A Phase 1, First-in-Human, Dose Escalation & Biomarker Trial of Liposomal Gemcitabine (FF-10832) in Patients with Advanced Solid Tumors

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Introduction

- **FF-10832 — a novel liposomal formulation of gemcitabine (GEM) with promising activity [Figure 1]**
  - Overcomes resistance through increased plasma stability and enhanced tumor drug delivery[1]
    - Prolonged half-life/reduced clearance
    - Preferential uptake and release in tumor vs normal tissues/marrow
      - Macrophage uptake
      - Enhanced permeability and retention (EPR) effect in tumor
  - Superior activity compared to GEM in sensitive & resistant tumor models (pancreatic, lung, ovarian, and biliary)[1,2]
  - Immune-modulating effects in the tumor microenvironment (TME) with greater synergy compared to GEM in combination with CTLA-4 and PD-L1 inhibitors.[1,2]

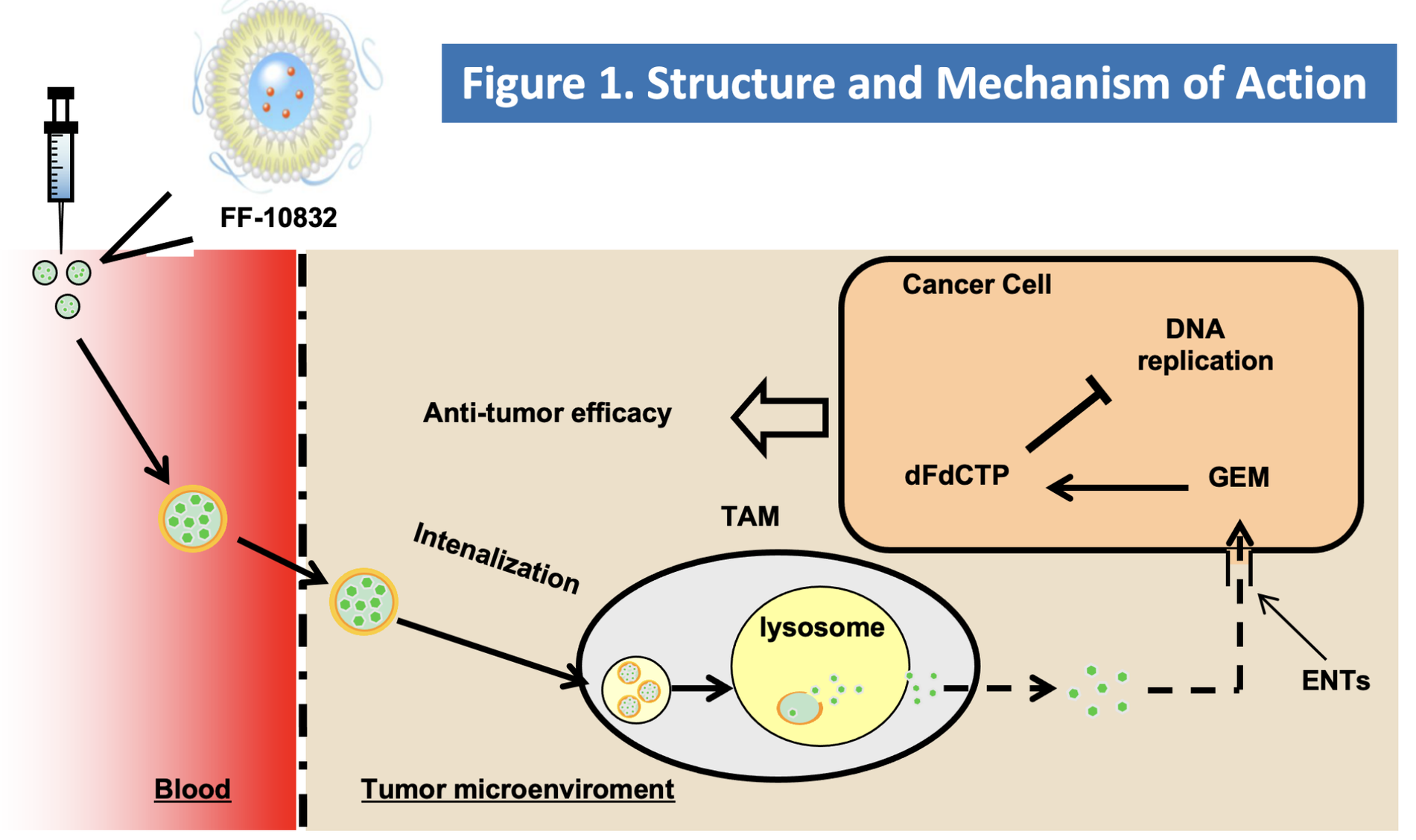


Figure 1. Structure and Mechanism of Action

Matsumoto et al. Pharm Res 2021; 38:1093–1106
TAM, tumor-associated macrophage; dFdCTP, GEM triphosphate; ENTs, equilibrative nucleoside transporters

Phase 1 study design

A Phase 1 dose escalation study was conducted in patients with advanced solid tumors, with initial clinical data supporting the immune-modulating effects of FF-10832 [**Figure 1**].

