The role of maintenance treatment in mCRC patients with disease control & appropriate endpoints

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Potential conflicts of interest:

- **1. Employment**
  - **no**
- **2. Consultancy**
  - **Amgen, Bayer, Celgene, Merck, Roche, Sanofi**
- **3. Stock/stock options**
  - **none**
- **4. Payment for lectures**
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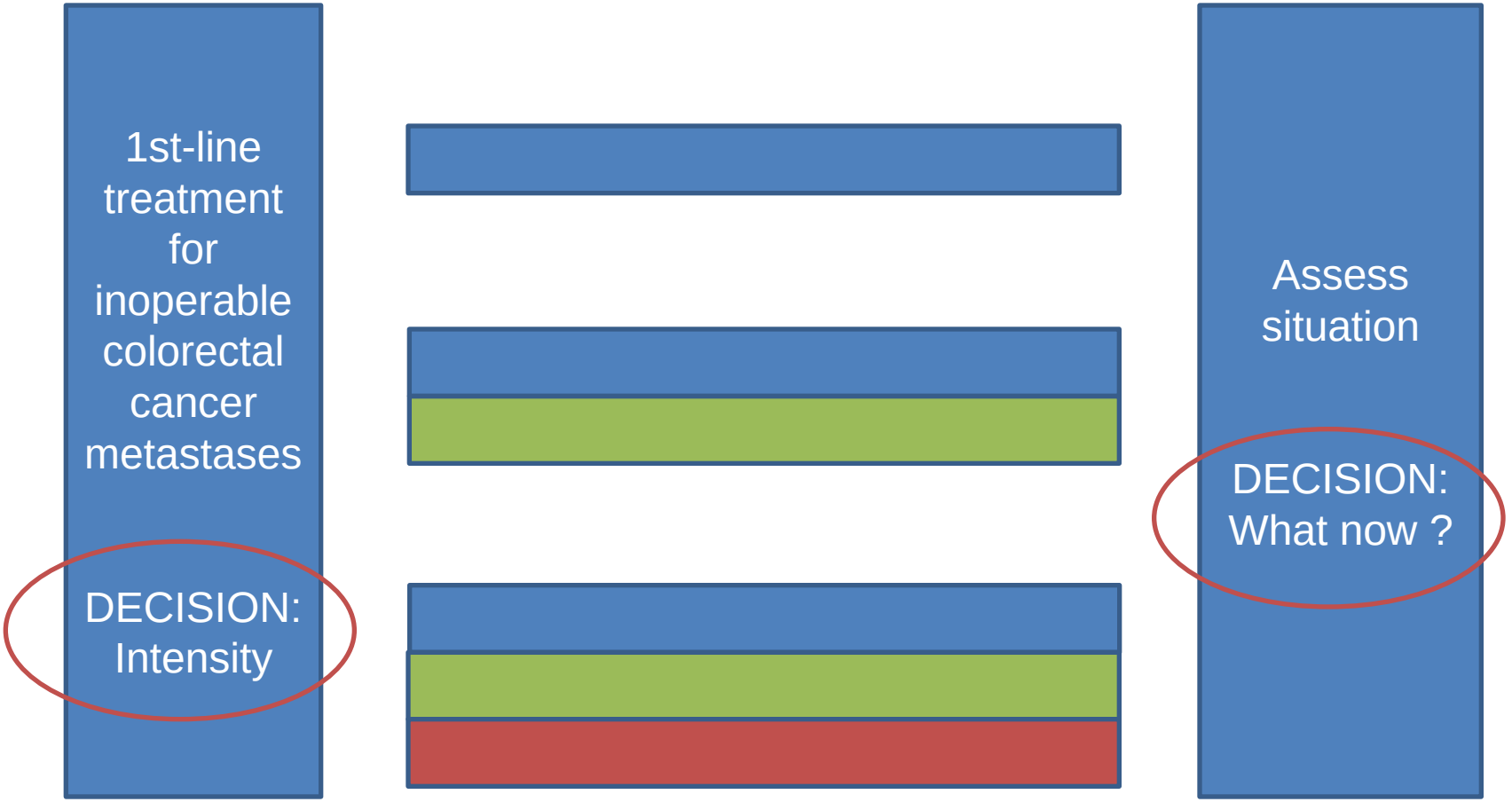
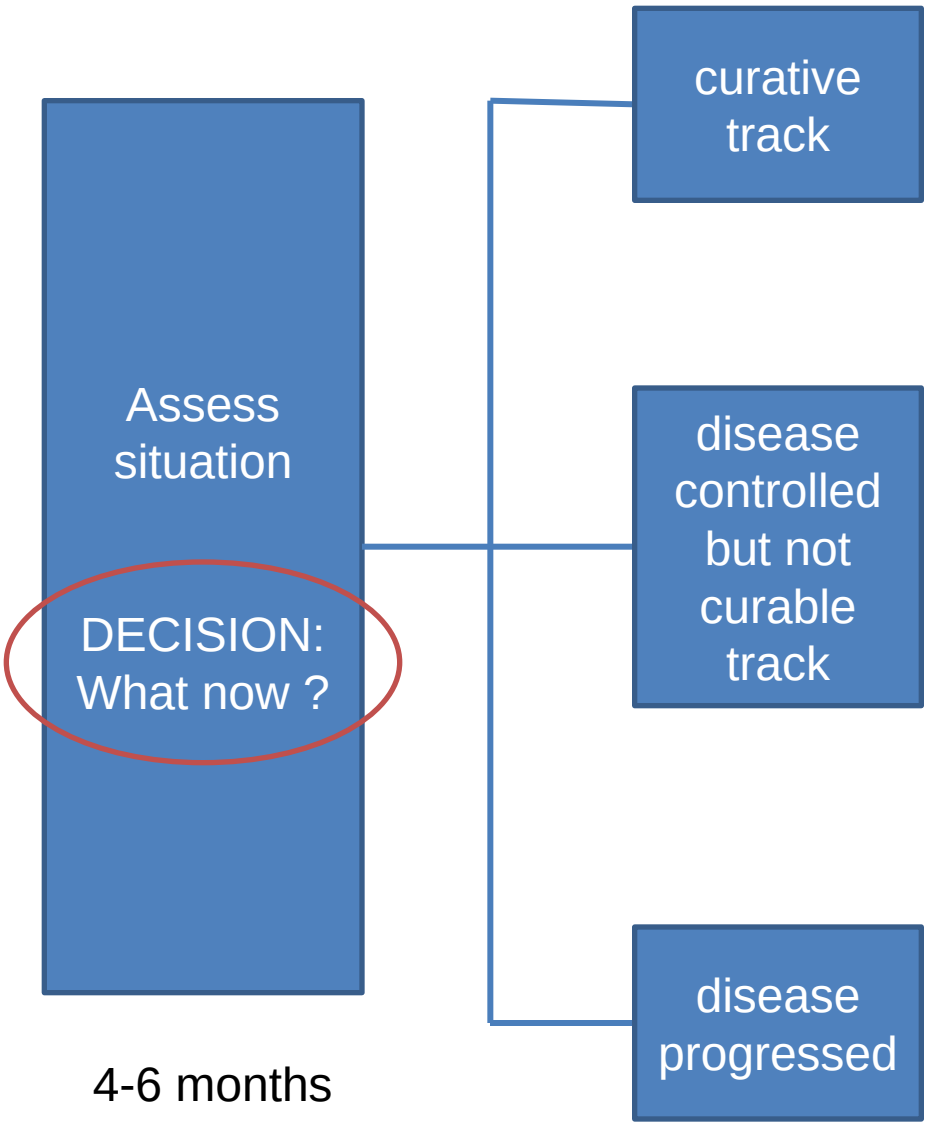
- **5. Grants/ grants pending**
  - **none**
- **6. Expert testimony**
  - **none**
- **7. Any other financial relationships**
  - **none**

