

Immuntherapie mit Antikörpern: Nicht nur eine wissenschaftliche Herausforderung

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Partnerstandort Tübingen

Medizinische Klinik II

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21. Januar 2015

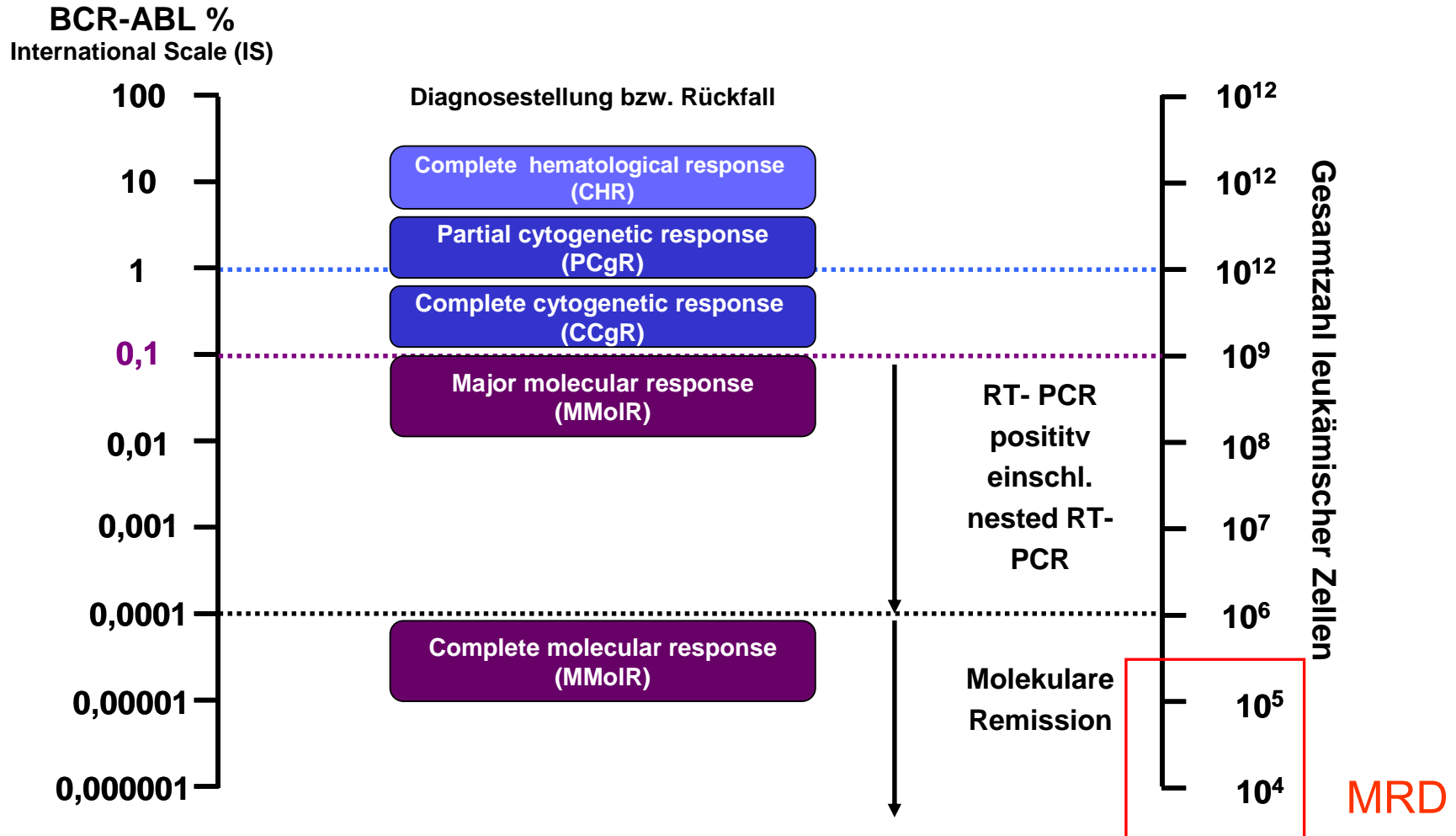
Wirkweise der „konventionellen Systemtherapie“

Konventionelle Systemtherapie:

Rasche und hochpotente Reduktion der Tumormasse, aber

- Wirkung nicht spezifisch auf Tumorzellen mit entsprechenden Nebenwirkungen
- Minimale Resterkrankung (MRD) als Ausgangspunkt für Rezidiv

Beispiel CML: Ansprechparameter und MRD



Konventionelle Systemtherapie versus Antikörpertherapie

Konventionelle Systemtherapie:

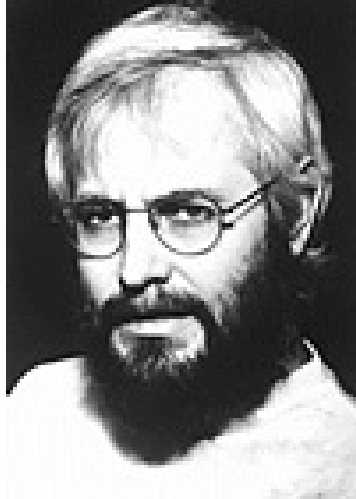
Rasche und hochpotente Reduktion der Tumormasse, aber

- Wirkung nicht spezifisch auf Tumorzellen mit entsprechenden Nebenwirkungen
- Minimale Resterkrankung (MRD) als Ausgangspunkt für Rezidiv

Immuntherapie mit Antikörpern - Ehrlichs Zauberkekeln ?

Eine Jahrhundertarbeit aus den 70igern ermöglicht die Antikörperrevolution

Georges Köhler



1946-1995

Cesar Milstein



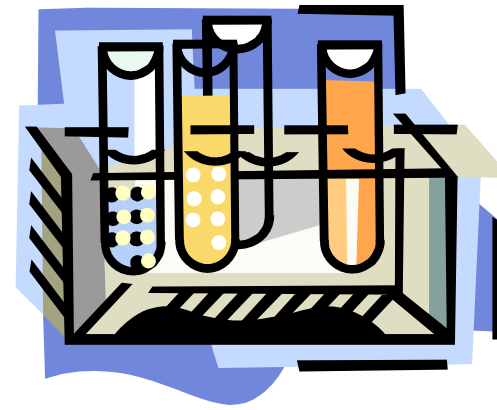
1927-2002

Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 256: 495-497 (1975)

