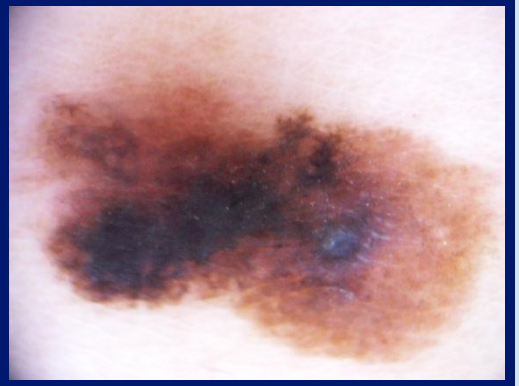


Ipilimumab:

Immuntherapie hilft doch!

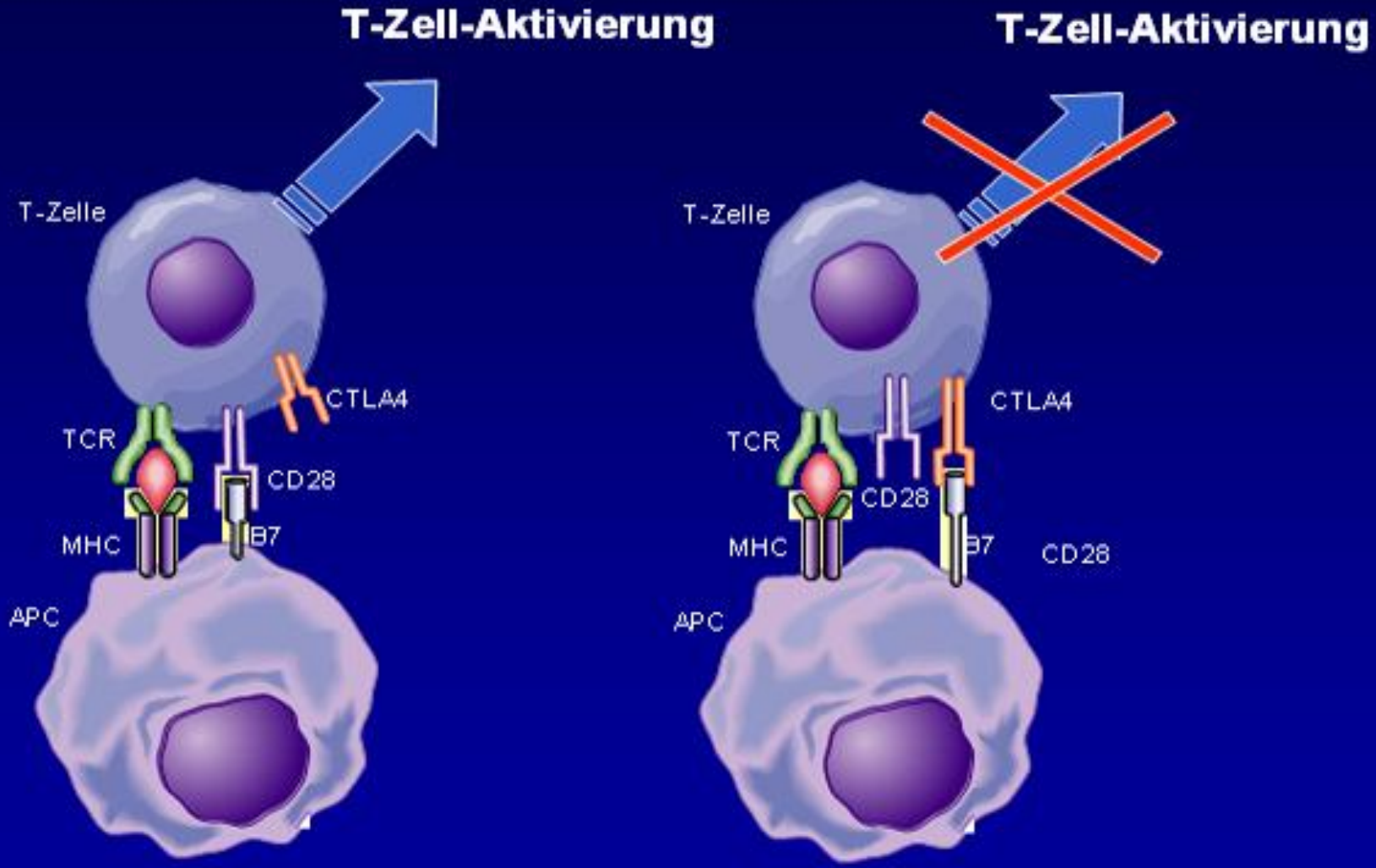
Jessica C. Hassel

Universitätshautklinik und

Nationales Centrum für Tumorerkrankungen Heidelberg

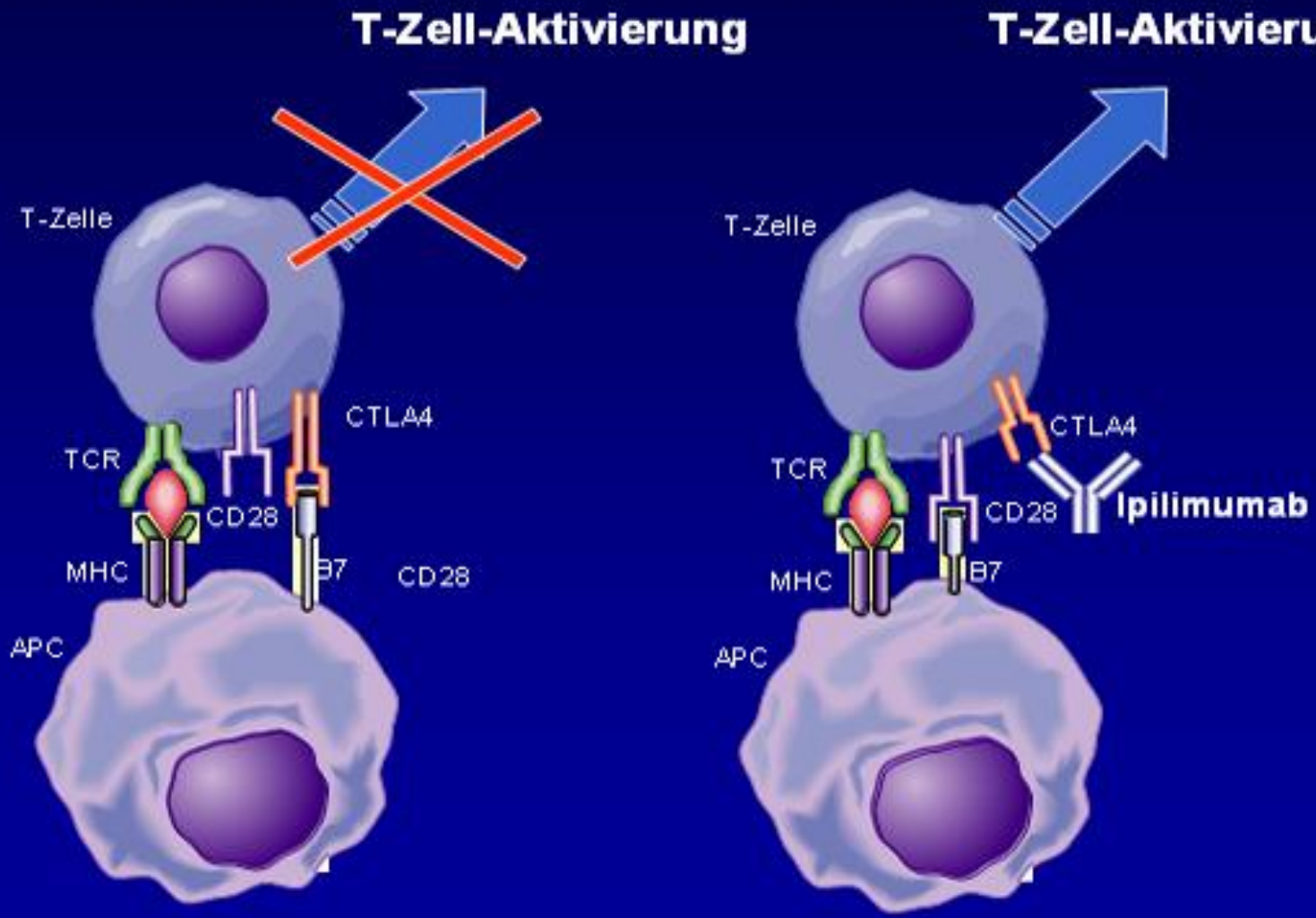
NCT | NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

Negative Signalübertragung von CTLA4 blockiert T-Zell-Aktivierung



ierend auf Lebbé et al. ESMO 2008

Ipilimumab vermindert die negative Signalübertragung von CTLA4



Basierend auf Lebbé et al. ESMO 2008

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

ABSTRACT

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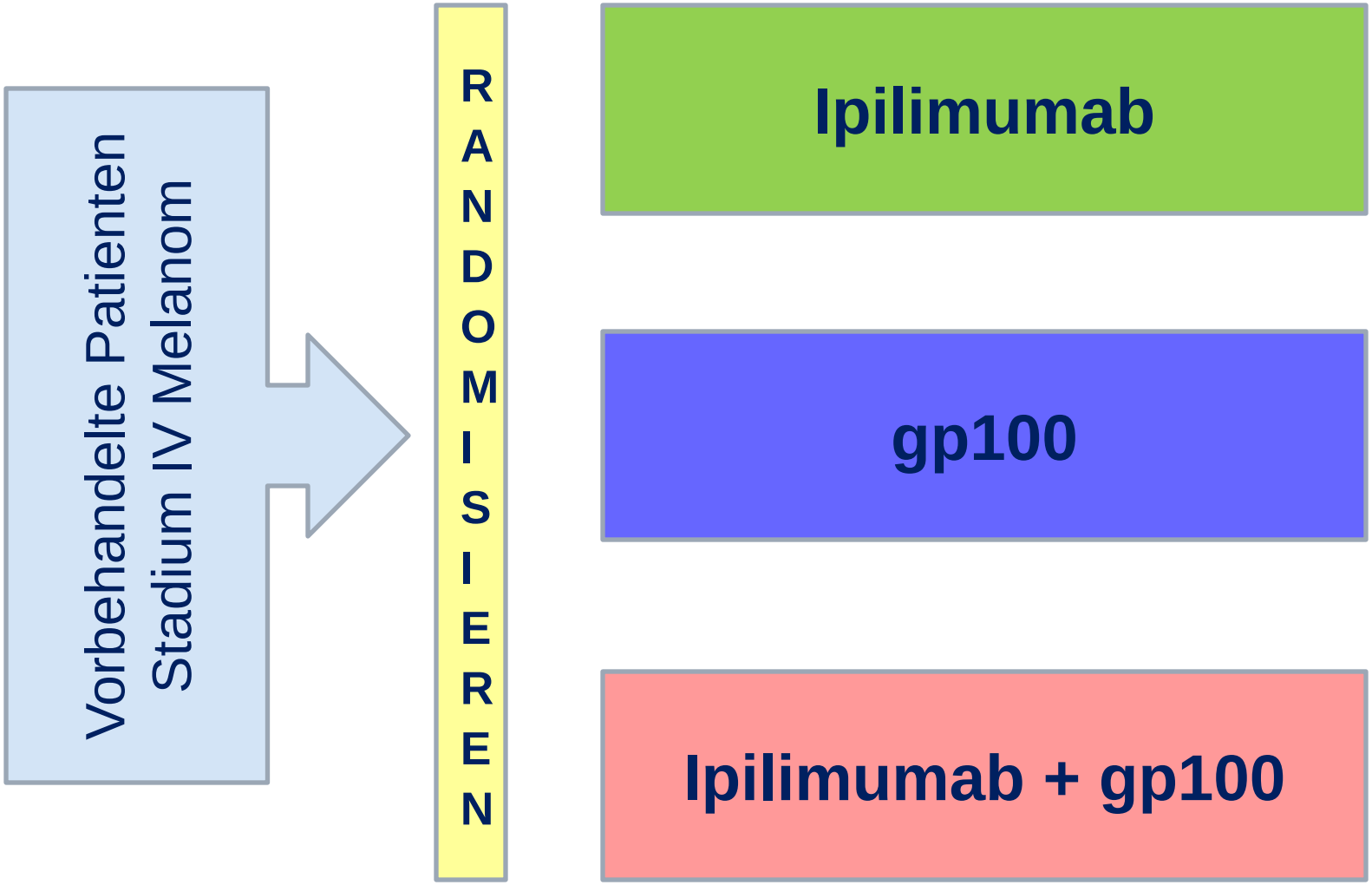
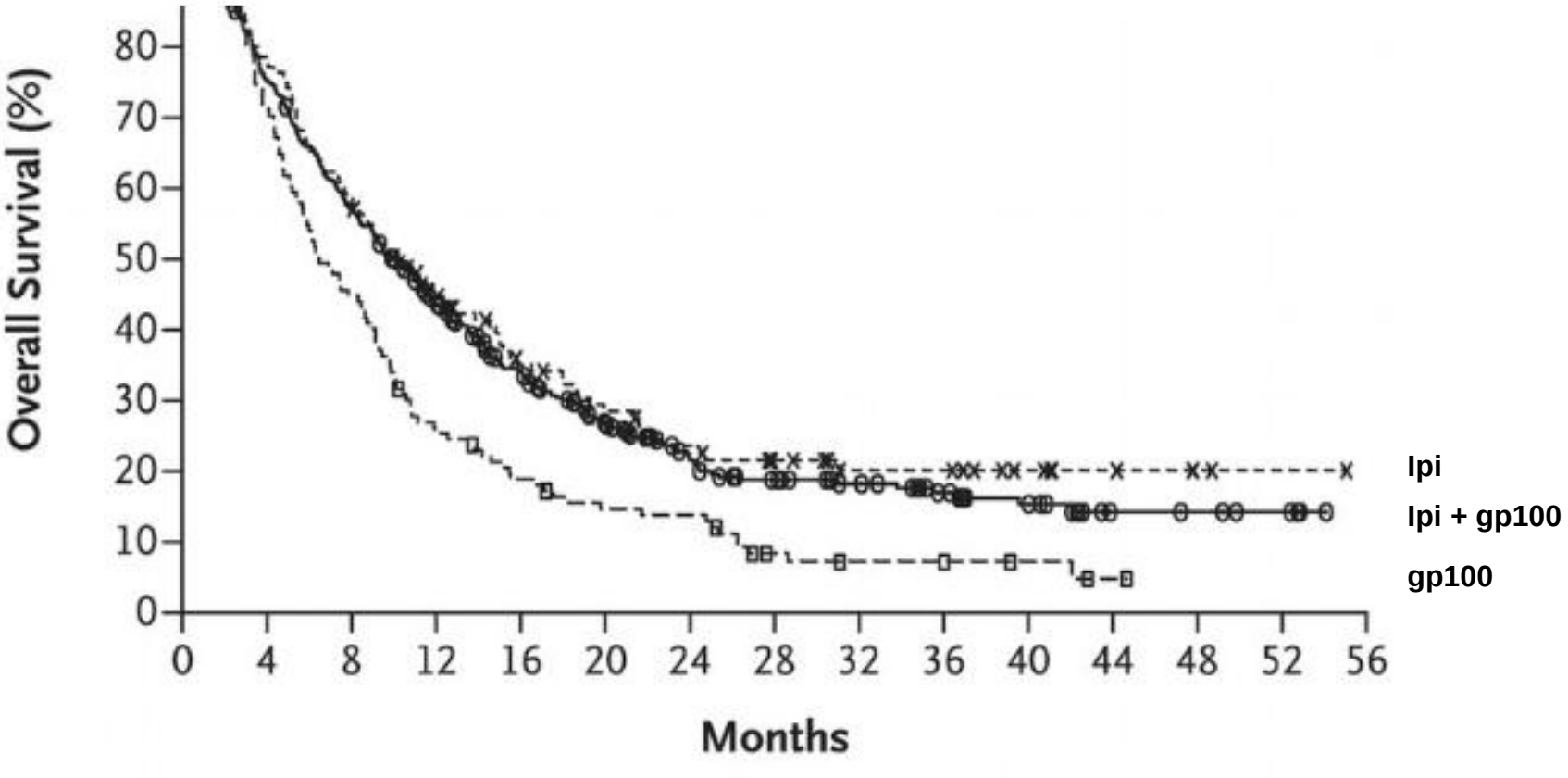




