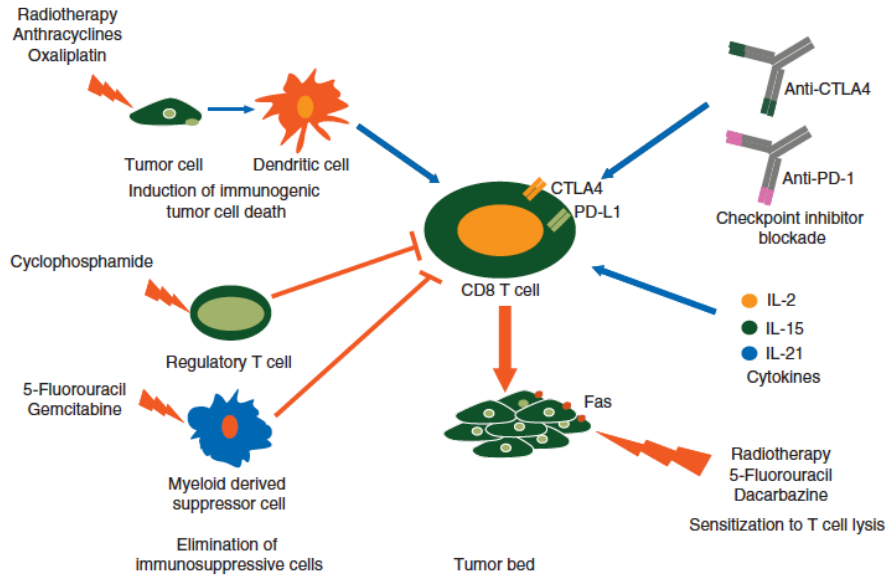
Avelumab, cetuximab and FOLFOX in 1st line MCRC Results of the phase II AVETUX-CRC trial (AIO-KRK-0216)

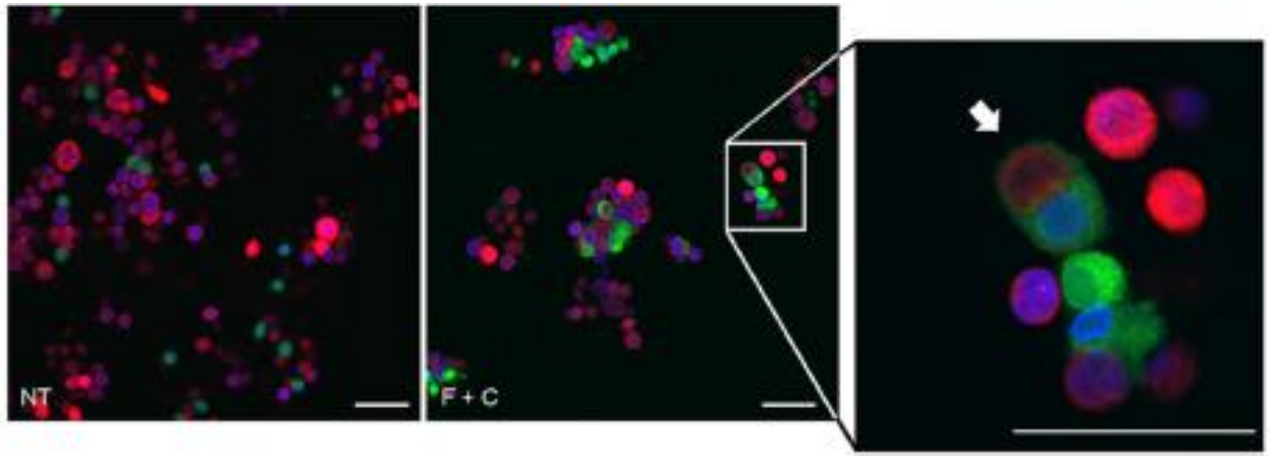
Tintelnot J, Stein A, Simnica D, Goekkurt E, Lorenzen S, Riera-Knorrenschild J, Depenbusch R, Ettrich T, Doerfel S, Al-Batran SE, Karthaus M, Pelzer U, Waberer L, Hinke A, Bokemeyer C, Hegewisch-Becker S, Binder M

Conflicts of interest and disclosure

I have NO financial disclosure or conflicts of interest with the presented material in this presentation