Figure 2. Phase 1 study design

- Starting dose 1.2 mg/m² escalated to 55 mg/m² (dose doubling from 1.2 to 8 mg/m², followed by modified Fibonacci)
- FF-10832: IV once or twice per cycle Q 21 or 28 days until progression or toxicity; twice per cycle discontinued due to skin toxicity

Open label, standard 3+3 dose-escalation in pts with advanced solid tumors; ClinicalTrials.gov NCT03440450					Expansion phase
Dose Level	Mono28D1D15 (Day 1 & 15 Q 28 days)	Mono28D1 (Day 1 Q 28 days)	Mono21D1D8 (Day 1 & 8 Q 21 days)	Mono21D1 (Day 1 Q 21 days)	
1.2–8 mg/m²	Cohorts 1–4	-	-	-	Expansion cohort ongoing in biliary tract cancer at RP2D/schedule: 40 mg/m² on Day 1 Q 21 days (n=15)
12 mg/m²	Cohort 5	-	Cohort 21	-	
17 mg/m²	Cohort 6	-	Cohort 22	-	
23 mg/m²	Cohort 7	-	Cohort 23	-	
30 mg/m²	Cohort 8	-	Discontinued	Cohort 41	
40 mg/m²	Discontinued	Cohort 31		**Cohort 42 (MTD/RP2D)**	
48 mg/m²		**Cohort 32 (RP2D Q 28d)**		-	
55 mg/m²		-		**Cohort 43 (DLT)**	

Primary objective:
Safety profile, MTD, DLTs, and RP2D

Secondary objectives:
- Overall response, duration of response, progression free survival
- Pharmacokinetics and pharmacodynamics

Exploratory objectives:
- Ferumoxytol (FMX) tumor uptake as a surrogate for nanoparticle penetration
- Immunomodulatory effects measured in peripheral blood

Major inclusion criteria:
- ≥18 years of age
- Advanced solid tumor with documented disease progression
- ≥3 weeks beyond previous therapy; recovered from acute toxicities (≤ Grade 1)
- ECOG performance status ≤2
- Adequate renal and hepatic function
- No history of significant cardiac disease

d, days; MTD, maximum tolerated dose; DLT, dose limiting toxicity; RP2D, recommended Phase 2 dose; ECOG, Eastern Cooperative Oncology Group

Methods

- 73 patients enrolled with a median of 3 (range, 1–11) 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.
- Pharmacokinetic (PK) parameters were determined from total and released (free) GEM, and dFdU (major metabolite) plasma concentrations using non-compartmental analysis (Phoenix WinNonlin V6.4, Pharsight Corp., St. Louis, MO).
- Circulating T cell populations were measured by flow cytometry at baseline and through Cycle 6 to explore the immunomodulatory effects of FF-10832.[3-6]
- Whole blood samples were collected pre-treatment to evaluate metabolic and transporter gene polymorphisms (SNPs) that may correlate with response or toxicity.

Results

Table 1. Phase 1 baseline demographics (n=73)

Parameter	
Median age, years (range)	64 (26–84)
Male/female, n	26 / 47
Dose/treatment schedule (n)	
Day 1 & 15 Q 28 days (1.2–30 mg/m²)	28
Day 1 & 8 Q 21 days (12–23 mg/m²)	13
Day 1 Q 28 days (40–48 mg/m²)	17
Day 1 Q 21 days (30–55 mg/m²)	15
Primary Cancer, n	
Pancreatic	32
Breast	5
Uterine/endometrial	5
Lung	5
Ovarian	4
Cervical	3
Cholangiocarcinoma	3
Gallbladder	2
Liposarcoma	2
Leiomyosarcoma	2
Other tumor types (n=1 each): appendiceal, bladder, mesothelioma, nasopharyngeal, neuroendocrine, penile, prostate, skin (melanoma), adeno of unknown primary; urachal	1
Screening ECOG performance status, n, (0 / 1)	9 / 64
Prior therapy	
No. of prior treatment regimens, median (range)	3 (1–11)
Prior gemcitabine therapy, n (%)	48 (66%)
Best response to prior gemcitabine, n	CR (2), PR (5), SD (12), PD (22), UNK (7)
Best response to most recent cancer therapy, n	SD (12), PD (48), UNK (13)

Clinical Safety

- Patients received a median of 2 (range, 1–17) cycles of FF-10832 treatment; median treatment duration = 7.1 (0.1–74) weeks.
- FF-10832 was well-tolerated with less myelosuppression compared to GEM; common (≥15%) treatment-related adverse events (AEs) were Grade (Gr) 1/2 nausea, rash, pyrexia, fatigue, and vomiting. Grade 3 anemia was observed in 6 pts (8%) [**Table 2**].
- Infusion reactions were observed at doses of 4.8–30 mg/m² (n=7); effectively managed with premedication/reduced infusion rate
- Dose-limiting dermal ulcerations were observed at doses ≥12 mg/m² on both schedules when administered twice per cycle:
  - More frequent with administration on a Days 1 & 8 schedule [DLTs: Gr 3 ulceration (n=2)/cellulitis (n=1) at 23 mg/m²]
  - Persistent circulating drug concentrations on Day 8 (pre-dose) suggested schedule- vs. dose-related dermal toxicity
  - Largely mitigated by reducing dose frequency to once-per-cycle (Day 1 only)
- Higher doses were explored on a once per cycle (Day 1) schedule: 30–55 mg/m² Q 21 days and 40–48 mg/m² Q 28 days
  - **Q 21 days:** DLT observed at 55 mg/m² [Gr 4 thrombocytopenia (n=2), Gr 3 pneumonitis (n=1)], early in the first cycle MTD/RP2D = 40 mg/m² Q 21 days [**Table 3**]
  - **Q 28 days:** One DLT in 6 patients observed at 40 mg/m² (Gr 3 pyrexia, C1D27 Intermediate dose of 48 mg/m² evaluated; well-tolerated without DLT (RP2D Q 28 days)
- SNP analysis: 50% of patients had polymorphisms associated with altered GEM metabolism and transport that may increase susceptibility to neutropenia (CDA, dCK, hENT1)[7], however, no events of FF-10832-related neutropenia observed.

