

A Phase 1B Study of Pegylated Liposomal Mitomycin-C Prodrug (Promitil®) with or without Capecitabine (CAP) and Bevacizumab (BEV) in chemotherapy of Colorectal Cancer

Abstract #1528

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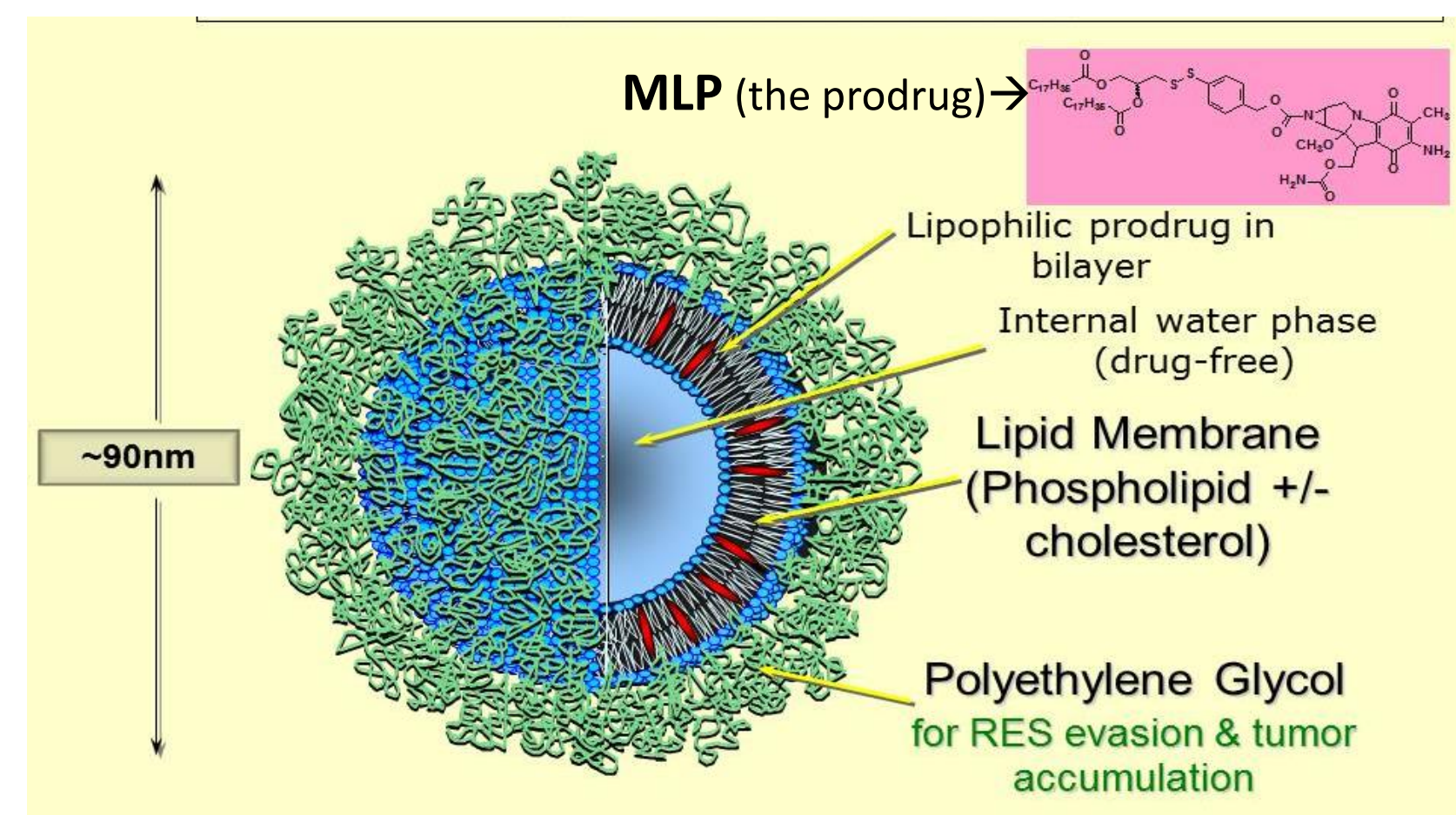
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Promitil Background

➤ Active ingredient (MLP): New Chemical Entity (MLP) based on Lipidated Prodrug of Mitomycin-C (MMC)

- Ease of formulation in Stealth liposomes
- Long shelf-life (36+ months at 5°C)
- Stability in absence of reducing agents
- Thiolytic cleavage generates active MMC¹
- Potent Therapeutic activity in various tumor models²
- Highly synergistic with Radiotherapy³
- Phase 1A study results confirm high plasma levels, prolonged circulation, and decreased toxicity (~3-fold less than MMC)⁴



