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CAPECITABINE PLUS IRINOTECAN VERSUS 5-FU/FA/IRINOTECAN +/- CELECOXIB IN FIRST LINE TREATMENT OF METASTATIC COLORECTAL CANCER (CRC). LONG-TERM RESULTS OF THE PROSPECTIVE MULTICENTER EORTC PHASE III STUDY 40015

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BACKGROUND

Oral fluoropyrimidines in combination with irinotecan may be an alternative to infusional 5-FU/FA plus irinotecan. Also, Cox-2 inhibitors may enhance the antineoplastic activity of chemotherapy (CT).

METHODS

STUDY DESIGN

Stratification

Institution
Prior adjuvant CT
Risk Group

RANDOMIZE

- FOLFIRI + Placebo (P)
- FOLFIRI + Celecoxib (C)
- CAPIRI + Placebo (P)
- CAPIRI + Celecoxib (C)

(Until progression)

Original Sample Size: 692 patients

FOLFIRI (Douillard's regimen)

Irinotecan IV	180 mg/m², 30-90 minute IV infusion	Days 1, 15, 29
Leucovorin IV	d/l-form 200 mg/m² or l-form 100 mg/m², 2-h infusion	Days 1-2, 15-16, 29-30
5-Fluorouracil IV	400 mg/m², bolus	Days 1-2, 15-16, 29-30
	600 mg/m², 22-hour continuous infusion	Days 1-2, 15-16, 29-30

CAPIRI

Irinotecan IV	250 mg/m², 30-90 minute IV infusion	Days 1, 22
Capecitabine PO	1000 mg/m², twice-daily (2000 mg/m² daily total)	Days 1-15, 22-36

PLACEBO / CELECOXIB

2 X 400 mg	Daily

MAIN ELIGIBILITY CRITERIA

- metastatic disease previously untreated with chemotherapy
- no previous adjuvant therapy except if completed at least 6 months prior to randomization
- no current or planned concomitant therapy with NSAIDs or COX-2 inhibitors
- WHO performance status ≤ 2
- adequate bone marrow, renal and liver functions
- no CNS metastases, second malignancy, uncontrolled severe medical condition
- informed consent

INITIAL OBJECTIVES

Primary:
- to demonstrate that infusional 5-FU in combination with IV irinotecan can be replaced by capecitabine in combination with IV irinotecan without compromising progression-free survival
- to demonstrate that celecoxib improves progression-free survival compared to placebo

Secondary:
- safety
- response rate, time to treatment failure and overall survival

RESULTS

HISTORY OF THE TRIAL

Open to patient entry in May 2003
Suspended in April 2004, after 85 patients had been entered, due to the occurrence of 8 fatal events not due to progression of disease (reported at ASCO 2005)

PATIENT POPULATION

N (%)	CAPIRI + C (N=23)	CAPIRI + P (N=21)	FOLFIRI + C (N=19)	FOLFIRI + P (N=22)	TOTAL (N=85)
Age					
Median	63.0	65.0	66.0	60.5	64.0
Range	42.0 - 75.0	43.0 - 78.0	54.0 - 77.0	45.0 - 75.0	42.0 - 78.0
≤ 65 years	15 (65.2)	11 (52.4)	9 (47.4)	14 (63.6)	49 (57.6)
> 65 years	8 (34.8)	10 (47.6)	10 (52.6)	8 (36.4)	36 (42.4)
WHO Performance Status					
0	14 (60.9)	12 (57.1)	10 (52.6)	14 (63.6)	50 (58.8)
1	8 (34.8)	8 (38.1)	9 (47.4)	8 (36.4)	33 (38.8)
2	1 (4.3)	1 (4.8)	0 (0.0)	0 (0.0)	2 (2.4)
Number of Metastatic Sites					
1	12 (52.2)	11 (52.4)	9 (47.4)	11 (50.0)	43 (50.6)
> 1	11 (47.8)	10 (47.6)	10 (52.6)	11 (50.0)	42 (49.4)
Risk Group*					
Good	12 (52.2)	10 (47.6)	9 (47.4)	11 (50.0)	42 (49.4)
Intermediate	6 (26.1)	6 (28.6)	7 (36.8)	8 (36.4)	27 (31.8)
Poor	5 (21.7)	5 (23.8)	3 (15.8)	3 (13.6)	16 (18.8)
Previous Adjuvant Therapy					
No	19 (82.6)	14 (66.7)	13 (68.4)	18 (81.8)	64 (75.3)
Yes	4 (17.4)	7 (33.3)	6 (31.6)	4 (18.2)	21 (24.7)