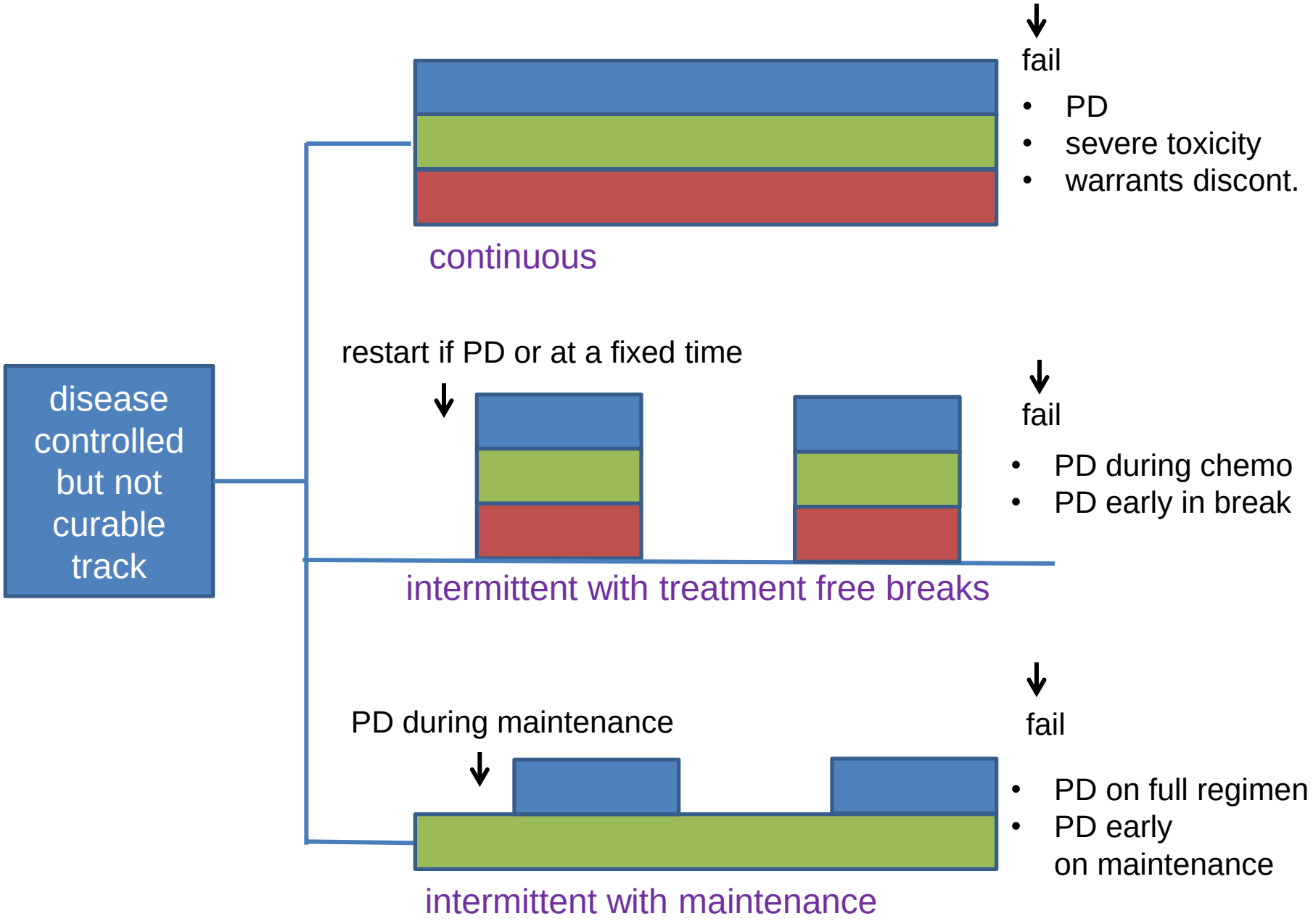
Strategic decisions in the care of patients with metastatic colorectal cancer (mCRC)



