Malignom unter immunsuppressiver Therapie – Strategien bei aktiver CED?

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Krebsrisiko bei Chronisch Entzündlichen Darmerkrankungen:

1) Entzündung begünstigt Krebsentstehung

2) Immunsuppression reduziert Entzündung

3) Immunsuppression kann Krebsenstehung begünstigen (Immunsurveillance ?)

Risk of Cancer in Patients With Inflammatory Bowel Diseases: A Nationwide Population-based Cohort Study With 30 Years of Follow-up Evaluation

13756 Pat. mit CD

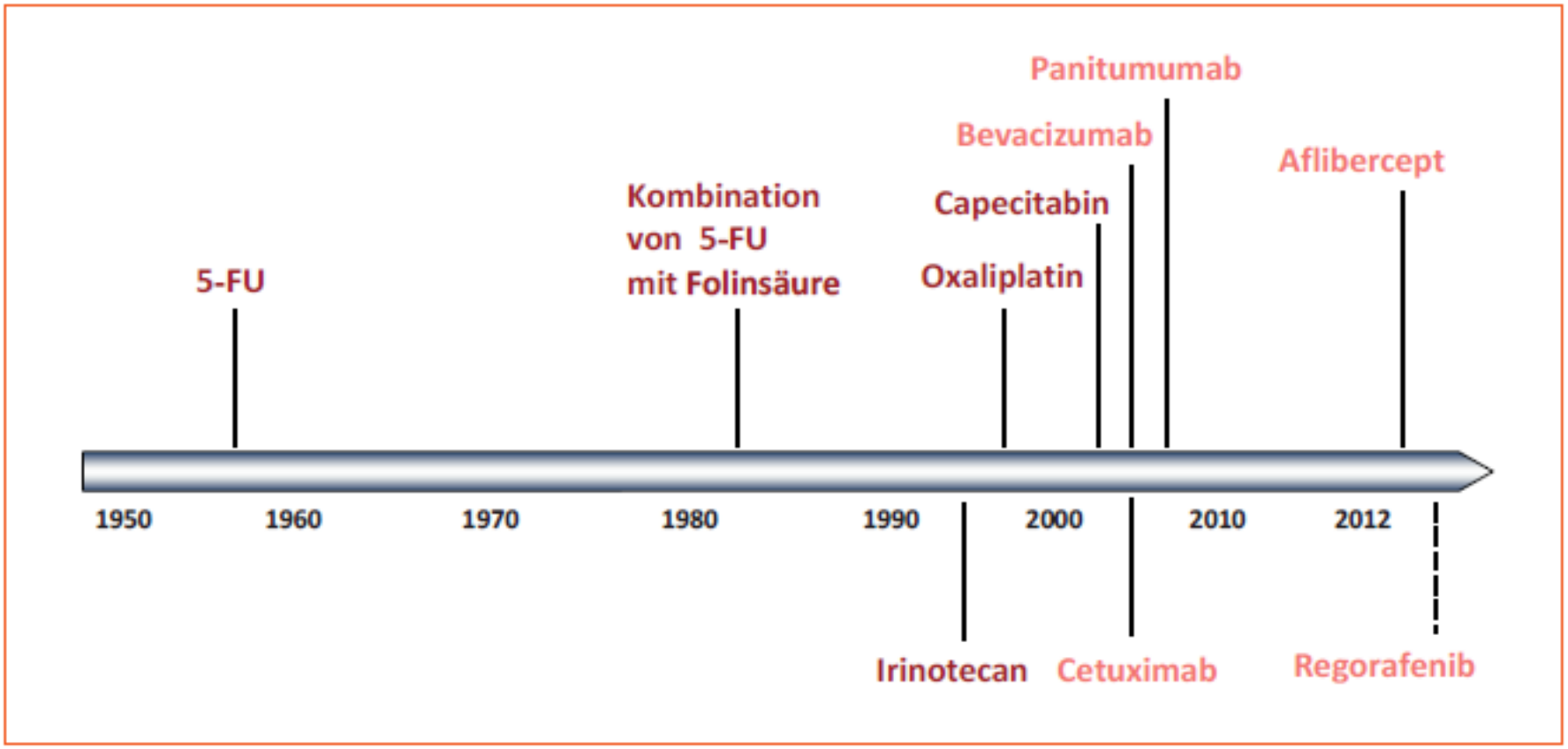
208 Tumoren im 1 Jahr	SIR 3.6
772 Tumoren im 2 J. od später	SIR 1.3

