Appendices (tables and figures)

Table A1: Further line treatments

	FOLFOX/bevacizumab		*FOLFOXIRI/bevacizumab*	
	N	**%**	**N**	**%**
Any second-line therapy	**82**	**67.8**	**89**	**73.6**
Chemotherapy with anti-EGFR	21	25.6	19	21.3
RAS wildtype patients treated with anti-EGFR/overall	16/32	50	17/38	44.7
Chemotherapy with anti-VEGF	34	41.5	44	49.4
Chemotherapy doublet regimen without anti-VEGF/EGFR	11	13.4	10	11.2
Chemotherapy single agent	11	13.4	4	4.5
anti-VEGF/EGFR single agent	4	4.9	9	10.1
Other	1	1.2	3	3.4
Any third-line therapy	**49**	**40.5**	**53**	**43.8**
Chemotherapy with anti-EGFR	6	12.2	12	22.6
RAS wildtype patients treated with anti-EGFR/overall	6/18	33.3	12/23	52.2
Chemotherapy with anti-VEGF	20	40.8	20	37.7
Chemotherapy doublet regimen without anti-VEGF/EGFR	6	12.2	3	5.7
Chemotherapy single agent	4	8.2	5	9.4
anti-VEGF/EGFR signle agent	12	13.3	12	22.6
Other	1	2.0	1	1.9

Table A2: Grade 3/4 adverse events and SAEs

	FOLFOX/bevacizumab **(N=121)**	*FOLFOXIRI/bevacizumab* **(N=121)**
Toxicity		
Grade 3/4 adverse events		
Diarrhea	12%	16%
Nausea	3%	8%
Vomiting	3%	3%
Mucositis	3%	3%
Neutropenia	14%	20%
Febrile Neutropenia	1%	1%
Infection	12%	10%
Hypertension	7%	9%
Neuropathy	4%	3%
Pulmonary embolism	3%	2%
Fatigue/Asthenia	3%	9%
SAEs		
Overall (n pts)	85 (51)	89 (49)
Fatal overall	2	5
Fatal treatment related	1	3

Table A3: Comparison of EORTC QLQ C30 and CR29 scales pooled over induction period

Scales	*FOLFOX/bevacizumab* **mean value ± SD**	*FOLFOXIRI/bevacizumab* **mean value ± SD**	**p-value (CI 95%)**
EORTC QLQ			
Global health	59.8 ± 18.8	58.8 ± 18.9	0.726 (-4.60 – 6.60)
Physical	76.7 ± 21.6	76.2 ± 24.2	0.889 (-6.45 – 7.42)
Role	64.9 ± 29.1	63.0 ± 32.2	0.686 (-7.31 – 11.10)
Emotional	73.3 ± 23.4	70.3 ± 20.8	0.335 (-3.36 – 9.31)
Cognitive	86.1 ± 18.0	83.5 ± 20.1	0.368 (-3.10 – 8.33)
Social	69.6 ± 26.9	66.0 ± 28.3	0.390 (-4.67 – 11.91)
Fatigue	40.4 ± 23.6	41.1 ± 24.5	0.842 (-7.94 – 6.48)
Nausea and	**9.4 ± 13.9**	**16.0 ± 20.7**	**0.015 (-11.84 – (-1.31)**
Pain	21.7 ± 25.9	23.9 ± 25.6	0.569 (-9.98 – 5.50)
Dyspnea	22.3 ± 26.2	25.2 ± 27.7	0.484 (-10.98 – 5.22)
Insomnia	27.8 ± 27.7	32.0 ± 27.6	0.321 (-12.48 – 4.11)
Appetite loss	22.3 ± 25.3	27.7 ± 28.3	0.186 (-13.50 – 2.63)
Constipation	11.0 ± 19.5	9.9 ± 16.8	0.689 (-4.36 – 6.59)
Diarrhea	**23.7 ± 26.6**	**32.1 ± 28.5**	**0.051 (-16.50 – 0.04)**
Financial	21.0 ± 28.3	28.3 ± 29.6	0.095 (-16.08 – 1.28)
EORTC QLQ			
Body image	78.5 ± 24.4	78.4 ± 22.6	0.971 (-6.99 – 7.26)
Anxiety	52.2 ± 27.4	51.3 ± 28.5	0.834 (-7.56 – 9.36)
Weight	76.2 ± 28.5	68.5 ± 26.8	0.069 (-0.62 – 16.16)
Sexual	34.3 ± 25.9	36.2 ± 23.2	0.697 (-11.03 – 7.39)
Sexual	16.9 ± 18.6	12.6 ± 21.7	0.439 (-6.65 – 15.11)
Urinary	36.1 ± 27.0	35.2 ± 23.0	0.809 (-6.67 – 8.54)
Blood and	5.7 ± 14.4	7.0 ± 11.9	0.539 (-5.24 – 2.75)
Urinary	4.0 ± 11.7	4.4 ± 10.6	0.790 (-3.85 – 2.94)
Dysuria	3.3 ± 12.4	5.6 ± 14.0	0.259 (-6.31 – 1.71)
Abdominal	17.8 ± 23.7	15.8 ± 20.5	0.554 (-4.71 – 8.75)
Buttock pain	13.1 ± 22.2	18.8 ± 22.2	0.095 (-12.44 – 1.00)
Bloated feeling	16.1 ± 21.3	17.8 ± 22.3	0.608 (-8.36 – 4.90)
Dry mouth	32.2 ± 29.2	29.7 ± 25.6	0.556 (-5.87 – 10.87)
Hair loss	**27.7 ± 27.5**	**36.8 ± 28.9**	**0.029 (-18.09 – (-1.01))**
Trouble with	39.1 ± 32.4	38.9 ± 30.1	0.958 (-922 – 9.73)
Impotence	40.1 ± 30.9	41.9 ± 31.2	0.768 (-13.75 – 10.19)
Dyspareunia	5.8 ± 11.3	4.5 ± 15.6	0.765 (-7.43 – 10.04)
Stool frequency with	25.1 ± 19.4	16.9 ± 17.3	0.132 (-2.56 – 19.01)
Stool frequency	**19.1 ± 18.9**	**28.1 ± 25.6**	**0.030 (-16.98 – (-0.87))**
Bloating with	28.7 ± 20.0	21.1 ± 17.6	0.169 (-3.39 – 18.75)
Bloatung	22.8 ± 26.6	22.8 ± 25.1	0.989 (-9.25 – 9.37)
Faecal incontinence	31.0 ± 29.0	10.9 ± 17.3	0.007 (5.71 – 34.46)
Faecal incontinence	5.5 ± 19.0	10.2 ± 22.7	0.218 (-12.22 – 2.82)