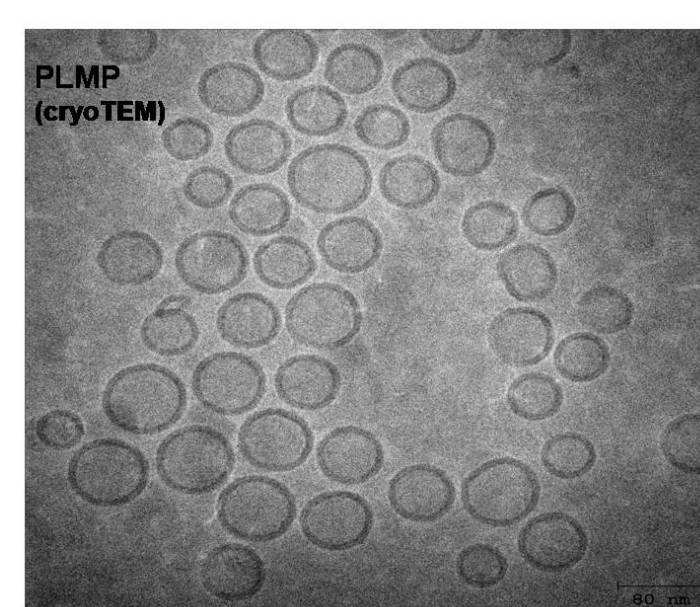
AIMS / Study Design / Methods

Primary Objective:

- To clear a safe dose-schedule of Promitil®, with or without CAP and BEV in advanced CRC patients

Secondary Objectives:

- To analyze the pharmacokinetics (PK) of Promitil®,
- To characterize the toxicity profile of Promitil®,
- To evaluate the anti-tumor response to Promitil® with or without CAP and BEV in advanced CRC patients