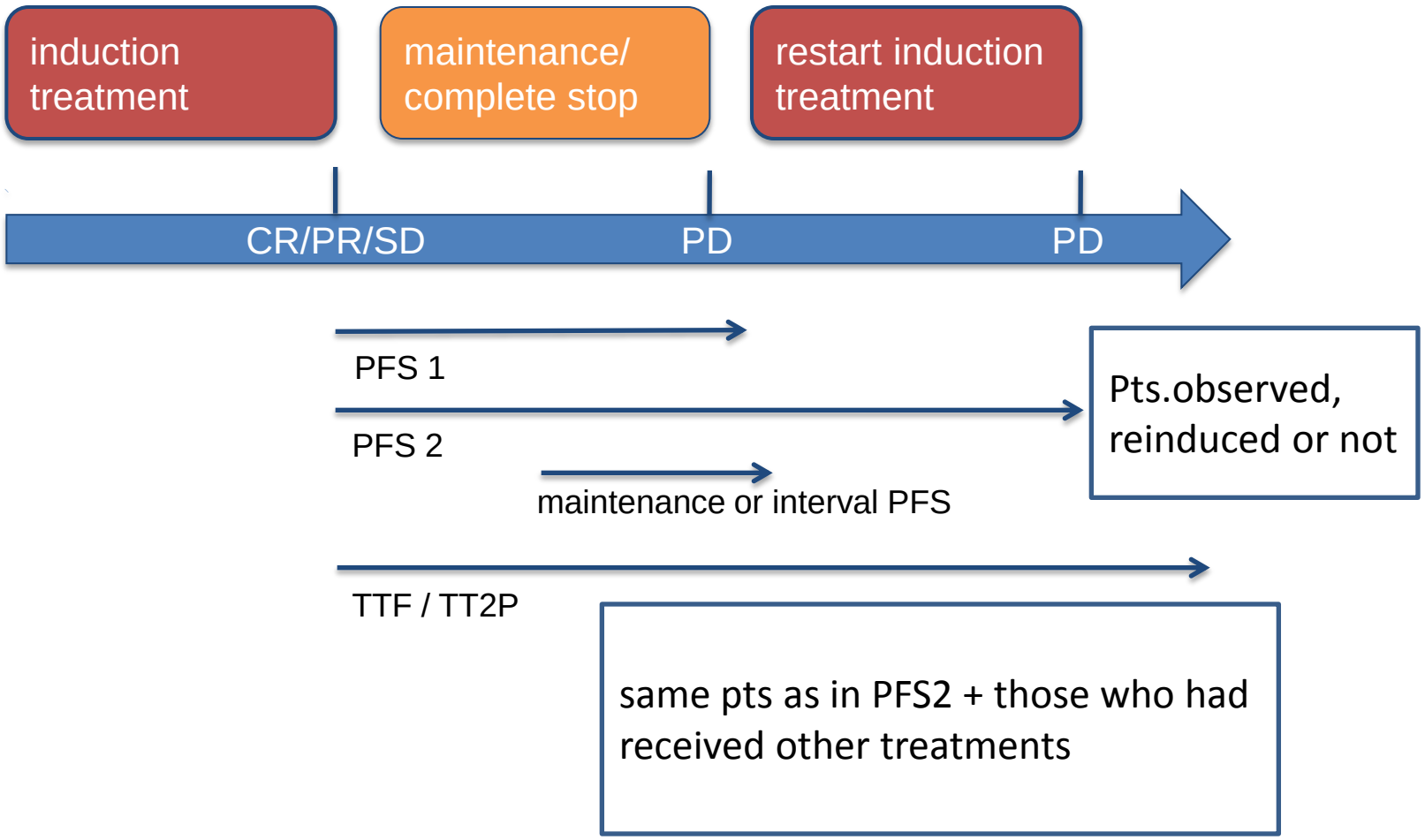


- resection(s)
- ablation(s)
- further chemotherapy

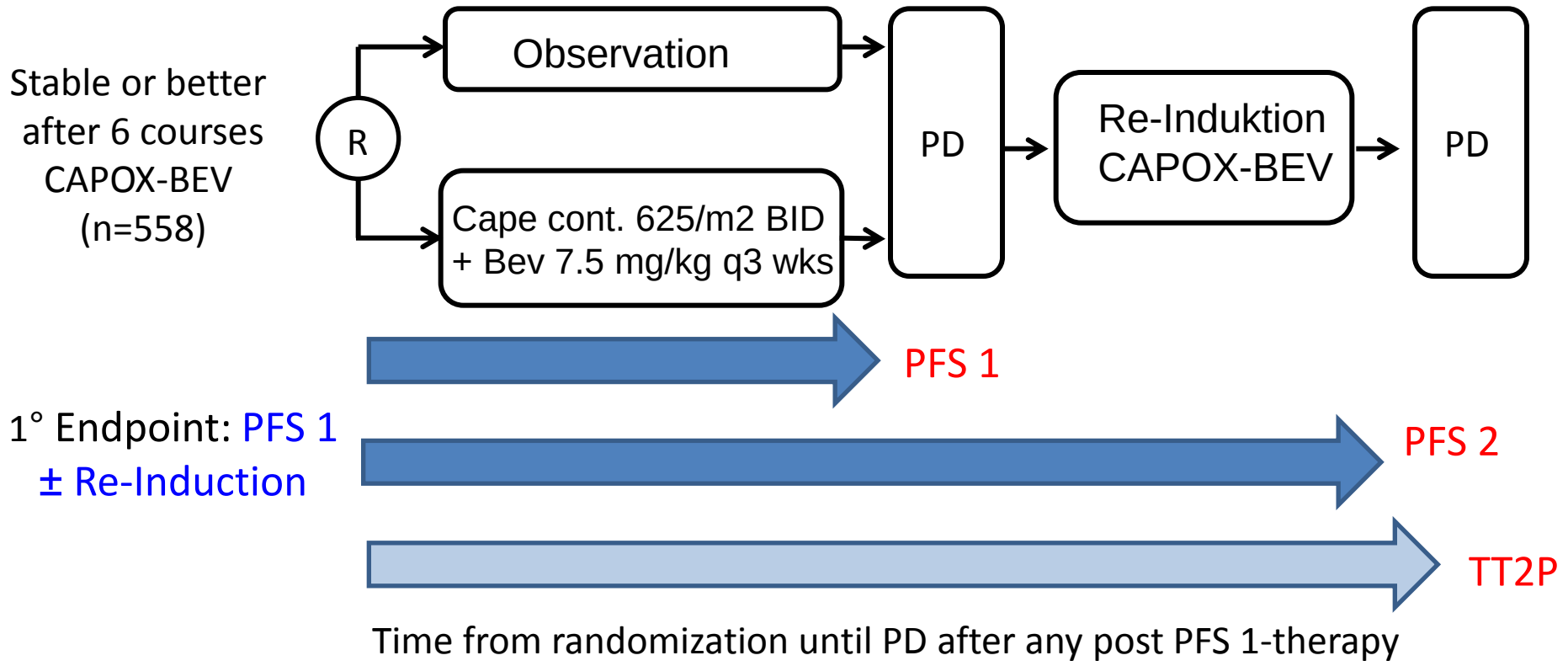
- intensify (if initially non-intensive)
- second-line drugs/trials
- palliative care


disease controlled but not curable track
continuous
fail
• PD
• severe toxicity
• warrants discont.
restart if PD or at a fixed time
intermittent with treatment free breaks
fail
• PD during chemo
• PD early in break
PD during maintenance
intermittent with maintenance
fail
• PD on full regimen
• PD early on maintenance

Study endpoints in case of maintenance therapy



CAIRO 3-Trial Koopman et al., ASCO GI 2014, LBA 388.