Sore skin with	34.1 ± 29.9	58.8 ± 18.9	0.110 (-2.96 – 28.02)
Sore skin	**14.2 ± 23.6**	76.2 ± 24.2	**0.034 (-19.26 – (-0.77))**
Embarrassed by bowel	41.5 ± 34.7	63.0 ± 32.2	0.086 (-2.44 – 35.31)
Embarrased by bowel	8.6 ± 21.5	70.3 ± 20.8	0.408 (CI -11.63 – 4.76)
Stoma care	23.9 ± 30.9	83.5 ± 20.1	0.033 (CI 1.34 – 29.36)

(Abbrev: SD standard deviation, CI confidence interval)

Table A4: Clinically relevant changes in EORTC QLQ C30 scales between baseline and week 8

	FOLFOXBevn (%)	FOLFOXIRIBevn (%)	p-value	FOLFOXBevn (%)	FOLFOXIRIBevn (%)	p-value
Patients	79**	78**		79**	78**	
	Increase of at least 10 points* (improvement)			**Decrease of at least 10 points* (deterioration)**		
Global health status	35 (44.3%)	31 (39.7%)	0.629	17 (21.5%)	21 (26.9%)	0.461
Physical functioning	27 (34.2%)	34 (43.6%)	0.254	20 (25.3%)	19 (24.4%)	1.00
Role functioning	26 (33.3%)	27 (35.1%)	0.866	29 (37.2%)	24 (31.2%)	0.499
Emotional functioning	40 (50.6%)	35 (44.9%)	0.524	15 (19%)	18 (23.1%)	0.562
Cognitive functioning	12 (15.2%)	13 (16.7%)	0.830	20 (25.3%)	21 (26.9%)	0.857
Social functioning	27 (34.2%)	17 (21.8%)	0.110	22 (27.8%)	25 (32.1%)	0.604
	Increase of at least 10 points* (deterioration)			**Increase of at least 10 points* (deterioration)**		
Fatigue	34 (43.2%)	30 (39.0%)	0.629	25 (31.6%)	31 (40.3%)	0.317
Nausea and vomiting	25 (31.6%)	34 (44.2%)	0.137	10 (12.7%)	12 (15.6%)	0.651
Pain	18 (22.8%)	16 (20.5%)	0.847	28 (35.4%)	29 (37.2%)	0.869
Dyspnea	17 (21.8%)	17 (22.7%)	1.00	11 (14.1%)	20 (26.7%)	0.070
Insomnia	17 (21.5%)	20 (26.0%)	0.574	20 (25.3%)	20 (26.0%)	1.00
Appetite loss	15 (19.2%)	27 (35.1%)	0.031	16 (20.5%)	18 (23.4%)	0.701
Constipation	10 (12.7%)	10 (12.8%)	1.00	7 (8.9%)	11 (14.1%)	0.328
Diarrhea	28 (35.9%)	33 (42.3%)	0.512	19 (24.4%)	12 (15.4%)	0.228
Financial difficulties	13 (16.7%)	23 (30.3%)	0.057	11 (14.1%)	7 (9.2%)	0.453

