Neue Wege in der Krebstherapie

Y. Ko

Patiententag – 16. August 2023

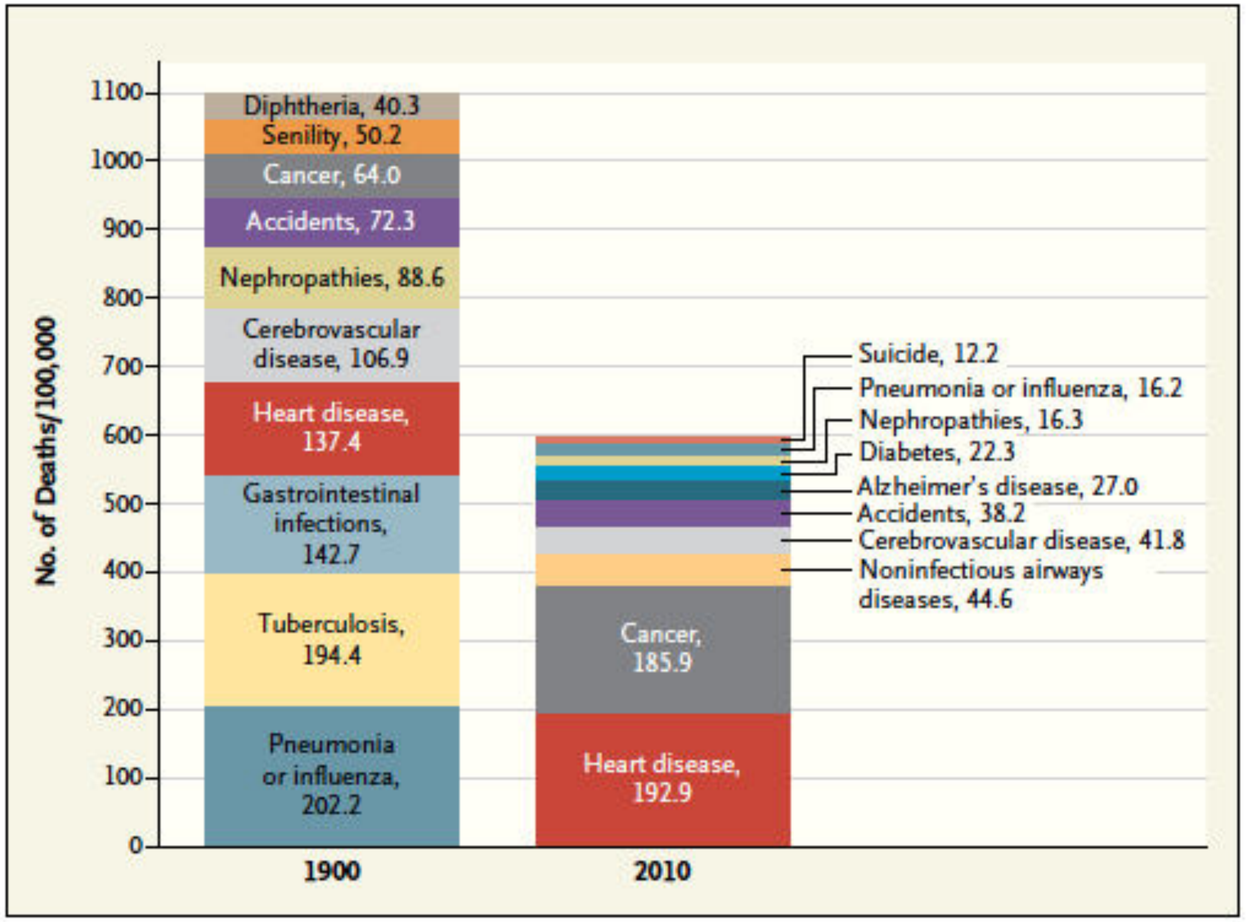
JOHANNITER
Competence Center

Volksgesundheit - Todesursachen

The DEATHS preceding were caused by Diseases and Casualties as follows, viz.

Abscesses	1	Hernia, or Rupture	3
Aneurism	1	Jaundice	10
Apoplexy	13	Inflammation of the bowels	1
Burns or Scalds	6	——— of the stomach	1
Cancer	5	Killed by lightning	1
Casualties	15	Insanity	1
Childbed	14	Intemperance	2
Cholera Morbus	6	Locked jaw	2
Colic	2	Mortification	11
Consumption	221	Old Age	26
Convulsions	36	Palsy	12
Cramp in the stomach	2	Pleurisy	8
Croup	1	Quinsy	15
Debility	28	Rheumatism	1
Decay	20	Rupture of blood vessels	1
Diarrhœa	15	Small-Pox,(at Rainsford's Island)	2
Drinking cold water	2	Sore throat	1
Dropsy	21	Spasms	2
——— in the head	23	Stillborn	49
Drowned	13	Suicide	1
Dysentery	14	Sudden death	25
Dispepsia or Indigestion	15	Syphilis	12
Fever, bilious	7	Teething	15
——— pulmonic	46	Worms	11
——— inflammatory	24	Whooping Cough	14
——— putrid	6	White swelling	2
——— typhus	33	Diseases not mentioned	48
Flux infantile	57		
Gout	3	Total,	942
Hoemorrhage	4		

Causes of Death in 1811. Abstract of the Bill of Mortality for the Town of Boston.

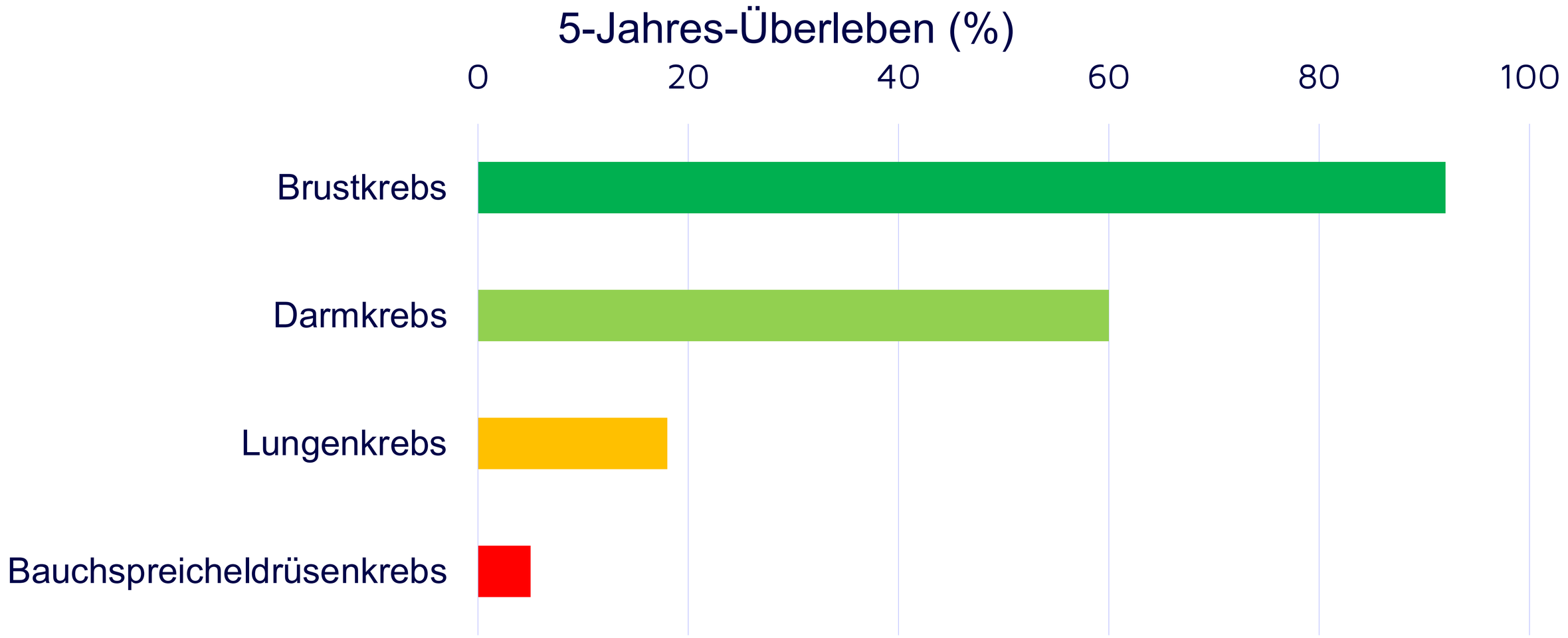


Top 10 Causes of Death: 1900 vs. 2010.

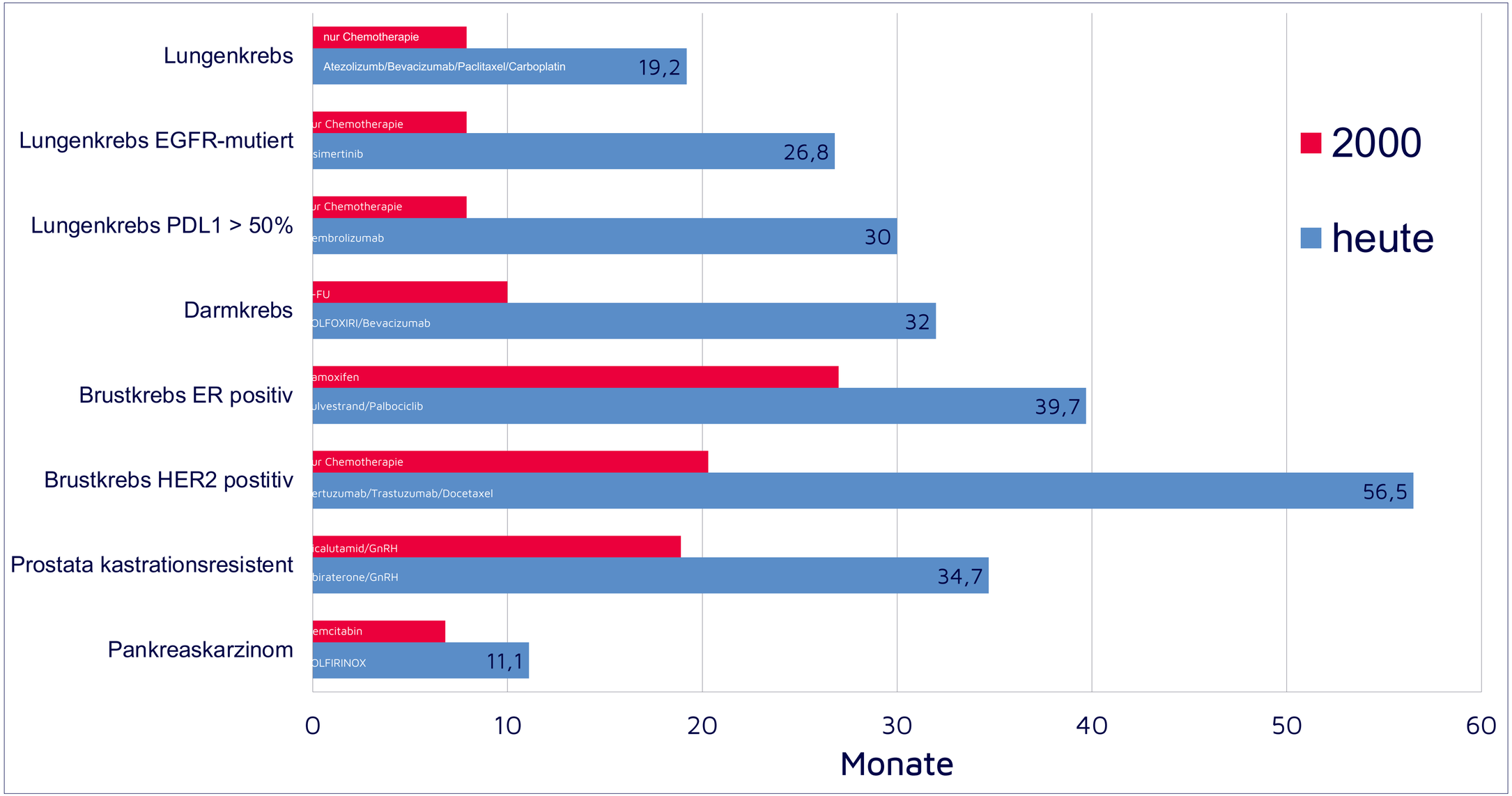
Data are from the Centers for Disease Control and Prevention.

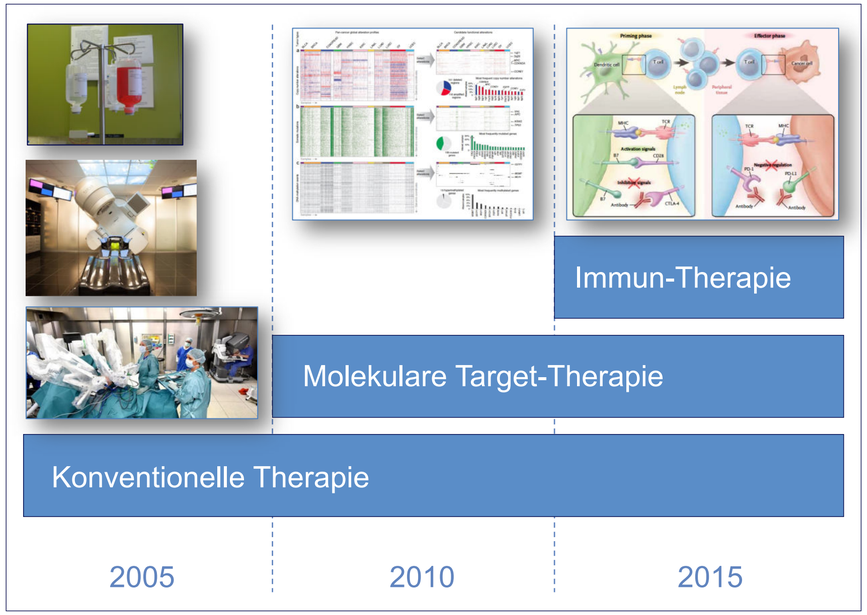
Jones et al. NEJM 2012;25:2333-8

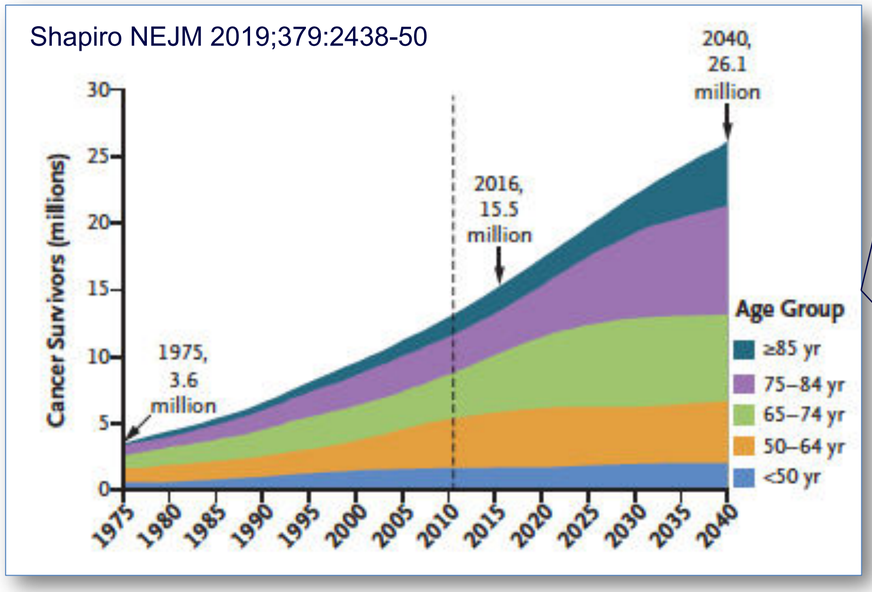
Überleben mit Krebs



Überleben mit Krebs und Metastasen – Gestern und Heute





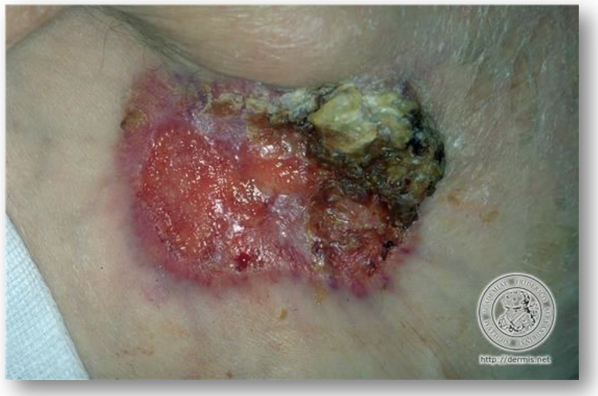


- Chronische Schmerzen
- Infertilität
- Gonadale Fehlfunktion
- Periphere Neuropathie
- Fatigue
- Schlaflosigkeit
- Sexuelle Dysfunktion
- Metabolisches Syndrom
- Knochenverlust
- Kognitive Störungen
- Kardiale Schäden
- Zweit-Neoplasien

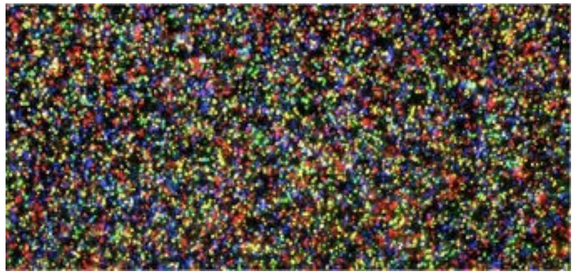
Onkologie im Wandel der Zeit

„… und an der Brust sahen wir häufig Tumoren, die der Gestalt eines Krebses sehr ähnlich waren. So wie die Beine des Tieres an beiden Seiten des Körpers liegen, so verlassen die Venen den Tumor, der seiner Form nach dem Krebskörper gleicht.“

Galenos von Pergamon 2. Jh. n. Chr.