die Zellbiologie

HUMAN					
CD # MW (kDa)	ANTIGEN EXPRESSION (NAME, FUNCTION)	CLONES	CD # MW (kDa)	ANTIGEN EXPRESSION (NAME, FUNCTION)	CLONES
CD1a	Corneal thymocytes, dendritic cell subset, Langerhans cells of skin, T cell subsets (Tc: thymus-associated in T cells)	B17.2.0.1 5.1L6 (D1.9) SPCHYTHYMA (D1)	CD2a	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	B8B (HRC20) H9B (D1) L26 (H)
CD1b	Corneal thymocytes, dendritic cell subset, Langerhans cells of skin, T cell subsets (Tc: thymus-associated in T cells)		CD2b	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	BL13 P178 (D2)
CD1c	Corneal thymocytes, dendritic cell subset, Langerhans cells of skin, T cell subsets (Tc: thymus-associated in T cells)		CD2c	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	5.1L6 (H1) H92B (B3)
CD1d	Corneal thymocytes, dendritic cell subset, Langerhans cells of skin, T cell subsets (Tc: thymus-associated in T cells)		CD2d	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	SP25 HDS (D6)
CD2	Thymus, most NK cells (Tc: TCR-mediated in T cells)	9F10.3 2.5C10.1 SP3 (DPR3) (T1)	CD2e	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	ALB9
CD2b	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2f	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	BI.0.9 33B.1 1H744H (L-Str)
CD2c	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2g	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	BA5 44C-1C7 (Tst)
CD2d	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2h	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	144C2D7
CD2e	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2i	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	CD2D.2 439.9
CD2f	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2j	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	K26 Luv.2 5.1L6 (HRC20)
CD2g	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2k	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	WDS4 K1
CD2h	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2l	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	2E1
CD2i	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2m	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	DH6.0.261 86.0 (H)
CD2j	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2n	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	5B1 (CD20) 10B.132 L475 (D4)
CD2k	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2o	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	J2D2
CD2l	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2p	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	FA8.102
CD2m	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2q	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	BL14
CD2n	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2r	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	T16
CD2o	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2s	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	L475B-4.3
CD2p	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2t	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	AC2
CD2q	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2u	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	MA8B9
CD2r	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2v	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	521
CD2s	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2w	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	822
CD2t	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2x	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	522
CD2u	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2y	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	523
CD2v	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2z	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	524
CD2w	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2aa	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	525
CD2x	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ab	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	526
CD2y	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ac	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	527
CD2z	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ad	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	528
CD2aa	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ae	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	529
CD2ab	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2af	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	530
CD2ac	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ag	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	531
CD2ad	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ah	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	532
CD2ae	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ai	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	533
CD2af	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2aj	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	534
CD2ag	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ak	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	535
CD2ah	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2al	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	536
CD2ai	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2am	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	537
CD2aj	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2an	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	538
CD2ak	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ao	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	539
CD2al	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ap	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	540
CD2am	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2aq	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	541
CD2an	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ar	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	542
CD2ao	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2as	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	543
CD2ap	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2at	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	544
CD2aq	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2au	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	545
CD2ar	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2av	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	546
CD2as	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2aw	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	547
CD2at	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ax	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	548
CD2au	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ay	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	549
CD2av	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2az	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	550
CD2aw	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ba	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	551
CD2ax	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bb	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	552
CD2ay	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bc	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	553
CD2az	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bd	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	554
CD2ba	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2be	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	555
CD2bb	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bf	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	556
CD2bc	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bg	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	557
CD2bd	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bh	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	558
CD2be	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bi	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	559
CD2bf	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bj	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	560
CD2bg	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bk	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	561
CD2bh	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bl	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	562
CD2bi	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bm	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	563
CD2bj	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bn	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	564
CD2bk	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bo	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	565
CD2bl	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bp	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	566
CD2bm	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bq	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	567
CD2bn	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2br	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	568
CD2bo	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bs	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	569
CD2bp	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bt	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	570
CD2bq	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bu	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	571
CD2br	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bv	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	572
CD2bs	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bw	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	573
CD2bt	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bx	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	574
CD2bu	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2by	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	575
CD2bv	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2bz	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	576
CD2bw	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ca	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	577
CD2bx	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cb	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	578
CD2by	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cc	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	579
CD2bz	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cd	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	580
CD2ca	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ce	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	581
CD2cb	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cf	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	582
CD2cc	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cg	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	583
CD2cd	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ch	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	584
CD2ce	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ci	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	585
CD2cf	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cj	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	586
CD2cg	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ck	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	587
CD2ch	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cl	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	588
CD2ci	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cm	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	589
CD2cj	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cn	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	590
CD2ck	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2co	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	591
CD2cl	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cp	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	592
CD2cm	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cq	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	593
CD2cn	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cr	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	594
CD2co	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cs	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	595
CD2cp	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ct	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	596
CD2cq	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cu	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	597
CD2cr	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cv	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	598
CD2cs	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cw	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	599
CD2ct	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cx	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	600
CD2cu	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cy	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	601
CD2cv	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2cz	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	602
CD2cw	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2da	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	603
CD2cx	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2db	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	604
CD2cy	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dc	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	605
CD2cz	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dd	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	606
CD2da	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2de	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	607
CD2db	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2df	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	608
CD2dc	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dg	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	609
CD2dd	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dh	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	610
CD2de	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2di	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	611
CD2df	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dj	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	612
CD2dg	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dk	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	613
CD2dh	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dl	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	614
CD2di	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dm	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	615
CD2dj	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dn	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	616
CD2dk	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2do	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	617
CD2dl	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dp	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	618
CD2dm	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dq	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	619
CD2dn	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dr	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	620
CD2do	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ds	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	621
CD2dp	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dt	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	622
CD2dq	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2du	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	623
CD2dr	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dv	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	624
CD2ds	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dw	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	625
CD2dt	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dx	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	626
CD2du	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dy	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	627
CD2dv	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2dz	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	628
CD2dw	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ea	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	629
CD2dx	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2eb	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	630
CD2dy	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ec	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	631
CD2dz	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ed	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus-associated in T cells)	632
CD2ea	Thymus, most NK cells (Tc: TCR-mediated in T cells)		CD2ee	Thymus of adult thymus, B cells, T cells and TCR-mediated cells (Tc: thymus	

die serologische Diagnostik



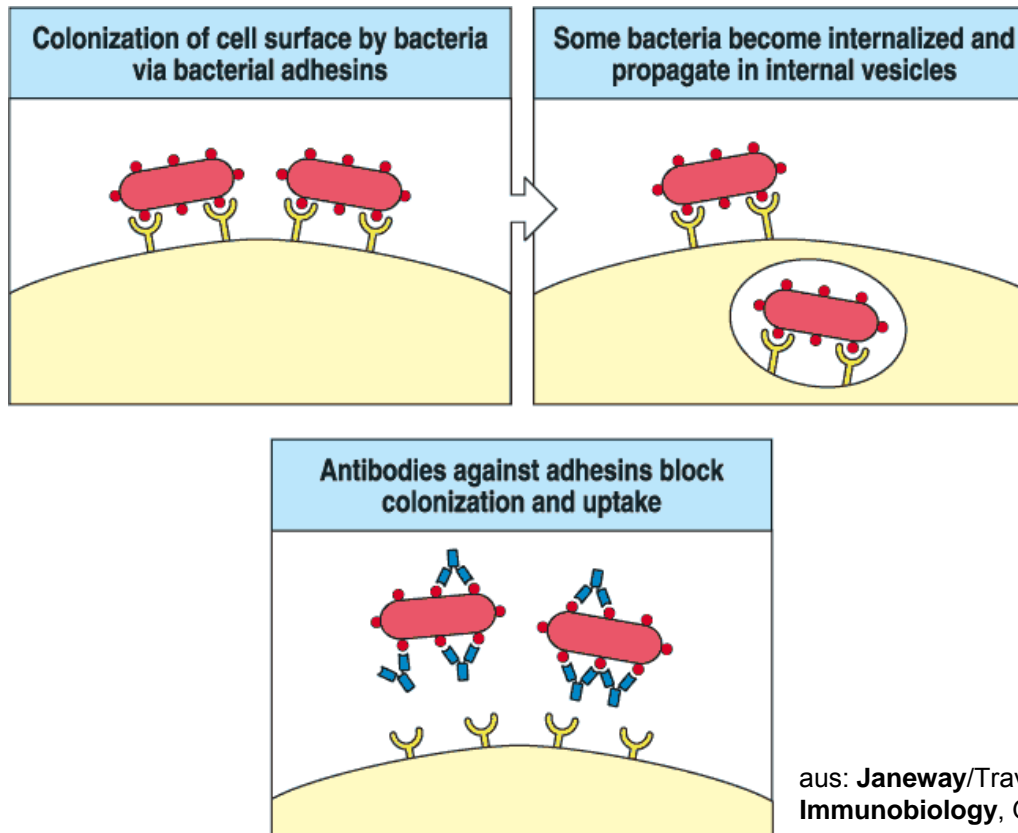
Zuverlässige Tests für HIV, Hepatitis....

...und die Therapie?

z.B. Kartographierung der Oberfläche
von Leukozyten (CD Klassifikation)...

Wie wirken Antikörper ?

1. Durch Blockade des Antigens



aus: **Janeway/Travers/Walport/Schlomchik**
Immunobiology, Garland Publishing, 2001

Fig 9.26 © 2001 Garland Science

Klinischer Einsatz blockierender Antikörper

- Immunsuppression bei Transplantatabstoßung und Autoimmunerkrankungen

Anti-CD3 [Orthoklone OKT3]

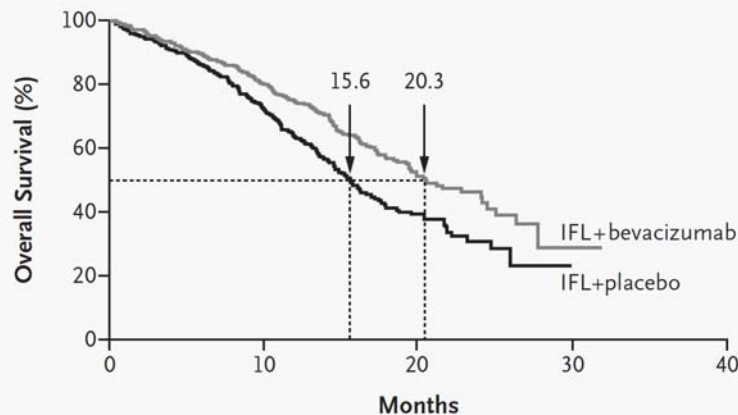
Anti-CD25(=IL2-Rezeptor) [Zenapax, Simulect]

Anti-TNF [Infliximab, Etanercept, etc.]

