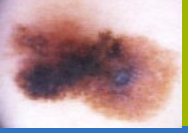


Neue Chancen bei metastasiertem schwarzen Hautkrebs

Jessica C. Hassel

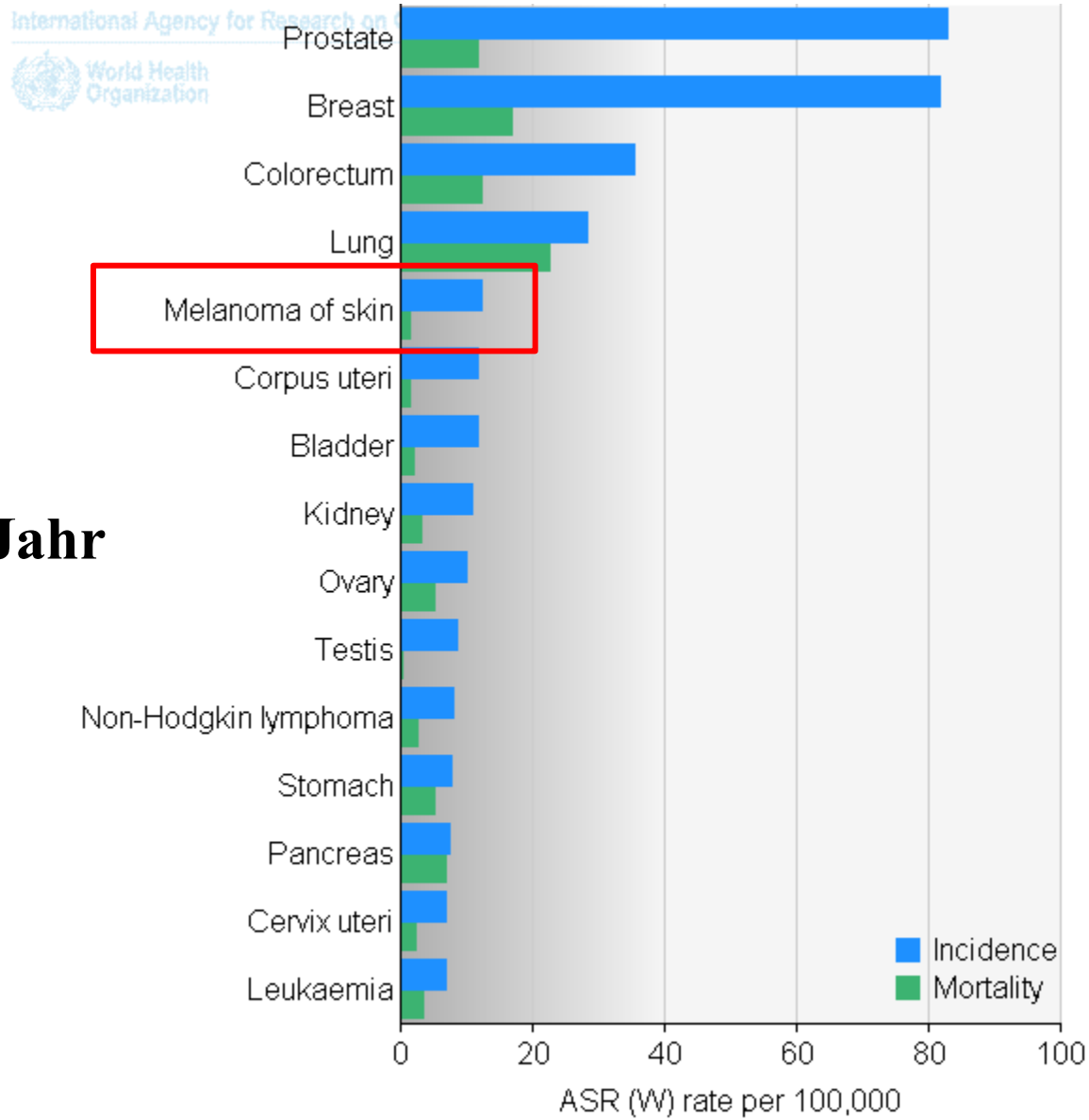
Universitätshautklinik und

Nationales Centrum für Tumorerkrankungen Heidelberg

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

22.000 Melanome / Jahr

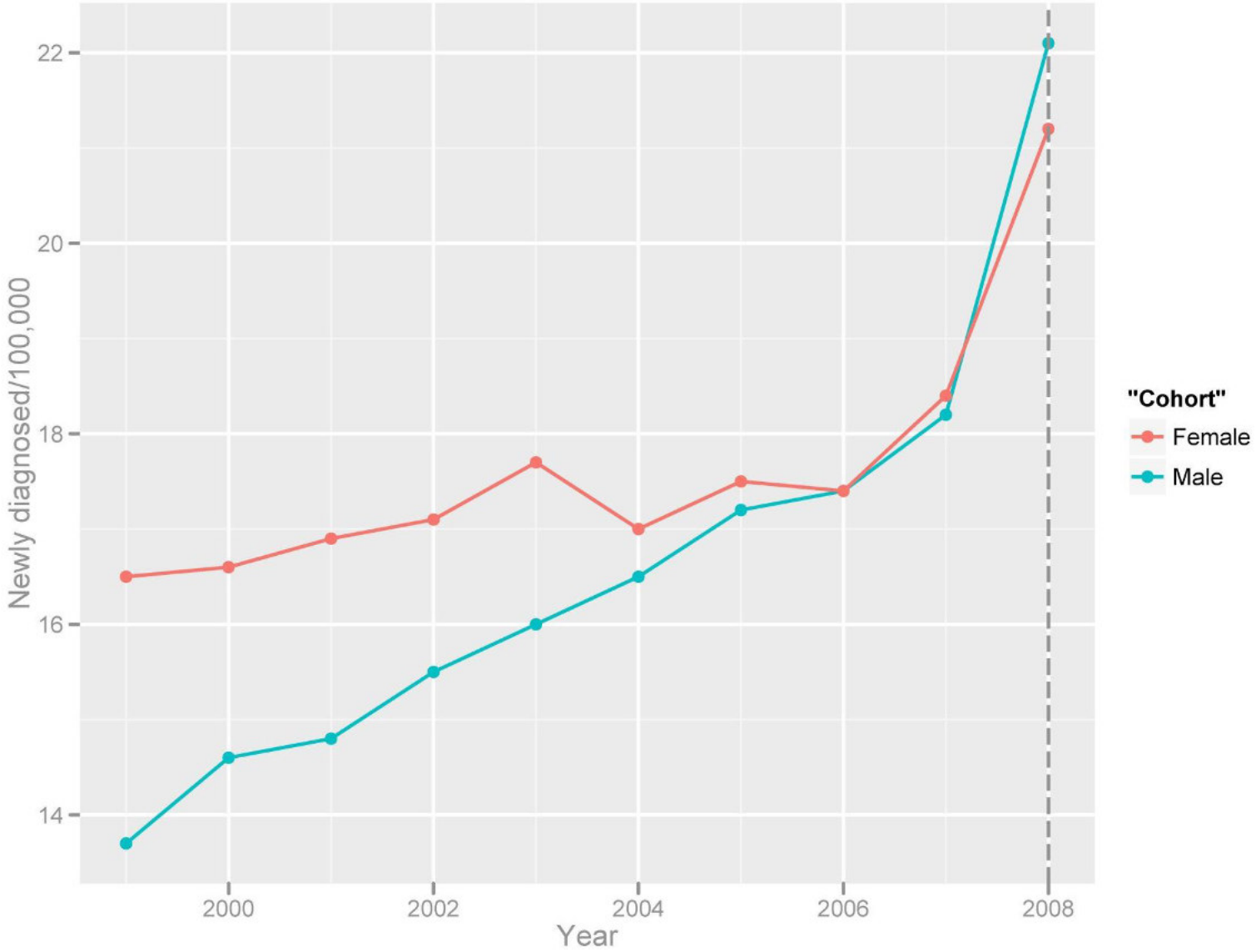
RKI 2008



Globocan 2008

NCT

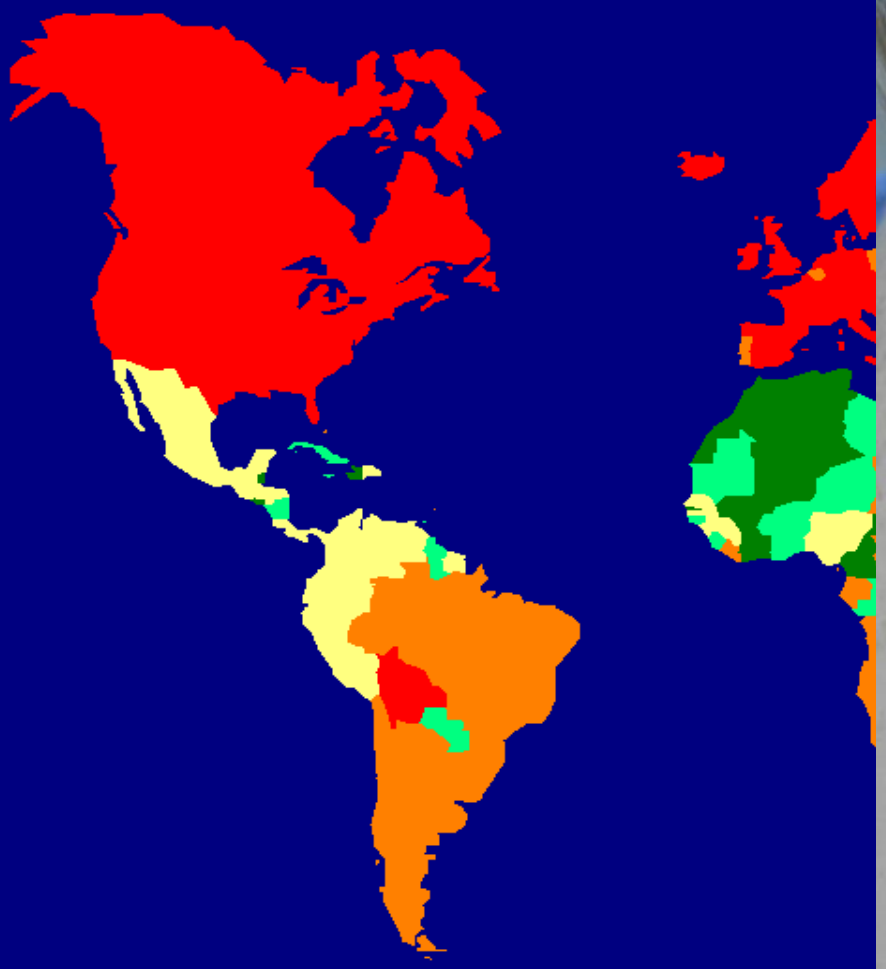
Inzidenz Melanom



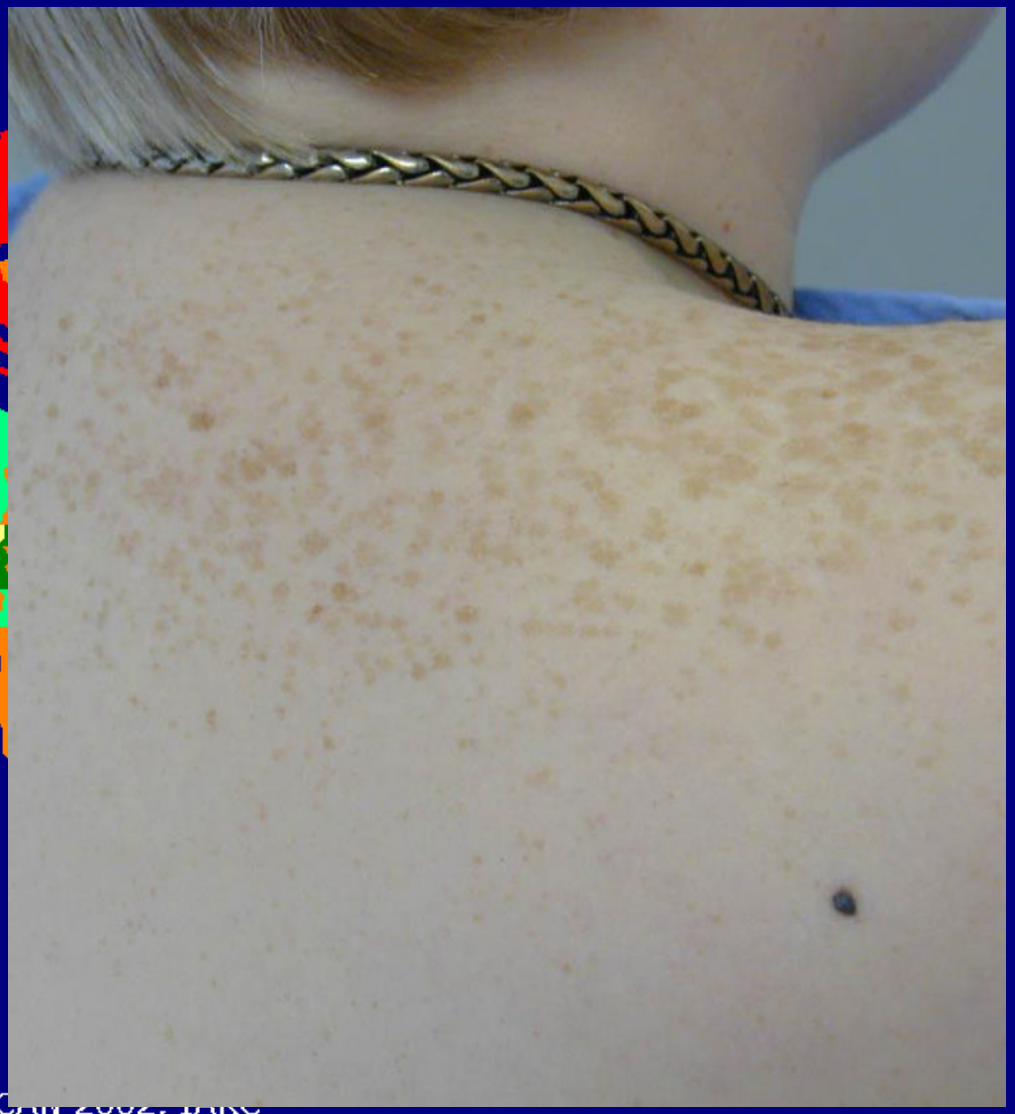
Rohe Raten, Robert-Koch-Institut.

