

RESULTS OF A PROSPECTIVE RANDOMIZED TRIAL ASSESSING SURVIVAL AT 30 MONTHS OF POLYVINYL ALCOHOL MICROSPHERES PRELOADED WITH IRINOTECAN (DEBIRI) VS. FOLFIRI IN PATIENTS WITH HEPATIC METASTASES FROM COLORECTAL CANCER

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Introduction (1)

- Liver metastases (LM) from colorectal cancer (CRC) occur in more than 50% of patients.
- 5-year survival after resection is 25-35%, but recurrence is common.
- For unresectable LM the survival is 5% at 5 years.
- Palliative chemotherapy is the mainstay of treatment.

Introduction (2)

- Toxicity is common and median survival is about 22 months with the addition of monoclonal antibodies.
- Ablative or trans-arterial techniques allow localised, minimally invasive therapy without systemic toxicity or morbidity.
- Catheter-delivered arterial treatments include TACE with polyvinyl alcohol microspheres .

Drug-Eluting Beads and Irinotecan: why selected ?

- DEB (DC Bead[®]) can be loaded with IRI 50mg/ml. The loading of IRI does not affect its ability to be suspended in contrast agent or delivered through a catheter.
- Following porcine hepatic artery infusion of DEBIRI, maximum plasma levels were 70-75% lower for both Irinotecan and SN-38, compared to intra-arterial bolus administration (Taylor RR Eur J Pharm Sci. 2007 Jan; 30(1):7-14.)

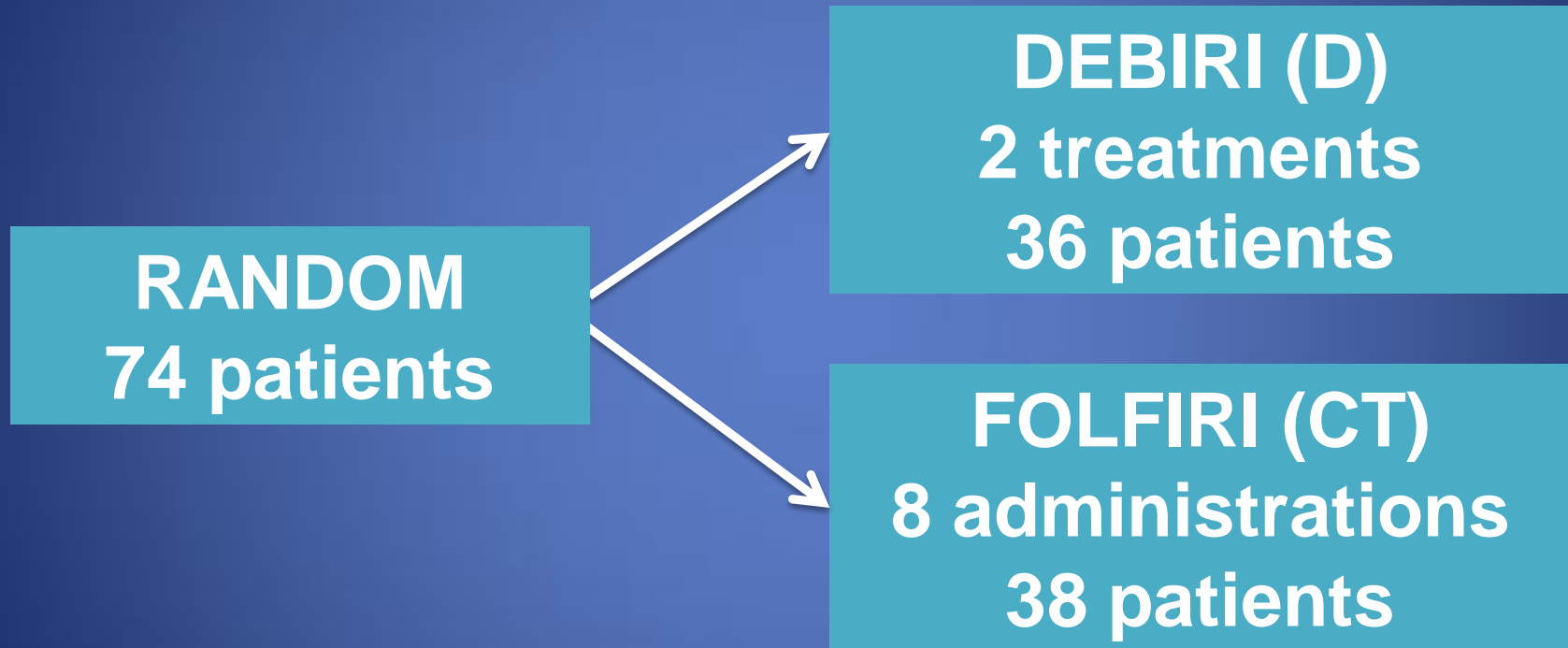
Development of the Study

Study was planned in March 2005, approved by Ethical Committee on May 2006 and from December 2006 to December 2008, 74 pts were randomized out of 134 observed.

