Wie gestalte ich Therapiepausen?

Susanna Hegewisch-Becker

Onkologische Schwerpunktpraxis Hamburg-Eppendorf

Erhaltungstherapie zur Optimierung der Palliation

Ziele:

- Toxizität einsparen
- Lebensqualität erhalten
- Behandlungserfolg bewahren

Erhaltungstherapie zur Optimierung der Palliation

Fragen:

- Welcher Zeitpunkt?

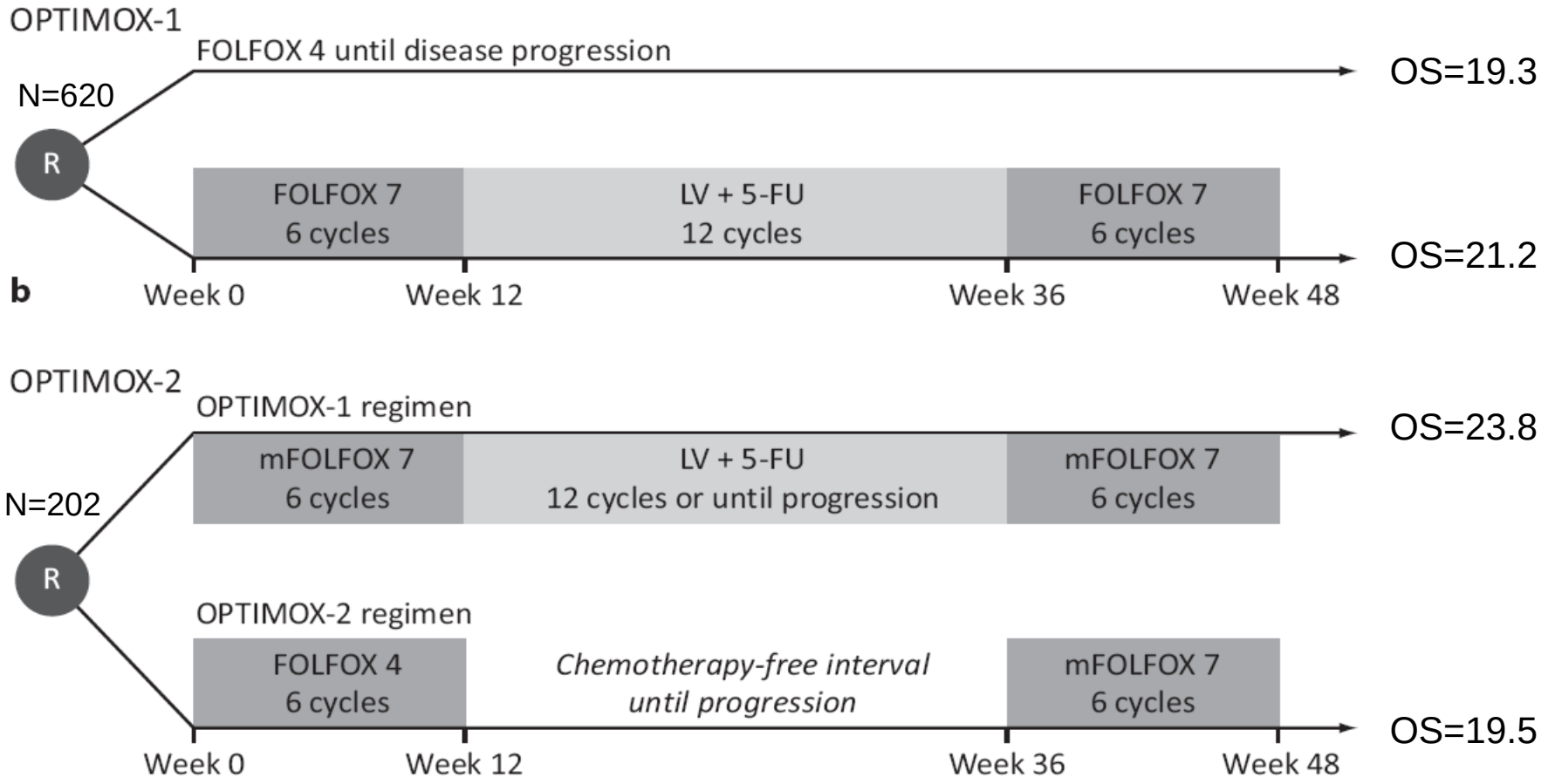
  - *Stop and Go über prädefinierten Behandlungsphasen oder*

    Maintenance nach Induktion bis zum Progress

- Welche Patienten sind geeignet?

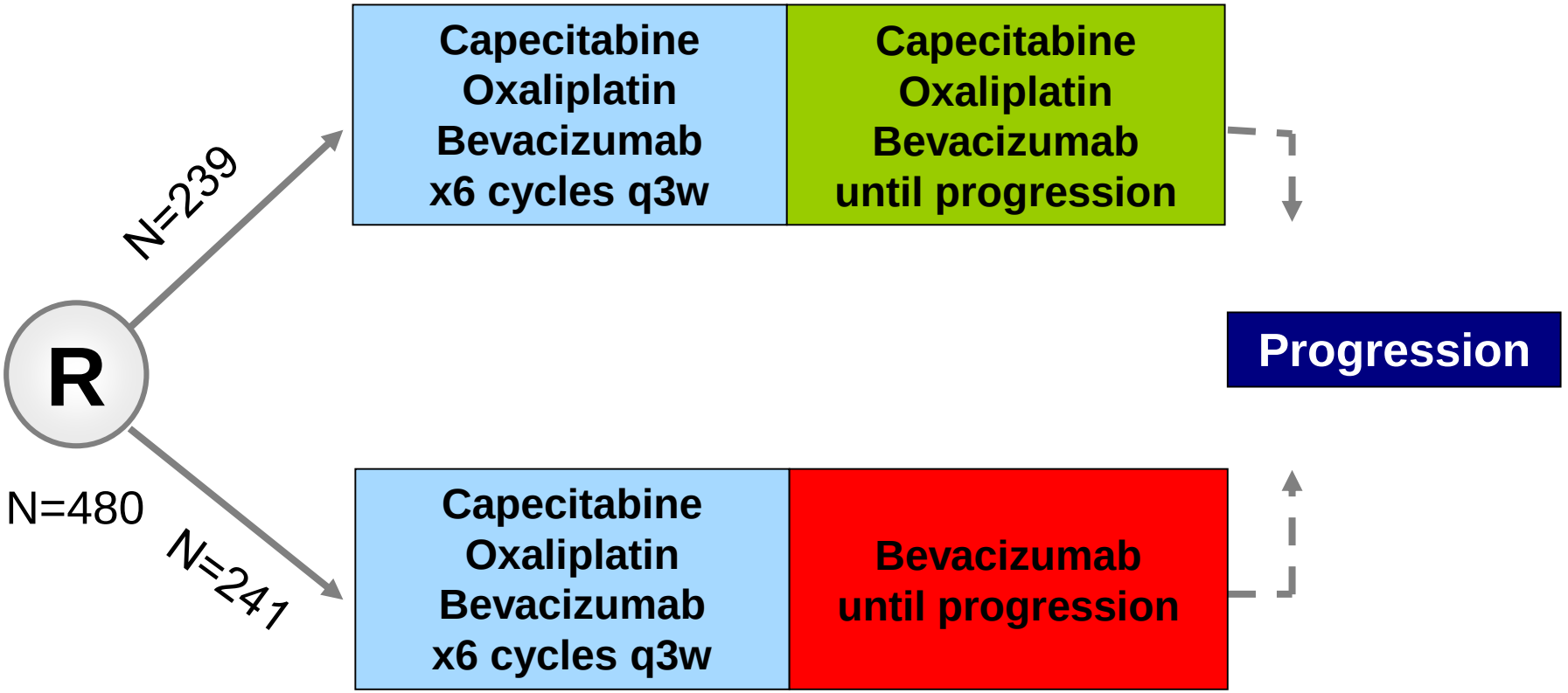
  - *CR, PR, SD, Resektabilität definitiv nicht gegeben*

OPTIMOX-1 und OPTIMOX-2



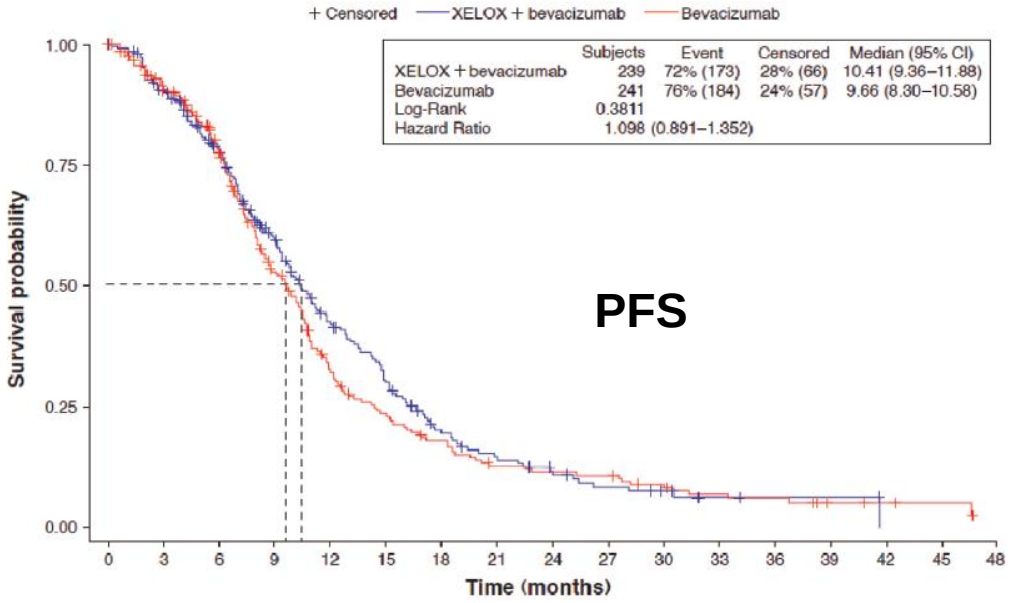
OPTIMOX-1: Tornigand et al., JCO 2006
OPTIMOX-2: Chibaudel et al. JCO 2009

MACRO TTD Study Design

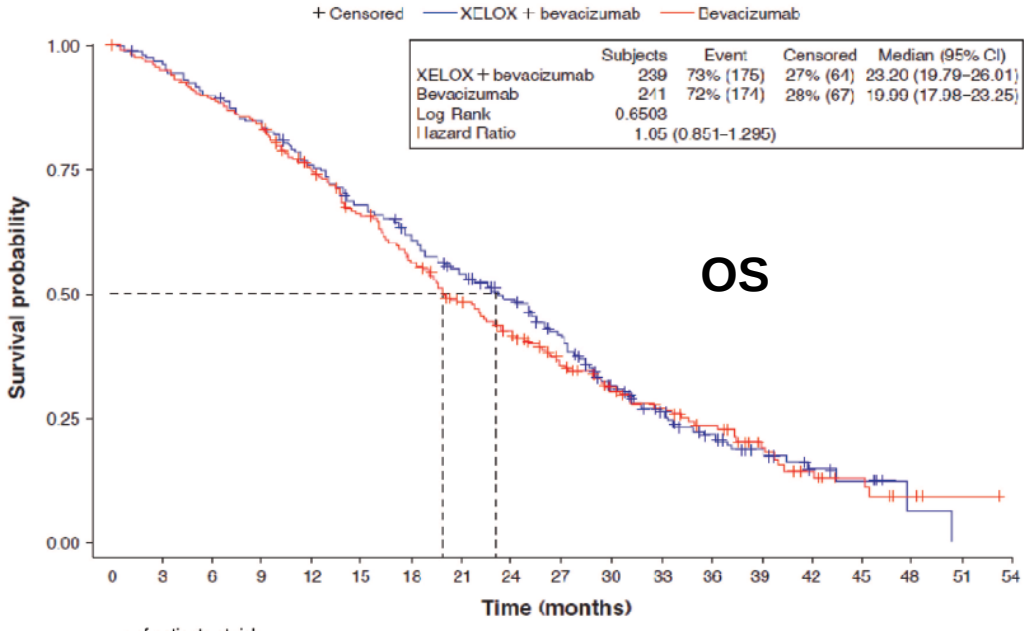


Diaz-Rubio et al., The Oncologist 2012

MACRO trial



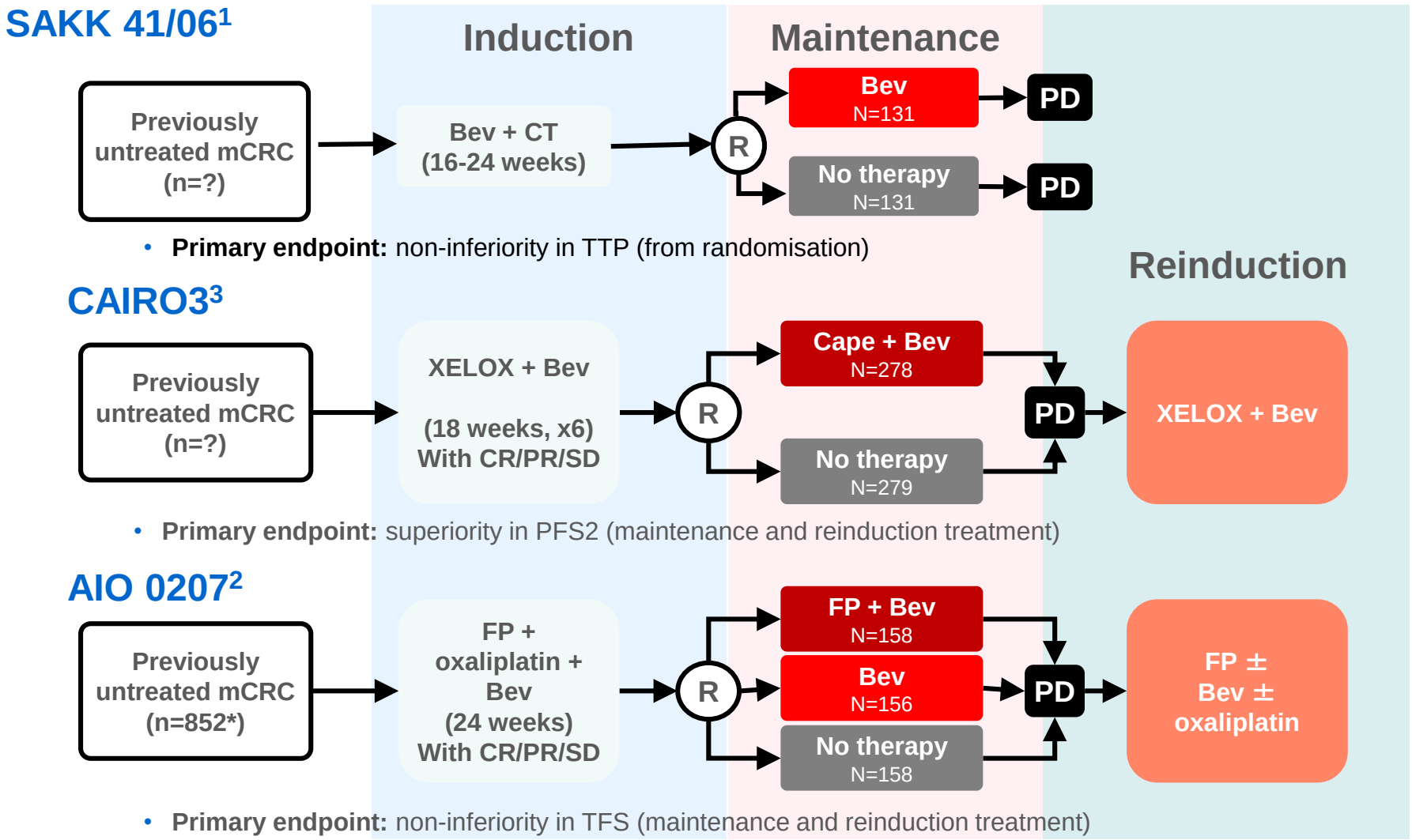
PFS



OS

Deeskalation oder Behandlungspause nach Fluoropyrimidin/Oxaliplatin/Bevacizumab basierter Induktionstherapie