Median OS:	Ipi + gp100	10,0 Monate	p<0,001
	Ipi	10,1 Monate	p=0,003
	gp100	6,4 Monate	

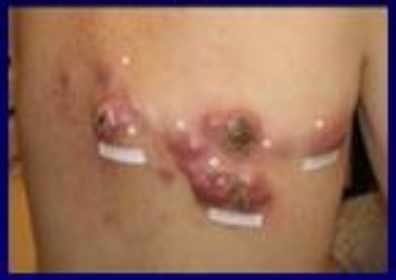
Ansprechen Ipilimumab-Gruppe

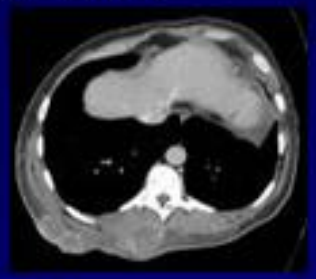
Ansprechen	%
CR	1,5
PR	9,5
SD	17,5
PD	51,1
Nicht evaluierbar	20,4

➔ **Median time to response: 3,2 Monate**

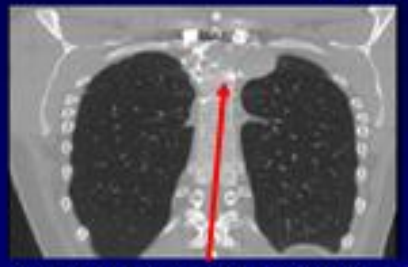
Entwicklung des Ansprechens
Patientenbeispiel

Beim Screening (Nov 2006)

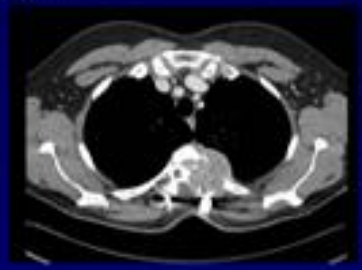




Woche 7 (ausgelassene Dosis)
Laminektomie

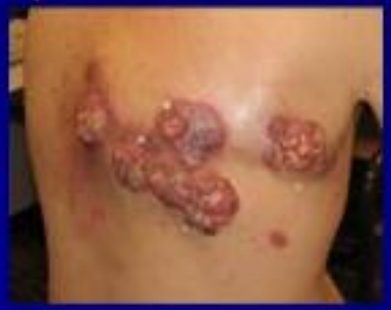


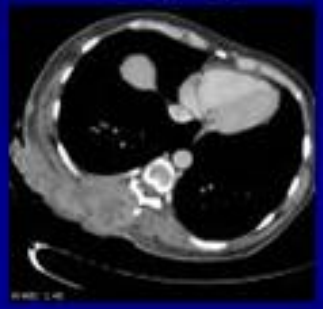
3.5 cm Metastase dorsale



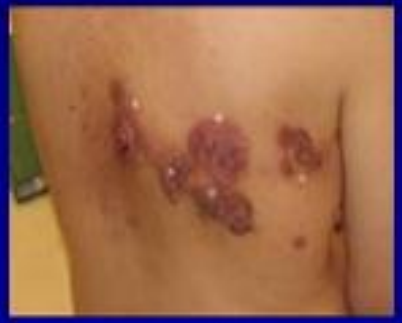
Nach
Laminektomie

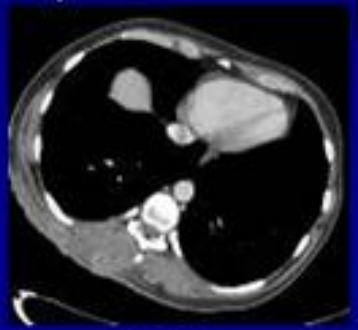
Woche 12
Anfänglicher Zuwachs in gesamter Tumorlast
(nach mWHO-Kriterien: Krankheitsprogression)





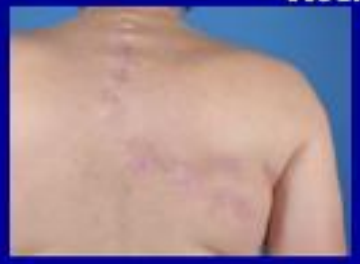
Woche 16
Partielles Ansprechen





Mit Genehmigung von K. Harmankaya
Dermatologie, Med. Univ. Wien, Österreich

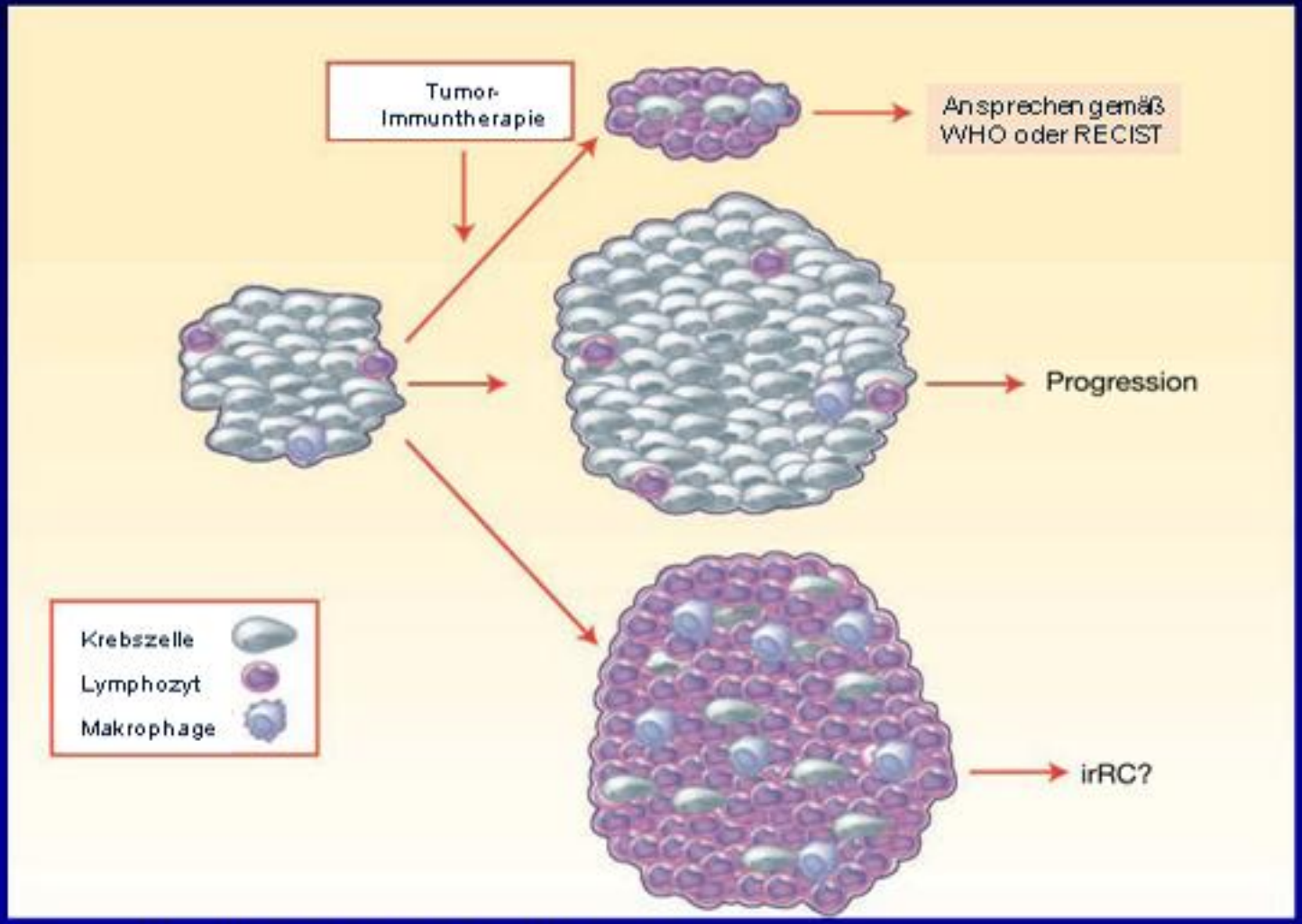
Woche 130



3+ Jahre unter Ipilimumab 10mg/kg (Erhaltungsphase)

Dauerhaftes und anhaltendes partielles Ansprechen ohne Anzeichen von irAE (residuelles Tumorgewebe links dorsal)

Ansprechkriterien (irRC) für die Tumor-Immuntherapie?



Ribas A *et al.* Clin Cancer Res 2009;15(23):7116–8) 2009;15: 7116-8.

Immune related Response Criteria (irRC)

	WHO	irRC
New, measurable lesions (ie, ≥5 x 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (ie, <5 x 5 mm)	Always represent PD	Do not define progression
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, PD	Contribute to defining irRC (complete disappearance required)
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 wk apart

Ipilimumab CU Heidelberg: 22 Patienten

- Ansprechrate:

CR	1 Pat / 4,5%
PR	2 Pat / 9%
SD	2 Pat / 9%
PD	16 Pat / 73%
nicht evaluierbar	1 Pat

- Nebenwirkungen:

  Therapieabbrüche aufgrund Nebenwirkung 6 Patienten

  ≥ Grad 3 ➔ 27%

  Diarrhoen: 2 Pat

  Hepatitis: 2 Pat

  Hypophysitis: 1 Pat (spät)

  Pankreatitis: 1 Pat

Fall 1

Patientenfall: Männlicher Patient, 76 Jahre

Melanom, TD 3 mm, Schulter links 2003

- Sentinellymphknoten nicht auffindbar
- Keine Interferontherapie
- Lymphknotendissektion axillär links (1+/13) 01/08
- Hochdosisinterferon, Abbruch nach 1 Woche
- Leberfiliae 07/09
- 3 Zyklen DTIC 08/09-10/09, pulmonale Filiae
- 3 Zyklen Gemcitabin 11/09-01/10, cerebrale Filiae
- 9 Zyklen Carboplatin/Paclitaxel 03-08/10, Progress Leberfiliae, cerebrale und pulmonale Metastasen nicht mehr nachweisbar 11/10

Männlicher Patient, 76 Jahre

- 11.01.11: 1. Zyklus Ipilimumab 3mg/kg
- 31.01.11: AZ-Verschlechterung, gespannter Bauch, epigastrischer Druckschmerz

  Labor:

  GOT 572 U/l

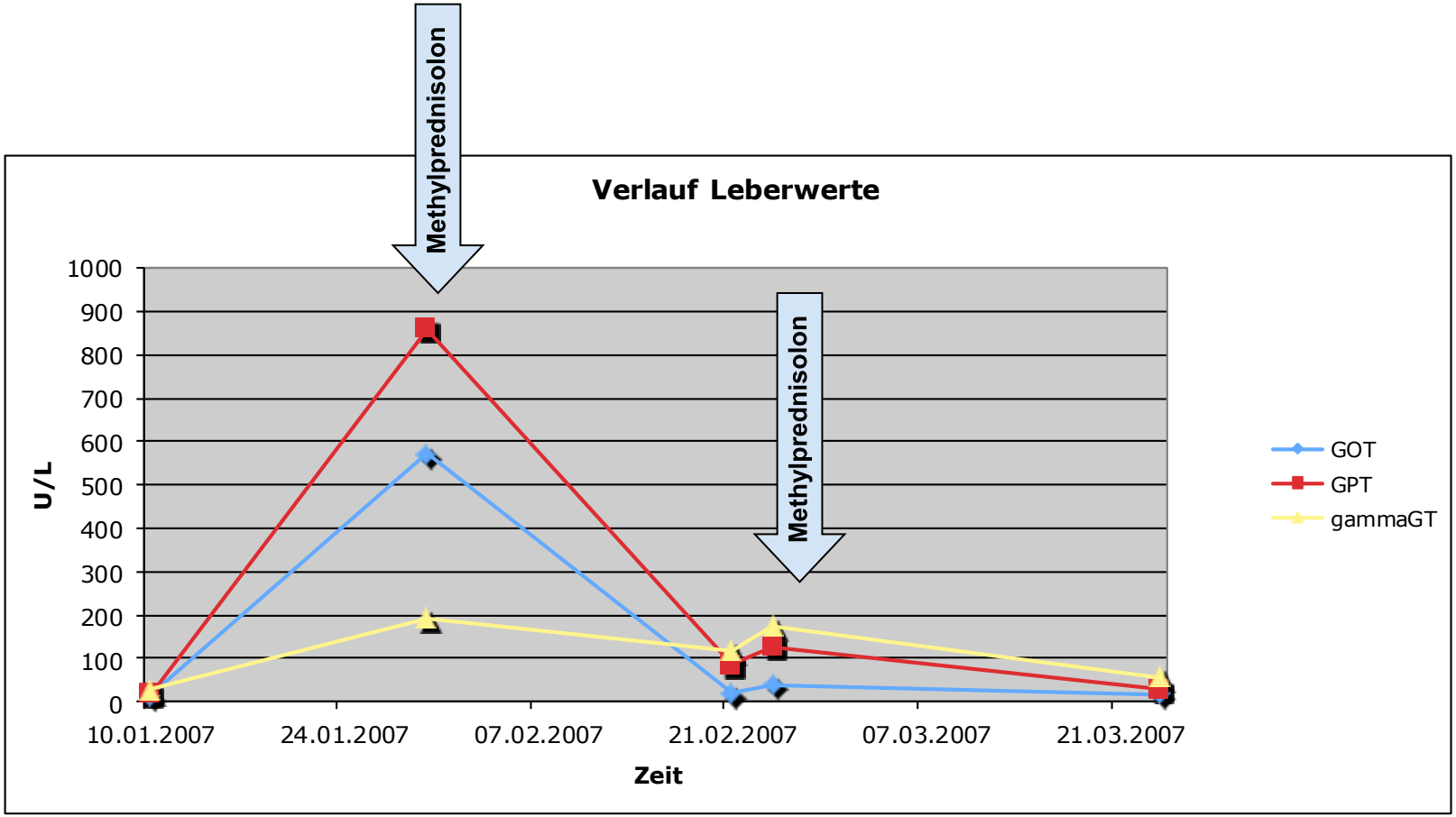
  GPT 859 U/l

  GammaGT 194 U/l

  Bilirubin 3,4 mg/dl

  → Methylprednisolon 150 mg 1-0-0 i.v., schrittweise Reduktion, Absetzen nach 3 Wochen