Next-Generation-Sequencing



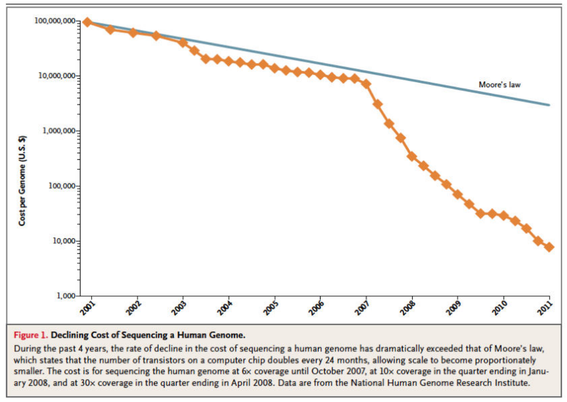
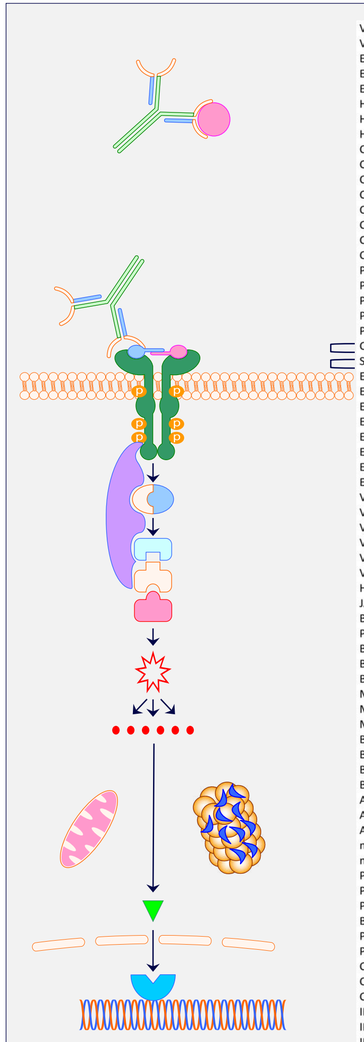
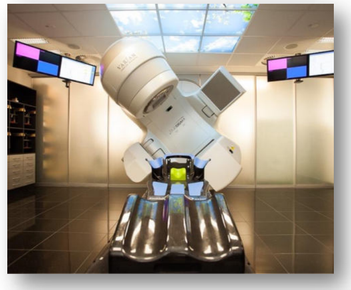


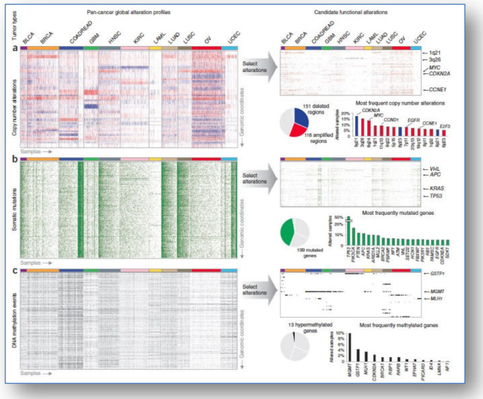
Figure 1. Declining Cost of Sequencing a Human Genome.
During the past 4 years, the rate of decline in the cost of sequencing a human genome has dramatically exceeded that of Moore's law, which states that the number of transistors on a computer chip doubles every 24 months, allowing scale to become proportionately smaller. The cost is for sequencing the human genome at 6× coverage until October 2007, at 10× coverage in the quarter ending in January 2008, and at 30× coverage in the quarter ending in April 2008. Data are from the National Human Genome Research Institute.

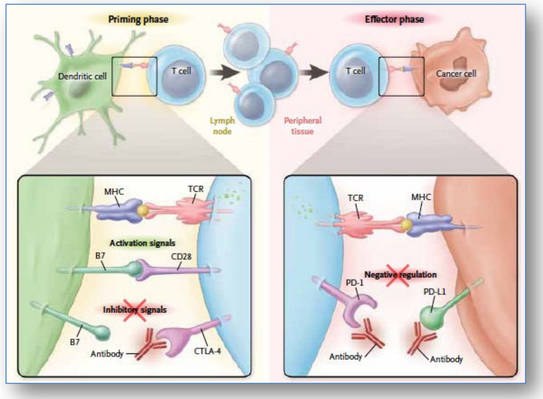


VEGF	Bevacizumab	Ak	BC,NSCLC, Ovar
VEGF	Ramucirumab	Ak	Magen,K KRK
EGF-R	Cetuximab	AK	KRK
EGF-R	Panitumumab	Ak	KRK
EGF-R	Necitumumab	Ak	NSCLC
HER2	Trastuzumab	Ak	BC
HER2	Pertuzumab	Ak	BC
HER2	TDM-1	IT	BC
CD38	Daratumumab	Ak	Myelom
CD19	Blinatumomab	Ak	ALL
CD20	Rituximab	Ak	NHL, CLL
CD20	Ofatumumab	Ak	CLL, MZL
CD20	Obinituzumab	Ak	NHL, CLL
CD22	Inotuzumab-V	IT	ALL
CD30	Brentuximab-V	IT	Hodgkin, T-NHL
CD33	Gemtuzumab-O	IT	AML
PD-1	Nivolumab	Ak	Melanom, NSCLC
PD-1	Pembrolizumab	Ak	Melanom, NSCLC
PD-L1	Atezolizumab	Ak	NSCLC, Urothel
PD-L1	Avelumab	Ak	Merkelzell-Karzir
PD-L1	Durvalumab	Ak	NSCLC
CTLA4	Ipilimumab	Ak	Melanom, RCC
SLAMF7	Elotuzumab	Ak	Myelom
EGF-R	Erlotinib	SM	NSCLC
EGF-R	Gefitinib	SM	NSCLC
EGF-R	Afatinib	SM	NSCLC
EGF-R	Osimertinib	SM	NSCLC
EGF-R	Dacomitinib	SM	NSCLC
EGF-R	Lapatinib	SM	BC
EGF-R	Neratinib	SM	BC
EGF-R, RET, VEG	Vandetanib	SM	SD
VEGF-R	Sorafenib	SM	RCC, HCC
VEGF-R	Sunitinib	SM	RCC
VEGF-R	Pazopanib	SM	RCC
VEGF-R	Axitinib	SM	RCC
VEGF-R	Cabozantinib	SM	RCC, SD
VEGF-R	Regorafenib	SM	KRK, GIST
Hedghog	Vismodegib	SM	Basaliom
JAK1/2	Ruxolitinib	SM	MPS
BTK	Ibrutinib	SM	CLL, MZL
PI3K	Idelalisib	SM	CLL
B-RAF	Vemurafenib	SM	Melanom
B-RAF	Dabrafenib	SM	Melanom
B-RAF	Encorafenib	SM	Melanom
MEK	Trametinib	SM	Melanom
MEK	Cobimetinib	SM	Melanom
MEK	Binimetinib	SM	Melanom
Bcr-Abl, c-kit	Imatinib	SM	CML, GIST
Bcr-Abl	Nilotinib	SM	CML
Bcr-Abl	Dasatinib	SM	CML
Bcr-Abl	Ponatinib	SM	CML
ALK-EML	Crizotinib	SM	NSCLC
ALK-EML	Ceritinib	SM	NSCLC
ALK-EML	Alectinib	SM	NSCLC
mTOR	Temsirolimus	SM	RCC
mTOR	Everolimus	SM	RCC,BC, NET
Proteasom	Bortezomib	SM	Myelom, MZL
Proteasom	Carfilzomib	SM	Myelom
Proteasom	Ixazomib	SM	Myelom
BCL-2	Venetoclax	SM	CLL
PARP	Olaparib	SM	Ovar
PARP	Niraparib	SM	Ovar
CDK4/6	Palbociclib	SM	BC,NSCLC, Ovar
CDK4/6	Ribociclib	SM	BC
CDK4/6	Abemaciclib	SM	BC
IMID	Thalidomid	SM	Myelom, MZL
IMID	Lenalidomid	SM	Myelom, MZL
IMID	Pomalidomid	SM	Myelom, MZL

Systemtherapie/ die 3 Säulen der Therapie heute







Immun-Therapie

Molekulare Target-Therapie

Konventionelle Therapie

2005 2010 2015

2000


Capecitabine
Doxorubicin
Topotecan
Capecitabine
Cabazitaxel
Nab-Paclitaxel
Epirubicin
Doxorubicin
Paclitaxel
Irinotecan
Cabazitaxel
Cisplatin
Irinotecan
Cisplatin
Epirubicin
Docetaxel
Carboplatin
Carboplatin
Docetaxel
Gemcitabin
Vinorelbin
5-FU
Paclitaxel
Cisplatin
Docetaxel
Doxorubicin
Gemcitabin
5-FU
Topotecan
5-FU
Nab-Paclitaxel
Carboplatin
Doxorubicin
Epirubicin
Paclitaxel
Irinotecan
Capecitabine
Vinorelbin

2023

2000

Capecitabine
Doxorubicin
Topotecan
Capecitabine
Cabazitaxel
Nab-Paclitaxel
Epirubicin
Doxorubicin
Paclitaxel
Irinotecan
Cisplatin
Epirubicin
Docetaxel
Carboplatin
Cabazitaxel
Gemcitabin
Gemcitabin
5-FU
Paclitaxel
Cisplatin
Docetaxel
5-FU
Topotecan
5-FU
Nab-Paclitaxel
Carboplatin
Doxorubicin
Carboplatin
Paclitaxel
Cisplatin
Irinotecan
Epirubicin
Capecitabine
Vinorelbin
Docetaxel
Gemcitabin
Vinorelbin
Capecitabine

Daratumumab
Ibrutinib
Nab-Paclitaxel
Trametinib
Trastuzumab
Carboplatin
Docetaxel
Cabazitaxel
Nintendanib
Ofatumumab
Gefitinib
Imatinib
Olaparib
Vemurafenib
Paclitaxel
Doxorubicin
Epirubicin
Ponatinib
Imatinib
Temsirolimus
Nivolumab
Ipilimumab
Pembrolizumab
Obinotuzumab
Afatinib
Gefitinib
Bortezomib
Docetaxel
Cisplatin
Lip-doxo
Venetoclax
5-FU
Topotecan
Dasatinib
Ibrutinib
Trametinib
Thalidomid
Necitumumab
Ponatinib
Gemcitabin
Vinflunin
Carboplatin
Panitumumab
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Dasatinib
Cisplatin
Paclitaxel
Rituximab
Lenalidomid
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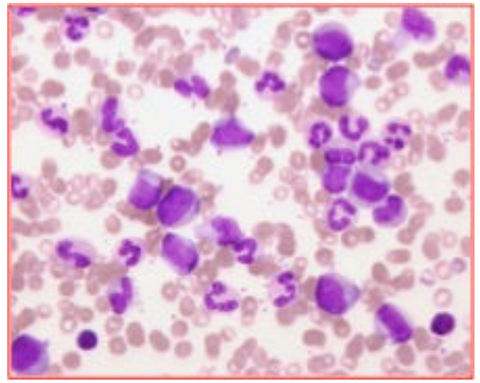
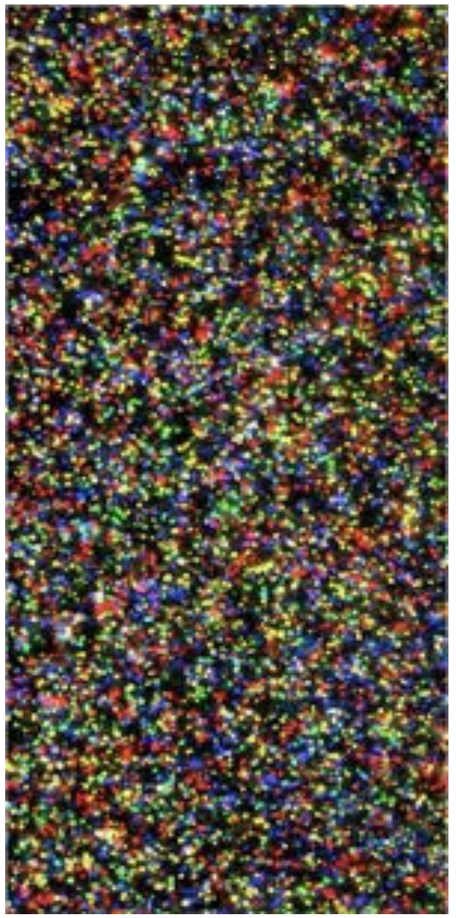
Peg-doxo
Nilotinib
Pomalidomid
Bortezomib
Imatinib
Olaparib
Cisplatin
Idelalisib
Lenalidomid
Pomalidomid
Axitinib
Irinotecan
Paclitaxel
Necitumumab
Pazopanib
Thalidomid
Aflibercept
Doxorubicin
Osimertinib
Carfilzomib
Osimertinib
Nilotinib
5-FU
Nivolumab
Cabozantinib
Cetuximab
Palbociclib
Crizotinib
Daratumumab
Vinorelbin
Bevacizumab
Trastuzumab
Idelalisib
Levantinib
Rituximab
Pembrolizumab
Niraparib
Topotecan
Trametinib
Vinflunin
Carfilzomib
Everolimus
Everolimus
Sunitinib
Vemurafenib
Ofatumumab
Gemcitabin
Elotuzumab
Ipilimumab
Pomalidomid
Peg-doxo
Ofatumumab
Trastuzumab
Vinorelbin
Thalidomid
Vinflunin
Lip-doxo
Gemcitabin
Lenalidomid
Daratumumab
Capecitabine
Venetoclax
Ponatinib
Afatinib
Sunitinib
Dabrafenib
Erlotinib
Axitinib
Erlotinib
Erlotinib
Ixazomib
Afatinib
Niraparib
Nilotinib
Trametinib
Rituximab
Irinotecan
Lip-doxo
Cabazitaxel
Olaparib
Paclitaxel
Ixazomib
Capecitabine
Ipilimumab
Ramucirumab
Bortezomib
Vinorelbin

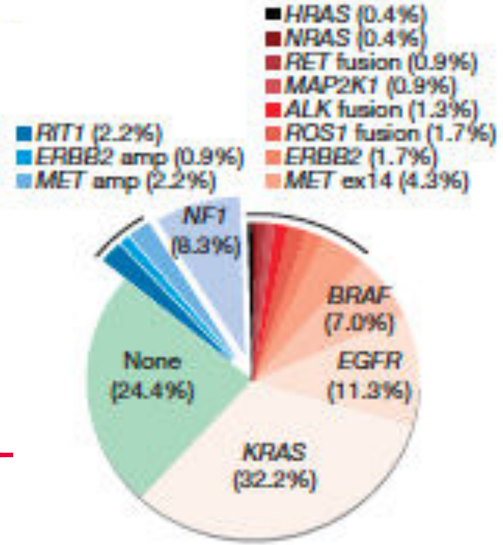
Target-spezifische Therapie

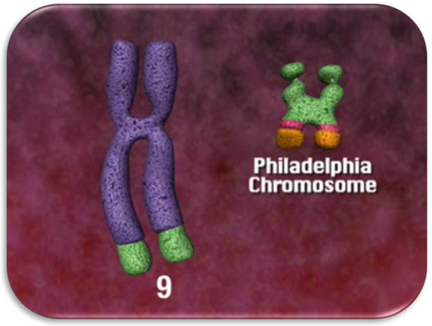
Vom Tumor zur Target-Mutation



NGS Illumina



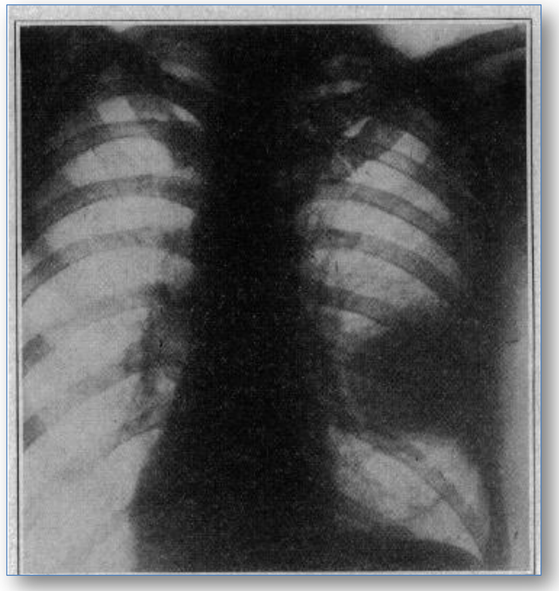




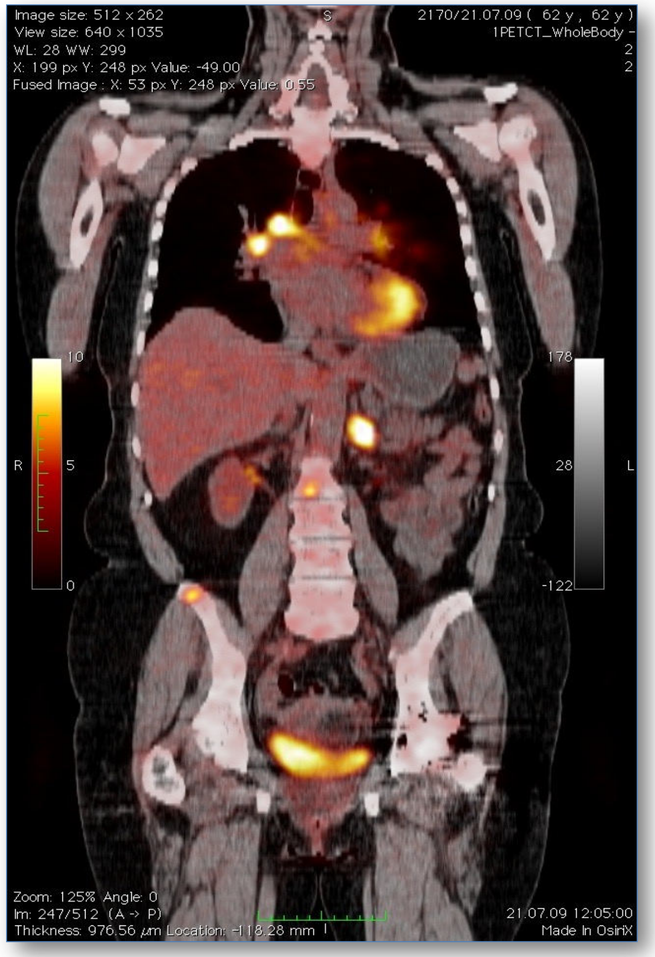
24 Stunden

Lungenkrebs - ein Umbruch

1936



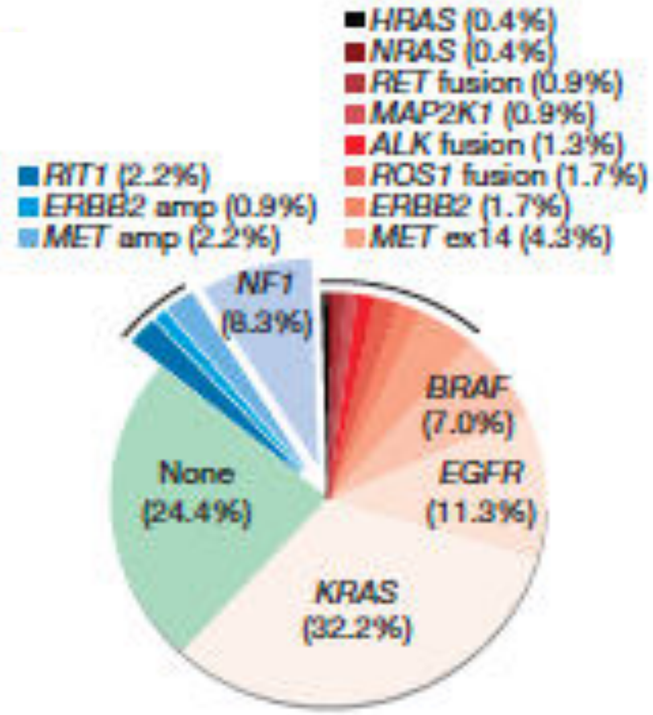
2022



ARTICLE OPEN
doi:10.1038/nature13385

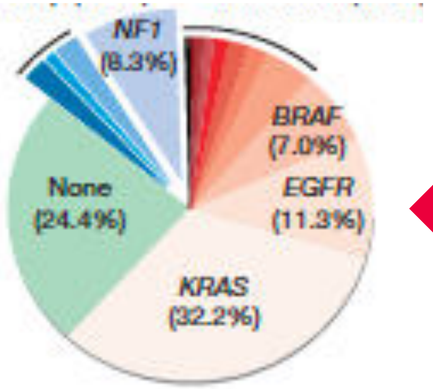
Comprehensive molecular profiling of lung adenocarcinoma