Background





untreated

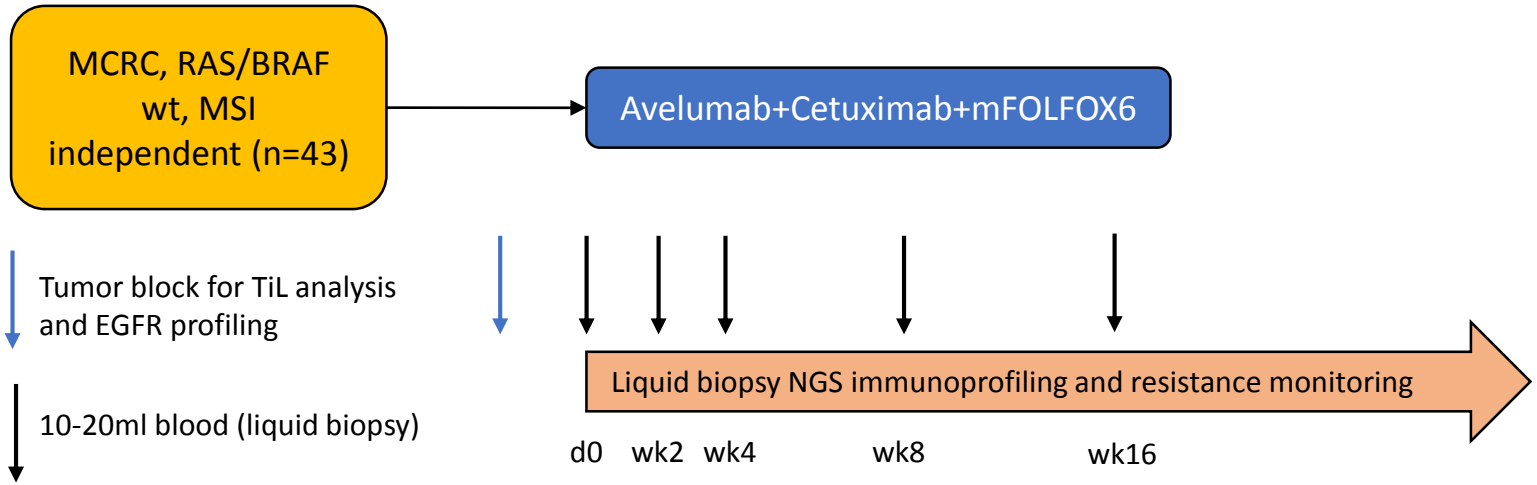
5FU based chemo + cetuximab

→ Combining anti-PD-L1 with chemotherapy may improve anti-tumor effects of immunotherapy

→ Cetuximab and chemotherapy triggers immunogenic cell death

Apetoh et al., Ann Onc 2015, Pozzi et al., Nature medicine 2016

Design

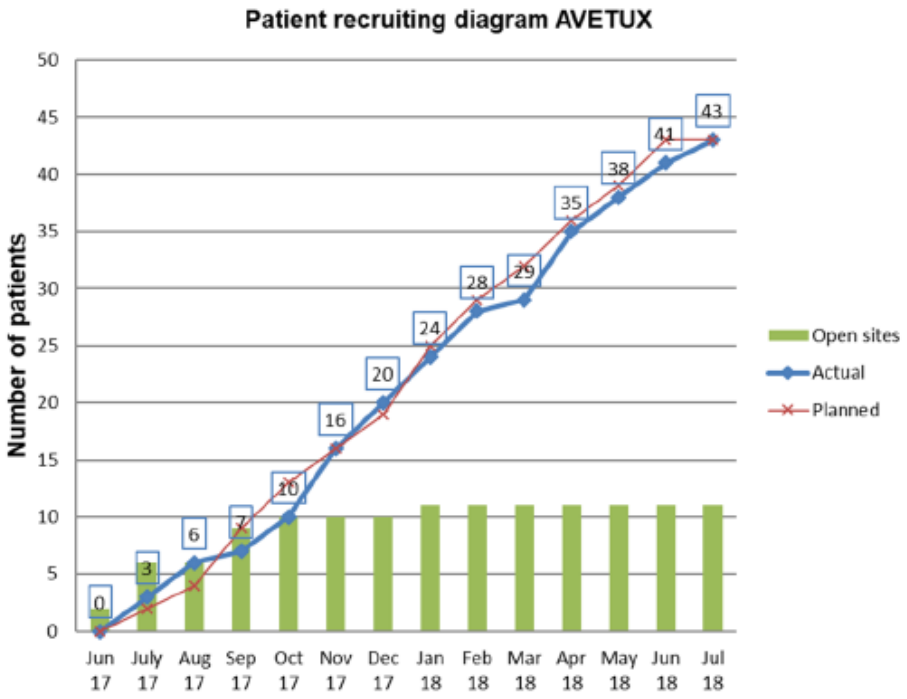


1° endpoint PFS rate after 12 months (PFSR@12)