35152 Pat. mit CU

376 Tumoren im 1 Jahr	SIR 1.8
2331 Tumoren im 2 J. od später	SIR 1.1

Kappelman et al., 2014, Clin Gastroenterol & Hepatol. 12:265

THERAPIE KOLOREKTALER KARZINOME



Patienten mit CED und Kolorektalem Karzinom sollten die Standardtherapie erhalten

(cave schwere Mukositis)

Clinical Features, Treatment, and Survival of Patients With Colorectal Cancer With or Without Inflammatory Bowel Disease

Table 1. Demographic Features of the IBD CRC and Non-IBD CRC Patients Diagnosed During 1994 to 2005 in Ireland

	IBD CRC, n (%)	Non-IBD CRC, n (%)	95% CI for the difference (Bonferroni adjusted)
Overall	170 (100)	22,155 (100)	
Sex			
Male	104 (61.2)	12,554 (56.7)	−0.03 to 0.12
Female	66 (38.8)	9601 (43.3)	−0.12 to 0.03
Mean age at CRC diagnosis, *y*	61.4 (13.9)	69.1 (12.0)	5.62–9.8
Smoking status			
Current	19 (11.2)	4002 (18.1)	−0.13 to −0.005
Ex-smoker	33 (19.4)	3678 (16.6)	−0.05 to 0.10
Never smoked	92 (54.1)	9415 (42.5)	0.02–0.21
Unknown	26 (15.3)	5060 (22.8)	−0.15 to −0.003

Ali et al., 2011, Clin Gastroenterol & Hepatol. 9:584

Clinical Features, Treatment, and Survival of Patients With Colorectal Cancer With or Without Inflammatory Bowel Disease

Table 2. The Extent of IBD and CRC Tumor Location for 139 Ulcerative Colitis CRC and 31 Crohn's Disease CRC Cases

	Extent of IBD	n	Tumor location
UC CRC	Rectum	49	37 rectum, 2 rectosigmoid, 5 sigmoid, 4 descending, 1 hepatic flexure
	Rectosigmoid	15	10 rectosigmoid, 1 descending, 4 transverse
	Descending	16	12 descending, 2 sigmoid, 2 splenic flexure
	Pancolon	1	1 ascending
	Other and unspecified UC	58	6 rectum, 7 descending, 2 splenic flexure, 16 transverse, 12 ascending, 3 cecum, 11 unspecified, 1 appendix
CD CRC	Large intestine	17	3 rectosigmoid, 4 descending, 9 ascending, 1 transverse
	Small intestine	6	2 transverse, 1 hepatic flexure, 3 unspecified
	Unspecified CD	8	4 transverse, 4 unspecified