FEASIBILITY, STATISTICS, END-POINTS

- DEBIRI is a combination of local drug infusion with selective embolisation of the Liver Metastases-feeding arteries. It is feasible and safe (ASCO-GI 2007, abs # 356; IN VIVO 2007, 21, 6; ASCO-GI 2008 abs # 480).
- The study was designed to show an increase of 40% of median overall survival (MS, primary endpoint) at 2 years follow-up (HR = 0.72 using Kaplan-Meier method).
- Response rate, progression-free survival and quality of life (Edmonton Symptom Score) were secondary endpoints.

Plan of the Study



PATIENTS CHARACTERISTICS	DEBIRI (D)	FOLFIRI (CT)
NUMBER OF PATIENTS	36	38
SEX (M – F)	20-16	24-14
AGE	64 (range 44-74)	63 (range 42-73)
LIVER INVOLVEMENT (≤ 25% - ≤ 50%)	26 - 10	26 - 12
SYNCHRONOUS/METACHRONOUS DISEASE	0/36	0/38
NUMBER OF METASTASES	4 (range 3 – 10)	4 (range 3 – 10)
LARGEST DIAMETER (cm)	4.5 (range 2.5 -8)	4 (range 2.5 – 8)
PERFORMANCE STATUS (0 – 1 and 2)	32 and 4	34 and 4
EXTRAHEPATIC METASTASES	0	0
PREVIOUS CHEMO (2–3 LINES)	23 - 13	25 - 14
TYPES OF PREVIOUS CHEMO	13 FUFA, 18 FOLFOX, 13 IFL, 3 FOLFOX+BEVACIZUMAB 3 FU+CETUXIMAB	12 FUFA, 20 FOLFOX, 14 IFL, 5 FOLFOX+BEVACIZUMAB 3 FU+CETUXIMAB
WEIGHT LOSS IN 2 MONTHS	20 (60%)	24 (63%)
ALBUMIN, g/dl (median)	4	3.9
CEA ng/mL	69 (range 3.5-673)	77 (range 2.5-611)
K-RAS (WT-M)	22 - 14	26 - 12
P53 (positive-negative)	22-12	20-18

DEBIRI : Supportive Therapy

(Fiorentini G. et al: Hepatogastroenterology 2008; 55(88):2077-82)

Intravenous (iv) hydration started Day-1 and continued on Day 0, +1, +2

- 2000ml bag/24h infusion (1000ml of saline solution 1000ml of glucose 5%) with the addition of Ranitidine 900mg

Prophylactic treatment against nausea

- Tropisetron 5mg, 1 vial iv before and 1 vial at +6 hours
- Prednisone 25mg orally (or Desamethasone 8mgr iv) at 08.00 am and at 08.00 pm on day 0,+1,+2,+3,+4,+5

Prophylactic treatment against pain

- Morphine 10mg 1 vial iv 30 minutes before DEBIRI and 1vial at +6 hours
- Intra-arterial Lidocaine 5ml just before DEBIRI

Prophylactic treatment against infection

- Cefazolin 2000mg iv at 08.00 am and at 08.00 pm day 0,+1,+2
- The supportive treatment is continued if required on day +3, +4, +5

DEBIRI : Administration

- Diagnostic angiography (DSA) was performed.
- Under fluoroscopic guidance, a solution of 4 ml of DEB 100-300 μ m loaded with IRI 200mg and mixed with non-ionic contrast medium was injected into the artery feeding the metastases.

Results

- 3 out of 38 FOLFIRI (CT) patients were not available for evaluation (1 declined, 2 refused).
- 1 out of 36 DEBIRI (D) patients had early disease progression.
- 35 (CT) and 35 (D) patients were analyzed for this report.
- 70 cycles of DEBIRI with a relative dose intensity of 99% and 272 FOLFIRI cycles with a relative dose intensity of 90% were administered.