- Angiogenesehemmung bei Makuladegeneration

Anti-VEGF [z.B. Bevacizumab]

- Hemmung der Neoangiogenese bei Krebserkrankungen



No. at Risk

IFL+bevacizumab	402	362	320	178	73	20	1	0
IFL+placebo	411	363	292	139	51	12	0	0

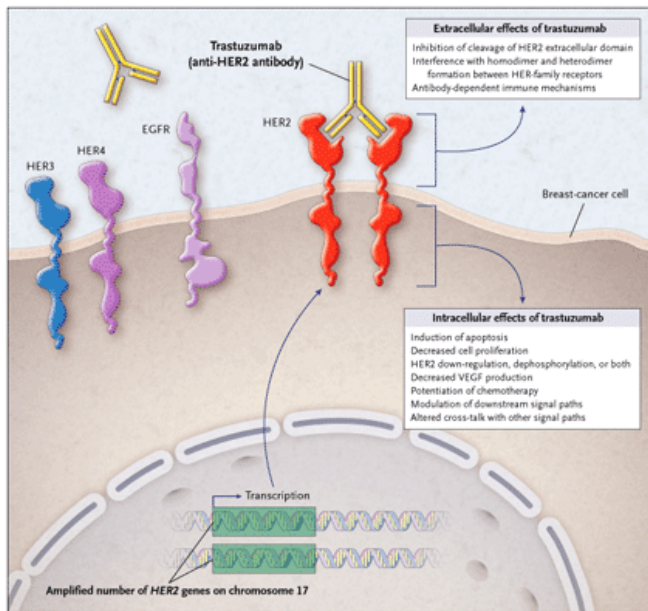
nicht vorbehandelte Patienten mit metastasiertem Kolonkarzinom, N=813

Hurwitz, H. et al. N.Engl.J.Med. 350:2336 (2004)

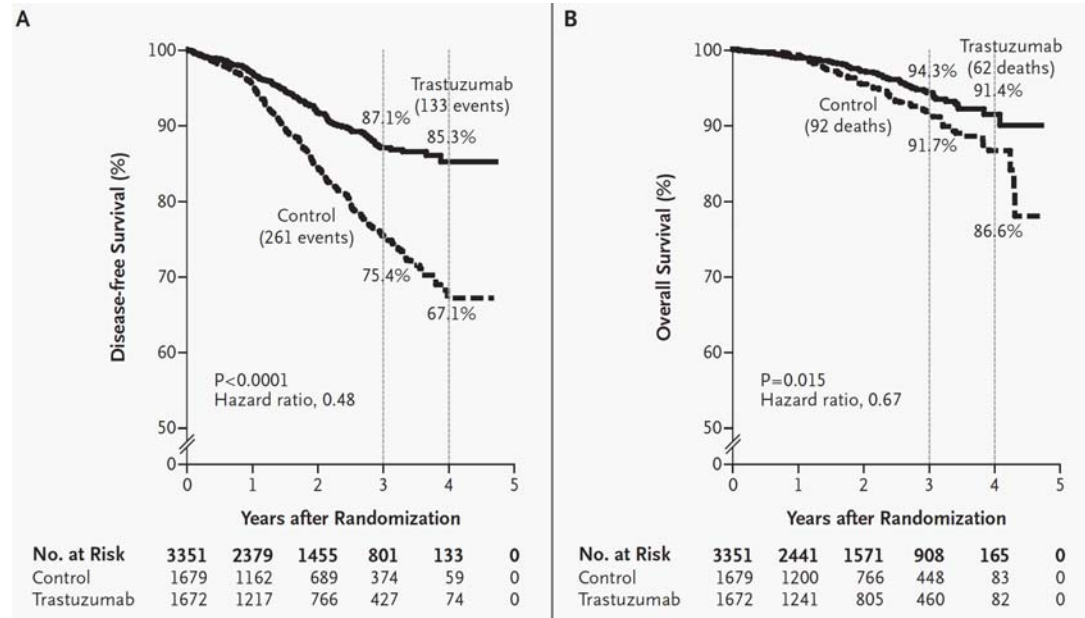
Klinischer Einsatz blockierender Antikörper

- Blockade „kanzerogener Signale“

Anti-Her2/neu [Trastuzumab], Mamma-Ca nach operativer Tumorentfernung



H.J.Burstein, N Engl Med 353:1652 (2005)

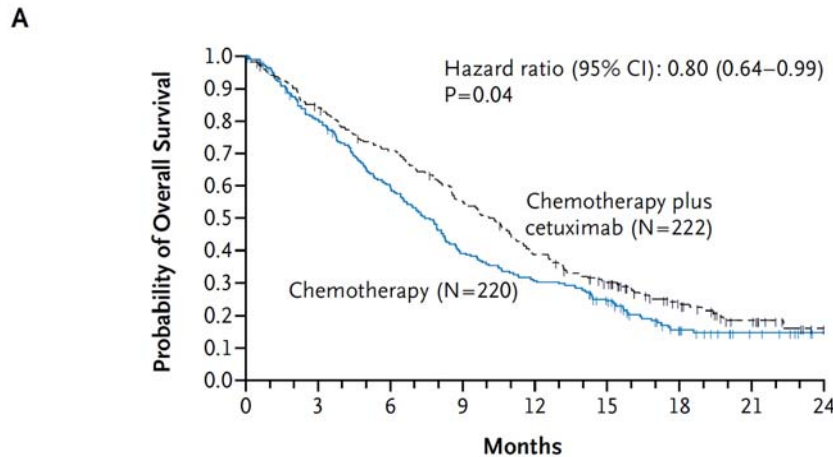


Romond et al. N.Engl.J.Med. 353:1673 (2005)

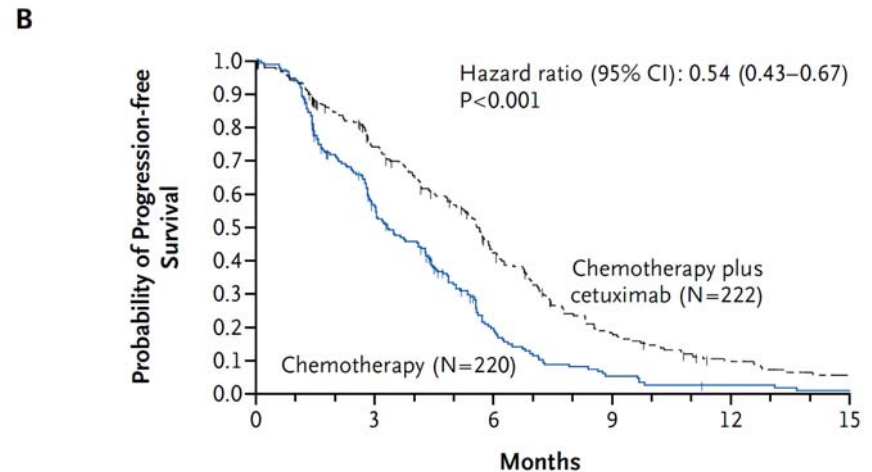
Klinischer Einsatz blockierender Antikörper

- Blockade „kanzerogener Signale“

Anti-EGFR [Cetuximab] bei rezidierten/metastasierten Kopf-Hals Tumoren



No. at Risk									
Chemotherapy	220	173	127	83	65	47	19	8	1
Chemotherapy plus cetuximab	222	184	153	118	82	57	30	15	3



No. at Risk									
Chemotherapy	220	103	29	8	3	1			
Chemotherapy plus cetuximab	222	138	72	29	12	7			

Vermorken et al., New Engl J Med 359:1116 (2008)

Wie wirken Antikörper ?