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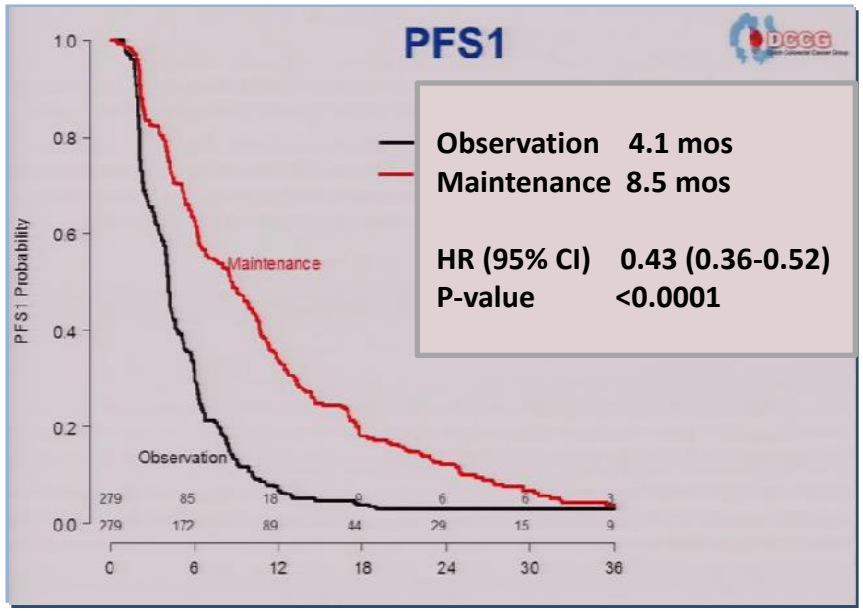
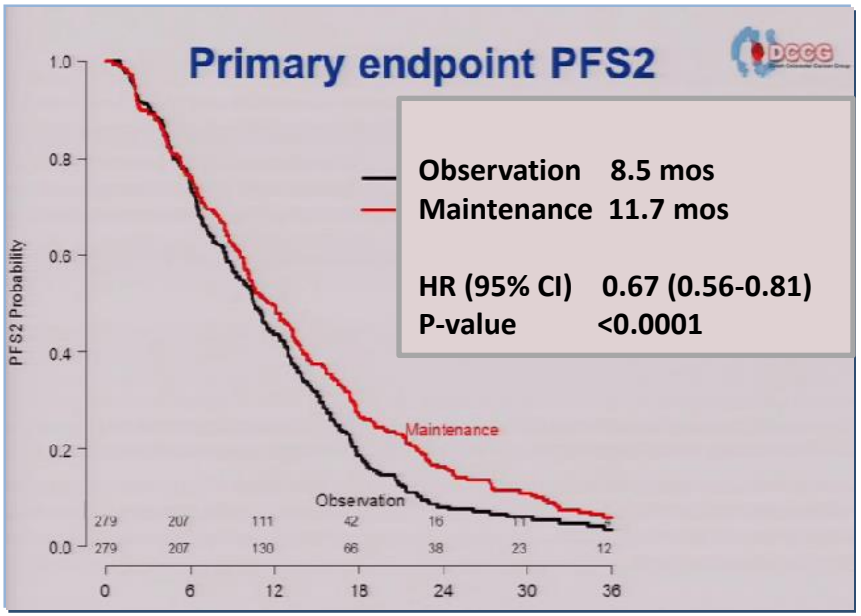


PFS1: Time from ® until 1. progression

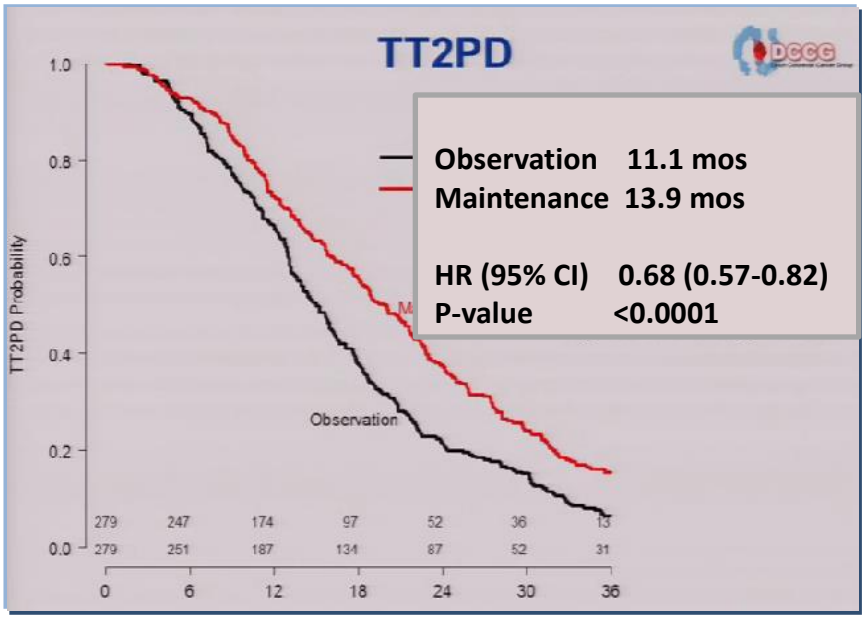


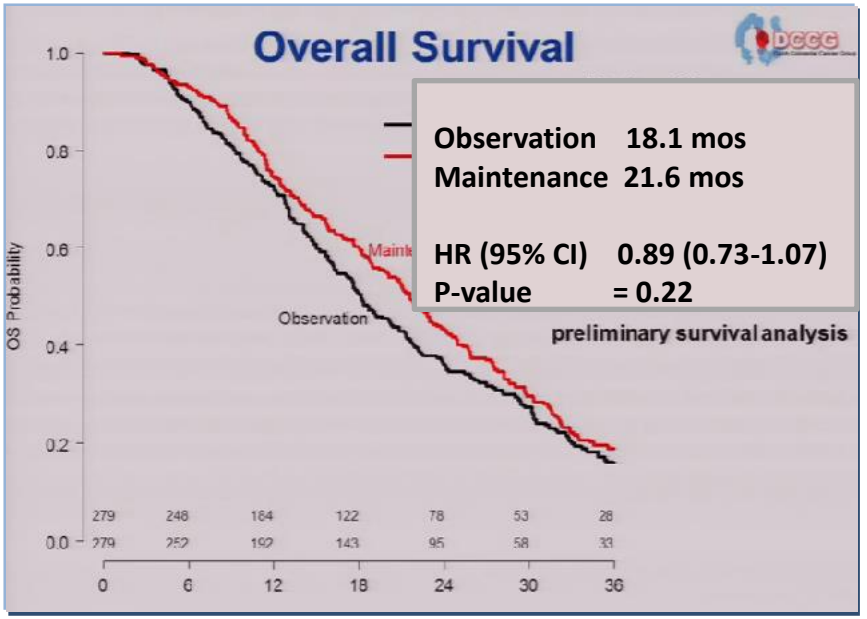
PFS2: Time from ® until PD ± re-induction

CAIRO 3-Trial Koopman et al., Proc ASCO 2013, #3502.