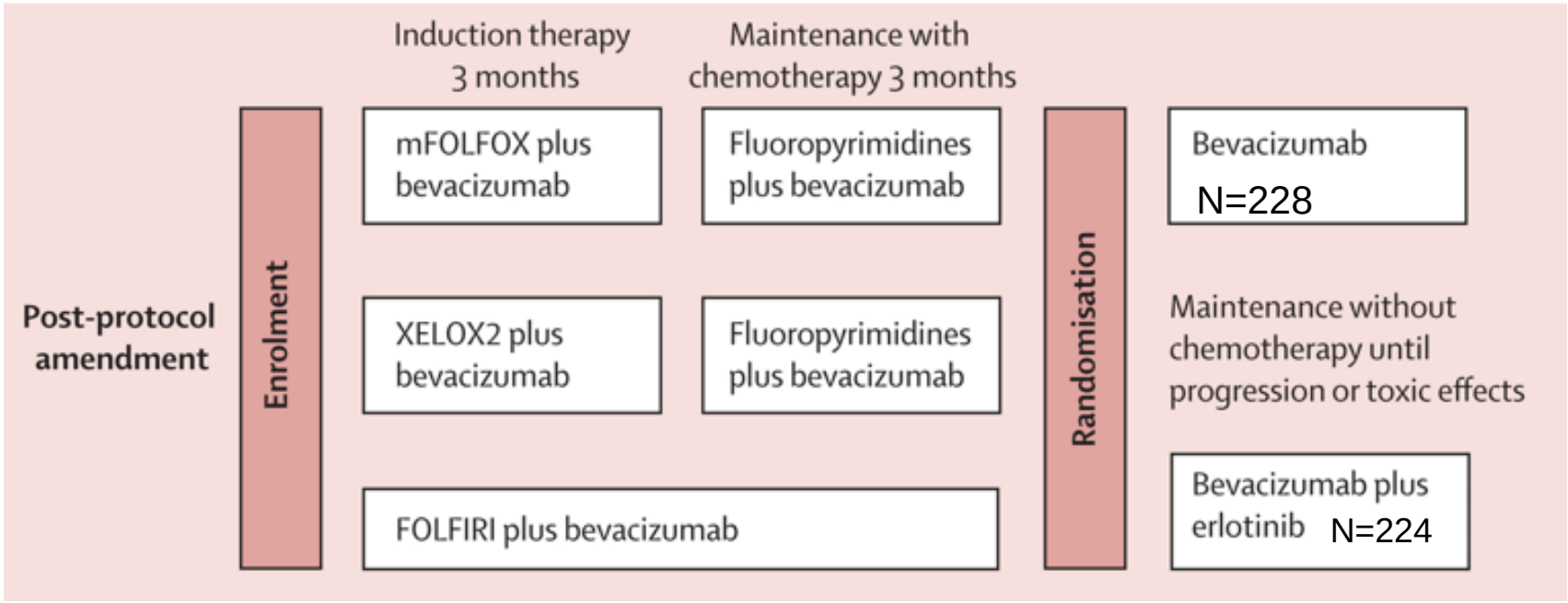
SAKK 41/06, CAIRO3 and AIO 0207:



*Assessed for eligibility; FP = 5-fluorouracil, folic acid, or capecitabine

1. Koeberle et al., Ann Oncol 2015
2. Hegewisch-Becker et. Al., Lancet Oncology 2015
3. Simkens et al., Lancet 2015

DREAM trial: Maintenance mit Bev vs. Bev/Erlotinib N=700)



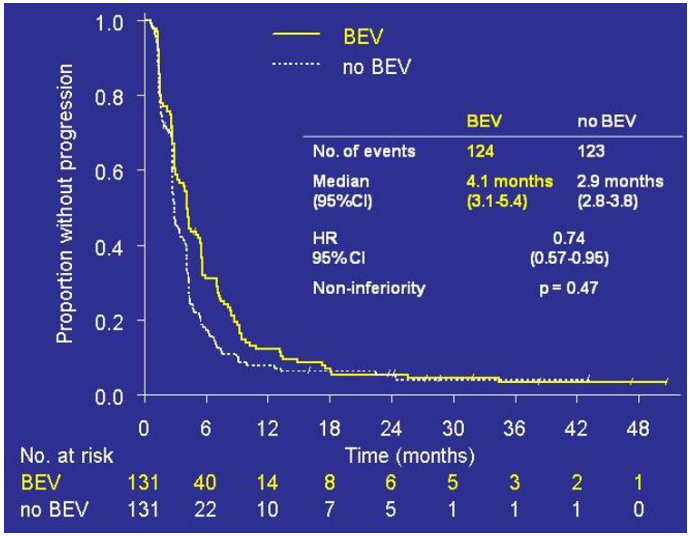
Chibaudel et al., Lancet Oncol 2015

Gründe für Randomisierungsversagen nach Induktionstherapie

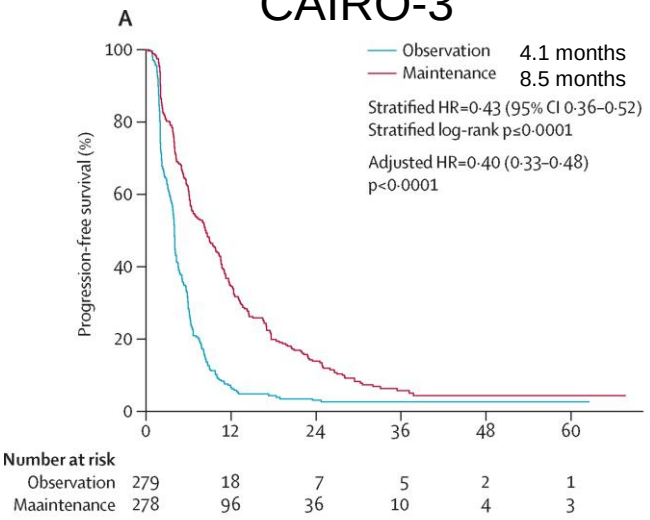
Induktion	AIO 0207 (N=852) 24 Wochen	DREAM (N=700) 12 od. 24 Wochen
Total	42 %	35 %
Progression während Induktion	35%	40%
Metastasenchirurgie	11%	11%
Toxizität	15%	20%
Patientenwunsch	15%	4%
Prüfarztentscheidung	8%	10%
Tod	8%	5%
Andere Gründe	8%	10%