The Cancer Genome Atlas Research Network*



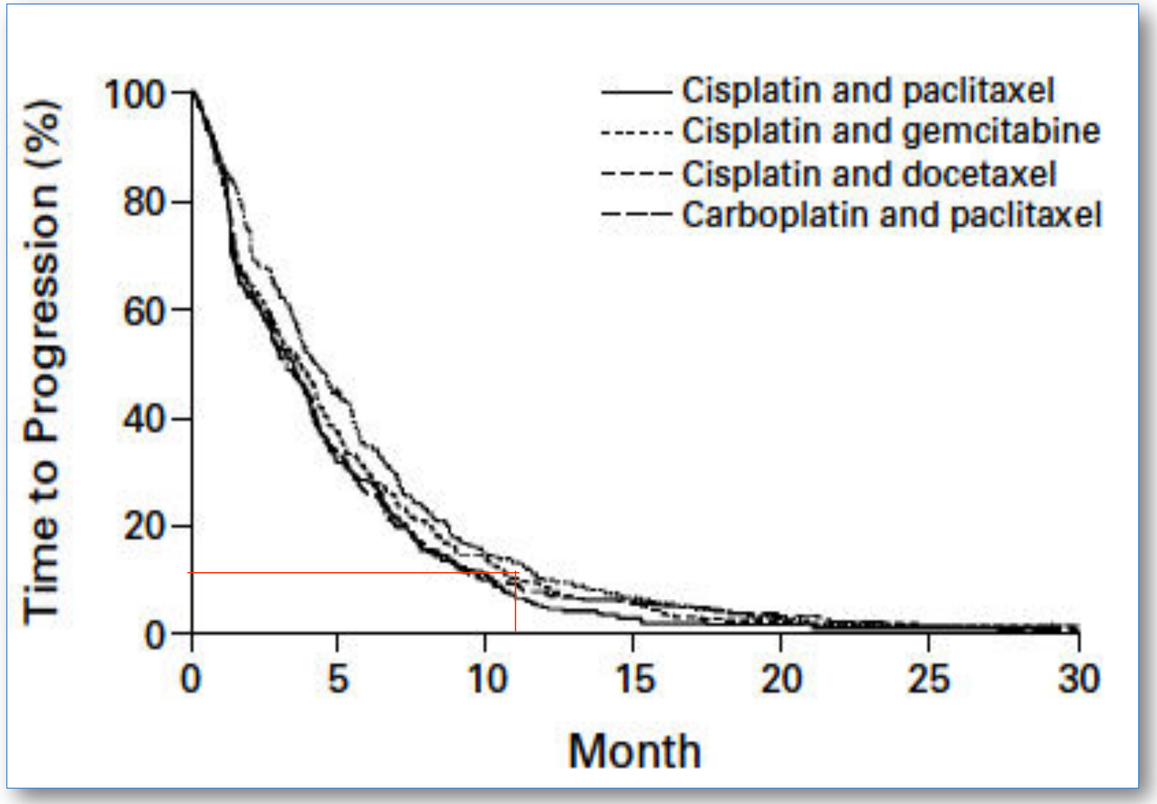
The Cancer Genome Atlas Research Network Nature 2014;511:543

Lungenkrebs



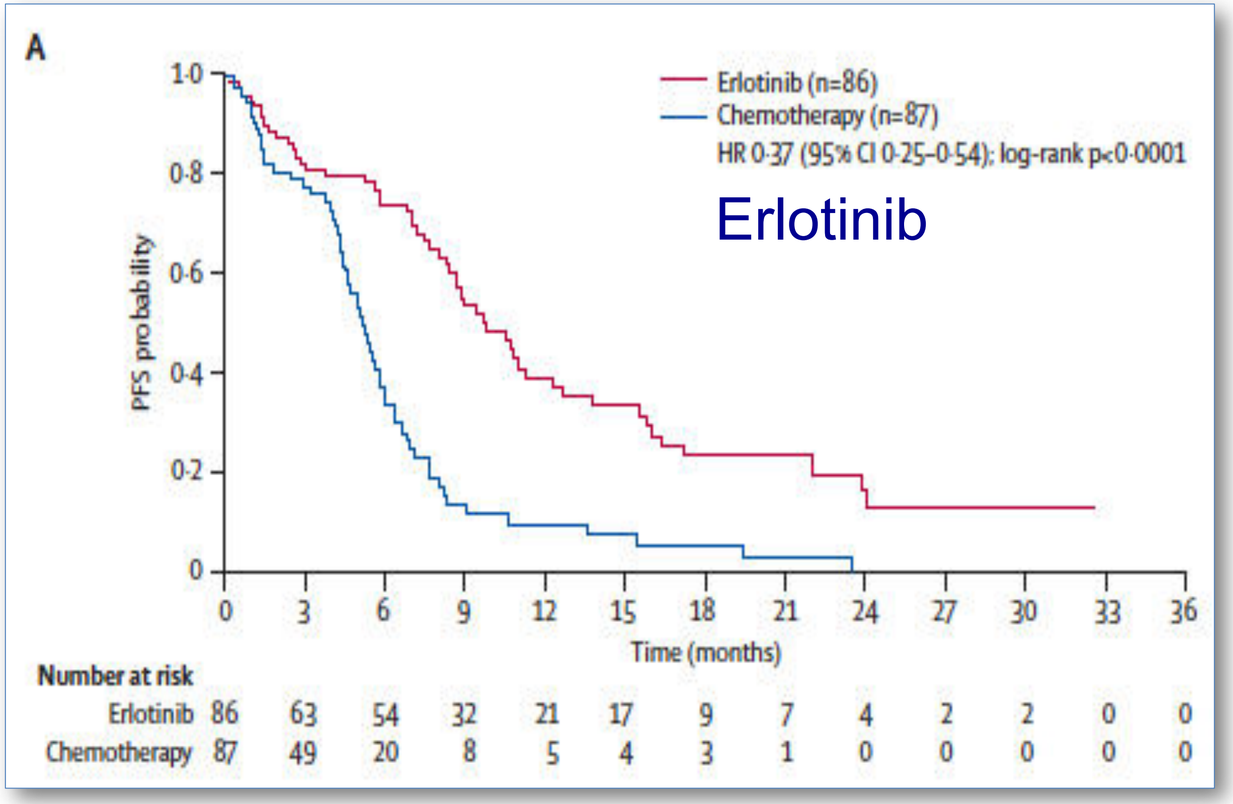
11,3%

2002



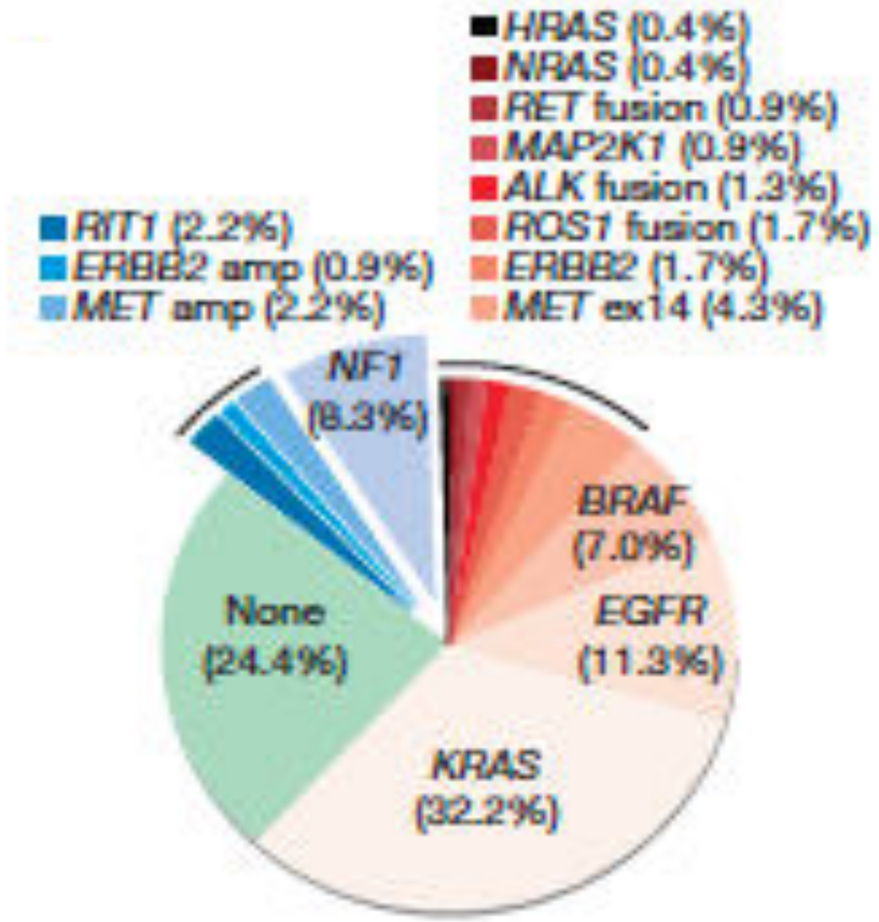
Schiller et el. NEJM 2002;346:92-98

2012



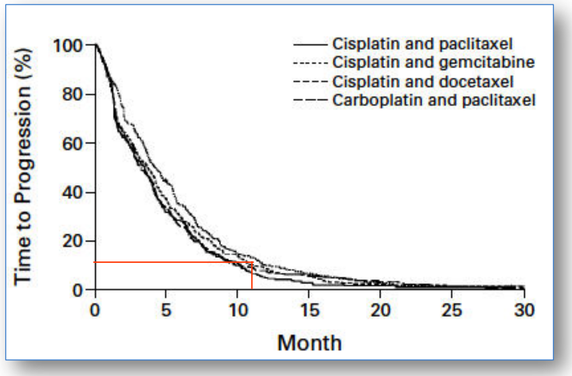
Rosell et al. Lancet Oncol 2012;13:239-46

Lungenkrebs



1,3%

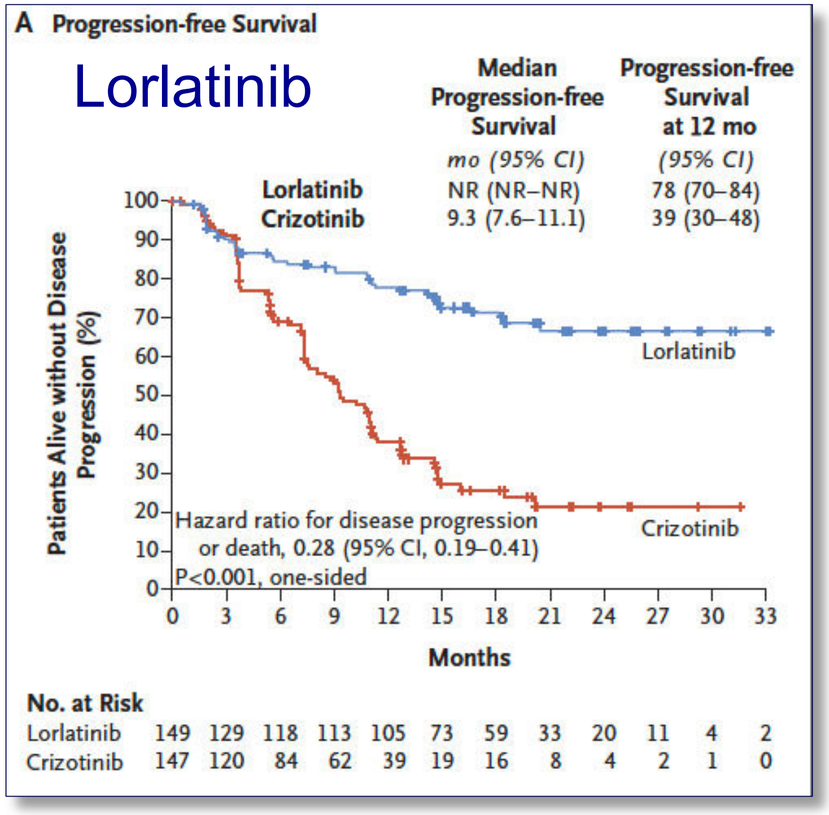
2002



Schiller et el. NEJM 2002;346:92-98

2020

Lorlatinib



Shaw et al. NEJM 2020:3843:2018-29

Lungenkrebs - Mutationsspezifische Therapien

	adjuvant	1st	2nd	3rd
EGF-R (Ex19/21)	Osimertinib (delEx19, Ex21 L858R)	Erlotinib Gefitinib Afatinib Osimertinib	Osimertinib (T790M)	Afatinib (Mutation Ex18 p.G724S)
EGF-R T790M		Osimertinib	Osimertinib	
EGF-R Exon (18)20			Mobocertinib Poziotinib	
ALK		Crizotinib Ceritinib Alectinib Brigatinib	Ceritinib (nach Crizotinib) Lorlatinib Brigatinib (nach Crizotinib)	Lorlatinib
ROS-1		Crizotinib	Lorlatinib	
B-RAF V600E		Dabrafenib+Trametinib		
RAS p.G12C		Sotorasib		
MET Ex14		Tepotinib Capmatinib	Tepotinib Capmatinib	
HER2 (ERBB2)			Trastuzumab-Deruxtecan	
NTRK			Larotrectinib	
RET			Selpercatinib Pralsetinib	

Immuntherapie

Immuntherapeutische Strategien

Immuntherapie 2004

nature medicine

PERSPECTIVE

2,6 %

Cancer immunotherapy: moving beyond current vaccines

Steven A Rosenberg, James C Yang & Nicholas P Restifo

Great progress has been made in the field of tumor immunology in the past decade, but optimism about the clinical application of currently available cancer vaccine approaches is based more on surrogate endpoints than on clinical tumor regression. In our cancer vaccine trials of 440 patients, the objective response rate was low (2.6%), and comparable to the results obtained by others. We consider here results in cancer vaccine trials and highlight alternate strategies that mediate cancer regression in preclinical and clinical models.

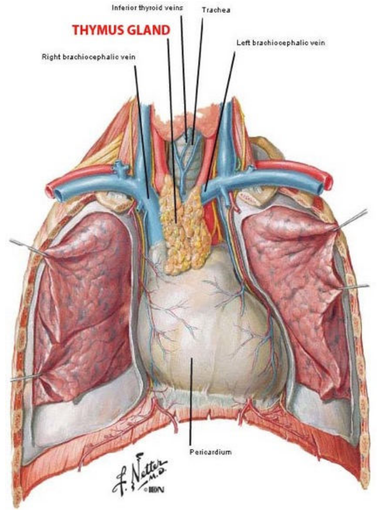
patients who achieved clinical responses, many cancer vaccine trials have been optimistically reported because surrogate or subjective endpoints were achieved. Sensitive techniques such as tetramer or ELISpot assays have been used to demonstrate the generation *in vivo* of antitumor T cells in vaccinated patients, but the scarcity of clinical responses in these patients has made it difficult to validate any of these assays as a useful surrogate of clinical response.

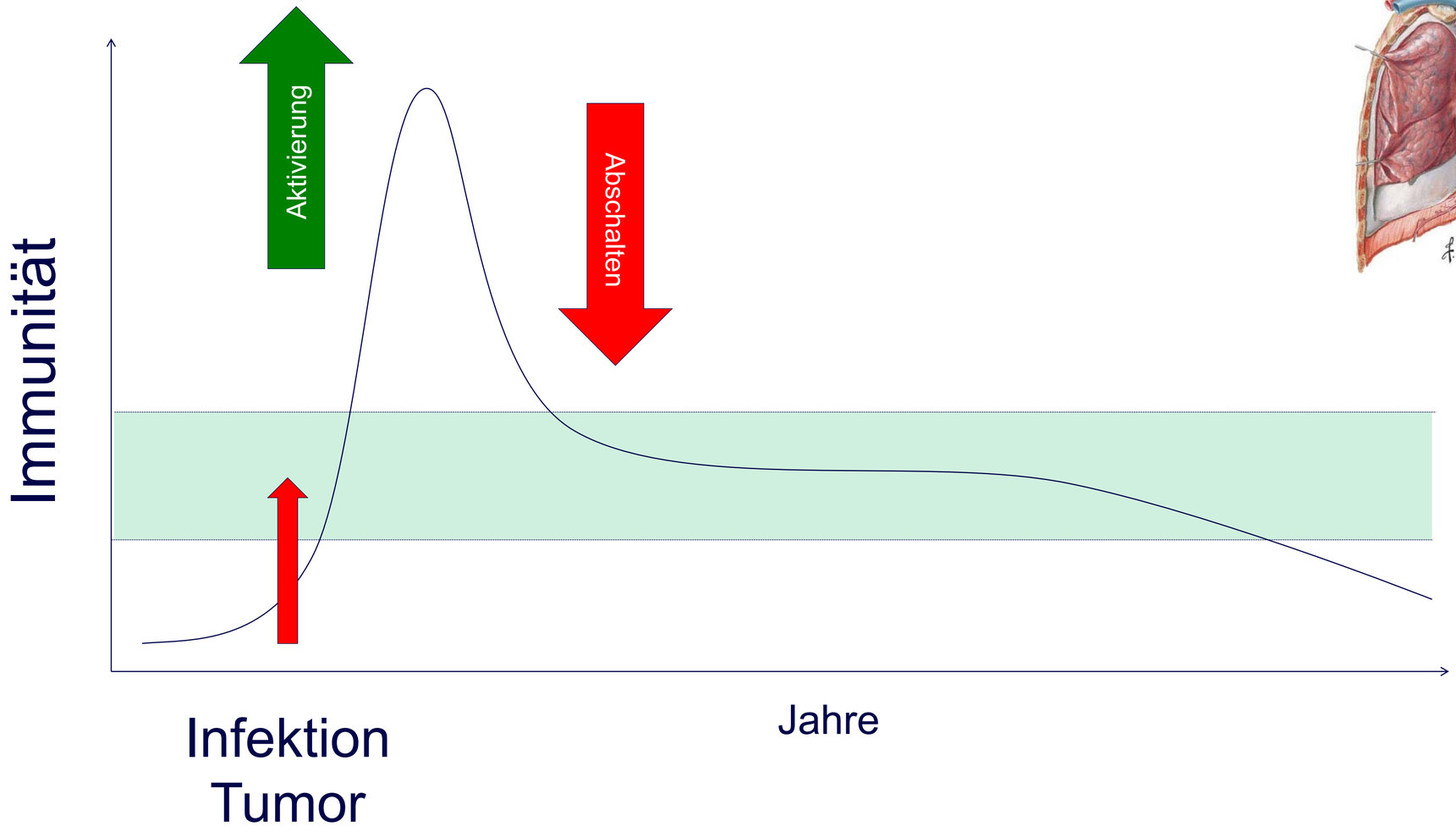
Analysis of trials using standard oncologic criteria