	Observation n=279	Maintenance n=279
Observation/Maintenance continuing	13 (5%)	20 (7%)
No re-induction with CAPOX-BEV	54 (19%)	125 (45%)
Persisting neurotoxicity	3 (6%)	15 (12%)
Other toxicities	-	26 (21%)
Patient‘s wish	8 (15%)	13 (10%)
Re-Induktion mit CAPOX-BEV	212 (76%)	131 (47%)
Pat. receiving additional/other drugs	49%/12%	49%/11%

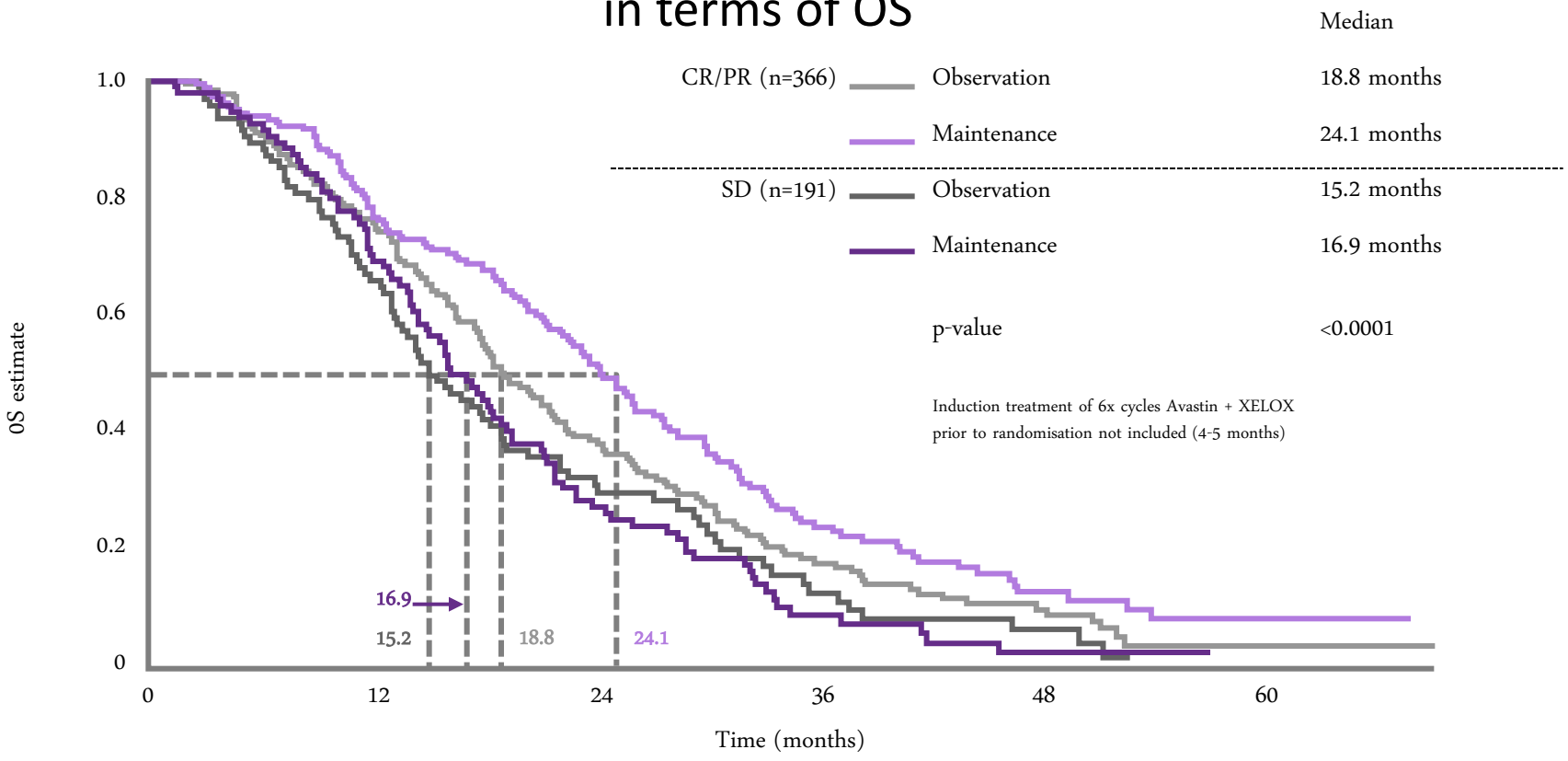
CAIRO 3-Trial Koopman et al., Proc ASCO 2013, #3502.





- **Significant improvements in PFS 1, PFS 2 (primary endpoint) & TT2P**
- **The difference in OS was borderline, but subgroup analyses suggest:**

