

Drug-Eluting Bead Irinotecan (DEBIRI) Therapy of Liver Metastases from Colon Cancer with Concomitant FOLFOX 6 and Anti-Angiogenic Therapy

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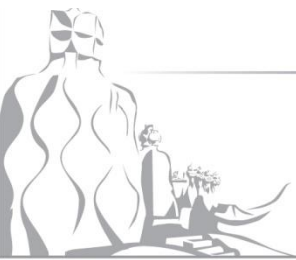
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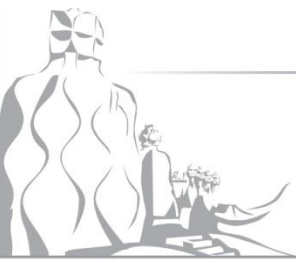


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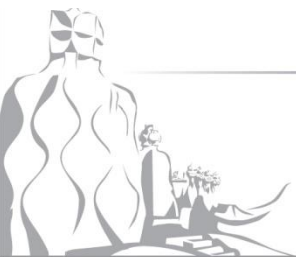
Objectives

- **The primary objective of this study:**
 - Evaluate the safety and efficacy of LC Bead, loaded with irinotecan in combination with intravenous chemotherapy versus intravenous chemotherapy alone
 - The treatment of chemo-naive unresectable liver metastases in patients with colorectal cancer
- **Multicenter, open label, prospective, Phase I followed by a randomized Phase II study**
- **LC Bead (DC Bead in Europe and ROW), loaded with irinotecan treatment with FOLFOX systemic chemotherapy who had not previously received chemotherapy**



Hypothesis

- **Adding Irinotecan Drug-Eluting Bead (DEBIRI) to standard FOLFOX + Avastin is Feasible, Safe, and Effective**



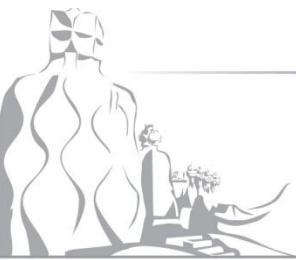
Endpoints

Primary Endpoint

Primary endpoint will be tumor response according to modified RECIST Criteria

Secondary Endpoint

- Safety
- Pharmacokinetics of systemic irinotecan and SN-38 (LC Bead loaded with irinotecan for feasibility group only)
- Progression-free survival
- Local tumor response (extent of necrosis in the treated lesions)
- Hepatic progression-free survival
- Change in tumor marker
- Time to progression
- Overall survival (telephone follow-up)

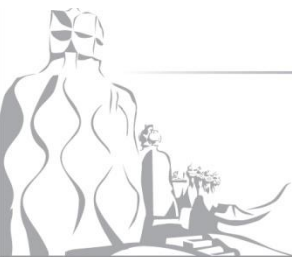


Feasibility Study: n=10 Patients

- **Concurrent full dose: mFOLFOX6 +/- Avastin**
 - Oxaliplatin 85mg/m²
 - with 2 LC Bead™ treatments (100mg irinotecan)
- **Schema:**

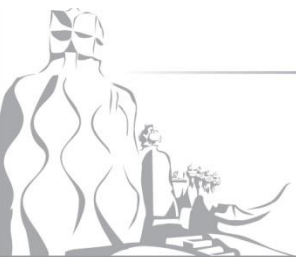
| Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 |
|---------------------|--------------------------------|--------------------|--------------------------------|---------------------|--------|---------------------|
| FOLFOX + Avastin | LC Bead 100mg Irinotecan | FOLFOX +Avastin | LC Bead 100mg Irinotecan | FOLFOX + Avastin | Break | FOLFOX + Avastin |

Then repeat CT to evaluate initial response



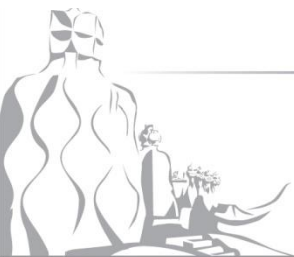
FOLFOXDEBIRI: Baseline – 10 Patients

| | |
|---|-----------------------------------|
| Median Age - Years (Range) | 63 (48-84) |
| Gender (M/F) | 6/4 |
| Race (AA/C) | 3/7 |
| Prior Cancer Therapy | |
| Lymphoma | 1 |
| Endometrial | 1 |
| Prior Liver Surgery | RFA = 2 |
| Laboratory Parameters | |
| T bili | 0.4 (0.3-0.6) |
| Creat | 0.9 (0.7-1.5) |
| CEA (median, range) | 386 (2.6 -2893) |
| ECOG Performance Status | |
| 0 | 5 |
| 1 | 5 |
| Colon/ Rectum Primary (In place) | |
| Colon | 7 (2) |
| Rectum | 3 (3) |
| Presence of Extra-Hepatic Disease (Yes/No) | 5/5 (Lung/Peritoneum) |
| Extent of Overall Tumor Burden in Liver | 100% = 5, 95% = 2, 80% = 3 |