Total amount of IRI received (calculated for patient of 1.8 sqm)

- **DEBIRI** **2 X 200= 400 mgr**
- **FOLFIRI** **8 X 320= 2600 mgr**

Observed Toxicity (G2-G3)

Toxicity (all procedures)	70 DEBIRI	272 FOLFIRI
Pain	11 (31%)	0%
Vomiting & Nausea	10 (28%)	54 (20%)
Fever	7 (10%)	6 (2%)
Diarrhoea	2 (6%)	95 (35%)
Asthenia	9 (26%)	136 (50%)
Leukopenia	2 (6%)	95 (35%)
Anaemia	2 (6%)	95 (35%)
Alopecia	2 (6%)	68 (25%)

Responses observed

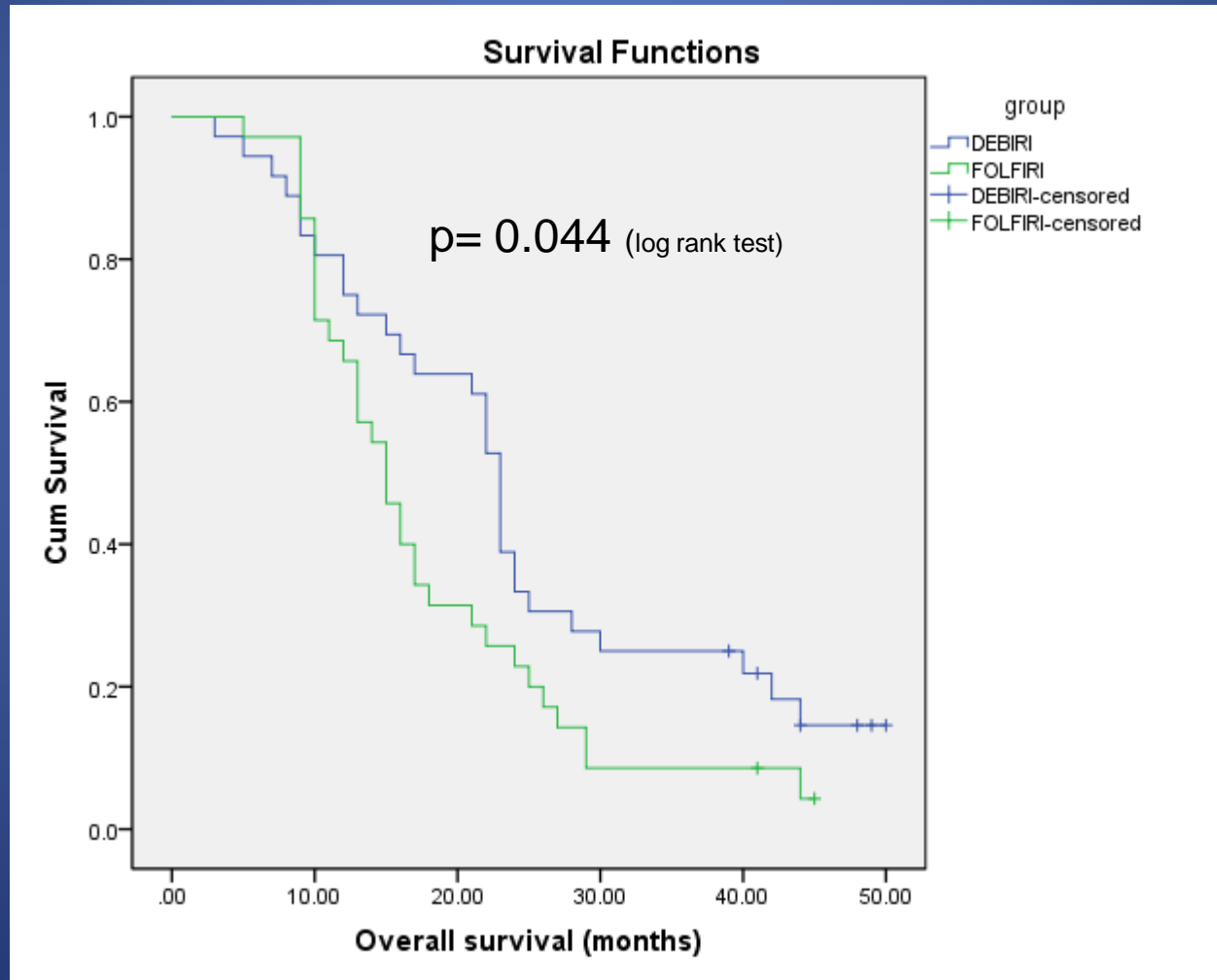
	DEBIRI 35 pts	FOLFIRI 35 pts
COMPLETE & PARTIAL RESPONSES	24 (68.6%)	5 (14,2%)
STABLE DISEASE	4 (11.4%)	13 (37,2%)
PROGRESSION	7 (20%)	17 (48,6%)