NCT

Melanoma of skin, Males
Age-Standardized incidence rate per 100,000



< 0.6 < 1.2



GLOBOCAN 2002, IARC

Diagnostik Melanom

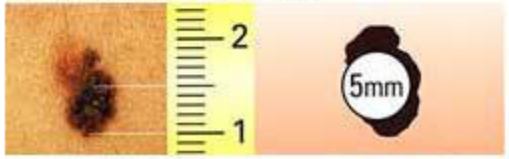
ABCDE-Regel

A = **A**symmetrie der Läsion

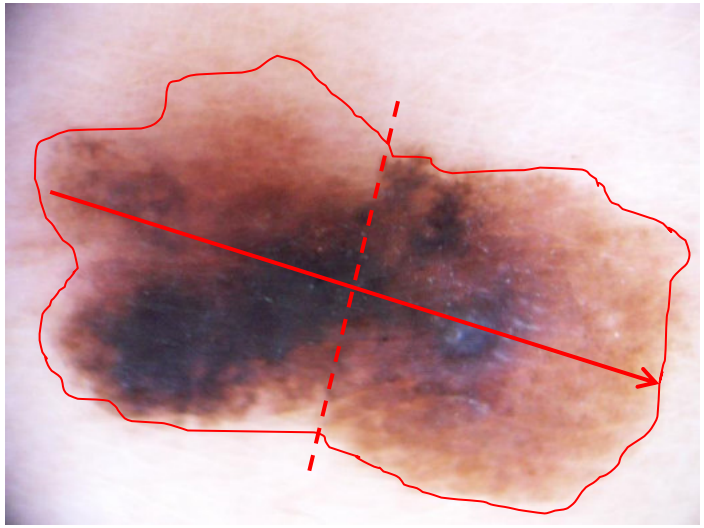
B = **B**egrenzung unregelmäßig, z. T. mit kleinen, zungenförmigen Ausläufern

C = **C**olorit der Läsion variierend, z. T. schwarze, rötliche oder graue Anteile neben brauner Pigmentierung

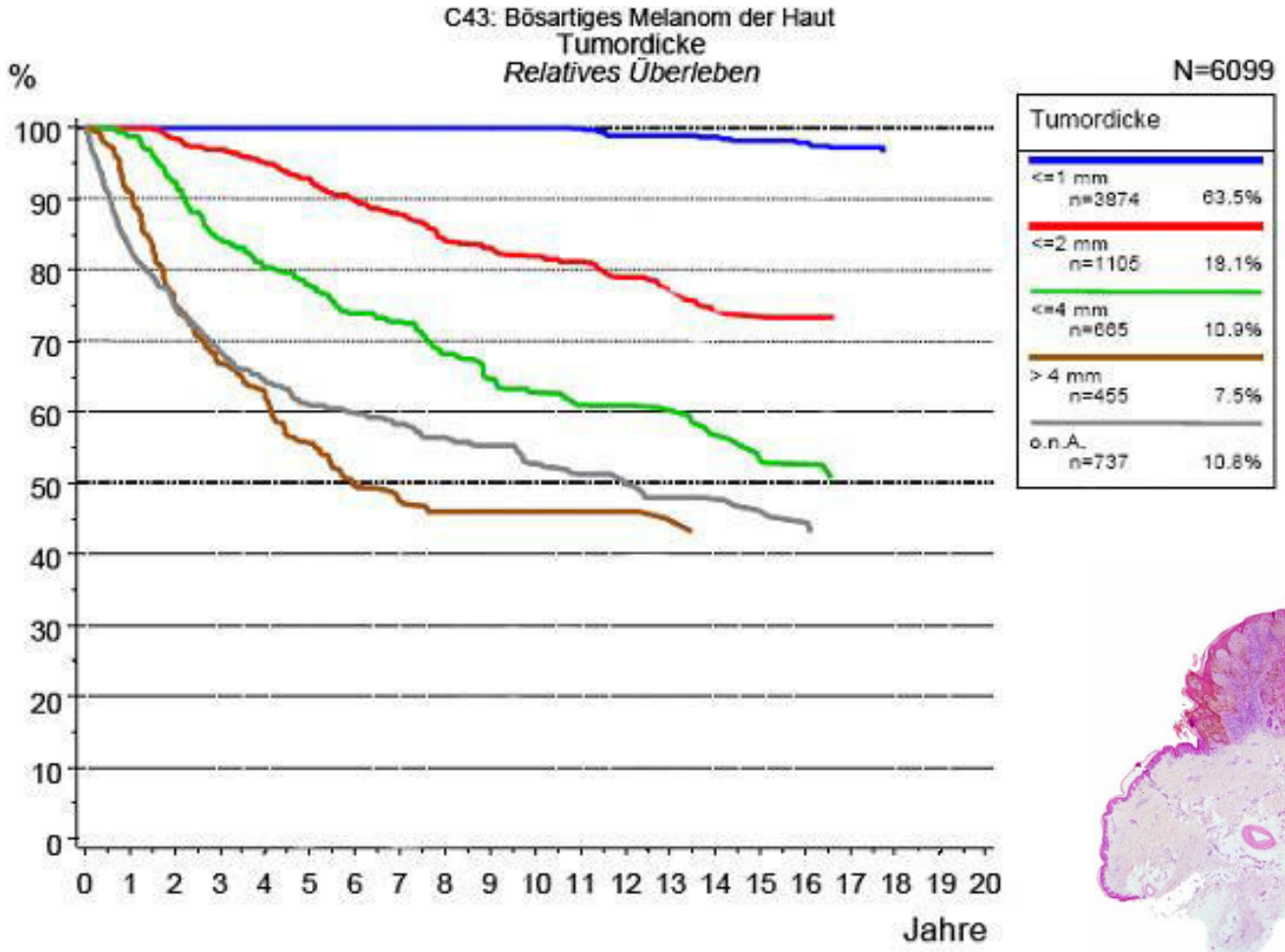
D = **D**urchmesser ³ 5 mm

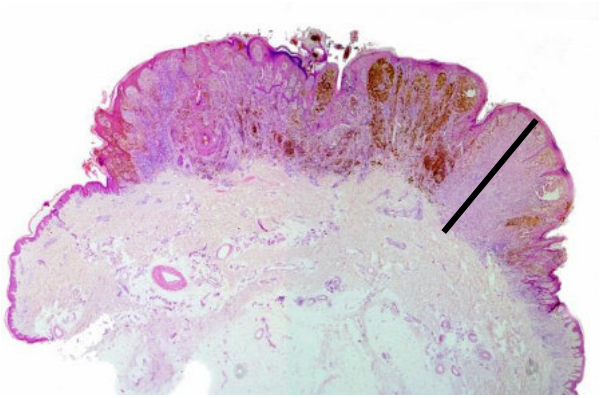


E = ~~Erhabenheit~~ Entwicklung



Warum Hautkrebsscreening?