2. Durch Aktivierung immunologischer Effektormechanismen

Komplementaktivierung: von C1-C9

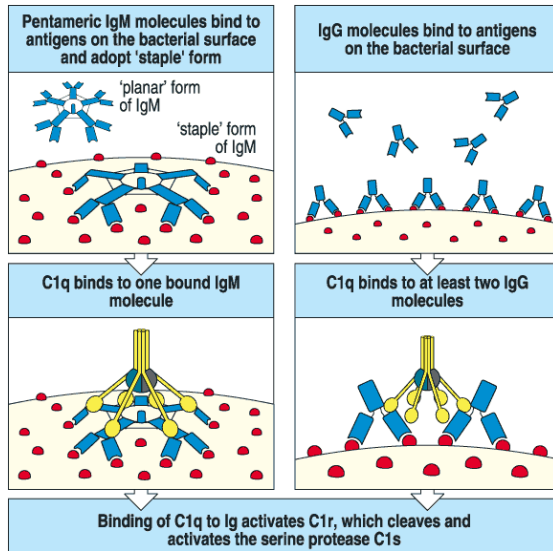


Fig 9.28 © 2001 Garland Science

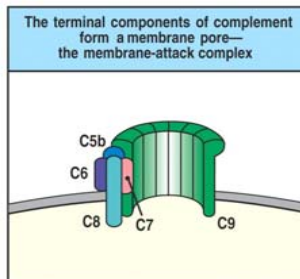


Figure 2-37 part 4 of 4 Immunobiology, 6/e. (© Garland Science 2005)

Phagozytose

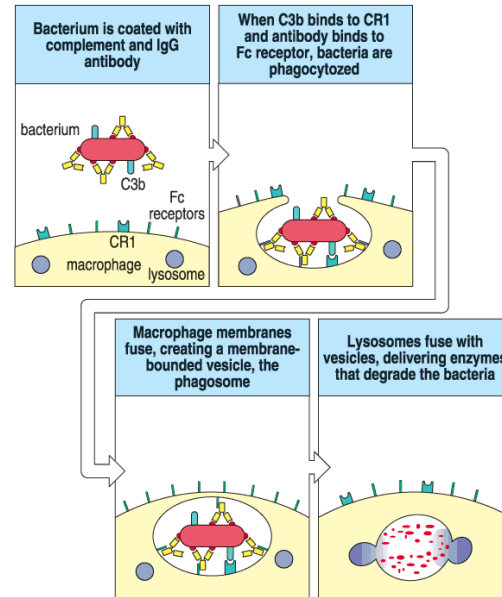


Fig 9.32 © 2001 Garland Science

Lyse (ADCC)

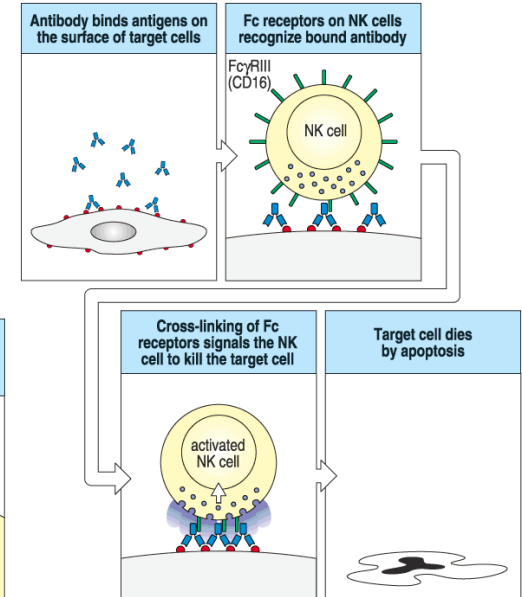
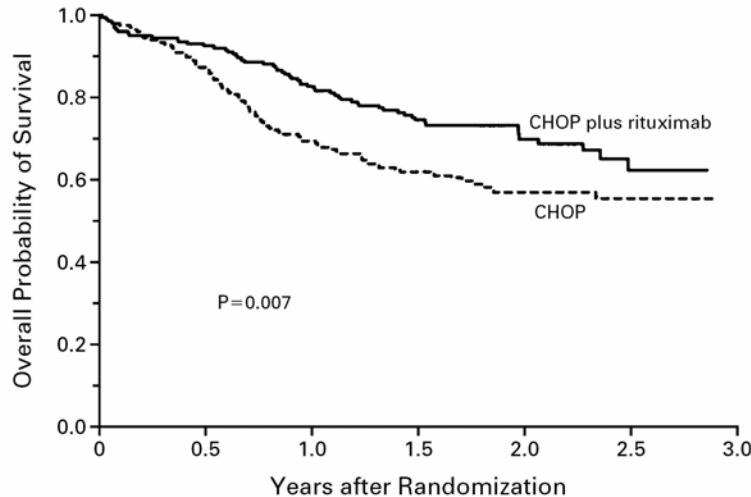


Fig 9.34 © 2001 Garland Science

Janeway, Immunobiology, Garland Publishing, 2001

Anti-CD20 Antikörper bei B Zell-Lymphomen

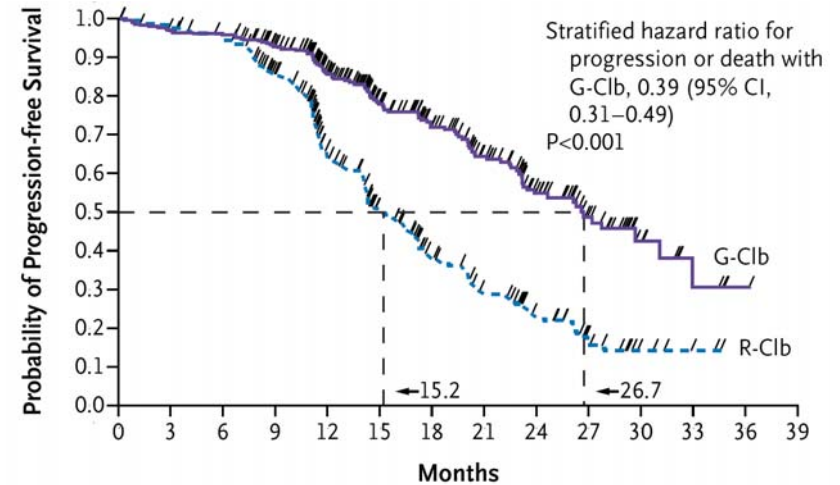
Chemo +/-Rituximab



No. AT RISK						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

Coiffier et al., NEJM 346:235-242 (2002)

Obinituzumab (Fc-optimiert) versus Rituximab



No. at Risk														
G-Clb	333	307	302	278	213	156	122	93	60	34	12	4	1	0
R-Clb	330	317	309	259	163	114	72	49	31	14	5	2	0	0

Goede et al., NEJM 370:1101-1 (2014)

→ Bedeutung der Antibody-Dependent Cellular Cytotoxicity (ADCC)

Ehrlichs Zauberkekeln wirken ! Aber.....



Paul Ehrlich, 1854-1915
Nobelpreisträger, Erfinder der
Zauberkekeln

- Rituximab und Trastuzumab etc. ermöglichen deutlich verbesserte Therapie. Umsatz in 2012 über 12 Milliarden US \$.
- Verbesserte Antitumor-Antikörper (ADCC-optimiert, bispezifisch) bereits zugelassen bzw. in Erprobung (z.B. Obinituzumab, Blinatumumab)
- Checkpoint Inhibitoren (anti-CTLA4 bzw. PD-1) induzieren Regression solider Tumore und anhaltende Remissionen

Verbliebene Herausforderungen:

- Begrenzte therapeutische Wirkung
- Für zahlreiche Tumorarten bislang keine Antikörper verfügbar
- Langsame Translation „from bench to bedside“ (10-25 Jahre)

Entwicklung neuer/besserer Antikörper: nur eine wissenschaftliche Herausforderung?