*Increase or decrease of at least 10 points between baseline and week 8
** Based on the completeness of data from the questionnaires patient numbers range between 75 and 79, displayed by the rate (%)

figure A1

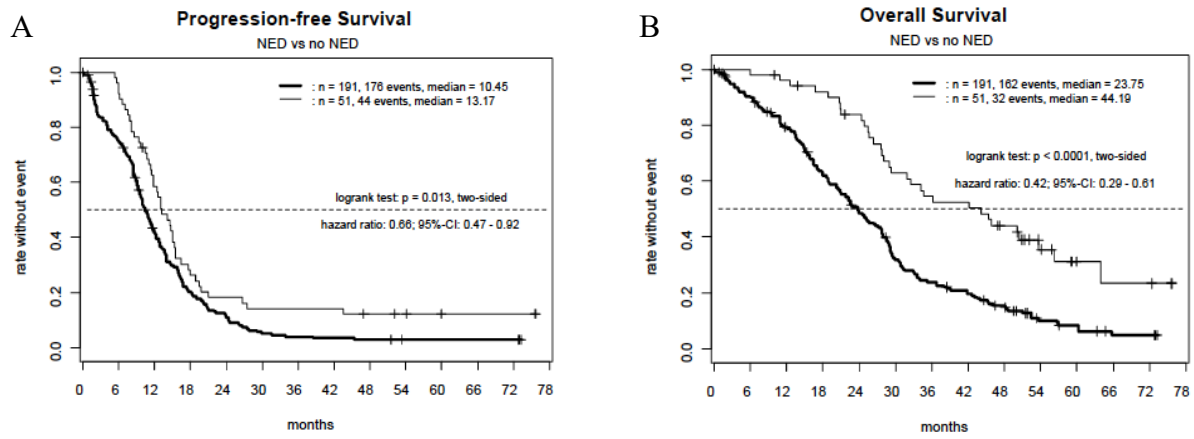

figure A1: Subgroup analysis for PFS and OS for achievement of No Evidence of Disease status (NED) defined as secondary R0/1 resection or complete remission on imaging vs. no NED status. (A) The Kaplan-Meier estimator for respective NED status of the total mITT population is shown. Number of patients per arm and median PFS interval is indicated. (B) as in A, except OS is shown for respective arms. Thick line indicates no NED and thin line NED.

figure A2

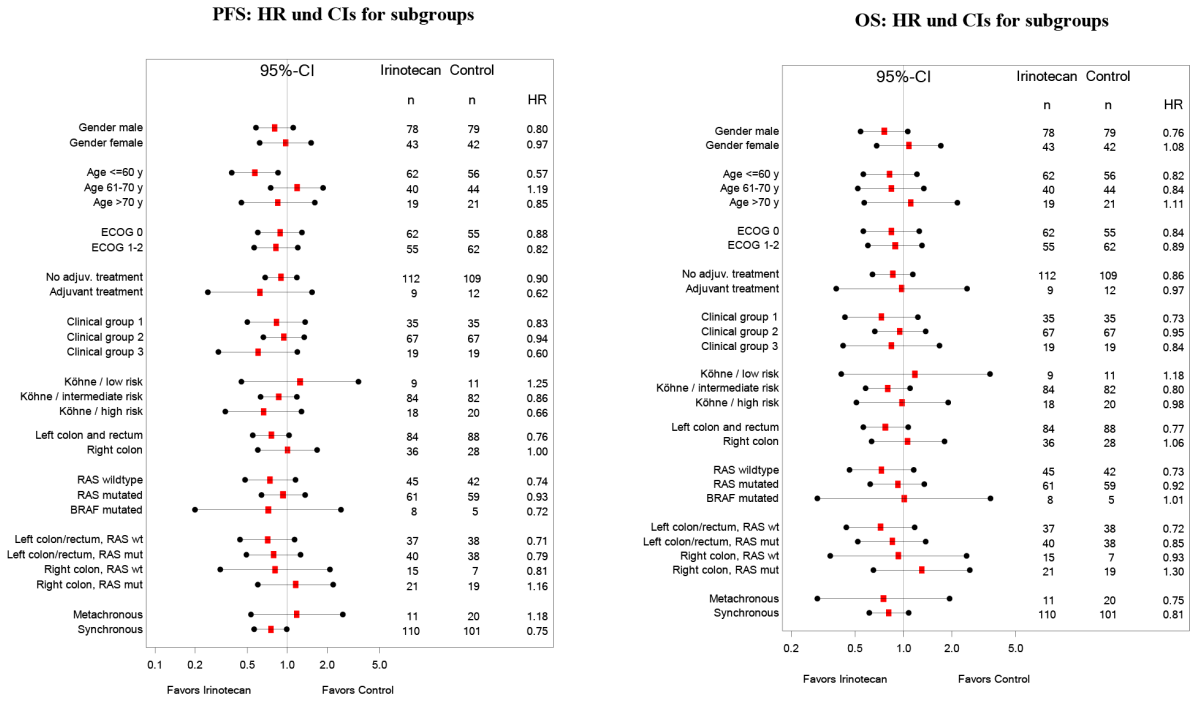

figure A2: Forest plot effect of clinico-pathological factors on PFS (left) and OS (right).