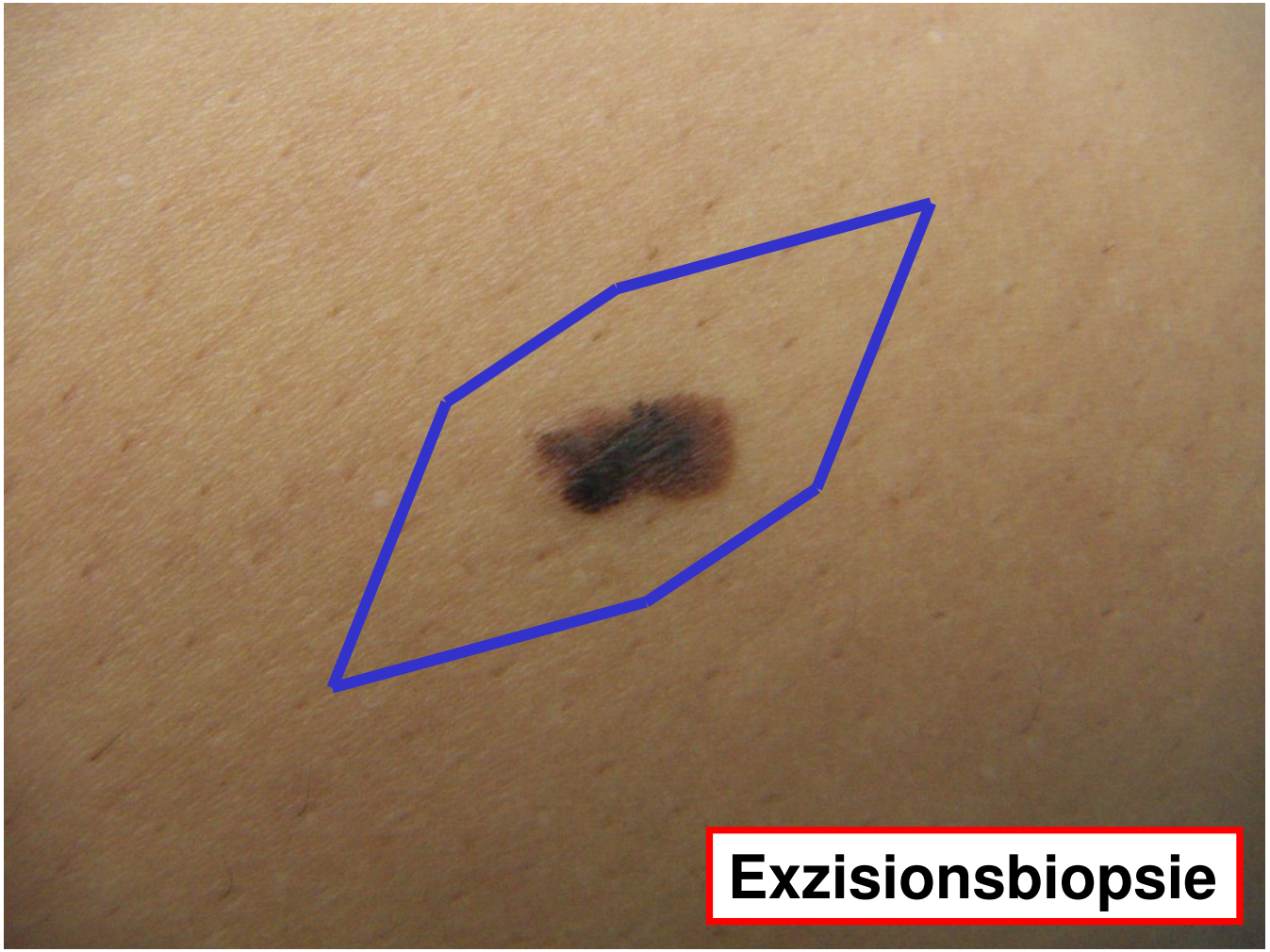




Tumorregister München

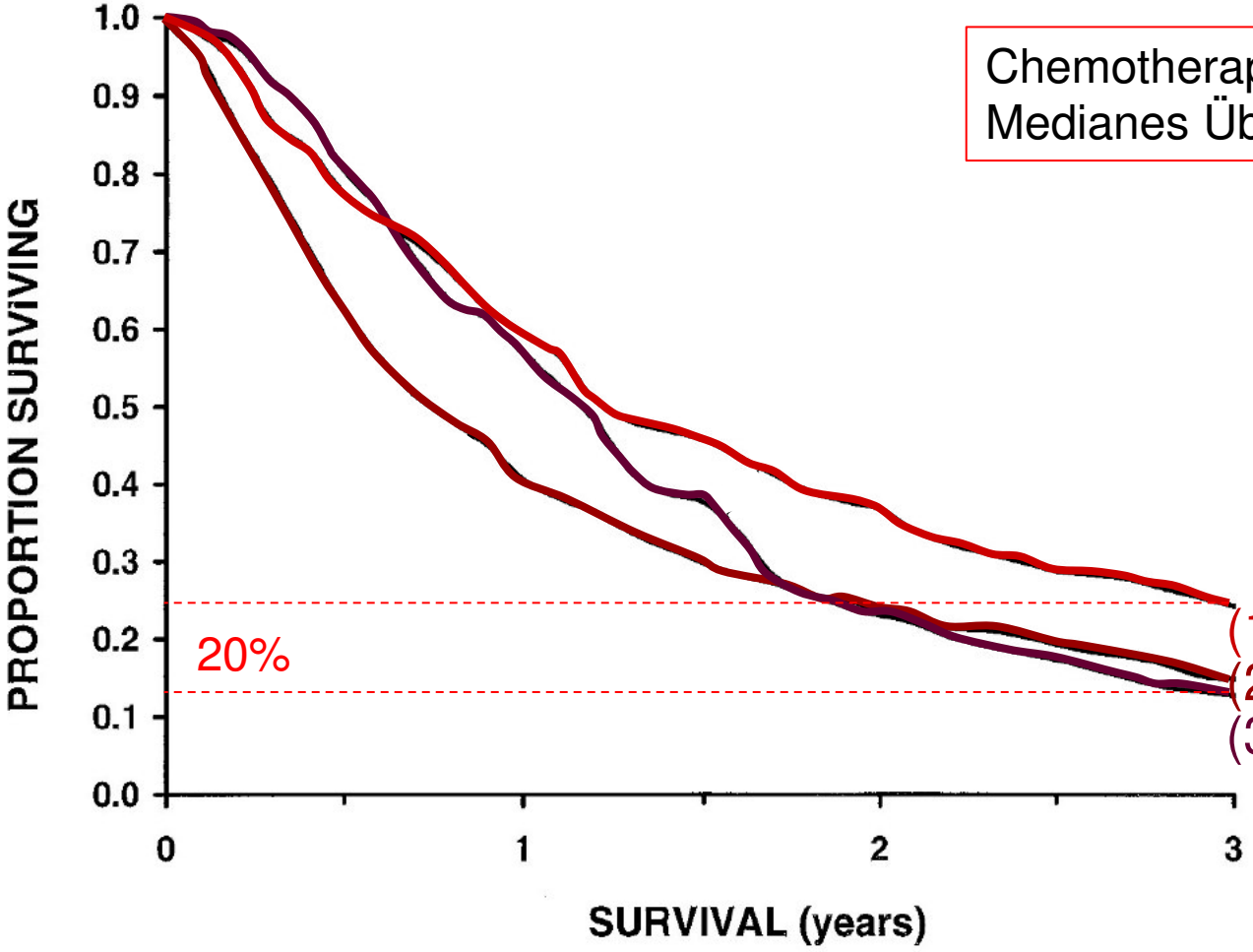
NCT

Melanom: Operative Therapie



NCT

Überleben bei Fernmetastasierung



Chemotherapie Ära
Medianes Überleben 6-9 Monate

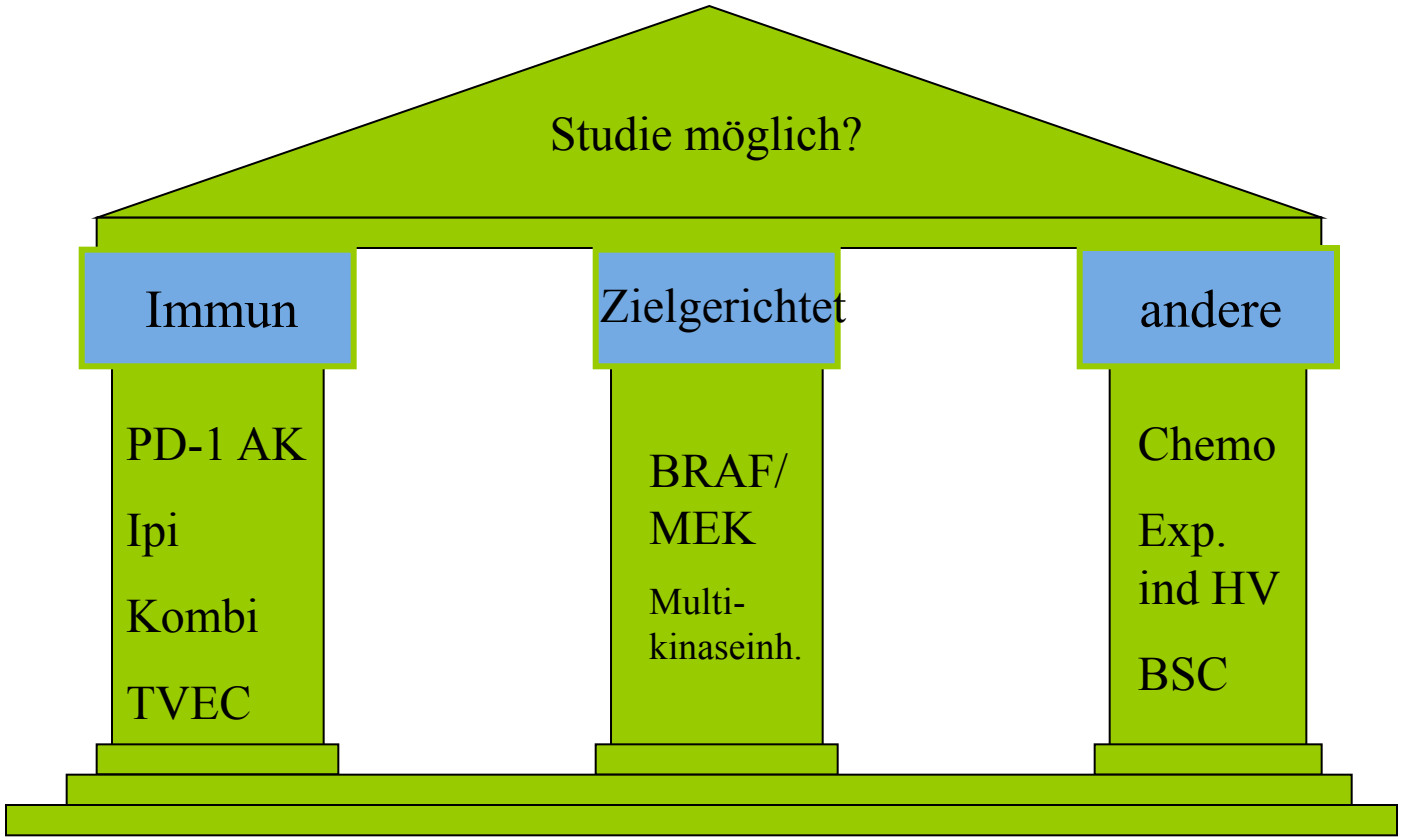
(1) **Haut, s.c., LK**
(2) **andere Organe**
(3) **Lunge**

n = 1158 Patienten

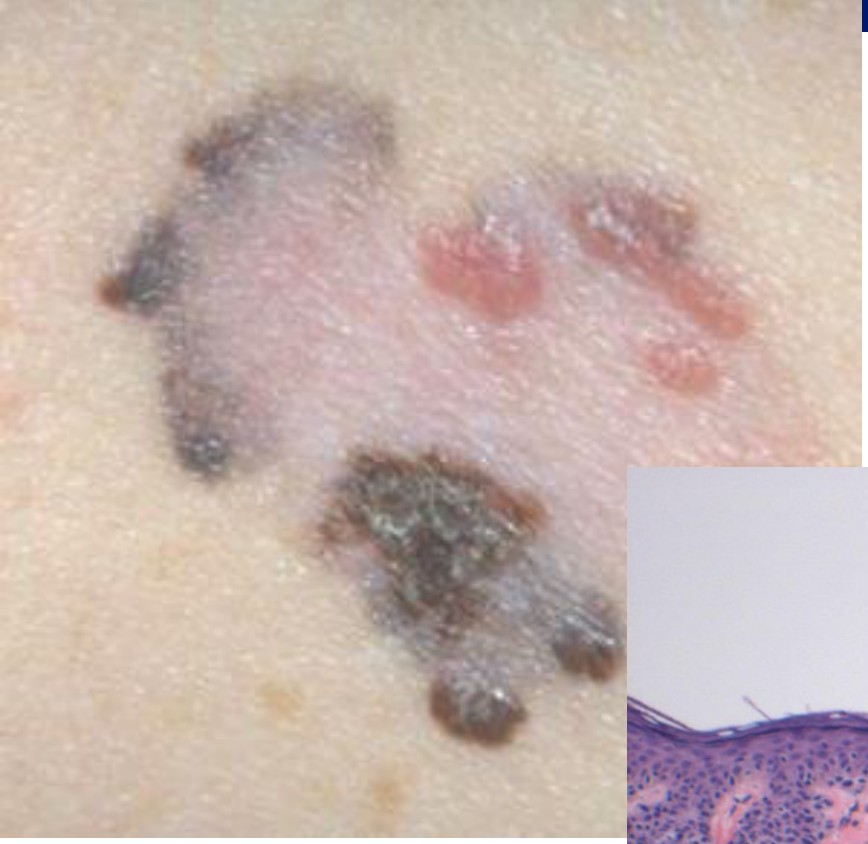
aus Balch CM et al.:
J Clin Oncol (2001)

NCT

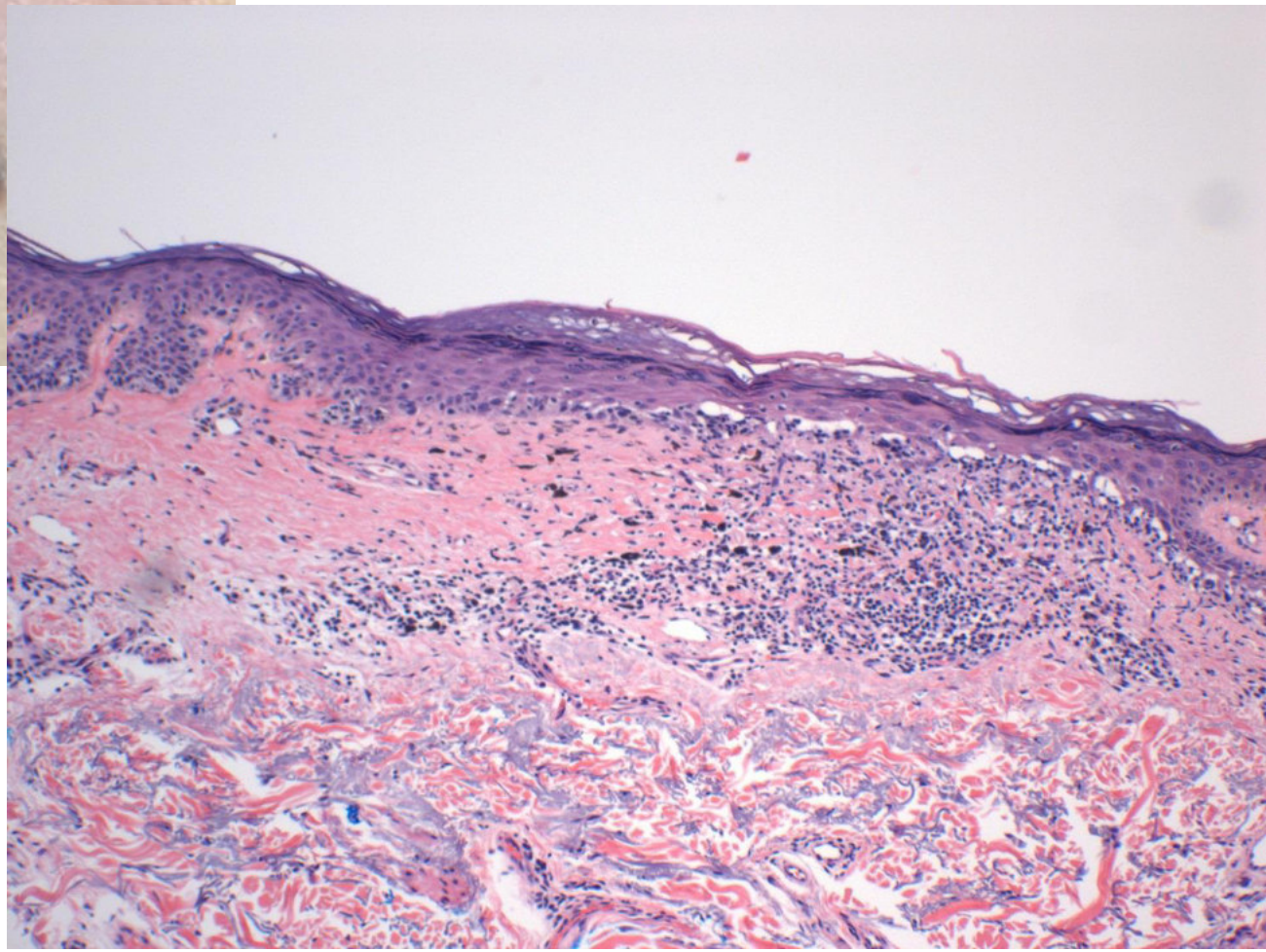
Systemische Therapien bei Melanom Stadium IV



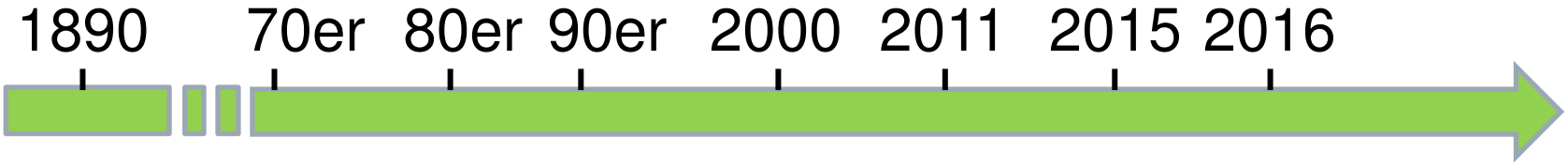
NCT



Regressives Melanom



Entwicklung der Immuntherapie



William Coley‘s Toxin

NCT

Entwicklung der Immuntherapie


The NEW ENGLAND JOURNAL of MEDICINE

AUGUST 19, 2010

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

ABSTRACT

1890 70er 80er 90er 2000 2011 2015 2016

William Coley‘s Toxin

Tuberkulosebakterien

Botenstoffen wie Interleukin-2 / Interferon

Impfstudien

MAGEA1, 1991
erstes TAA

Immuncheckpointblockern

Ipilimumab / PD-1 AK

Onkoloytisches Virus (TVEC)