* C.-H. Köhne et al. Annals of Oncology 13: 308–317, 2002

NUMBER OF CYCLES OF CT

N (%)	CAPIRI + C (N=23)	CAPIRI + P (N=21)	FOLFIRI + C (N=19)	FOLFIRI + P (N=22)	TOTAL (N=85)
0	0 (0.0)	1 (4.8)	1 (5.3)	1 (4.6)	3 (3.5)
1 - 2	11 (47.8)	8 (38.0)	6 (31.6)	3 (13.6)	28 (33.0)
3 - 4	7 (30.4)	6 (28.6)	4 (21.0)	3 (13.6)	20 (23.5)
5 - 6	**5 (21.8)**	**6 (28.6)**	**8 (42.1)**	**15 (68.2)**	**34 (40.0)**
Median [Range]	**3 [1 - 6]**	**3 [0 - 6]**	**4 [0 - 6]**	**6 [0 - 6]**	**4 [0 - 6]**

TREATMENT MODIFICATIONS AND DOSE INTENSITY (patients who started CT)

N (%) Median [Range]	CAPIRI + C (N=23)	CAPIRI + P (N=20)	FOLFIRI + C (N=18)	FOLFIRI + P (N=21)	TOTAL (N=82)
Dose modifications	**13 (56.5)**	**10 (50.0)**	**3 (16.7)**	**10 (47.6)**	**36 (42.4)**
hematological toxicity	2 (8.7)	0 (0.0)	1 (5.6)	7 (33.3)	10 (12.2)
non hematological toxicity	11 (47.8)	7 (35.0)	2 (11.1)	1 (4.8)	21 (25.6)
Delays	**8 (34.7)**	**5 (25.0)**	**8 (44.5)**	**13 (61.9)**	**34 (41.5)**
hematological toxicity	0 (0.0)	1 (5.0)	3 (17.0)	9 (42.9)	13 (15.9)
non hematological toxicity	5 (21.7)	2 (10.0)	2 (11.1)	2 (9.5)	11 (13.4)
Relative dose intensity (%)					
Capecitabine	66.4 [6.6 - 110.3]	82.4 [47.5 - 119.6]	/	/	73.7 [6.6 - 119.6]
5-FU	/	/	92.1 [21.2 - 107.4]	83.8 [51.7 - 103.1]	86.8 [21.2 - 107.4]
CPT-11	83.1 [32.6 - 103.3]	83.6 [47.5 - 101.7]	88.4 [20.9 - 98.6]	84.0 [51.6 - 103.3]	84.1 [20.9 - 103.3]
Celecoxib / Placebo	99.2 [66.7 - 100.0]	98.3 [59.5 - 101.2]	96.2 [37.6 - 100.0]	94.4 [81.6 - 100.0]	96.9 [37.6 - 101.2]

WORST ADVERSE EVENTS (patients who started CT, CTCAE version 2.0)

N (%)		CAPIRI + C (N=23)	CAPIRI + P (N=20)	FOLFIRI + C (N=18)	FOLFIRI + P (N=21)
Cardiovascular Gr. 3-4		3 (13.0)	2 (10.0)	2 (11.1)	0 (0.0)
Hand & Foot syndrome Gr. 3*		1 (4.3)	1 (5.0)	0 (0.0)	0 (0.0)
Alopecia Gr. 2		2 (8.7)	6 (30.0)	0 (0.0)	0 (0.0)
Diarrhea Gr. 3-4		**9 (39.1)**	**7 (35.0)**	**3 (16.7)**	**2 (9.5)**
Mucositis Gr. 2**		4 (17.4)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea Gr. 3*		1 (4.3)	1 (5.0)	1 (5.6)	2 (9.5)
Stomatitis Gr. 2**		3 (13.0)	1 (5.0)	0 (0.0)	0 (0.0)
Vomiting Gr. 3-4		2 (8.7)	1 (5.0)	1 (5.6)	1 (4.8)
Other Gastrointestinal Gr. 3-4		2 (8.7)	0 (0.0)	0 (0.0)	1 (4.8)
Catheter related infection Gr. 3*		0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)
Febrile Neutropenia Gr. 3-4		0 (0.0)	2 (10.0)	2 (11.1)	0 (0.0)
Infection Gr. 3-4 without neutropenia		1 (4.3)	0 (0.0)	2 (11.1)	0 (0.0)
WBC	Gr. 1-2	4 (17.4)	7 (35.0)	5 (27.8)	7 (33.3)
	Gr. 3-4	**3 (13.0)**	**3 (15.0)**	**2 (11.1)**	**4 (19.0)**
Hemoglobin	Gr. 1-2	15 (65.2)	14 (70.0)	15 (83.3)	12 (57.1)
	Gr. 3*	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Platelets	Gr. 1-2	3 (13.0)	2 (10.0)	5 (27.8)	2 (9.5)
	Gr. 3*	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)