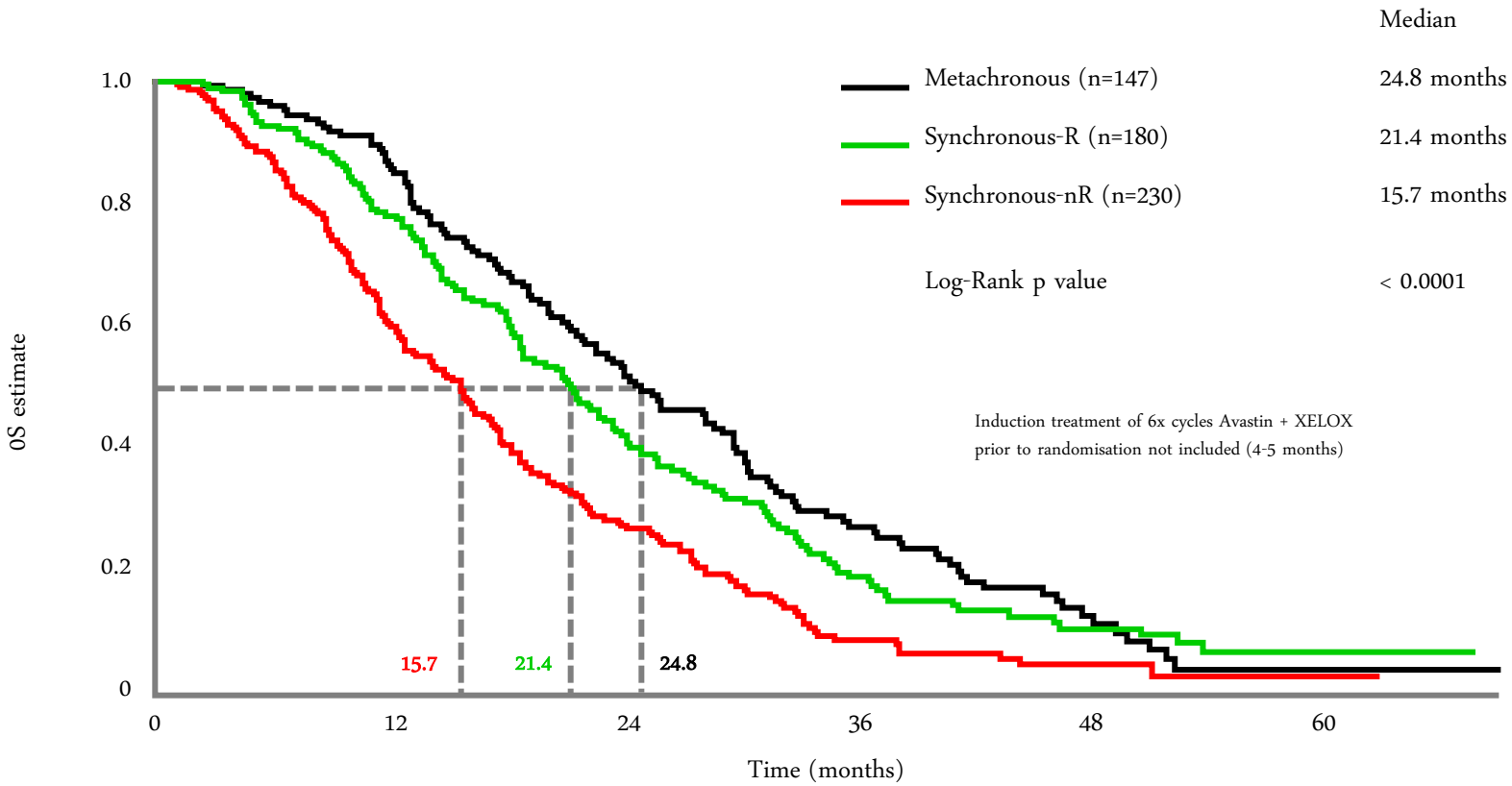
CAIRO-3: patients with a CR/PR as best response on induction treatment benefit most from maintenance Avastin + Xeloda in terms of OS



No. at risk:							
	184	136	65	26	11	2	CR-PR/O
	95	62	24	9	3	0	SD/O
	182	140	86	32	11	4	CR-PR/M
	96	66	26	7	2	0	SD/M

Koopman, et al. ASCO GI 2014. Abstract LBA388

CAIRO-3: patients with metachronous disease or synchronous disease with resected primary tumour have higher OS

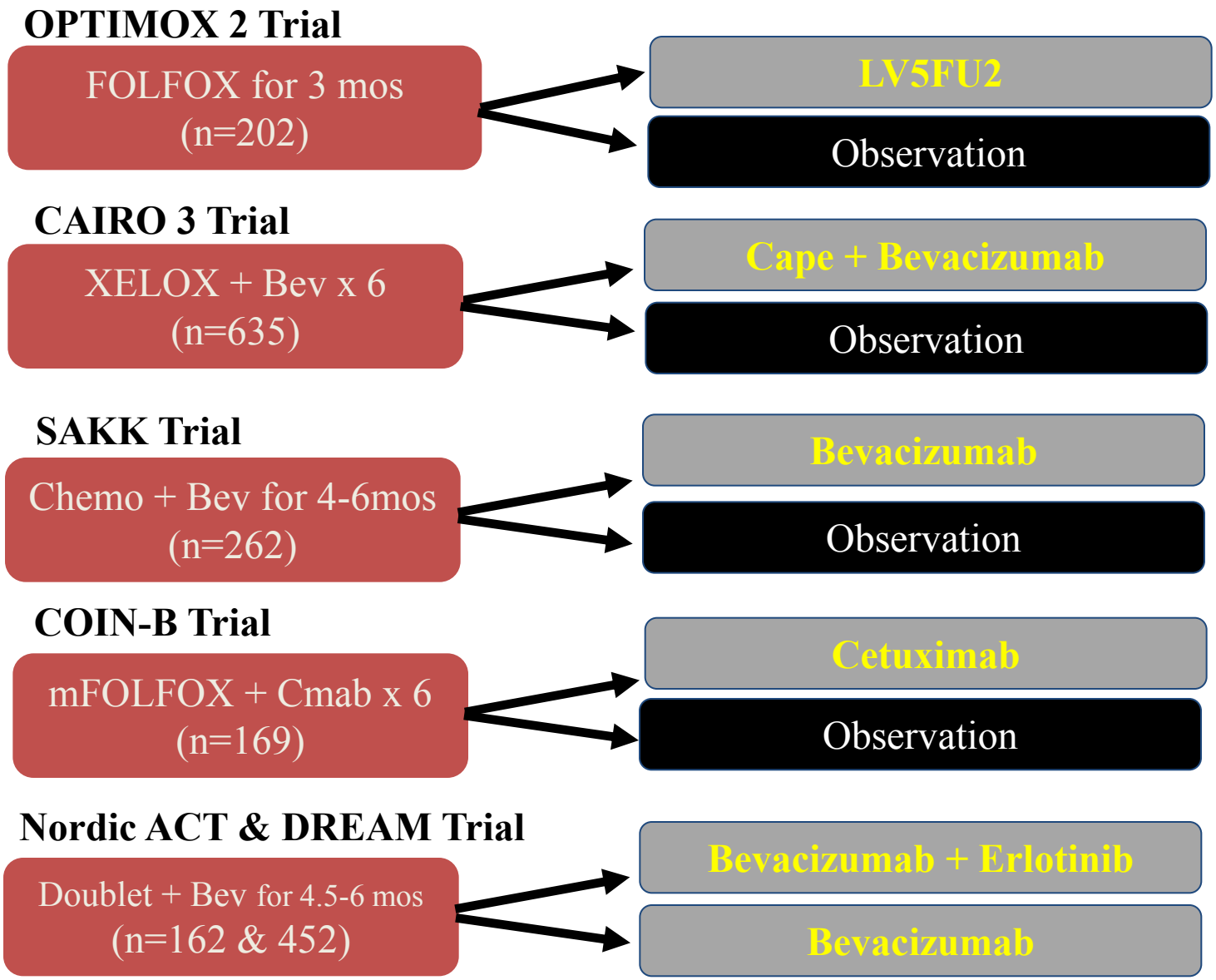


No. at risk:	147	127	72	33	10	2	M
	230	139	57	14	5	2	S n/R
	180	138	72	27	12	2	SR