Standard oncologic criteria for evaluating and reporting objective clinical responses to treatment are well established in oncology, and

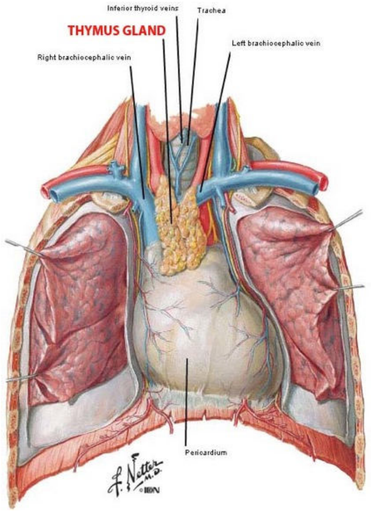
Rosenberg et al. Nat Med 2004;10:909-15

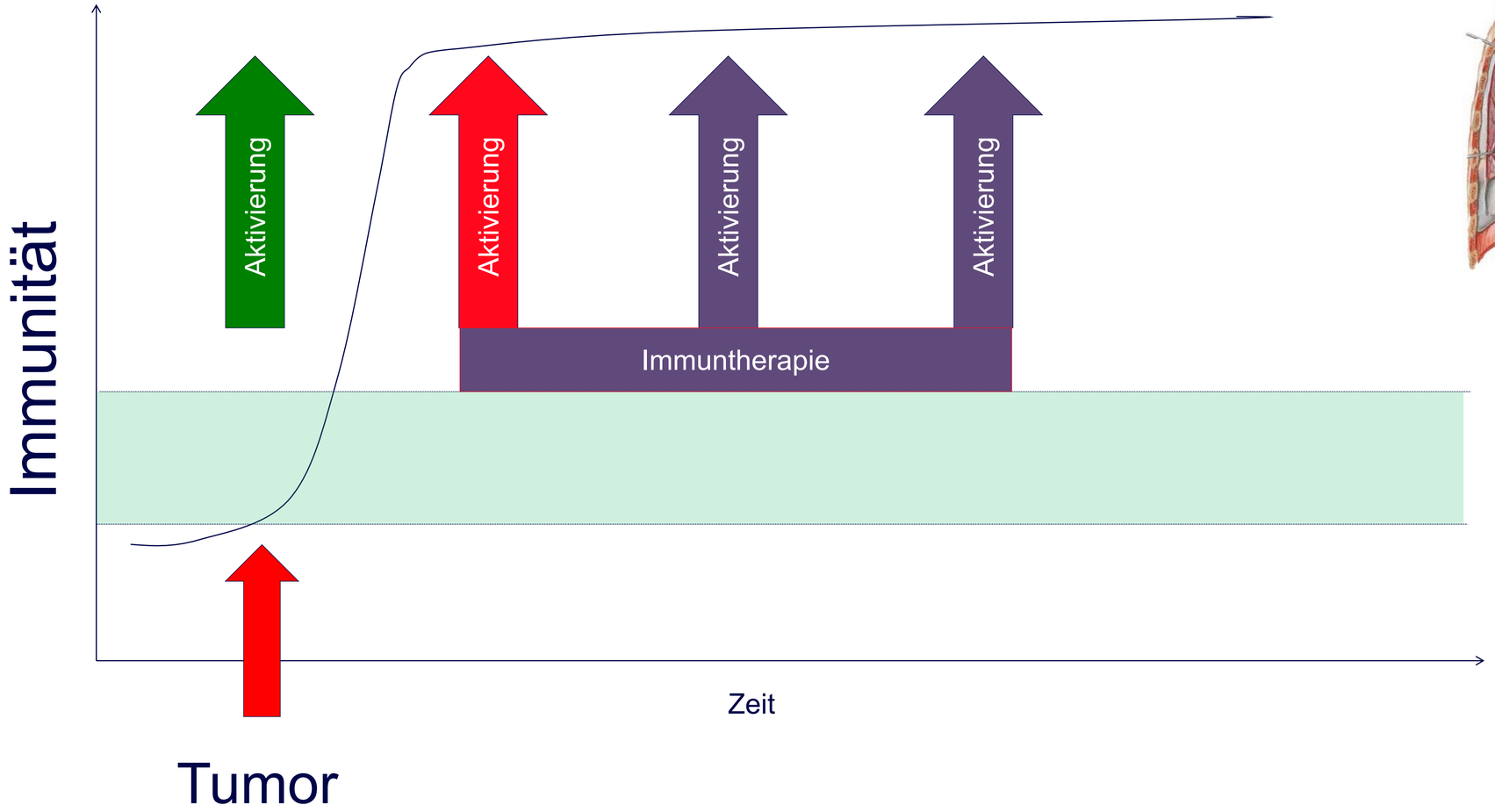
An- und Abschalten der Immunität



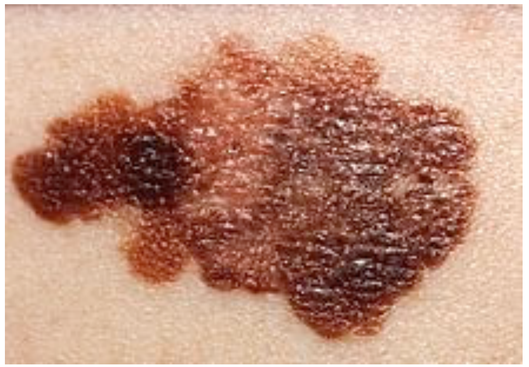


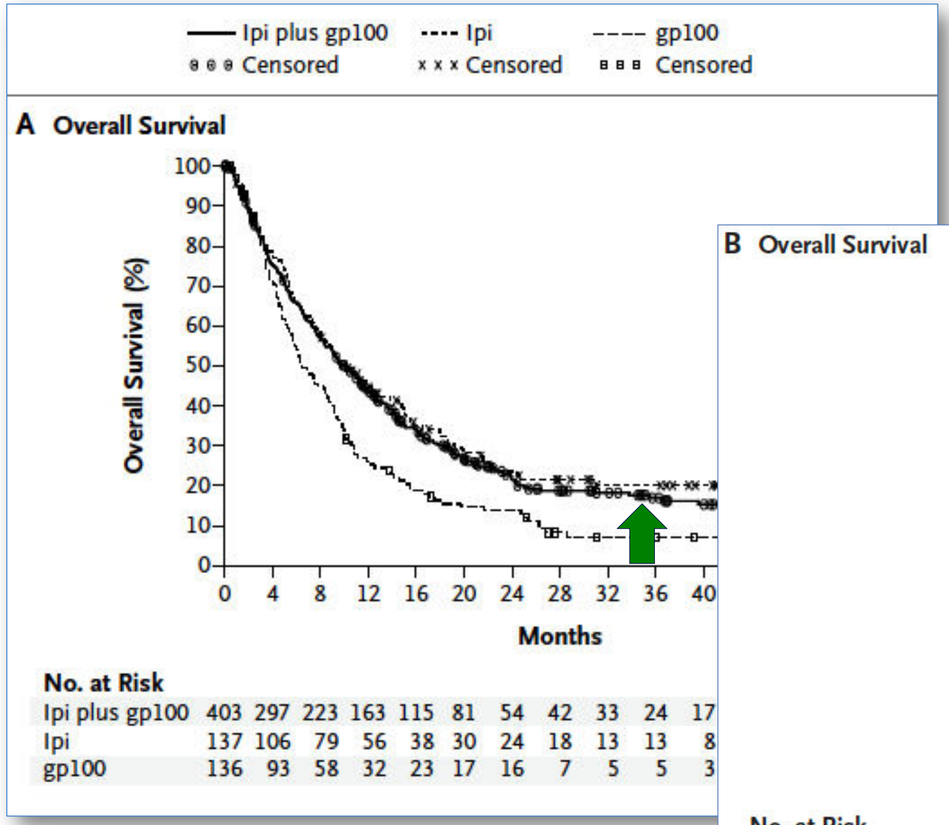
Aktivierung der Immunität durch Immuntherapie

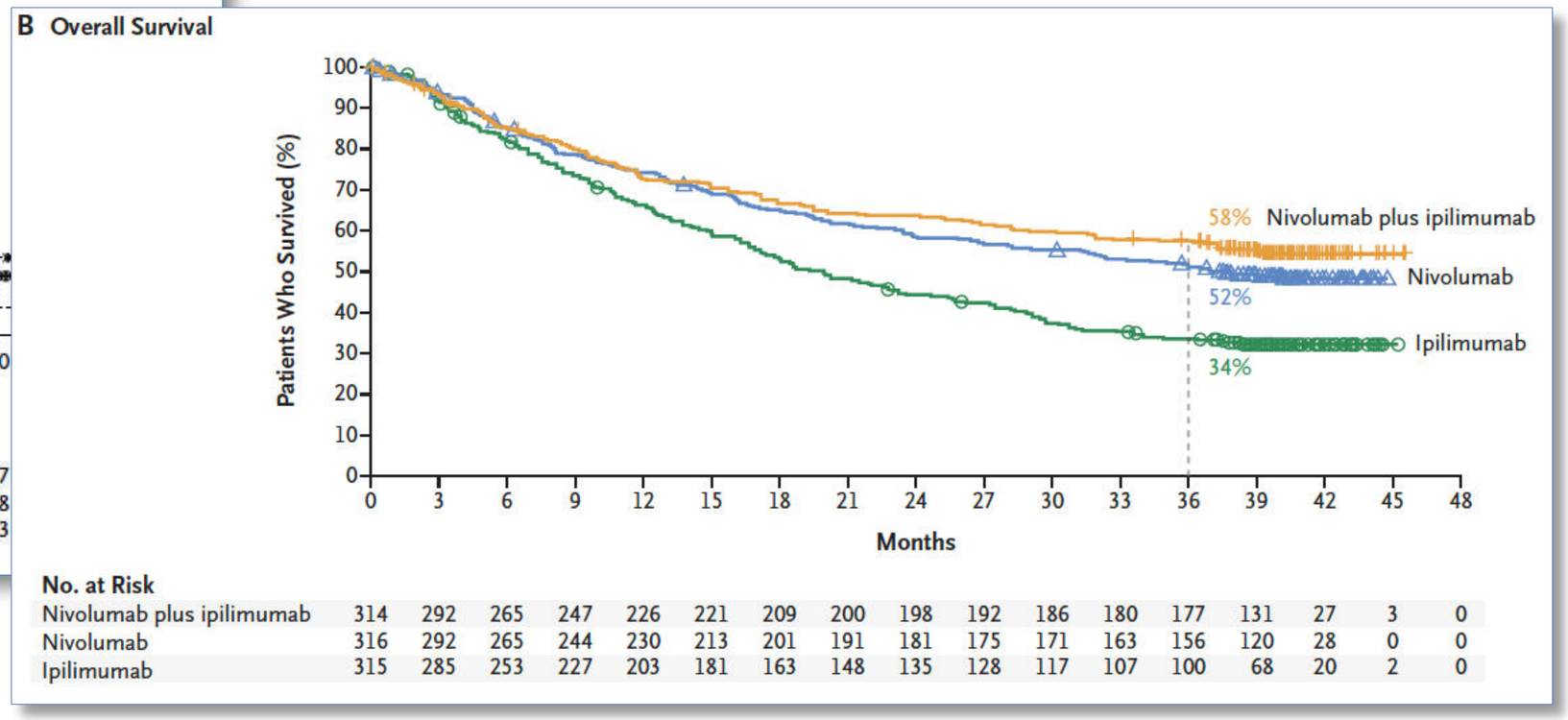




Melanom





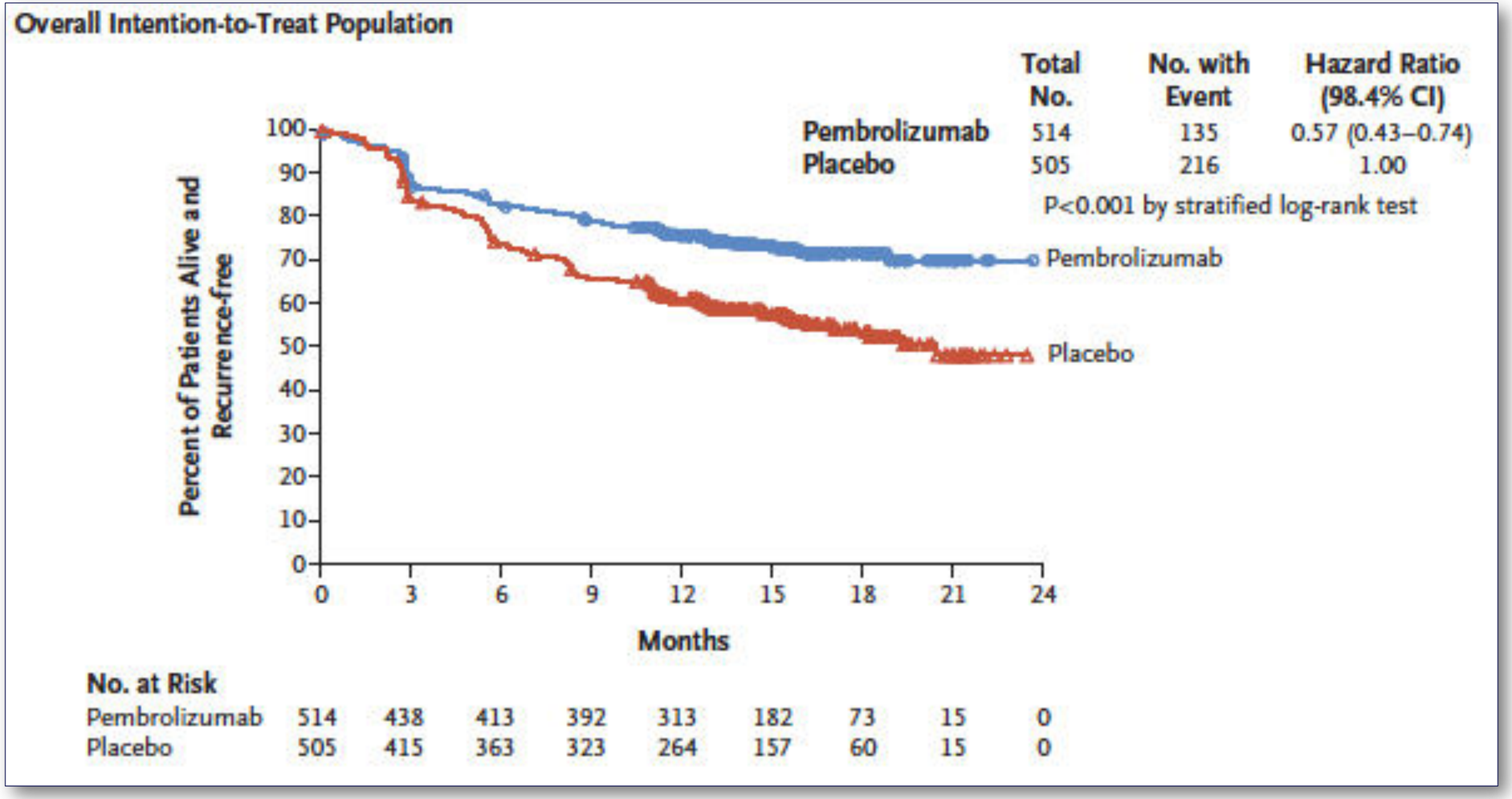


Hodi et al. NEJM 2010;363:711-23

Wolchok et al. NEJM 2017;377:1345-56

Immuntherapie adjuvant - Melanom

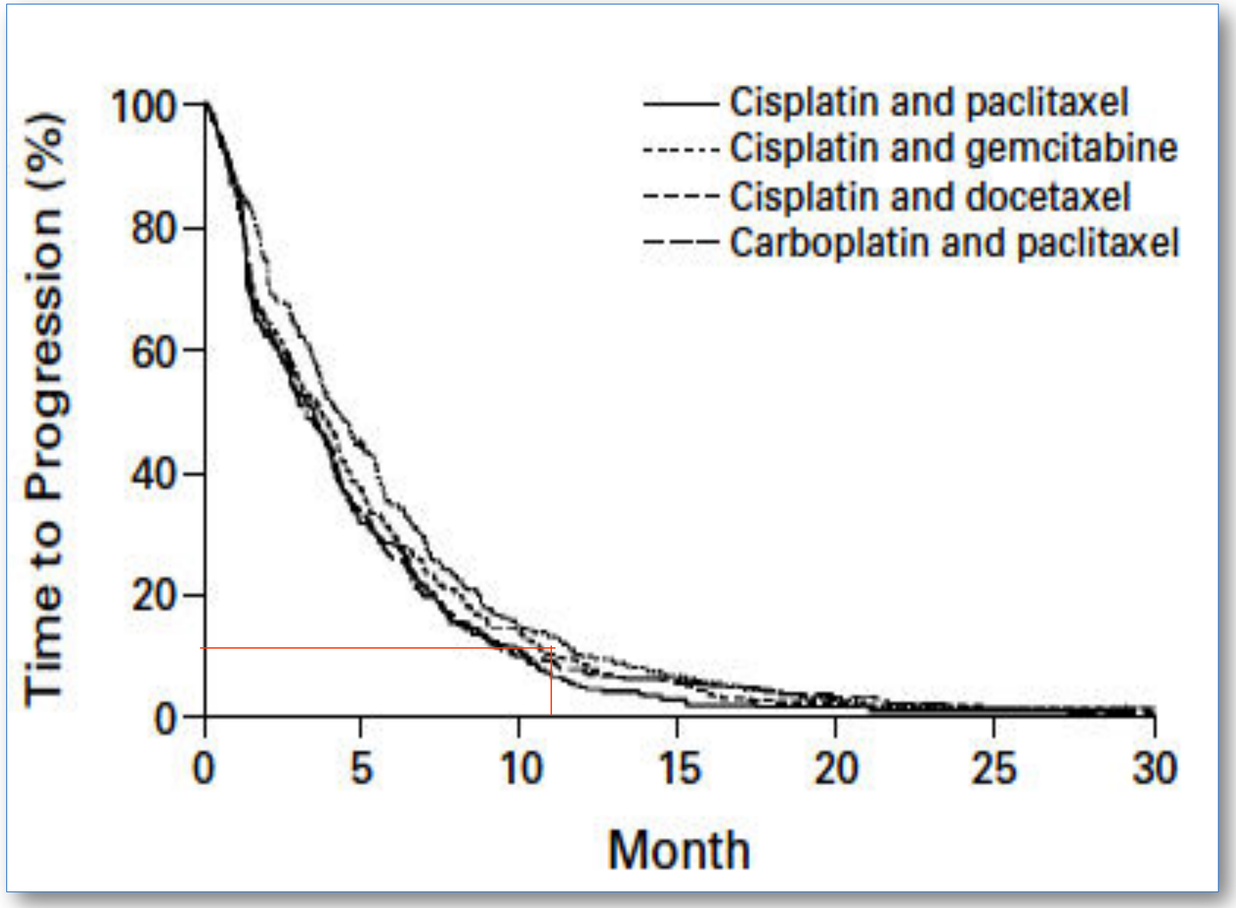
Phase III-Studie Malignes Melanom Stadium III (T1-4b N1-3 M0)