Gesetzgebung fordert strikte Einhaltung von GMP- und GCP-Richtlinien auch für Studien mit universitär entwickelten Substanzen/Antikörpern

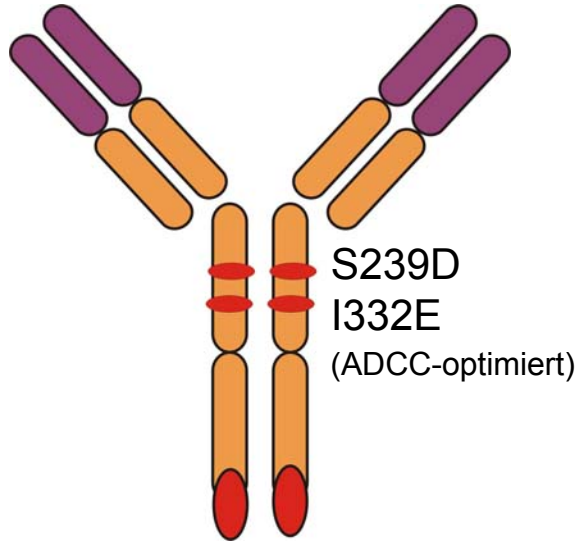
→ seit AMG Novelle 2004 Entwicklung an der Akademie kaum mehr möglich.



→ Entwicklung neuer Medikamente nahezu ausschließlich durch Industrie

→ beeinflusst durch zahlreiche „nicht-wissenschaftliche“ Faktoren

4G8-SDIEM: ADCC-verstärkter anti-Flt3 Antikörper



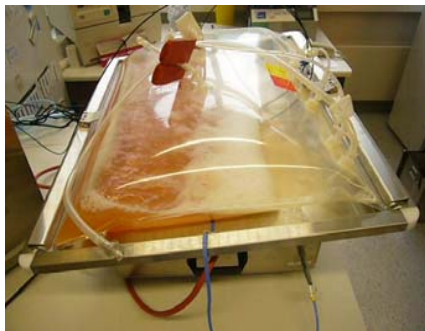
An der Universität:

- generiert
- humanisiert
- ADCC-optimiert
- funktionell charakterisiert
- GMP-konform produziert

Hofmann et al.,
Leukemia 2012



GMP facility



25 g aus 100 L !



single use-Technology



Closed filling



Einsatz im individuellen Heilversuch – aktive Erkrankung

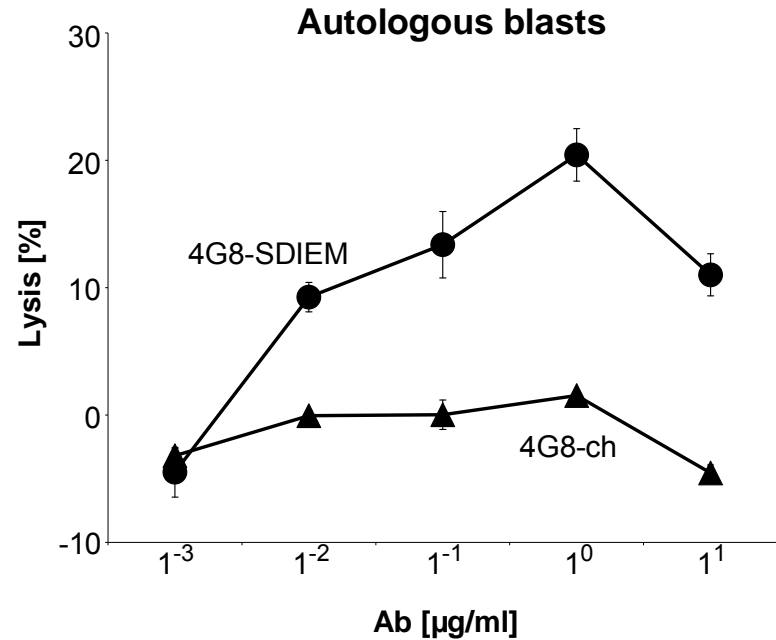
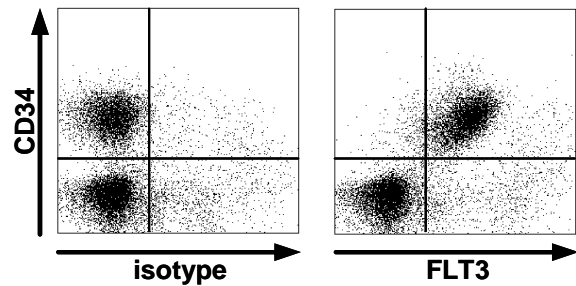
Pat. X:

AML, 45XY, komplex rearrangiert, u.a. inv(3)(q21q26), -7;

- keine Remission nach mehrfachen Induktions-Chemotherapien
- allogene Stammzelltransplantation (SZT), Regeneration mit Leukämiezellen
- Haploidente SZT (Schwester), Rezidiv nach 6 Monaten

➔ Heilversuch: 4G8-SDIEM

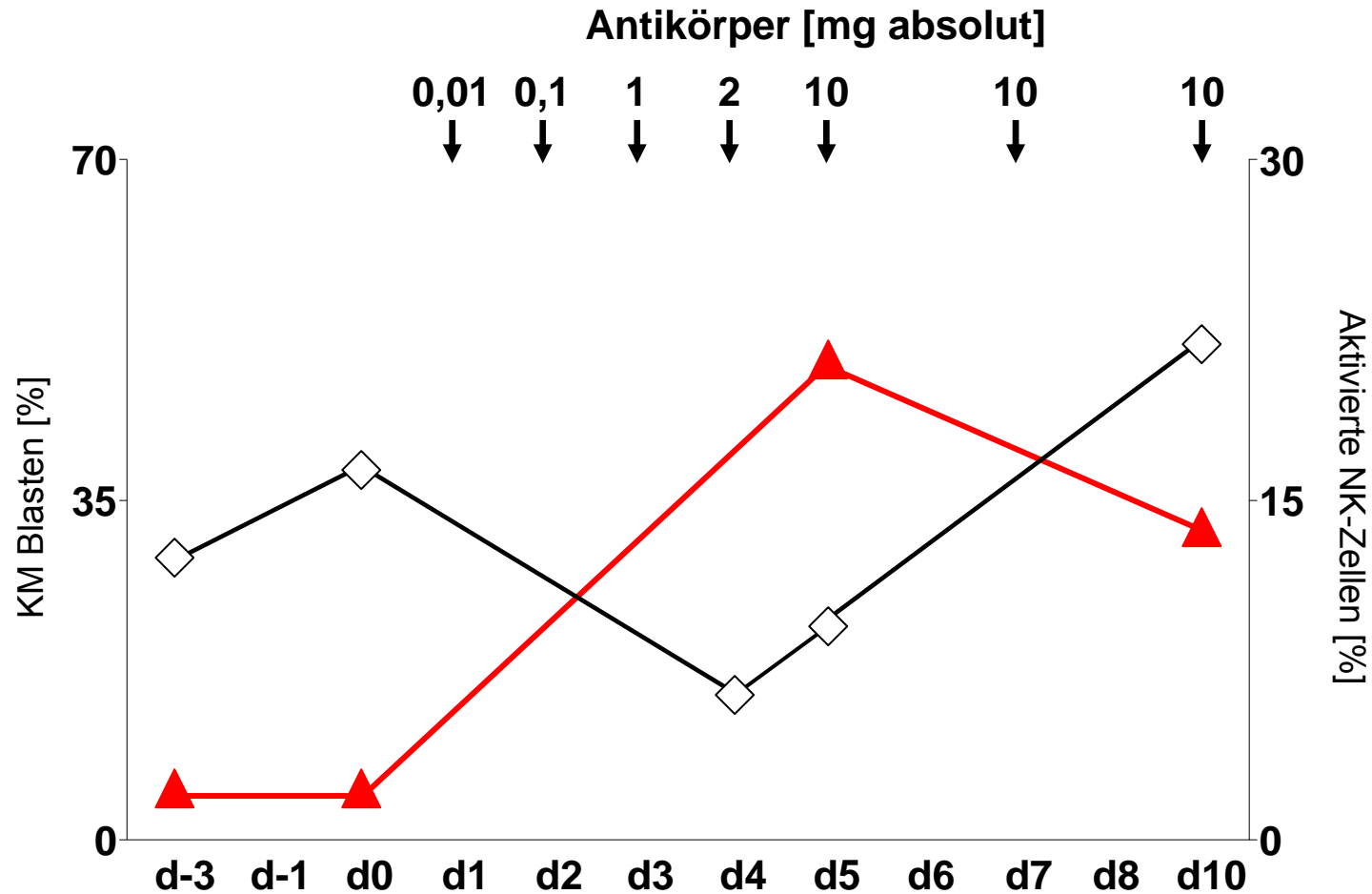
Einsatz im individuellen Heilversuch – aktive Erkrankung