R = resected; nR = not resected

Koopman, et al. ASCO GI 2014. Abstract LBA388

Randomised phase II/III trials comparing maintenance therapy versus chemo free interval in advanced CRC



Randomised phase II/III trials comparing maintenance therapy versus chemo free interval in advanced CRC

Trial	No.of pts	Maintenance	Interval PFS	HR (P-value)
OPTIMOX 2	202	LVFU2 vs. 0	+2.0 mos	n.s.
CAIRO 3	558	Bev + Cape vs. 0	+4.4 mos	0.41 (<0.001)
SAKK	262	Bev vs. 0	+1.8 mos	0.74 (0.47)
COIN B	169	Cmab vs. 0	+3.1 mos	0.67 (0.039)
Nordic ACT	162	Bev + Erlotinib vs. Bev	+1.5 mos	0.79 (0.19)
DREAM	452	Bev + Erlotinib vs. Bev	+1.0 mos	0.77 (0.012)

- **Interval PFS is the clearest surrogate endpoint for drug activity.**
- **Cape + Bev maintenance showed the best activity.**

Chibaudel B, J Clin Oncol 2009;43:5727–33; Koopman M, ASCO GI 2014 (LBA. 388); Koeberle D, Proc ASCO 2013 (abstr. 3503); Wasan H, Eudract No. 2006-003049-17; Johnsson A, Ann Oncol 24:2335-41, 2013. Tournigand C, Proc ASCO 2014 (in press)

Randomised phase II/III trials comparing maintenance therapy versus chemo free interval in advanced CRC

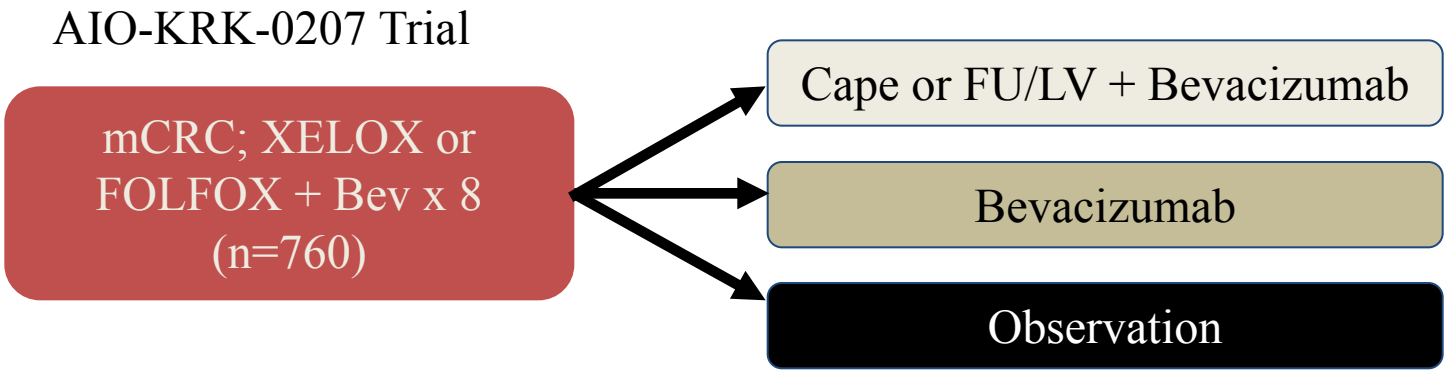
Trial	No.of pts	Maintenance	Interval PFS	OS	HR (P-value)
OPTIMOX 2	202	LVFU2	+2.0 mos	+4.3 mos	0.88 (0.42)
CAIRO 3	558	Bev + Cape	+4.4 mos	+3.5 mos	0.89 (0.22)
SAKK	262	Bev	+1.8 mos	+2.3 mos	0.83 (0.49)
COIN B	169	Cmab	+3.1 mos	-1.5 mos	n.s.
Nordic ACT	162	Bev + Erlotinib vs. Bev	+1.5 mos	-1.3 mos	0.88 (0.51)
DREAM	446	Bev + Erlotinib vs. Bev	+1.0 mos	+3.0 mos	0.80 (0.034)

- **Overall survival would be the key end point to change clinical practice.**
- **Cape + Bev showed no significant benefit in the ITT population, but in soubgroups & might thus be a reasonable option.**

Chibaudel B, J Clin Oncol 2009;43:5727–33; Koopman M, ASCO GI 2014 (LBA. 388); Koeberle D, Proc ASCO 2013 (abstr. 3503); Wasan H, Eudract No. 2006-003049-17; Johnsson A, Ann Oncol 24:2335-41, 2013. Tournigand C, Proc ASCO 2014 (in press)

Conclusions concerning maintenance treatment & remaining questions:

- **Was the benefit in the CAIRO 3 Trial due to cape alone or both cape + bev ?**



Conclusions concerning maintenance treatment & remaining questions:

- **Which patients really need maintenance therapy ?**

group	factor
patient related	follow-up compliance
	treatment tolerance
	treatment response
	personal preference
tumour related	multiple metastatic sites
	peritoneal involvement
	extensive liver disease
biochemical	alkaline phosphatase ≥300 U/l
	high LDH
	low serum albumin
	white blood cell count ≥$10x10^9$/l
	platelets ≥$400x10^9$/l
molecular/genetic	BRAF-mutation; KRAS codon G13D mutation

Personal preference……

survival time

time free of cancer symptoms

time free of treatment side effects

wellbeing & lethargy

time to life as normal

time free of clinical visits

impact on career

worries of CT scan results

financial pressure

What are my priorities, lets‘ discuss them, inform about choices, trade offs

Maintenance therapy - take home messages:

- **According to the CAIRO-3 trial, Cape + Bev maintenance shows clinical benefit over no maintenance therapy & seems to be a reasonable option.**
- **In view of the SAKK "mCRC triple negative trial" (failure to demonstrate noninferiority of no maintenance treatment), use of Bev-monotherapy can not be recommended.**
- **Efforts should be undertaken to resolve remaining questions….**