Männlicher Patient, 76 Jahre



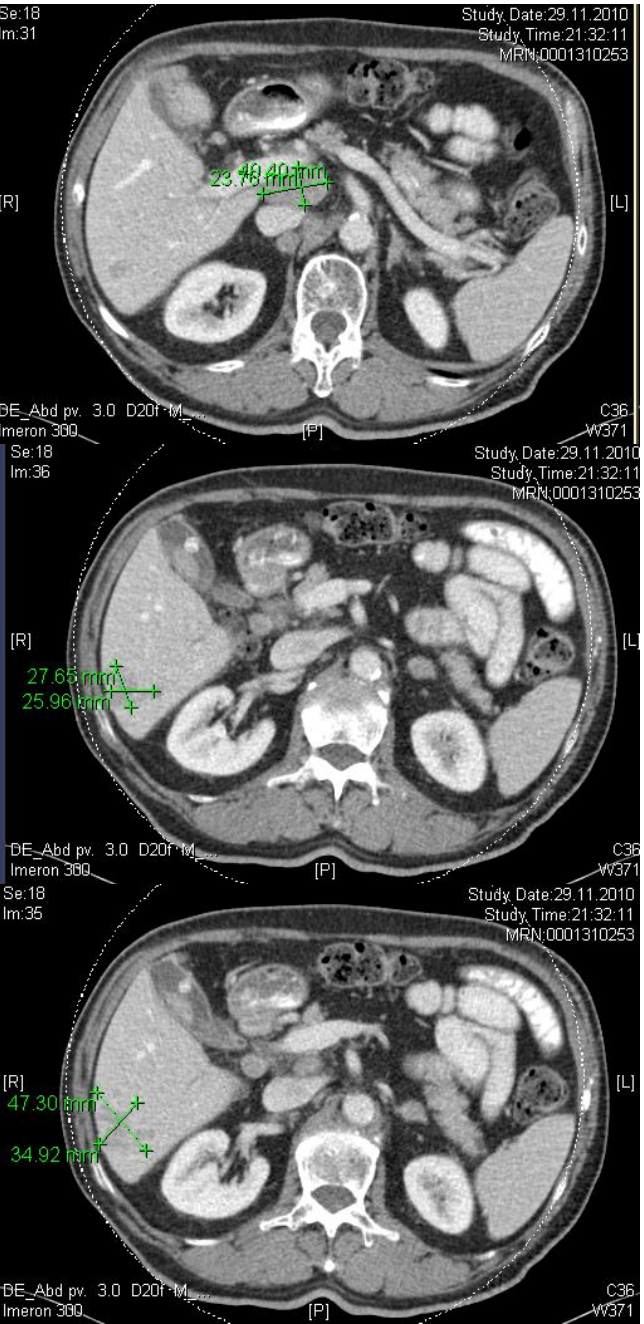
Männlicher Patient, 76 Jahre

- Methylprednisolon schrittweise reduziert bis 05/11
  - Insulinpflichtiger steroidinduzierter Diabetes mellitus
  - Leberwerte und Bilirubin normwertig

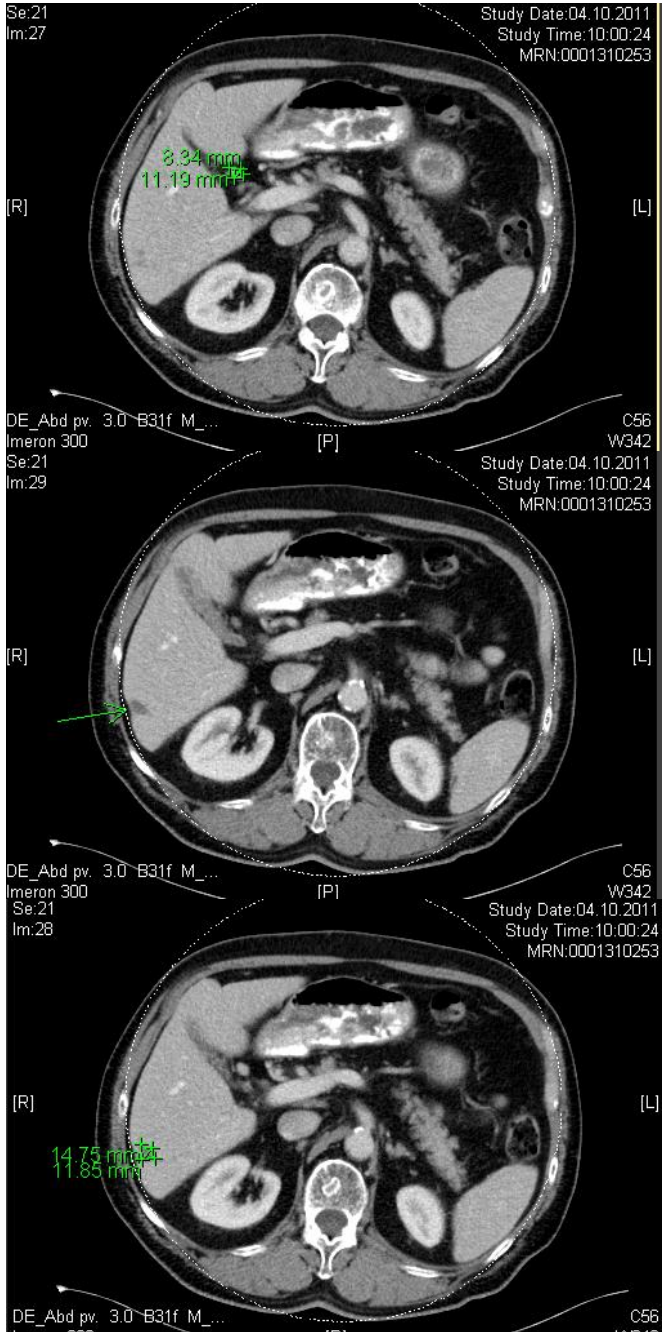
- Staging vom 21.03.11:
  - Lungenarterienembolie
  - Regrediente Lebermetastase Segment VI
  - Im Leberhilus deutlich regrediente Metastasen
  - Kein Nachweis von cerebralen Filiae

- Staging vom 4.10.11:
  - Leber- und LK-Metastasen Leberhilus weiter rückläufig

vor Ipi



nach Ipi



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Männlicher Patient, 76 Jahre

- Staging vom 16.1.12 (1 Jahr später):
  LK-Leberpforte progredient, grössenkonstante Lebermetastasen

- Vorstellung Tumorboard: noch operabel
  ➔ Explorative Laparotomie mit anatomischer Lebersegmentresektion 6, 7 sowie atypischer Leberresektion Segment 4a, Cholecystektomie und LK-Exzision 02/12

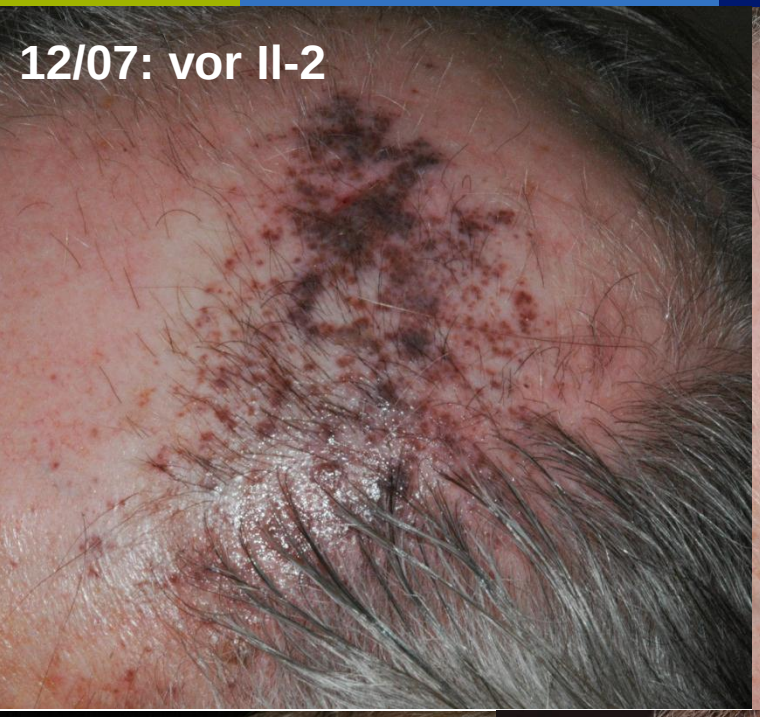
- Pathologischer Befund:
  MM-Metastase Gallenblase
  Leberresektate mit bindegewebig substituiertem Nekroseareal
  LK mit Sinushistiozytose ohne MM-Nachweis

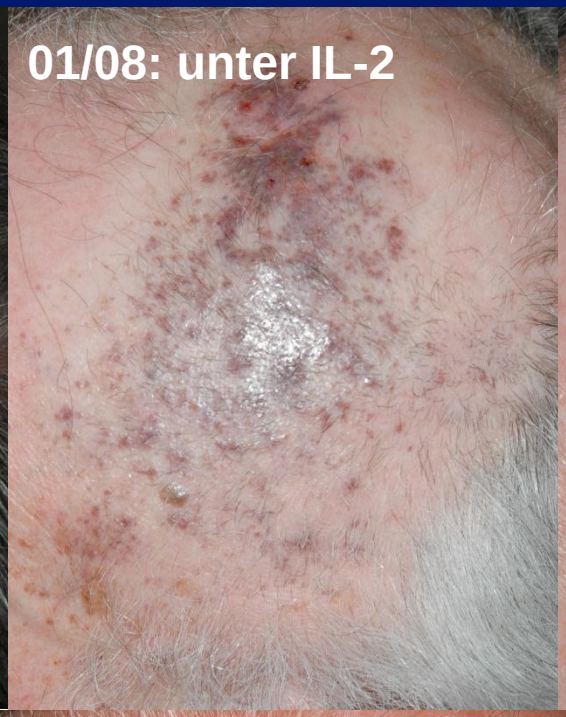
Fall 2

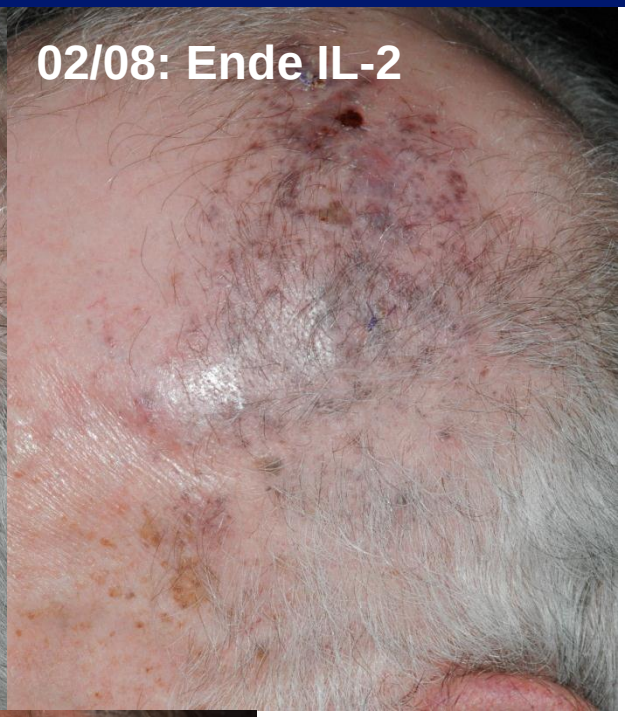
76j. Patient

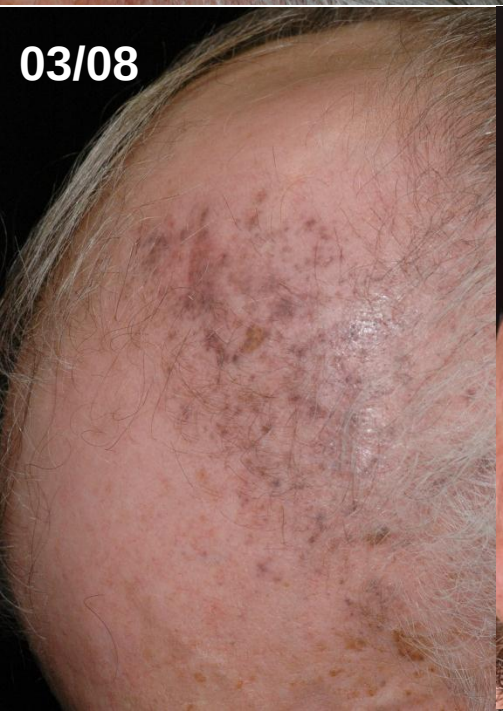
- Z.n. Exzision Melanom Kapillitium 11/07 (non in sano, TD mind. 2,4mm)
- Multiple Satelliten- und Intransitmetastasen Kapillitium 12/07

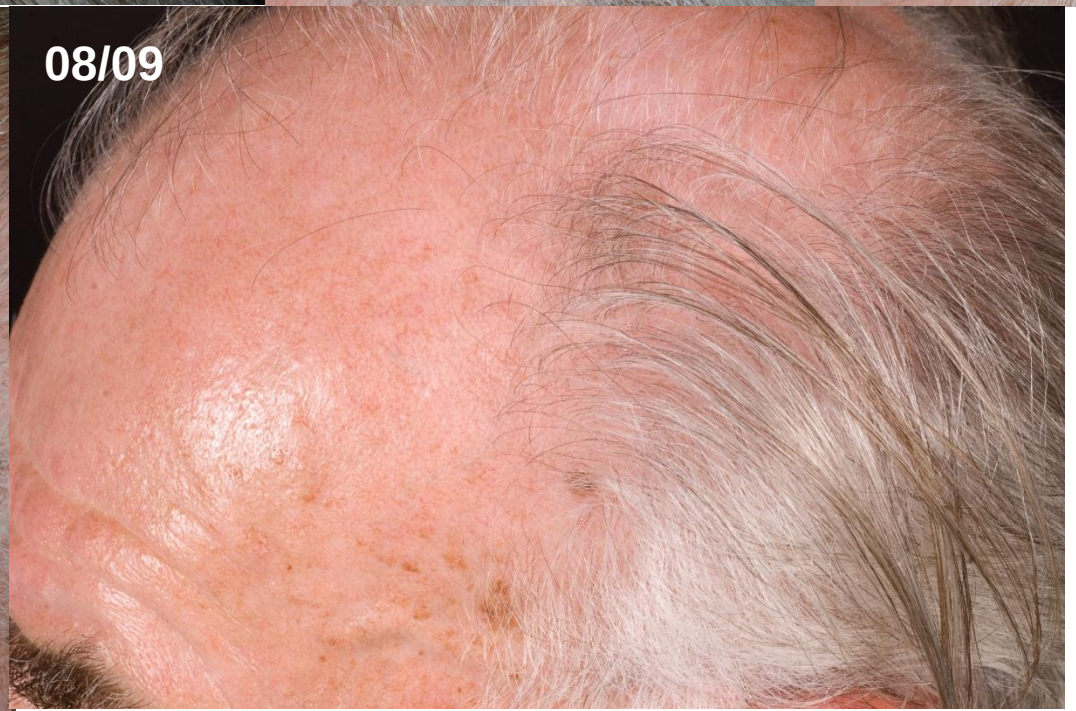
  ➔ intraläsional IL-2 12/07-02/08, CR











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Fall: Verlauf

- CR der Satelitten/Intransitmetastasen bis heute
- 11/09 ED Stadium IV: Leber- und LK-Metastasen
- 12/09-07/10 DTIC, 9 Zyklen, zunächst SD, dann PD
- 09-10/10 2 Zyklen Ipilimumab (CU), Abbruch bei Diarrhoen Grad III, Behandlung mit Budesonid, PR
- 09/11 Addison-Krise bei Hypophysitis, weiterhin in PR

Fall 3

53j. Patient

- 02/08 Exzision SSM Td 3,5mm / Oberschenkel links
- 02/08 SLNB inguinal links negativ
- 04/08-03/10 LD-IFN adjuvant
- 04/10 ED IV: Hemikolektomie rechts +

  Ileumsegmentresektion bei Darmmetastasen
- 06-07/10 3 Zyklen DTIC, PD mit Lebermet, Kolonmet

53j. Patient

- Behandlung mit 2 Zyklen Ipilimumab 09-10/2010, Abbruch bei Colitis Grad 3
- Staging nach 12 Wochen: PR
- Staging 04/12 (1,5J. nach Ipi): CR !!!