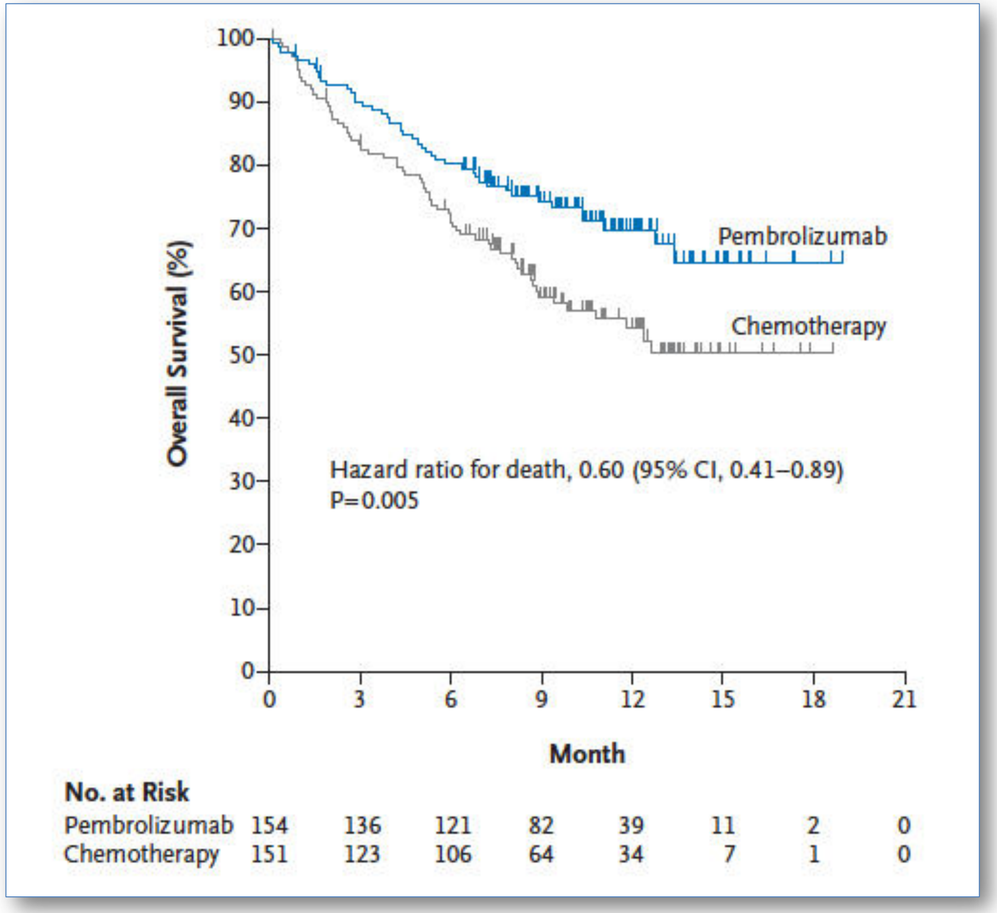


Eggermont et al. NEJM 2018;378:1789-801

Lungenkrebs - Immuntherapie - PDL1-Blockade

NSCLC N=305, PDL1-Expression > 50%: Platin+X vs. Pembrolizumab

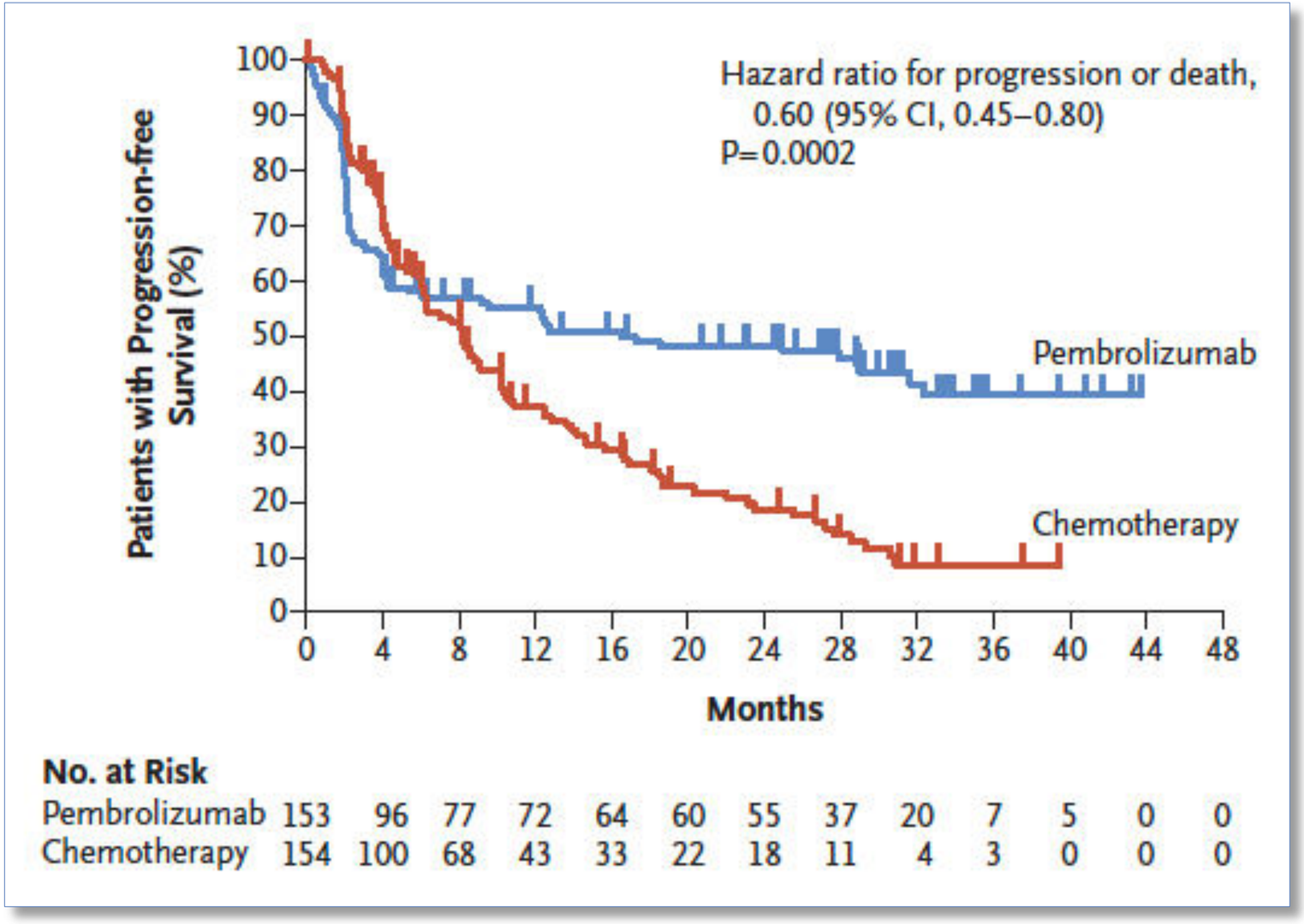




Schiller et el. NEJM 2002;346:92-98

Reck et el. NEJM 2016;375:1823-33

Darmkrebs - MSI-dMMR

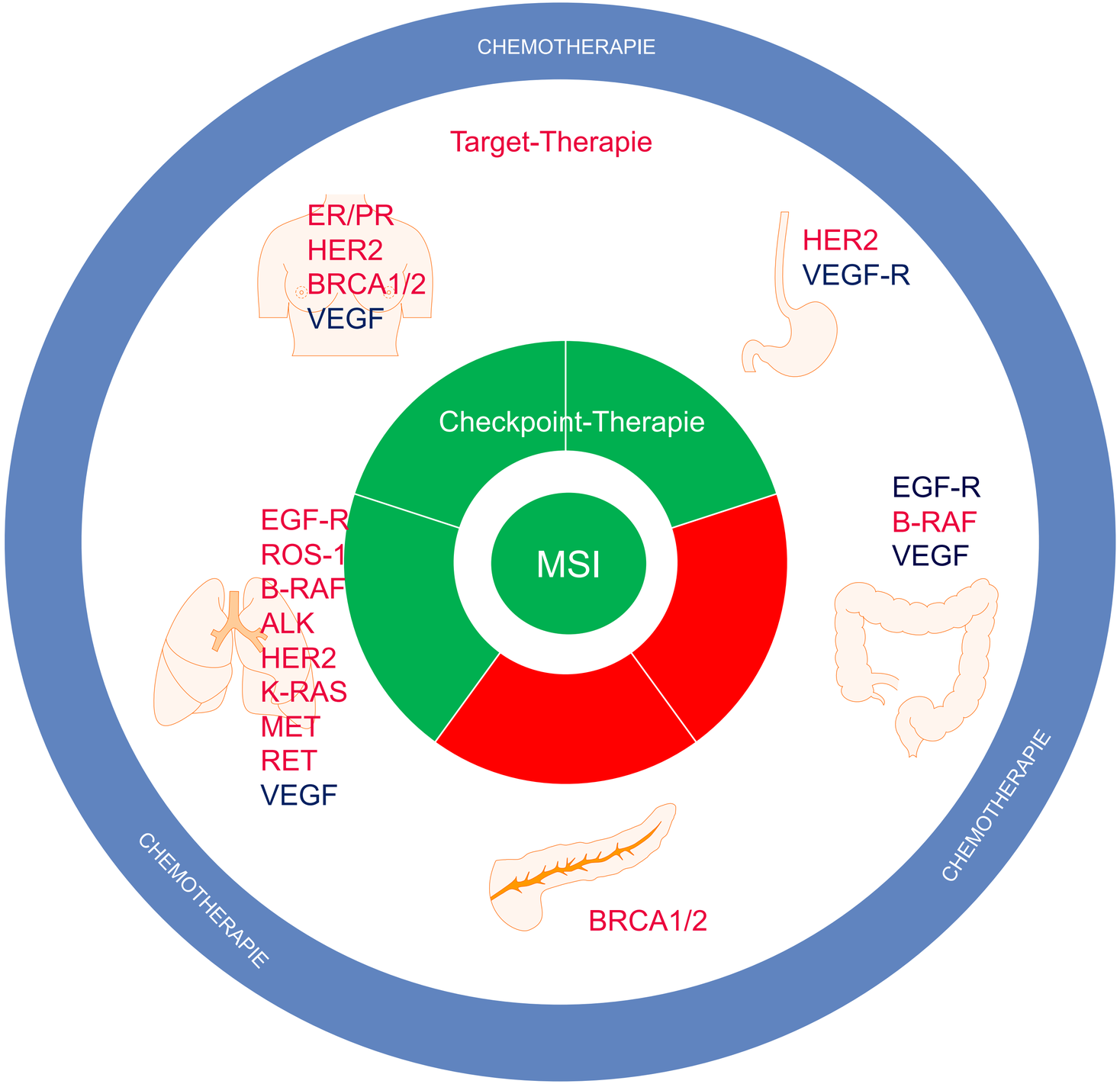


Andre et al. NEJM 2020;383:2207-18

Immuntherapie 2022

Immuntherapie 2022		Melanom	Merkelzell-Karzinom	Plattenepithel-karzinom der Haut	Basalzellkarzinom	Lungenkrebs NSCLC Adeno	Lungenkrebs NSCLC Platte	Lungekrebs SCLC	Pleurameotheliom	Brustkrebs TNBC	Ösopahgus-karzinom/AEG	Magenkarzinom	Darmkrebs MSI-high	HCC	Nierenkrebs	Urothel-karzinom	Kopf-Hals-Krebs	Endometrium-karzinom	M. Hodgkin
Ipilimumab Yervoy®	CTLA-4	+				+	+		+				+ 2nd		+				
Nivolumab Opdivo®	PD-1	+				+	+		+		+	(+)	+ 2nd		+	+	+		+
Pembrolizumab Keytruda®	PD-1	+				+	+				+		+ 1st		+	+	+		+
Avelumab Bavenico®	PD-L1		+												+				
Durvalumab Imfinzi®	PD-L1					+	+												
Atezolizumab Tecentric®	PD-L1					+		+		+				+		+			
Cemiplimab Libtayo®	PD-L1			+	+	+	+												
Dostarlimab Jemperli®	PD-1																	+	

Systemtherapie 2023



Target-spezifisch
Mutations-spezifisch

Immuntherapie

Haut

Augen

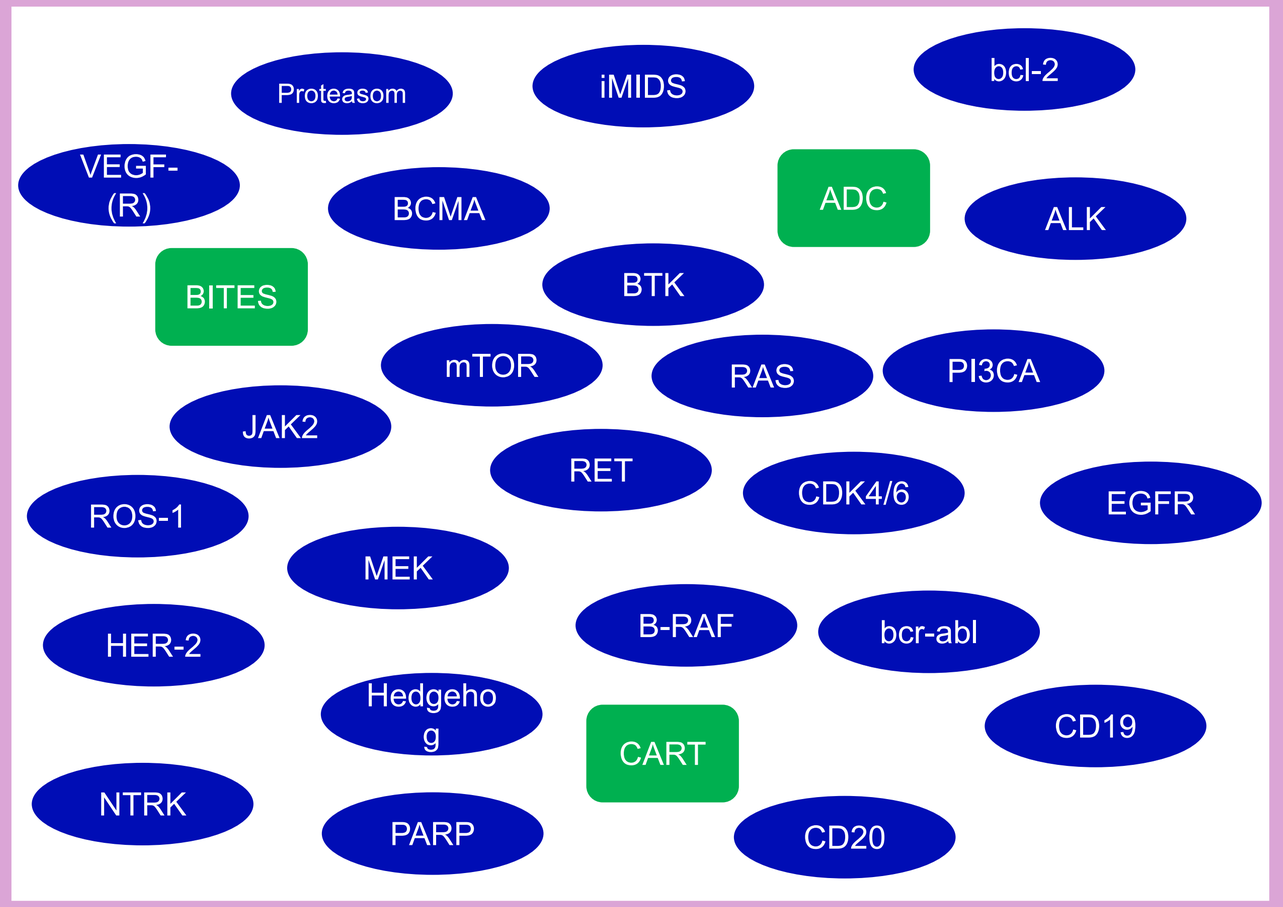
Hormone

ZNS

Nerven

Herz

Thromb-Embolien



Darm

Niere

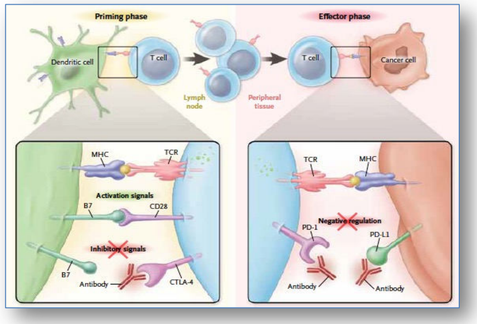
Leber

Lunge

Blutbild

Immunsystem

Fatigue



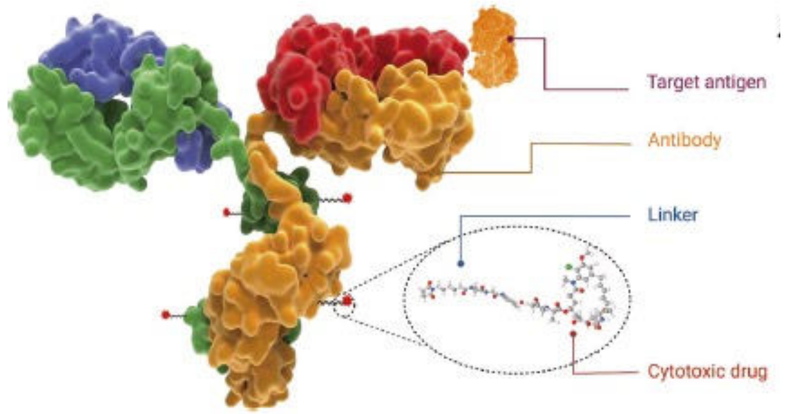
Immun-Therapie

Molekulare Target-Therapie

Konventionelle Therapie

2005 2010 2015

Antikörper – Drug – Konjugate (ADC)



ADC (Antibody Drug Conjugate)