Treatment Summary

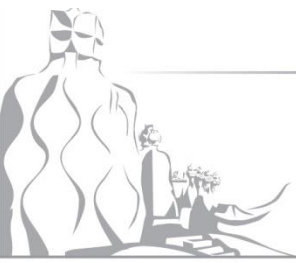
- **Percent of liver tumor involvement was a median of 45% (range 20-55%)**
- **All patients have undergone at least 4 cycles of FOLFOX and bevacizumab, in combination with 2 DEBIRI bead treatments during the patients' off week**
- **All patients have received full dose FOLFOX without the need for dose reduction or delay**



Response Rates & Pharmacokinetics

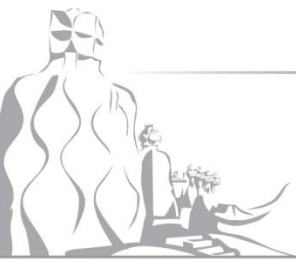
- **Currently: One related SAE (grade 2) HTN**
- **3-month and 6-month response rate: 100% (2 CR, 8 PR)**
- **PK data minimal detectable levels of CPT-11 and SN-38**
 - **After 1st, 2nd and 3rd DEBIRI treatments**

| Sample | 1 hour (nm/ml) | 4 hours (nm/ml) | 24 hours (nm/ml) |
|-----------------------------------|------------------|-----------------|------------------|
| Irinotecan (median, range) | | | |
| DEBIRI 1 | 281 (207-484) | 112 (101-215) | 18.6 (11.8-31) |
| DEBIRI 2 | 261 (218-494) | 114 (84-202) | 21 (15.5-28.5) |
| DEBIRI 3 | 237 (217-270) | 127 (108-167) | 18.6 (14.8-34.3) |
| SN-38 (median,range) | | | |
| DEBIRI 1 | 16.4 (11.4-27.8) | 6.2 (3.5-10.6) | 1.06 (0.9-1.6) |
| DEBIRI 2 | 9.3 (6.8-19.0) | 5.85 (3.0-6.78) | 1.47 (1.12-1.90) |
| DEBIRI 3 | 12.0 (8.2-15.8) | 8.8 (4.8 -10.5) | 1.55 (1.37-1.67) |



Surgical Downstaging

- **5 (50%) patients downstaged to resection**
- **All tolerated surgical resection**
- **Pathologic response rates >90%**



Summary: FOLFOXDEBIRI

- **Combination Systemic FOLFOX +/- Avastin with DEBIRI is:**
 - Safe
 - Effective
 - Superior Surgical Downstaging
- **Current Phase 2 study is needed to demonstrate superiority**



Design: First-Line Metastatic Colorectal Cancer

Pilot: N=60



Randomize: N=60

1:1

Arm A (Standard)

Chemotherapy

1. Bevacizumab 5mg/kg on d1 if indicated based on last surgical date
2. FOLFOX regimen (oxaliplatin 85mg/sqm d1, I-LV 200mg/sqm d1 and 5FU 3200mg/sqm 48- flat continuous infusion starting on d1) repeated every 2 weeks

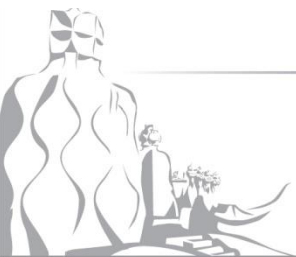
Arm B (Experimental)

Chemotherapy

1. Bevacizumab 5mg/kg on d1 if indicated based on last surgical date
2. FOLFOX regimen (oxaliplatin 85mg/sqm d1, I-LV 200mg/sqm d1 and 5FU 3200 mg/sqm 48- flat continuous infusion starting on d1) repeated every 2 weeks

i.a. LC Bead™ Irinotecan

2ml LC Bead™ + irinotecan 100mg at week 1 and week 3
2-6 cycles at investigator's discretion based on response, toxicity, tumor burden.



Thank You

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