Ipilimumab nach Zulassung Heidelberg: 26 Patienten

- davon 3 Uvea-MM: 2 PD, 1 SD
- davon 2 postjuvant Stadium IV: bislang ohne Rezidiv
- <u>Ansprechrate:</u>

CR	0 Pat / 0%
PR	2 Pat / 9%
SD	5 Pat / 21%
PD	16 Pat / 70%

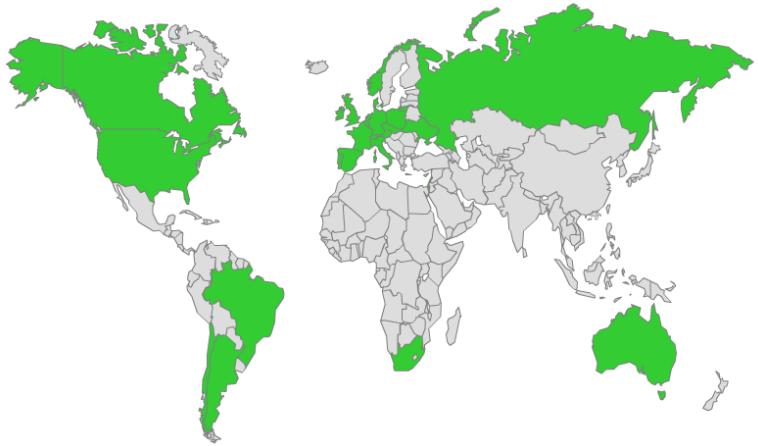
- PR: beide auch Nebenwirkungen (Hypophysitis + Kolitis), Zyklenzahl 4 bzw 3

- Reexposition aktuell 1 Patient geplant

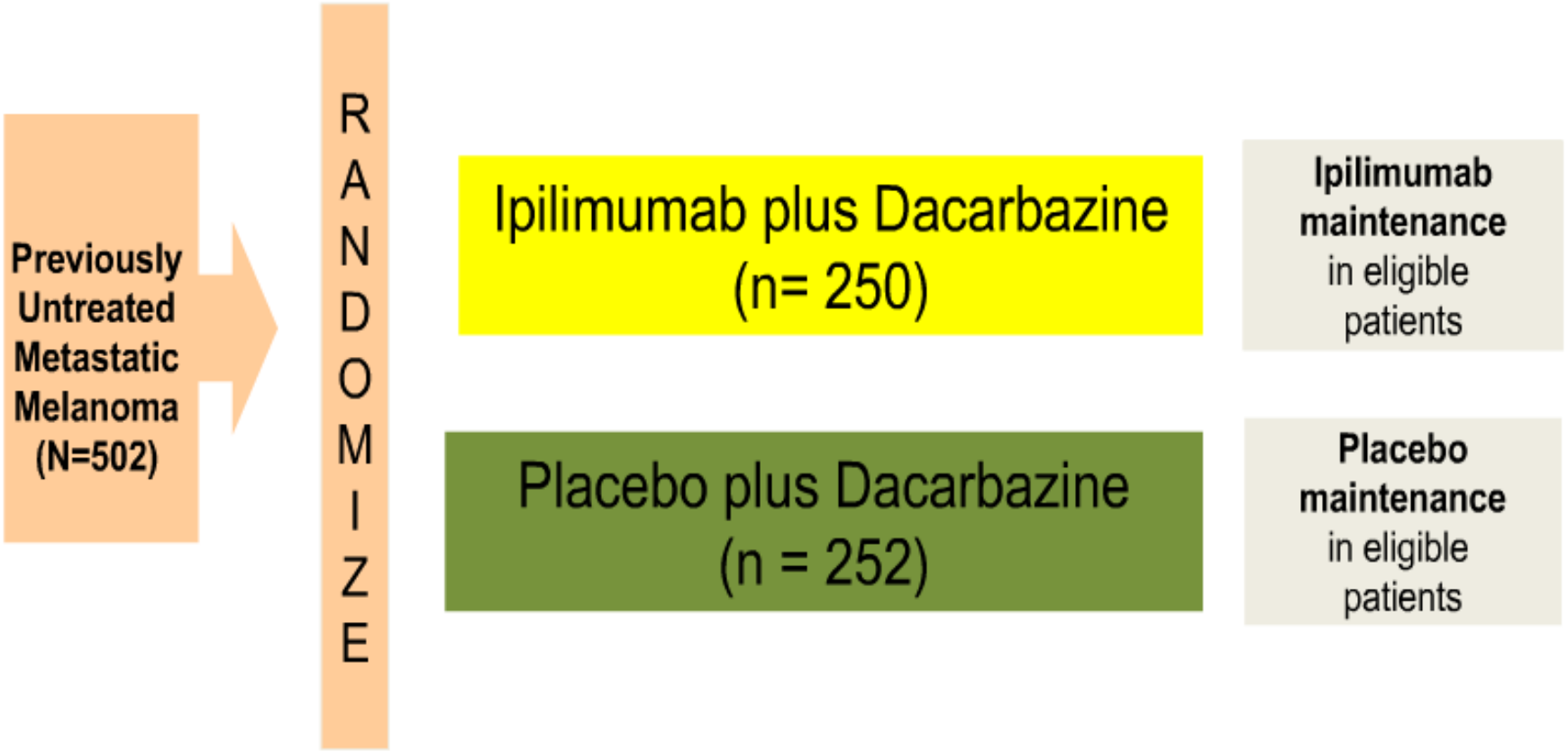
A Multi-Center, Randomized, Double-Blind, Two-Arm, Phase 3 Study in Patients with Untreated Stage III (Unresectable) or Stage IV Melanoma Receiving Dacarbazine plus 10mg/kg of Ipilimumab vs. Dacarbazine with Placebo

Worldwide Study Sites

502 patients randomized in 24 countries worldwide



Study Design



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Dose and Schedule

- Induction:
  - Ipilimumab 10mg/kg or placebo q3 weeks for 4 doses (wks 1, 4, 7,10)
  - DTIC 850mg/m2 q3 weeks for 8 doses (wks 1, 4, 7, 10, 13, 16, 19, 22)
- Maintenance therapy (in the absence of PD/unacceptable toxicities):
  - Ipilimumab 10mg/kg or placebo q3 months starting at week 24 till disease progression, unacceptable toxicity or withdrawal of consent

Study Objectives

- Primary endpoint: Overall Survival
- Secundary endpoint: PFS, DCR, BORR

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Baseline Characteristics

	Ipilimumab + DTIC N=250	Placebo + DTIC N=252
Age (years)		
Mean	57.5	56.4
Gender (%)		
Male	60.8%	59.1%
Female	39.2%	40.9%
M Stage (%)		
M0	2.4%	3.2%
M1a	14.8%	17.1%
M1b	25.6%	24.6%
M1c	57.2%	55.2%

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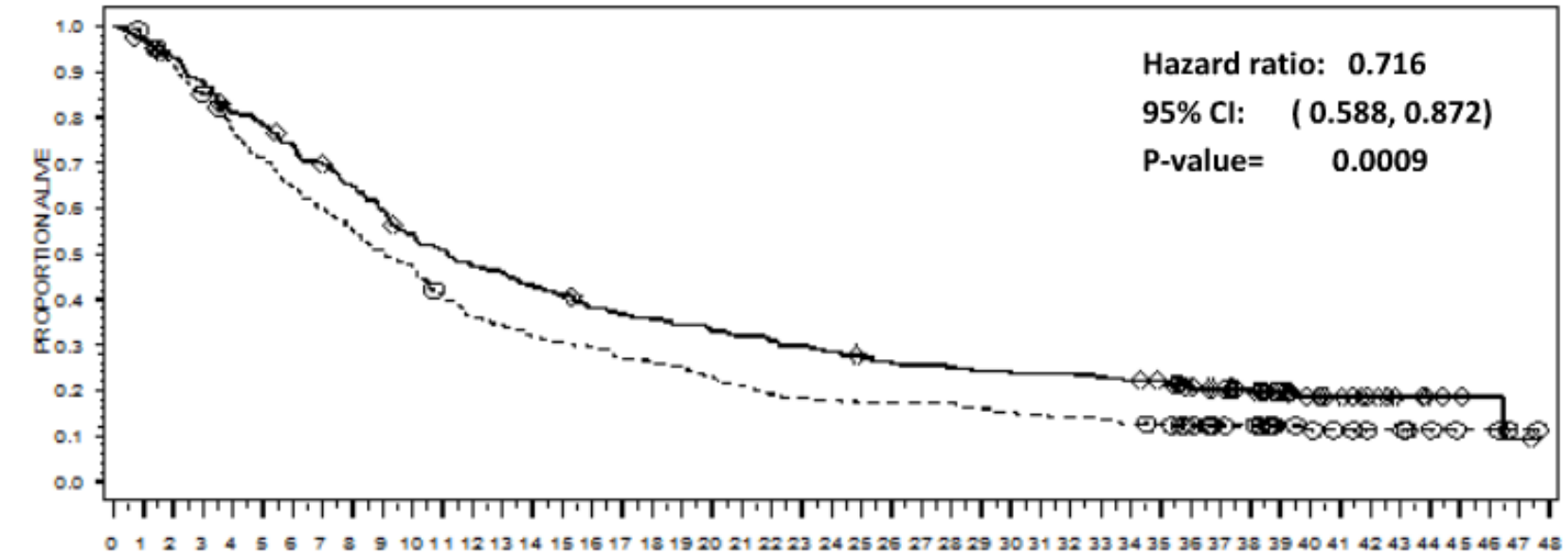
K-M Analysis: Overall Survival (414 deaths)



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
Dacarbazine + 10 mg/kg Ipilimumab	196/250	11.2 (9.40 - 13.6)
Dacarbazine + Placebo	218/252	9.07 (7.75 - 10.5)

Survival Rates

	Ipilimumab+ DTIC N=250	Placebo+ DTIC N=252
12 months	47.3%	36.3%
24 months	28.5%	17.9%
36 months*	20.8%	12.2%

*Heavy censoring around ~34 months

Protocol-specified Response Endpoints: IRC Assessment

	Ipilimumab+ DTIC N=250	Placebo + DTIC N=252	Comparison between arms Weighted difference (Mantel-Haenszel)
Disease Control Rate %	33.2	30.2	+3.4% * (-4.5, +11.1)
BORR, %	15.2	10.3	+5.0% (-0.8, +10.7)
Complete Response	1.6	0.8	N/A
Partial Response	13.6	9.5	N/A
Stable Disease	18.0	19.8	N/A
Progressive Disease	44.4	52.0	N/A

*p= 0.4067

The pre-specified hierarchical test (1.OS, 2.PFS, 3.DCR, 4.BORR) stops with the non-significant p-value for DCR

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Duration of Response and Stable Disease: IRC Assessment

	Ipilimumab+ DTIC N=250	Placebo + DTIC N=252
Median Duration of Response, Months	19.3	8.1
Median Duration of Stable Disease, Months	4.7	4.6

Adverse Events

N(%) Patients		
	Ipilimumab + DTIC N=247	Placebo + DTIC N=251
Any AE Regardless of causality	244(99)	236(94)
Grade 1-2	60 (24)	103(41)
Grade 3-4	139 (56)	69(28)
Grade 5	45 (18)	64(26)
Any drug related AEs	221(90)	192(77)
Grade 1-2	95 (39)	162(65)
Grade 3-4	125 (51)	29(12)
Grade 5	0*	1(0.4)

Aber: Keine Ipilimumab-verursachten Todesfälle

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Ipilimumab

➔ Überlebensvorteil für Patienten bestätigt

Aber:

- Mehr Nebenwirkung in Kombination mit DTIC (Leber!)
- Geringere Verlängerung OS bei Kombination mit Chemotherapie? (Firstline!)

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Ipilimumab in Combination With Paclitaxel and Carboplatin As First-Line Treatment in Stage IIIB/IV Non–Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase II Study

Thomas J. Lynch, Igor Bondarenko, Alexander Luft, Piotr Serwatowski, Fabrice Barlesi, Raju Chacko, Martin Sebastian, Joel Neal, Haolan Lu, Jean-Marie Cuillerot, and Martin Reck

See accompanying editorial doi: 10.1200/JCO.2011.41.4912 and articles doi: 10.1200/JCO.2011.39.5848 and doi: 10.1200/JCO.2011.40.1315

Thomas J. Lynch, Yale Cancer Center and Smilow Cancer Hospital, New Haven, CT; Igor Bondarenko, City Clinical Hospital, Dnipropetrovsk, Ukraine; Alexander Luft, Leningrad Regional Clinical Hospital, St Petersburg, Russia; Piotr Serwatowski, Oddzial Chemioterapii, Szczecin, Poland; Fabrice Barlesi, University of Mediterranée–Assistance Publique Hopitaux de Marseille, Marseille, France; Raju Chacko, Christian Medical College, Vellore, India; Martin Sebastian, Universitaetsmedizin Mainz, Mainz, Germany; Joel Neal, Stanford Cancer Institute, Stanford, CA; Haolan Lu and Jean-Marie Cuillerot, Bristol-Myers Squibb Research and Development, Wallingford, CT; and

ABSTRACT

Purpose

Ipilimumab, which is an anti–cytotoxic T-cell lymphocyte-4 monoclonal antibody, showed a survival benefit in melanoma with adverse events (AEs) managed by protocol-defined guidelines. A phase II study in lung cancer assessed the activity of ipilimumab plus paclitaxel and carboplatin.