Table 2. Treatment-related AEs in ≥5 patients – All Doses

Adverse event	All patients (N=73)	
	All (%)	Gr 3/4
Nausea	16 (22%)	0
Rash	16 (22%)	0
Pyrexia*	15 (21%)	2 (3%)
Fatigue	14 (19%)	0
Vomiting	12 (16%)	1(1%)
Anemia	11 (15%)	6 (8%)
Appetite, decreased	10 (14%)	0
Thrombocytopenia*	8 (11%)	3 (4%)
Infusion related reaction	7 (10%)	2 (3%)
Chills	6 (8%)	0
Skin ulcer*	6 (8%)	2 (3%)
Skin lesion	5 (7%)	0

Table 3. Safety profile at the RP2D

Adverse event	MTD/RP2D Q21 days (40 mg/m²) (n=6)	
	All (%)	Gr 3/4
Thrombocytopenia	2 (33%)	1 (17%)
Asthenia	1 (17%)	0
Decreased appetite	1 (17%)	0
Erythema	1 (17%)	0
Oral Candidiasis	1 (17%)	0
Orthostatic Hypotension	1 (17%)	0

*Dose-limiting toxicities; treatment-related cellulitis also observed in 3 patients (2 Gr 3/4)

Total and released GEM PK following FF-10832 administration improves drug delivery

- **Total and Released (Free) Gemcitabine PK Following FF-10832 Administration**
  - Dose proportional exposure from 1.2–55 mg/m² without accumulation; no dose dependency observed in PK [**Figure 3, Table 4**]
  - Prolonged plasma $t_{1/2}$ (total ~26 hours, free ~39 hours), with 3-log difference between total vs released GEM concentrations (<1% free)
  - Measurable concentrations >200 hours support prolonged exposure/delivery to TME
  - No evidence of accelerated blood clearance due to anti-PEG IgM

Figure 3.