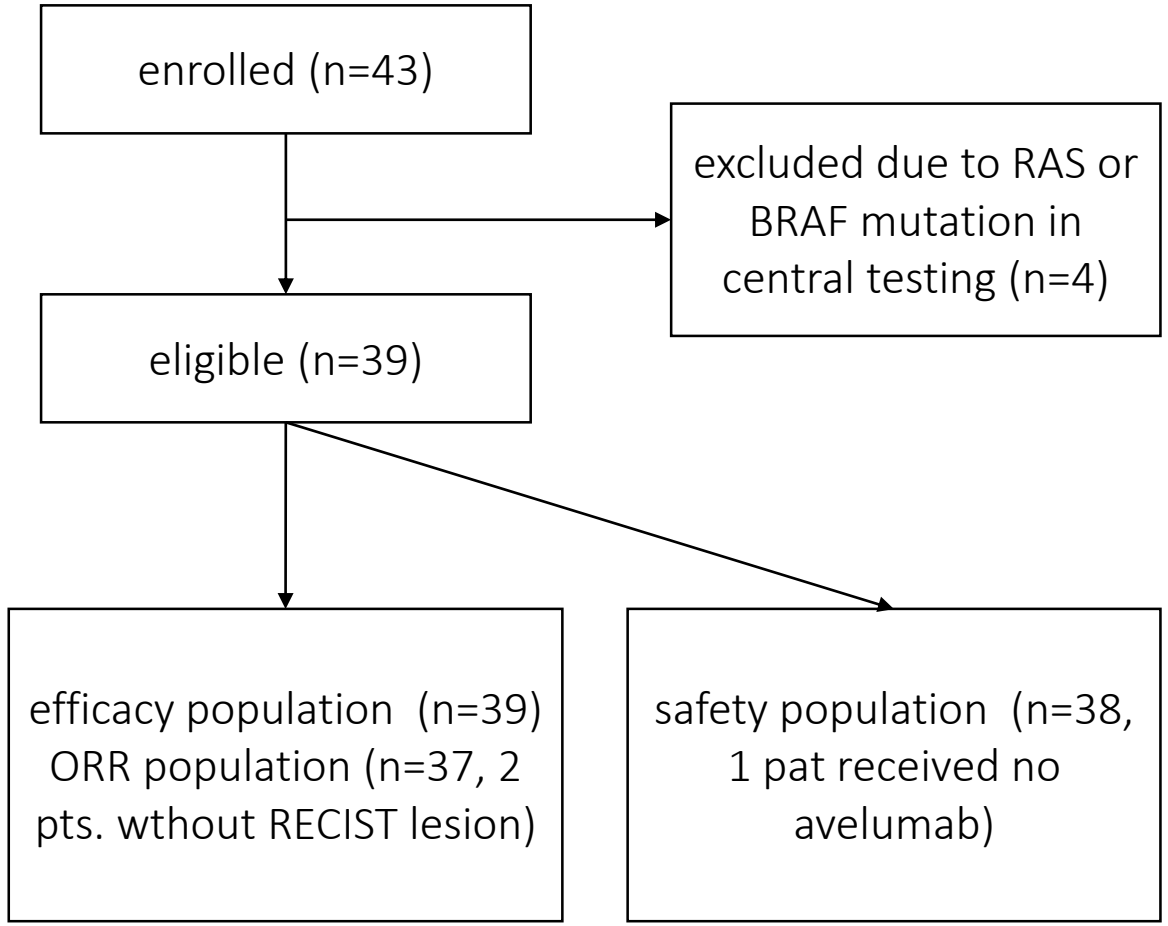
Statistical consideration PFSR@12 40% → 57%

alpha 10%, power 80%, one sided test with 5% drop out 43 patients

Study status/patient population



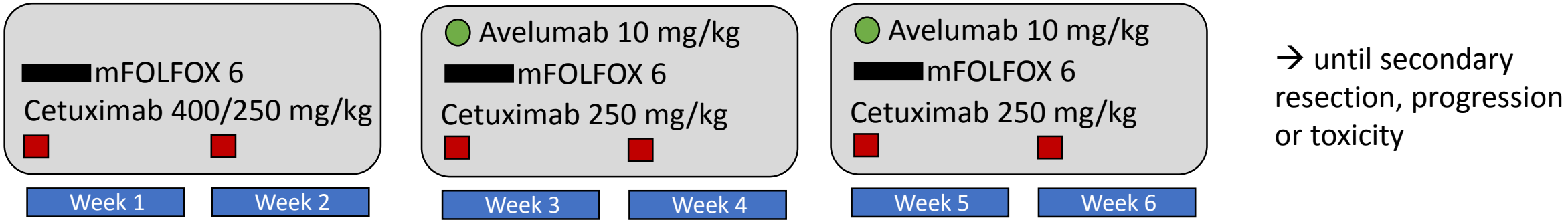
10 sites in Germany (university and community hospitals and private practices)



Results - patients characteristics (n=39)

characteristic		number (%)
median age (range)		62 (29-82)
gender	female	13 (33%)
	male	26 (67%)
primary tumor location	**left**	**36 (92%)**
	right	3 (8%)
prior adjuvant chemotherapy	single agent	3 (8%)
	oxaliplatin-based	**9 (23%)**
synchronous metastases		28 (72%)
location of metastases	liver	30 (77%)
	lung	12 (31%)
	lymph nodes	18 (46%)
microsatellite status (local, partly central)	**MSI-H/MSI-L**	**2/1 (5%/3%)**
	MSS	36 (92%)
RAS/BRAF status (central tissue)	mutated (low frequent 15-30%)	4/43

Treatment



→ until secondary resection, progression or toxicity

Median number of treatment cycles (range)

oxaliplatin	8 (1-34)
5FU	13 (1-35)
cetuximab	12 (1-35)
avelumab	16 (0-34)