PFS

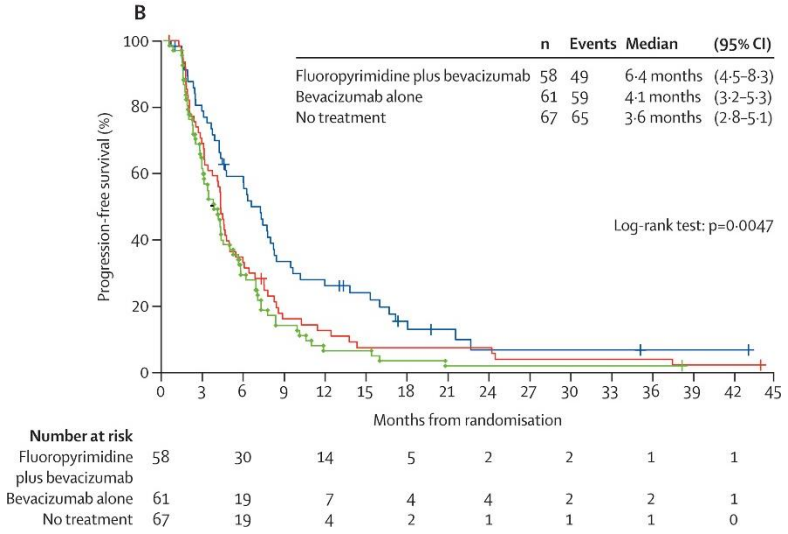
SAKK 41/06



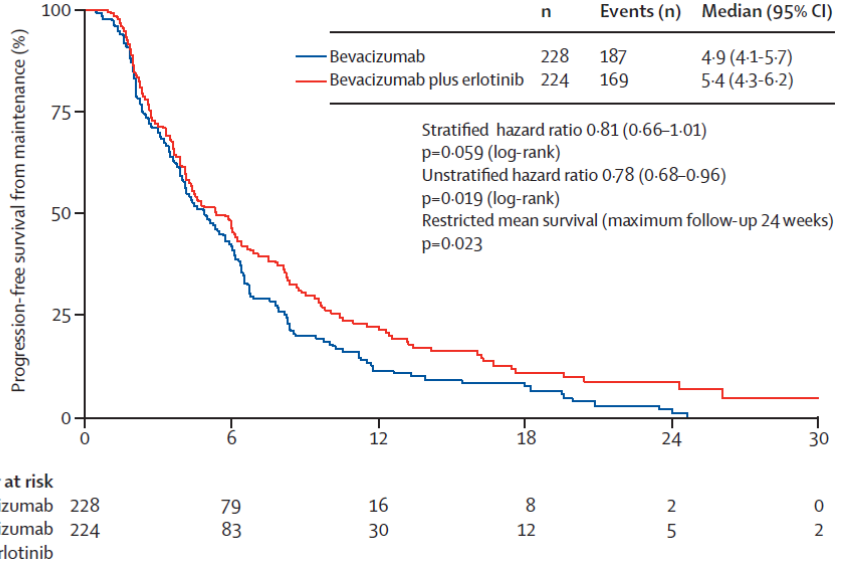
CAIRO-3



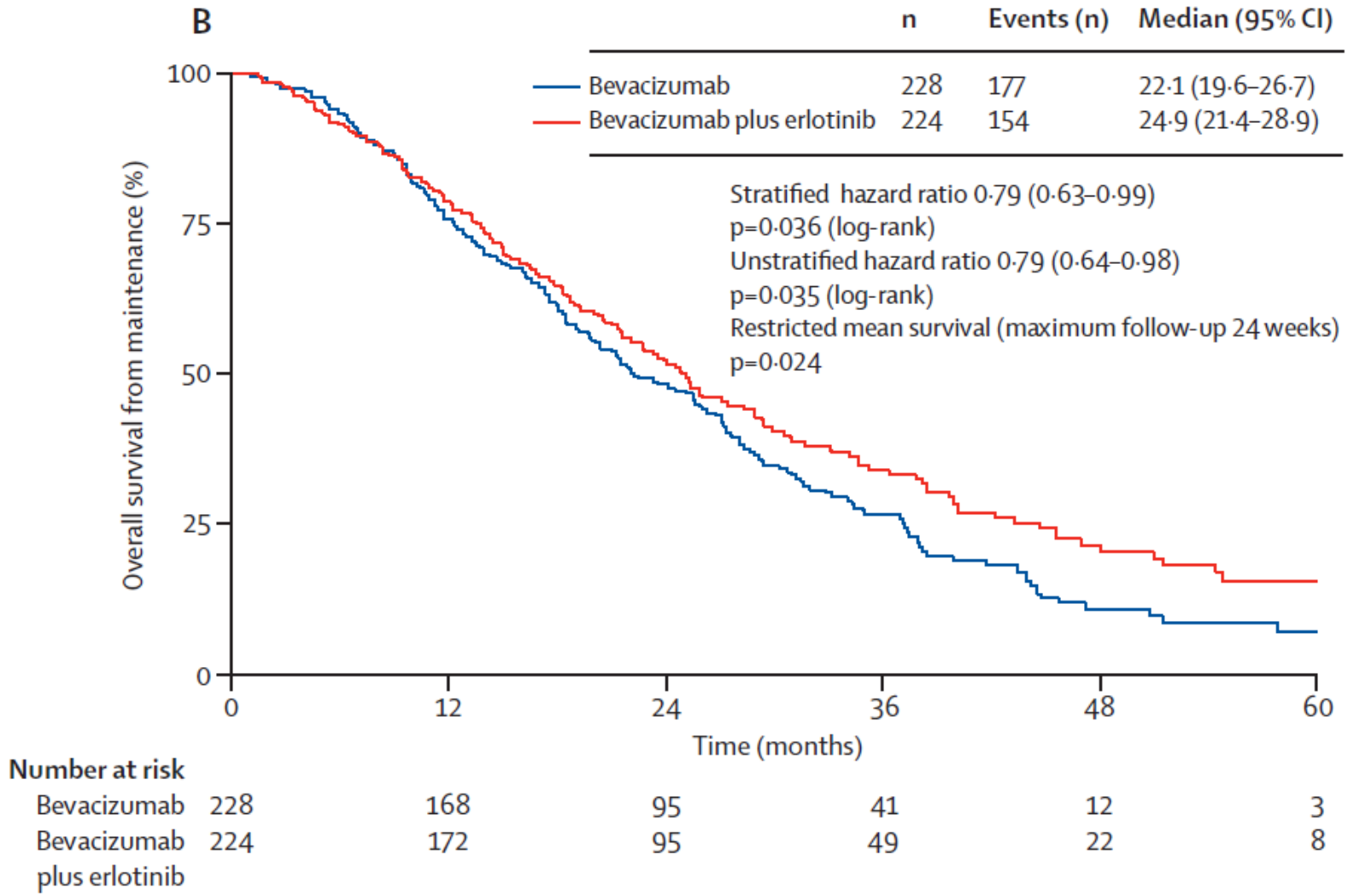
AIO KRK 0207



DREAM



Overall Survival DREAM



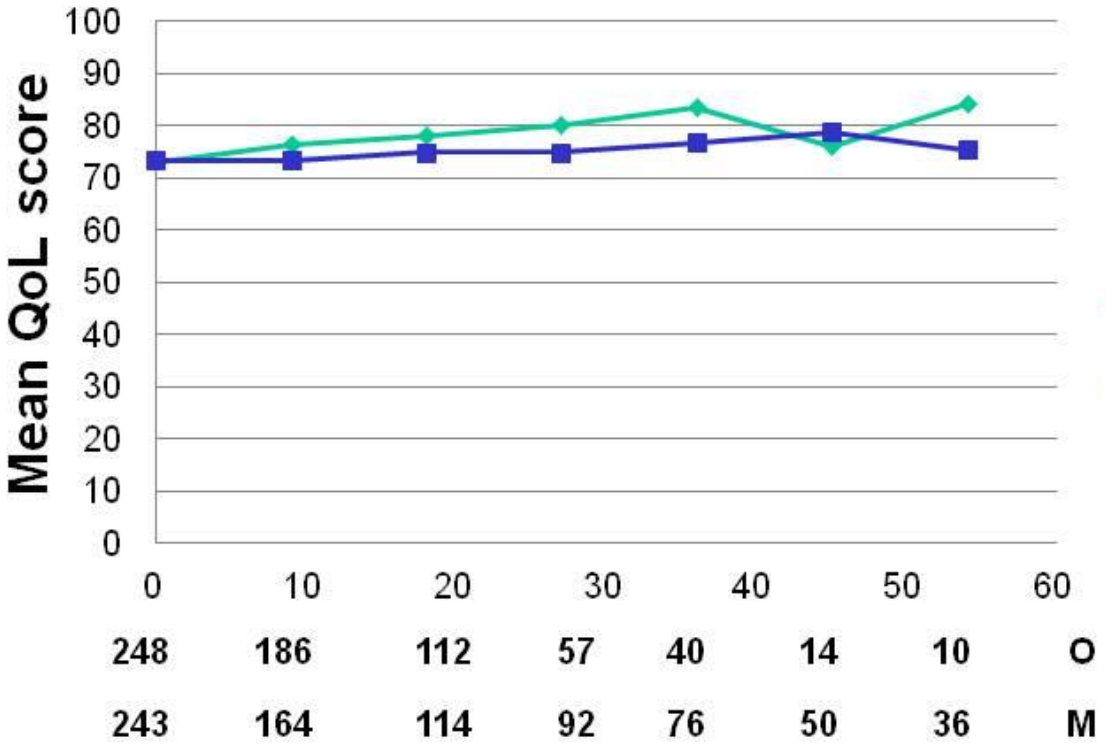
Auszug aus der Stellungnahme der AIO-KRK Leitgruppe zu Deeskalationsstrategien nach FP/Ox/Bev

- Eine aktive Erhaltungstherapie verlängert das PFS-1 signifikant.
- Eine Deeskalation auf FP/Bev ist Standardvorgehen und ist effektiver als Bev mono.
- Eine Therapieunterbrechung ist möglich ohne signifikanten Einfluß auf OS. Auf das signifikant kürzere PFS müssen die Pat. hingewiesen werden.
- Die optimale Dauer der Induktionstherapie ist nicht abschließend geklärt und sollte ausserhalb von Studien vom individuellen Verlauf abhängig gemacht werden.

Gibt es Entscheidungshilfen?

- Ansprechen
- Lebensqualität
- Einfluß klinischer und molekulargenetischer Faktoren
- Tumorlokalisation

CAIRO3 Quality of life during maintenance/observation

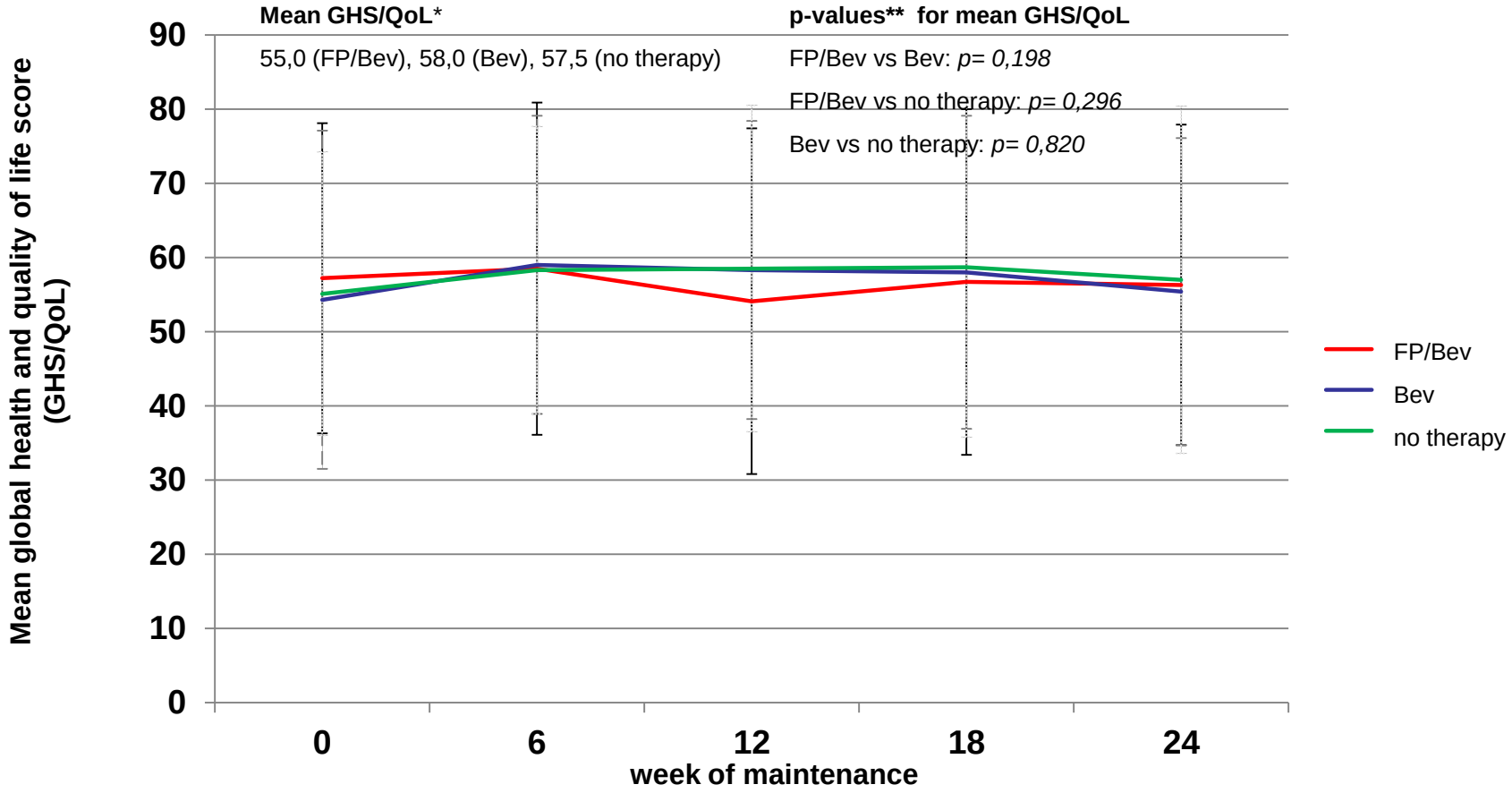


Between-group difference:
3.9 (95%CI 1.2; 6.5) p=0.004
(not clinically relevant, < 10)

observation
maintenance

- QoL was maintained during maintenance treatment, and was clinically not inferior compared to QoL in observation arm

AIO KRK 0207

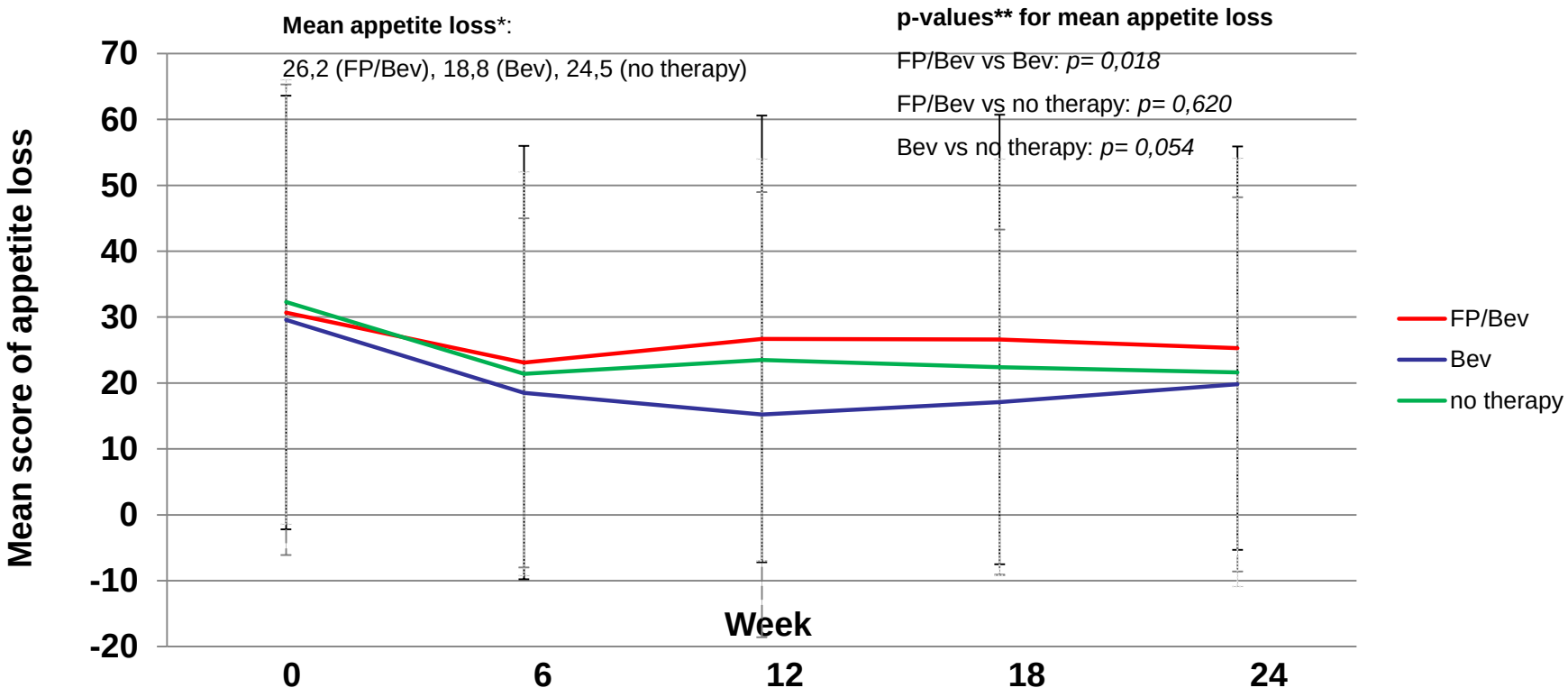


	0	6	12	18	24
FP/Bev	57,2 (SD 20,9) *n=128*	58,5 (SD 22,4) *n=129*	54,1 (SD 23,3) *n=124*	56,7 (SD 23,3) *n=114*	56,3 (SD 21,6) *n=106*
Bev	54,3 (SD 22,8) *n=132*	59,0 (SD 20,1) *n=138*	58,3 (SD 20,1) *n=120*	58,0 (SD 21,1) *n=123*	55,4 (SD 20,7) *n=112*
no therapy	55,1 (SD 19,1) *n=128*	58,3 (SD 19,4) *n=128*	58,5 (SD 22,0) *n=124*	58,7 (SD 22,9) *n=120*	57,0 (SD 23,4) *n=112*

***Figure 1*: Mean global health status and quality of life score at different maintenance assessment timepoints**

* analyzed according to protocol: mean value, calculated as the average of all available time points after randomization (week 6, 12, 18, 24)
**analyzed by t-test

AIO KRK 0207



FP/Bev	30,7 (SD 32,9)	23,1 (SD 32,9)	26,7 (SD 33,9)	26,6 (SD 34,1)	25,3 (SD 30,6)
Bev	29,6 (SD 35,7)	18,5 (SD 26,5)	15,2 (SD 22,8)	17,1 (SD 26,2)	19,8 (SD 28,4)
no therapy	32,3 (SD 33,7)	21,4 (SD 30,6)	23,5 (SD 30,5)	22,4 (SD 31,6)	21,6 (SD 32,5)