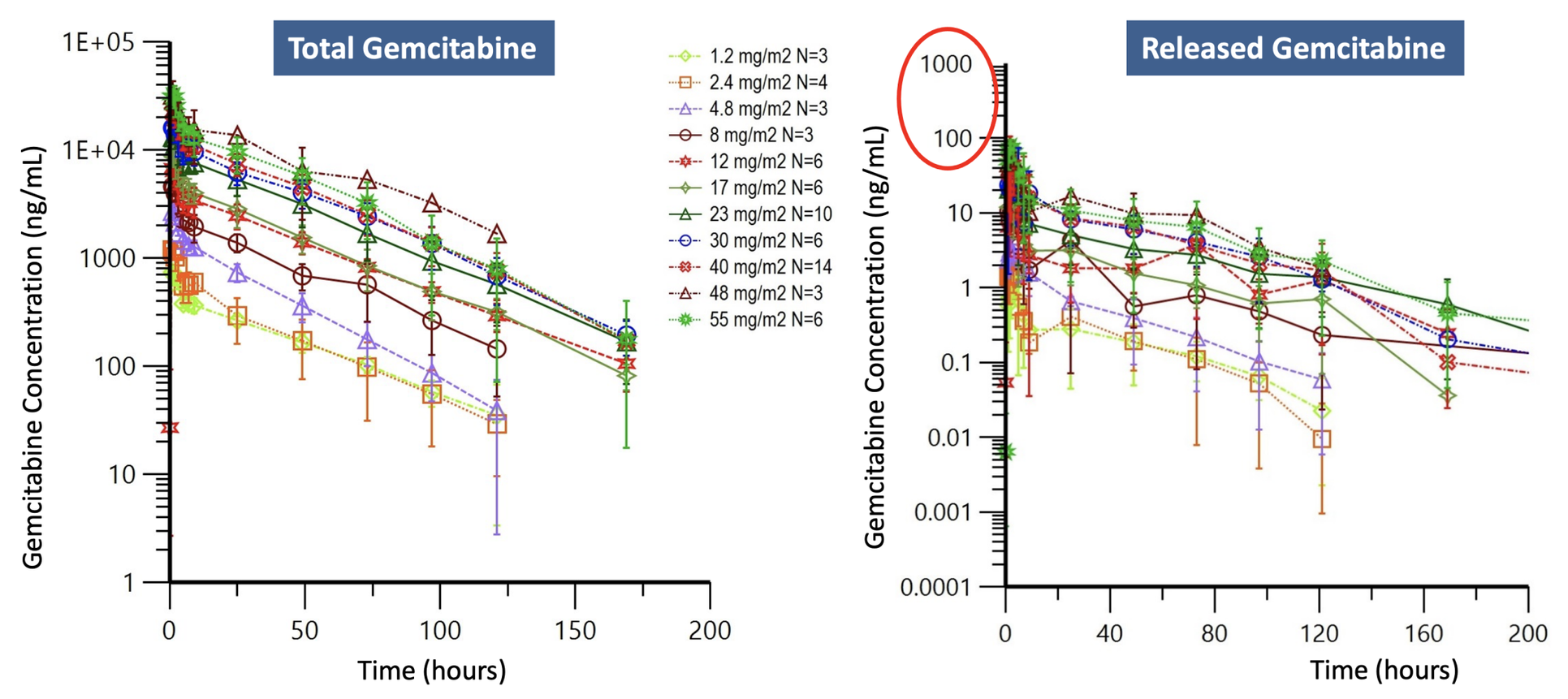


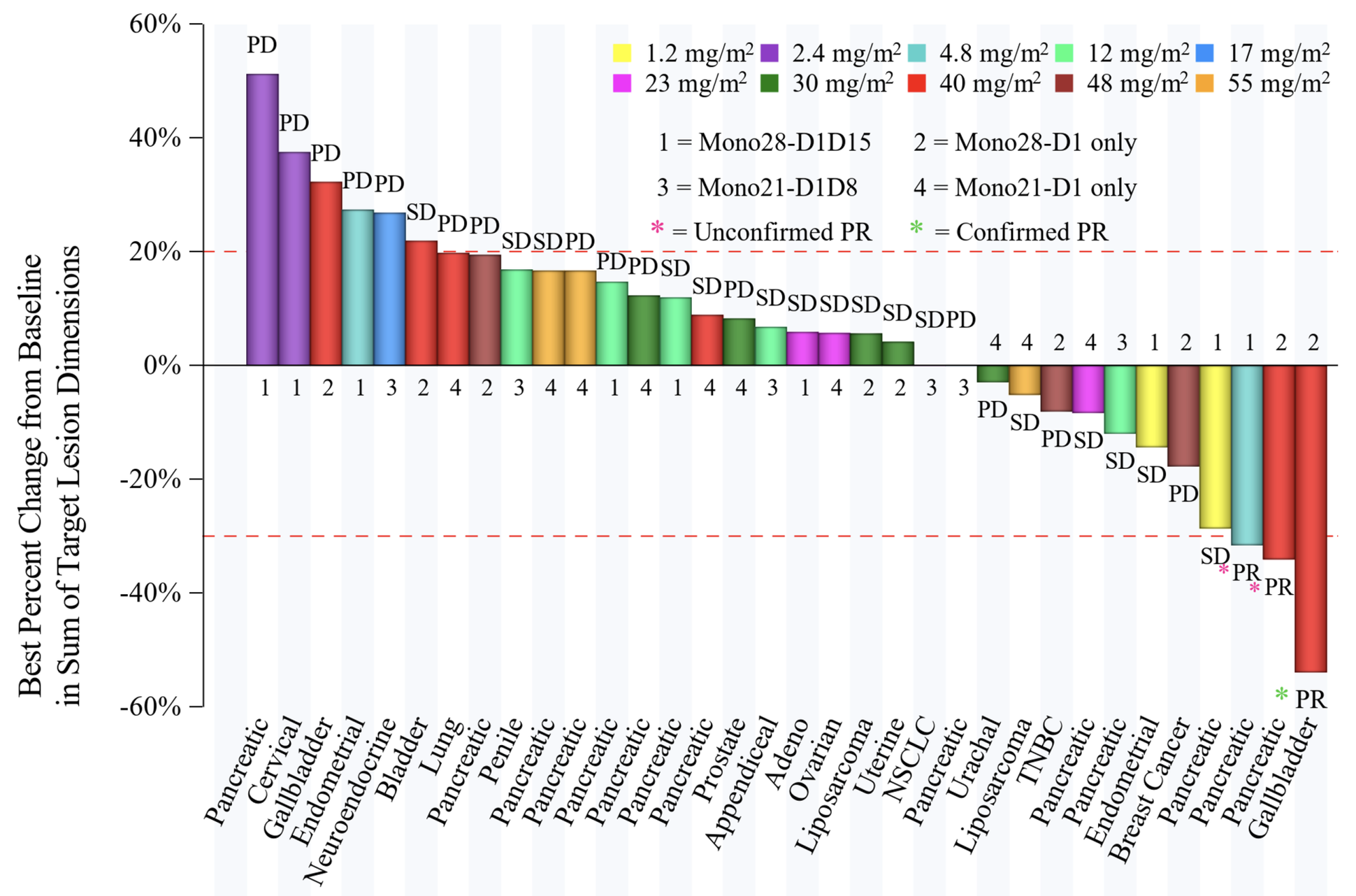
Table 4. Mean (CV%) Cycle 1 Day 1 GEM PK parameters

Dose (mg/m²)	n	C_{max} (ng/ml)		$T_{½}$ (hrs)		$AUC_{0-\infty}$ (ng/ml*hr)		V_{ss} (L/m²)	Cl (L/hr/m²)
		Total GEM	Free GEM	Total GEM	Free GEM	Total GEM	Free GEM	Total GEM	Total GEM
1.2	3	748 (12)	1.08 (27)	35.7 (20)	49.6 (37)	22700 (15)	26.1 (58)	2.66 (18)	0.053 (15)
2.4	4	1240 (10)	1.86 (32)	24.1 (34)	19.6 (63)	25000 (42)	25.7 (42)	3.33 (11)	0.106 (63)
4.8	3	2970 (9)	5.10 (18)	23.2 (17)	21.4 (52)	51900 (23)	59.1 (32)	2.79 (5)	0.089 (23)
8	3	4710 (9)	13.3 (36)	28.4 (31)	46.6 (90)	107000 (25)	207 (47)	3.10 (23)	0.074 (26)
12	6	6712 (19)	24.3 (100)	30.8 (10)	27.8 (100)	186000 (21)	218 (100)	2.82 (20)	0.064 (18)
17	6	9277 (17)	19.3 (22)	26.5 (18)	23.5 (14)	206000 (27)	288 (27)	3.10 (17)	0.067 (31)
23	10	12455 (21)	28.8 (64)	25.4 (24)	35.3 (20)	381000 (31)	581 (93)	2.44 (17)	0.060 (53)
30	6	16300 (12)	41.6 (68)	29.5 (14)	38.3 (13)	499000 (26)	768 (42)	2.60 (19)	0.060 (28)
40	14	22078 (18)	53.5 (137)	27.5 (13)	29.0 (68)	572000 (23)	800 (81)	2.78 (16)	0.069 (26)
48	3	30800 (36)	68 (23)	26.4 (35)	21.6 (32)	625000 (80)	971 (33)	2.56 (40)	0.067 (88)
55	6	32500 (21)	78 (21)	24.3 (9)	29.4 (49)	689000 (47)	1070 (47)	2.93 (22)	0.087 (47)

C_{max}, peak concentration; $t_{1/2}$, half-life; AUC, area under the concentration-time curve; V_{ss}, steady-state volume of distribution; Cl, clearance