Results

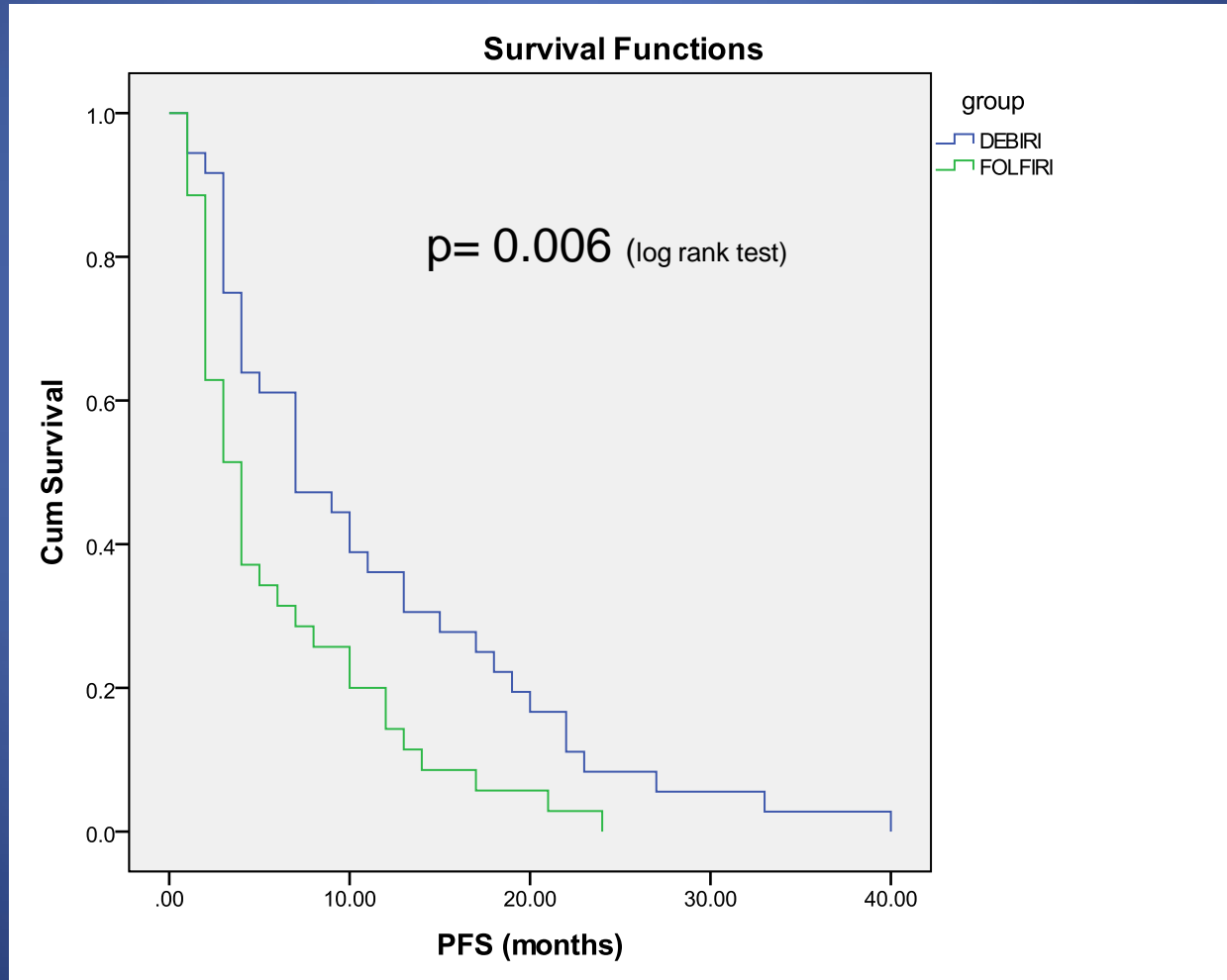
(at median follow up 30 months range 26-48)

Arm	Median Overall Survival (Months)	PFS (Months)	Acute Toxicity (G2-G3)	Late Toxicity (G2)	Edmonton Score Improvement (from baseline)	Cost per Patient (Euros)
DEBIRI (D) (n=34)	23	7	40%	24%	60%	7,000 (2 D)
FOLFIRI (CT) (n=35)	15	4	22%	80%	22%	24,000 (8 CT)