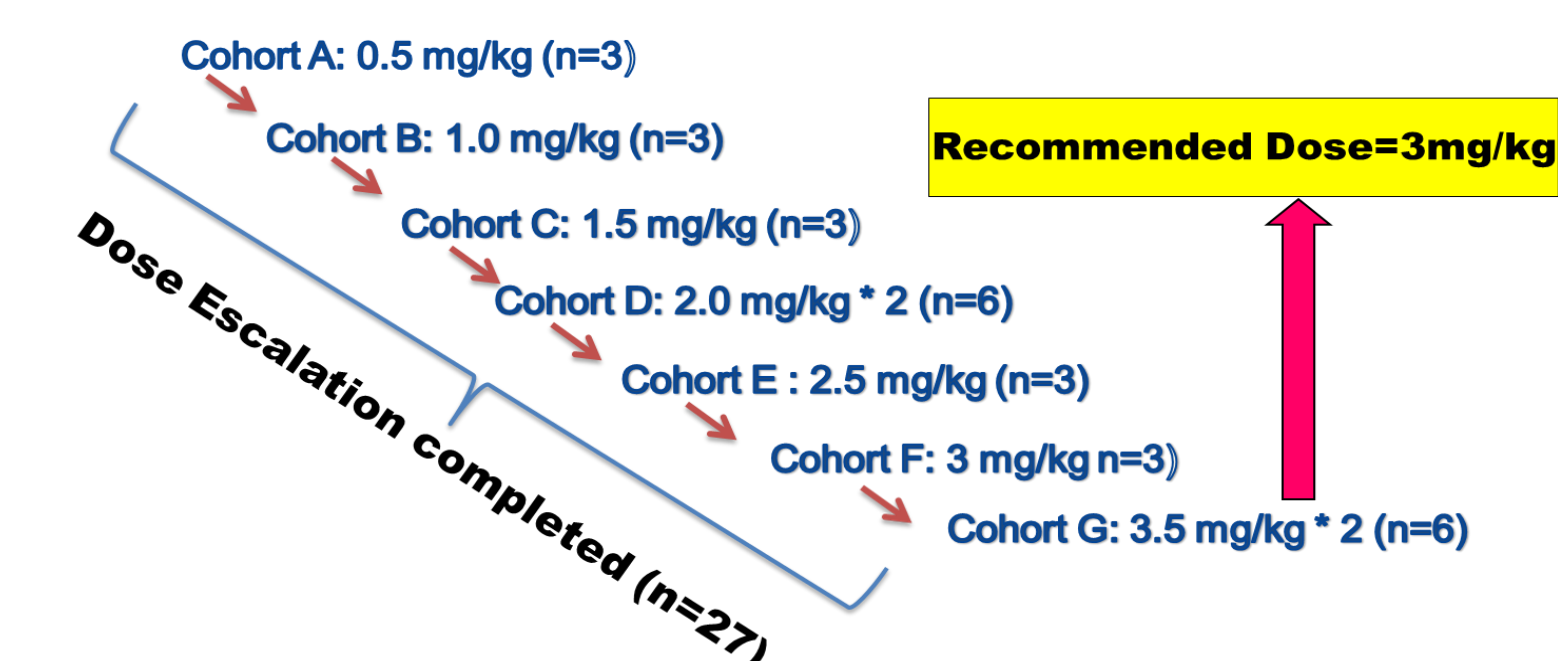
Study Drug Administration

Promitil Treatment:
i.v. drip ~2h
250 ml 0.9% Saline
every 4 weeks



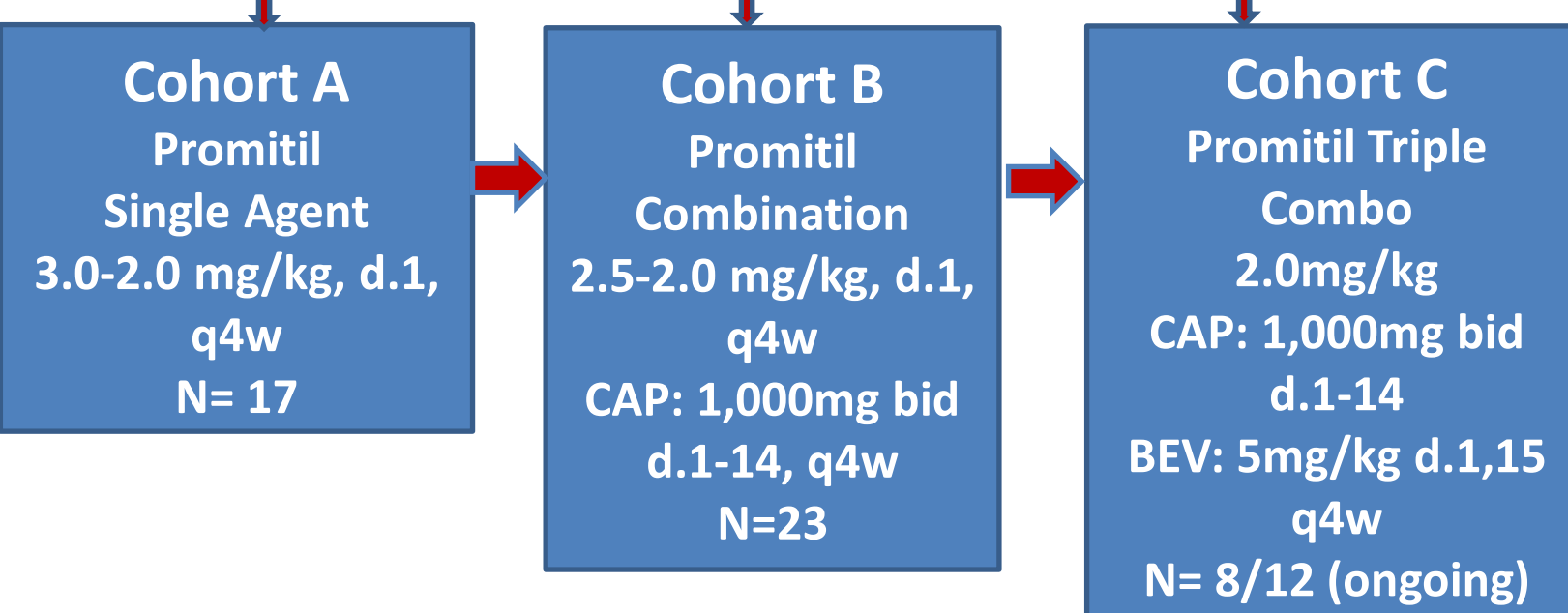
Day -21: Screening → Day 1, Cycle 1, PK, Weekly Clin-Lab and AE check → Day 29, Cycle 2, Bi-weekly Clin-Lab and AE check → Day 57, Cycle 3, Bi-weekly Clin-Lab and AE check → Day 84, End of Study with evaluation of tumor response → Extended Treatment at physician's discretion with monthly F/U

Initial Open Study: Phase 1A



Recommended Dose=3mg/kg

Current Study: Phase 1B* Patients with mCRC on ≥3rd line chemotherapy



Methods

- DLT will be cleared if <2 DLTs are observed in the first 6 treated patients during their first cycle. For cumulative DLT, 3 cycles will be evaluated.
- PK: Plasma levels of MLP measured by HPLC assay after the 1st cycle of treatment in blood samples obtained 15 min - 7 days after end of infusion
- All patients reaching 3 cycles will be evaluated for tumor response, and will be followed for survival.

* **Note:** 1 patient withdrew consent. The data from two patients have not yet been fully analyzed.