Patients and Methods

Patients (N = 204) with chemotherapy-naive non–small-cell lung cancer (NSCLC) were randomly assigned 1:1:1 to receive paclitaxel (175 mg/m^2) and carboplatin (area under the curve, 6) with either placebo (control) or ipilimumab in one of the following two regimens: concurrent ipilimumab (four doses of ipilimumab plus paclitaxel and carboplatin followed by two doses of placebo plus paclitaxel and carboplatin) or phased ipilimumab (two doses of placebo plus paclitaxel and carboplatin followed by four doses of ipilimumab plus paclitaxel and carboplatin).Treatment was administered intravenously every 3 weeks for ≤ 18 weeks (induction). Eligible patients continued ipilimumab or placebo every 12 weeks as maintenance therapy. Response was assessed by using

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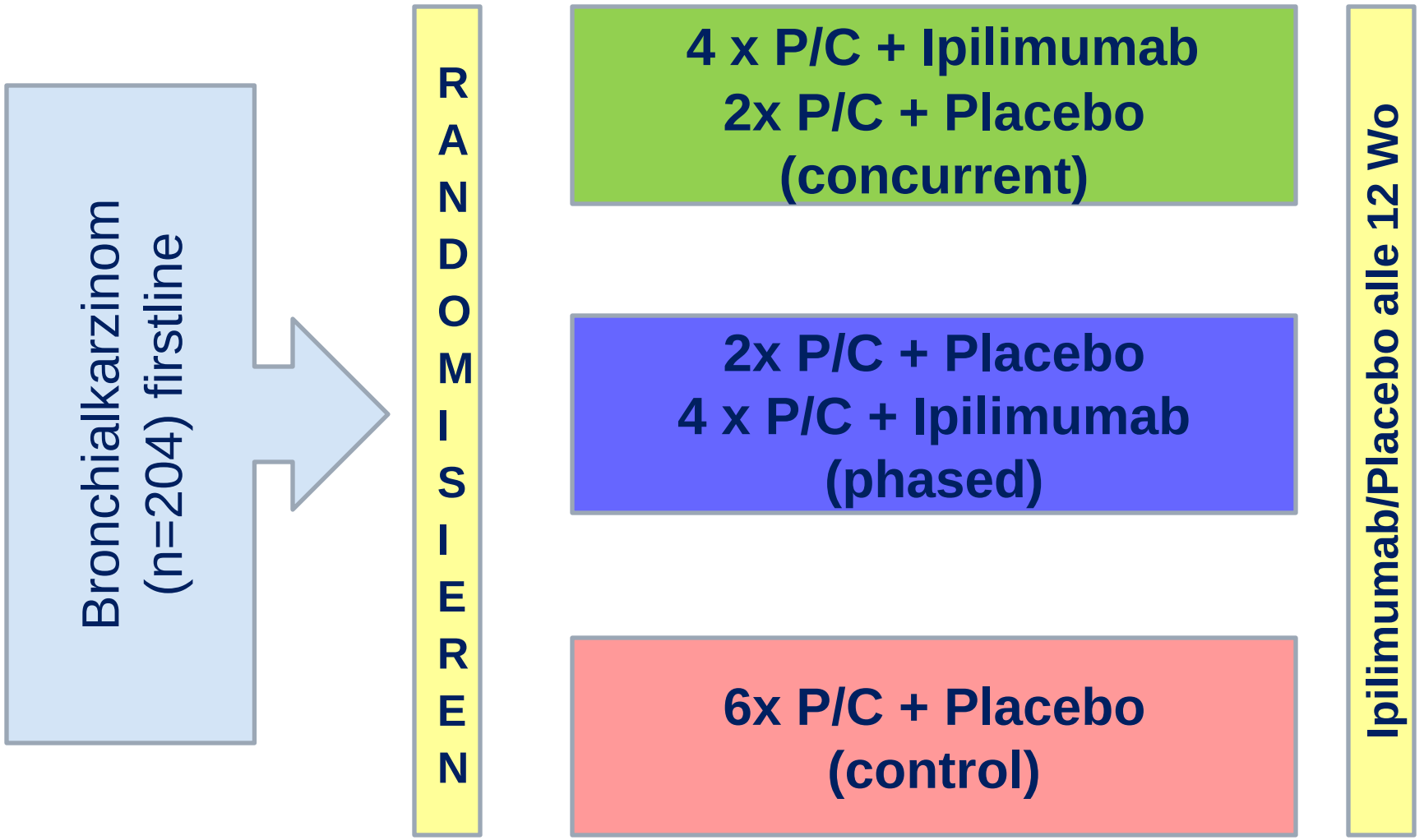
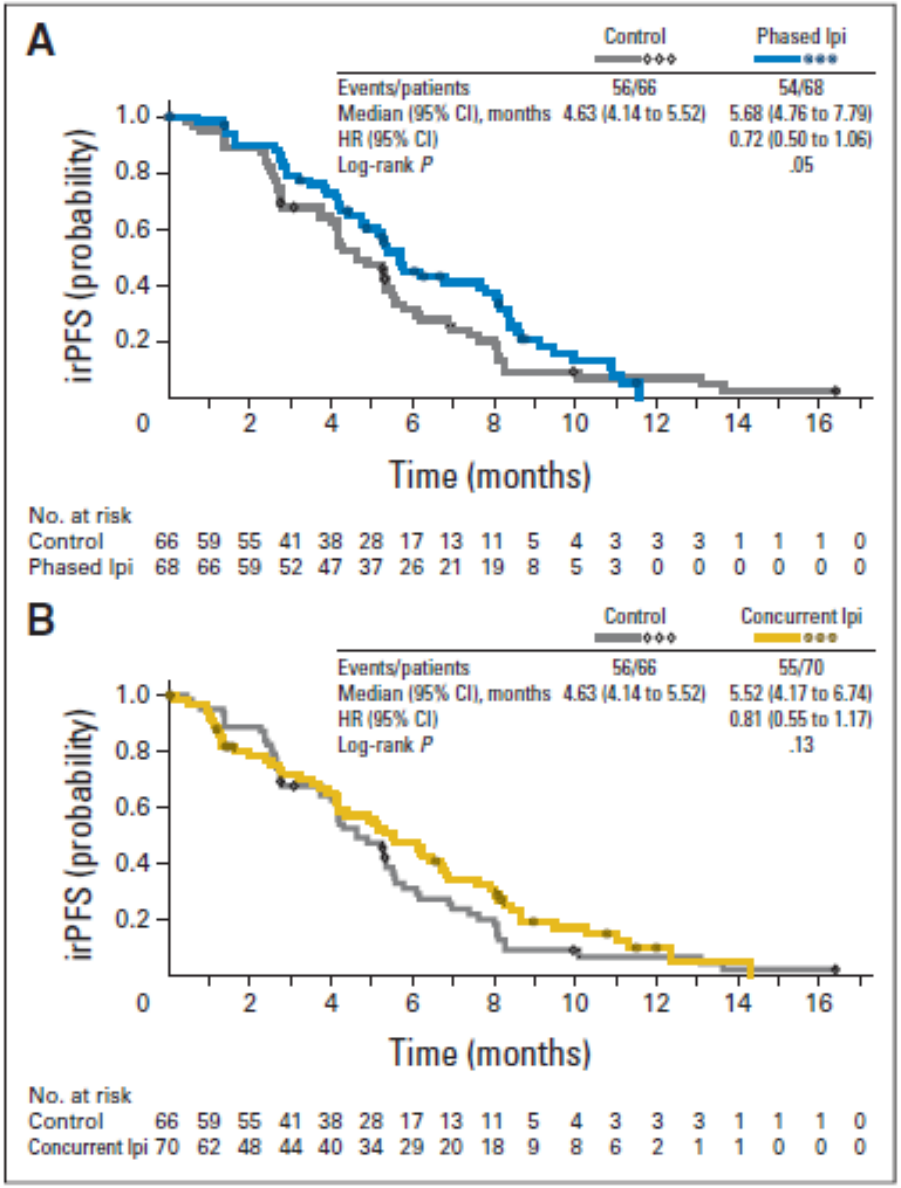


Ergebnisse

Table 2. Tumor Response and Disease Control

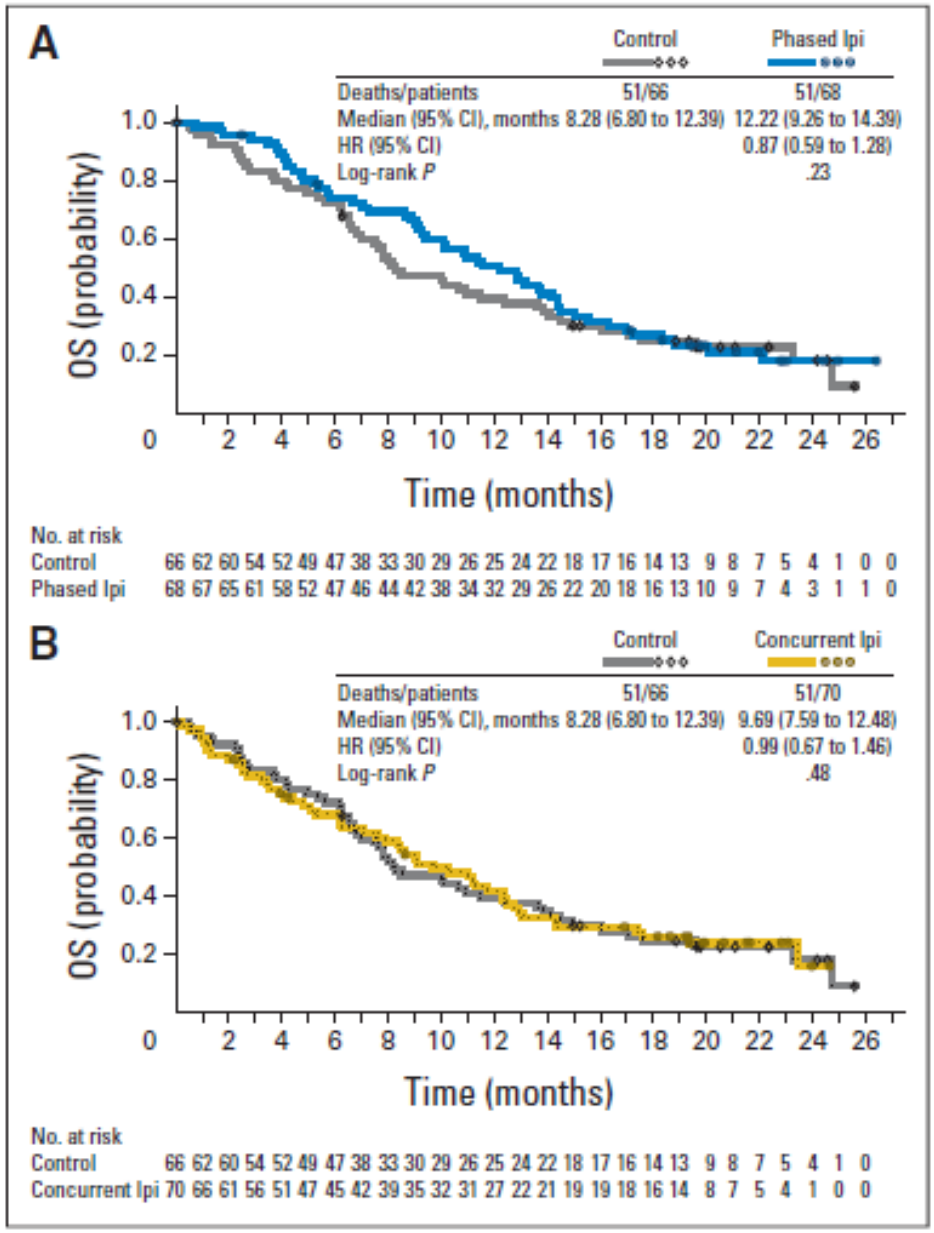
Response	Control (n = 66) No. of Patients	%	Concurrent Ipilimumab (n = 70) No. of Patients	%	Phased Ipilimumab (n = 68) No. of Patients	%
irBOR						
irCR	0		0		0	
irPR	12	18	15	21	22	32
irSD	42	64	34	49	37	54
irPD	2	3	6	9	5	7
Unknown	10	15	15	21	4	6
irBORR						
%	18		21		32	
95% CI	10 to 30		13 to 33		22 to 45	
irDCR						
%	82		70		87	
95% CI	70 to 90		58 to 80		76 to 94	
mWHO-BOR						
CR	0		0		0	
PR	9	14	15	21	22	32
SD	39	59	25	36	31	46
PD	11	17	16	23	11	16
Unknown	7	11	14	20	4	6
mWHO-BORR						
%	14		21		32	
95% CI	6 to 24		13 to 33		22 to 45	
mWHO-DCR						
%	73		57		78	
95% CI	60 to 83		45 to 69		66 to 87	

Ergebnisse



NCT

Ergebnisse


A
Control
Phased Ipi
Deaths/patients 51/66 51/68
Median (95% CI), months 8.28 (6.80 to 12.39) 12.22 (9.26 to 14.39)
HR (95% CI) 0.87 (0.59 to 1.28)
Log-rank P .23
OS (probability)
1.0
0.8
0.6
0.4
0.2
0
2 4 6 8 10 12 14 16 18 20 22 24 26
Time (months)
No. at risk
Control 66 62 60 54 52 49 47 38 33 30 29 26 25 24 22 18 17 16 14 13 9 8 7 5 4 1 0 0
Phased Ipi 68 67 65 61 58 52 47 46 44 42 38 34 32 29 26 22 20 18 16 13 10 9 7 4 3 1 1 0
B
Control
Concurrent Ipi
Deaths/patients 51/66 51/70
Median (95% CI), months 8.28 (6.80 to 12.39) 9.69 (7.59 to 12.48)
HR (95% CI) 0.99 (0.67 to 1.46)
Log-rank P .48
OS (probability)
1.0
0.8
0.6
0.4
0.2
0
2 4 6 8 10 12 14 16 18 20 22 24 26
Time (months)
No. at risk
Control 66 62 60 54 52 49 47 38 33 30 29 26 25 24 22 18 17 16 14 13 9 8 7 5 4 1 0
Concurrent Ipi 70 66 61 56 51 47 45 42 39 35 32 31 27 22 21 19 19 18 16 14 8 7 5 4 1 0 0

Offene Fragen:

- Erhaltungstherapie?

  ➔ noch ungeklärt

- Kombinationen: z.B. Chemotherapie, Vemurafenib

- Dosierung? 3 vs 10mg/kg

  ➔ BMS169-Studie

Therapiestudien beim Melanom

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

Ansprechpartner:

Dr. med. Jessica C. Hassel
Oberärztin
Tel: 06221 – 56-38503
jessica.hassel@med.uni-heidelberg.de

Version 03/2012

Stadium II
pT > 2,0 mm

tumorfrei (nach OP) → Low-dose IFN Therapie
Aktuell keine Studien

Stadium III
LK Metastasen

vor OP (R0 erreichbar) → **Multiferon (ADO)**
Einschluss: StadiumIIIB+C (2-10 Met)
Ausschluss: SH-MM, Uvea-MM, Herzerkr, Autoimmunerkr

tumorfrei (nach OP) → High oder Low-dose IFN Therapie
Aktuell keine Studien

Stadium IV
Fernmetastasen

mit Tumorlast (nach OP)

Second-line

Ipilimumab Multibasket (ADO)
Einschluss: ≥ 2ndline Uvea-MM, auch Hirnmet
Ausschluss: aktive Autoimmunerkr.

NY-ESO Ipilimumab (Jäger)
Einschluss: spontane Immunantwort gegen NY-ESO1, eine Vorther
Ausschluss: ECOG >1, KI gg Ipi

Tadalafil (TaMe, IIT)
Einschluss: Stadium IIIunres o IV, Biopsierbare Metastasen
Ausschluss: Immunsuppression, Hirnmet

Firstline

Chemotherapie nach TCA vs DTIC (ChemosensMM-ADO)
Einschluss:Firstline Stadium IV, max 1 Vorther (ausser Chemo), auch MUP, SH-MM
Ausschluss: ZNS-Met, Uvea-MM

E7080-206 (Eisai)
Einschluss: Stadium IIIunres/IV, 1-2 Vorther, BRAF-Mut+, BRAF-Inhib. Vorther
Ausschluss: Z.n. anti-VEGF-Ther, Uvea- MM, Hirnmet, QT-Verlängerung, Gerinnungsstörung

Ipilimumab 3 vs 10mg/kg (BMS184-169)
Einschluss: Stadium IIIunres/IV, auch asympt Hirnmet
Ausschluss: Immunsuppression, aktive Autoimmunerkr, Vorbehandlung mit BRAF-Inh.