Signal Transduction and Targeted Therapy

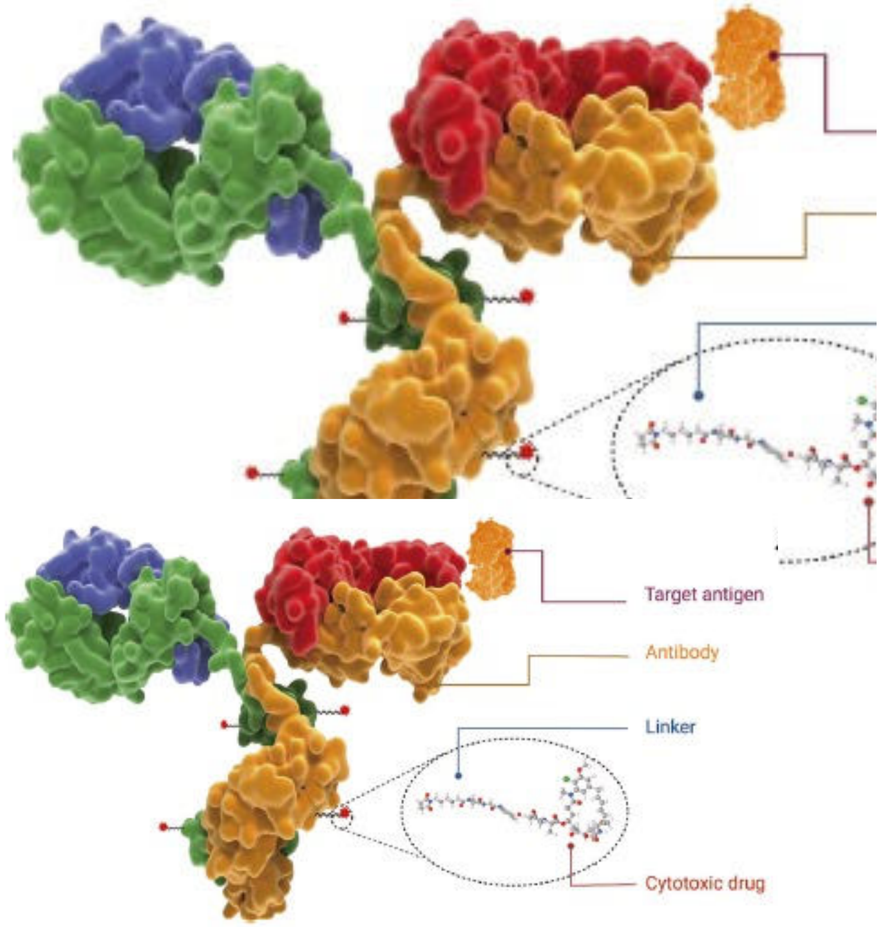
www.nature.com/sigtrans

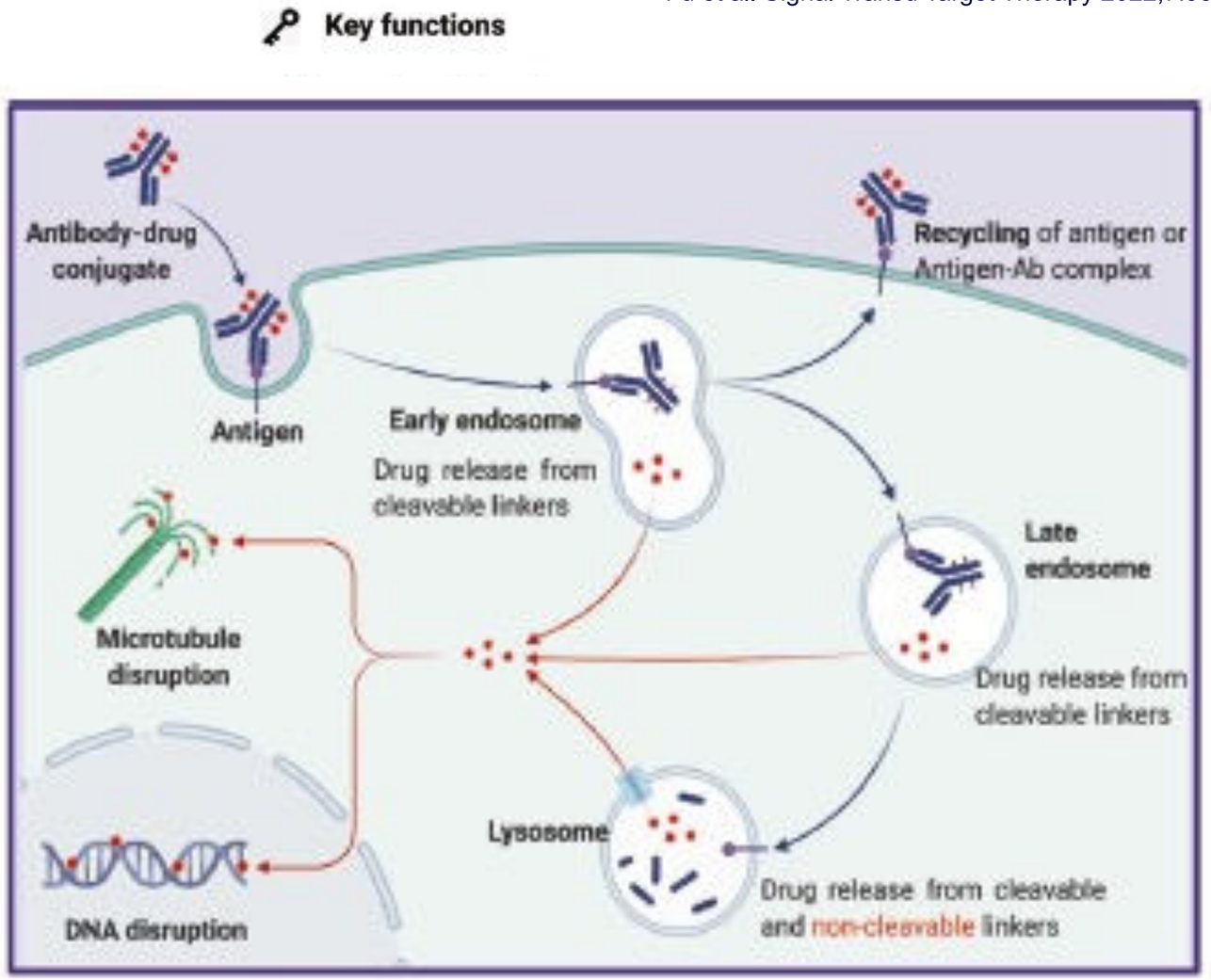
REVIEW ARTICLE OPEN

Antibody drug conjugate: the "biological missile" for targeted cancer therapy

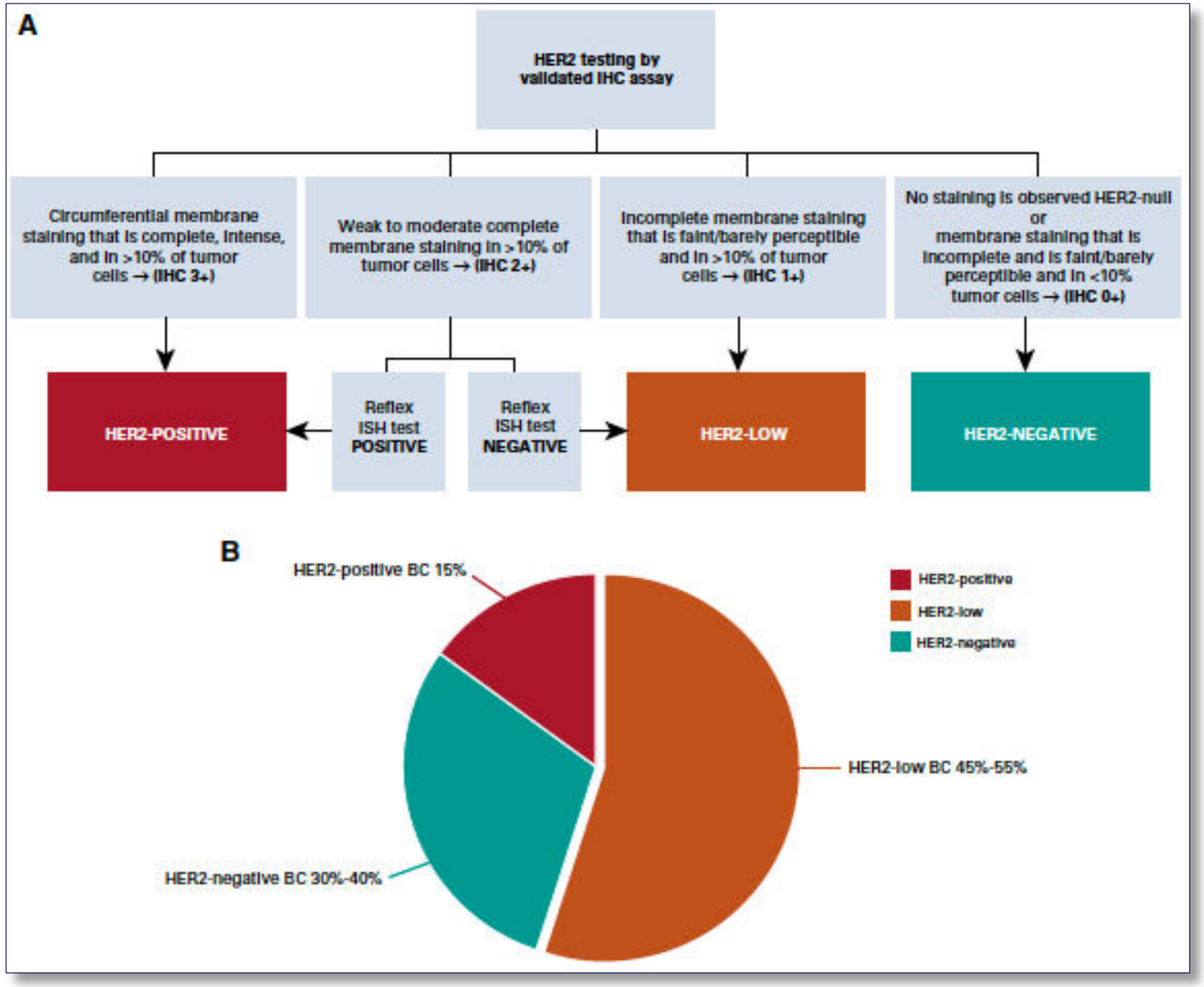
Zhiwen Fu[1,2], Shijun Li[1,2], Sifei Han[3,4], Chen Shi[1,2]✉ and Yu Zhang[1,2]✉

Fu et al. Signal Transd Target Therapy 2022;7:93





HER-low positives Mammakarzinom



Tarantino et al. JCO 2020;38:1951-62

HER-low positives Mammakarzinom

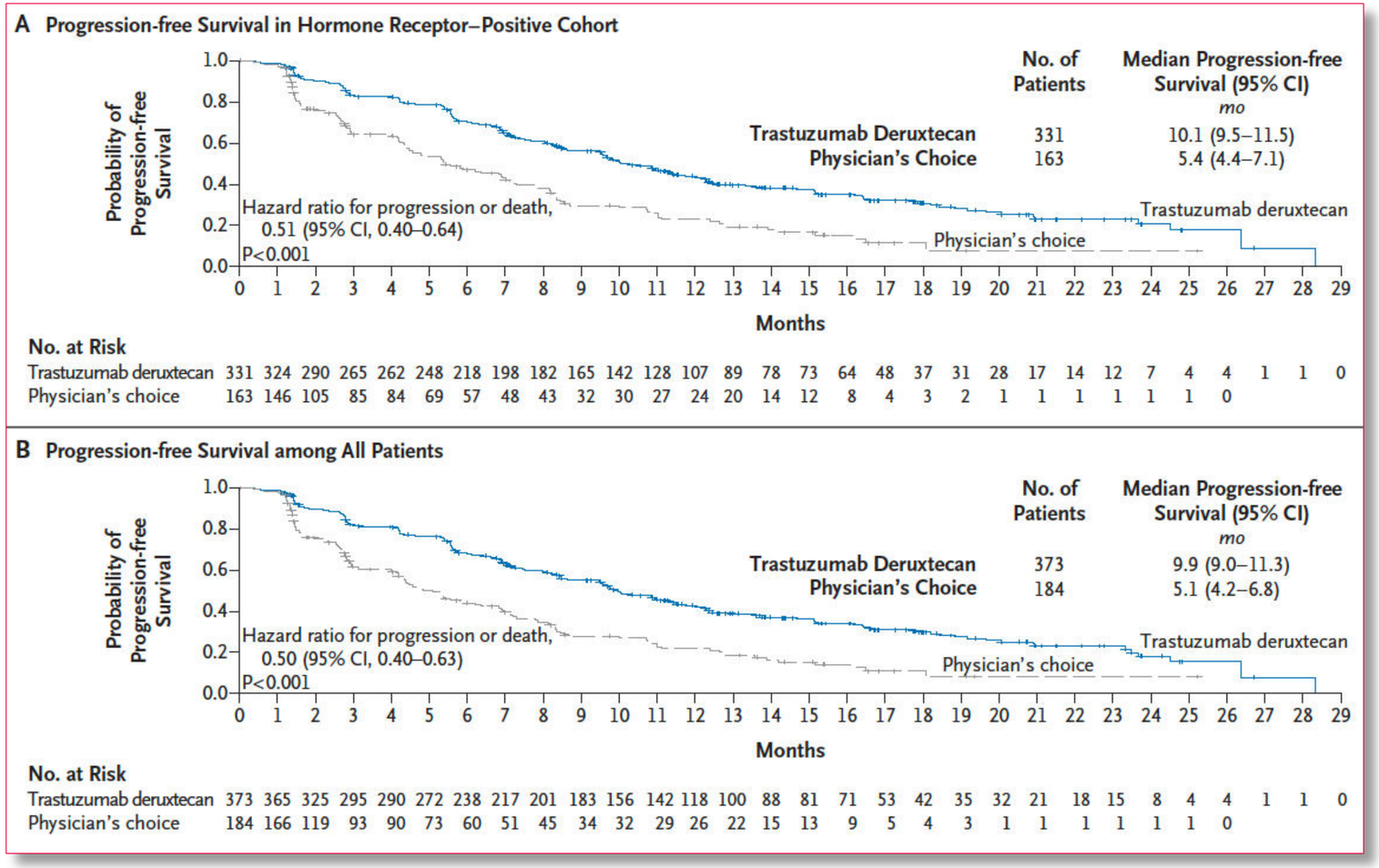
Trastuzumab Deruxtecan (TDx)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

≥2. Linie; HER2 ICH 1+/2+; überwiegend HR positiv



Modi et al. NEJM 2022;387:9-20

HER-low positives Mammakarzinom
Trastuzumab Deruxtecan (TDx)

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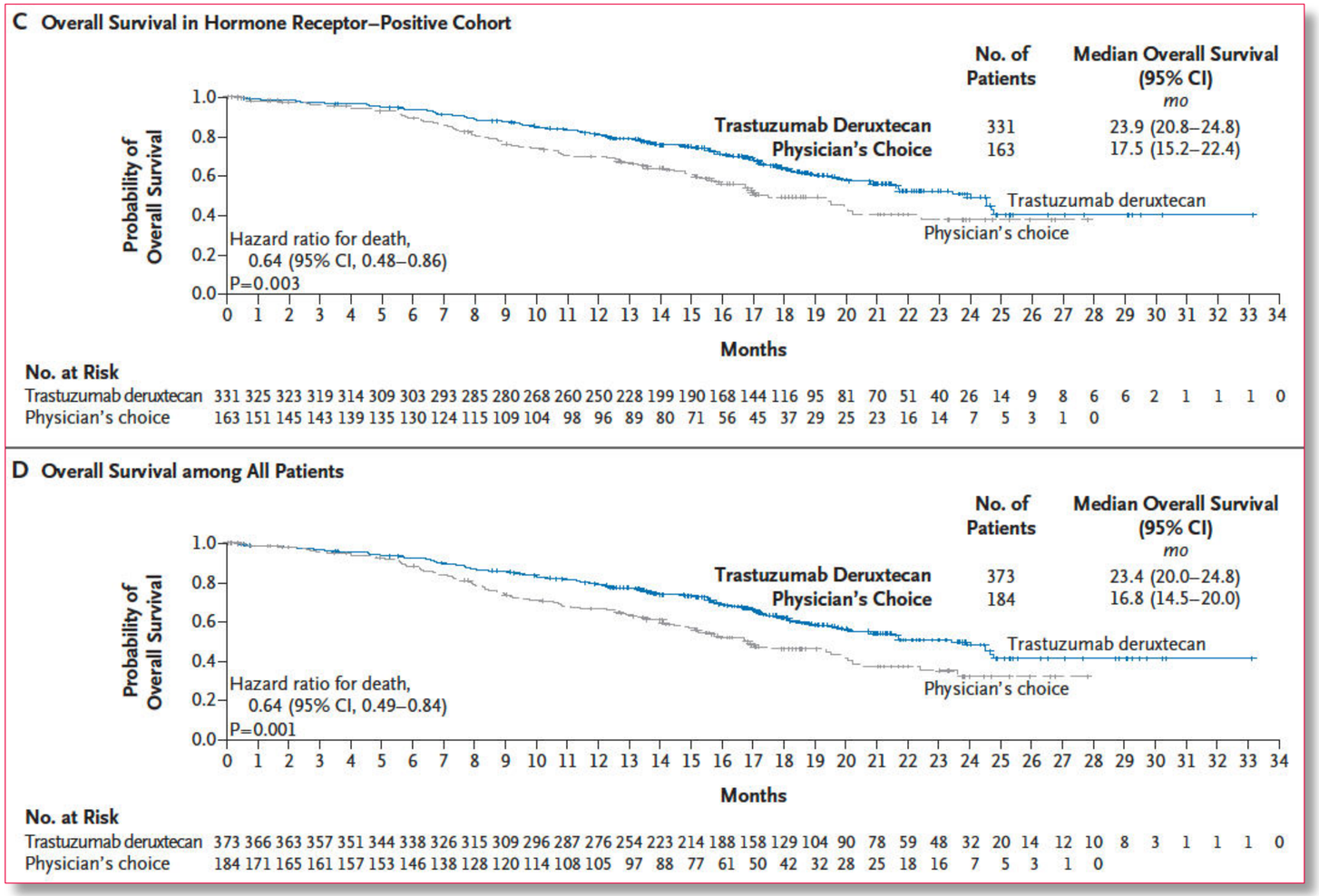
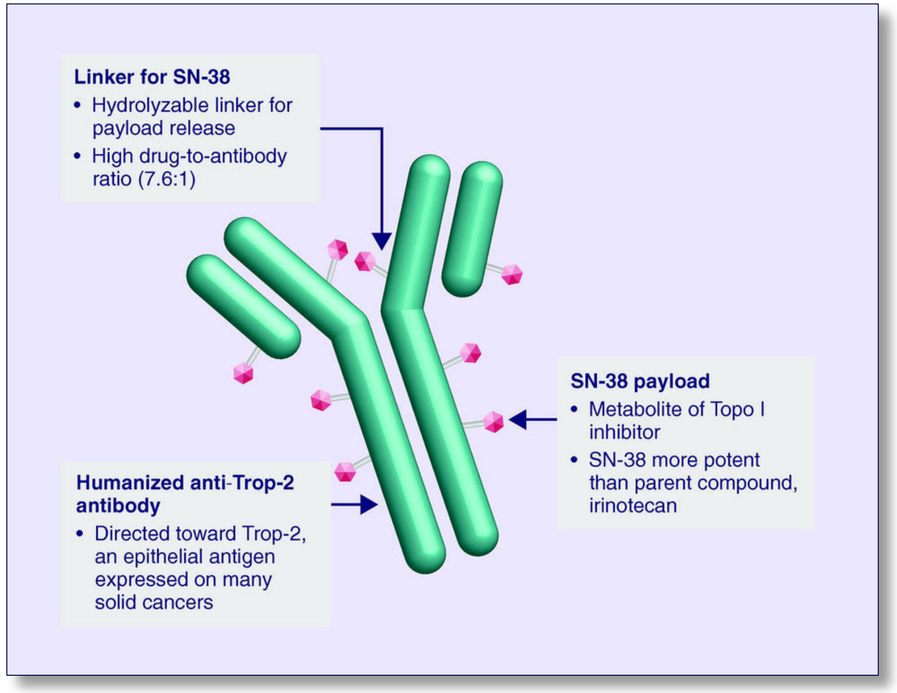


