A First-in-Human Phase 1 Dose Escalation Study of FF-10850 (Liposomal Topotecan) in Patients with Advanced Solid Tumors

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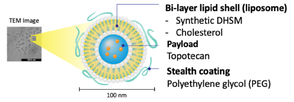
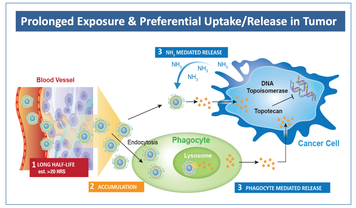
Introduction

- FF-10850 (liposomal topotecan, TPT) [**Figure 1**]
  - Unique dihydrosphingomyelin (DHSM)-based carrier
  - Enhanced tumor drug delivery and retention[1]
  - Superior anti-tumor activity in preclinical models with less myelosuppression compared to topotecan[1]
  - Pharmacokinetic (PK) profile supporting a Q 2-week dosing schedule

Figure 1.





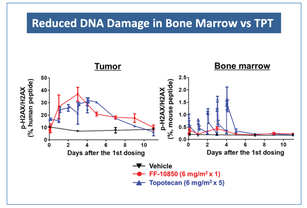
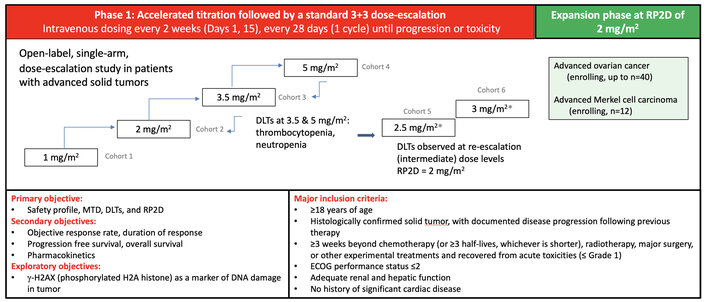


Figure 2. Phase 1 study design and dose escalation cohorts

- Phase 1 starting dose of 1 mg/m^2 was escalated to 2, 3.5 and 5 mg/m^2, followed by dose de-escalation and expansion at 2 mg/m^2. Intermediate doses of 2.5 and 3 mg/m^2 were subsequently evaluated.



MTD, maximum tolerated dose; DLT, dose limiting toxicity; RP2D, recommended Phase 2 dose; ECOG, Eastern Cooperative Oncology Group. ClinicalTrials.gov NCT04047251

Methods and Baseline Demographics

- 29 patients were enrolled, with a median of 5 (range, 1–10) prior treatment regimens [**Table 1**].
- Safety was assessed by adverse events (AEs), clinical laboratory parameters, physical exam, vitals, and electrocardiograms.
- Disease assessments were performed at the end of Cycle 2 (Week 8) and every 8 weeks (2 cycles) according to the Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1).
- PK parameters were determined from total and released (free) topotecan plasma concentrations by non-compartmental analysis using Phoenix WinNonlin V6.4 (Pharsight Corp., St. Louis, MO).
- Serum Anti-PEG IgM was measured to assess the potential for accelerated blood clearance phenomenon.

Table 1. Phase 1 baseline demographics (n=29)

Parameter	
Median age, years (range)	64 (37–79)
Male/female, n	4 / 25
Tumor types enrolled, n	
Ovarian	15
Cervical	3
Endometrial	2
Pancreatic	2
Prostate	2
Uterine	2
Adrenocortical carcinoma	1
Breast	1
Merkel cell carcinoma	1
Screening ECOG performance status, n	
0	5
1	24
Prior therapy	
No. of prior treatment regimens, median (range)	5 (1–10)
Best response to most recent cancer therapy	CR (1), PR (2), SD (1), PD (17), UNK (8)

