2615 A Phase 2a Safety Run-in and Preliminary Efficacy Study Of Liposomal Gemcitabine (FF-10832) in Combination with Pembrolizumab in Patients with Advanced Solid Tumors

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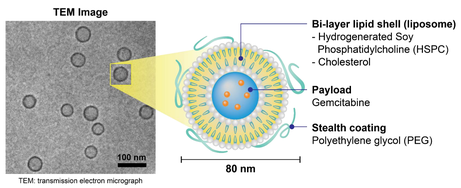
This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

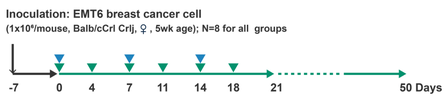
Liposomal Encapsulation Provides Stable, Consistent Delivery of Gemcitabine

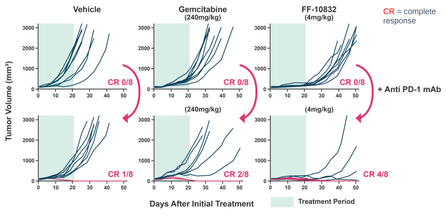
FF-10832 - a Novel Liposomal Formulation of Gemcitabine



- A Phase 1 dose escalation study was conducted in patients with advanced solid tumors (NCT03440450)[1]; the recommended phase 2 dose was determined to be 40 mg/m^2 q 21 days

FF-10832 + Anti-PD-1 Has Increased Anti-tumor Activity



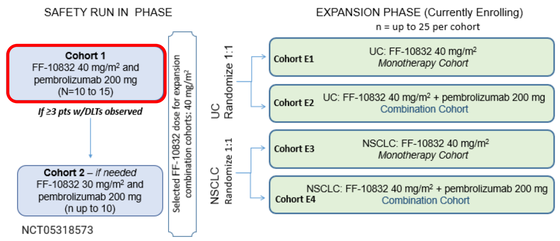


- Preclinical data demonstrate enhanced anti-tumor activity with FF-10832 compared to gemcitabine when combined with an anti-PD-1 monoclonal antibody

Safety Run-in Key Entry Criteria

- ≥ 18 years of age with advanced/metastatic cancer
- No limit on prior lines of therapy
- 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 and bilirubin ≤1.5X ULN; AST/ALT ≤2.5X ULN (≤5X ULN for patients with hepatic metastases)
- Serious cardiac conditions (e.g. NYHA class III or IV) exclusionary

Study Design: Data Are Presented For Safety Run-in Phase (Cohort 1)



- FF-10832 & pembrolizumab administered on Day 1 of a 21-day cycle
- Treatment continued until unacceptable toxicity or disease progression
- RECIST 1.1 and iRECIST evaluation performed every 2 cycles
- DLT defined per Phase 1 FF-10832 monotherapy trial[1]

Baseline Demographics

Baseline demographics (n=12 treated patients)	
Median age, years (range)	69 (42–82)
Male/female, n	6 / 6
Primary cancer, n	
NSCLC	6
Urothelial carcinoma	4
Renal cell carcinoma	2
ECOG performance status, n, (0 / 1)	2 / 10
Prior cancer therapy	
Number of prior regimens, median (range)	5 (1 - 7)
Best response to most recent therapy, n	PR(1), SD(4), PD(6), UNK(1)
Prior gemcitabine therapy, n (%)	5 (42%)
Best response to prior gemcitabine, n	PR(2), SD(1), PD(1), UNK(1)
Prior PD-1/PD-L1 therapy, n (%)	12 (100%)
Best response to prior PD-1/L1 therapy, n	PR(2), SD(5), PD(4), UNK(1)

Patient Disposition

- All patients have discontinued treatment:
  - 9 patients had disease progression by either radiography (8) or clinical progression (1)
  - 1 patient died during treatment of an unrelated cardiac event*
  - 1 patient discontinued due to physician recommendation**
  - 1 patient discontinued due to grade 2 pyrexia related to FF-10832***

*82 yo M with history of hypertension and stroke. Four days after the first infusion was admitted for hypotension. Hospitalization was complicated by COVID infection with progressive decline ending in cardiac arrest (Patient 5)

**65 yo M who developed a new lesion at the end of Cycle 2 which was considered disease progression requiring a change in therapy (Patient 4)

***69 yo M who developed grade 2 fever, which in context of other unrelated adverse events of weakness and atrial fibrillation prompted removal from study (Patient 10)

Dose Intensity & Safety of the Combination

- 1 DLT occurred (grade 3 pain, malaise and arthralgia)
- Median (range) cycles received: 2 (1-8)
- 2 patients required FF-10832 dose reduction to 30 mg/m^2 after C1
- 1 patient discontinued FF-10832 due to grade 2 pyrexia
- 1 discontinued pembrolizumab due to grade 3 maculopapular rash
  - Entered study with grade 1 rash due to enfortumab vedotin (immediate prior therapy)
- FF-10832 infusion interruptions/dosing delays:
  - 1 patient had C1D1 dose interrupted due to infusion reaction (facial flushing, HTN, dyspnea, tachycardia); resolved with treatment (steroid/H_2 antagonist) & dosing completed
  - 1 patient had treatment delayed due to an embolic stroke prior to Cycle 6, unrelated to FF-10832; recovered but taken off study due to PD.
- Most common AEs considered related to FF-10832 + pembrolizumab were Gr≤2 fatigue (50%) & nausea (25%)