Immunabwehr

Fresszelle

Melanom

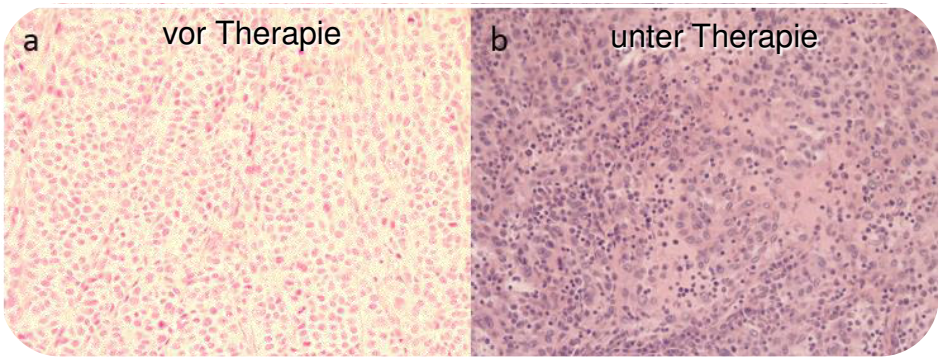
Lymphozyt

Autoimmunität

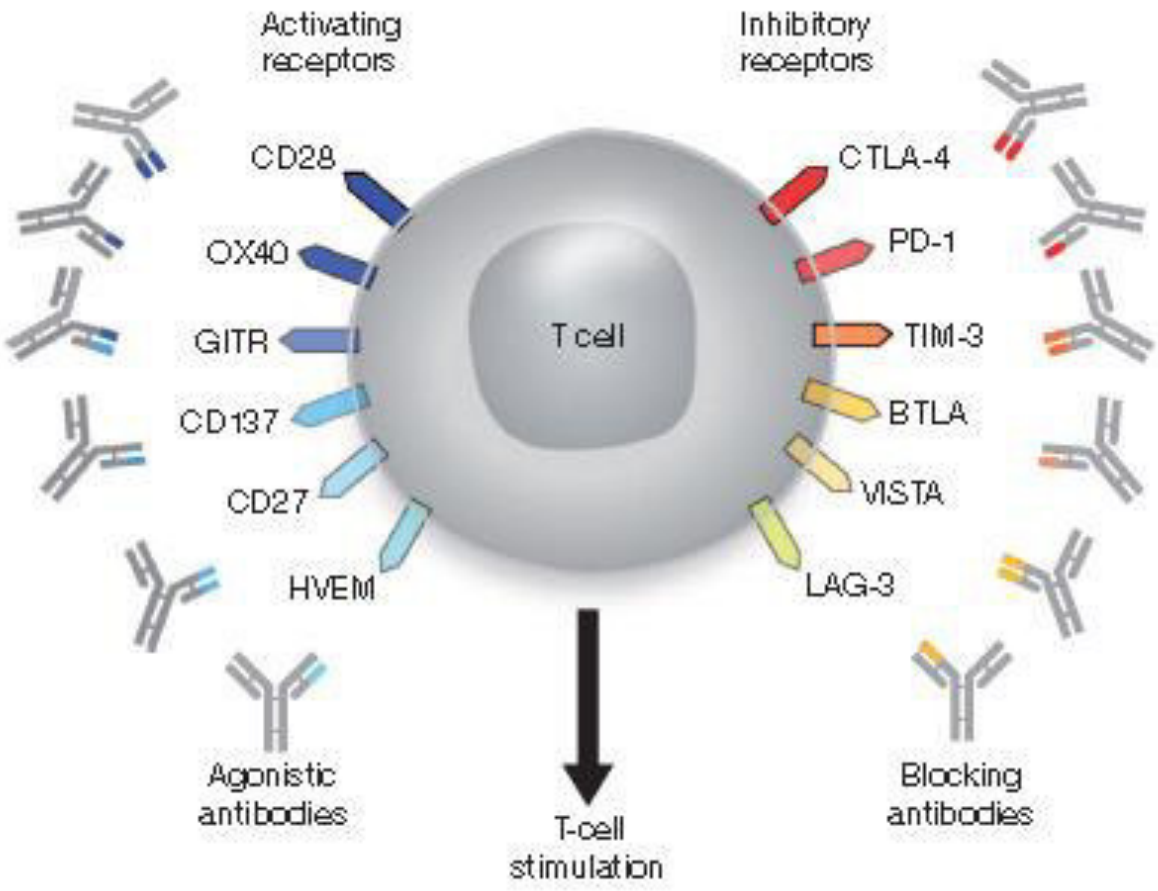
CTLA-4

Ipilimumab

Immune Checkpoints



Immuncheckpoints



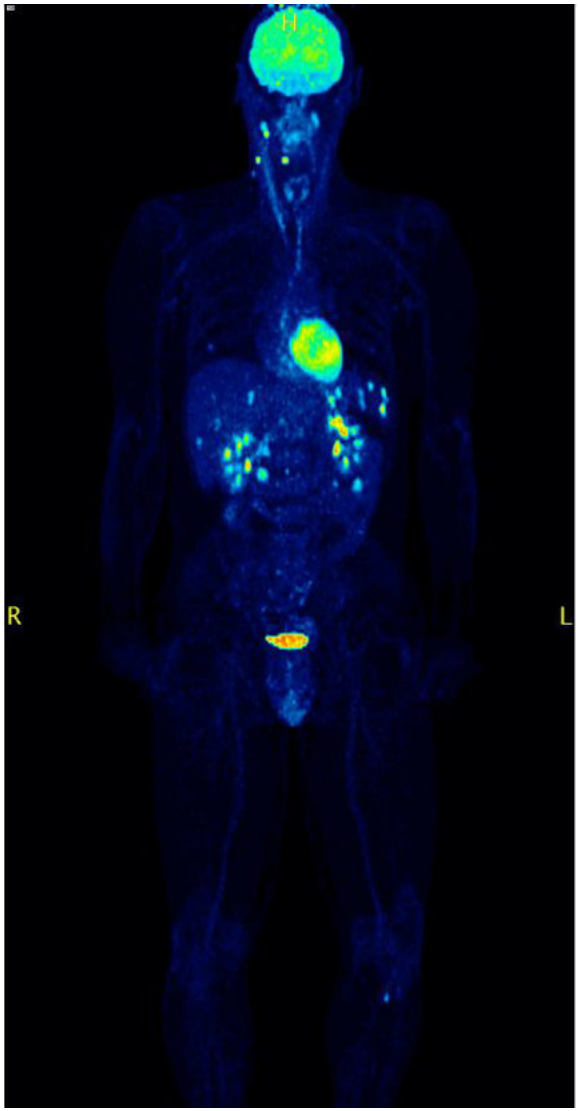
Ipilimumab

PD-1 Antikörper:
Pembrolizumab
Nivolumab

LAG-3 Antikörper

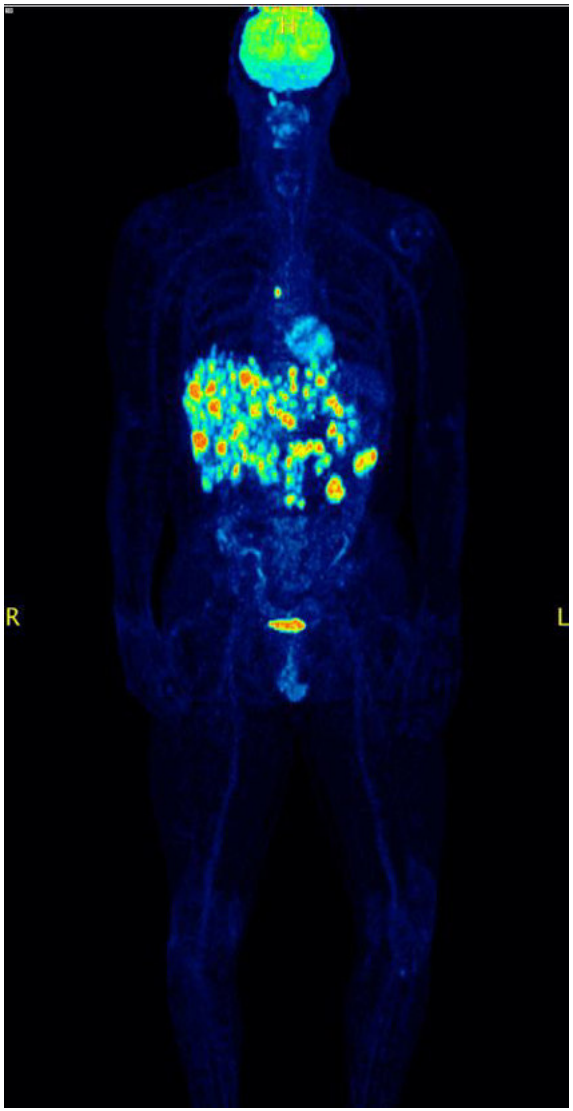
NCT

vor Ipilimumab
07/2014



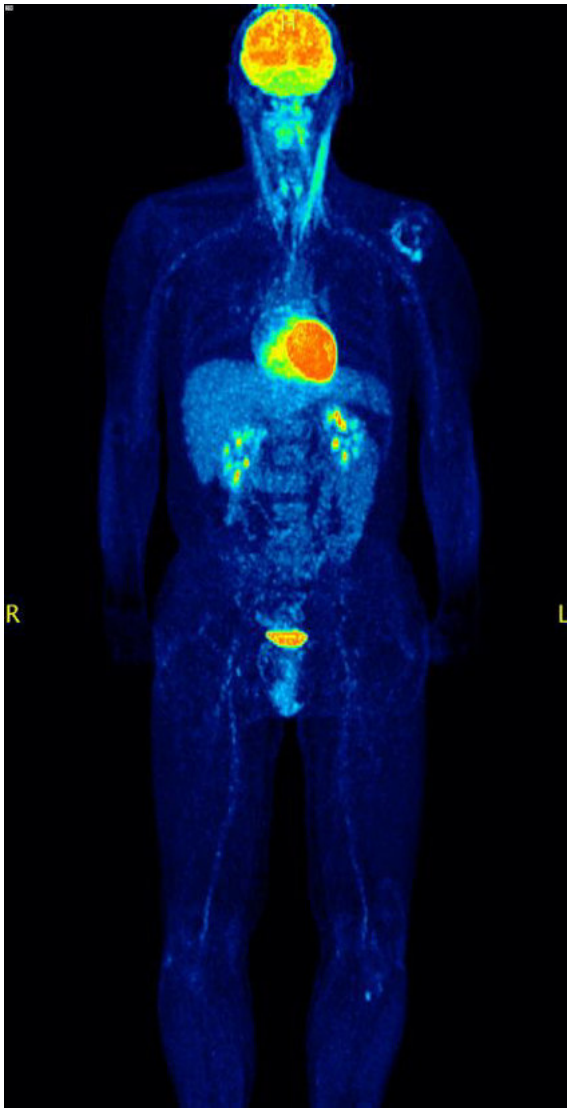
S100 0,165

nach 4 Zyklen Ipilimumab
10/2014



S100 0,962

nach 4 Zyklen Pembrolizumab
01/15

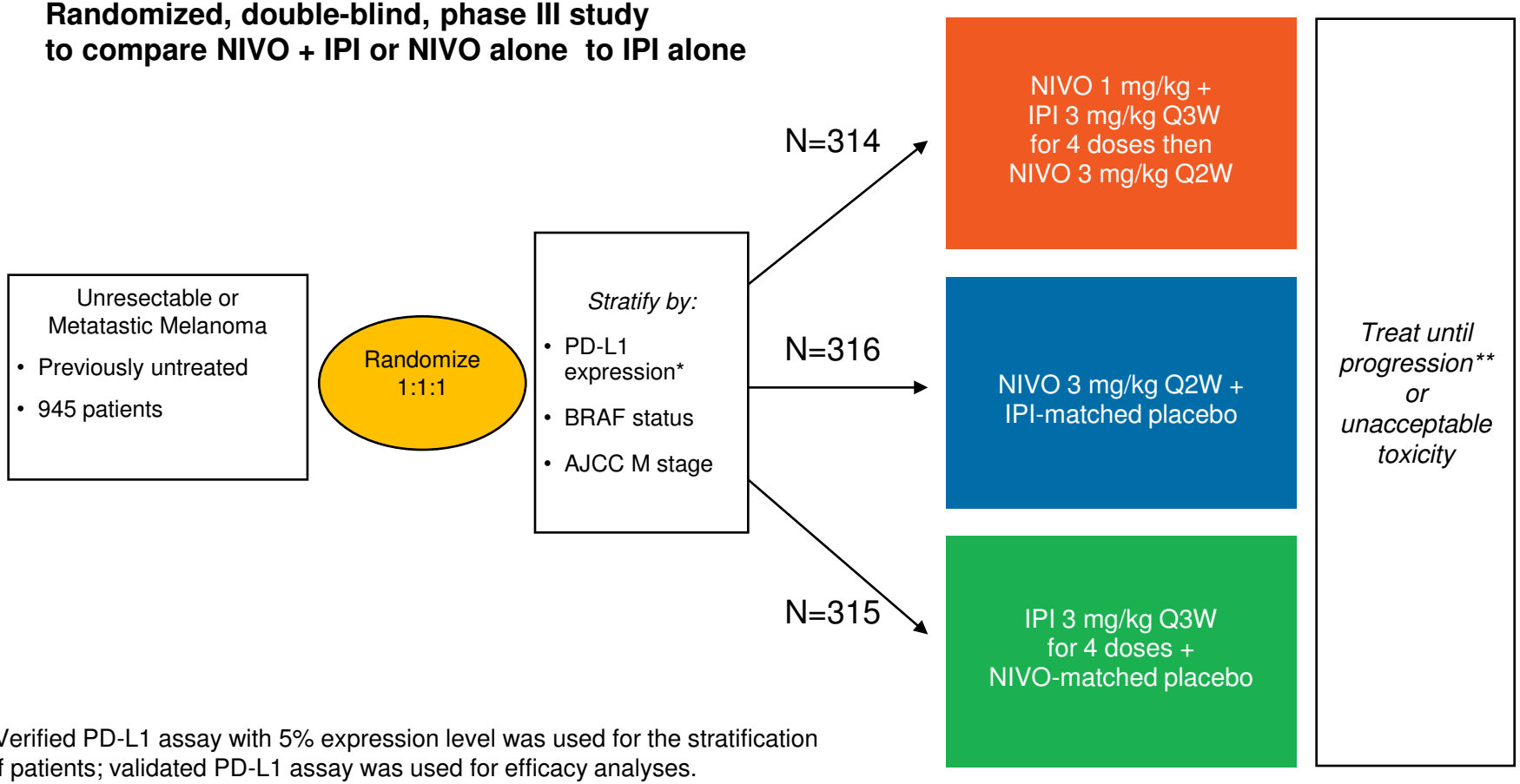


S100 0,07

NCT

CheckMate 067 Studie

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone



*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

NCT

Therapieansprechen

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	**57.6** (52.0–63.2)	**43.7** (38.1–49.3)	**19.0** (14.9–23.8)
Two-sided *P* value vs IPI	<0.001	<0.001	--
Best overall response — %			
Complete response	11.5	8.9	2.2
Partial response	46.2	34.8	16.8
Stable disease	13.1	10.8	21.9
Progressive disease	22.6	37.7	48.9
Unknown	6.7	7.9	10.2
Duration of response (months)			
Median (95% CI)	NR (13.1, NR)	NR (11.7, NR)	NR (6.9, NR)

*By RECIST v1.1.
NR, not reached.

*mindestens 30% Abnahme im Tumorvolumen

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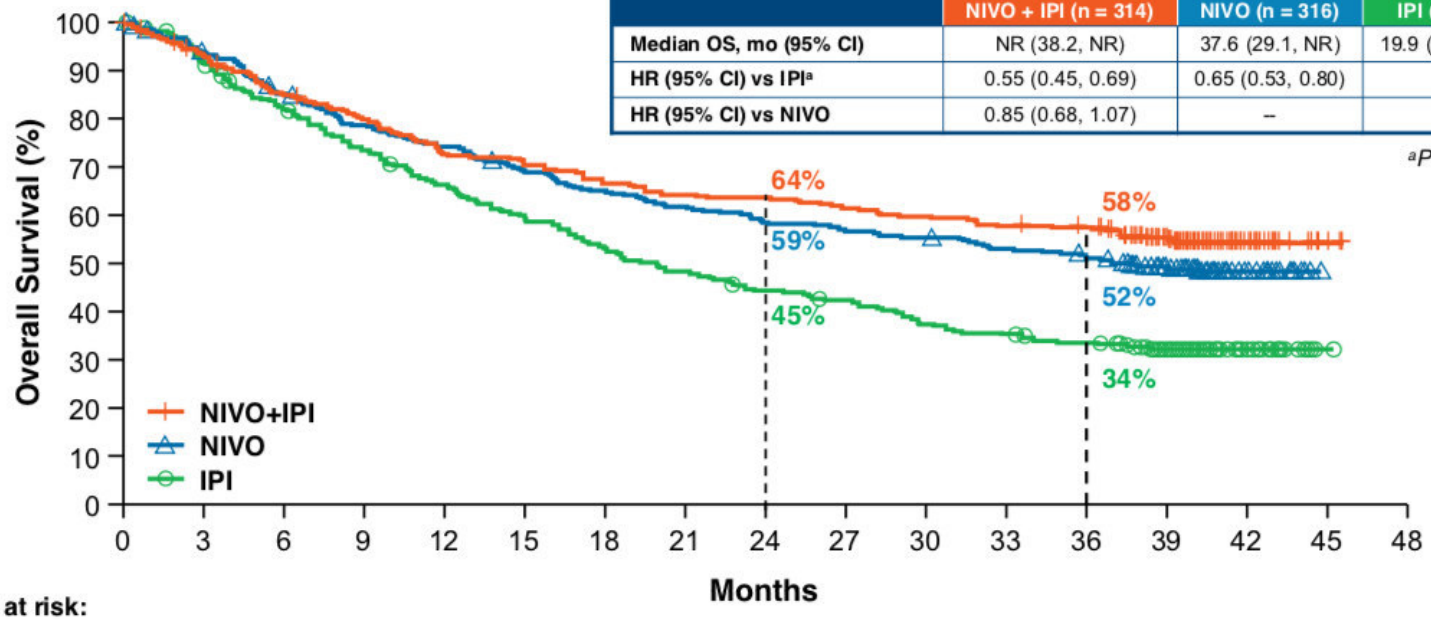
CheckMate 067 Gesamtüberleben

OS (Intent-to-Treat)[1]

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	37.6 (29.1, NR)	19.9 (16.9, 24.6)
HR (95% CI) vs IPI[a]	0.55 (0.45, 0.69)	0.65 (0.53, 0.80)	--
HR (95% CI) vs NIVO	0.85 (0.68, 1.07)	--	--

[a]$P < 0.0001$



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
NIVO	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
IPI	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

1. Wolchok JD et al. *N Engl J Med*. In press.

Wolchok et al, NEJM 2017

NCT

CheckMate 067 Verträglichkeit

	NIVO + IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
Patients reporting event, %	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Treatment-related AE	95.8	58.8	86.3	21.4	86.2	27.7
Treatment-related AE leading to discontinuation	39.3	30.4	11.8	7.7	15.8	13.8
Treatment-related death, n (%)	2 (0.6)[a]		1 (0.3)[b]		1 (0.3)[c]	

ABER:

➔ 67.5% der Patienten (81/120), die NIVO + IPI aufgrund von Nebenwirkungen abbrechen mussten, hatten auch ein Therapieansprechen

Grob et al, ESMO 2017

NCT

Autoimmune Nebenwirkungen

Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Skin	59.1	5.8	41.9	1.6	54.0	2.9
Pruritus	33.2	1.9	18.8	0	35.4	0.3
Rash	28.4	2.9	21.7	0.3	20.9	1.6
Rash maculo-papular	11.8	1.9	4.2	0.3	11.9	0.3
Gastrointestinal	46.3	14.7	19.5	2.2	36.7	11.6
Diarrhea	44.1	9.3	19.2	2.2	33.1	6.1
Colitis	11.8	7.7	1.3	0.6	11.6	8.7
Hepatic	30.0	18.8	6.4	2.6	7.1	1.6
Increase in alanine aminotransferase	17.6	8.3	3.8	1.3	3.9	1.6
Increase in aspartate aminotransferase	15.3	6.1	3.8	1.0	3.5	0.6
Endocrine	30.0	4.8	14.4	0.6	10.9	2.3
Hypothyroidism	15.0	0.3	8.6	0	4.2	0