Clinical activity of FF-10832 in advanced solid tumors

Figure 4. Best overall tumor response

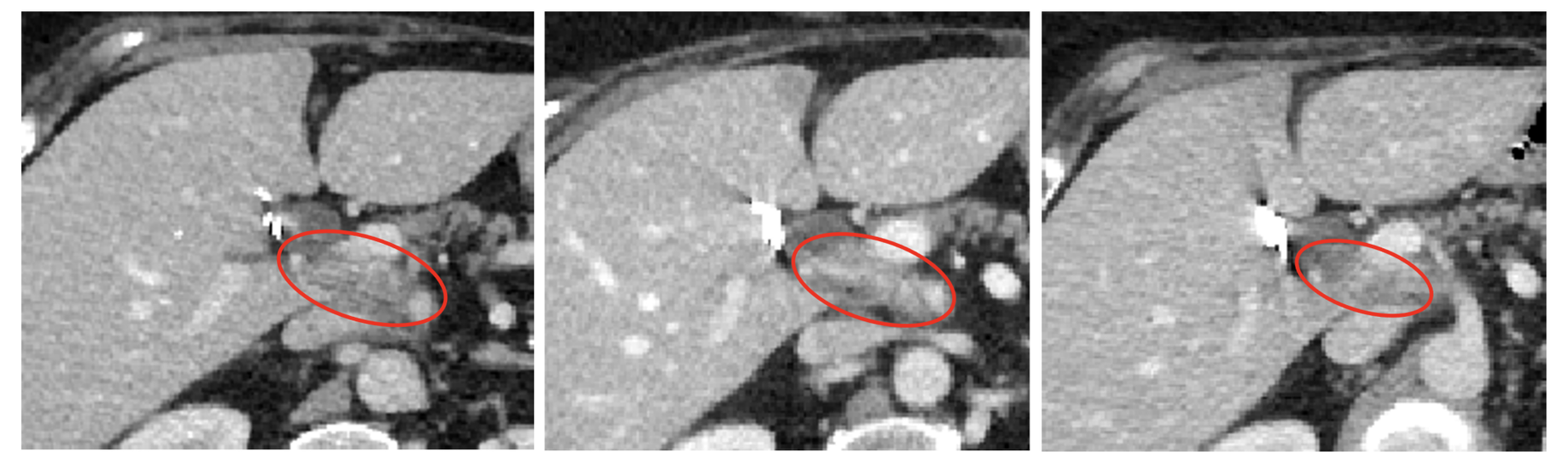


- **Partial responses (PR) were observed in 3 of 37 (8%) patients evaluable for response [Figure 4]**
  - **Confirmed PR in a gallbladder cancer patient at 40 mg/m² Q 28 days [Figure 5]**
  - **Unconfirmed PRs observed in two pancreatic cancer patients:**
    - **pancreatic adenocarcinoma [4.8 mg/m² Days 1 & 15 Q 28 days, Figure 6]**
    - **pancreatic acinar carcinoma [40 mg/m² Q 28 days, Figure 7]**
- Tumor shrinkage and/or stable disease (SD) ≥20 weeks was observed in 9 patients, including at low doses:
  - At the lowest dose level of 1.2 mg/m² Days 1& 15 Q 28 days, a 28.6% decrease in target lesions was observed after 4 cycles in a pancreatic cancer patient who had previously progressed on GEM; CA-19-9: 2731 → 1752
  - Disease control was observed in a variety of other tumor types including endometrial, bladder, appendiceal, uterine, adenocarcinoma of unknown primary, and liposarcoma.

Durable response in biliary cancer

Figure 5. Confirmed durable PR in a 74 y/o female with metastatic gallbladder adenocarcinoma

- Sept 2016: Cholecystectomy, Dx: adenocarcinoma, T3, Grade 1, margin+
- Nov 2016: Gallbladder fossa resection, no residual malignancy
- Mar 2020: CT chest/abdomen/pelvis: progressive disease (PD)
- April 2020: Gemcitabine/cisplatin x 5 cycles; complicated by thrombocytopenia → PD
- Oct 2020: **FF-10832 40 mg/m² Q 28 days**
  PR: 46% decrease in target lesions after 4 cycles; 54% decrease after 15 cycles
  Treatment delayed at Cycle 13 (2 weeks) and Cycle 16 (1 week) for resolution of Grade 1 skin toxicity
  Remained on study 72 weeks (17 cycles) before progressing



Oct 2020 Baseline | Feb 2020 – Week 16 (PR) | Mar 2020 – Week 20 (Confirmed PR)

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Anti-tumor activity of FF-10832 in pancreatic cancer

Figure 6. 57 y/o male

- Nov 2016: Dx: metastatic pancreatic adenocarcinoma
  3.1 cm mass, pancreatic head
- Dec 2016: Whipple, pT3N1
- April 2017: Adjuvant GEM x 3 cycles
- July 2017: IMRT (50.4 Gy over 28 fractions) + capecitabine
- Sept 2017: Adjuvant GEM (plan for 6 cycles)
- Mar 2018: Recurrent disease; FOLFIRINOX with PD after 4 cycles
- Sept 2018: Clinical trial of MLN0128 + Alisertib
  Discontinued due to neutropenia and fatigue
- Jan 2019: **FF-10832 4.8 mg/m2 Days 1 & 15 Q 28 days**
  PR: 32% reduction in target lesions after 2 cycles before progressing after Cycle 3

Baseline | Week 8 (PR)