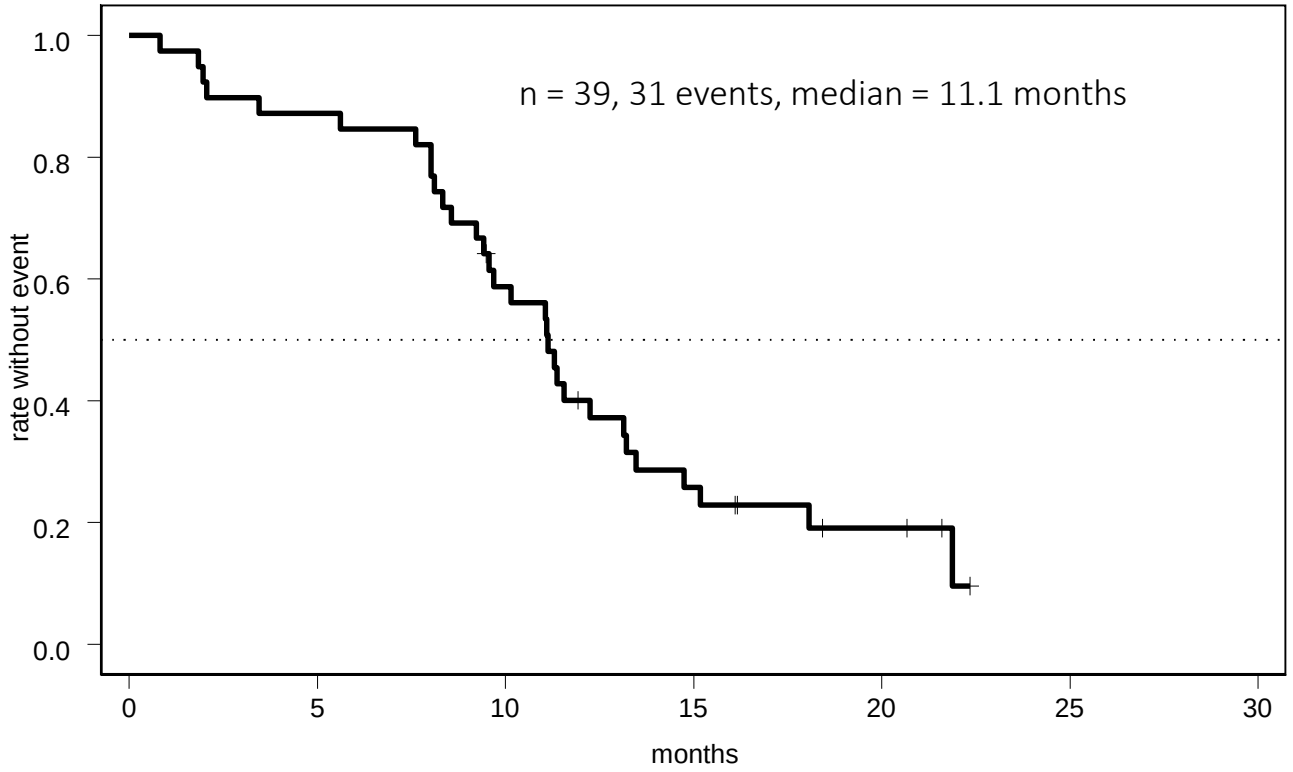
Duration of cetuximab and avelumab treatment **median 5.4 months** (range 0.7-18.4)

Results – safety (n=43)

Grade 3/4 event (>5%)	Incidence n (% per patient)
Anemia, blood disorders, HUS	7 (18%)
Abdominal pain, Diarrhea, others	9 (24%)
Vomiting, Nausea	5 (13%)
Fever, Fatique	4 (10%)
Administration, Infusion related, Allergic	6 (16%)
Infection of Catheter, Device, Urinary tract, others	12 (32%)
Elevated creatinine, liver enzymes	5 (13%)
Cognitive disturbance, Meningism, Syncope, Psychiatric disorders	6 (16%)
Peripheral sensory polyneuropathy, Paresthesia	6 (16%)
Skin reaction	8 (21%)
Hematoma, Thromboembolic events	5 (13%)
Hypertension	3 (8%)