- With immune modulatory agents, resolution rates for the majority of grade 3–4 select AEs were: 85-100% for NIVO + IPI, 50-100% for NIVO, and 83-100% for IPI
- As observed in prior studies, most endocrine events did not resolve

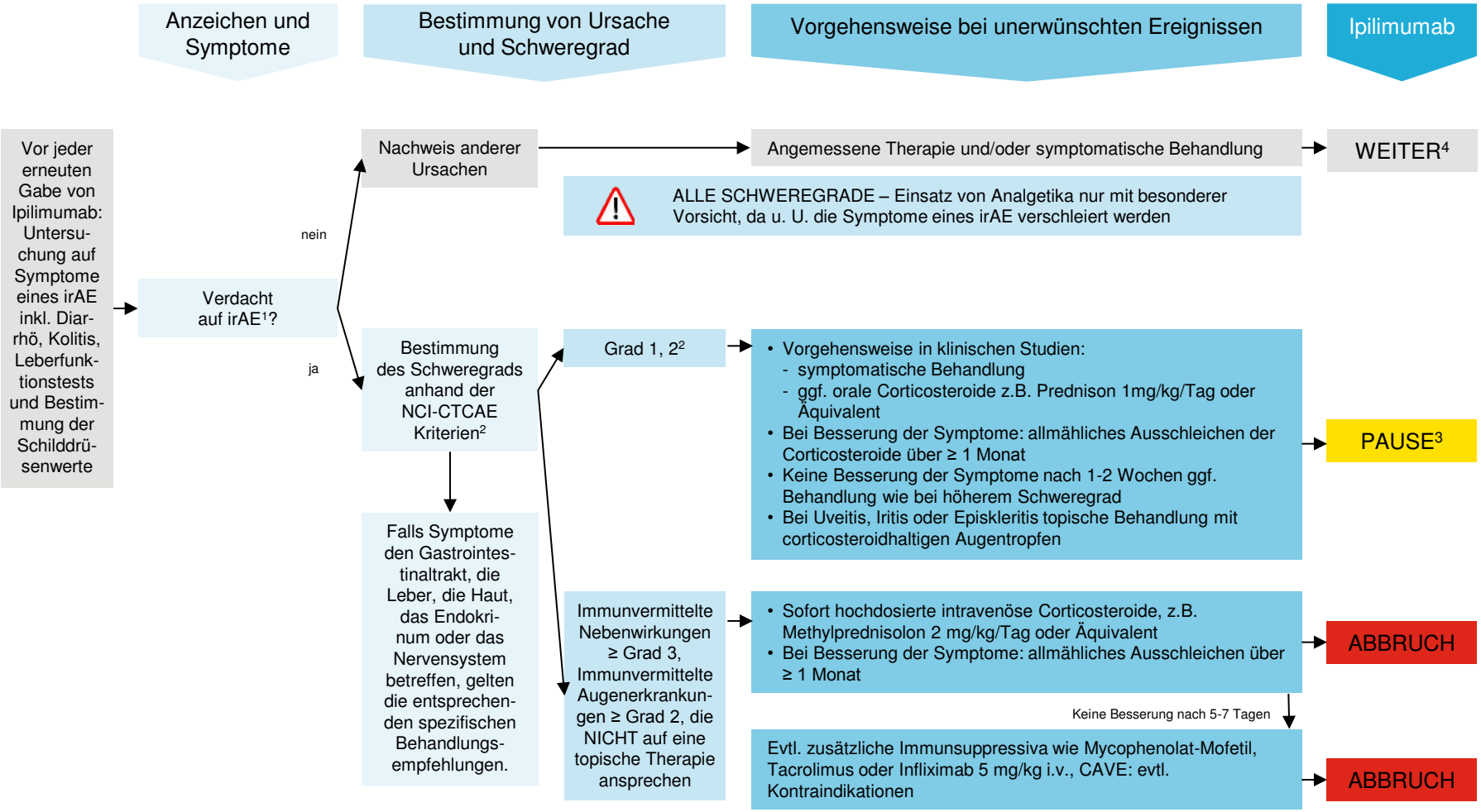
CheckMate 069: Grade 2–4 Treatment-related Select AEs Across Organ Categories

Number of organ categories, % (n/N)[a]	All treated patients	
	NIVO + IPI	IPI
0	21 (20/94)	52 (24/46)
1	47 (44/94)	41 (19/46)
2	23 (22/94)	7 (3/46)
3	7 (7/94)	0 (0/46)
>3	1 (1/94)	0 (0/46)

- A higher proportion of patients treated with the combination experienced ≥1 grade 2–4 AEs across organ categories during treatment

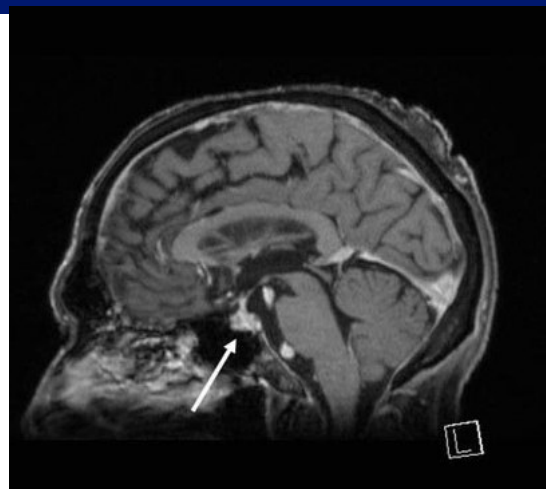
[a]Organ categories: Skin, gastrointestinal, endocrine, hepatic, pulmonary, renal

Allgemeine Empfehlungen zu immunvermittelten Nebenwirkungen



➔ Immunsuppressive Therapie mit Kortison und ggf. anderen Medikamenten

NCT



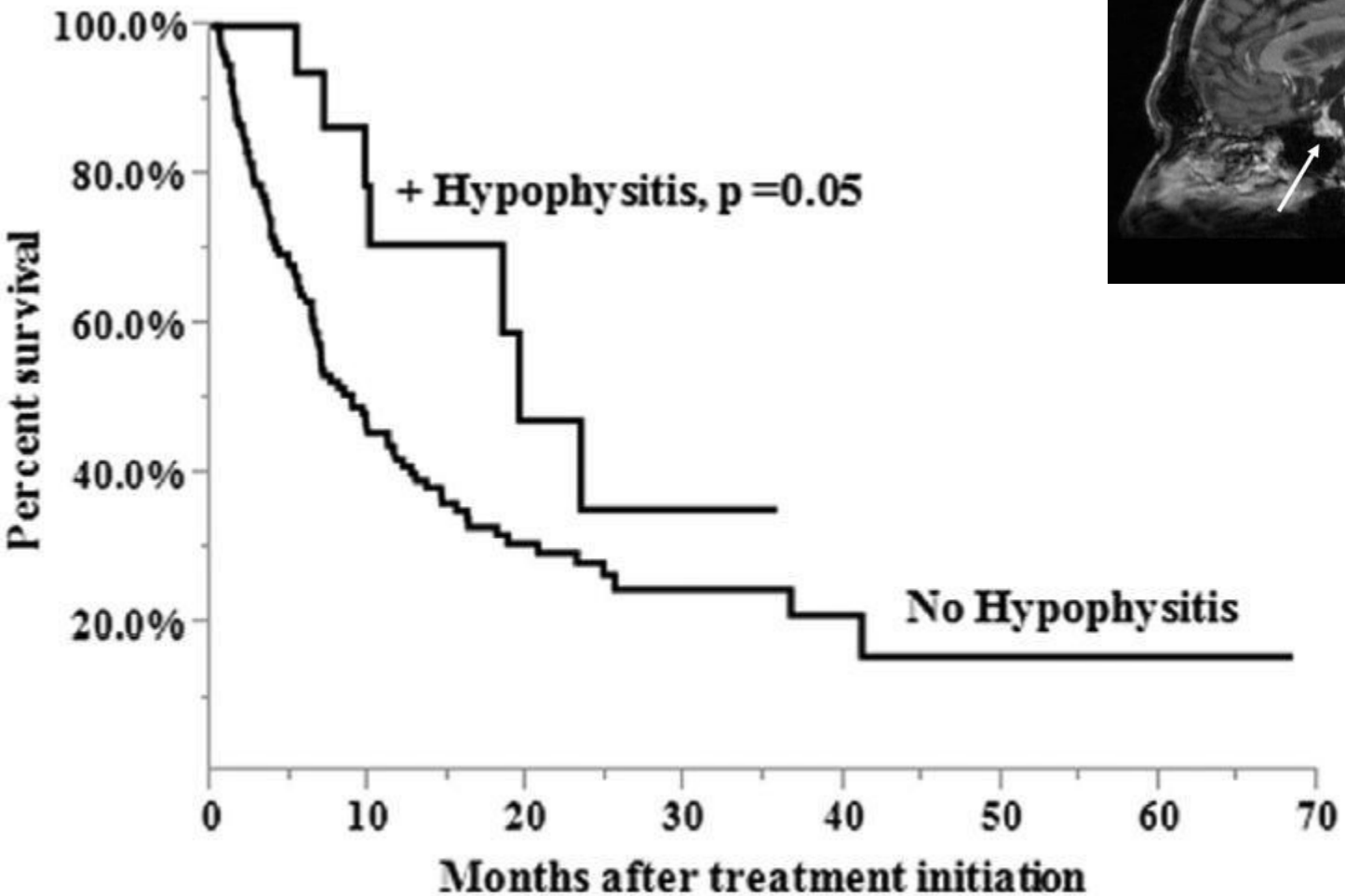


Figure 1. Kaplan-Meier plots for survival in metastatic melanoma patients, with and without hypophysitis, after the initiation of Ipi.

Faje et al, 2014

NCT

PD-1ab induzierte Arthralgien und Therapieansprechen

	Patienten ohne Arthralgien	Patienten mit Arthralgien *
Patienten gesamt	149	24
Komplette Remission (CR)	6 (4%)	4 (17%)
Partielle Remission (PR)	32 (22%)	15 (63%)
Stabilisierung (SD)	34 (23%)	5 (21%)
Progress (PD)	77 (52%)	0

26%

80%

** Differenz des Ansprechen (CR+PR) versus kein Ansprechen (SD+PD) zwischen Patienten mit und ohne Arthralgien war statistisch signifikant (Chi-Quadrat Test: $p < 0.0001$).*

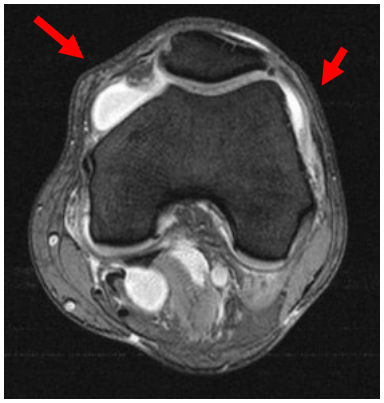
Buder et al, 2017

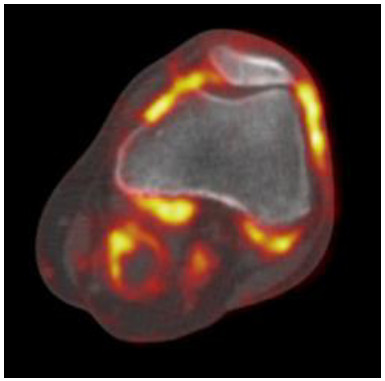
NCT

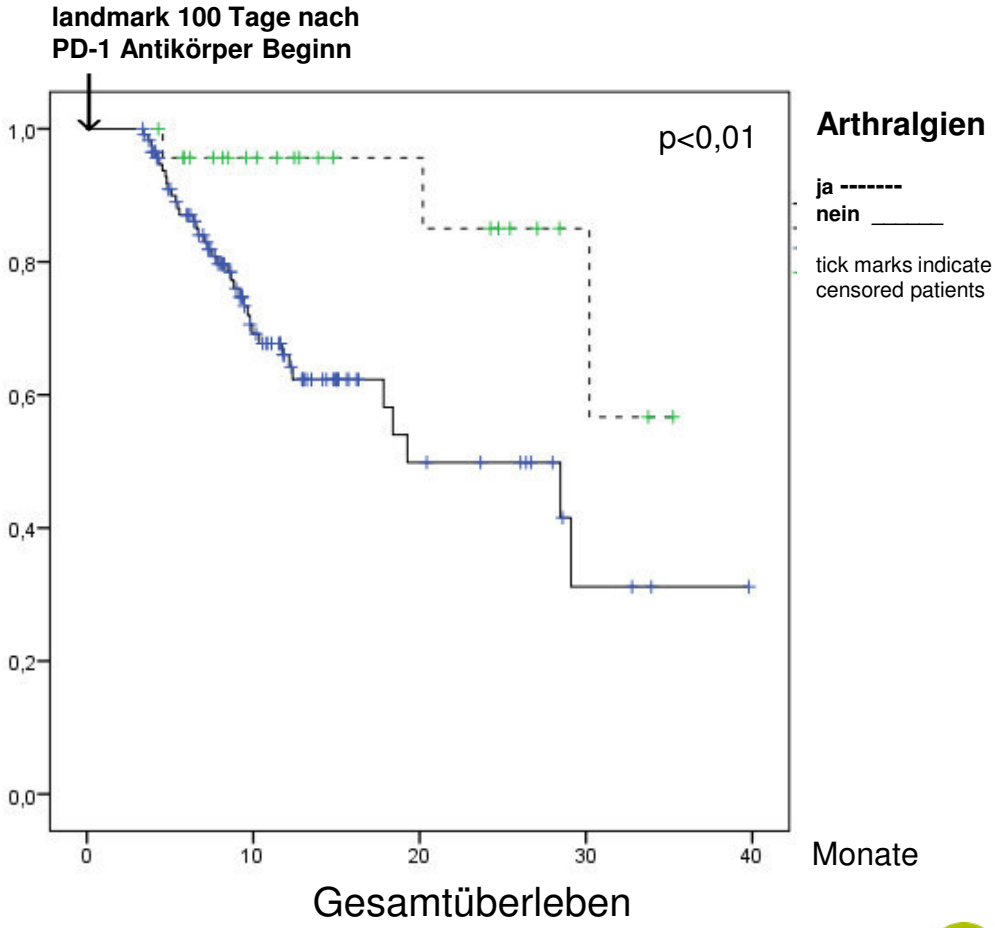
Arthralgien unter PD-1 gerichteter Therapie

Retrospektive Analyse von 195 Patienten

Patient mit Oligoarthritis der Kniegelenke





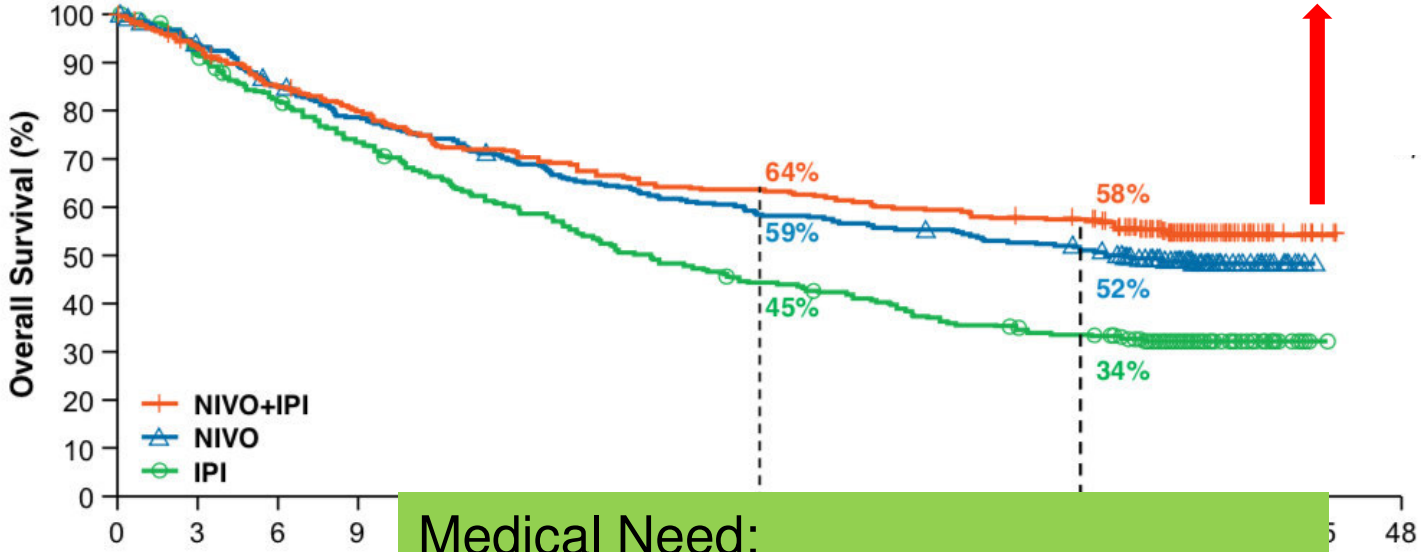


Buder et al, 2017

NCT

Wer profitiert von der Immuntherapie?