➤ Major Criteria of Eligibility

- Metastatic CRC, 18-80 yr-old, BMI: 18-36.
- ECOG P.S. ≤2; Creat≤1.5mg/dl; Bil≤2mg/dl; Plats≥100K
- Progression on two lines or more of chemotherapy/biological therapy (irinotecan, oxaliplatin, 5FU) and prior treatment with anti-EGFR antibodies in case of K-ras wild type tumors. Prior BEV optional.

Supporting References:

1. Amitay et al., Pharm Res. 2016; 33:686-700
2. Gabizon et al., J Control Release. 2012;160:245-53
3. Tian et al., Int J Rad Oncol Biol Phys, 2016; 96:547-55
4. Golan et al., Cancer Med. 2015; 4:1472-83

Results

Patient Demographics:

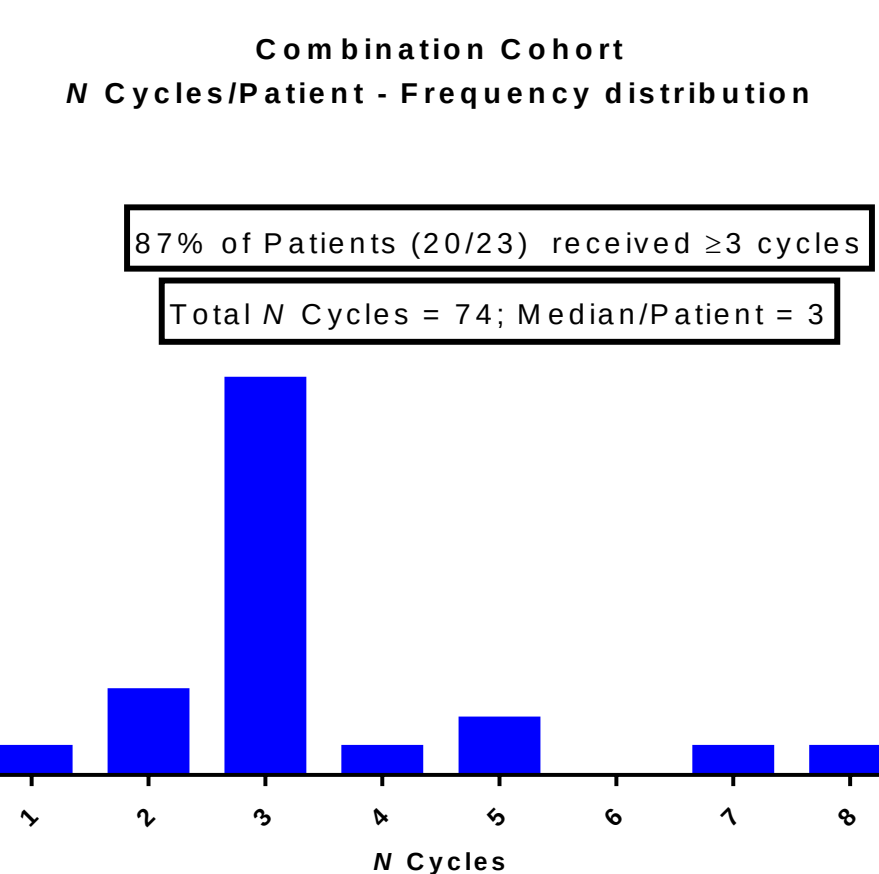
- ❖ **Median Age: 63 (40-79)**
- **Single Agent Cohort: 65 (51-79)**
- **Combination Cohort: 62 (40-75)**
- ❖ **Female / Male: 20 / 20**
- **Single Agent Cohort F/M = 7/10**
- **Combination Cohort F/M = 13/10**
- ❖ **ECOG P.S. – Median (range): 1 (0-2)**
- ❖ **All patients received at least 2 prior chemotherapies (oxaliplatin, irinotecan, 5FU)**

SAFETY

- No single dose-limiting toxicity after 1st cycle of Promitil
- The majority of the AE's were mild to moderate and not related to the study drug.
- 10 and 16 SAE's in Cohorts A and B respectively, NOT related to study drug.
- No alopecia, mucocutaneous toxicity or diarrhea.
- Thrombocytopenia, and fatigue were the most frequent drug-related AE's

Most Frequent Drug-Related AEs

Preferred Terms	Cohort	
	Single Agent N=17	Combined N=21
#Events (% subjects)		
Thrombocytopenia	10 (35%)	28 (52%)
Fatigue	4 (12%)	8 (29%)
Infusion Reaction	8 (18%)	3 (14%)
Anemia		6 (10%)
Nausea	1 (6%)	3 (10%)
Loss Of Appetite		3 (14%)