- 52 SAEs in 23 out of 38 patients (61%)
- 1.37 SAEs per patient

Results – progression free survival



PFS Rate at 12 months 40%, thus primary endpoint not met

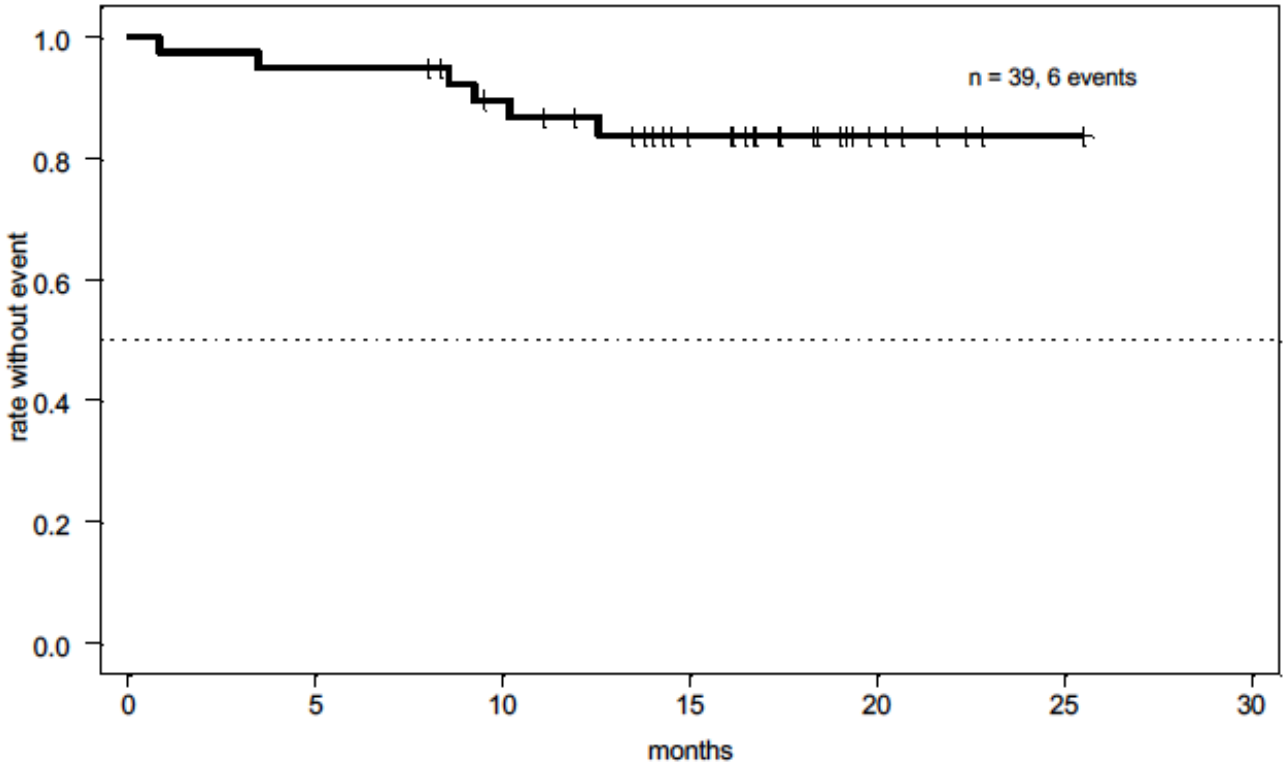
Results – overall response rate

Response	Response rate (n)	Response rate (%)
Complete response	4/37	11%
Partial response	26/37	70%
Stable diseae	4/37	11%
Progressive disease	3/37	8%

→**ORR 81%** and **DCR 92%**

→Secondary resection rate 15%

Results – preliminary overall survival



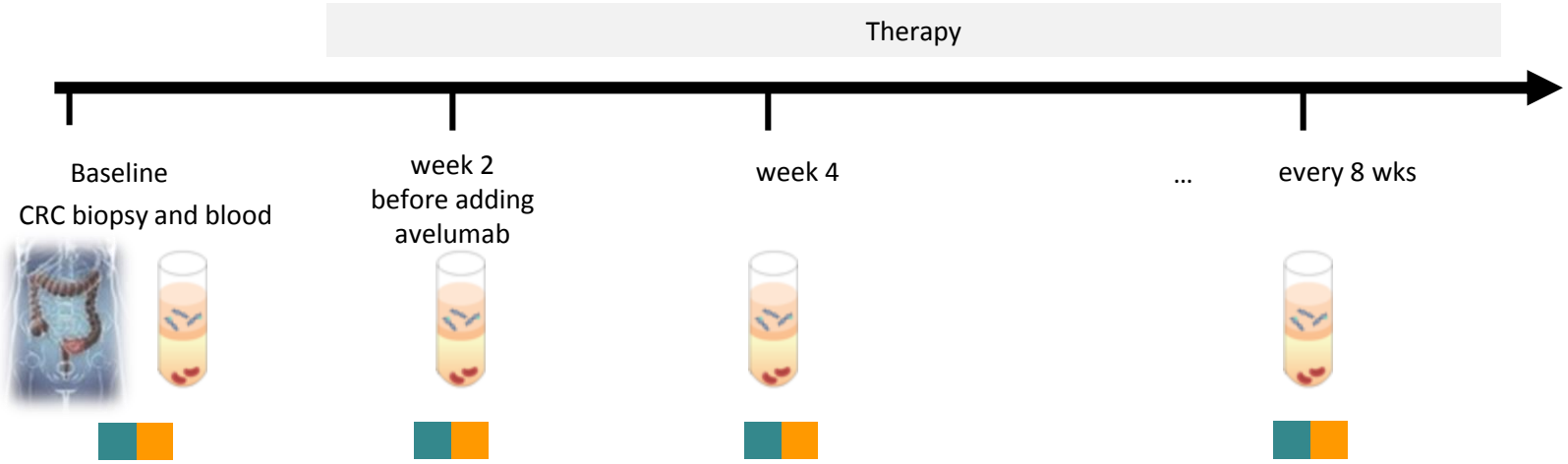
With a median duration of follow-up of 16.2 months
OS plateaus at 84%