Einsatz im individuellen Heilversuch – aktive Erkrankung

▲ NK Zell-Aktivierung

◇ Leukämiezellen in Knochenmark



Schlussfolgerung nach Applikation bei aktiver Erkrankung

Fazit Applikation Fc-optimierte Antikörper (FLT3 und CD19) bei aktiver Erkrankung:

- from bench to bedside in <2 Jahren für <2M €
- werden gut vertragen
- sind therapeutisch E:T Ratio-abhängig wirksam
- können „aktive“ Leukämie nicht aufhalten

→ Einsatz zur Therapie der Minimal Residual Disease (MRD)

Einsatz im MRD Setting - Patientenhistorie

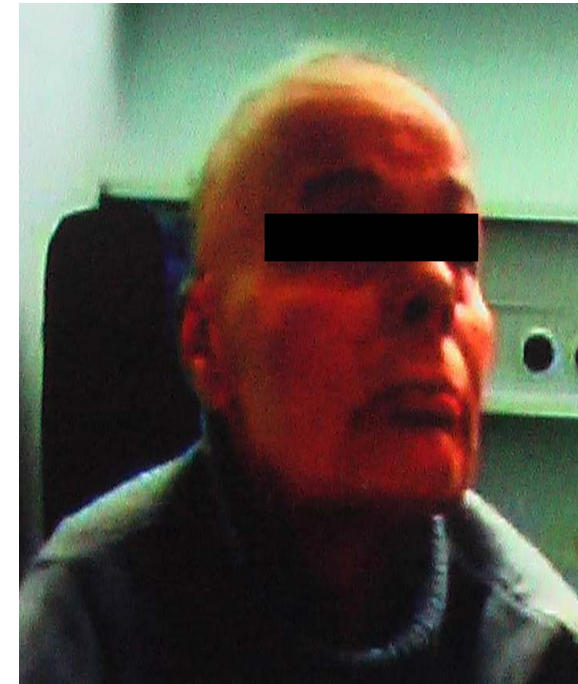
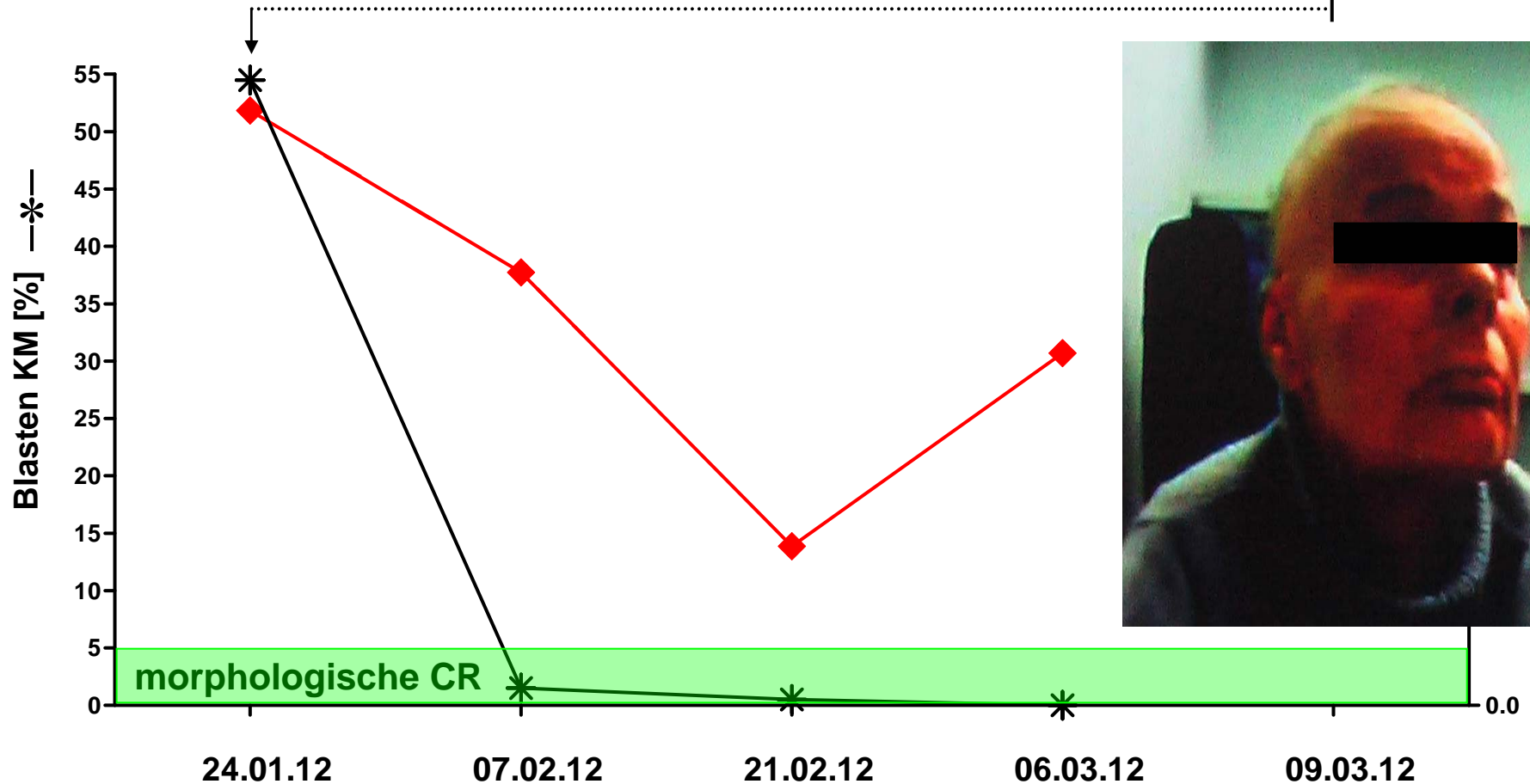
Pat. K.S., geb. 1959