Medical Need



Patients at risk:

NIVO+IPI	314	292	265	247	0
NIVO	316	292	265	244	0
IPI	315	285	253	227	0

1. Wolchok JD et al. *N Engl J Med.* In press.

<u>Medical Need:</u>

- Biomarker für Therapieansprechen
- Erhöhung der Ansprechrate

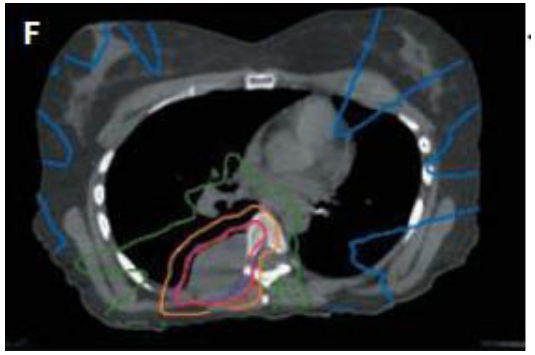
Wolchok et al, NEJM 2017

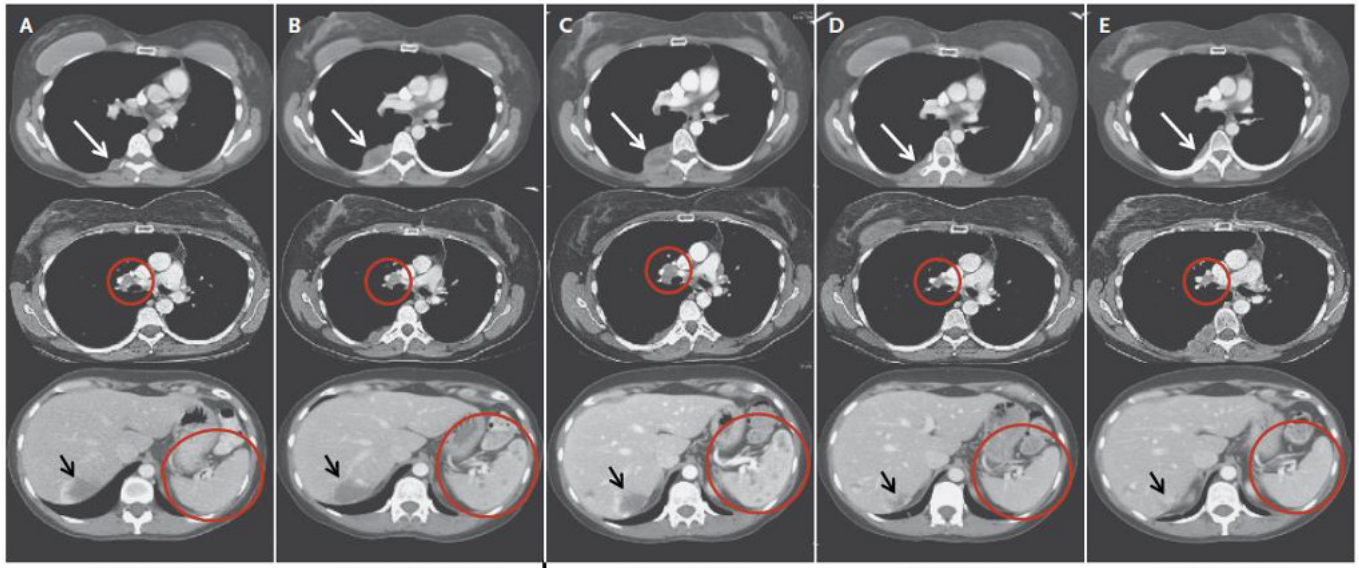
NCT

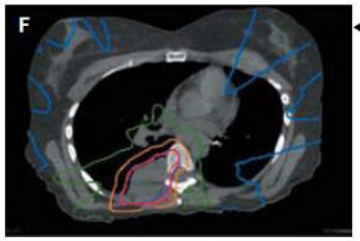
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

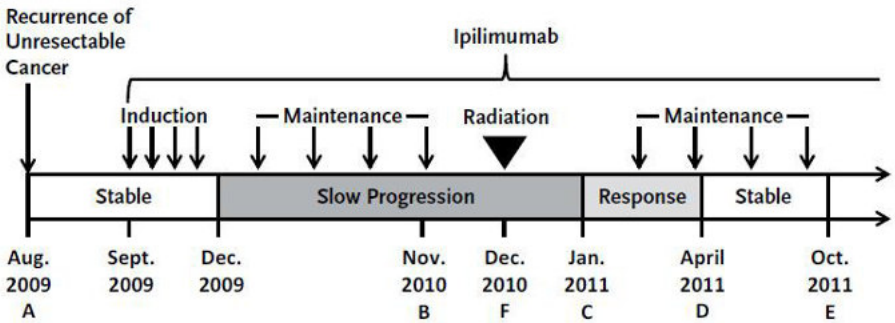
Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma







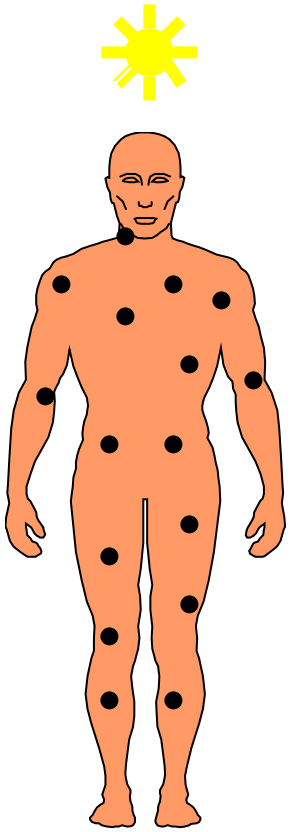
December 2010



Postow et al, 2012

NCT

Zielgerichtete Therapie

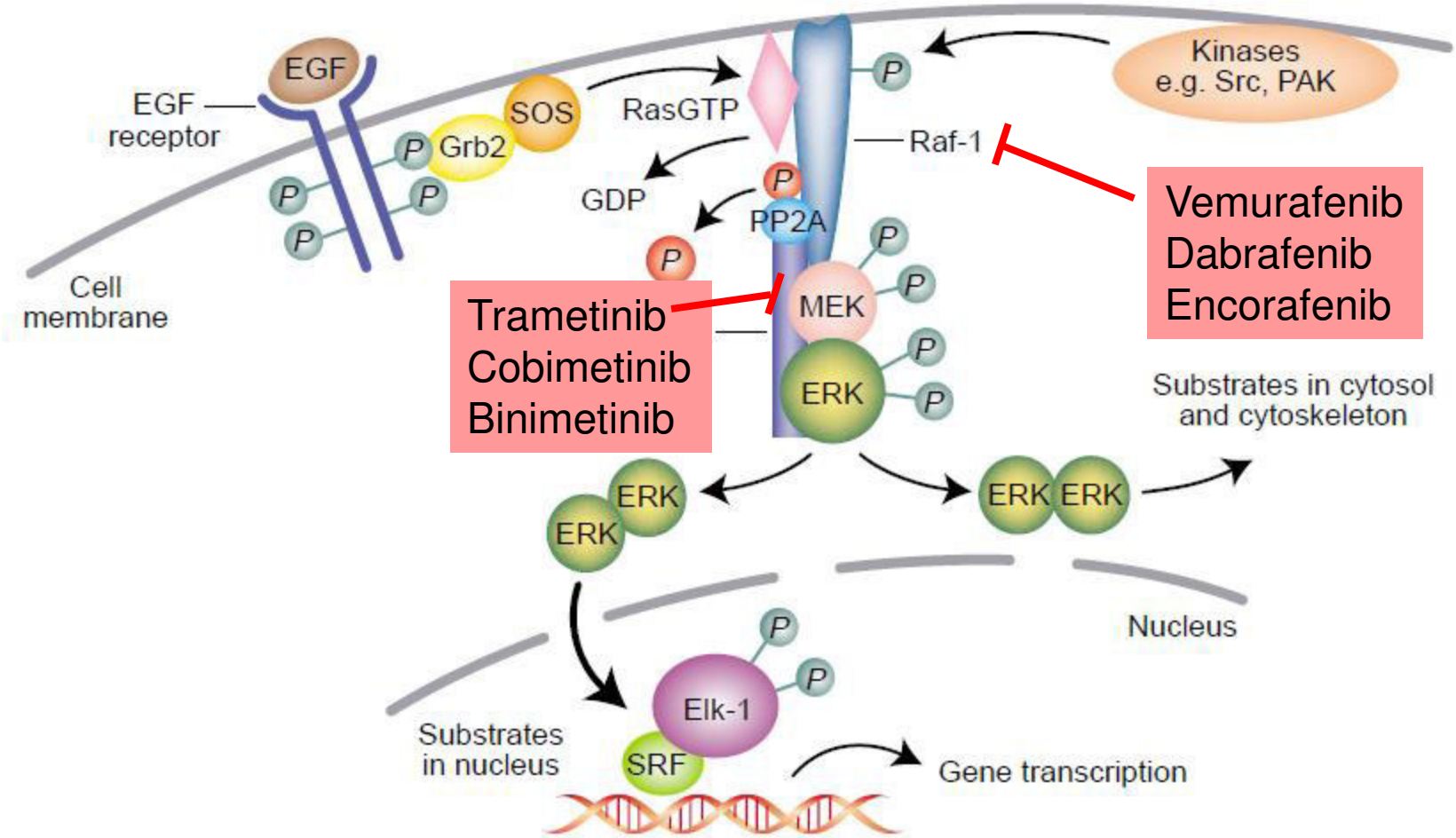


- BRAFV600E Mutation = Ziel
- Biomarker für Therapieansprechen!
- Primäre Resistenzen ausgesprochen selten