***Figure 2c*: Mean appetite loss score at different maintenance assessment timepoints**

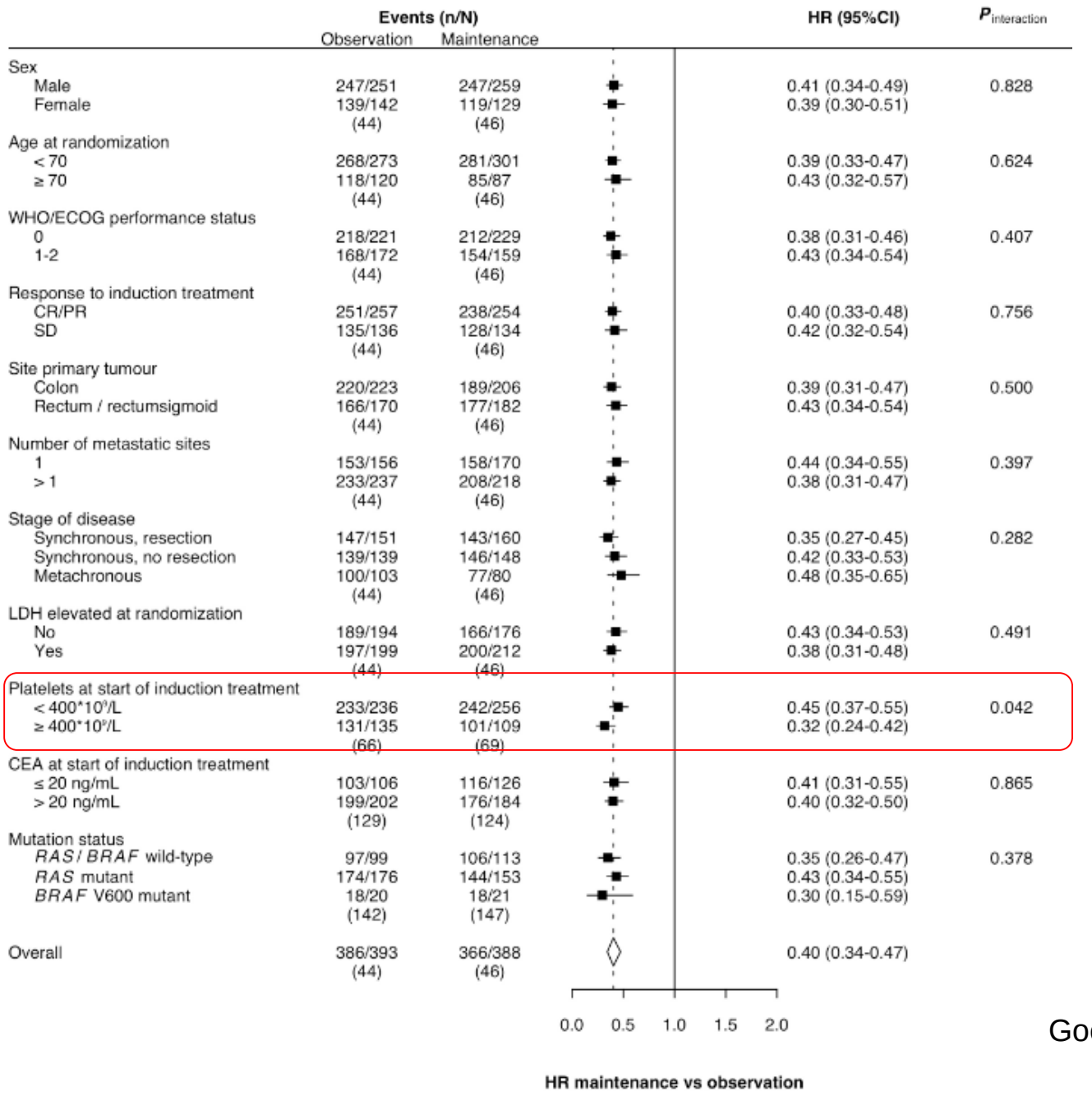
* analyzed according to protocol: mean value, calculated as the average of all available time points after randomization (week 6, 12, 18, 24)
**analyzed by t-test

Resultate einer gepoolte Analyse von CAIRO-3 und AIO 0207
FP/Bev vs. Beobachtung
Cave: unterschiedliche Studiendesigns

Analysierte Faktoren:

Interaktion mit Geschlecht, Alter, WHO-PS, SD vs PR, Tumorlokalisation, Stadium, Zahl der Metastasenlokalisationen, Resektion des Primarius, TZ-Zahl, CEA, RAS/BRAF Mutationsstaus

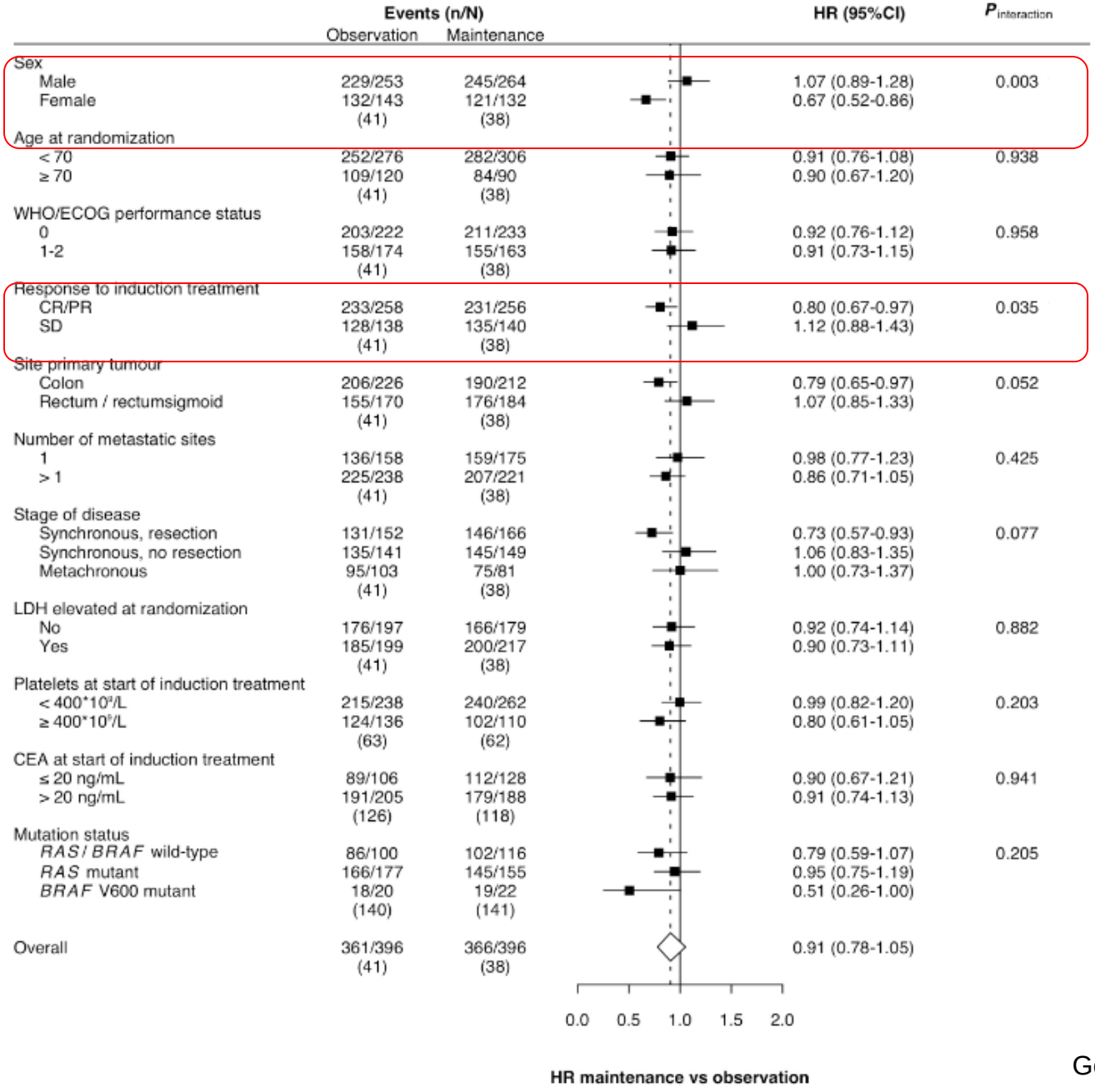
Pooled analysis: PFS, CAIRO-3, AIO 0207



	Events (n/N) Observation	Events (n/N) Maintenance	HR (95%CI)	$P_{interaction}$
Sex				
Male	247/251	247/259	0.41 (0.34-0.49)	0.828
Female	139/142	119/129	0.39 (0.30-0.51)	
	(44)	(46)		
Age at randomization				
< 70	268/273	281/301	0.39 (0.33-0.47)	0.624
≥ 70	118/120	85/87	0.43 (0.32-0.57)	
	(44)	(46)		
WHO/ECOG performance status				
0	218/221	212/229	0.38 (0.31-0.46)	0.407
1-2	168/172	154/159	0.43 (0.34-0.54)	
	(44)	(46)		
Response to induction treatment				
CR/PR	251/257	238/254	0.40 (0.33-0.48)	0.756
SD	135/136	128/134	0.42 (0.32-0.54)	
	(44)	(46)		
Site primary tumour				
Colon	220/223	189/206	0.39 (0.31-0.47)	0.500
Rectum / rectumsigmoid	166/170	177/182	0.43 (0.34-0.54)	
	(44)	(46)		
Number of metastatic sites				
1	153/156	158/170	0.44 (0.34-0.55)	0.397
> 1	233/237	208/218	0.38 (0.31-0.47)	
	(44)	(46)		
Stage of disease				
Synchronous, resection	147/151	143/160	0.35 (0.27-0.45)	0.282
Synchronous, no resection	139/139	146/148	0.42 (0.33-0.53)	
Metachronous	100/103	77/80	0.48 (0.35-0.65)	
	(44)	(46)		
LDH elevated at randomization				
No	189/194	166/176	0.43 (0.34-0.53)	0.491
Yes	197/199	200/212	0.38 (0.31-0.48)	
	(44)	(46)		
Platelets at start of induction treatment				
< 400*10^9/L	233/236	242/256	0.45 (0.37-0.55)	0.042
≥ 400*10^9/L	131/135	101/109	0.32 (0.24-0.42)	
	(66)	(69)		
CEA at start of induction treatment				
≤ 20 ng/mL	103/106	116/126	0.41 (0.31-0.55)	0.865
> 20 ng/mL	199/202	176/184	0.40 (0.32-0.50)	
	(129)	(124)		
Mutation status				
RAS/*BRAF* wild-type	97/99	106/113	0.35 (0.26-0.47)	0.378
RAS mutant	174/176	144/153	0.43 (0.34-0.55)	
BRAF V600 mutant	18/20	18/21	0.30 (0.15-0.59)	
	(142)	(147)		
Overall	386/393	366/388	0.40 (0.34-0.47)	
	(44)	(46)		

Goey et al, BJC in print

Pooled analysis: Overall survival CAIRO-3, AIO 0207



Goey et al, BJC in print

AIO 0207

Einfluß der Lokalisation des Primärtumors:

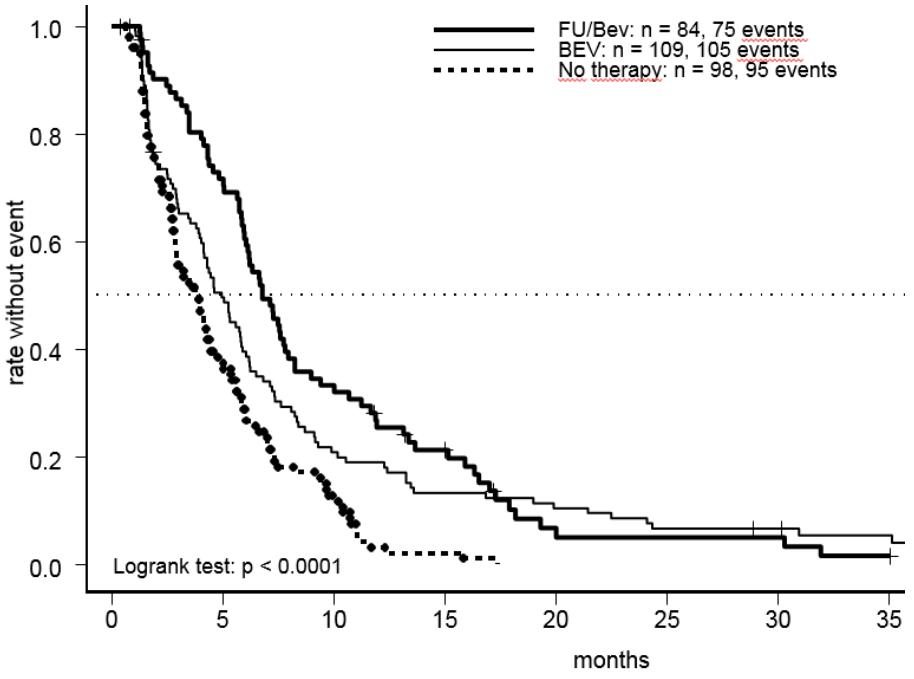
Rechts: Zökum, Colon ascendens, Colon transversum bis zur splenischen Flexur

Links: Splenische Flexur, Colon descendens, Sigma, Rektum

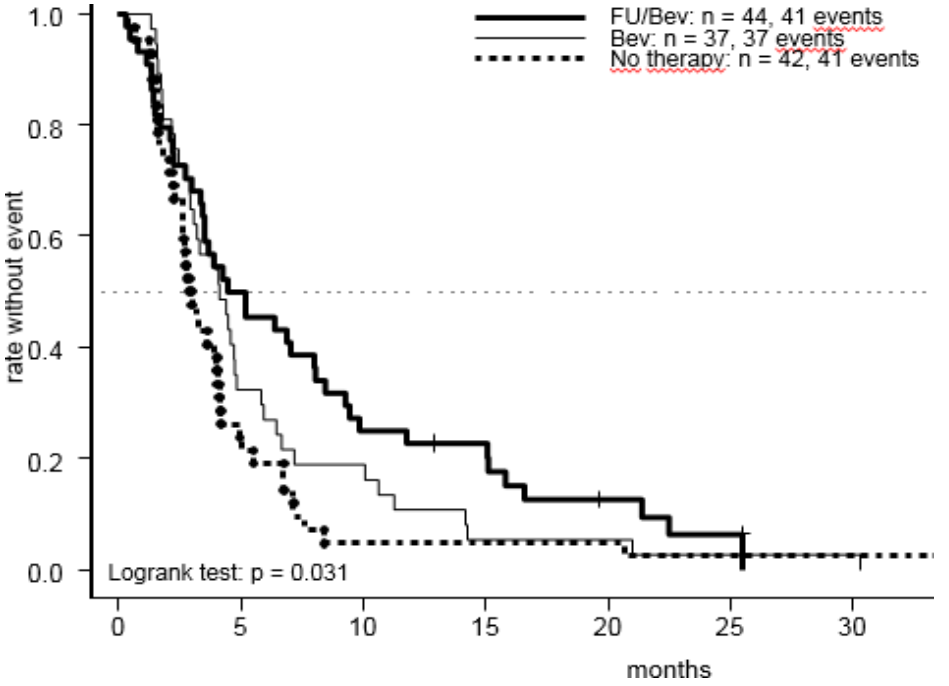
Reinacher-Schick et al. ASCO 2017

PFS während der Maintenance in Abhängigkeit von der Tumorlokalisation (AIO 0207)