Tasigna (TEAM-Novartis)
Einschluss: Stadium IIIc o IV, c-kit Mutation, Vorbehandlung mit DTIC erlaubt
Ausschluss: Herzinsuffizienz

Welche Patienten profitieren?

- Wenig Tumorlast?
- Adjuvant?
- Biomarker?
- Vorhersage des Ansprechens durch frühe Bildgebung

Fall 4

49j. Patientin, Allgemeinärztin

- 01/2007 Exzision SSM, TD1,2mm / Flanke links
- Kein Sentinel (extern)
- 03/10 LK-Metastasen axillär links (15+/21)
- 04-07/10 EORTC18071-Studie adjuvant, keine NW
- 07/10 OP LK-Metastasen-Rezidiv axillär links
- 08/10 OP LK-Metastase inguinal links (2+/3)
- 11-12/10 LD-IFN adjuvant
- 12/10 OP LK-Metastasen inguinal rechts (disseminiert)

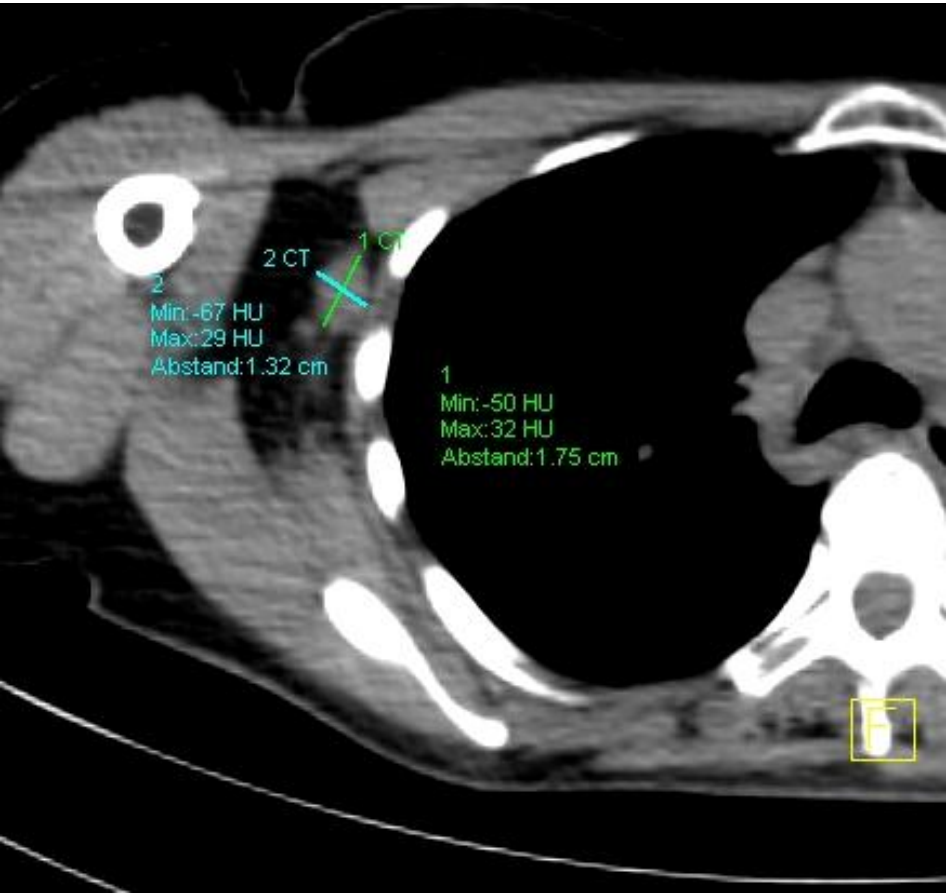
49j. Patientin, Allgemeinärztin

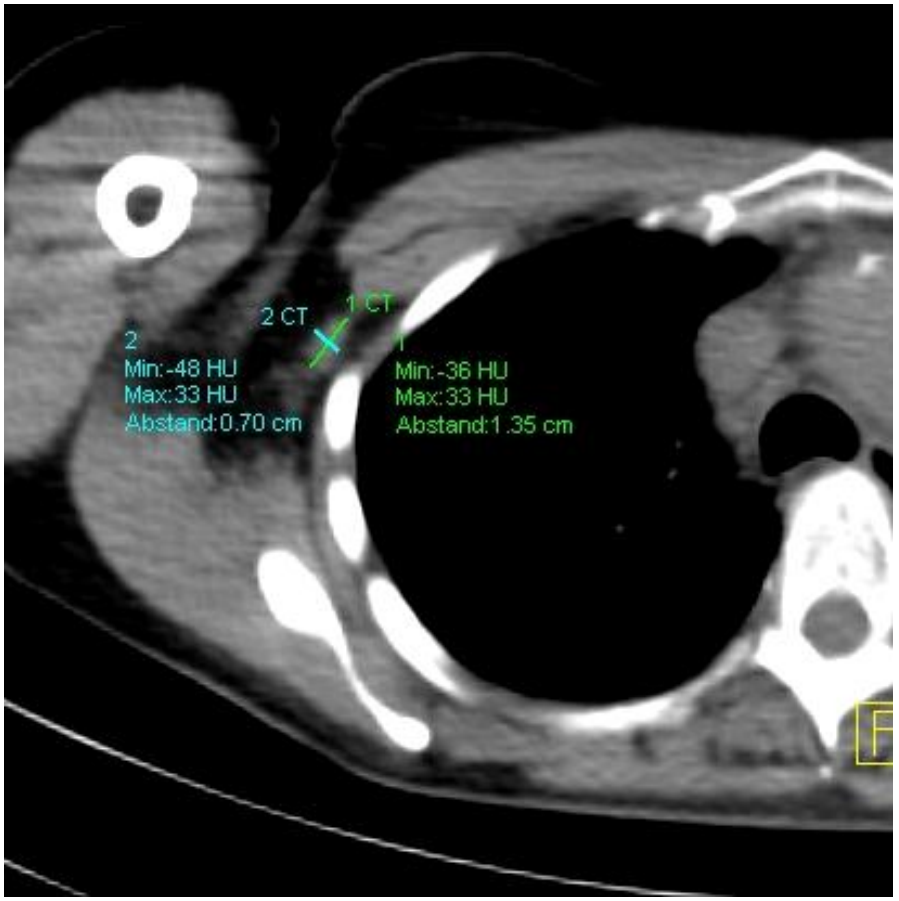
- 10/11 erneut OP LK-Metastasen inguinal links
- 11/11-02/12 4 Zyklen Ipilimumab postjuvant, keine NW
- 02/12 V.a. LK-Metastasen axillär rechts (sonografisch), im GK-MRT zudem V.a. LK-Metastasen mediastinal, retroperitoneal und inguinal (sonografisch reaktiv)

  ➔ Pseudoprogress?

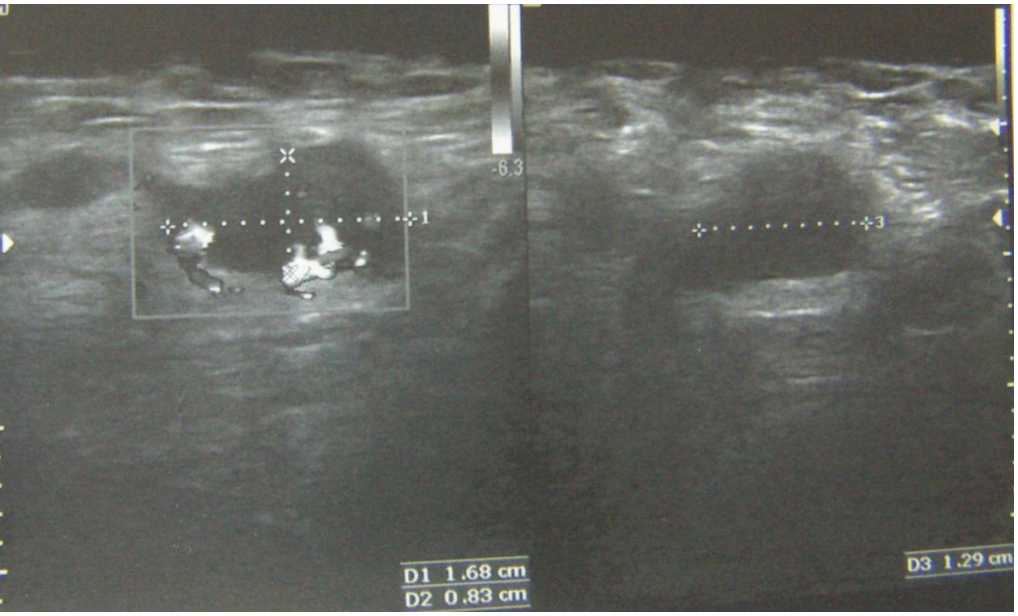
  ➔ Kontrolle in 6 Wochen vereinbart

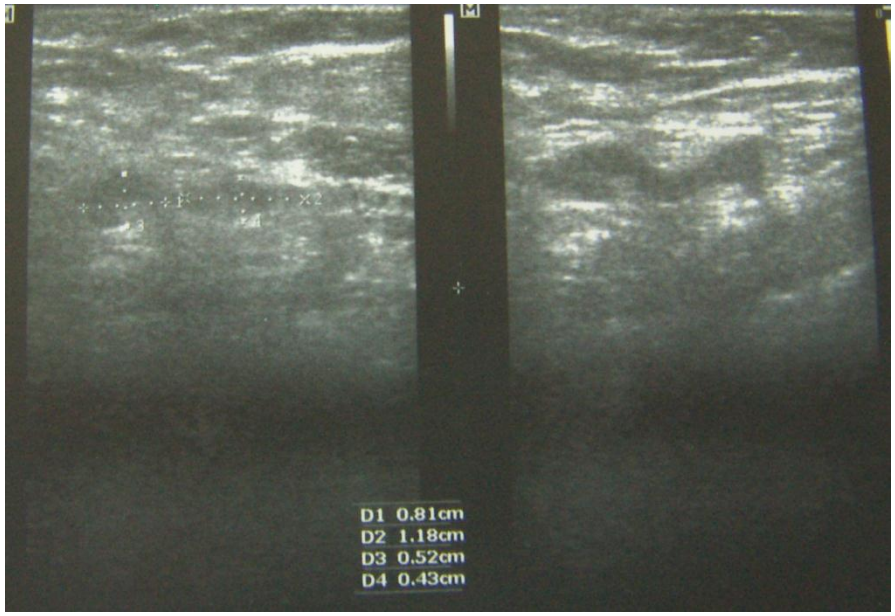
Staging


2 CT
1 CT
2
Min:-67 HU
Max:29 HU
Abstand:1.32 cm
1
Min:-50 HU
Max:32 HU
Abstand:1.75 cm


2 CT
1 CT
2
Min:-48 HU
Max:33 HU
Abstand:0.70 cm
1
Min:-36 HU
Max:33 HU
Abstand:1.35 cm

Staging





Biomarker?

Published in final edited form as:
Cancer. 2010 April 1; 116(7): 1767–1775. doi:10.1002/cncr.24951.

Single institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting: lymphocyte count after two doses correlates with survival

Geoffrey Y. Ku[a,#], **Jianda Yuan**[a,#], **David B. Page**[b], **Sebastian E.A. Schroeder**[b], **Katherine S. Panageas**[c], **Richard D. Carvajal**[d], **Paul B. Chapman**[d], **Gary K. Schwartz**[d], **James P. Allison**[a,e,f], and **Jedd D. Wolchok**[a,d]

[a]Ludwig Center for Cancer Immunotherapy, Memorial Sloan-Kettering Cancer Center, New York, NY

Dosierung: 10mg/kg + Erhaltungszyklen
N = 53

NCT

Lactate dehydrogenase (LDH)	
≤ upper limit of normal (ULN; 200 units/L)	23 (43%)
1.1 - <2× ULN	13 (25%)
>2× ULN	17 (32%)
Prior therapy	
Radiation therapy	21 (40%)
Cytotoxic chemotherapy	49 (93%)
Biologic therapy	
• Adjuvant IFN-α (adjuvant)	9 (17%)
• High-dose IL-2 (metastatic disease)	8 (15%)
Vaccine therapy	4 (7%)
Others (e.g. small molecule inhibitors)	23 (43%)
No. of prior systemic therapies	
Median	2
Range	0-6

Clinical characteristics of patients with objective responses

Age/sex	Baseline LDH	No. of prior therapies	Disease sites	Best response	Time-to-response (mos)	Response duration (mos)	OS (mos)
76/M	113	3	Lung, soft tissue	irCR[a]	3.5	10.2+	13.7+
78/F	160	3	Lung, soft tissue, bone	irPR	2.4	2.8	8.3
62/M	92	4	Soft tissue	irCR[b]	5.2	6.2+	11.4+
66/M	121	2	Lung, soft tissue, lymph node	irCR	5.6	5.6+	11.2+
62/M	171	3	Lung, lymph node	irPR	4.3	6+	10.3+
47/M	210	1	Lymph node	irCR[c]	2.6	4.4+	7.0+

CR, complete response; LDH, lactate dehydrogenase; mos, months; OS, overall survival; PR, partial response

[a] This patient experienced a CR to ipilimumab and surgery;

[b] This patient received radiotherapy prior to study entry;

[c] This patient was found to have achieved a pathologic CR when the only metastatic site was resected.