* No grade 4   ** No grade 3-4

BEST OVERALL RESPONSE

N (%)	CAPIRI + C (N=23)	CAPIRI + P (N=20)	FOLFIRI + C (N=18)	FOLFIRI + P (N=21)	TOTAL (N=82)
Complete Response	**0 (0.0)**	**1 (4.8)**	**1 (5.3)**	**0 (0.0)**	**2 (2.4)**
Partial Response	**5 (21.7)**	**9 (42.9)**	**5 (26.3)**	**10 (45.5)**	**29 (34.1)**
Stable Disease	12 (52.2)	5 (23.8)	7 (36.8)	9 (40.9)	33 (38.8)
Progression	2 (8.7)	2 (9.5)*	2 (10.5)	3 (13.6)	9 (10.6)
Early death, cancer	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.2)
Early death, toxicity	1 (4.3)	3 (14.3)	2 (10.5)	0 (0.0)	6 (7.3)
Early death, other	1 (4.3)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Not assessable	2 (8.7)	1 (4.8)	1 (5.3)	0 (0.0)	4 (4.7)

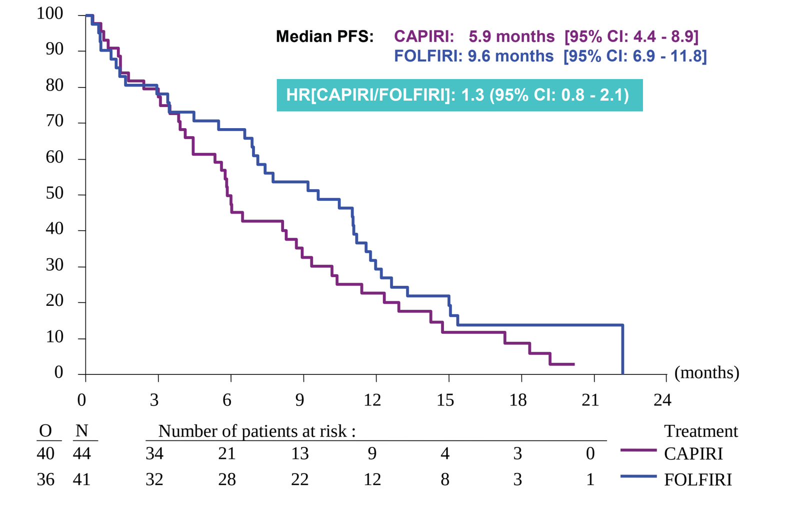
* Of which one patient died from toxicity after 2 cycles of therapy
** Severe GI bleeding

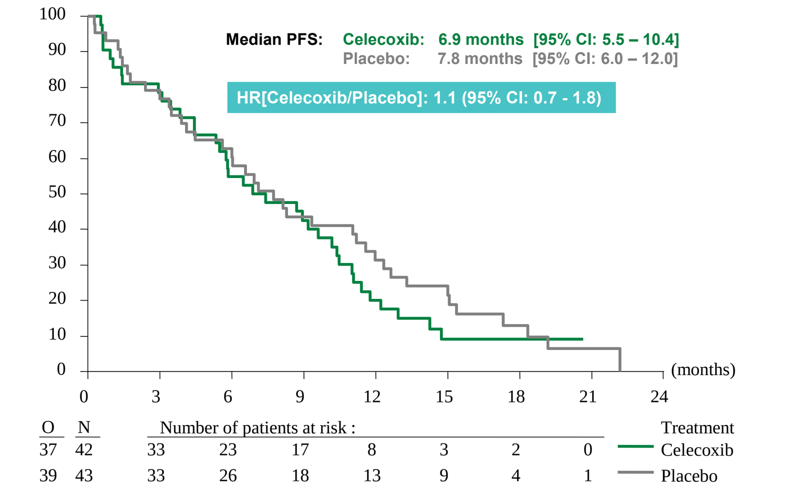
DESCRIPTION OF TOXIC DEATHS (early and other)