Ali et al., 2011, Clin Gastroenterol & Hepatol. 9:584

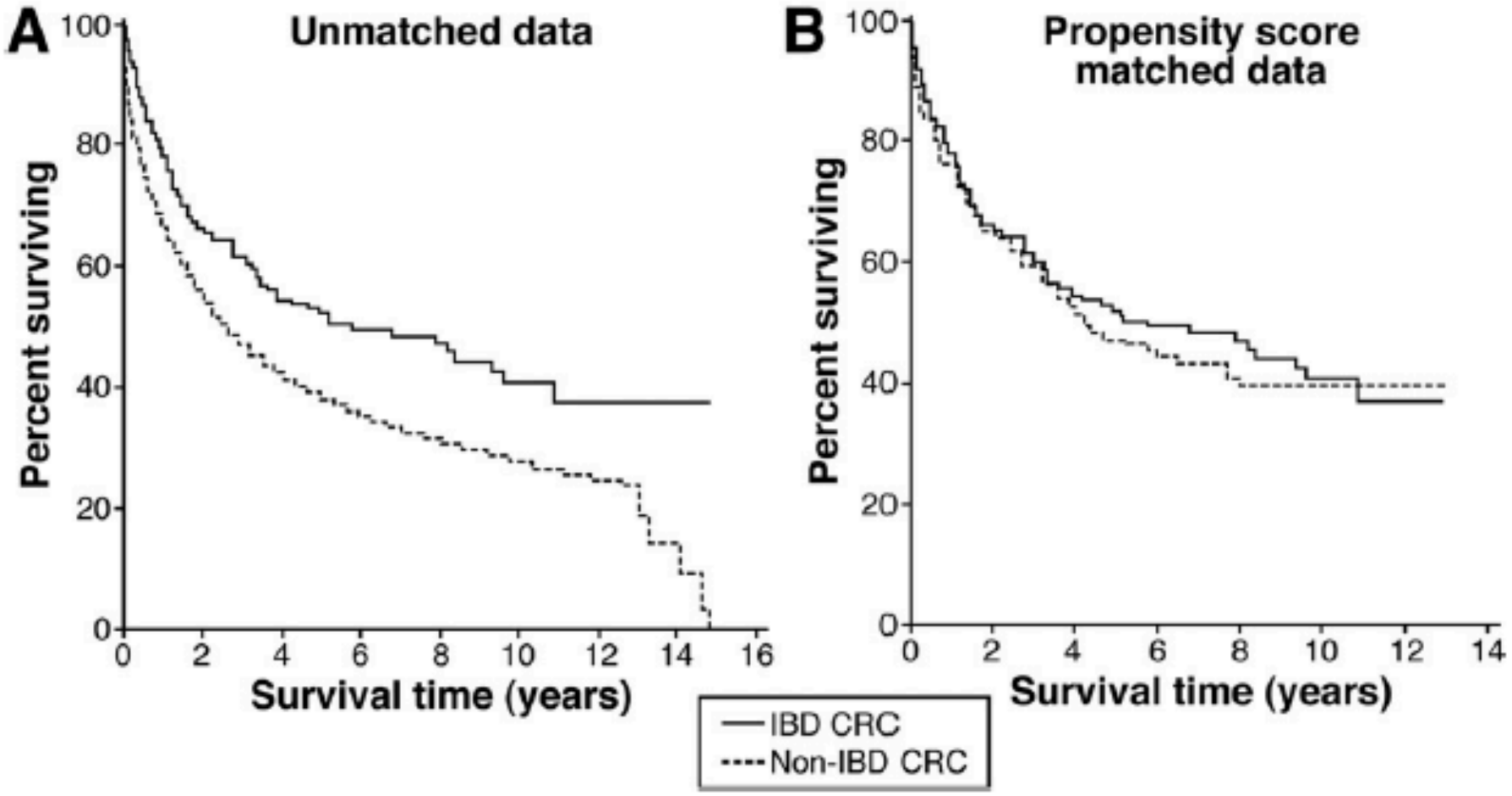
Clinical Features, Treatment, and Survival of Patients With Colorectal Cancer With or Without Inflammatory Bowel Disease

Table 4. Comparison of the Treatments Received Between IBD CRC and Non-IBD CRC Patients

Treatments ever received	IBD CRC, n (%)	Non-IBD CRC, n (%)
Surgery only	91 (53.5)	11,254 (50.8)
Surgery and chemotherapy	42 (24.7)	4696 (21.2)
Chemotherapy only	9 (5.4)	686 (3.1)
Surgery and radiotherapy	7 (4.1)	642 (2.9)
Radiotherapy only	5 (2.9)	465 (2.1)
Surgery, chemotherapy, and radiotherapy	1 (0.6)	1728 (7.8)
Chemotherapy and radiotherapy	0 (0)	376 (1.7)
No treatment	15 (8.8)	2308 (10.4)
Total	170 (100)	22,155 (100)

Ali et al., 2011, Clin Gastroenterol & Hepatol. 9:584

Clinical Features, Treatment, and Survival of Patients With Colorectal Cancer With or Without Inflammatory Bowel Disease



Ali et al., 2011, Clin Gastroenterol & Hepatol. 9:584

Pat. mit langjähriger CED u. behandelter Tumorerkrankung: Wideraufnahme der Immunsuppression?

Pat. mit Tumorerkrankung welche „late-onset CDE entwickeln: Immunsuppressiv behandeln?

Wiederaufnahme der Immunsuppression nach Chemotherapie?

Use of Immunosuppressants and Biologicals in Patients with Previous Cancer

Laurent Beaugerie

Empfehlung Beaugerie (Dig Dis. 2013, 31:254-259):

Abstand von 2 Jahren (5-ASA, Corticosteroide, Chirurgie ja)
Falls die Tumorerkrankung ein hohes Rezidivrisiko hat, Abstand von 5 Jahren

Use of Immunosuppressants and Biologicals in Patients with Previous Cancer

Beaugerie, Dig Dis 2013; 31: 254

Table 2. Risk of recurrence of preexisting cancers under posttransplant immunosuppressive therapy

Risk level	Organ
Low	Kidney (asymptomatic) Lymphoma Testicle Uterine cervix Thyroid
Intermediate	Breast Uterine body Colon Prostate
High	Bladder Kidney (symptomatic) Sarcoma Melanoma NMSC Myeloma

Wiederaufnahme der Immunsuppression nach Chemotherapie?