Ausserdem:

- Patienten mit Grad3/4 NW korrelierten mit Ansprechrate

NCT

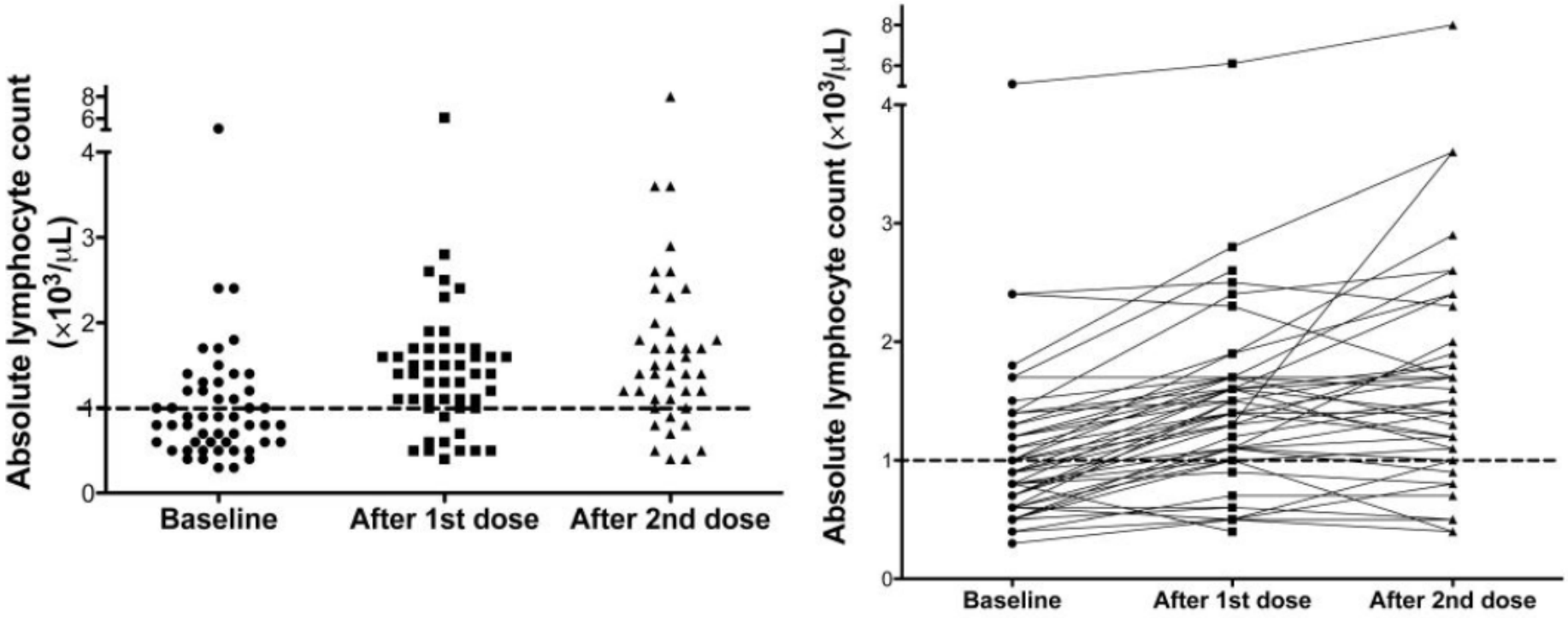


Figure 2. Changes in absolute lymphocyte count (ALC) with ipilimumab therapy
(A) represents the ALC of all patients at baseline and after one and two ipilimumab doses while (B) represents the change in ALC for each patient with therapy.

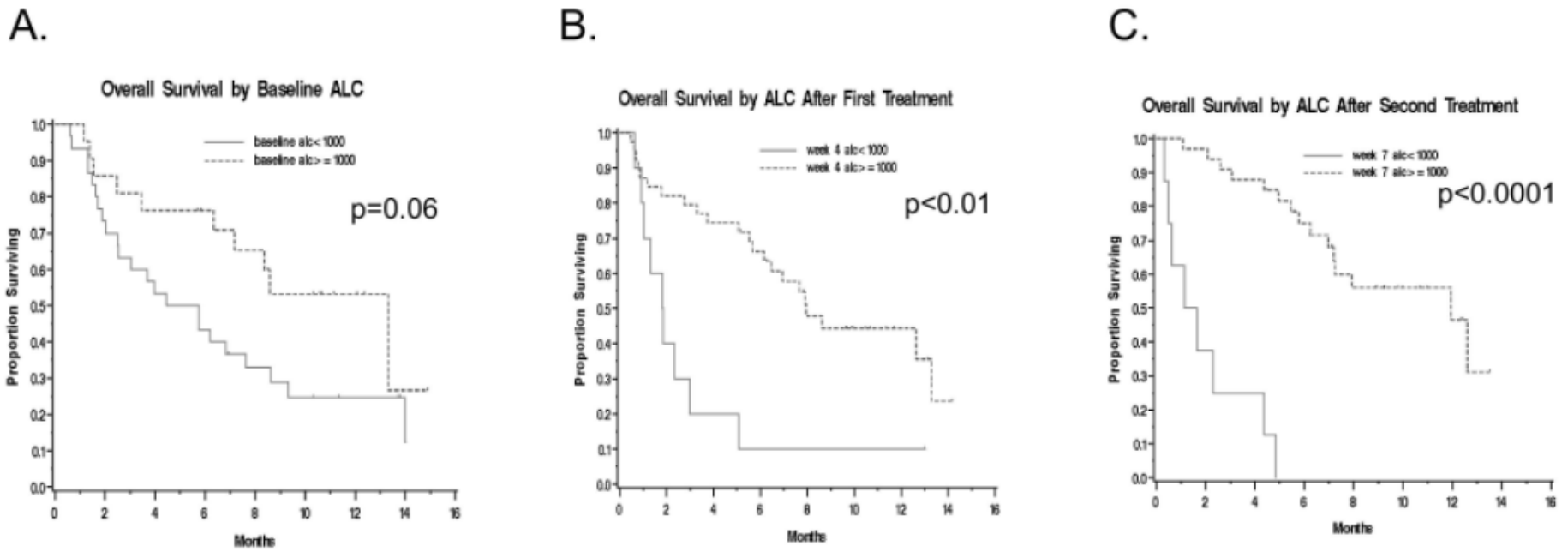


Figure 3. Kaplan-meier survival curves stratified by absolute lymphocyte count (ALC) at (A) baseline and after (B) the first and (C) second ipilimumab doses

➔Keiner der Patienten ALC<1000 hatte klinischen Benefit!

➔ORR 18 vs 0% (p=0.33)

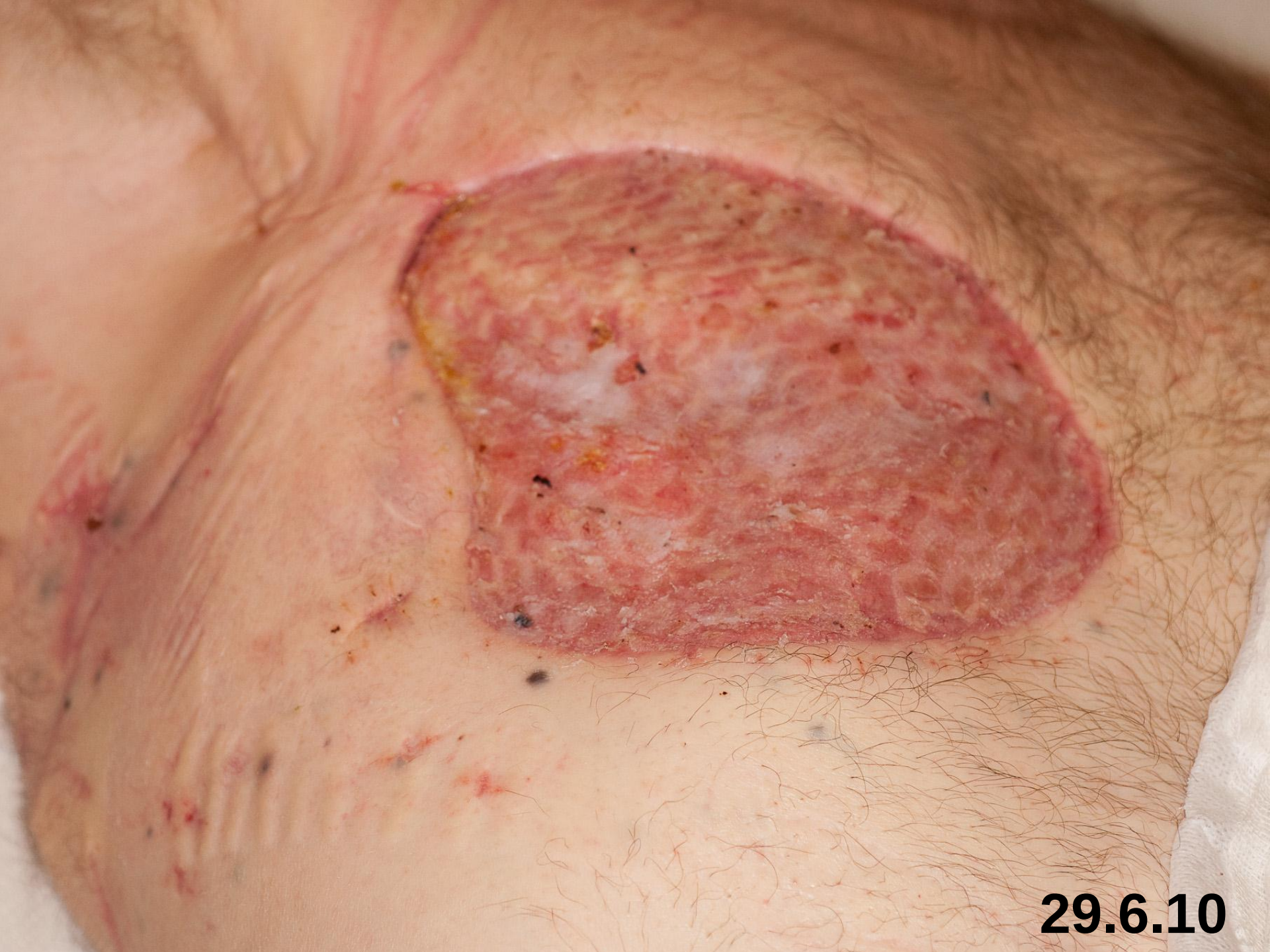
Fall 5

47j. Patient

- Exzision Melanom TD4,1mm Oberbauch rechts 10/08
- Nachexzision und SLNB axillär rechts (1+/2) 10/08
- LK-Dissektion axillär rechts (0+/10) 11/08
- Exzision multipler Intransit-Metastasen + Radiatio

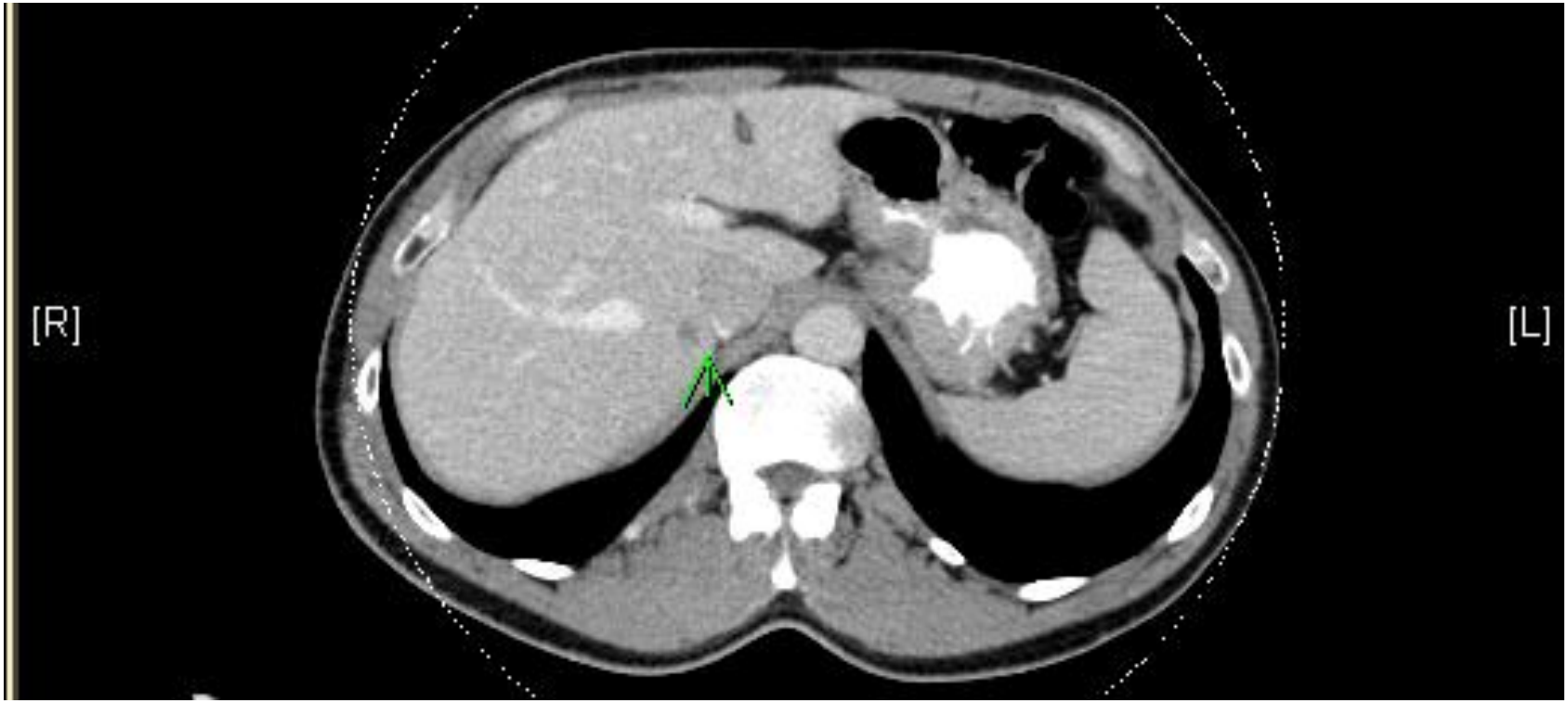
  rechte Thoraxwand + Lymphabstromgebiet GD 50 Gy

  09-11/09
- 6 Zyklen DTIC 11/09-07/10, Abbruch bei Progress


29.6.10

Staging vom 7.7.10

- Zusätzlich Multiple Lebermetastasen



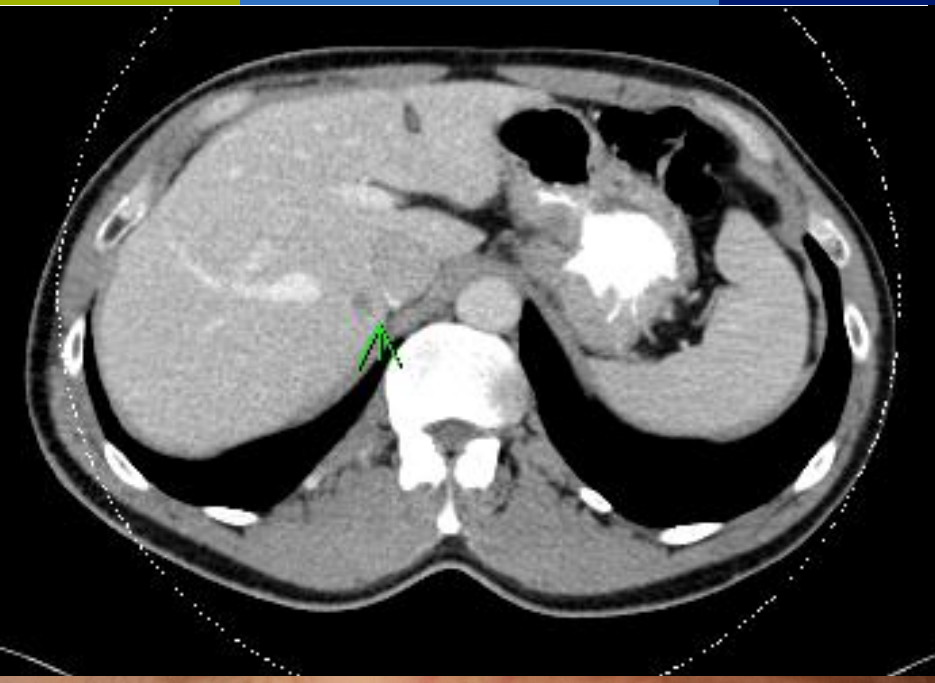
Therapieentscheidung: Ipilimumab CU

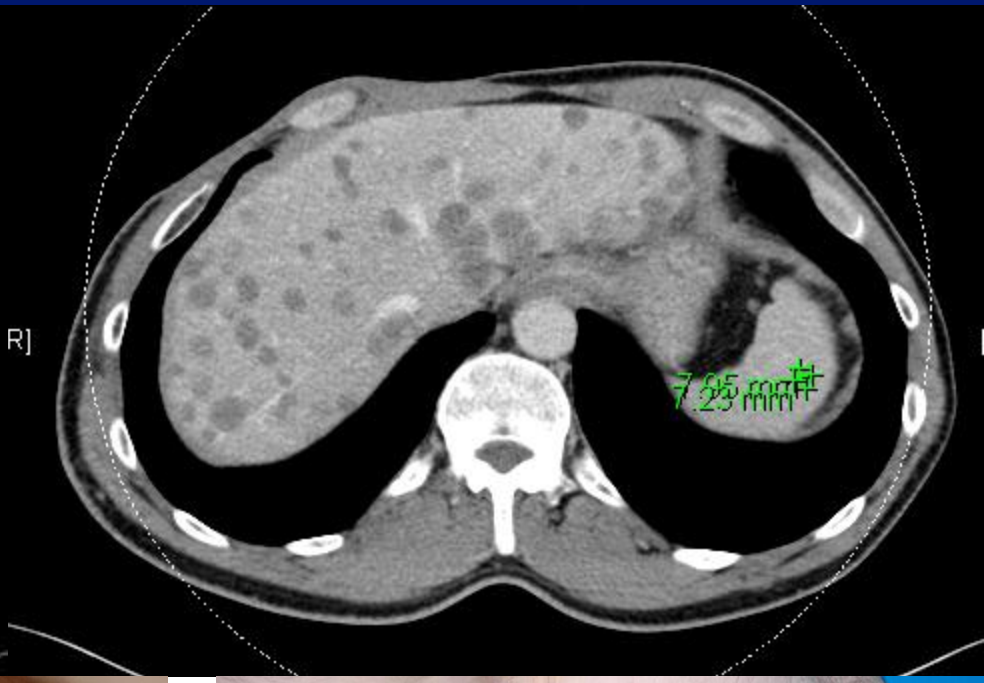
⇒ 4 Gaben 3mg/kg KG alle 3 Wochen 9/10-11/10