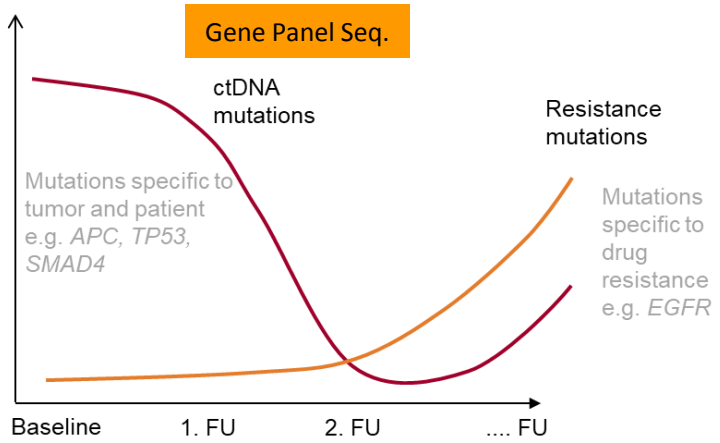
Discussion - results in perspective

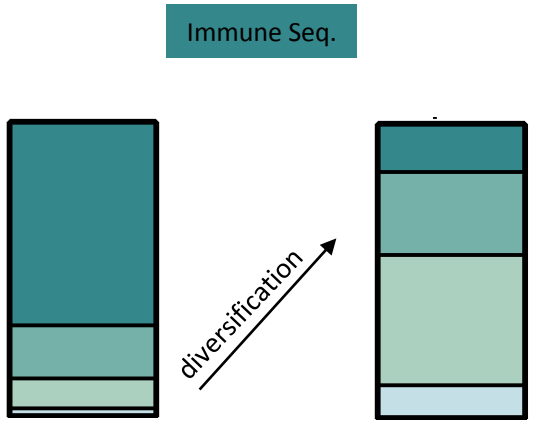
	No of patients	RAS/BRAF	PTL	ORR (%)	ETS >=20% (%)	mPFS (months)
randomized trials						
OPUS	72	KRAS/BRAFwt	uk	60	69.2	8.3
TAILOR	146	RASwt	left sided	66.4	uk	9.2
CALGB 80405	198	RASwt	left sided	(68.6)*		11.3
single arm trials						
APEC	110	RASwt	uk	62.7	80.6	13.3
AVETUX	**39**	**RAS/BRAFwt**	**Left sided**	**81%**	**76%**	**11.1**

Bokemeyer et al., Ann Onc 2011, Venook et al., JAMA 2017,
Qin et al J Clin Oncol 2018, Cheng et al Clin Colorectal Cancer 2017

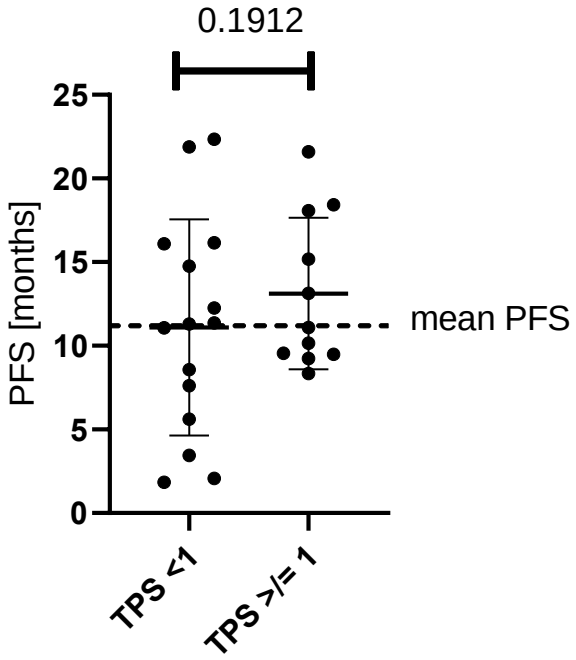
Translational research



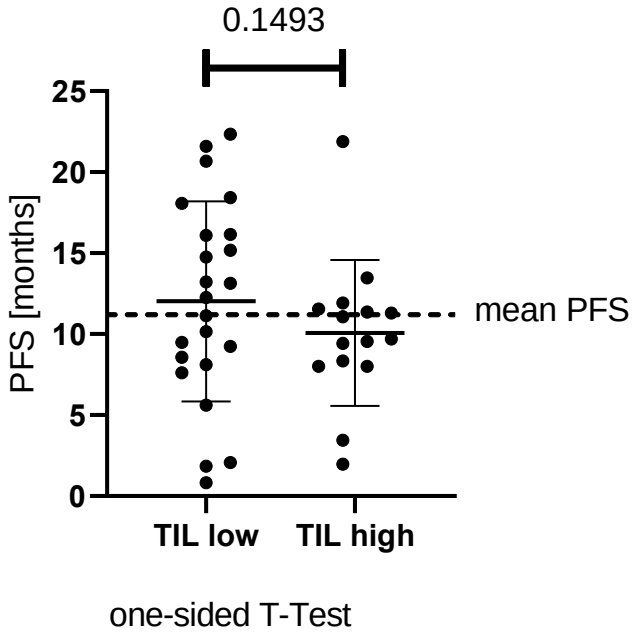




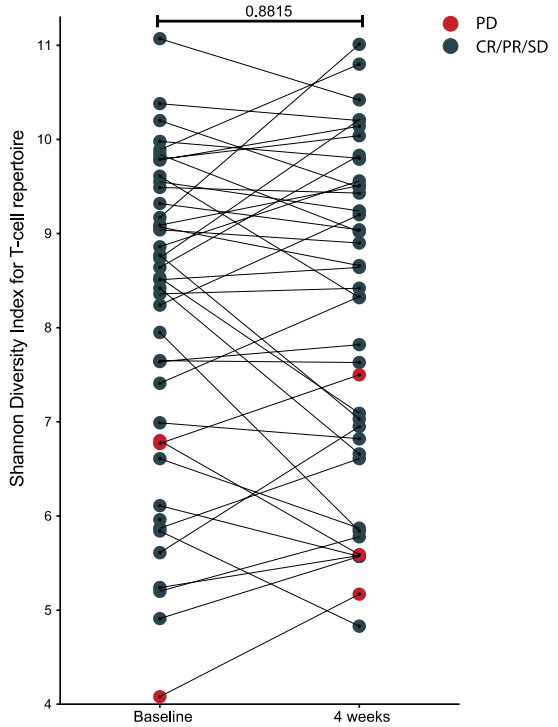
TR – Predictive value of T cell repertoire TiL and TPS (PD-L1)