ECOG, Eastern Cooperative Oncology Group

Results

Clinical safety

- Patients received a median of 2 (range, 1–12) cycles of FF-10850 treatment; median time on study was 8.3 (1.7–50) weeks.
- FF-10850 was well-tolerated at doses up to 2 mg/m^2. Common drug-related adverse events (AEs) in ≥5 patients: anemia (83%), thrombocytopenia (62%), neutropenia (59%), nausea (38%), fatigue (28%), alopecia (24%), & hypokalemia (17%) [**Table 2**].
- Dose-limiting toxicity was observed at doses ≥2.5 mg/m^2:
  - Grade 4 thrombocytopenia and neutropenia were observed at doses of 3.5 mg/m^2 (n=2 of 6 patients) and 5 mg/m^2 (n=2 of 2), which exceeded the MTD.
  - Intermediate dose levels of 2.5 and 3.0 mg/m^2 were subsequently evaluated, with Grade ≥3 thrombocytopenia, anemia, neutropenia, and fatigue observed, requiring dose holds (2 weeks) and dose reductions (25% or one dose level).
- Treatment-related SAEs were reported in 7 (24%) patients overall, including thrombocytopenia (6 patients, 21%), neutropenia (5 patients, 17%), anemia (2 patients, 7%), and asthenia (1 patient, 3%); SAEs of Gr 4 thrombocytopenia/neutropenia led to treatment discontinuation in one subject at 5 mg/m^2.
- Only one patient on study at 3.0 mg/m^2 experienced an infusion-related reaction.
- **The RP2D = 2 mg/m^2 administered on Day 1 and 15 of a 28-day cycle.**

Table 2. Treatment-related adverse events in ≥ 3 patients

Adverse event	All patients (N=29)		(n=6) 2.0 mg/m²		(n=6) 2.5 mg/m²		(n=7) 3.0 mg/m²		(n=7) 3.5 mg/m²		(n=2) 5.0 mg/m²	
	All (%)	Gr 3/4	All	Gr 3/4	All	Gr 3/4	All	Gr 3/4	All	Gr 3/4	All	Gr 3/4
Anemia	24 (83%)	15 (52%)	5	4	4	2	6	3	7	4	2	2
Thrombocytopenia	18 (62%)	10 (35%)	3	1	2	1	6	3	5	3	2	2
Neutropenia	17 (59%)	13 (45%)	1	0	4	2	5	5	5	4	2	2
Nausea	11 (38%)	0	3	0	3	0	4	0	1	0	0	0
Fatigue	8 (28%)	2 (7%)	0	0	3	2	1	0	2	0	2	0
Alopecia	7 (24%)	0	1	0	1	0	2	0	0	0	0	0
Hypokalemia	5 (17%)	1 (3%)	1	0	1	0	0	0	2	0	1	1
Rash	4 (14%)	0	0	0	0	0	2	0	1	0	1	0
Vomiting	4 (14%)	0	1	0	1	0	2	0	0	0	0	0
Diarrhea	3 (10%)	0	0	0	1	0	1	0	0	0	1	0
Pruritis	3 (10%)	0	0	0	0	0	0	0	2	0	1	0

All, all grades; Gr, grade; Dose was escalated from 1, 2, 3.5, and 5 mg/m^2, then intermediate dose levels evaluated at 2.5 and 3.0 mg/m^2. No treatment-related AEs were reported in Cohort 1 at 1 mg/m^2 (n=1)

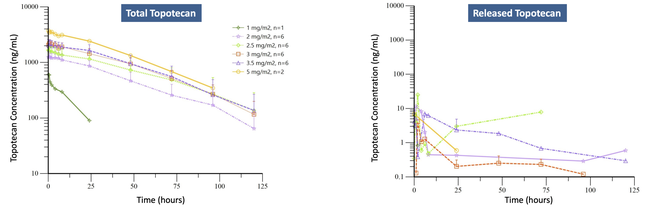
FF-10850: Superior PK profile compared to topotecan