AML, 46XX, NPM1 mutiert, FLT3-ITD, *

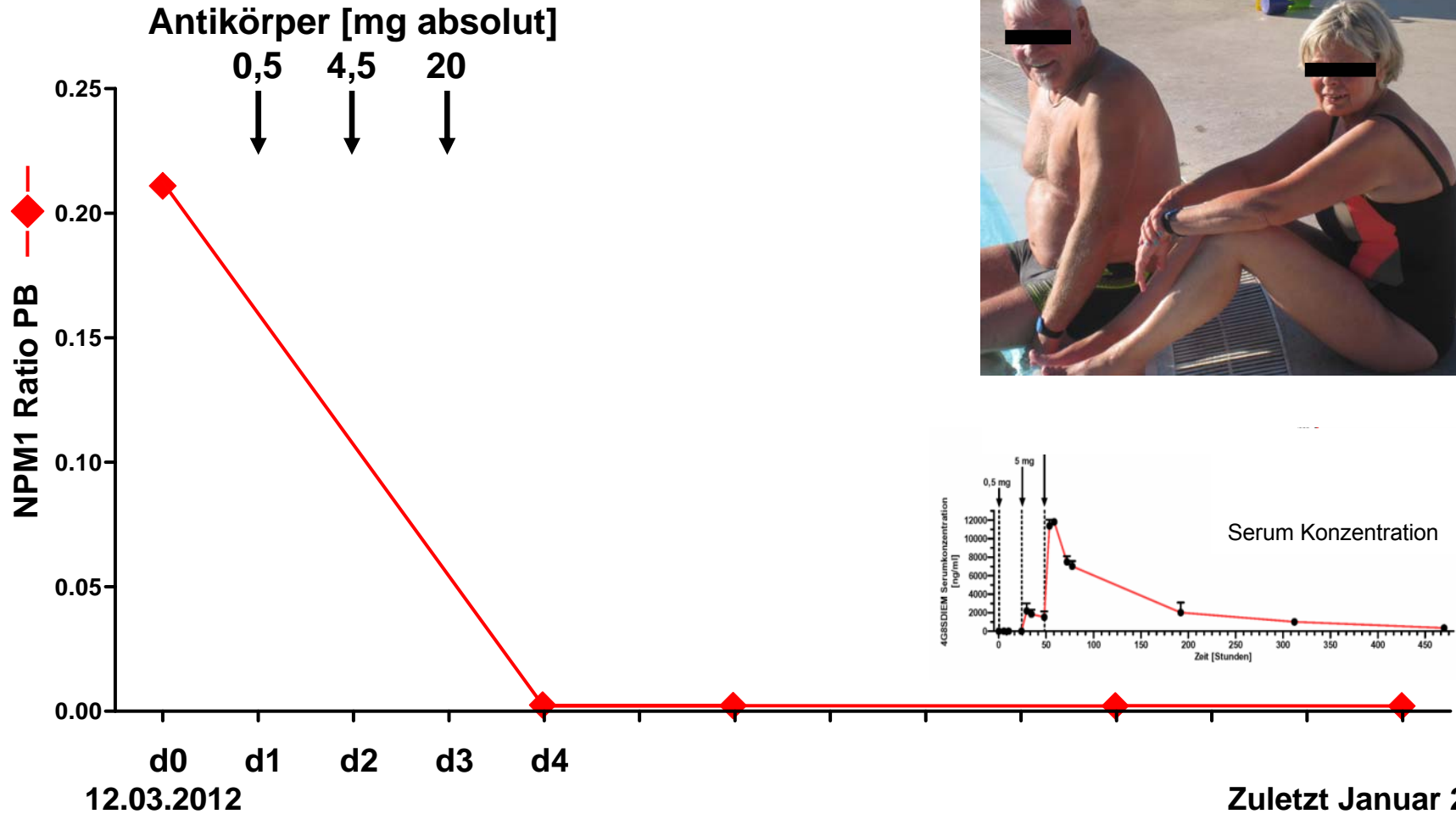
- Frührezidiv nach allo SZT

Sorafenib

abgesetzt



Einsatz im MRD Setting – Applikation 4G8-SDIEM

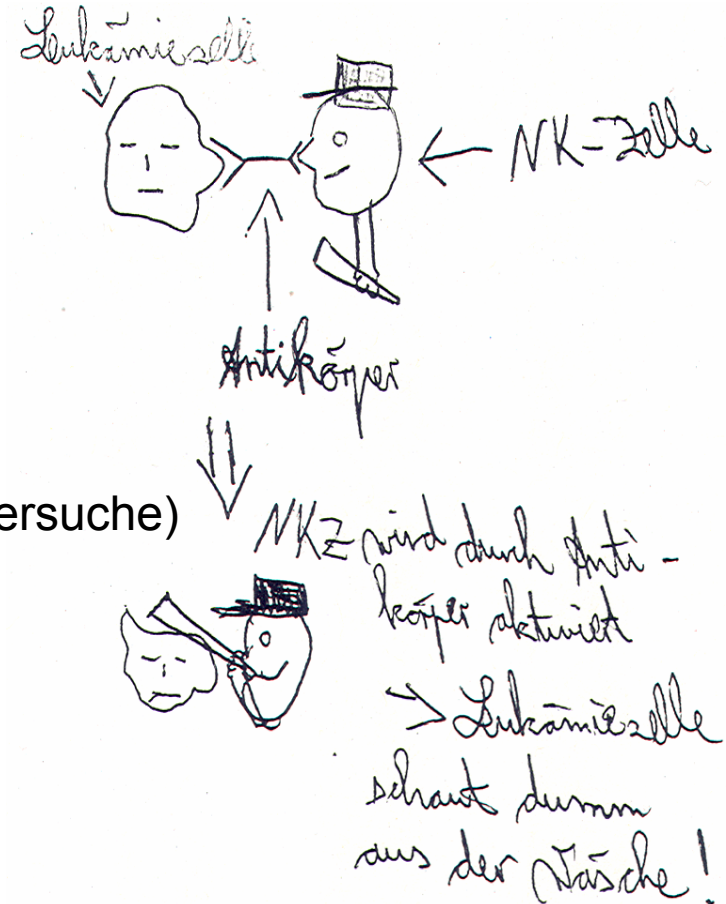


Zuletzt Januar 2015

Fazit und zukünftiger Einsatz 4G8-SDIEM

Fazit Applikation Fc-optimierte Antikörper (FLT3 und CD19) bei aktiver Erkrankung:

- from bench to bedside in <2 Jahren für <2M €
- werden gut vertragen
- sind therapeutisch E:T Ratio-abhängig wirksam
- können „aktive“ Leukämie nicht aufhalten



Fazit Applikation in „MRD Situation“

- Aktuell 7 Patienten behandelt (individuelle Heilversuche)
- Molekulare Remissionen in 3 Patienten

Phase I/II Studie Start Q3/2015:

AML in morphologischer CR,

nach 1. SZT/keine SZT Option, steigende MRD

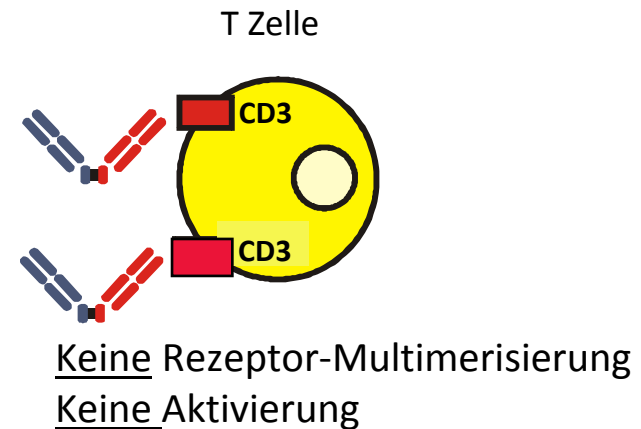
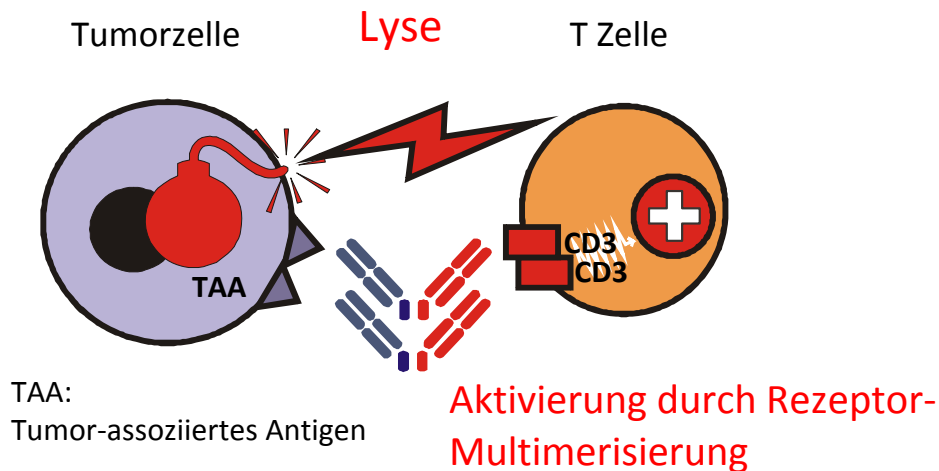
Bispezifische Antikörper