Empfehlung Beaugerie (Dig Dis. 2013, 31:254-259):

Abstand von 2 Jahren (5-ASA, Corticosteroide, Chirurgie erlaubt)
Falls die Tumorerkrankung ein hohes Rezidivrisiko hat, Abstand von 5 Jahren

falls die Krankheitsaktivität hoch ist, Immunsuppression ja
(Beginn mit MTX)

In jüngeren Patienten Anti-TNF besser als Azathioprin (bes. falls EBV-assoziierte PTLD)

Ähnliche Empfehlungen auch in Mantzaris,2014 Dig Dis. 32: 122-127

Association Between Tumor Necrosis Factor-α Antagonists and Risk of Cancer in Patients With Inflammatory Bowel Disease

Nynne Nyboe Andersen, MD; Björn Pasternak, MD, PhD; Saima Basit, MSc; Mikael Andersson, MSc; Henrik Svanström, MSc; Sarah Caspersen, MD; Pia Munkholm, MD, DMSc; Anders Hviid, MSc, DMSc; Tine Jess, MD, DMSc

56.146 patienten 15 J alt oder älter mit CED im Dänischen Nationalregister
4.553 (8.1%) wurden mit TNF-α Antagonisten behandelt

TNF-α Antagonist Exposure	Person-years	Cases, No.	Adjusted Rate Ratio (95% CI)
Accumulated doses, No.			
1-3	6694	31	1.02 (0.71-1.47)
4-7	4664	18	0.89 (0.55-1.42)
≥8	7083	32	1.29 (0.90-1.85)
Time since first exposure, y			
<1	3115	16	1.10 (0.67-1.81)
1-<2	3591	19	1.22 (0.77-1.93)
2-<5	7190	23	0.82 (0.54-1.24)
≥5	4545	23	1.33 (0.88-2.03)

Andersen et al., 2014, JAMA 311; 2406

New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000

Curtis et al., NIH Publ 05-5302, 2006

Table 1.A: Risk of subsequent primary cancer after any initial cancer, by age at initial diagnosis, SEER 1973-2000.

Age at initial diagnosis	Total		
	O	O/E	EAR
All ages	**185,407**	**1.14***	**21**
00–17	351	6.13*	15
18–29	1,401	2.92*	22
30–39	4,909	2.37*	39
40–49	13,537	1.61*	39
50–59	34,159	1.27*	32
60–69	62,286	1.13*	23
70–79	52,321	1.02*	4
80–115	16,443	0.92*	-19

2,036,597 patients die mindestens 2 Monate nach Diagnose beobachtet wurden 1973 to 2000

The relative risk of second primary cancers in Queensland, Australia: a retrospective cohort study