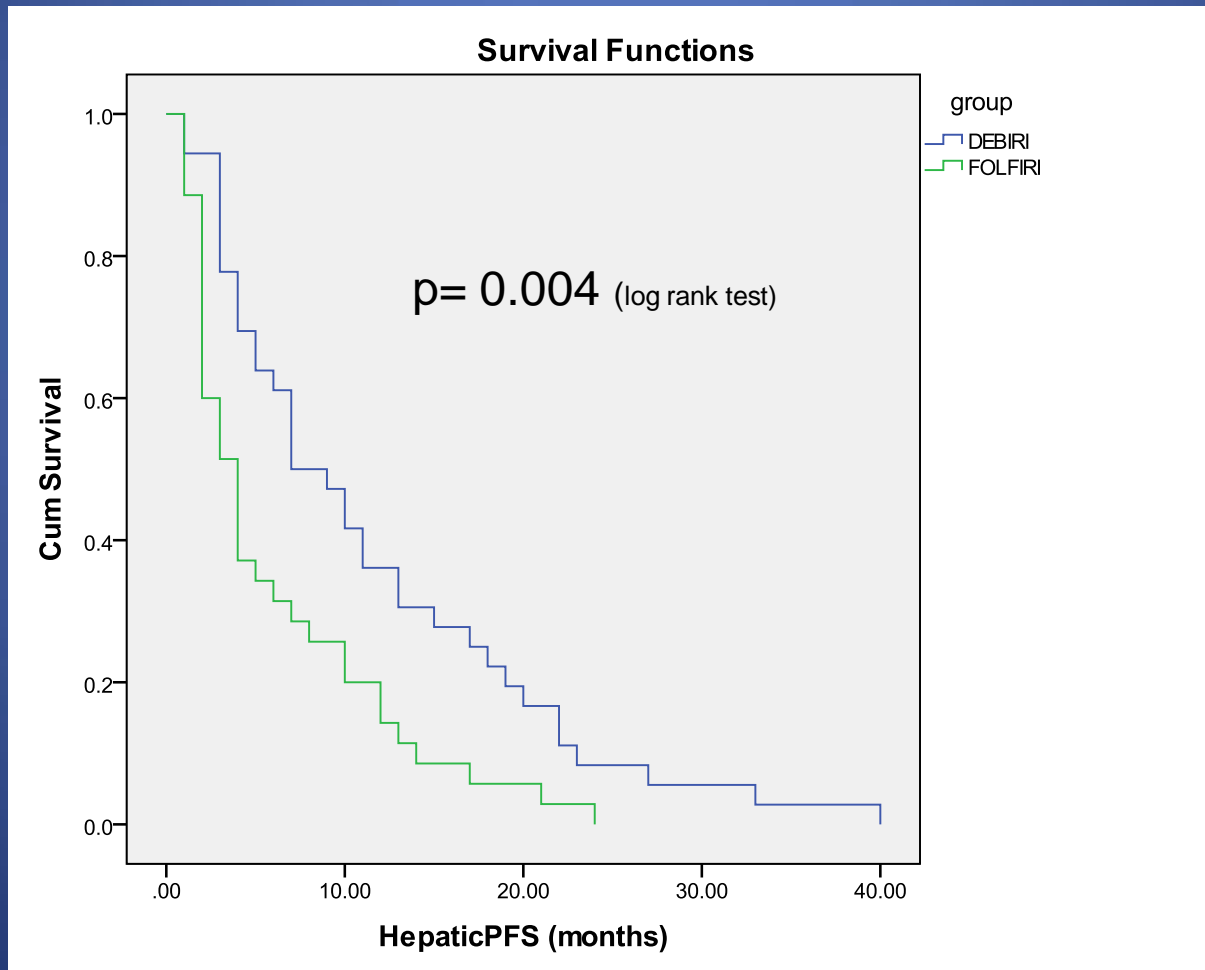
Kaplan-Meier Curve: Overall Survival (OS)