Links



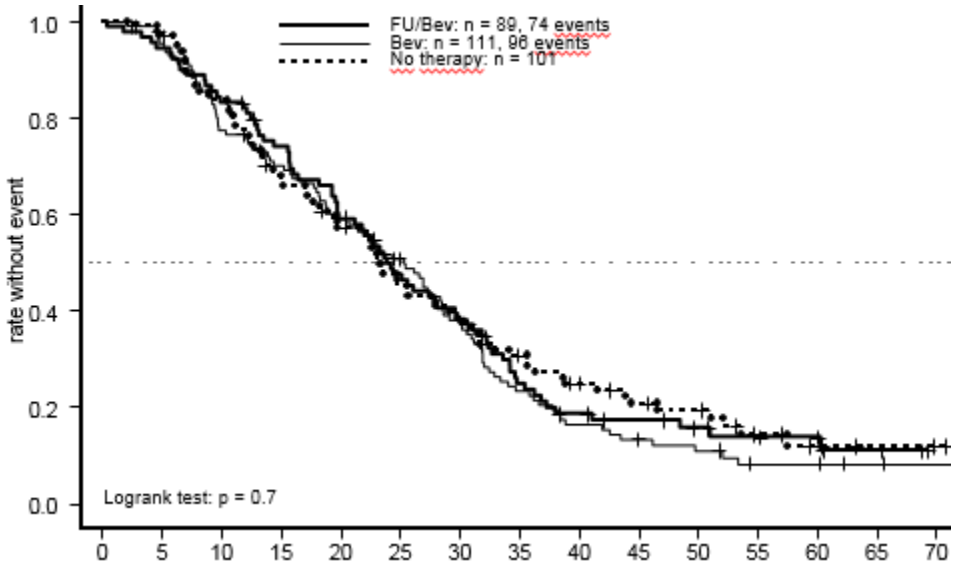
Rechts



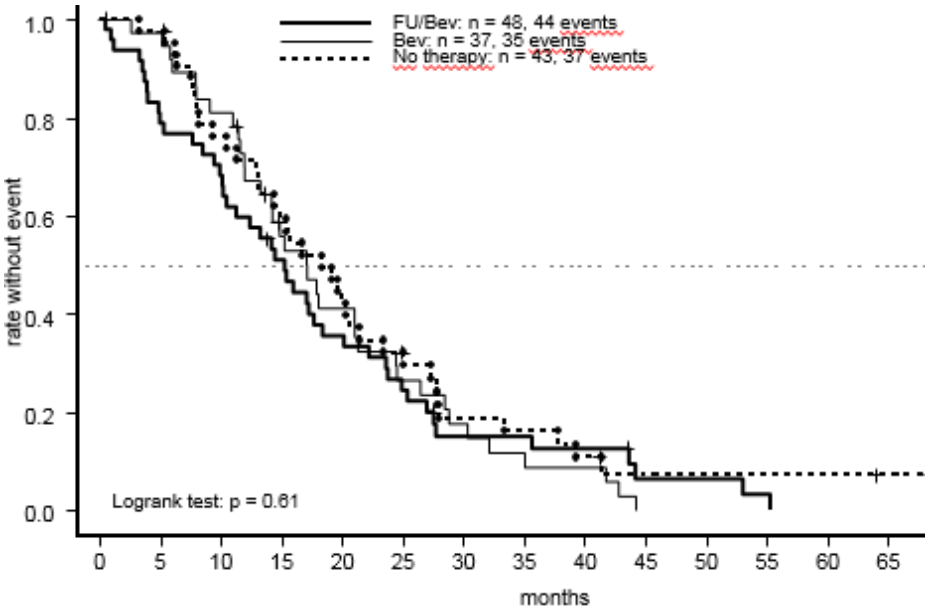
PFS (Monate)	Links	Rechts
FP/BEV	6.8	5.2
BEV mono	5.0	4.1
Keine Therapie	3.9	2.9

OS seit Randomisierung in Abhängigkeit von der Tumorlokalisation (AIO 0207)

Links



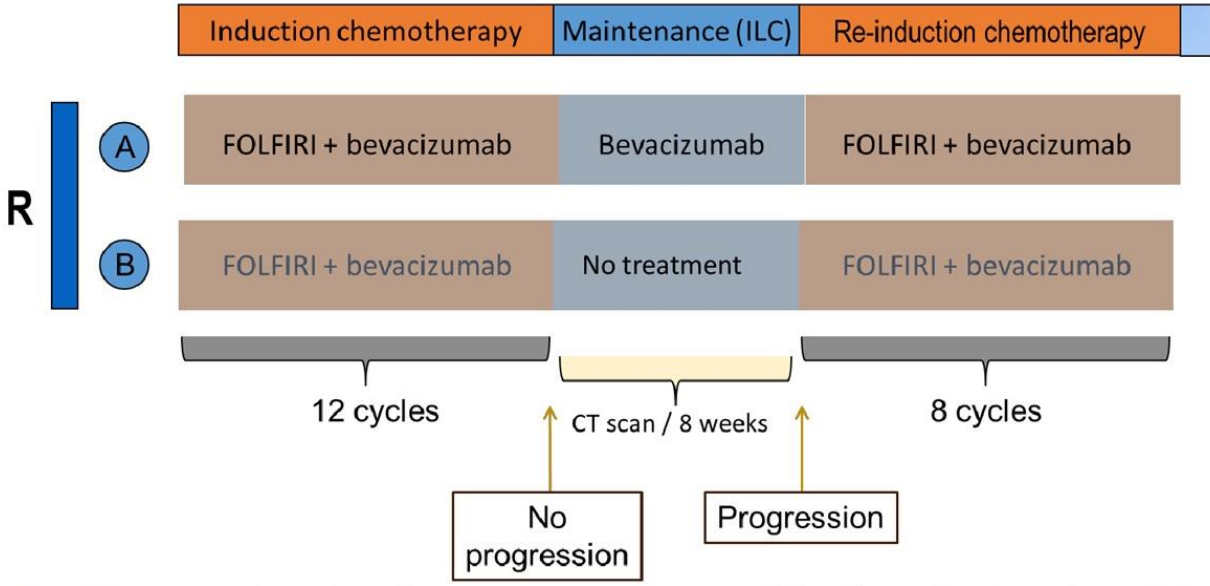
Rechts



OS (Monate)	Links	Rechts
FP/BEV	24.0	15.3
BEV mono	25.3	17.0
Keine Therapie	23.3	18.3

Deeskalation oder Behandlungspause nach Fluoropyrimidin/Irinotecan/Bevacizumab basierter Induktionstherapie

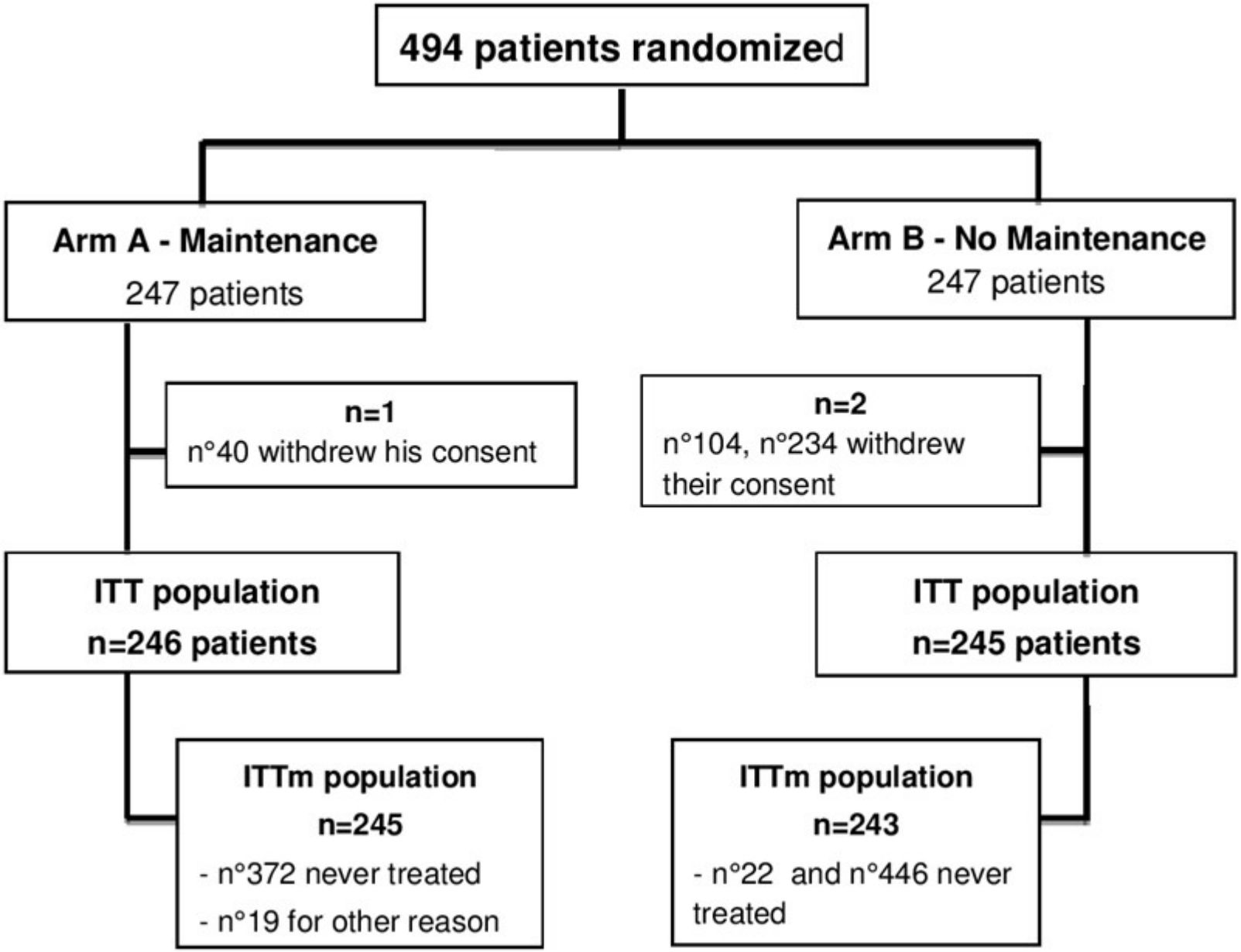
PRODIGE 9: Bevacizumab-Erhaltung vs. Behandlungspause während der Chemotherapie-freien Intervalle nach 12 Zyklen FOLFIRI-Bev Induktion



Aparicio T et al, Dig Liver Dis. 2015 ; 47

Alternate sequences of maintenance and re-induction until progression under CT, than 2nd line if appropriate

Aparicio et al., ASCO 2016


494 patients randomized
Arm A - Maintenance
247 patients
Arm B - No Maintenance
247 patients
n=1
n°40 withdrew his consent
n=2
n°104, n°234 withdrew their consent
ITT population
n=246 patients
ITT population
n=245 patients
ITTm population
n=245
- n°372 never treated
- n°19 for other reason
ITTm population
n=243
- n°22 and n°446 never treated

PRODIGE 9:

Treatment received	Arm A (Bevacizumab)	Arm B (Observation)	All
	N=245	N=243	N=488
Progression during induction CT	39 (15.9%)	46 (18.9%)	85 (17%)
At least one re-induction	124 (50.6%)	137 (56.3%)	261 (53.5%)
At least two re-induction	46 (18.8%)	61 (25.1%)	107 (22%)
At least three re-induction or more	16 (6.5%)	35 (14.4%)	51 (10%)
Second line treatment	150 (61.2%)	150 (61.7%)	300 (61.4%)
Chemotherapy alone	49 (20.0%)	54 (22.2%)	103 (21.1%)
Anti-VEGF	69 (28.2%)	72 (29.6%)	141 (28.9%)
Anti-EGFR	30 (12.2%)	24 (9.9%)	54 (11.1%)
R0 surgery	13 (5.3%)	10 (4.1%)	23 (4.7%)

Aparicio et al., ASCO 2016

PRODIGE 9: Ergebnisse

Bevacizumab Observation

Efficacy result Intent to treat modified	Arm A	Arm B	HR [95% CI]; p-value
	N=245	N=243	
Tumor control duration (months)	15.01	14.98	1.09 [0.87 ; 1.37]; p=0.43
First progression free survival (months)	9.20	8.90	0.92 [0.76 ; 1.10]; p=0.34
Overall survival (months)	21.65	21.98	1.05 [0.86 ; 1.28]; p=0.65
Time to treatment faillure (months)	11.07	12.12	1.14 (0.95 ; 1.37); p=0,14
First CFI duration (months)	4.30	4.34	-
Overall tumor response rate	119 (48.6%)	129 (53.1%)	-

Per protocol: Pat. mit ≥ 1 Re-Induktion

Efficacy result *Per protocol*	Arm A	Arm B	HR [95% CI]; p-value
	N=124	N=137	
Tumor control duration (months)	17.77	23.26	1.18 [0.87 ; 1.59]; p=0.29
First progression free survival (months)	9.86	9.49	0.89 [0.69 ; 1.13]; p=0.33
Overall survival (months)	27.47	28.58	1.09 [0.82 ; 1.45]; p=0.56

Aparicio et al., ASCO 2016

Deeskalation oder Behandlungspause nach FOLFOX/Cetuximab basierter Induktionstherapie