➢ **Was the benefit in the CAIRO 3 trial due to cape alone or both cape + bev ?**

➢ **Which patients really need maintenance therapy ?**

➢ **Can we use novel therapies in molecularly selected patients in the interval to improve tumour control & overall survival ?**

➢ **Are there any alternatives to "de-escalation maintenance treatment" ?**

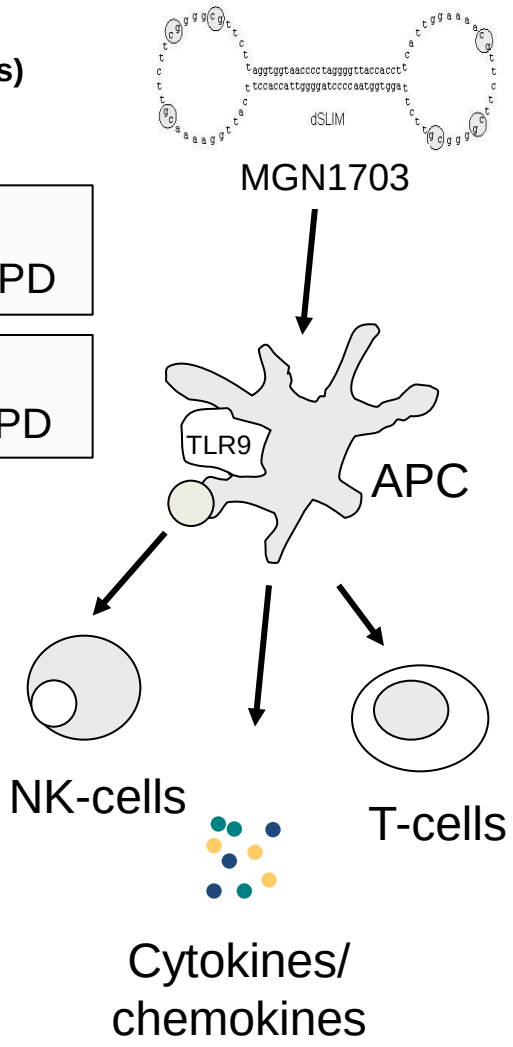
Maintenance treatment with immunomodulator MGN1703* following induction with standard 1st line therapy – The IMPACT TRIAL

Schmoll HJ et al. J. Cancer Res. Clin Oncol 2014 (in press)

mCRC patients with disease control after standard first-line therapy: combination chemotherapy ± bevacizumab

Randomization 2:1

- 60mg MGN1703 x2 / week s.c. until PD
- Placebo x2 / week s.c. until PD



Primary endpoint:
- PFS from randomization

Secondary endpoints:
- PFS from induction therapy
- Overall survival
- Safety (CTCAE v4.0)
- Pharmacodynamics
- Biomarker (incl. immunologic response)
- QoL (QLQ-C30 and -CR29)

* A DNA molecule with broad activation of the innate & adaptive immune system

Maintenance treatment with immunomodulator MGN1703* following induction with standard 1st line therapy – The IMPACT TRIAL

Primary and secondary endpoints

Progression free survival (PFS)

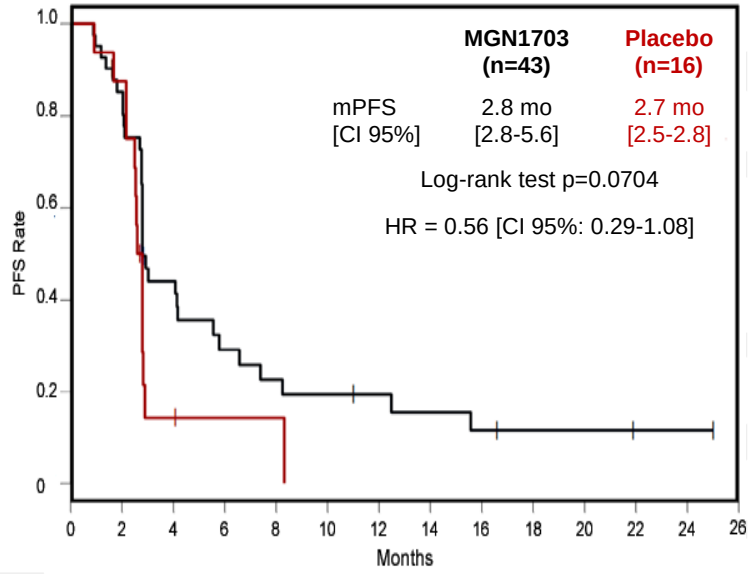


Figure 2: Primary endpoint - PFS on maintenance from start of MGN1703 or placebo. Abbreviations: HR, hazard ratio; CI, confidence interval.

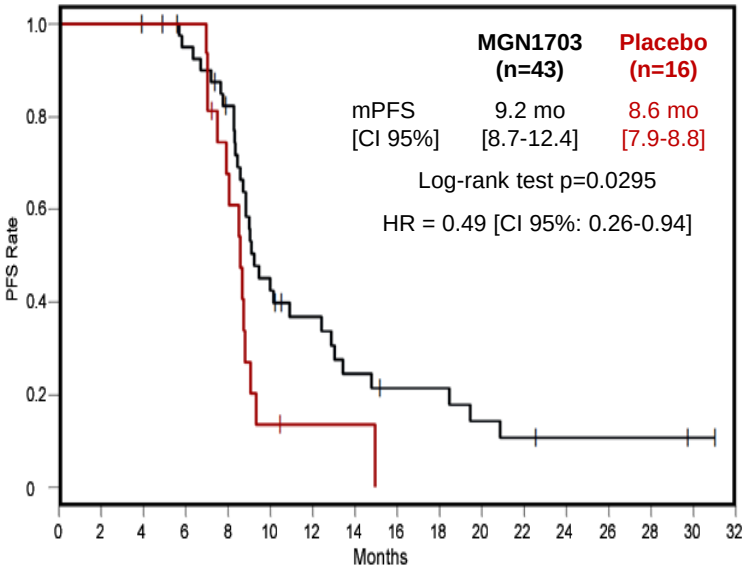


Figure 3: Secondary endpoint - PFS from start of induction chemotherapy. Abbreviations: HR, hazard ratio; CI, confidence interval.

Schmoll HJ et al. J. Cancer Res. Clin Oncol 2014 (in press)

Maintenance therapy - appropriate endpoints:

- **Interval PFS is the clearest surrogate endpoint for drug activity.**
- **Overall survival is the key end point to change clinical practice.**