one-sided T-Test



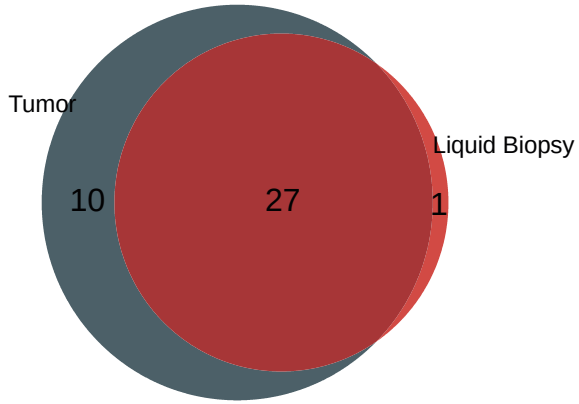
one-sided T-Test

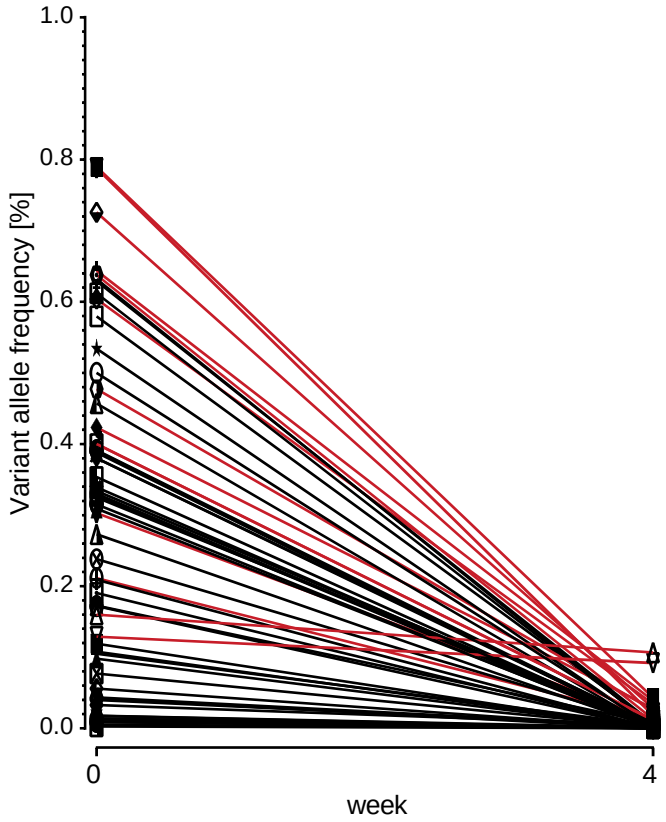


→ No clear correlation between T cell diversification, TiLs or TPS and PFS likely due to interaction with chemo and EGFRi

TR - NGS data

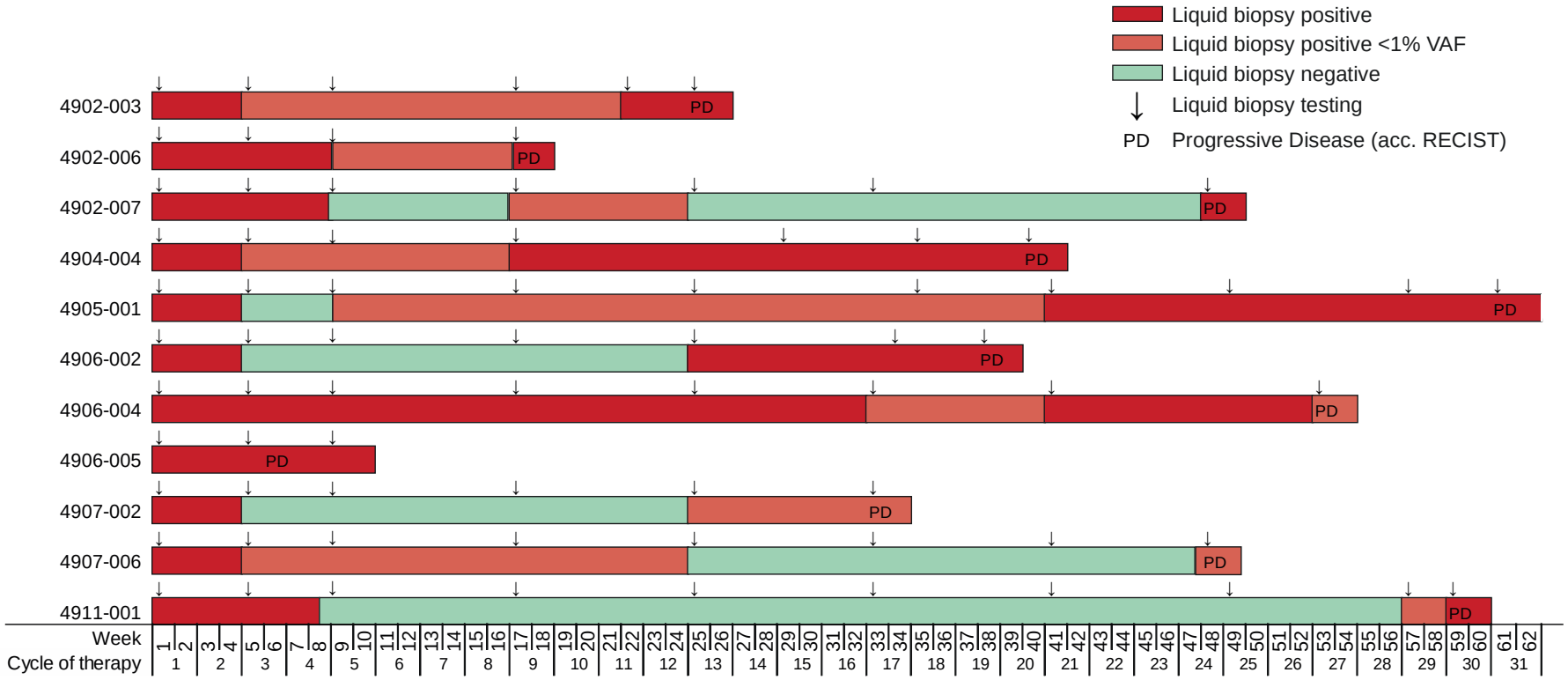
Gene	Target Region
AKT1	codons 10-30
APC	codons 789 - 1589
B2M	entire coding region
BRAF	codons 582-605
CTNNB1	codons 30-46
EGFR	exon 12,13,18,19,20,21
ERBB3	codons 85-105
FCGR3A	codon 158
FCGR2A	codon 131
HRAS	codons 10-15
JAK1	entire coding region
JAK2	entire coding region
KRAS	codons 10-15, 51-63, 98-150
NRAS	codons 10-15, 51-63
PIK3CA	codons 64-94, 316-346, 418-434, 527-560, 1002-1054
PD-L1	entire coding region
PTEN	codons 71-124,130,173,267,268,320
SMAD4	entire coding region
TP53	entire coding region