Modi et al. NEJM 2022;387:9-20

Triple negatives Mammakarzinom

ADC (Antikörper-Drug-Conjugat)

Sacituzumab-Govitecan ≥2. Linie

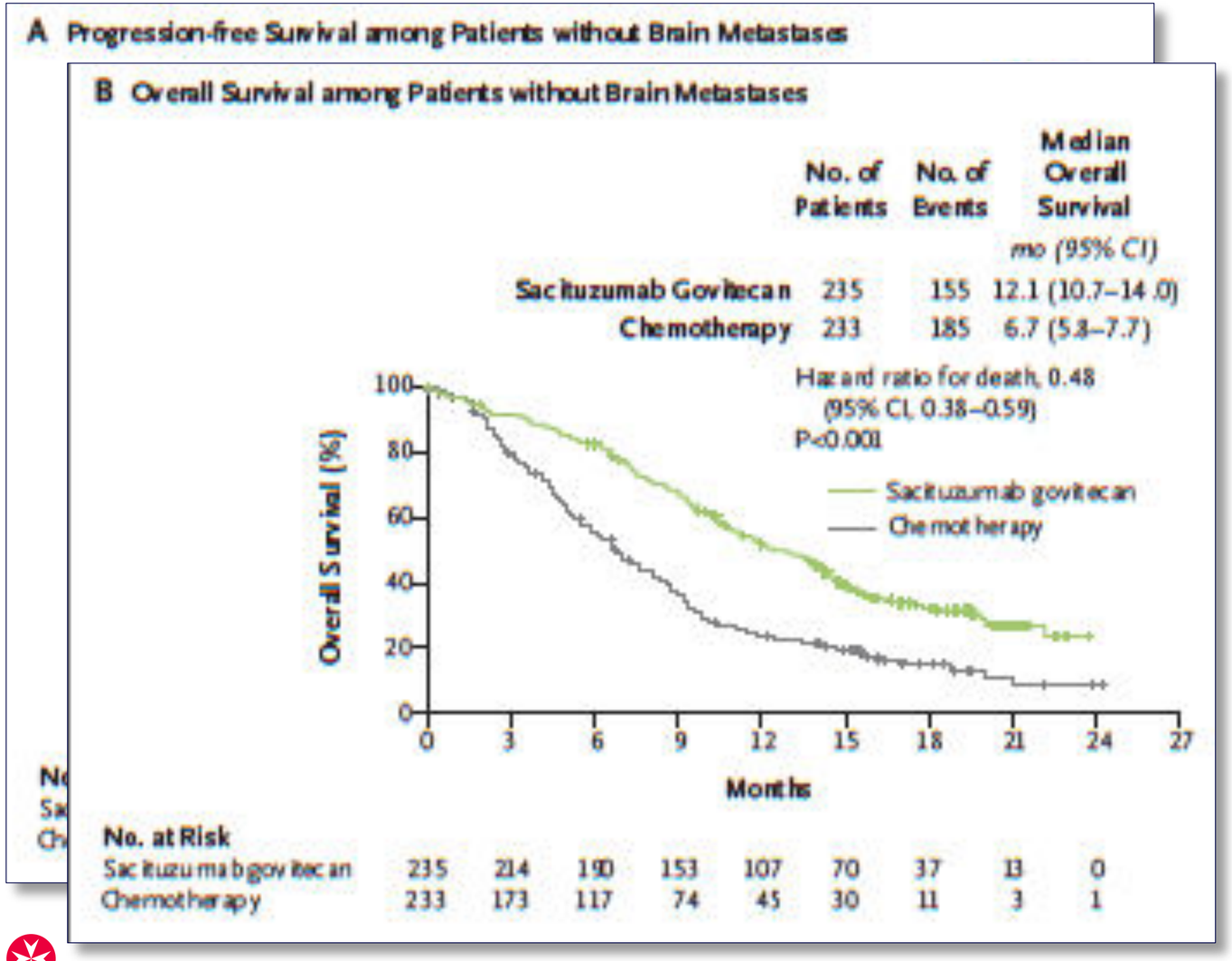


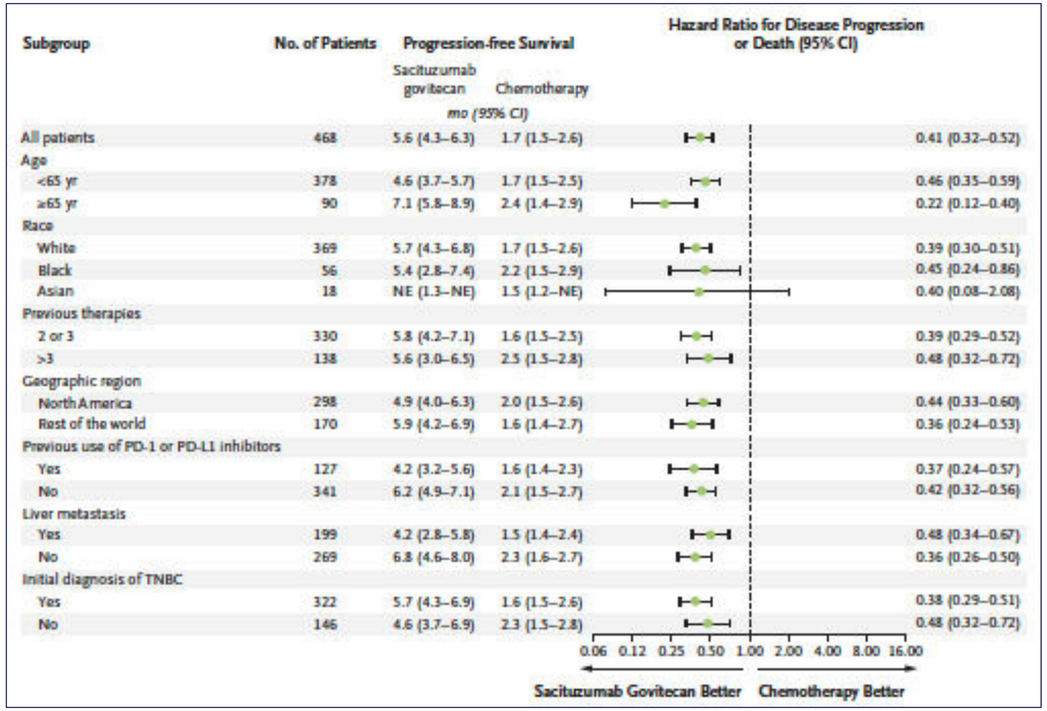
Characteristic	Sacituzumab Govitecan (N=235)	Chemotherapy (N=233)†
Sex — no. (%)		
Female	233 (99)	233 (100)
Male	2 (1)	0
Median age (range) — yr	54 (29–82)	53 (27–81)
Race or ethnic group — no. (%)‡		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG performance-status score at screening — no. (%)§		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
Germline *BRCA1* or *BRCA2* mutation status — no. (%)¶		
Negative	133 (57)	125 (54)
Positive‖	16 (7)	18 (8)
Triple-negative breast cancer at initial diagnosis — no. (%)		
Yes	165 (70)	157 (67)
No**	70 (30)	76 (33)
Median time from diagnosis of metastatic disease to enrollment (range) — mo††	15.8 (0–202.9)	15.2 (0–140.1)
Major tumor locations — no. (%)‡‡		
Lung	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Axillary lymph nodes	57 (24)	73 (31)
Bone§§	48 (20)	55 (24)
Median no. of previous anticancer regimens (range) ¶¶	3 (1–16)	3 (1–12)
Previous chemotherapy regimens — no. (%)		
2 or 3	166 (71)	164 (70)
>3	69 (29)	69 (30)
Previous chemotherapy drugs — no. (%)‖‖		
Taxanes	235 (100)	233 (100)
Anthracyclines	191 (81)	193 (83)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Previous use of PARP inhibitors — no. (%)	17 (7)	18 (8)
Previous use of PD-1 or PD-L1 inhibitors — no. (%)	67 (29)	60 (26)

Bardia et al. NEJM 2021;DOI:https//doi.org/10.1056/NEJMoa2028485

Triple negatives Mammakarzinom

ADC (Antikörper-Drug-Conjugat)





Neutropenie

Diarrhoen

Urothelkarzinom
Enfortumab-Vedotin

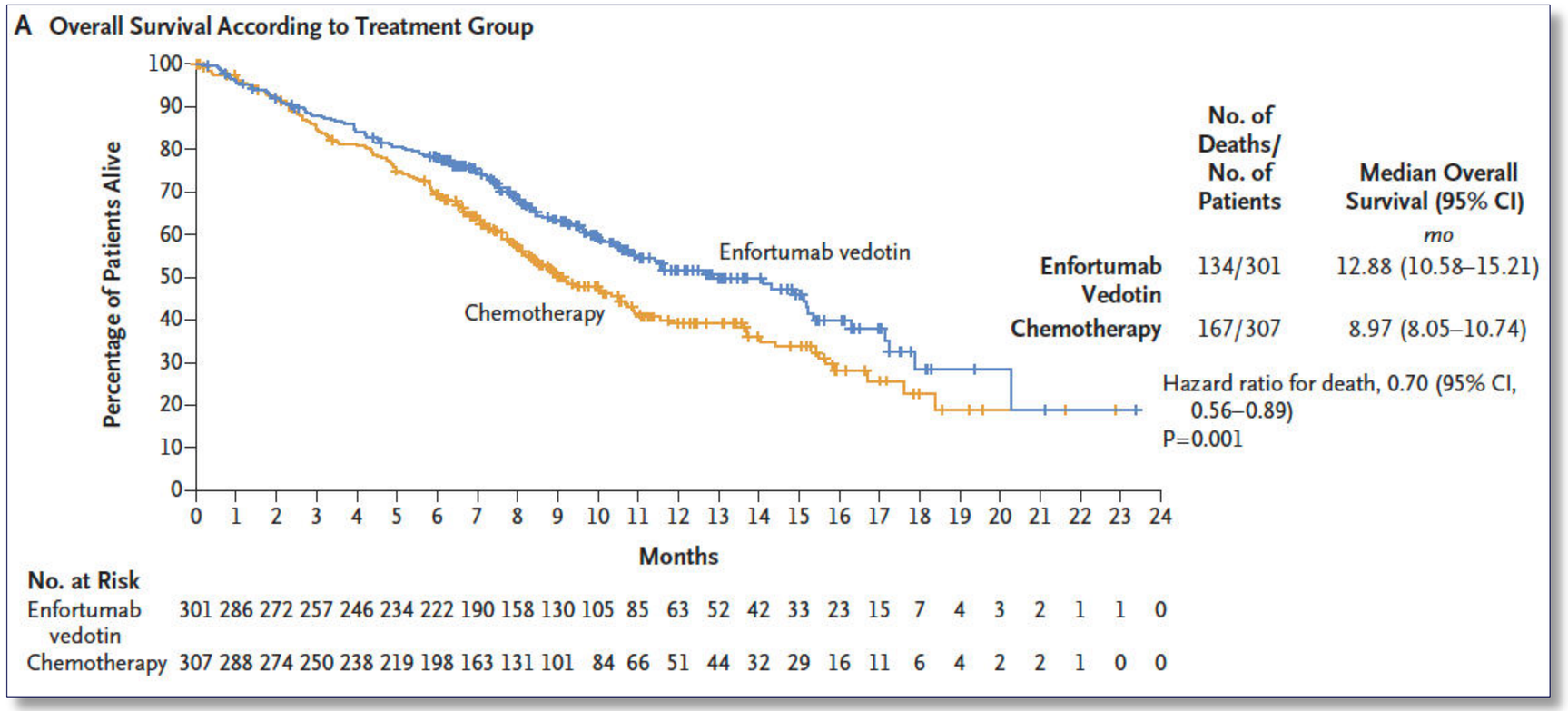
nach Chemotherapie und Immuntherapie

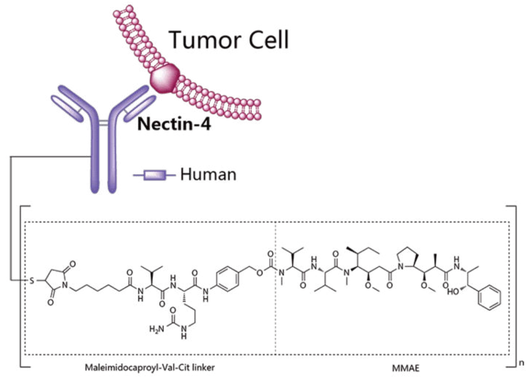
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

Thomas Powles, M.D., Jonathan E. Rosenberg, M.D., Guru P. Sonpavde, M.D., Yohann Loriot, M.D., Ph.D., Ignacio Durán, M.D., Ph.D., Jae-Lyun Lee, M.D., Ph.D., Nobuaki Matsubara, M.D., Christof Vulsteke, M.D., Ph.D., Daniel Castellano, M.D., Chunzhang Wu, Ph.D., Mary Campbell, M.D., Maria Matsangou, M.B., Ch.B., M.D., and Daniel P. Petrylak, M.D.





Tumor-Vakzination
Neo-Antigene

2018

"...a personalized mutanome vaccine has the potential to become a universally applicable therapy irrespective of cancer type."

SPECIAL SECTION CANCER IMMUNOTI

REVIEW

Personalized vaccines for cancer immunotherapy

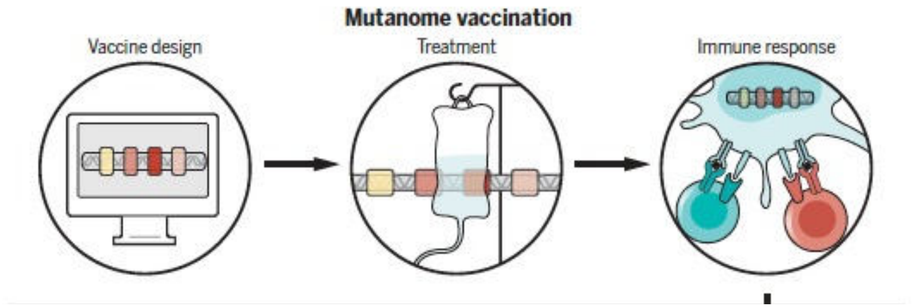
Ugur Sahin[1,2,3*] and Özlem Türeci[4]

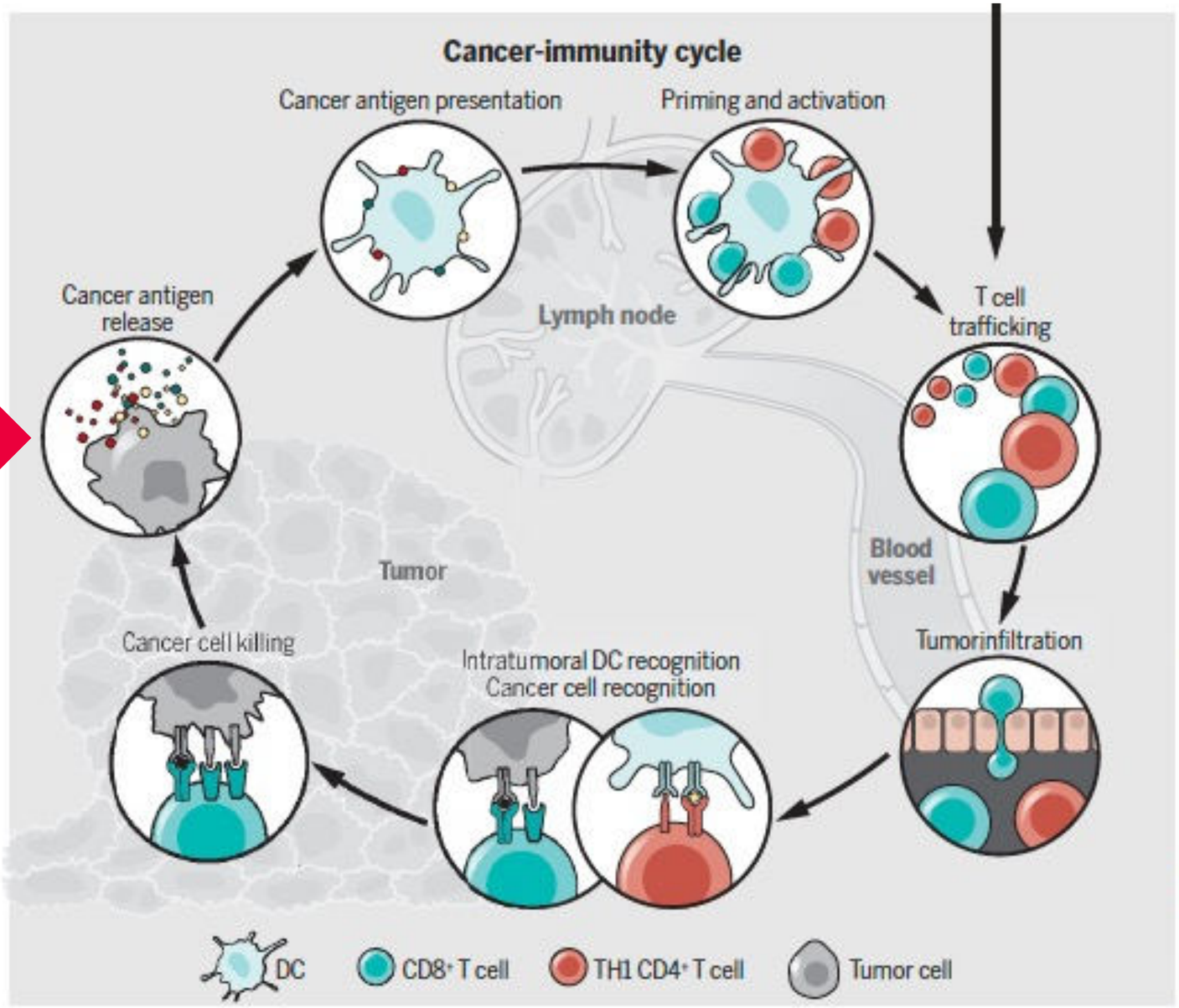
Sahin et al. Science 2018;359:1355-60

Neo-Antigene

Zerstörung von Tumorzellen und Freisetzung von Tumorantigenen

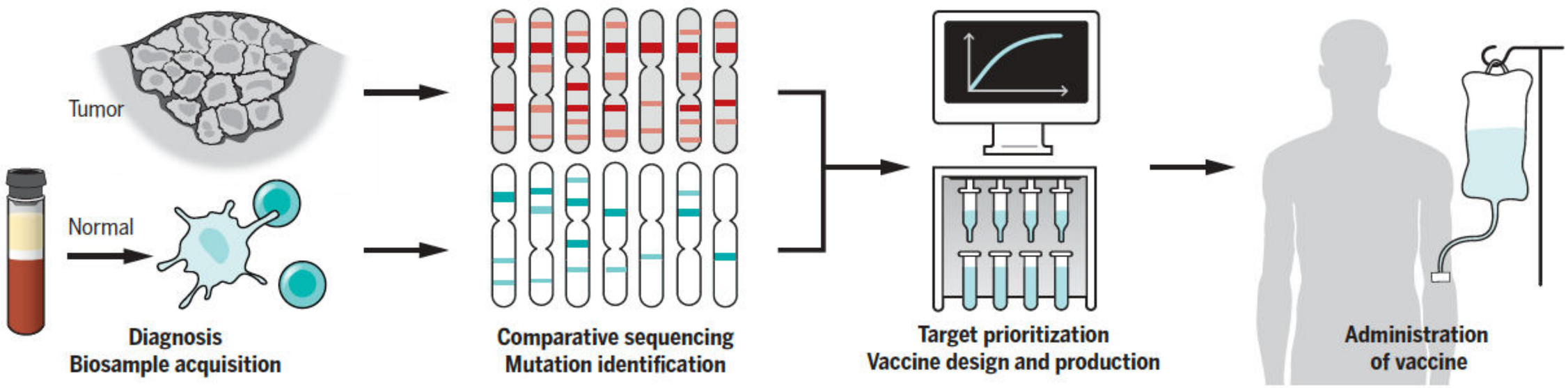
Nur Neo-Antigene werden als fremd erkannt





