles) on study; dose was reduced to 23 mg/m^2 by cycle 3 due to fatigue; treatment schedule was shifted to Q 4 weeks at cycle 11

Radiographic Response (n=16 evaluated per RECIST 1.1*)



*1 of 16 patients evaluated per RECIST 1.1 had a response of NE at cycle 2 prior to progressing

iCCA, intrahepatic cholangiocarcinoma; pCCA, perhilar cholangiocarcinoma; dCCA, distal cholangiocarcinoma

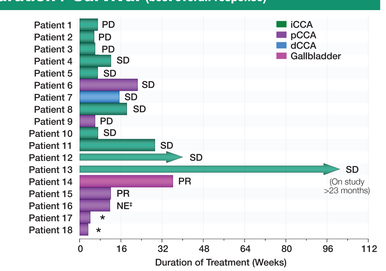
Treatment Duration / Survival (best overall response)

Patient Disposition

- Treatment ongoing (2)
- Discontinued treatment (16)
  - Disease progression (11)
  - Withdrew consent (1*)
  - AE: sepsis/resp failure (1*)
  - Patient decision (2)
  - Pursued hospice (1)

Treatment Duration (n=18 treated)

- Median time on study: 18 (3.3–169.1) weeks
- mPFS: 2.8 months (95%CI: 1.3–6.7)
- mOS: 9.1 months (95% CI: 5.6–NR)

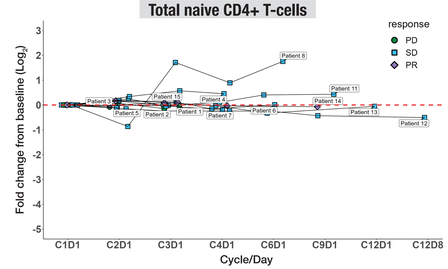


‡RECIST 1.1 response: cycle 2, NE; cycle 4, PD; *2 patients off study prior to first RECIST 1.1 evaluation

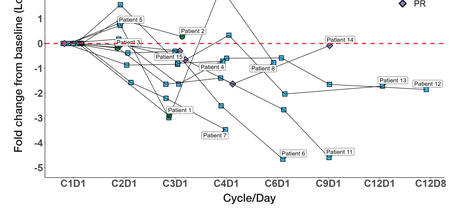
Peripheral Blood T-cells

- Antitumor immune activation in the TME has been shown with gemcitabine, including ↓'s in immune suppressive CD4+ Tregs and M2 macrophages and ↑'s in antitumor CD8+ T cells and M1 macrophages[6]. Released gemcitabine from FF-10832 has also induced this antitumor microenvironment[2,5]
- Circulating T-cells were measured by flow cytometry in patients as a surrogate of immunocompetency in the tumor microenvironment
- Consistent with previously reported dose-escalation data[3], circulating naïve CD4+ T-cells were unchanged, while 4 to 32-fold (2–5 log$_2$) decreases were observed in circulating immune suppressive CD4+ Effector Tregs (Signature II) in patients with longer term SD, which share highly similar cellular markers with intra-tumoral Tregs[7]

Total naive CD4+ T-cells



CD4+ Effector Tregs (Signature II)



Pharmacokinetics

- PK profile & extended gemcitabine plasma $t_{1/2}$ (~30 hrs) demonstrated in this patient population was consistent with patients receiving the RP2D of 40mg/m^2 in the dose escalation phase[3]

Summary

- FF-10832 monotherapy has demonstrated anti-tumor activity in heavily pre-treated patients with advanced BTC who progressed on gemcitabine-based therapy
- Activity of single agent FF-10832 (ORR, 12.5%; mPFS & mOS, 2.8 & 9.1 months) compares favorably to 2nd line combination therapies in larger trials (ORR, 4–11%; mPFS & mOS, 4 & 7.4 months)[8,9]
- Prolonged (>6 cycles) disease control was observed in an additional 4 of 18 treated patients; 2 patients remain on study after 9 and 23 months
- FF-10832 was tolerable with a predictable and manageable adverse event profile; dose intensity was 90.6% with a median of 3.5 (1–28) cycles received
- PK was consistent with the dose finding trial[3]; prolonged circulating $t_{1/2}$ of ~30 hrs observed
- T-cell analysis shows immune modulation indicative of anti-tumor immune activation that correlates with clinical response; results are consistent with ongoing trial of FF-10832 + pembrolizumab in NSCLC and urothelial carcinoma (NCT 05318573)[4]

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