- Total and Released Topotecan PK Following FF-10850 Administration
  - Dose proportional exposure over 1.0–5.0 mg/m^2 [**Table 3, Figure 3**]
  - Extended plasma $t_{1/2}$ (~27 hours) allowing Q 2-week dosing (vs TPT 3-hour half-life[3]), with no observed accumulation:
    - Total concentration >1000 ng/m> for >24 hours at doses ≥2 mg/m^2
    - Released (free) concentration <3% of simultaneous total concentrations.
  - No evidence of accelerated blood clearance due to anti-PEG IgM

Table 3. Cycle 1 Day 1 – Mean Total Topotecan Pharmacokinetics

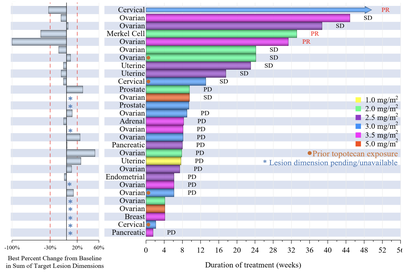
Dose (mg/m²)	Subjects (n)	Cmax (ng/ml)	AUC0-inf (hr*ng/ml)	T1/2 (hr)	Vss (ml/m²)	Cl (ml/hr/m²)
1.0	1	606	7340	10.2	1960	136
2.0	6	1320	60700	27.6	1440	37.7
2.5	6	1670	88700	27.7	1350	34.4
3.0	6	2270	107000	27.1	1200	29.5
3.5	6	2190	108000	23.8	1360	37.0
5.0	2	3860	164000	24.2	1180	30.7

Figure 3.



Clinical activity of FF-10850 in advanced solid tumors

Figure 4.



- **Partial responses (PR) were observed in 3 of 24 patients evaluable for response [Figure 4]:**
  - **Confirmed PR in ovarian cancer [Figure 5]**
  - **Confirmed PR in cervical cancer [Figure 6]**
  - **Confirmed PR in Merkel cell carcinoma [Figure 7]**
- Patients with PR or SD ≥10 weeks remained on FF-10850 treatment for a longer duration compared to immediate prior therapy
  - Mean of 28.2 (10–50) weeks [FF-10850] vs 16.2 (6 – 8) weeks [immediate prior therapy]
- Stable disease was observed in an additional 8 of 24 (33%) evaluable patients for ≥10 weeks:
  - Five ovarian, 2 uterine and 1 cervical cancer patient:
    - Five maintained disease control for ≥24 weeks; including one (ovarian) who had previously progressed on topotecan, and two (ovarian) who maintained SD for 38–45 weeks
- The median OS was 31.7 (95% CI:13.6 – 62.7) weeks, with a PFS of 9.4 (95% CI: 7.6 – 22.1) weeks

Activity demonstrated in ovarian and cervical cancer

Figure 5. 71 y/o female

- Aug 2019: Dx: Stage IVA ovarian cancer
  Neoadjuvant chemotherapy: 3 cycles carboplatin/paclitaxel
- Oct 2019: Surgery + 3 cycles carboplatin/paclitaxel
  End of treatment scan: no appreciable disease, small stable pulmonary nodules
- June 2020: Rising CA-125, 2 cycles carboplatin/gemcitabine/bevacizumab
- Aug 2020: **FF-10850 3.5 mg/m^2 Days 1 & 15 Q 28 days**; dose reduced 75% (2.6 mg/m^2) due to Gr 4 thrombocytopenia for Cycle 2+
  Complete response (CR, 100% decrease) in target lesions with stable non-target lesions
  Decline in CA-125: 2248 (Baseline) → 17 (Cycle 6 Day 1)
  Maintained response > 30 weeks (8 cycles)

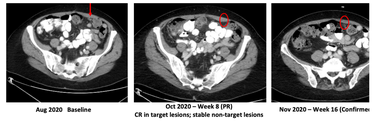
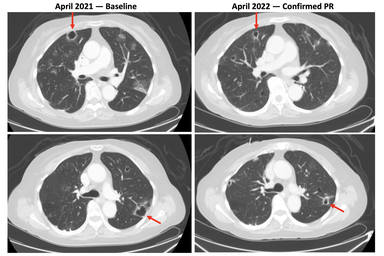