COIN-B

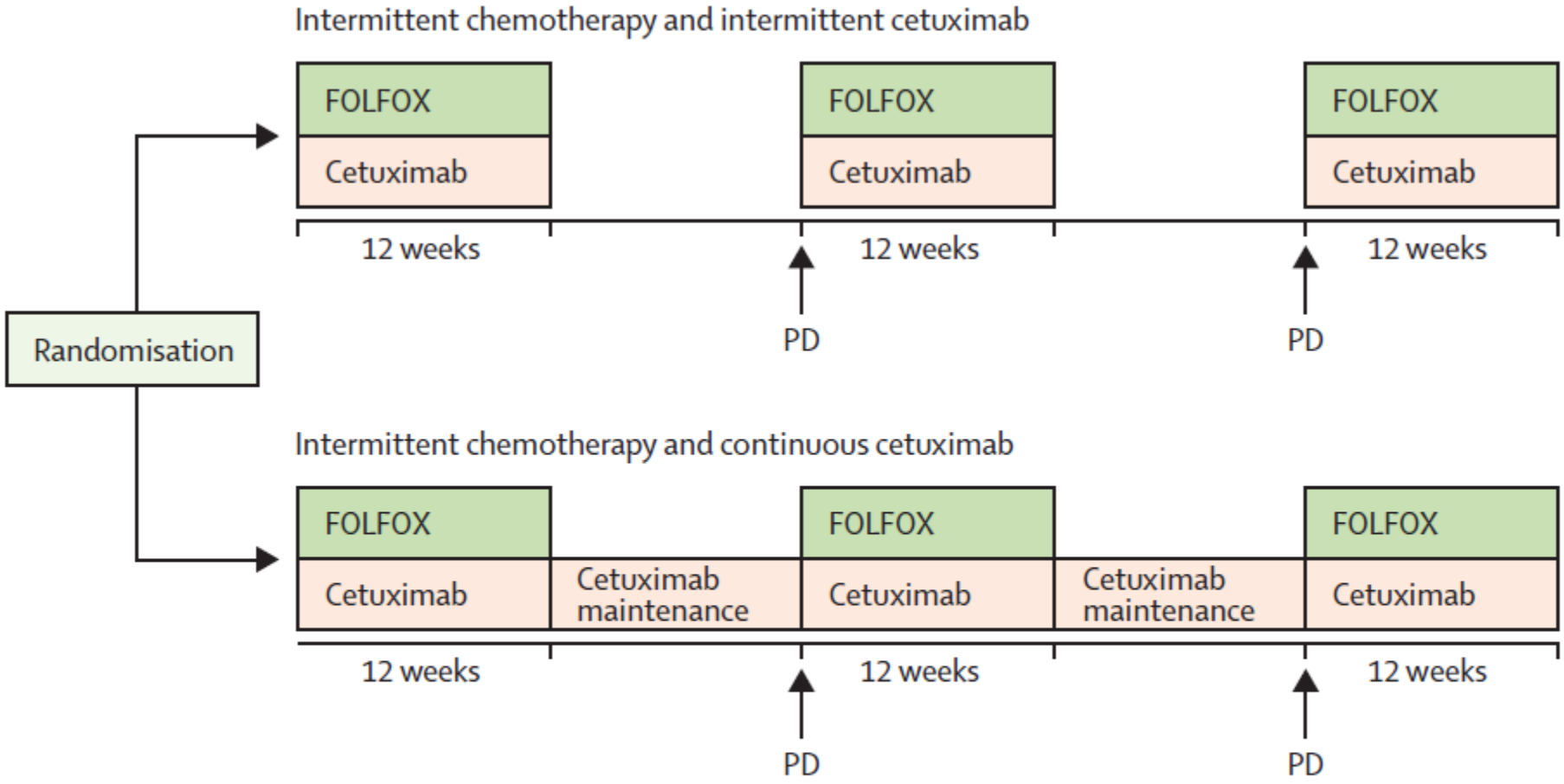


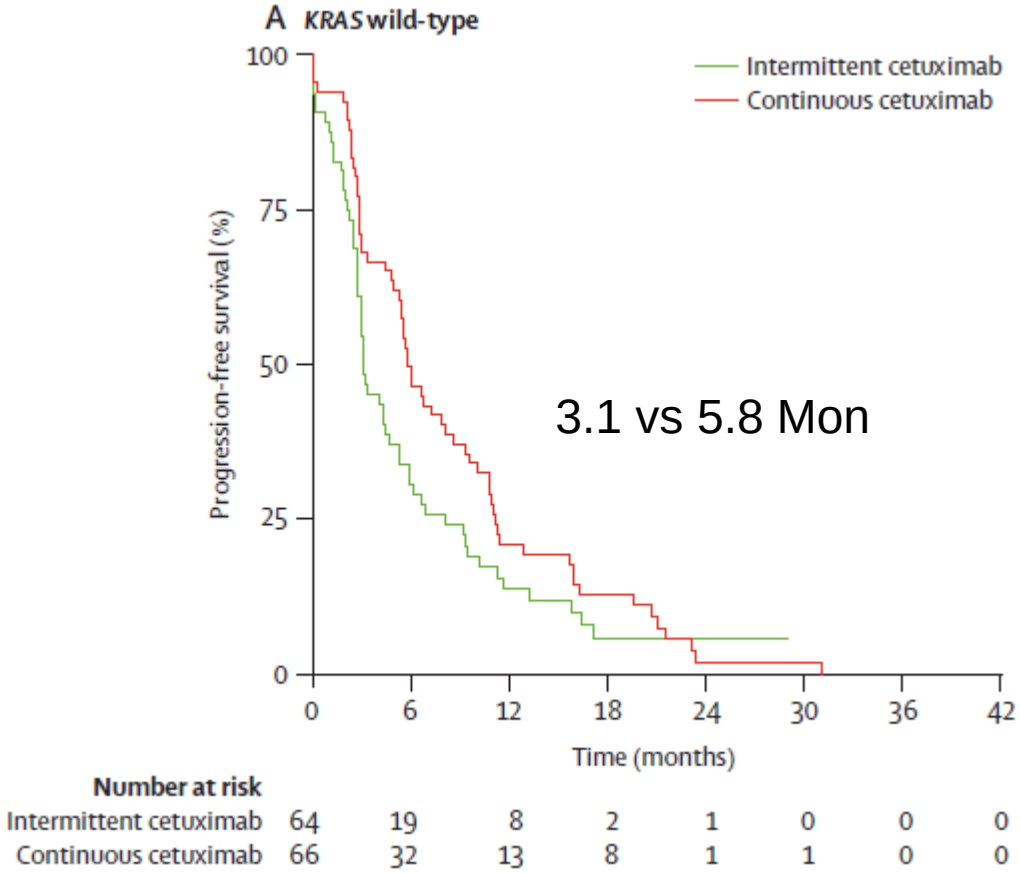
Figure 1: **Trial design**

Treatment cycles continued until progressive disease (PD) with maximally tolerated treatment, or patient choice. FOLFOX=folinic acid and oxaliplatin followed by bolus and infused fluorouracil.

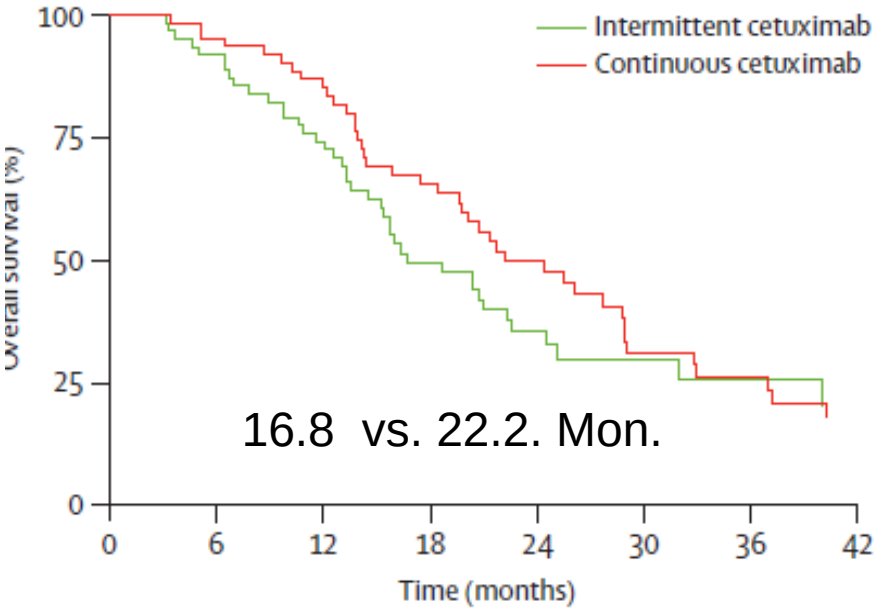
Wasan et al. Lancet Oncology 2014

COIN B: PFS und OS in KRAS^{wt} Patienten

PFS



OS



Wasan et al., Lancet Oncol 2014

Phase II study of first-line mFOLFOX plus cetuximab (C) for 8 cycles followed by mFOLFOX plus C or single agent (s/a) C as maintenance therapy in patients (p) with KRAS wild type metastatic colorectal cancer (mCRC): the MACRO-2 trial

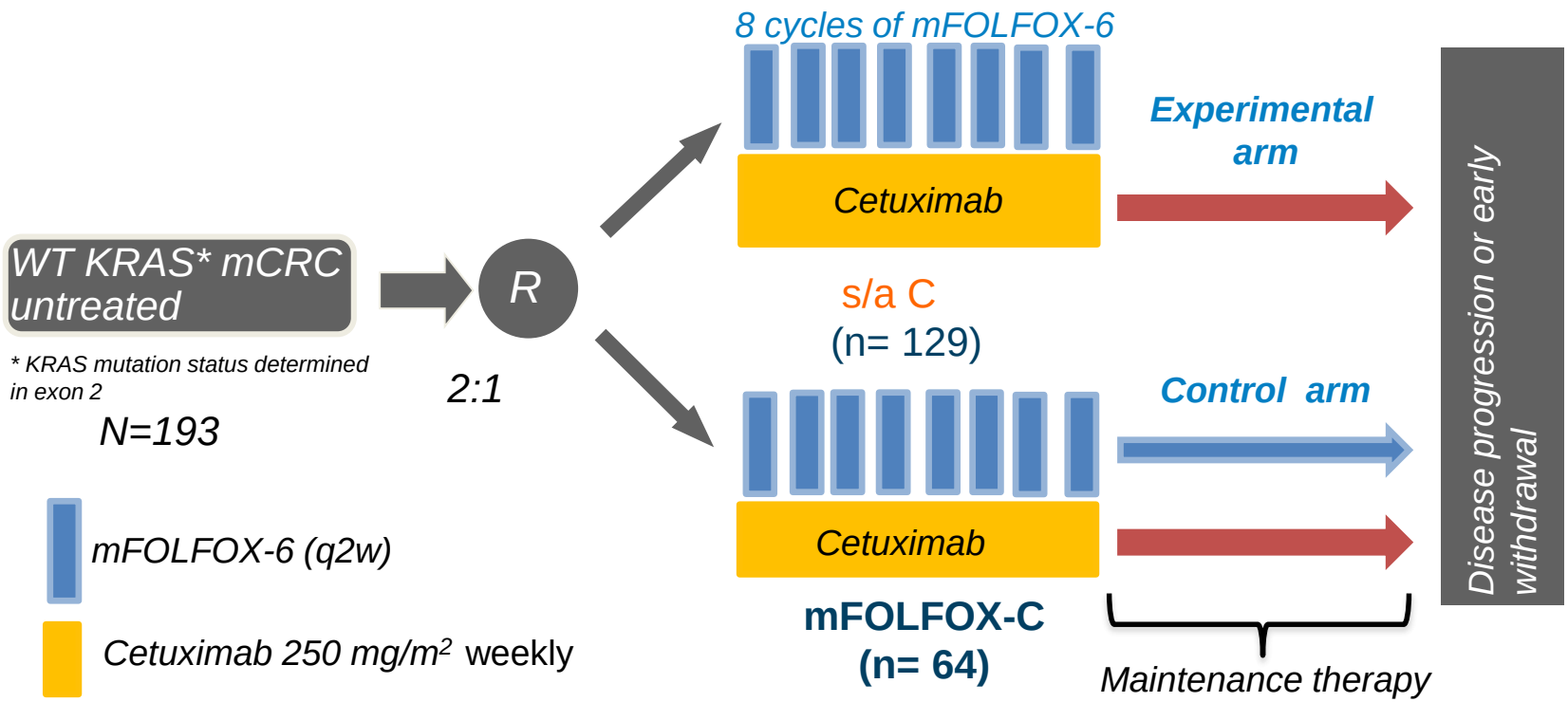
P. García Alfonso, M. Benavides, A. Sánchez Ruiz, C. Guillén-Ponce, M.J. Safont, J. Alcaide, A. Gómez, R. López, J.L. Manzano, M. Méndez Ureña, F. Rivera, J. Sastre, C. Grávalos, T. García García, J.I. Martin-Valadés, E. Falcó, E. González Flores, M. Navalón, E. Díaz Rubio, E. Aranda

On behalf of the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

MADRID 2014 ESMO congress

TTD
GRUPO DE TRATAMIENTO DE LOS TUMORES DIGESTIVOS

MACRO-2 trial



- *Sponsor: Spanish Cooperative Group for Digestive Tumour Therapy (TTD)*
- *Study:* TTD-09-04
- *Principal investigators: Dr. Eduardo Díaz Rubio & Dr. Enrique Aranda Aguilar*
- *ClinicalTrials.gov identifier:* NCT01161316