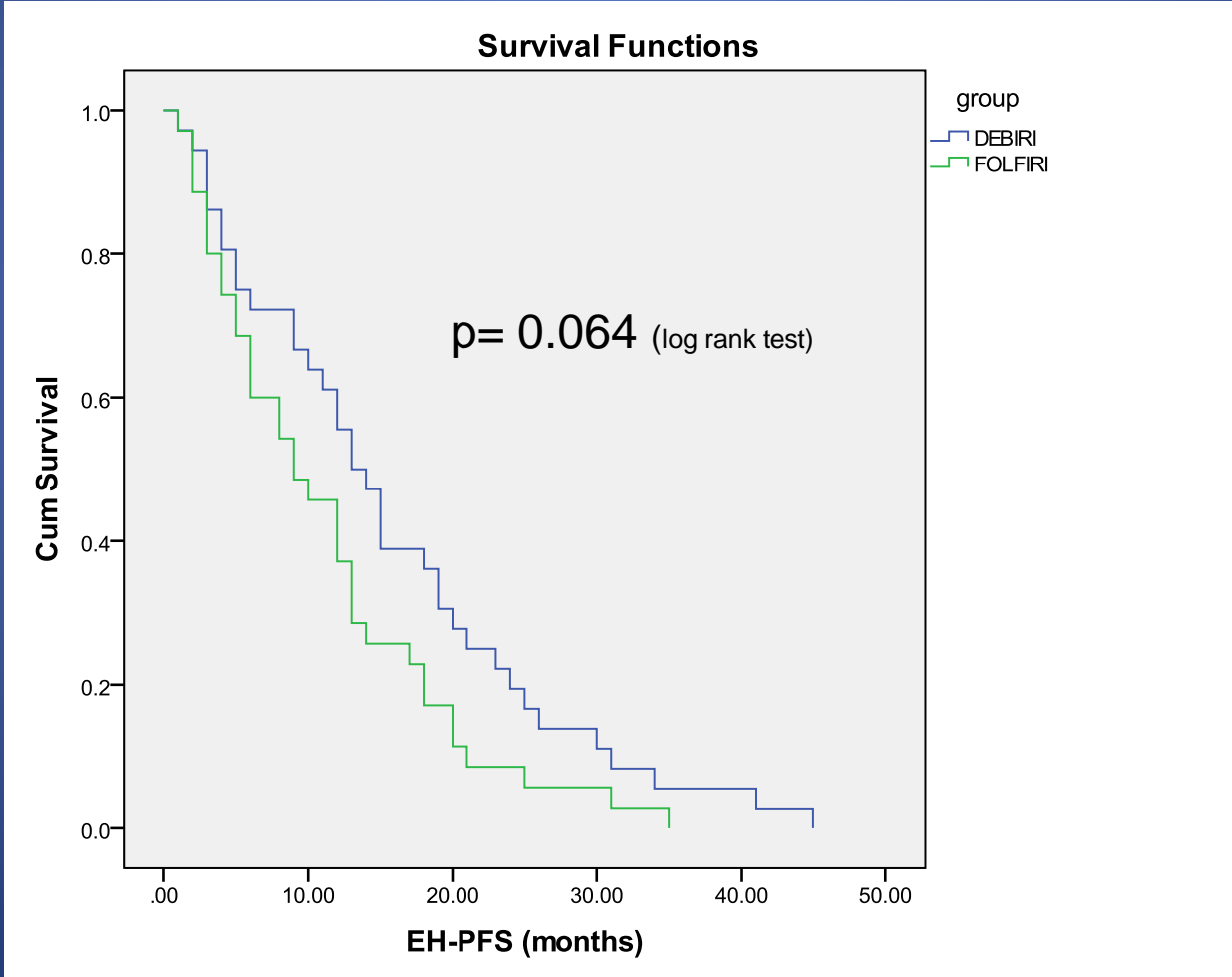
Kaplan-Meier Curve: Progression-Free Survival (PFS)



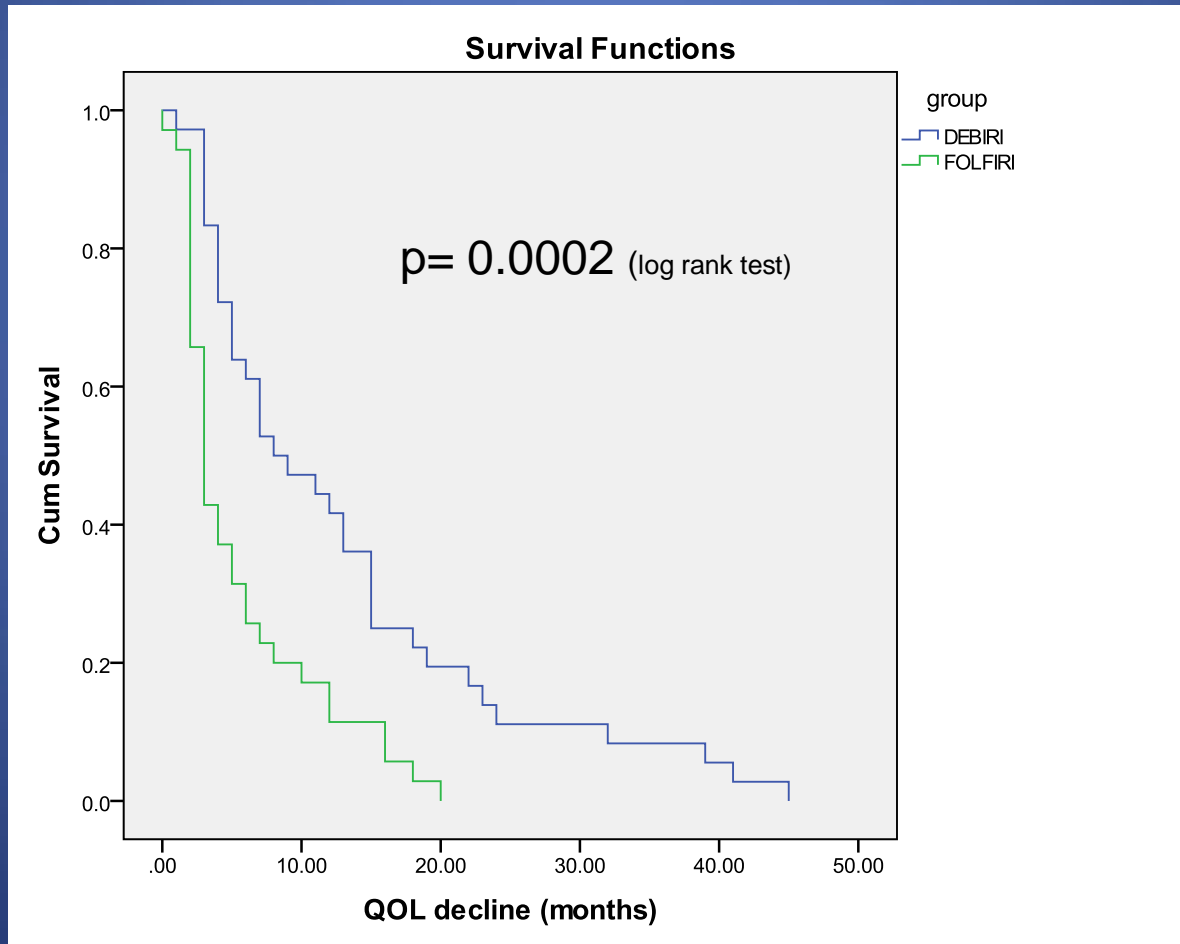
Kaplan-Meier Curve: Time to Hepatic Progression