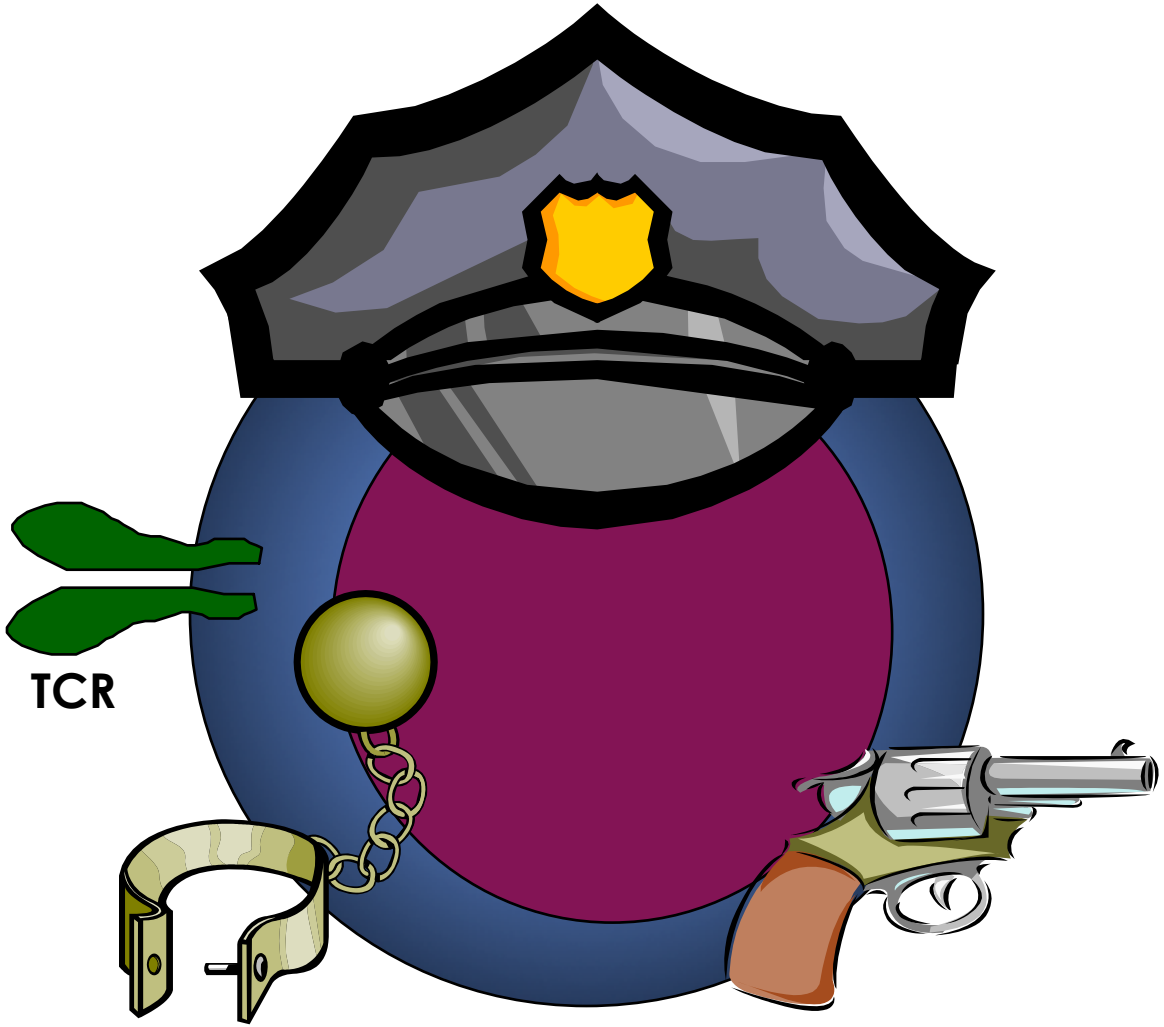
Danny R Youlden[1*†], Peter D Baade[1,2†]

A total of 23,580 second invasive primary cancers were observed over 1,370,247 years of follow-up among 204,962 cancer patients.

	MALES (SIR)	FEMALES (SIR)
All Cancers	**1.22**	**1.36**
Head & Neck	**1.7**	**1.84**
Oesophagus	**1.43**	**1.06**
Stomach	**0.83**	**1.0**
Lung	**1.18**	**1.41**
Melanoma	**1.77**	**1.70**
Breast		**1.31**
Prostate	**0.83**	
Kidney	**1.39**	**1.69**
Bladder	**1.40**	**1.61**
Lymphoma	**1.37**	**1.36**
Myeloid Leukemia	**1.44**	**1.25**

Youlden and Baade *BMC Cancer* 2011, **11**:83

Immunosurveillance ?




HELP SUPPORT YOUR BODY'S DEFENCES
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ORIGINAL
0·1%
HELP SUPPORT YOUR BODY'S DEFENCES
SCIENTIFICALLY PROVEN
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gibt es eine tumorspezifische Immunüberwachung ?

- Nacktmäuse (ohne funktionierende T-Zellen) sterben an Infektionen, haben aber nicht eine erhöhte Tumorinzidenz
- die meisten Tumoren, die bei Patienten mit Immundefekten auftreten, haben eine virale Genese
- bei Patienten mit schwerer HIV-Infektion ist die Inzidenz der häufigsten Tumoren (Darm-, Lungen-, Brustkrebs) nicht oder nur minimal erhöht (Ausnahme: Lymphome und Virus-assoziierte Tumoren!)