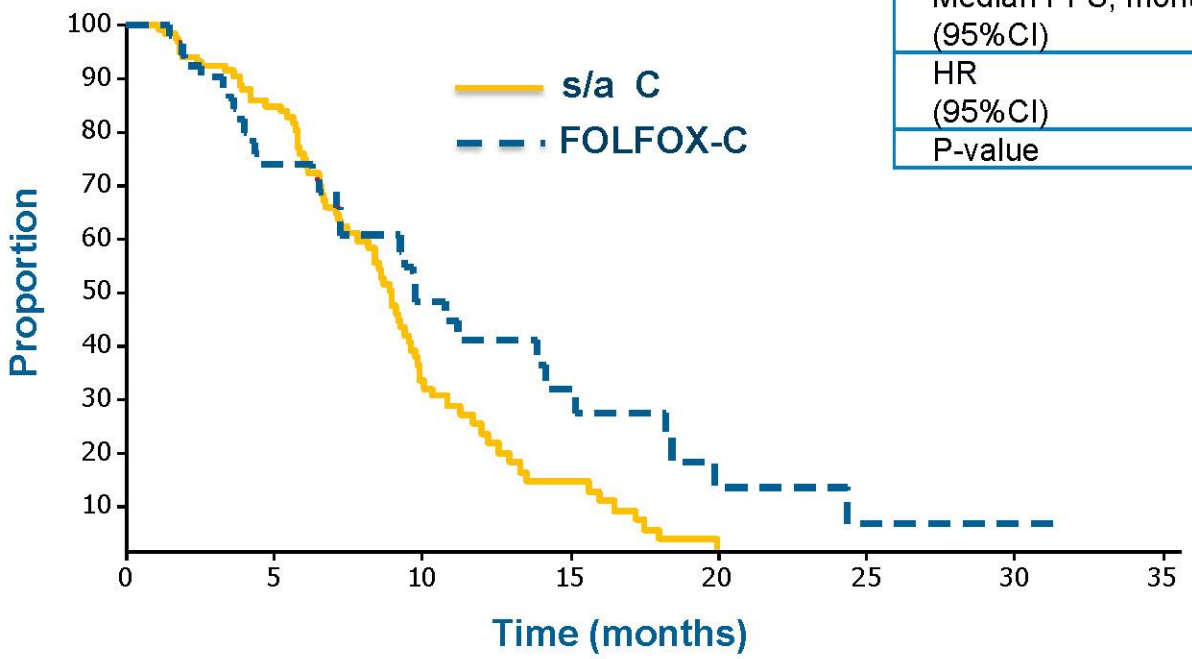
Garcia Alfonso et al., ESMO 2014

GRUPO DE TRATAMIENTO DE LOS TUMORES DIGESTIVOS

MACRO-2 trial

Results: secondary endpoint

Progression free-survival



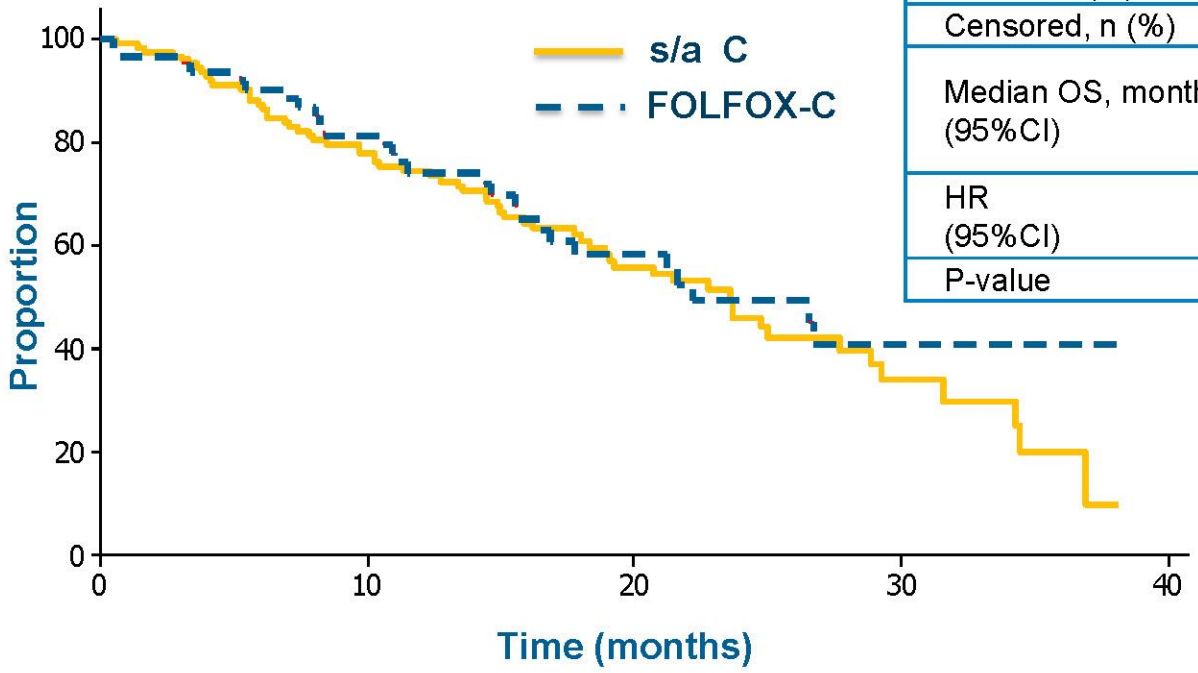
	s/a C N = 129	FOLFOX-C N = 64
Events, n (%)	75 (58.1)	31 (48.4)
Censored, n (%)	54 (41.9)	33 (51.6)
Median PFS, months (95%CI)	8.9 (7.8 to 9.6)	9.8 (7.2 to14.2)
HR (95%CI)	0.690 (0.4498 to 1.0580)	
P-value	0.09	

Median duration of follow-up was 13.9 months (range, 0-38)

MACRO-2 trial

Results: secondary endpoint

Overall survival



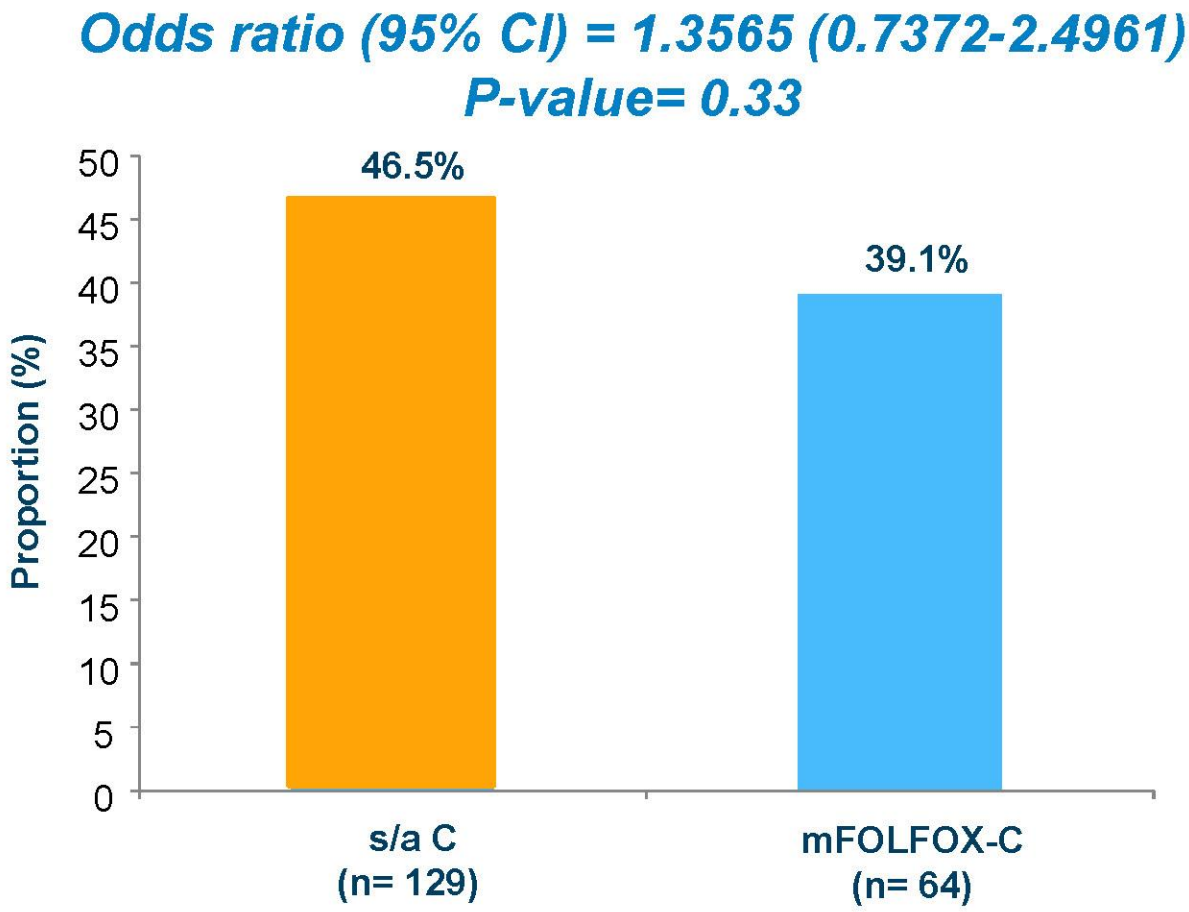
	s/a C N = 129	FOLFOX-C N = 64
Events, n (%)	63 (48.8)	27 (42.1)
Censored, n (%)	66 (51.2)	37 (57.8)
Median OS, months (95%CI)	**23.6** (18.3 to 28.9)	**22.2** (16.4 –not estimable)
HR (95%CI)	1.151 (0.7330 to 1.8070)	
P-value	0.54	

Median duration of follow-up was 13.9 months (range, 0-38)

MACRO-2 trial

Results : secondary endpoint

Objective response rate (confirmed responses)



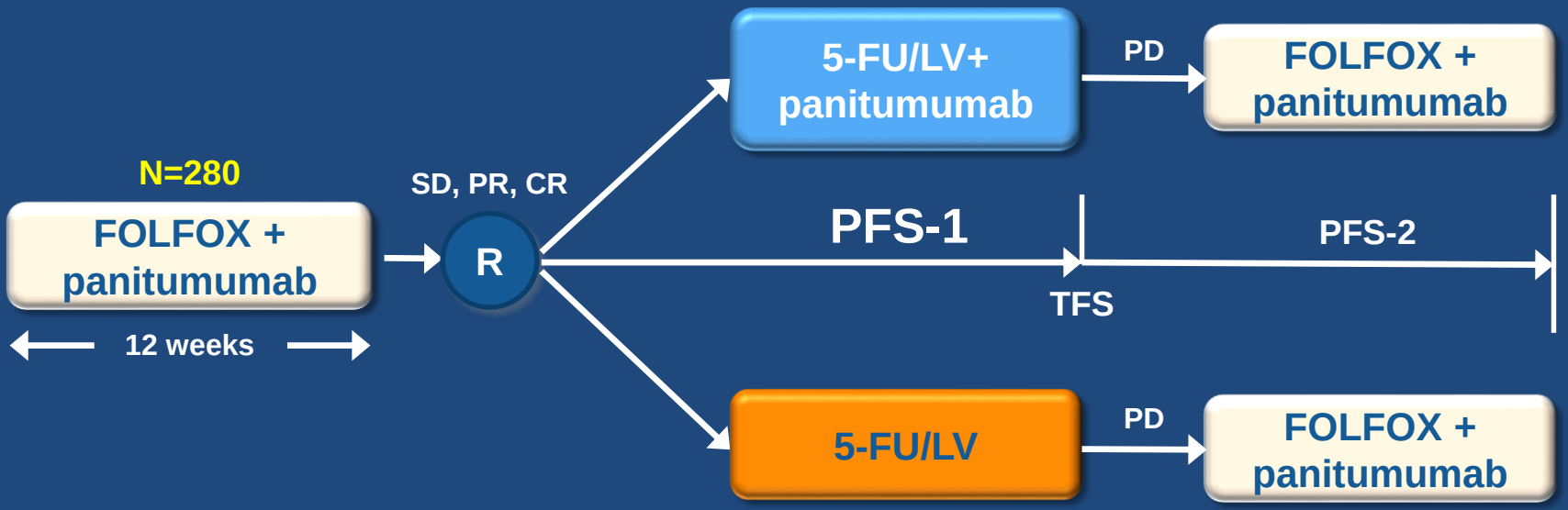
MACRO-2 trial

Conclusions

- The results of the present hypothesis-generating phase II exploratory trial with a non-inferiority design suggest that maintenance therapy with single agent cetuximab following mFOLFOX plus cetuximab induction is not inferior to continuing treatment with mFOLFOX plus cetuximab with respect to PFS at 9 months.
- Analysis of *RAS* status (KRAS and NRAS exon 2,3,4) and its predictive role in efficacy variables is ongoing.
- Analysis of resectability of the disease (R0), hypomagnesaemia as predictor efficacy factor and CTC enumeration is ongoing.
- Phase III studies are needed to confirm the benefit of cetuximab as maintenance therapy following induction chemotherapy

PanaMA- AIO KRK0212

Open-label, randomized, multicenter Phase II, mCRC, RAS wt, 1st-line treatment



Primary endpoint: PFS-1

Secondary endpoints: overall survival, PFS-2, response rates during induction and maintenance, time to failure of strategy, QoL-health and skin, safety

Aktivierung des angeborenen Immunsystems

Toll like receptors: expremiert auf NK-Zellen und dendritischen Zellen

MGN1703 = Toll like receptor 9 agonist,
Verstärkung des angeborenen (innate) Immunsystems