Treatment	Number cycles	Cause of death
CAPIRI + C	1	Thrombo-embolic event / pulmonary embolism
CAPIRI + P	1	Pulmonary embolism
CAPIRI + P	1	Diarrhea / neutropenia / septic shock
CAPIRI + P	2	Diarrhea / Myocardial infarction
CAPIRI + P	1	Diarrhea / suspected pulmonary embolism
FOLFIRI + C	1	Pulmonary embolism
FOLFIRI + C	1	Diarrhea / neutropenia / septic shock

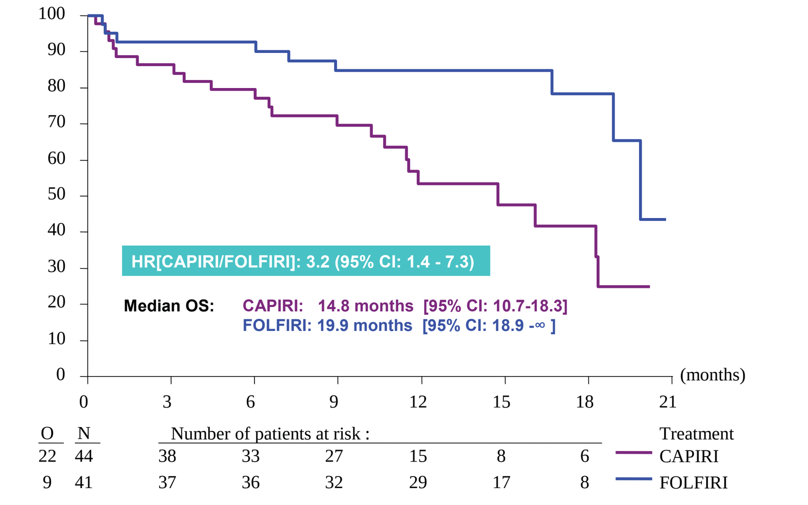
PFS AND OVERALL SURVIVAL

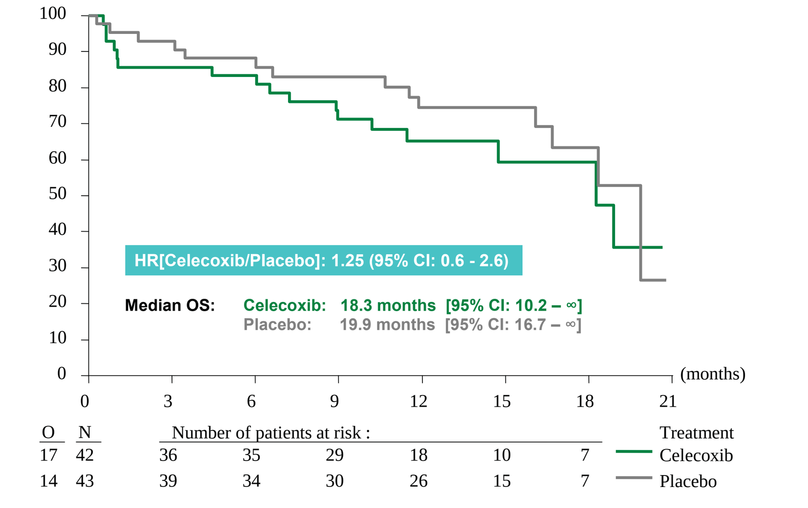
Progression-free survival





Overall survival





CONCLUSION

The data suggest that celecoxib might reduce response to CT and this warrants further preclinical investigation. The stratified analysis failed to demonstrate the non-inferiority of CAPIRI as compared to FOLFIRI. Small patient number and confounding safety issues prevent us from drawing definitive conclusions. Results of larger studies are needed.