- etwa 50% der Melanome: B-Raf Mutation
- intermitt. UV-Exposition
- viele Nävi

NCT

BRAF- und MEK-Inhibitoren

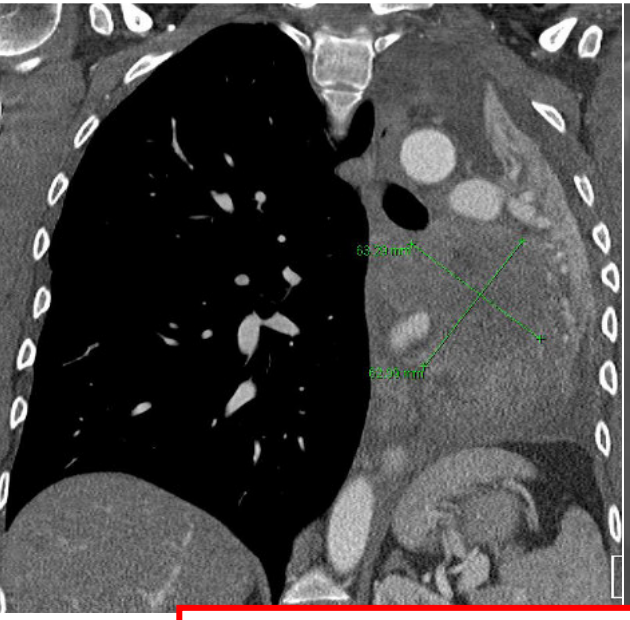


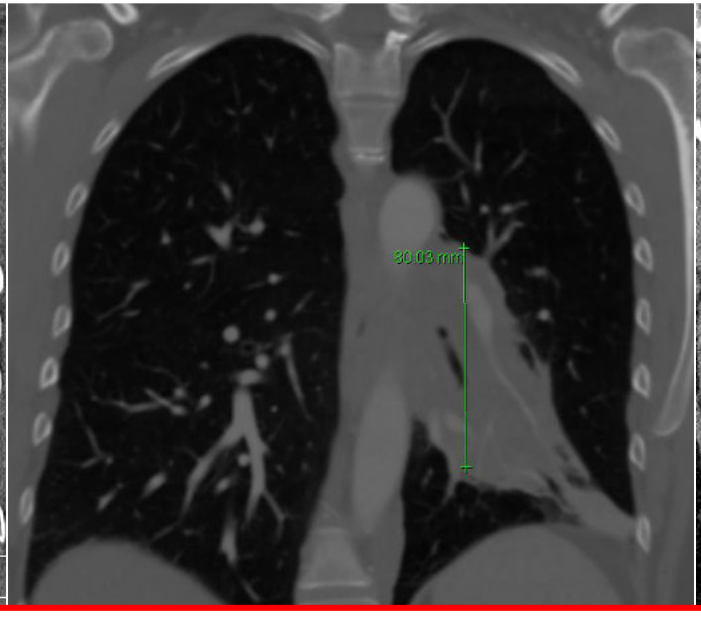
➔ Zellwachstum und Unsterblichkeit

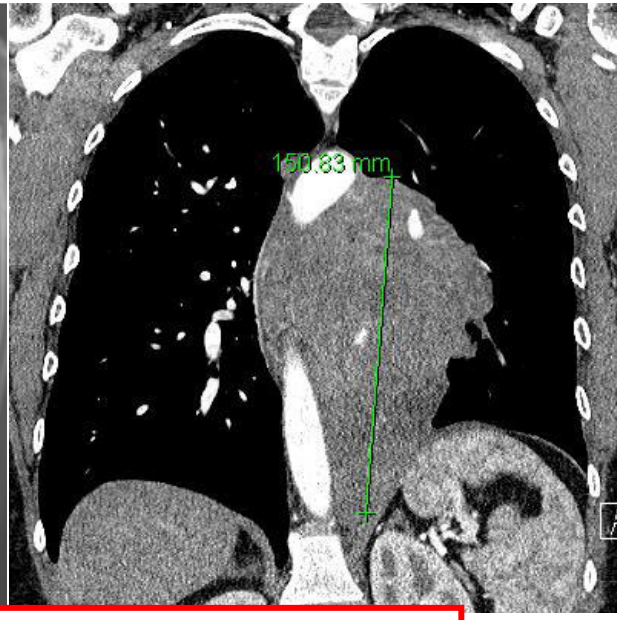
Kolch et al, 2002

NCT

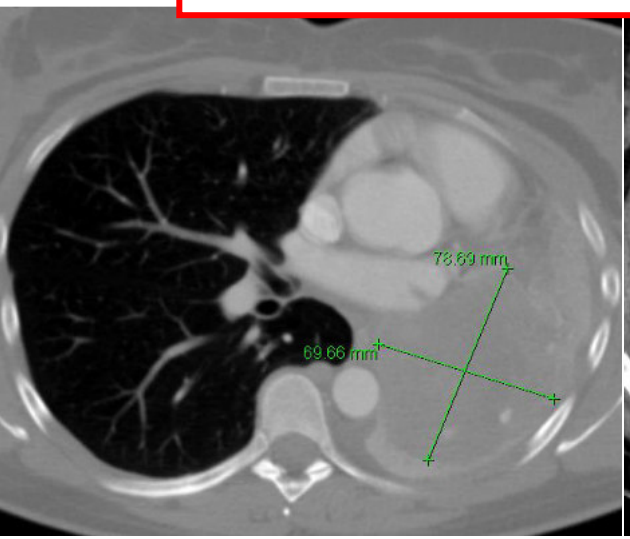
vorher -23% PD

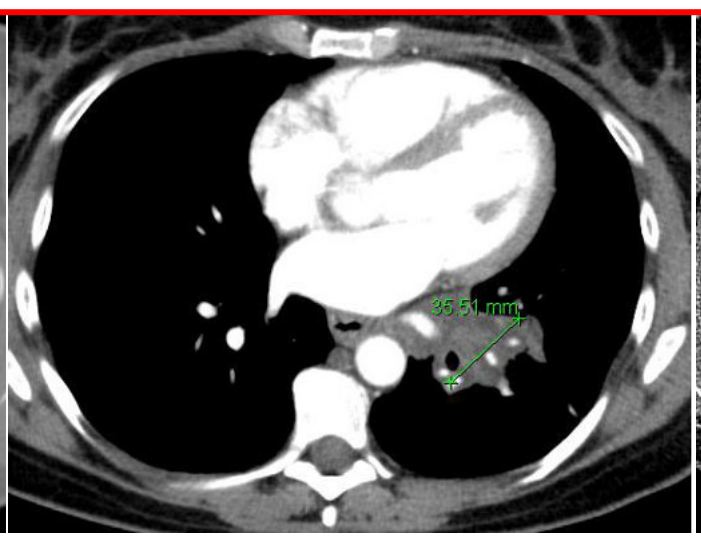


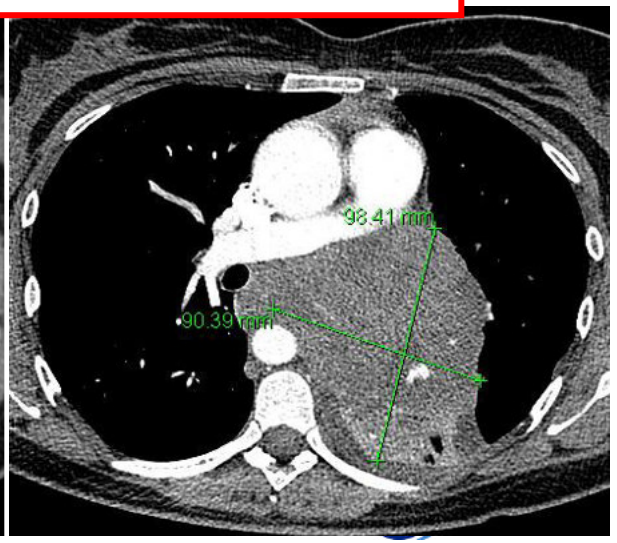




Mediane Dauer des Therapieansprechens liegt bei etwa einem Jahr





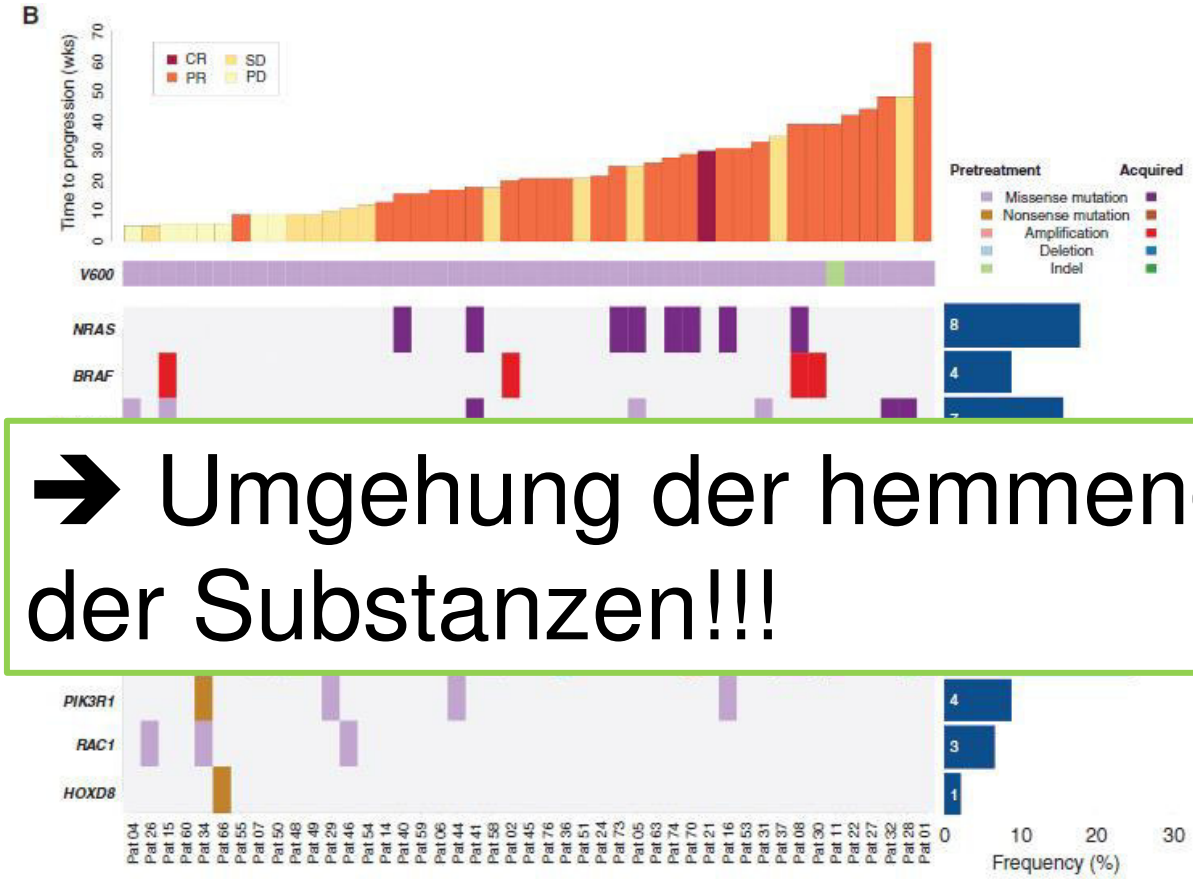


RESEARCH ARTICLE

The Genetic Landscape of Clinical Resistance to RAF Inhibition in Metastatic Melanoma

Eliezer M. Van Allen[1,3], Nikhil Wagle[1,3], Antje Sucker[5,6], Daniel J. Treacy[1], Cory M. Johannessen[3], Eva M. Goetz[1], Chelsea S. Place[1,3], Amaro Taylor-Weiner[3], Steven Whittaker[3], Gregory V. Kryukov[3], Eran Hodis[1,3,4], Mara Rosenberg[3], Aaron McKenna[3,15], Kristian Cibulskis[3], Deborah Farlow[3], Lisa Zimmer[5,6], Uwe Hillen[5,6], Ralf Gutzmer[8], Simone M. Goldinger[16], Selma Ugurel[9], Helen J. Gogas[17], Friederike Egberts[10], Carola Berking[6,11], Uwe Trefzer[6,12], Carmen Loquai[6,13], Benjamin Weide[6,14], Jessica C. Hassel[6,7], Stacey B. Gabriel[3], Scott L. Carter[3], Gad Getz[2,3], Levi A. Garraway[1,3], and Dirk Schadendorf[5,6] on behalf of the Dermatologic Cooperative Oncology Group of Germany (DeCOG)

Cancer Discovery 2014



➔ Wiederaktivierung des MAPK-

➔ Umgehung der hemmenden Wirkung der Substanzen!!!

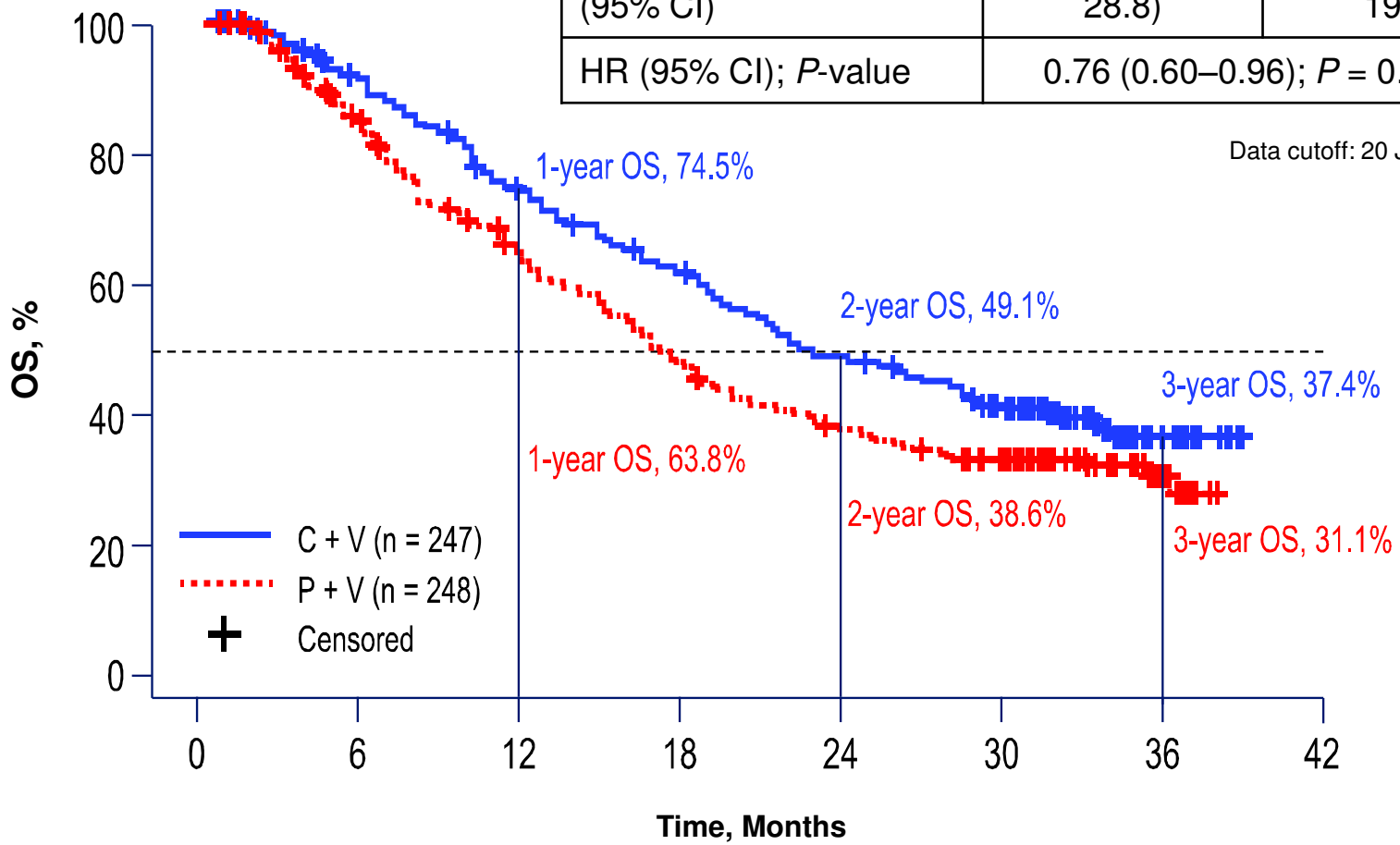
anderen Signalweges

NCT

CoBRIM: 3-yr Überleben Vemurafenib + Cobimetinib

	C + V	P + V
Median OS, months (95% CI)	22.5 (20.3, 28.8)	17.4 (15.0, 19.8)
HR (95% CI); *P*-value	0.76 (0.60–0.96); *P* = 0.0188	