Kaplan-Meier Curve: Time to Extrahepatic Progression



Kaplan-Meier Curve: Time to Decline in QoL



Sites of Progression

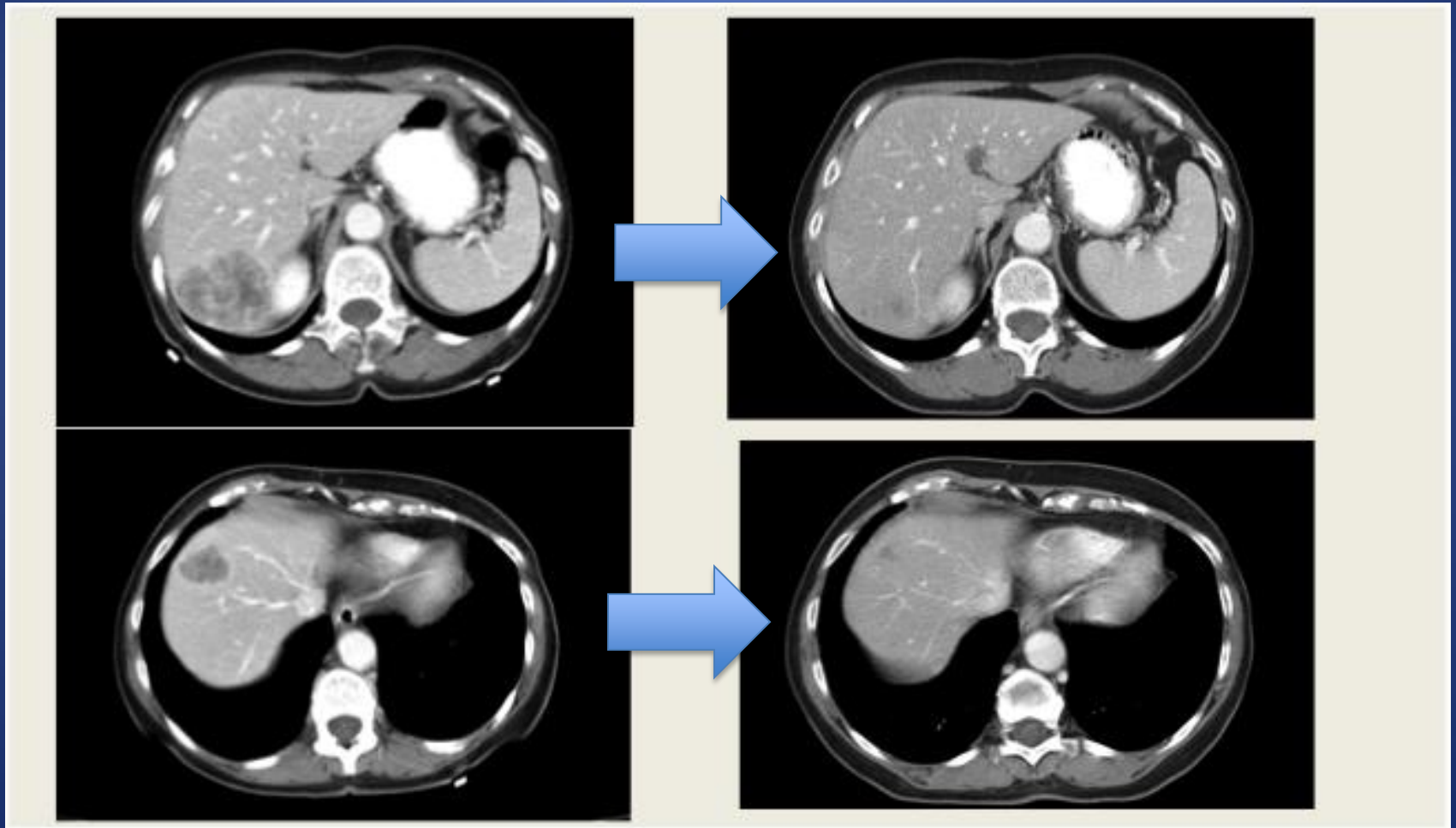
ARM	DEBIRI (D)	FOLFIRI (CT)
Number of patients	35	35
Liver	17	23
Liver + Lung	8	7
Liver + Lung + Bones	3	3
Liver + Perit. Carcinosis	2	1
Liver + Lung + Brain	1	1
Lymphonodes + Peritoneal Carcinosis	2	0