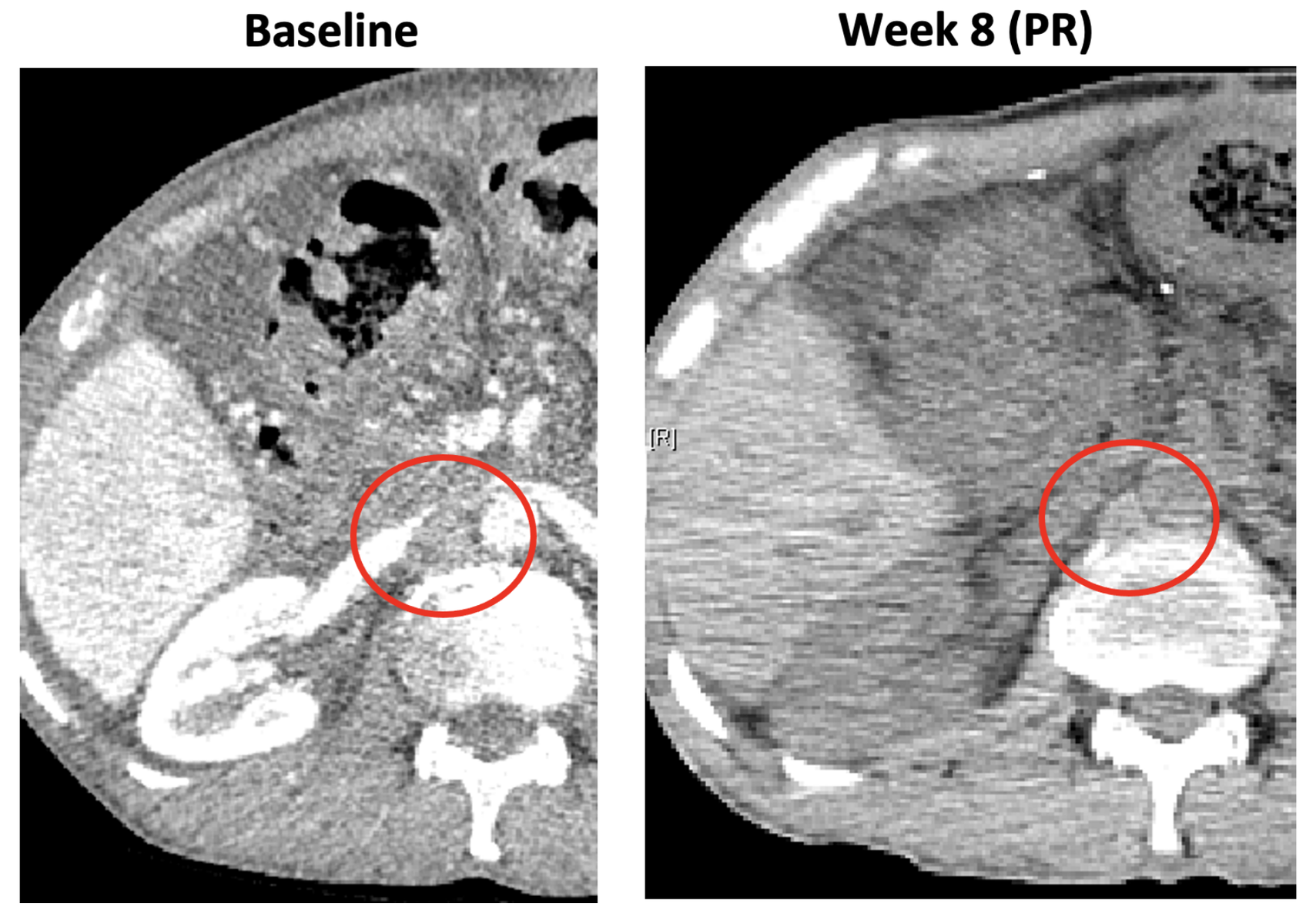
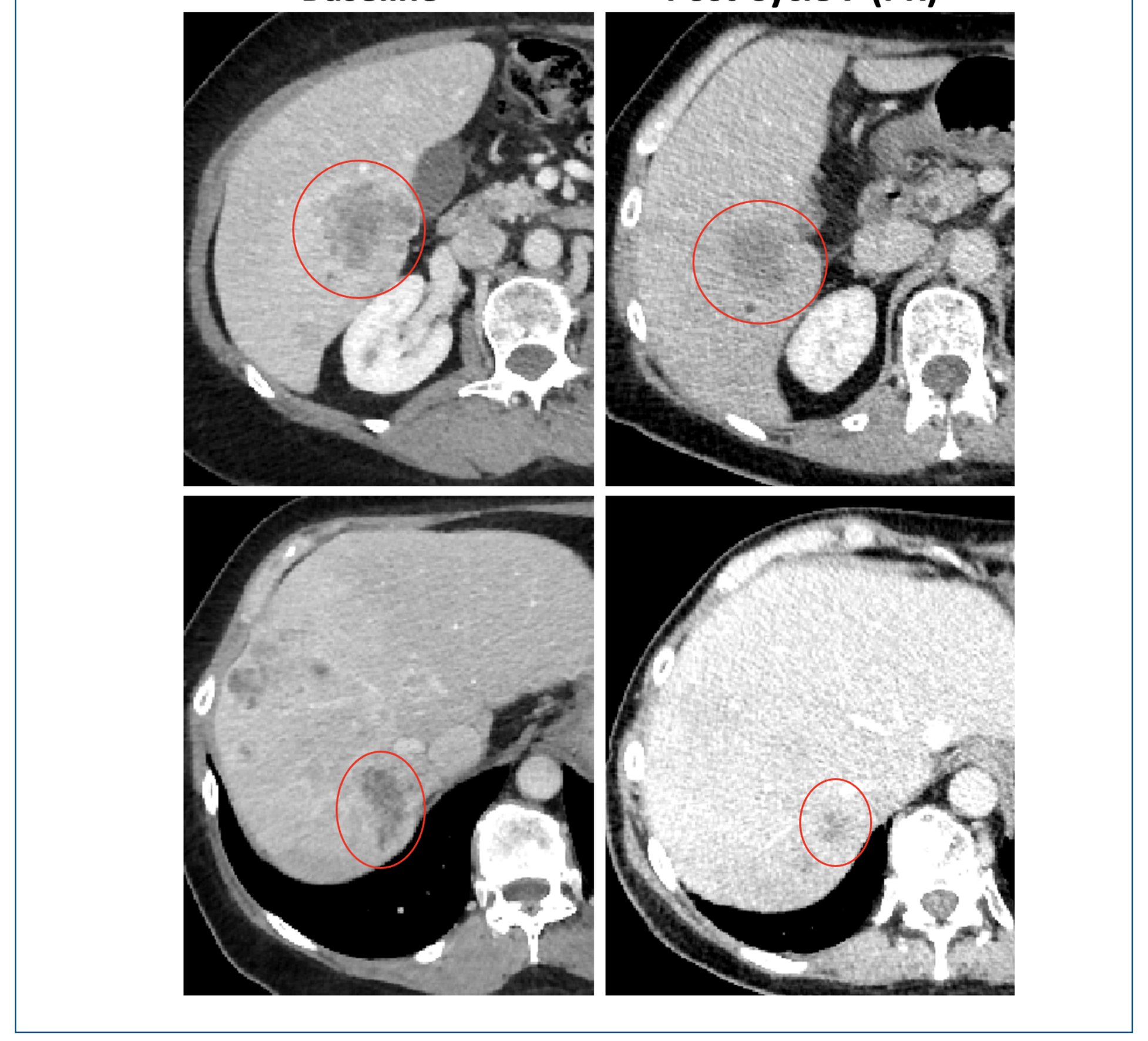