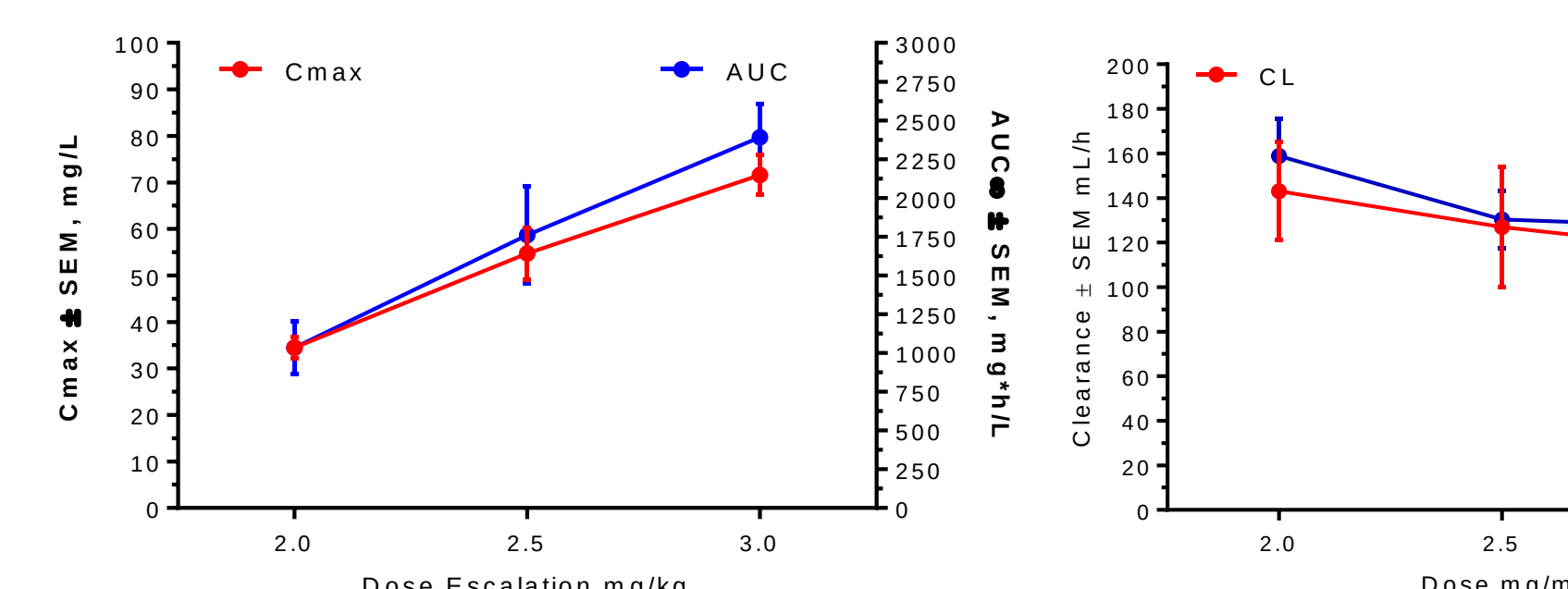
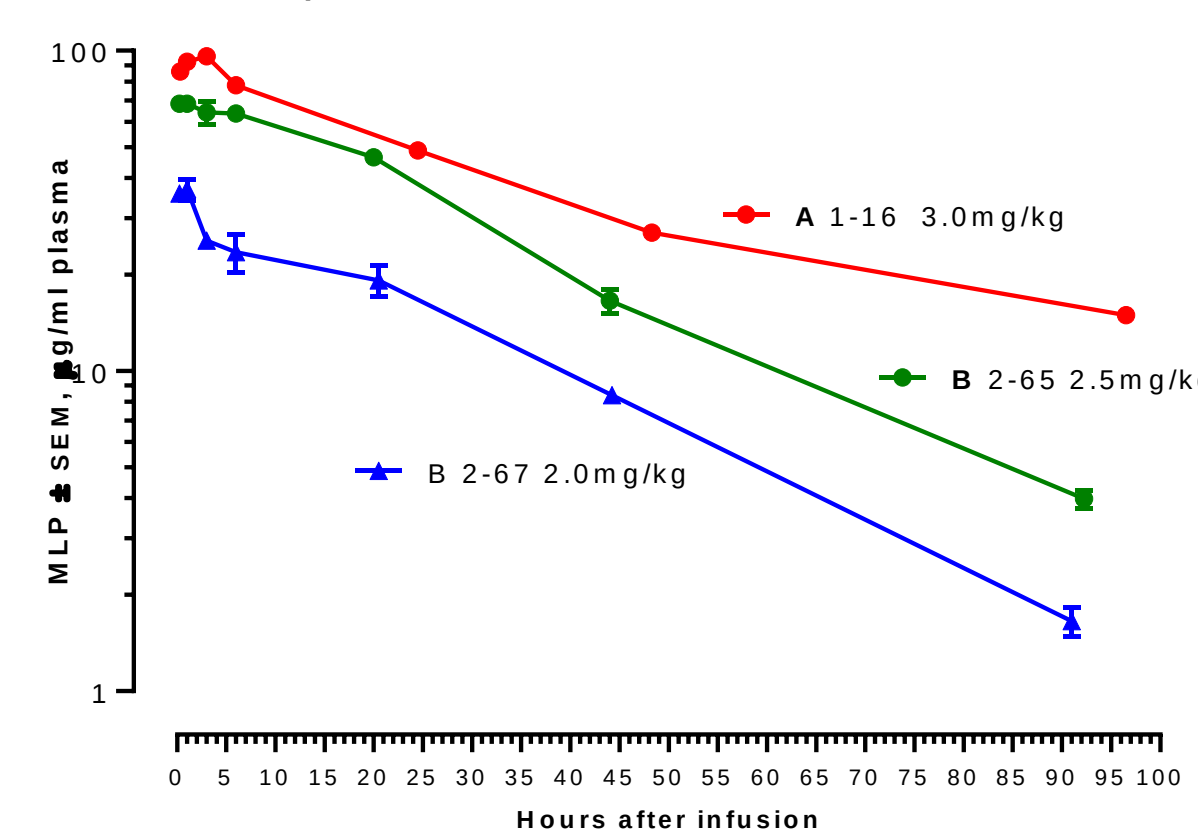
Administered Dose as % of Planned Dose/Cycle [Range] N patients