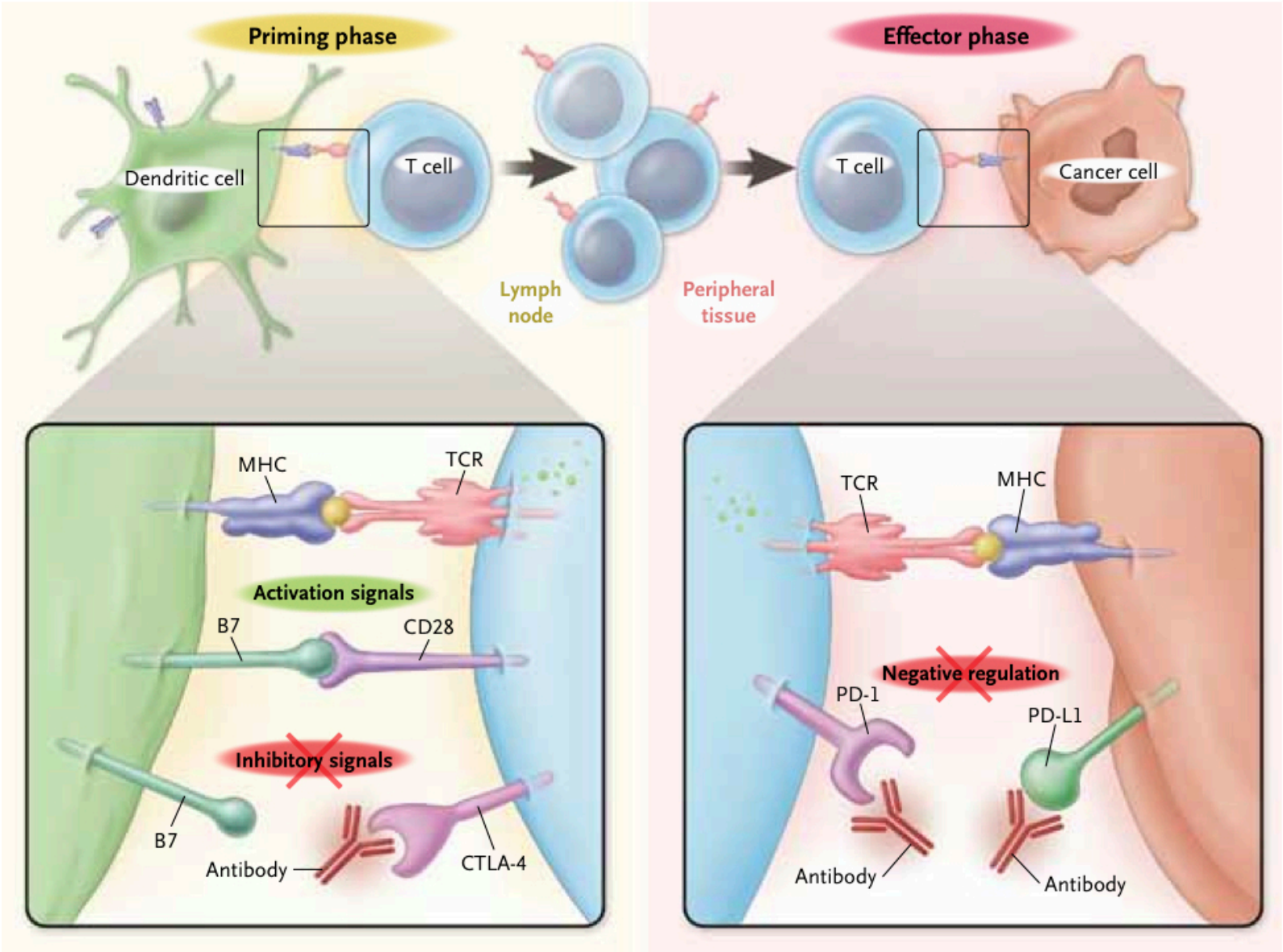
Relatives Krebsrisiko in HIV infizierten Pazienten

	Rel Risiko	Virus assoziiert
Kaposi sarcoma	> 10.000	HHV8 (100%)
Mal. Lymphoma	> 200	EBV (38-66%)
CNS Lymphoma	1000-3900	EBV (100%)
Cervical Carcinoma	2.9 -4	HPV (100%)
Hodgkin Lymphoma	7.6	EBV
Leiomyosarcoma	10000	EBV
Squamous carcinoma (skin)	13	HPV
Seminoma	2.9	?
Myeloma	4.5	? (HHV8)
Anal cancer	24-84	HPV