Figure 7. 64 y/o female

- May 2009 Dx: Pancreatic acinar cell carcinoma, Stage IB.
  Chemoradiation with mitomycin C + 5FU
- Nov 2015: Recurrence in the liver
- Jan 2016: FF-10502-01 (20% decrease then PD)
- Oct 2017: New tumor in T5
  XRT; HSP90 inhibitor conjugate; CSF1R inhibitor; PD-1 inhibitor
- Mar 2021: **FF-10832 40 mg/m² Q 28 days**;
  PR: 34% decrease in target lesions after 7 cycles;
  CA19-9: 4038 → 2753
- Treatment held after Cycle 7 (~5 months) due to unrelated hospitalization
- Patient restarted treatment at Cycle 8 and **remains on study with SD at Cycle 12**

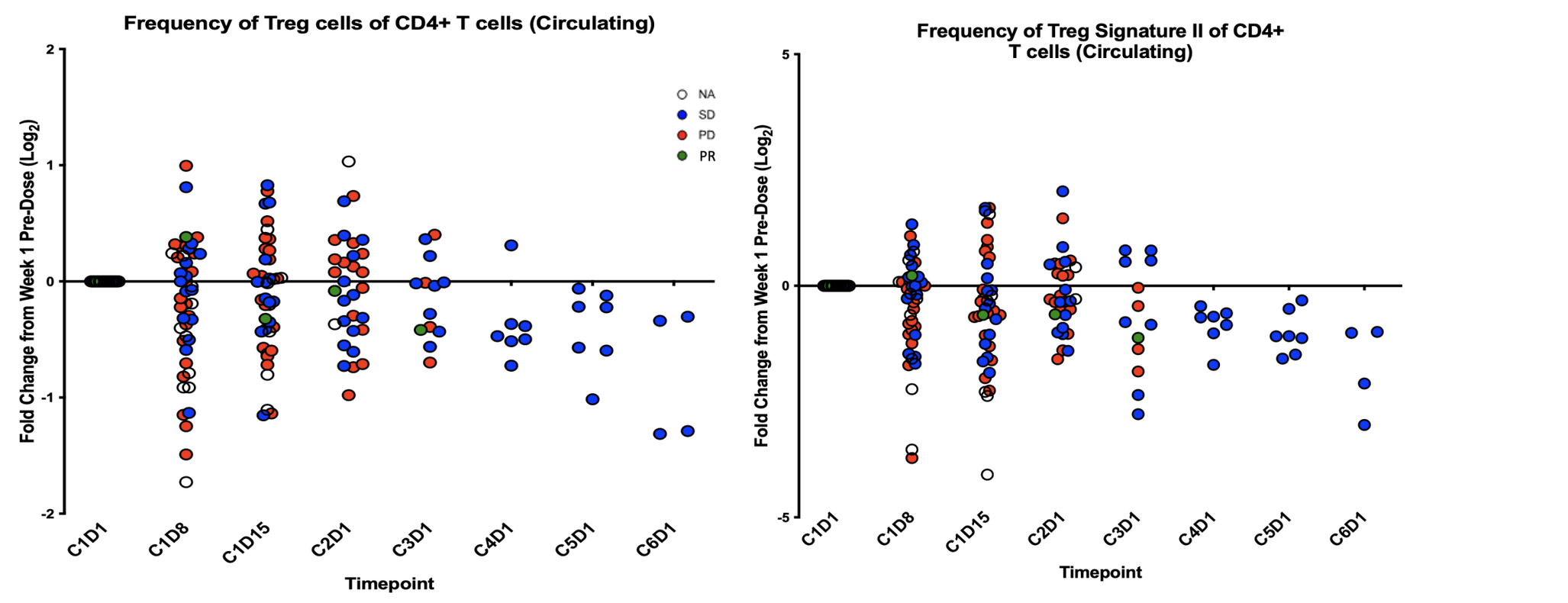
Baseline | Post Cycle 7 (PR)