Treatment-related AEs in ≥3 Patients*

Adverse Event	Related to FF-10832 + pembrolizumab	Related to FF-10832 only
	All patients (n=12), n (%)	
Fatigue	6 (50)	1 (8)
Nausea	3 (25)	0
Anemia	2 (17)	3 (25)
Muscular weakness	2 (17)	2 (17)
AST, increased	1 (8)	2 (17)
Decreased appetite	1 (8)	3 (25)
Diarrhea	1 (8)	2 (17)
Pyrexia	1 (8)	2 (17)

*Columns are mutually exclusive

Grade ≥3 Treatment-related AEs*

Adverse Event	Related to FF-10832 + pembrolizumab	Related to FF-10832 only
	All patients/all related grade ≥3 events (n=12), n (%)	
Amylase, increased	1 (8)	0
Arthralgia	1 (8)**	0
Lipase, increased	1 (8)	0
Maculopapular rash	1 (8)	0
Malaise	1 (8)**	0
Pain	1 (8)**	0
Anemia	0	2 (17)
Fatigue	0	1 (8)

*Columns are mutually exclusive. All events were grade 3 except for one grade 4 lipase elevation that resolved (grade 3 amylase elevation in same patient)

**Dose-limiting toxicity of grade 3 arthralgia, malaise, pain in same patient

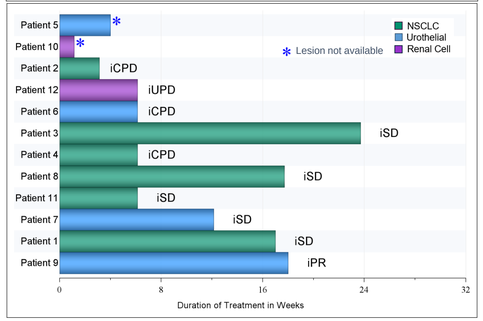
Anti-tumor Activity: iRECIST Response

Best Response by iRECIST	n (%)
iCR	0
iPR	1 (10)
iSD	5 (50)
iCPD	3 (30)
iUPD	1 (10)
Not Available	2*

*2 of 12 treated patients were not evaluable for disease response. Patient 10 discontinued treatment due to related grade 2 fever and other unrelated AEs before scheduled scans were performed. Patient 5 died due to a cardiac event prior to scheduled scans.

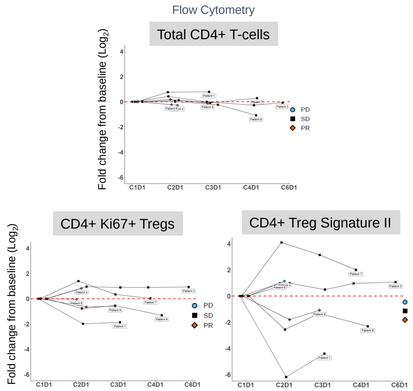
- A partial response (PR/iPR) was observed in a 69 yo F with urothelial carcinoma (Patient 9)
  - Prior therapy (best response): gemcitabine/cisplatin (SD), pembrolizumab (unknown), and enfortumab (SD)
  - Two target lesions in anterior and posterior right lung; 8 non-target lesions in lung (2), bone (3), liver (2) and LN (1)
- Median PFS was 6 weeks (95%CI: 3.1–NR); median OS was 23.3 weeks (95% CI: 4–– NR)

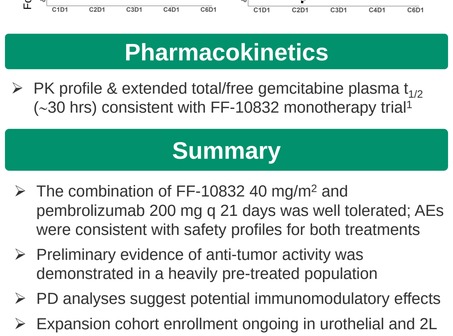
Radiographic Response / Treatment Duration



Peripheral Blood T-Cells

- Circulating T-cells measured as a surrogate of immunocompetency in the tumor microenvironment[2-4]
- While overall population density of Total CD4+ T-cells did not change, 2 - 6-fold log ↓'s were observed in immune suppressive CD4+ Treg lineages in patient achieving PR & some maintaining SD; consistent with Phase 1 FF-10832 monotherapy trial[1]





Pharmacokinetics

- PK profile & extended total/free gemcitabine plasma $t_{1/2}$ (~30 hrs) consistent with FF-10832 monotherapy trial[1]

Summary

- The combination of FF-10832 40 mg/m^2 and pembrolizumab 200 mg q 21 days was well tolerated; AEs were consistent with safety profiles for both treatments
- Preliminary evidence of anti-tumor activity was demonstrated in a heavily pre-treated population
- PD analyses suggest potential immunomodulatory effects
- Expansion cohort enrollment ongoing in urothelial and 2L non-small cell lung carcinoma

References

1. *J Clin Oncol* 2022; 40(16-suppl):3097
2. *Nature, Sci Reports* 2021; 11:14426
3. *J Immuno Cancer* 2022; 10(6):1
4. *Cancer Med* 2023; 12(8):9069

Acknowledgements

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