Individualisierte Vakzination (Impfung)

Neo-Antigen-Strategie



Neo-Antigene

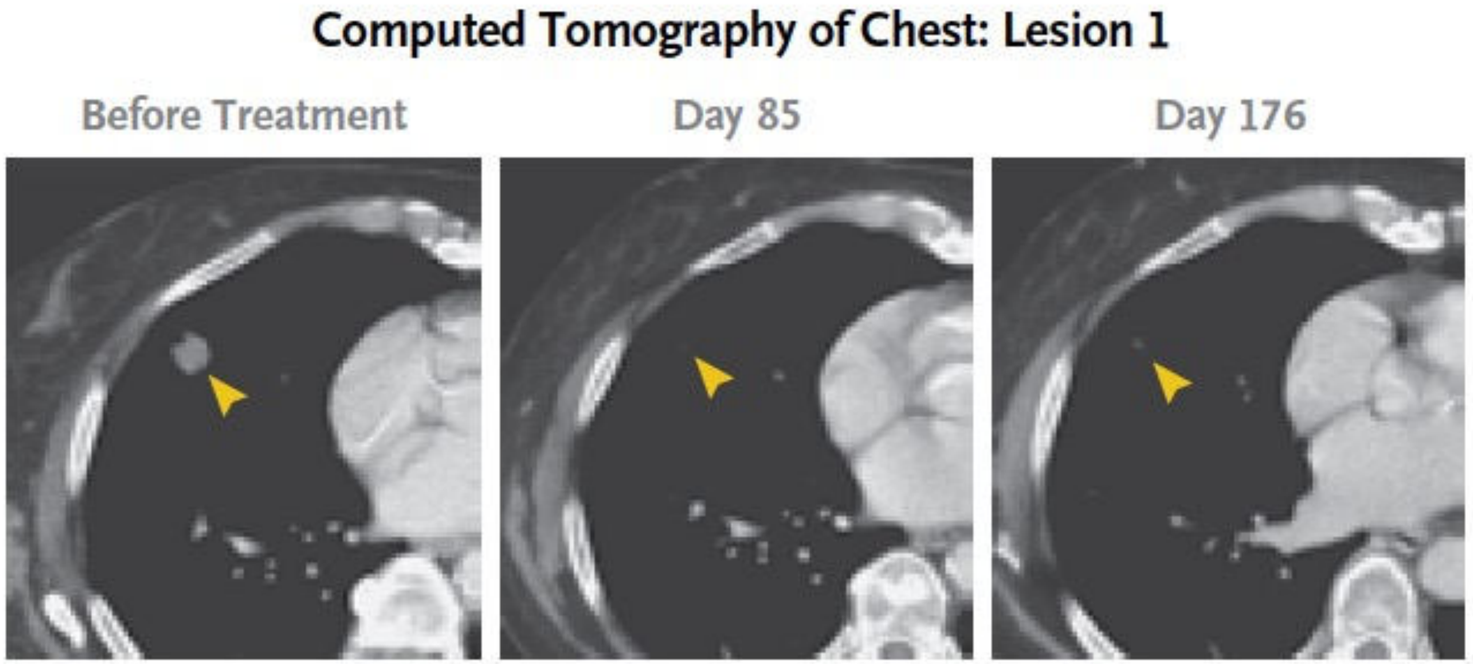
Neoantigen T-Cell Receptor Gentherapie
Pankreaskarzinom

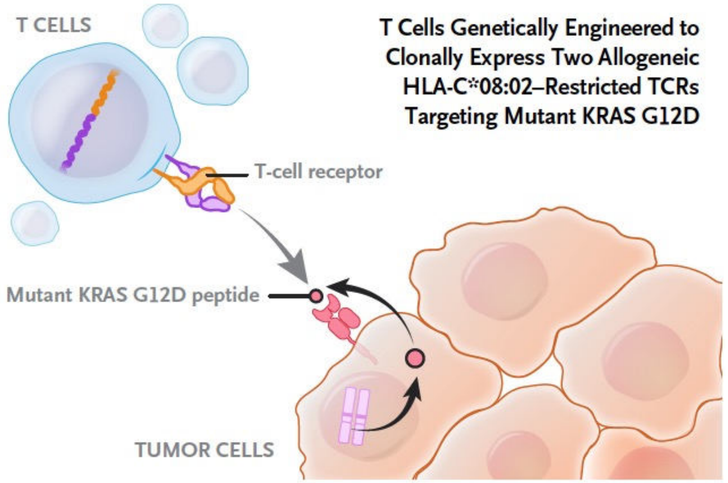
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer

Rom Leidner, M.D., Nelson Sanjuan Silva, B.S., Huayu Huang, M.S., David Sprott, B.S., Chunhong Zheng, Ph.D., Yi-Ping Shih, Ph.D., Amy Leung, B.S., Roxanne Payne, M.N., Kim Sutcliffe, B.S.N., Julie Cramer, M.A., Steven A. Rosenberg, M.D., Ph.D., Bernard A. Fox, Ph.D., Walter J. Urba, M.D., Ph.D., and Eric Tran, Ph.D.

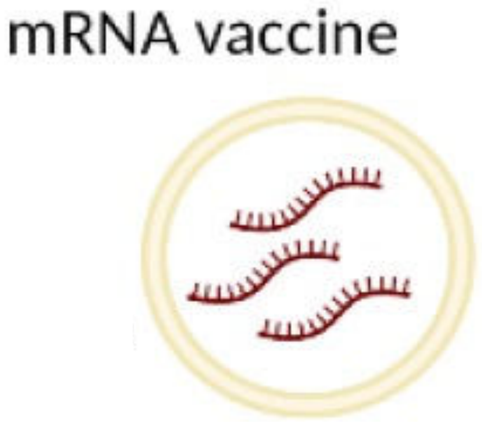


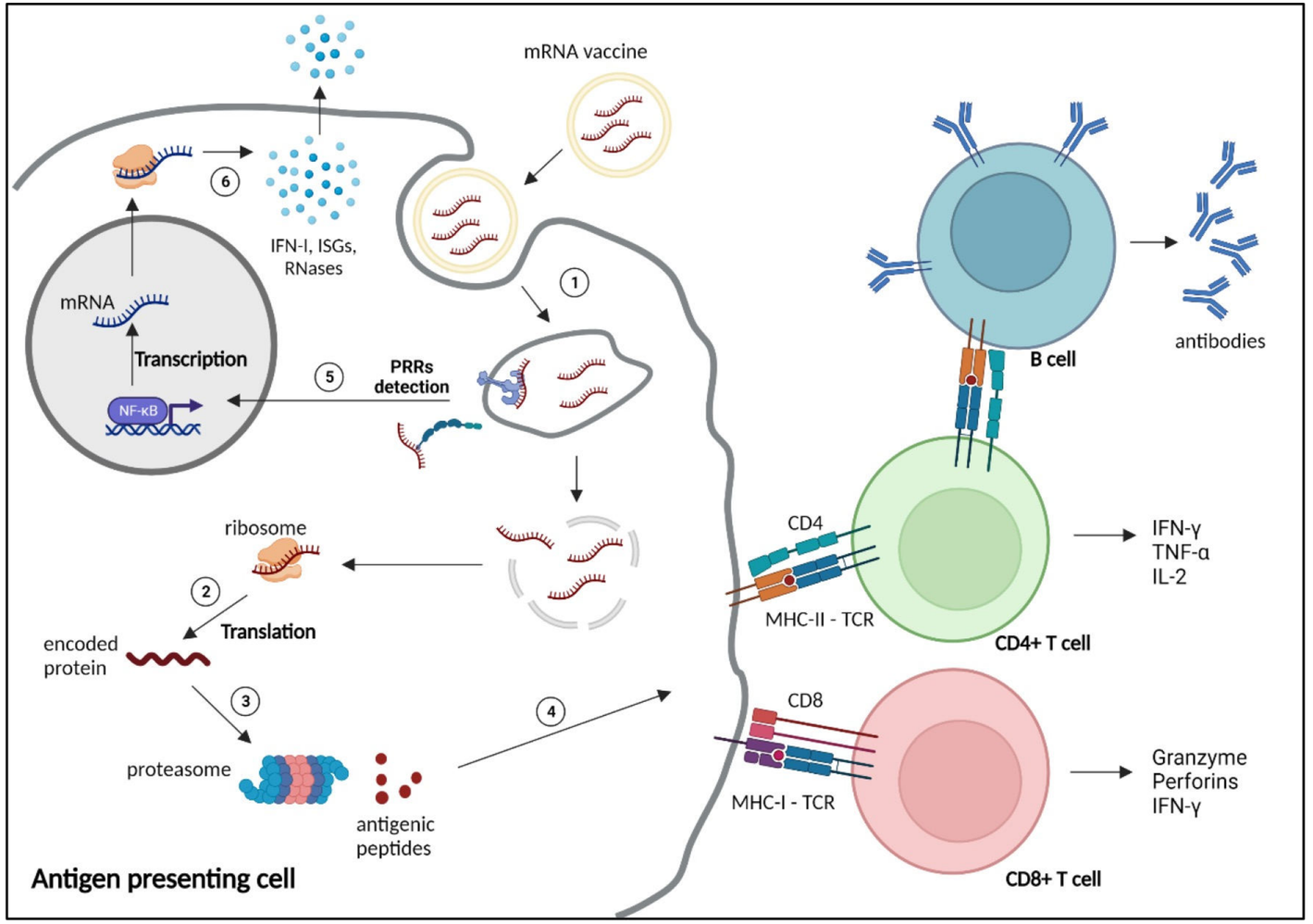


Leidner et al. NEJM 202;386:2112-9:

Neoantigen Vakzinierung
Malignes Melanom

34 Neo-Antigene Patienten-spezifisch





Neoantigen Vakzinierung
Malignes Melanom

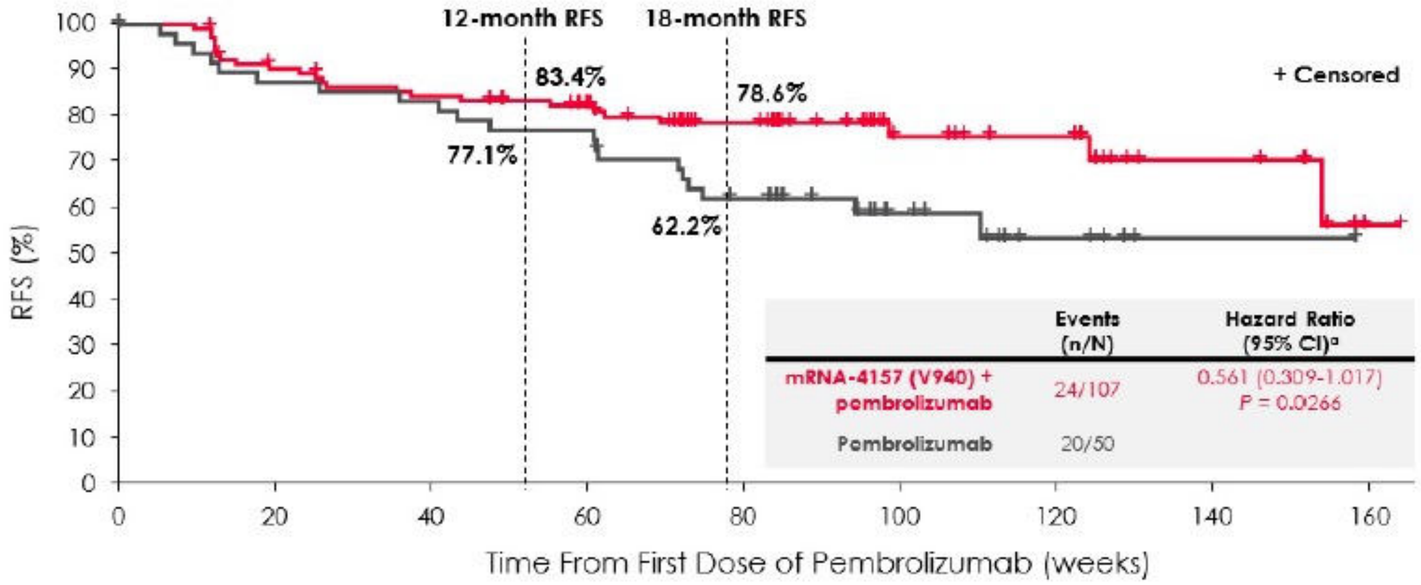
American Association for Cancer Research
FINDING CURES TOGETHER

Embargoed for Release: 11 a.m. ET, Sunday, April 16, 2023

To interview Jeffrey Weber or Ryan Sullivan, please contact Julia Gunther at julia.gunther@aacr.org or 770-403-7690. For a photo of Weber, click here; for a photo of Sullivan, click here. Visit our newsroom.

Adding a Personalized mRNA Cancer Vaccine to Immunotherapy May Prolong Recurrence-free Survival in Patients With High-risk Melanoma

Clinical benefit was independent of patients' tumor mutational burden



Number at Risk									
mRNA-4157 (V940) + Pembrolizumab	107	92	85	73	49	24	20	8	1
Pembrolizumab	50	42	40	37	28	13	6	1	0

CI, confidence interval; mRNA, messenger RNA; RFS, recurrence-free survival.
aThe hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIB or IIIC or IIID vs stage IV) used for randomization. The *P* value is based on a 1-sided log-rank test stratified by disease stage (stages IIB or IIIC or IIID vs stage IV) used for randomization.

Entschlüsselung der DNA
(Watson & Crick 1953; NP1962)

Sequenzierung der DNA
(Sanger 1975; NP 1980)

Entwicklung der PCR
(Mullis 1983; NP 1993)

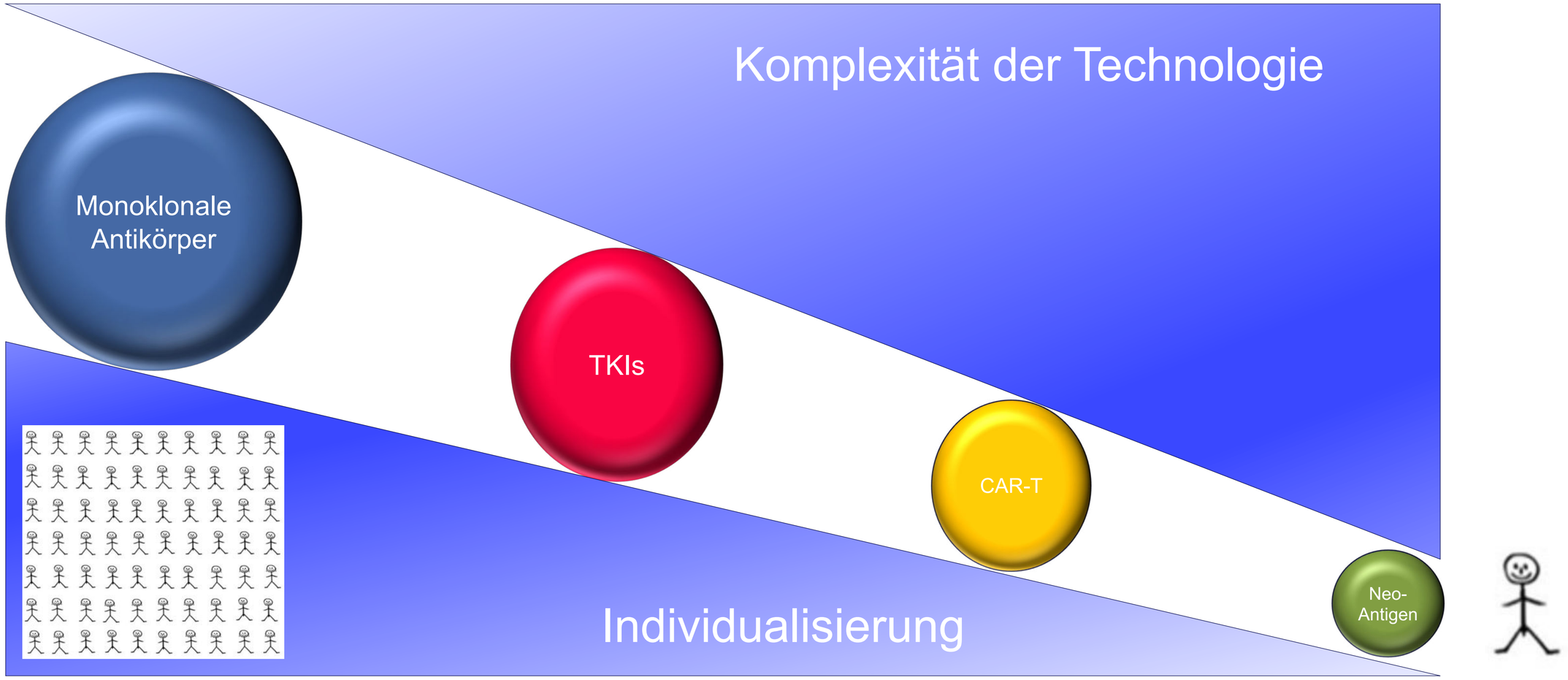
NGS Sequencing
(Illumina 2004)

Genome Editing
Crisp-Cas Genschere
(Charpentier 2015)

Herstellung monoklonaler Antikörper
(Köhler 1975; NP 1984)

Entschlüsselung des Genoms
(HGP 2003)

Tumor-Genom-Atlas
(2013)



Vielen Dank

JOHANNITER
Competence Center