Cycle	Dose (mg/kg)	Cohort	
		Single Agent	Combined
1	3.0	100% [95-101]	
	2.5		100% [99-100]
	2.0		100% [96-101]
2	2.0	100% [97-100]	100% [80-101]
	2.0	100% [100-100]	100% [79-101]
3	2.0		

	Median Cumulative Dose mg/kg (Range)
Single Agent Cohort	7.0 (3.0-15.0)
Combination Cohort	6.0 (4.0-15.5)

Pharmacokinetics of Promitil in CRC Patients

PK of 3 CRC patients at 3 dose levels of Promitil in Phase 1B



			Cmax (µg/ml)		AUC _{0-inf} (µg*h/ml)		T _{1/2} (h)		CL (mL/h)		Vd (L)	
Dose (mg/kg)	Cohort	N	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
2.0	Combination	7	34.5	2.3	1034	167	20.7	2.1	143	22	3.97	0.42
2.5	Combination	5	54.7	5.6	1760	313	19.1	1.6	127	27	3.26	0.32
3.0	Single Agent	17	71.6	4.3	2391	212	20.9	1.0	116	19	3.17	0.29

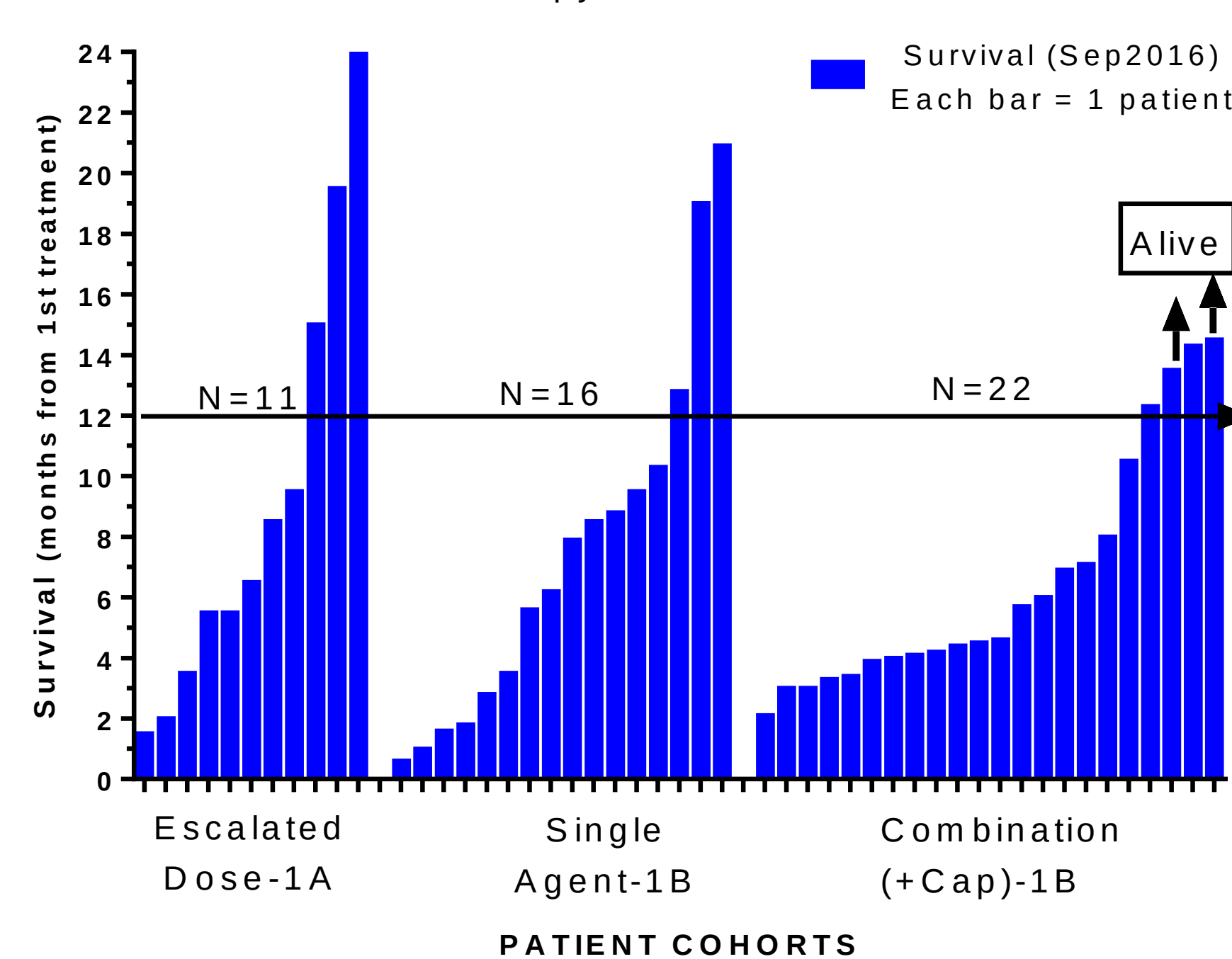
- ❖ Slow, mono-exponential clearance of MLP, with high plasma levels, half-life of ~20 hours and small volume of distribution.
- ❖ Dose Effect: Slight deviation from linearity suggesting saturation trend.
- ❖ No measurable free MMC in plasma