Konzept: Bestehend aus Ziel- und Effektorarm

→ Zielzell-restringierte Aktivierung von T Zellen

Zielzelle vorhanden

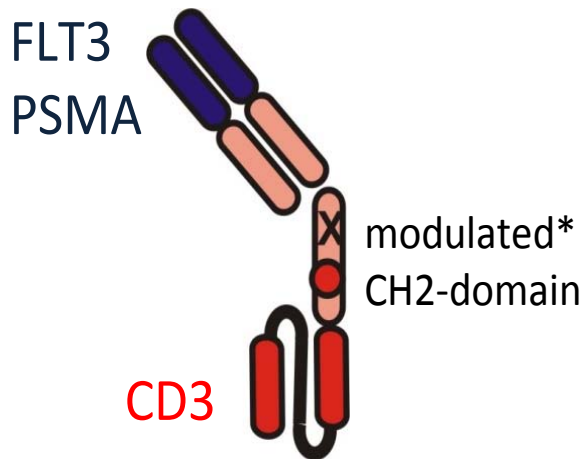
Zielzelle abwesend



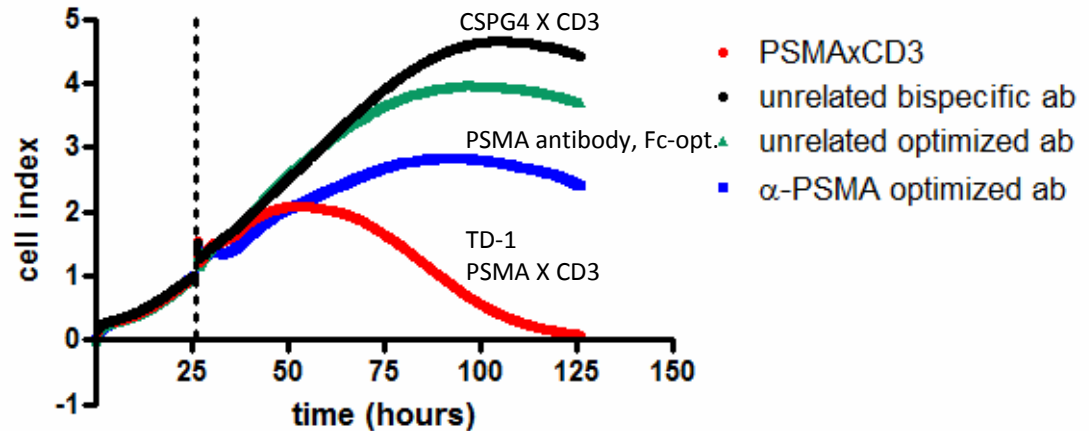
Prototyp: BiTE Antikörper Blinatumumab (CD19 x CD3);
Zielantigen jedoch auch auf gesunden Zellen → Nebenwirkungen →
nur geringe Dosen applizierbar

Bispezifische Antikörper

Reduktion von Nebenwirkungen durch geeignete Zielantigene und neues Format:



*cystein-depletiert, Fc-attenuiert



Langzeit-Zytotoxizitätsassay mit PBMC

Vorteile des Fabsc- versus BiTE-Format:

- Erhöhte Produktionsraten
- Höhere Affinität
- Verminderte Aggregation → verringerte Nebenwirkungen

Durben et al., Mol Ther 2014

Wesentliche Schritte der Antikörper-Entwicklung und Rolle der Akademie

Gute Wissenschaftler
und Ideen



Präklinische
Entwicklung

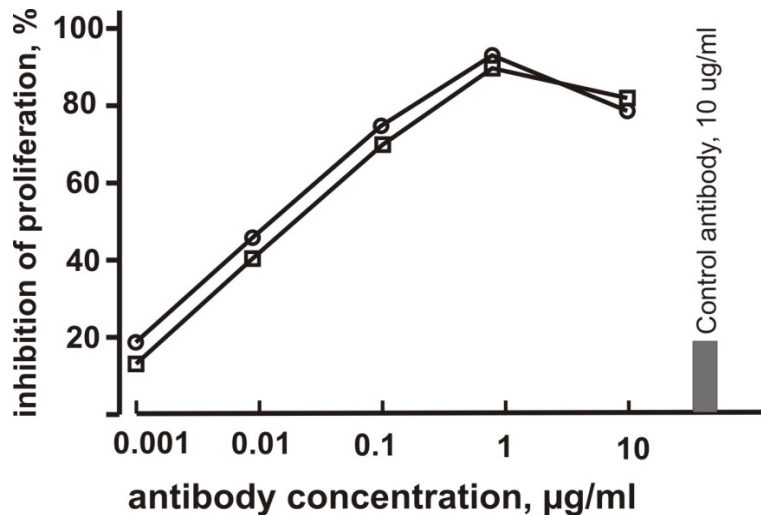
Valley of death

GMP
Produktion



Nahe am Patient

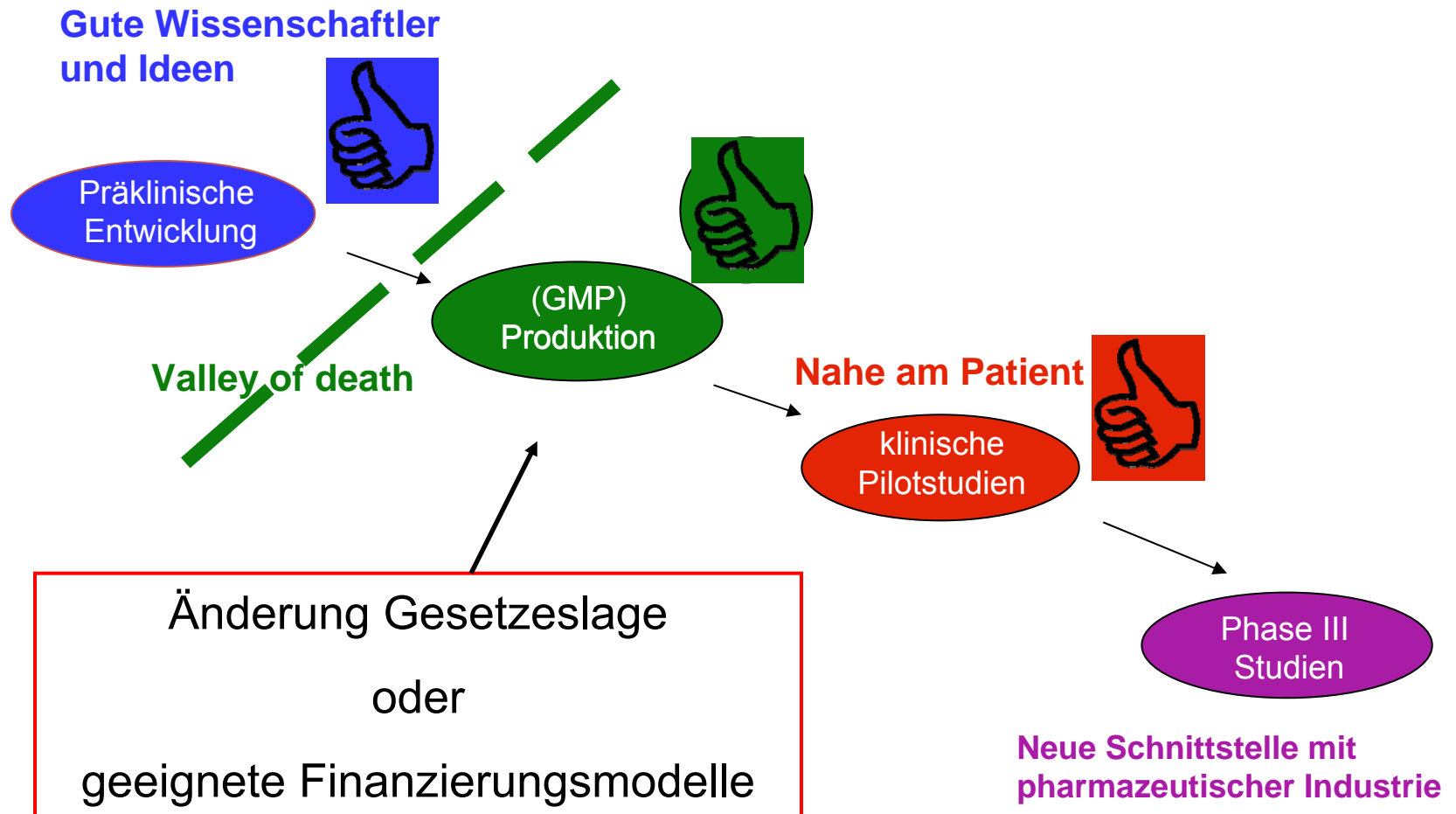
klinische
Pilotstudien



Unterschiede GMP versus non-GMP CD19-Antikörper:

- Biologische Aktivität: keine
- Kosten: € 1 Million
- Zeit: ≥3 Jahre Verzögerung

Wesentliche Schritte der Antikörper-Entwicklung und Rolle der Akademie



Danksagung

- DKTK, Otmar Wiestler
- Lothar Kanz
- Hans-Georg Rammensee
- Alle Kooperationspartner
- Labormitarbeiter
- Gundram Jung