Figure 6. 73 y/o female

- Dec 2018: Well-differentiated gastric type endocervical adenocarcinoma; parametrial involvement
- Mar 2019: XRT + brachytherapy
- Jan 2020: Bilateral metastasis to lung
- Feb 2020: Surgery/wedge resections
- Mar 2020: Carboplatin+ paclitaxel + bevacizumab x 6 cycles; Bevacizumab maintenance
- Jan 2021: Nivolumab + lucitanib x 4 cycles
- May 2021: **FF-10850 3.0 mg/m^2**
  Days 1 & 15 Q 28 days;
  Dose reduced to 2.5 mg/m^2 for Cycle 2+ due to Gr 4 thrombocytopenia
- April 2022: **Confirmed PR with 32% reduction in target lesions**; Continues on study at Cycle 13



Acknowledgements

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References

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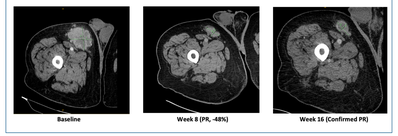
Durable response in refractory Merkel cell carcinoma

Figure 7. 62 y/o male

- April 2019: Dx with metastatic Merkel cell carcinoma; right leg/right arm
  Wide local excision + regional lymph node dissections, followed by adjuvant radiation
- Sept 2019: Recurrent disease; new lower extremity nodules
  Pembrolizumab Q 3 weeks; disease progression after 8 cycles
  Subsequent antibody drug conjugate clinical trial: enapotamab vedotin (anti-Axl-ADC); disease progression after 3 cycles
- Oct 2020: **FF-10850 2.0 mg/m^2 Days 1 & 15 Q 28 days**
  Treatment was well-tolerated
  Marked clinical response with a 48% reduction in sum of diameters of target lesions
  Maintained response > 30 weeks (8 cycles), including after hold post Cycle 2 x 1 month (unrelated hospitalization



Summary

- FF-10850 is a liposomal formulation of topotecan developed to improve topotecan exposure, efficacy and safety. Preclinical studies demonstrated superior anti-tumor activity with less myelosuppression compared to topotecan, with a PK profile supporting a more optimal twice monthly dosing schedule.
- In the Phase 1 trial, treatment was well-tolerated at doses up to 2 mg/m^2 administered on a Q 2-week schedule (Days 1 and 15 Q 28 days).
  - The most common drug-related AEs were anemia, thrombocytopenia, neutropenia, nausea and fatigue
  - Dose-limiting myelosuppression was observed at doses ≥2.5 mg/m^2 on the Q 2-week dosing schedule
- Anti-tumor activity was demonstrated in heavily pre-treated patients with advanced solid tumors:
  - Three PRs were observed in 24 evaluable patients (12.5%), including patients with ovarian cancer, cervical cancer, and Merkel cell carcinoma.
  - Stable disease was observed in an additional 8 of 24 (33%) patients for ≥10 weeks (10–45 weeks)
  - The median OS was 31.7 (95% CI:13.6–62.7) weeks, with a PFS of 9.4 (95% CI: 7.6–22.1) weeks
- Linear/dose proportional PK was observed following FF-10850 administration, with higher, continuous exposures compared to topotecan HCl
  - Mean $t_{1/2}$ for total topotecan following FF-10850 administration was ~27 hours (versus 3-hour topotecan HCl $t_{1/2}$), with total and released topotecan measurable for >120 hours; <3% of circulating topotecan was in the free (released) form
  - No apparent dose-dependency or accumulation was observed
- Expansion is ongoing in patients with ovarian and Merkel cell carcinoma at the RP2D of 2 mg/m^2 IV on Day 1 & 15 of a 28-day cycle