Results (continued)

EFFICACY and SURVIVAL

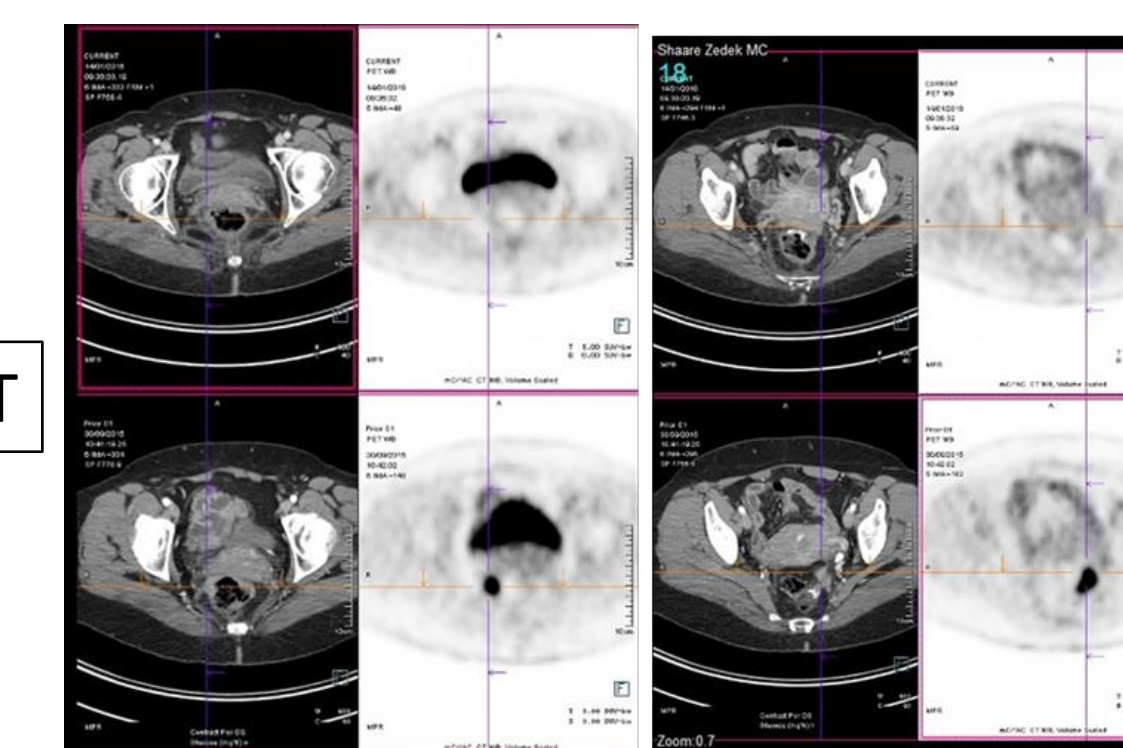
- Survival analysis of 3rd Line CRC patients treated with Promitil in Phase 1 (A+B) includes a total of 49 patients who received between 1-3mg/kg. Median Survival was 5.7mth (range: 1-24) for all patients, and **7.9 mth** (N=35, range: 3-24) for patients who received ≥ 3 treatment doses.
- **12-mth Survival** was **21%** for all patients, and **26%** for patients receiving ≥ 3 treatment doses.
- Evaluation of Tumor Response in 36 patients reaching week 12 after 3 cycles: **SD = 33%** (12/36). There were no PR. (See below for response to Promitil and Radiotherapy.)