Weitere Tumoren: Hepatitis assoziiertes Leber-Ca

Launay et al..: Bull Cancer 2003; 90:387

Blockade of CTLA-4 and PD-1 signaling in tumor immunotherapy



Ribas, NEJM, 2012

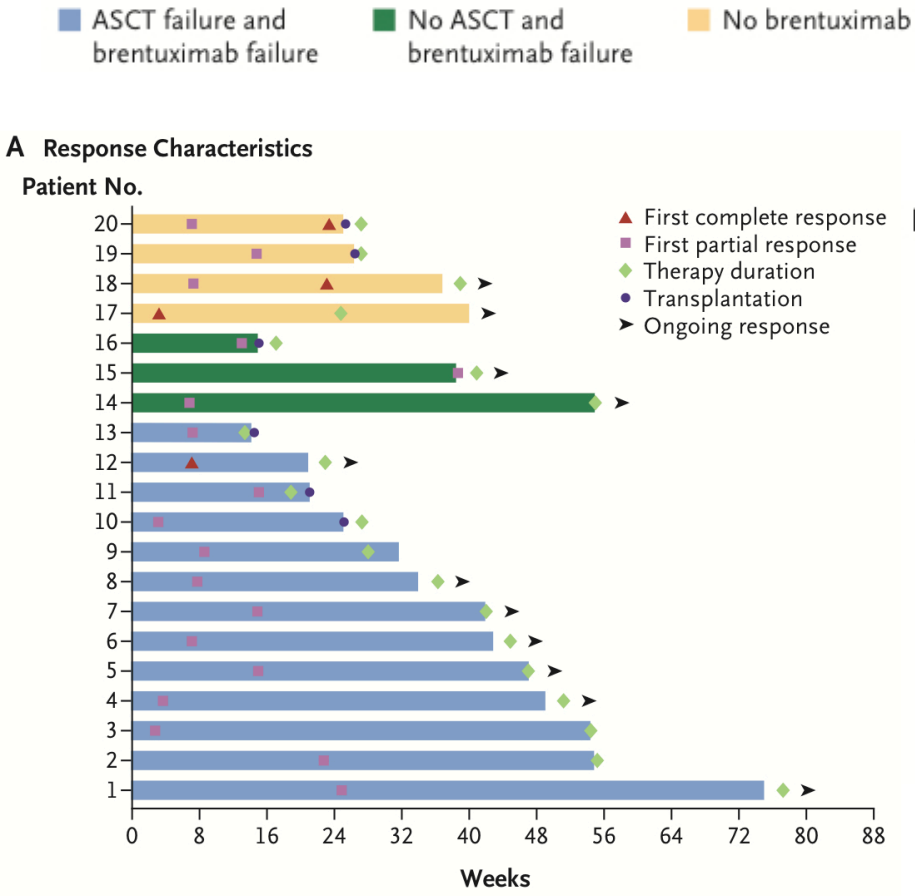
Clinical Activity of anti-PD-1

Tumor Type	Dose (mg/kg)	No. pts	ORR (CR/PR) No. pts (%)	SD ≥24 wk No. pts (%)
MEL	0.1-10	106	33 (31)	6 (6)
NSCLC	1-10	122	20 (16)	11 (9)
RCC	1 or 10	34	10 (29)	9 (27)

- 294 patients started treatment in 2008 and 1 year follow-up.
- No ORs were observed in 19 CRC or 13 CRPC patients
- 28/54 responses lasted ≥1 year in patients with ≥1 year follow-up

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma, Ansell et al., NEJM 2014

78% of pts. previous treatment with brentuximab and/or autologous SCT



12/23 pts. discontinued treatment during follow-up:

- **2 pts. toxicity (MDS, thrombocytopenia and pancreatitis)**
- **4 pts. progressive disease**
- **5 pts. allogeneic SCT, 1 pt. autologous SCT**

ORR 87% (20/23 pts.)

CR 17% (4/23 pts.)
PR 70% (16/23 pts.)

??

Keine übertriebene Angst vor einer Immunsuppression bei Krebspatienten !

(cave Melanom – RCC)

aber.....

das könnte sich ändern bei Patienten die auf neue Immuntherapien (Immun-Checkpoint-Blockade inhibitoren) angesprochen haben !

Danke für die Aufmerksamkeit