Therapy at Progression

TYPE OF THERAPY	DEBIRI (D)	FOLFIRI (CT)
FU c.i.	8	4
FU c.i. + Mitomycin	4	4
FOLFOXIRI	2	2
HERBAL MEDICINE + HOLISTICS	2	5
FOLFIRI + CETUXIMAB	3	2
FOLFOX + BEVACIZUMAB	2	3
PALLIATIVE MEDICINE	14	14

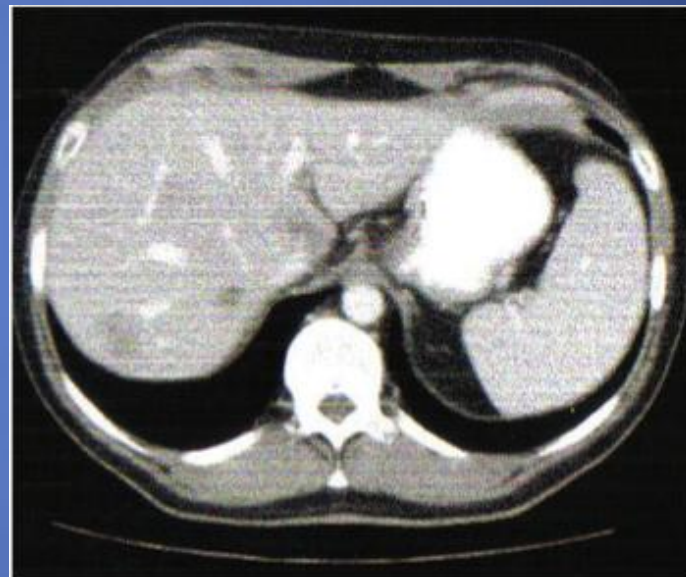
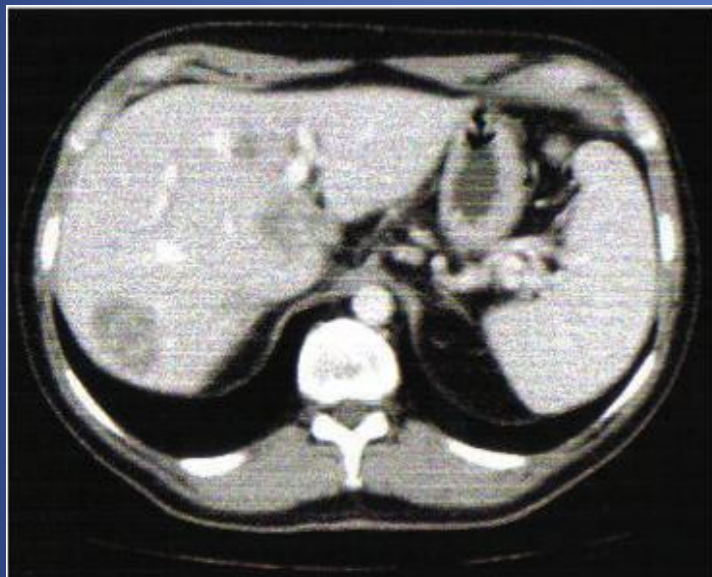
DEBIRI Case 1

Partial remission lasting 190 days



DEBIRI Case 2

Partial remission lasting 150 days



Conclusions (1)

- DEBIRI achieved the primary study endpoint by improving median overall survival when compared to FOLFIRI
- DEBIRI statistically produced a significant increase in overall survival, progression-free survival and quality of life
- DEBIRI significantly reduced costs when compared to systemic FOLFIRI

Conclusions (2)

- DEBIRI reported more immediate toxicity than FOLFIRI. These symptoms can be reduced with periprocedural medications
- Late toxicity (diarrhoea, leukopenia, anemia, asthenia and alopecia) were more common with FOLFIRI. These symptoms cannot be reduced with medications
- Our study is the first in literature which reports a survival benefit of an loco-regional therapy over systemic chemotherapy in patients with metastases limited to the liver pretreated with at least 2 lines of chemotherapy.