→ 26 patients with tumor mutations detectable in liquid biopsy with immediate drop during treatment

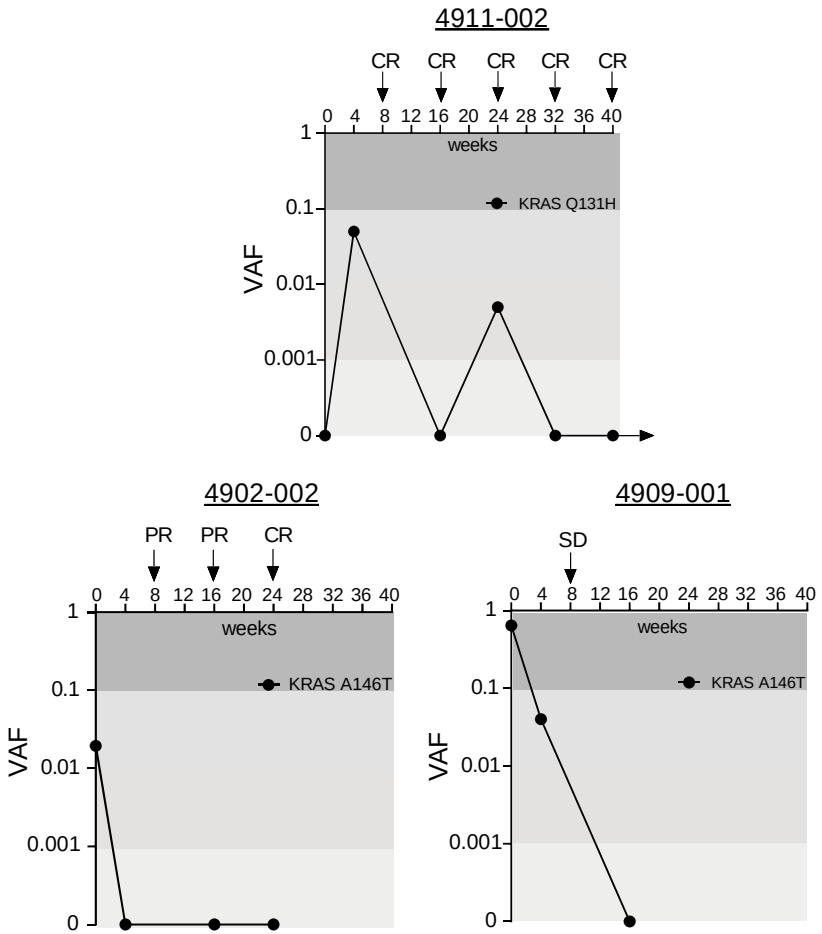
TR - NGS data


Liquid biopsy positive
Liquid biopsy positive <1% VAF
Liquid biopsy negative
Liquid biopsy testing
PD Progressive Disease (acc. RECIST)
4902-003
4902-006
4902-007
4904-004
4905-001
4906-002
4906-004
4906-005
4907-002
4907-006
4911-001
PD
Week
Cycle of therapy

TR – Monitoring for EGFR resistant clones

- Only 1 patient developed a resistant clone (KRAS mutation)
- **No EGFR mutation was detected during follow-up (or at baseline)**

- In 2 RAS mutant patients the RAS mutation was immediately and consistenly supressed beside potential stimulation of the RAS mut clone by cetuximab



Conclusion

- **Tolerable regimen** with no unexpected or additive toxicities
- **Highly active regimen** in terms of **response** induction, but only moderate effect on PFS (ideal endpoint?) and promising, yet **preliminary OS**
- Translational data indicate
  - **Classical predictive factors** for PD-1/L1 inhibtor treatment (e.g. TiL , T cell receptor diversification, TPS) may have only **limited role** in combination regimen
  - **NGS data feasible** with immediate decline of ctDNA during treatment and increase prior to radiological progression
  - The **AVETUX regimen suppressed** the development of **EGFR resistant clones**

Acknowledgement

We would like to thank

- The patients and their families
- The study sites
- The study teams (namely) at Merck (Michael Baum), AIO (Tobias Meyer) and IKF (Lisa Waberer)