Promitil in 3rd Line Therapy of Advanced CRC - Survival Results

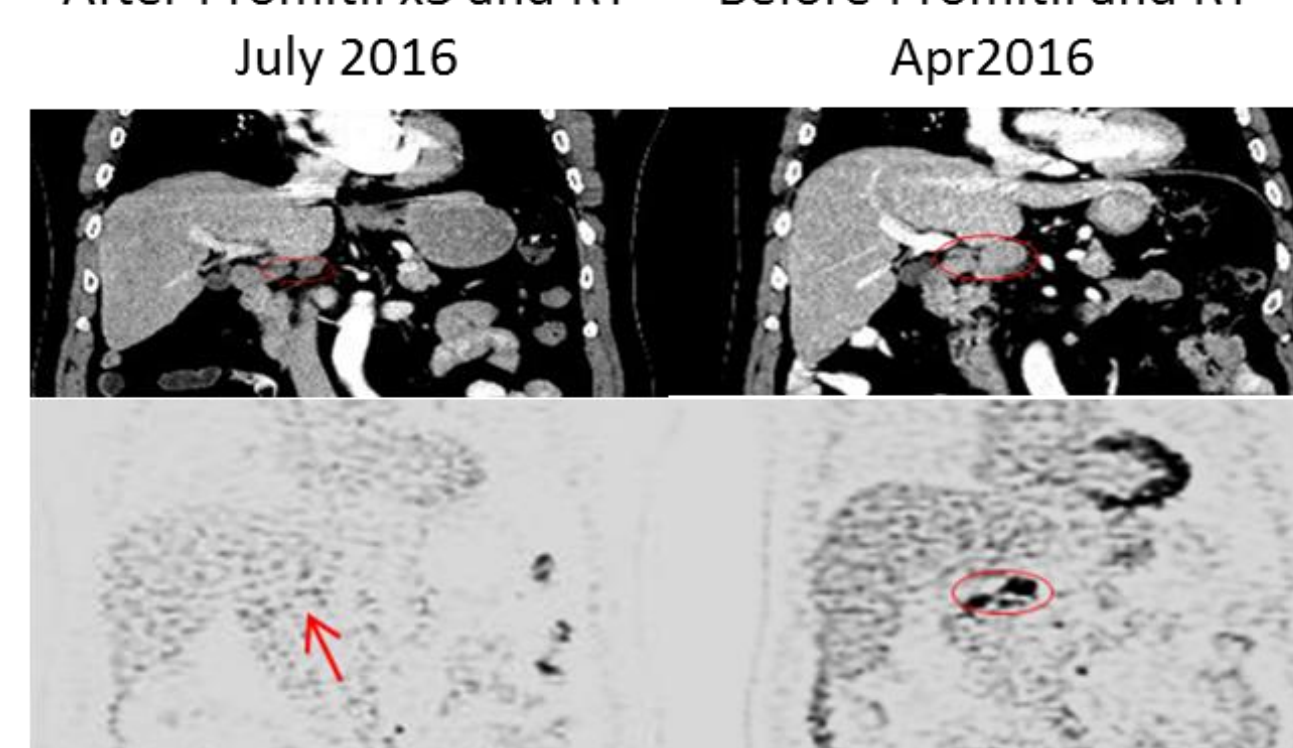


Promitil and Radiotherapy (based on Ref. 3) in off-protocol CRC 3rd Line patients

Case 1: Pelvic LN



Case 2: Retroperitoneal LN



Conclusions

- Promitil is well-tolerated, and safe to administer in CRC patients with or without CAP.
- Thrombocytopenia is the most frequent AE and is cumulative dose limiting.
- Recommended dose is 2.5 mg/kg q4w as Single Agent, and 2.0mg/kg in combo with CAP 1,000 mg b.i.d. days 1-14, q4weeks.
- The PK is Stealth-like as reported previously with long T_{1/2} (~20h) and is not affected by CAP intake.
- >20% of patients reached >12 mth survival. Accrual to Cohort C, combining Promitil with CAP and BEV in CRC patients, is ongoing.
- Sustained and near-CR in 2 patients with Colo-Rectal Ca receiving Promitil and Radiotherapy