Conversion to anti-tumor immune environment

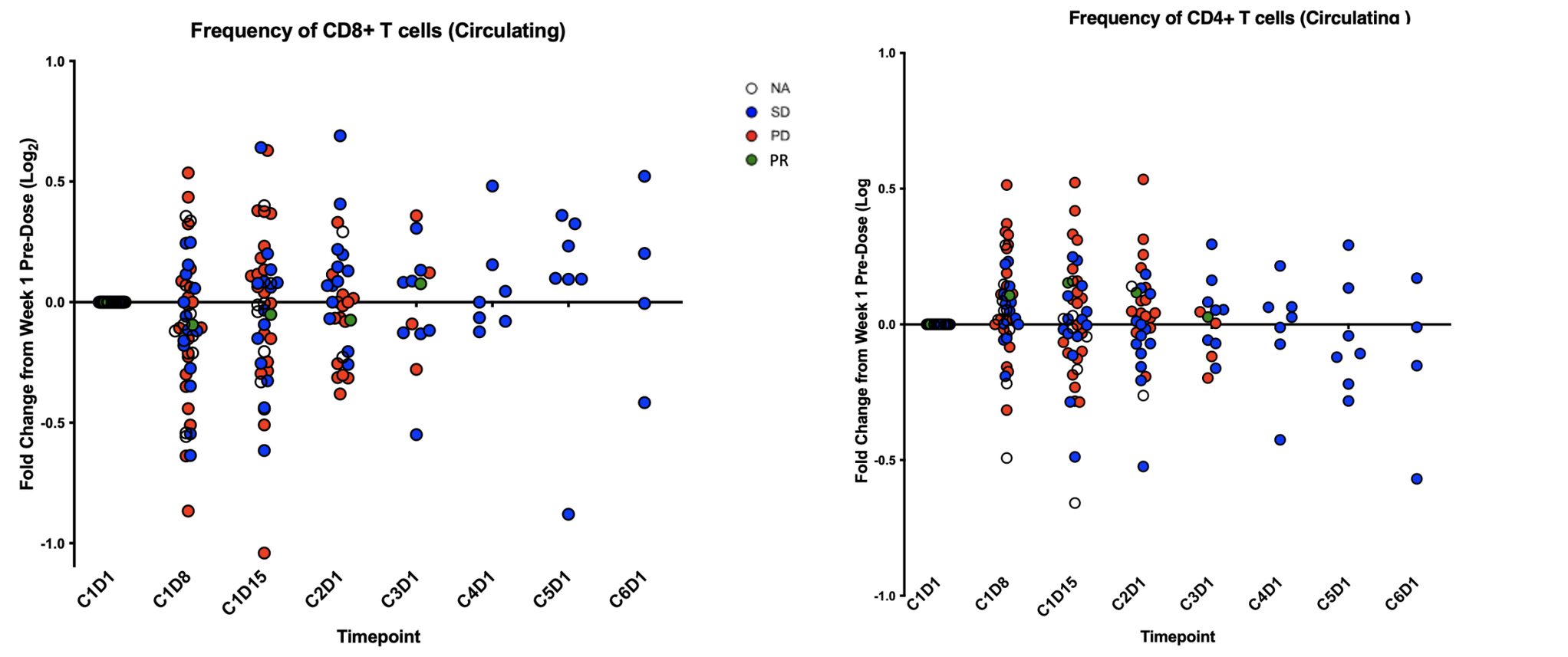
- **Statistically significant changes in circulating T-cell populations were observed**
  - Log decreases in the frequency of proliferating immune suppressive Ki67+ Tregs of CD4+ T-cells and Treg Signature II of CD4+ T-cells
  - Highly statistically significant through time (p-values 0.000 and 0.000, q values 0.000 and 0.007, respectively)

Log Decreases in Ki67+ Tregs | Log Decreases in Treg Signature II of CD4+ T-cells



- **In contrast, log increases observed in the frequency of total anti-tumor CD8+ T-cells (w/no decrease in total CD4+ T-cells)**

Log Increases in CD8+ T-cells | No change in Total CD4+ T-cells



- Overall:
  - Changes were related to both time and dose.
  - Patients with PR/SD overall demonstrated more positive changes (↓ Tregs relative to total CD4+ T-cells with ↑CD8+ T-cells).
  - Results suggest a shift in the general immune profile from an immunosuppressive environment to one that is more immunocompetent.

Summary

- FF-10832 is a novel liposomal formulation of GEM with increased plasma stability and enhanced tumor drug delivery. Macrophage uptake and immune activation in the TME play a role in the superior efficacy of FF-10832 compared to GEM, with selective, marrow-sparing biodistribution contributing to an improved safety profile.
- FF-10832 was well-tolerated administered on Day 1 of a 21-day or 28-day cycle, with minimal myelosuppression
  - Common drug-related adverse events were Gr ≤2 nausea, rash, pyrexia, fatigue, and vomiting.
  - Dose-limiting Gr ≥3 cellulitis/skin ulcers were observed at ≥23 mg/m² with twice per cycle dosing and those regimens discontinued.
  - The MTD was confirmed at 40 mg/m² (Q 21 days) and 48 mg/m² (Q 28 days) administered once per cycle on Day 1.
- Anti-tumor activity was shown in heavily pre-treated patients with advanced solid tumors, even at low FF-10832 doses:
  - Three PRs were observed in pancreatic and biliary tumors, with a durable response in a patient with gallbladder cancer who had progressed on prior GEM.
  - Disease control was maintained ≥20 weeks in patients with a variety of solid tumor types: sarcoma, bladder, endometrial, uterine, pancreatic, and appendiceal cancer.
- Dose proportional PK was observed, with a prolonged plasma $t_{1/2}$ (~26 hrs) and free fraction <1% of total GEM concentrations, suggesting continuous release in the TME.
- Dose and treatment duration-related immunomodulatory effects were shown that correlate with preclinical data[1], and suggest the combination of FF-10832 with immune checkpoint inhibitors as a promising future therapeutic approach.
- Expansion is ongoing in biliary tract cancer patients at the RP2D of 40 mg/m² Q 21-days.