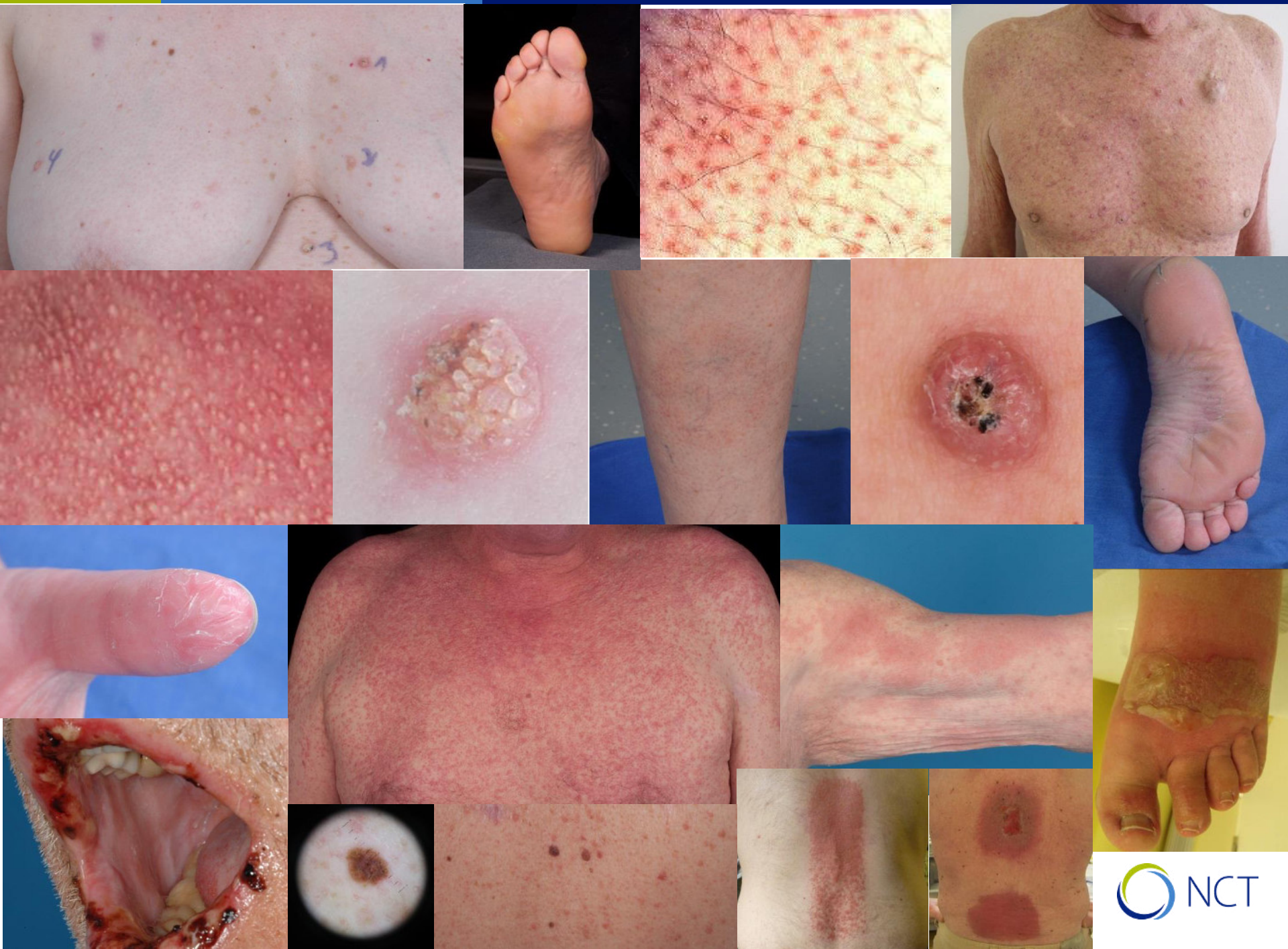
Data cutoff: 20 June 2016



Patients at risk, n

C + V	247	210	210	192	169	152	139	123	109	99	83	50	16
P + V	248	230	194	165	142	126	107	93	84	76	65	37	15

Presented as a poster at: the Society for Melanoma Research 2016 Congress; McArthur G et al. November 6-9, 2016; Boston, MA, USA.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coBRIM: Nebenwirkungen

	Vemurafenib + Plazebo (n = 239)		Vemurafenib + Cobimetinib (n = 254)	
Unerwünschte Ereignisse (UE), n (%)	**Alle Grade**	**Grad ≥ 3**	**Alle Grade**	**Grad ≥ 3**
Häufigste UE				
Diarrhoe	67 (28)	0 (0)	144 (56)	16 (6)
Übelkeit	57 (24)	2 (1)	99 (40)	2 (1)
Hautausschlag/Rash	85 (35)	12 (5)	99 (39)	15 (6)
Arthralgie	96 (40)	12 (5)	83 (32)	6 (2)
Fatigue	73 (31)	7 (3)	81 (32)	9 (4)
Erhöhte Kreatinkinase	7 (3)	0 (0)	76 (31)	26 (11)
Photosensitivität	37 (15)	0 (0)	72 (28)	6 (2)
Fieber	53 (22)	0 (0)	66 (26)	4 (2)
Erhöhte Alanin-Aminotransferase	43 (18)	15 (6)	60 (24)	29 (11)
Erhöhte Aspartat-Aminotransferase	30 (13)	5 (2)	56 (22)	21 (8)
Erbrechen	29 (13)	2 (1)	54 (21)	3 (1)
Alopezie	70 (29)	1 (< 1)	35 (14)	1 (< 1)
Hyperkeratose	68 (29)	5 (2)	26 (10)	0 (0)
Ausgewählte UE				
Seröse Retinopathie	1 (< 1)	0 (0)	51 (20)	7 (2)
Verringerte Ejektionsfraktion	7 (3)	3 (1)	19 (8)	3 (1)
Verlängertes QT-Intervall	13 (5)	3 (1)	9 (3)	1 (< 1)
Kutanes Plattenepithelkarzinom	27 (11)	27 (11)	7 (2)	6 (2)
Keratoakanthom	20 (8)	18 (8)	2 (1)	2 (1)

➔ In 18% der Patienten wurde Therapie wegen AEs vollständig beendet

NCT

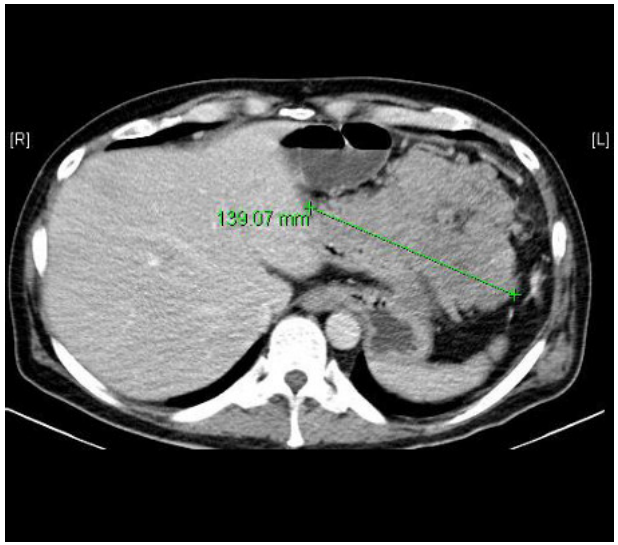
Modifiziert nach: Larkin et al. ASCO 2015, Oral Abstract Session Melanoma/Skin Cancers, Abstract No. 9006.

Kombinationstherapie?

➔ Hohe Ansprechrate + Langzeitremissionen?

NCT

57j. Patient



- Überweisung durch die Chirurgie bei durchbrechenden Bauchmetastasen (Not-OP)
- ein Jahr lang indonesische Heilkräuter bei nachgewiesener Metastasierung
- Gewicht: knapp 50kg
- Grösse: > 1,80m
- bettlägerig

➔ Start einer Therapie mit Vemurafenib 02/2012
➔ Zügige Besserung des Allgemeinzustandes
➔ Insgesamt 30kg Gewichtszunahme!

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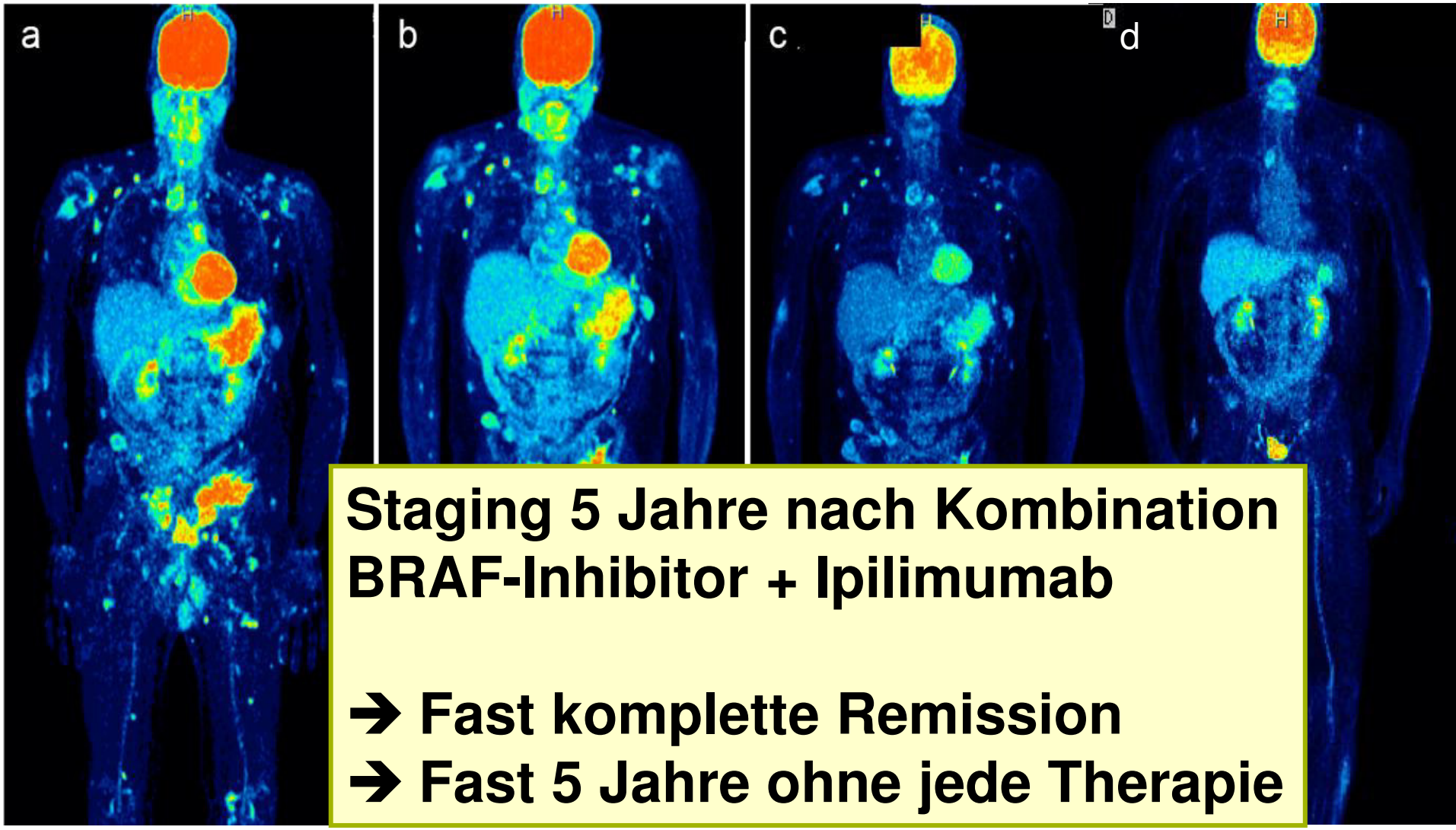
Kombination Ipilimumab + Vemurafenib als individueller Heilversuch

07/12 10/12 02/13 09/17



Staging 5 Jahre nach Kombination BRAF-Inhibitor + Ipilimumab

➔ Fast komplette Remission
➔ Fast 5 Jahre ohne jede Therapie

nach 5 Mo Vem vor Ipi | nach 4 Zyklen Ipi | bei Absetzen Vem | aktuell

NCT

Hassel et al, OncoImmunology 2016

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

Therapiestudien - Melanom

am Hauttumorzentrum der Univ.-Hautklinik Heidelberg
im Nationalen Centrum für Tumorerkrankungen (NCT)

Kontakt: Tel: 06221 - 56-8562
Hauttumorzentrum@med.uni-heidelberg.de

Stadium II
pT > 2 mm

Stadium III
lokoregionäre Metastasen

Stadium IV
Fernmetastasen

First-in-Human

Second-Line

First-Line

neoadjuvant (vor OP)

tumorfrei (nach OP)

mit Tumorlast (unresektabel)

L19IL2+L19TNF+ OP vs nur OP (PIVOTAL, Philogen)
Einschluss: St. IIIB/C, vollst. resezierbare bzw. injizierbare Läsionen (>10 mm)
Ausschluss: Uvea-/Schleimhaut-MM, Infektionserkr., Herzerkr., Autoimmunerkr.

adj. Nivo + Ipi vs Nivo vs Ipi (CA209-915, BMS)
Einschluss: tumorfrei St. IIIB-IV (max. 12 Wo)
Ausschluss: Uvea-MM, syst. MM-Vortherapie, Checkpoint-Vortherapie

Pembro +/- Onkolyt. Virus T-VEC (MASTERKEY-265, Amgen)
Einschluss: unres. Stadium IIIB-IV, erreichbare Metastasen für intraläsionale Therapie
Ausschluss: aktive Hirnmetastasen, Uvea-/Schleimhaut-MM, Vortherapie mit Immun-Checkpoint-Blocker, Autoimmunerkr.

Cobimetinib + Vemurafenib +/- Atezolizumab (TRILOGY/CO39262, Roche)
Einschluss: St. IIIunres/IV, BRAF V600- Mut.
Ausschluss: Vortherapie (Ausnahme: adj. INF, IL-2), aktive Hirnmet., Herzerkr., Autoimmunerkr., Immunsup., HIV/HBV/HCV

Cobimetinib + Vemurafenib gefolgt von Atezolizumab (ImmunoCobiVem, UK Essen)
Einschluss: St. IIIunres/IV, BRAF V600- Mut.
Ausschluss: Vortherapie (Ausnahme: adj. INF, IL-2), aktive Hirnmet., Herzerkr., Autoimmunerkr., Immunsup., HIV/HBV/HCV

PDR001 + Dabrafenib + Trametinib (COMBI-i, Novartis)
Einschluss: St. IIIunres/IV, BRAF V600- Mut., Part 2: ≥2 erreichbare Läsionen
Ausschluss: Vortherapie (St. IIIunres/IV), Uvea-/Schleimhaut-MM, Part 2/3: aktive Hirnmet., Autoimmunerkr.,

RNA-Lipoplex Vakzinierung (Lipo-MERIT, Biontech)
Einschluss: Stadium IIIB-IV, keine andere Therapieoption
Ausschluss: Uvea-Melanom, Hirnmet., Splenektomie, Infektion, Autoimmunerkr.

Ipilimumab + Radiatio (Hirnmet.) (ELEKTRA, IIT)
Einschluss: Stadium IV mit Hirnmetastasen
Ausschluss: frühere Radiatio (Hirnmet.)

IMCgp100 + Durvalumab und/oder Tremelimumab (IMCgp100-201, Immunocore)
Einschluss: Stadium IIIunres/IV, HLA-A2 positiv, erlaubte Vortherapien Phase-abh.
Ausschluss: Uvea-/Akral-/Schleimhaut-MM, aktive Hirnmet., Interstitielle Lungenerkr., Herzerkr., Autoimmunerkr.

Paclitaxel +/- Nintedanib (Nipawilma, UK Essen)
Einschluss: Stadium IIIunres/IV, BRAF wt, messbare Läsionen
Ausschluss: aktive Hirnmet., Taxan-/Kinase-Inh.-Vortherapie, Thrombosen

Masitinib vs DTIC (AB08026, AB Science)
Einschluss: Stadium IIIC/IV, c-kit Mutation
Ausschluss: aktive Hirnmet., Herzinsuffizienz

Dabrafenib +/- Trametinib (BOTTOM, UK Essen)
Einschluss: Stadium IIIunres/IV, BRAF V600-Mutation, biopsierbare Metastasen, auch Reexposition BRAFi/MEKi
Ausschluss: Uvea-/Schleimhaut-MM, aktive Hirnmet., Herzerkr., HIV/HBV/HCV

Nivolumab vs Nivolumab+Ipilimumab vs Placebo (IMMUNED, UK Essen)
Einschluss: tumorfrei St. IV/St. III mit unbek. Primarius, BRAF-Status, Gewebe f. PD-L1-Test
Ausschluss: Uvea-/Schleimhaut-MM, α-CTLA4-/α-PD1-Vortherapie, Autoimmunerkr.

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Dankeschön!