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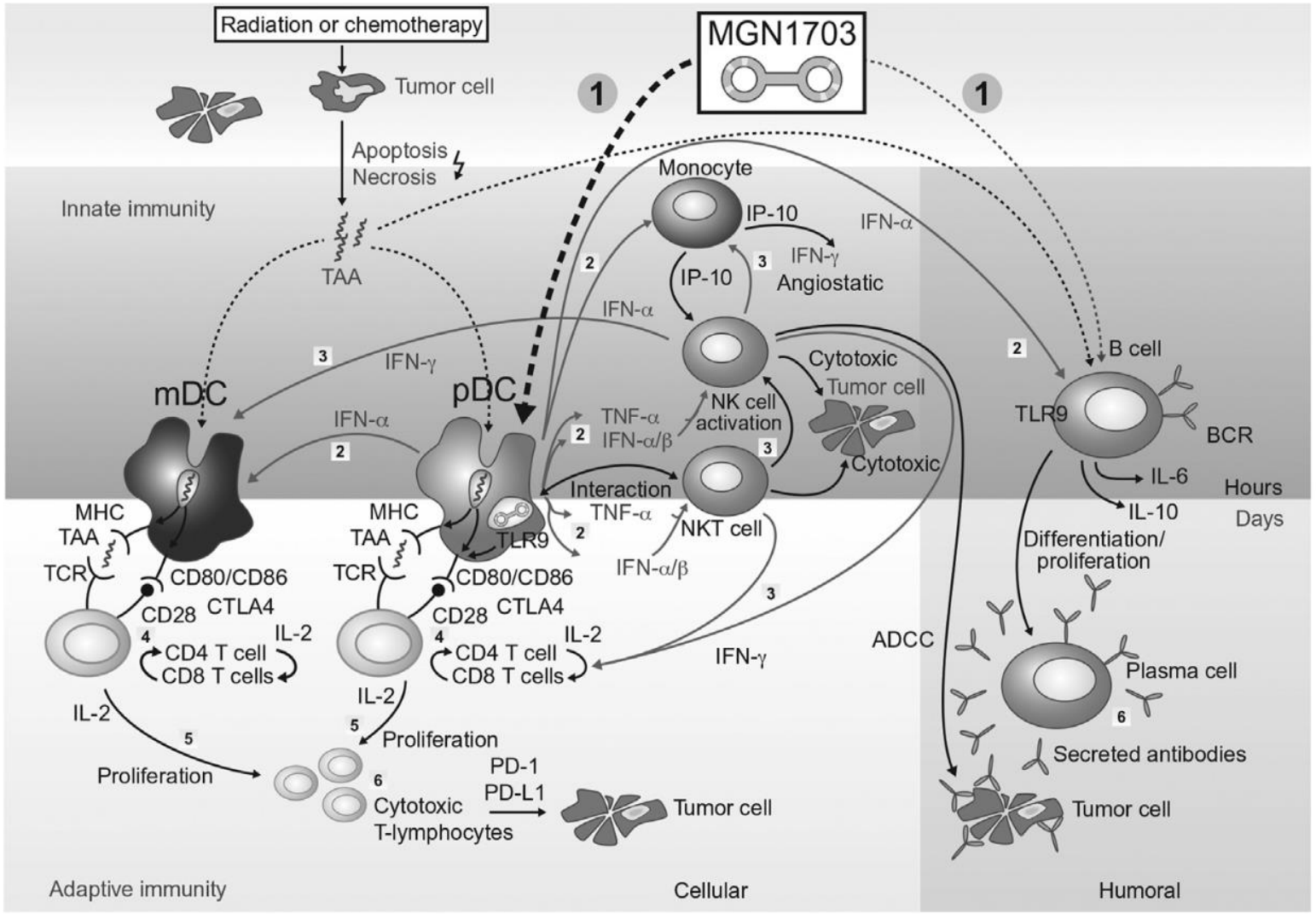
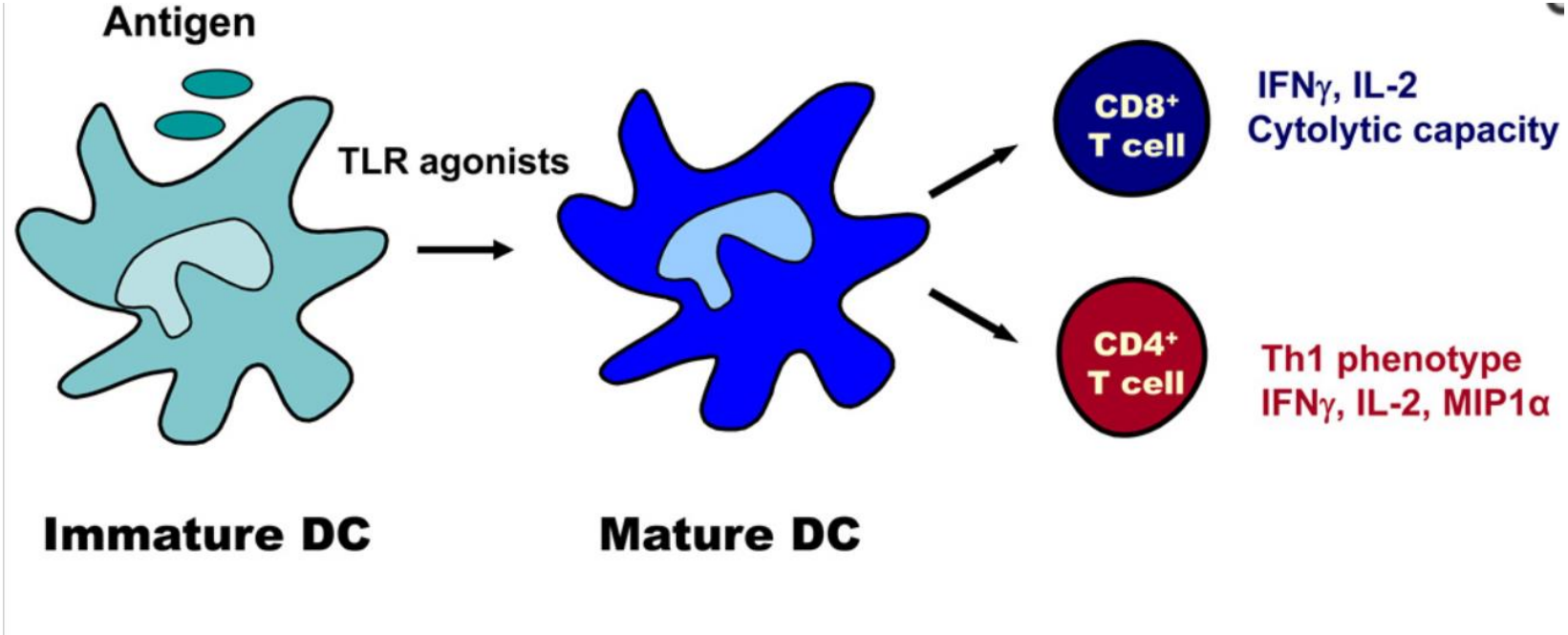
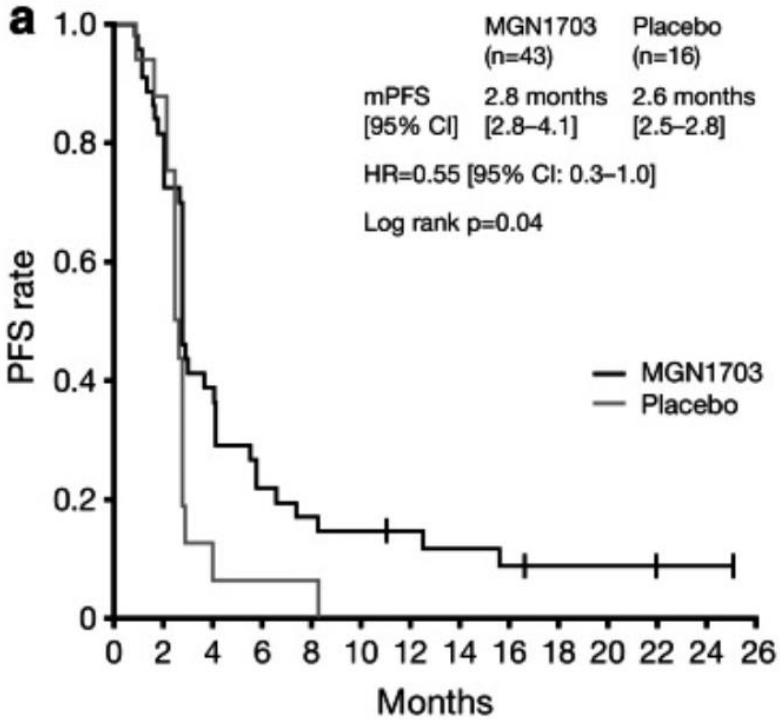
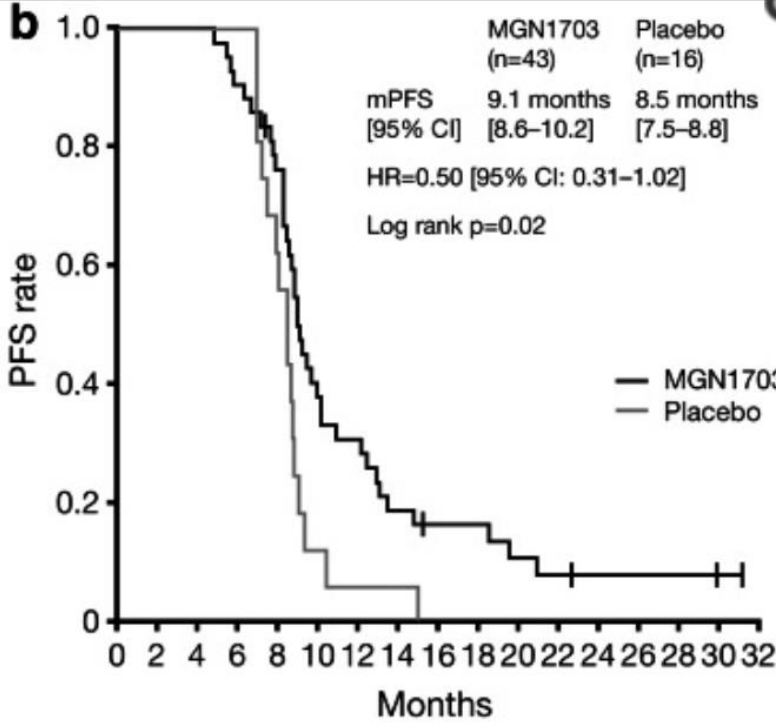


Verstärkung des angeborenen (innate) Immunsystems



IMPACT trial



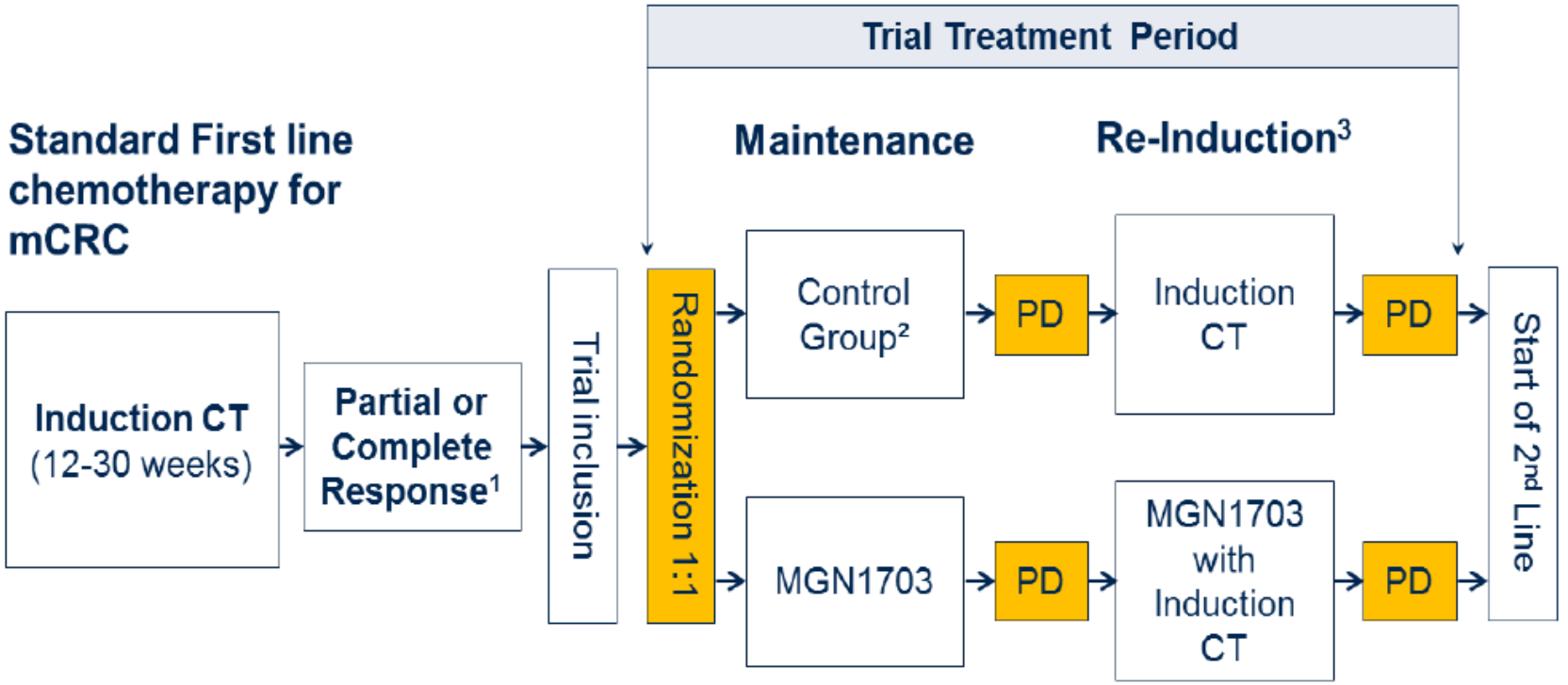


[a]Similar results were obtained for the independent review assessment:

	mPFS, months (95% CI)		HR (95% CI)	P
	MGN1703 (n=43)	Placebo (n=16)		
From randomisation	2.8 (2.8–5.6)	2.7 (2.5–2.8)	0.56 (0.29–1.08)	0.07
From start of induction therapy	9.2 (8.7–12.4)	8.6 (7.9–8.8)	0.49 (0.26–0.94)	0.03

Schmoll et al., J Cancer Res Clin Oncol 2014

IMPALA Study Design



1. RECIST 1.1. Responses are assessed locally. No need of response confirmation or independent review
2. Control Group patients may either continue induction therapy or halt some of the agents or interrupt all therapies
3. Re-introduction of prior induction therapy mandated whenever feasible in all patients of the MGN1703 arm and in those of the control group who reduced treatment intensity during maintenance

MGN1703 = Toll like receptor 9 agonist

Maintenance-Studien im Vergleich: Bewertungskriterien

- Randomisierungszeitpunkt (zu Beginn oder nach Induktion)
- Art und Dauer der Induktionstherapie, Chemotherapie-Backbone
- Wahl der zielgerichteten Therapie
- Folgetherapien
- Biomarker

Optionen in der Sequenz u. Erhaltungstherapie

- Deeskalation auf aktive Erhaltungstherapie oder Therapiepause ist ohne Beeinträchtigung des OS möglich
- Standardempfehlungen können nicht ausgesprochen werden. Die Wahl einer Maintenance-Strategie sollte die Patienten-Präferenz berücksichtigen.
- Maintenance-Switch (z.B. Einführung eines Immuntherapeutikums)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