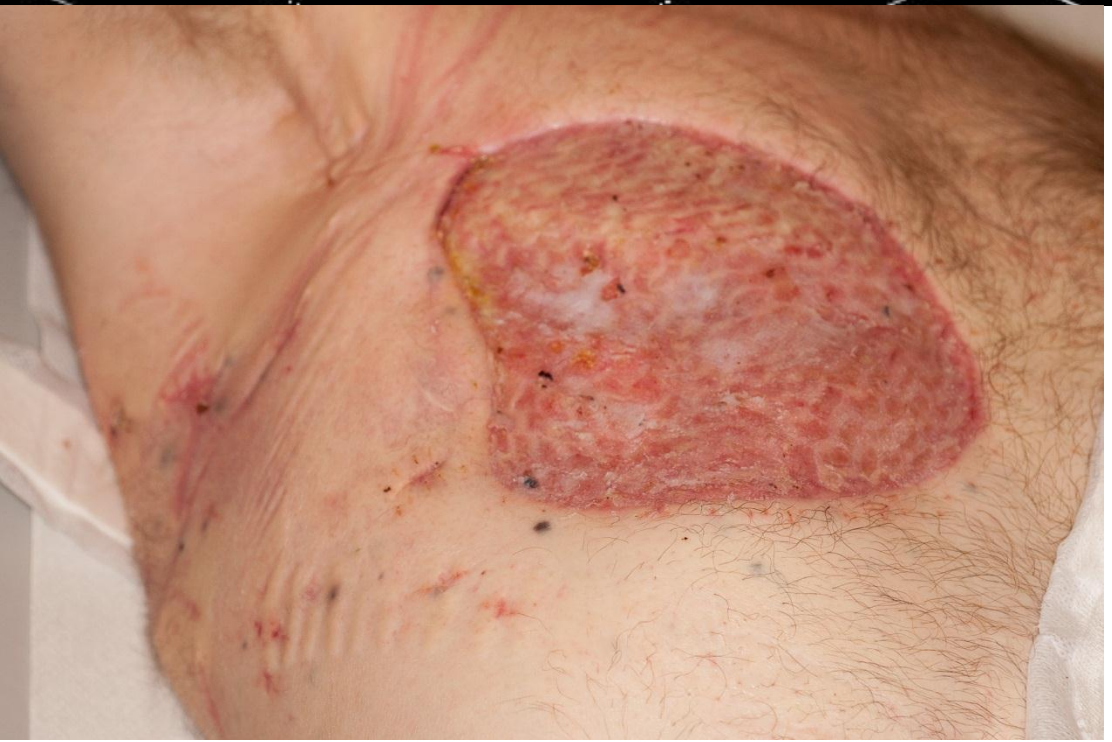
⇒ Gute Verträglichkeit, nach 4 Zyklus z.T. Juckreiz und diskrete Erytheme an den Beinen

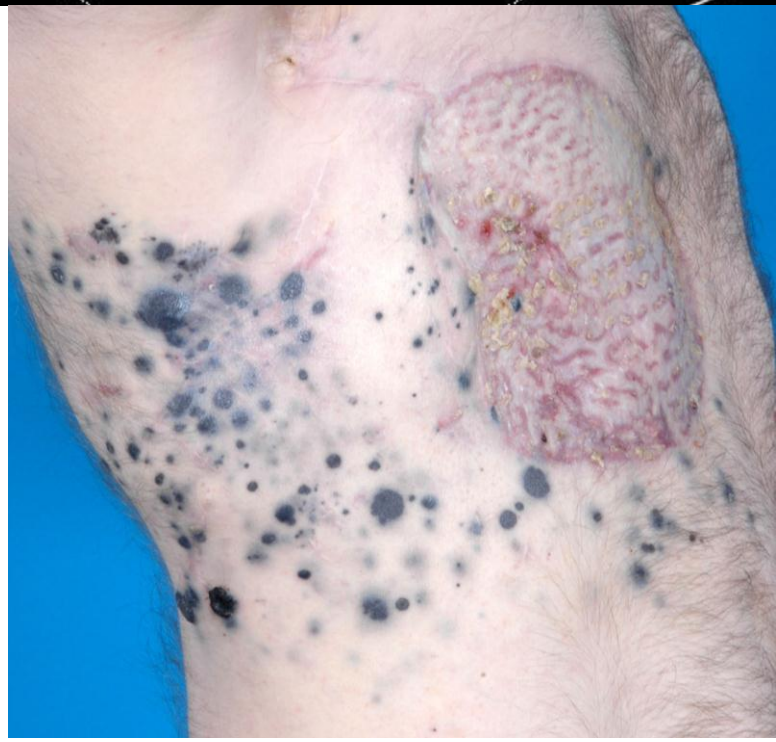
⇒ Staging 6.12.10: PD in Leber (Grösse und Anzahl), zudem Milz, pulmonal, neue kutane (>50%)

⇒ Staging 10.1.11: im kurzfristigen Verlauf stabil




R]
7.95 mm
7.23 mm





Welche Patienten profitieren?

Geplante Projekte:

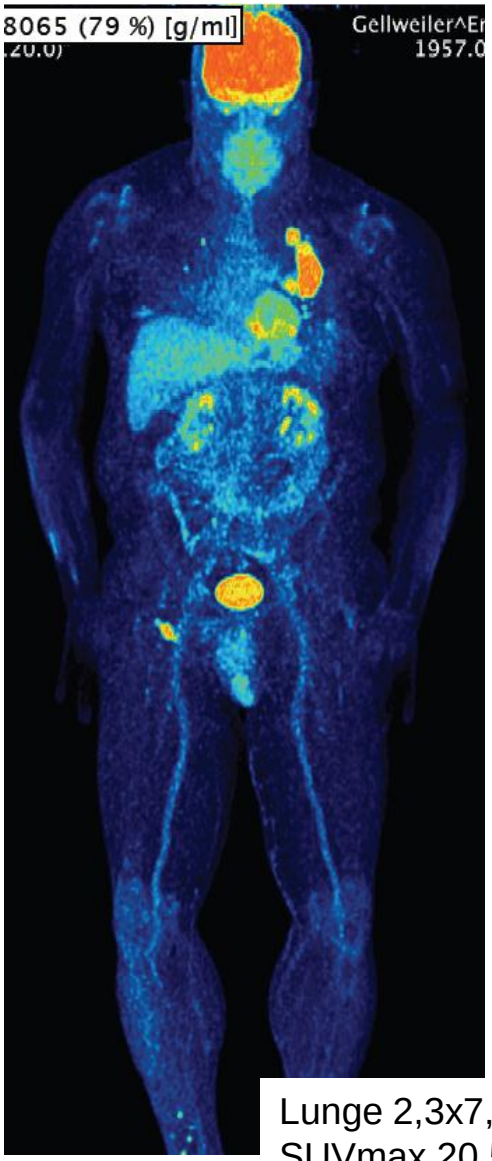
- Frühzeitige Bildgebung zur Vorhersage Ansprechen möglich?

  Studieninitiierung geplant mit GK-Diffusions-MRT (M. Ganten) sowie PET-CT (Prof. Strauss) vor Ipi, nach 2 Gaben sowie nach 4 Gaben Ipi

- Immunmonitoring im Rahmen der Elektrastudie

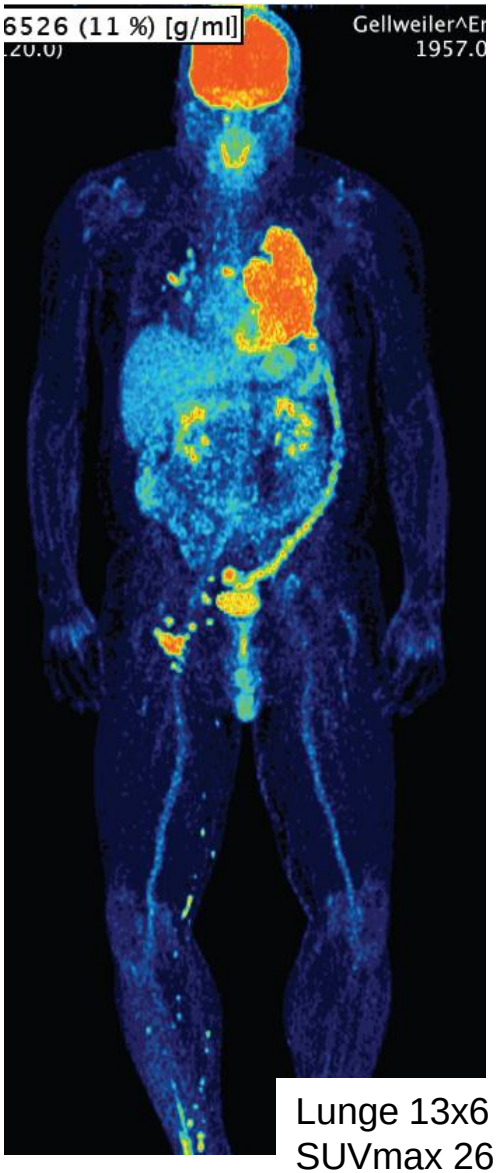
57j. Patient

vor Ipi



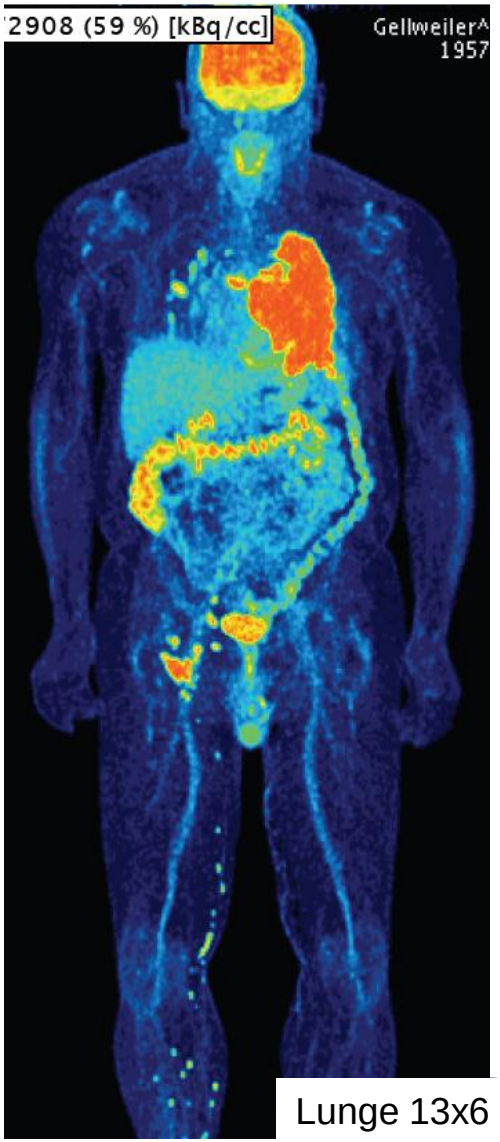
Lunge 2,3x7,4
SUVmax 20,5

nach 2 Zyklen



Lunge 13x6
SUVmax 26,1

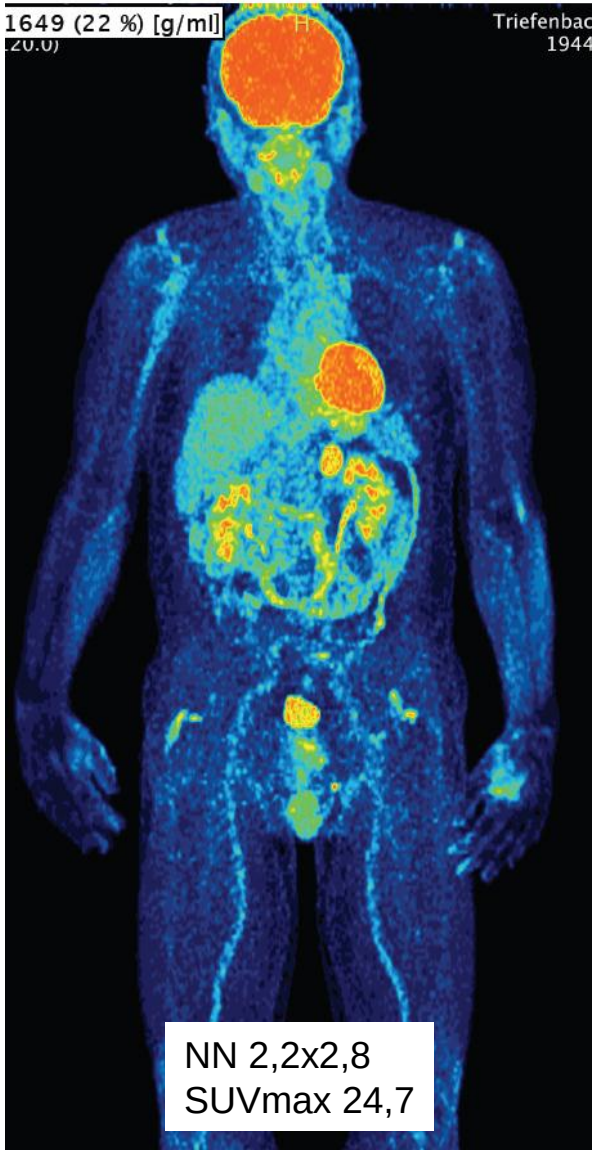
nach 4 Zyklen



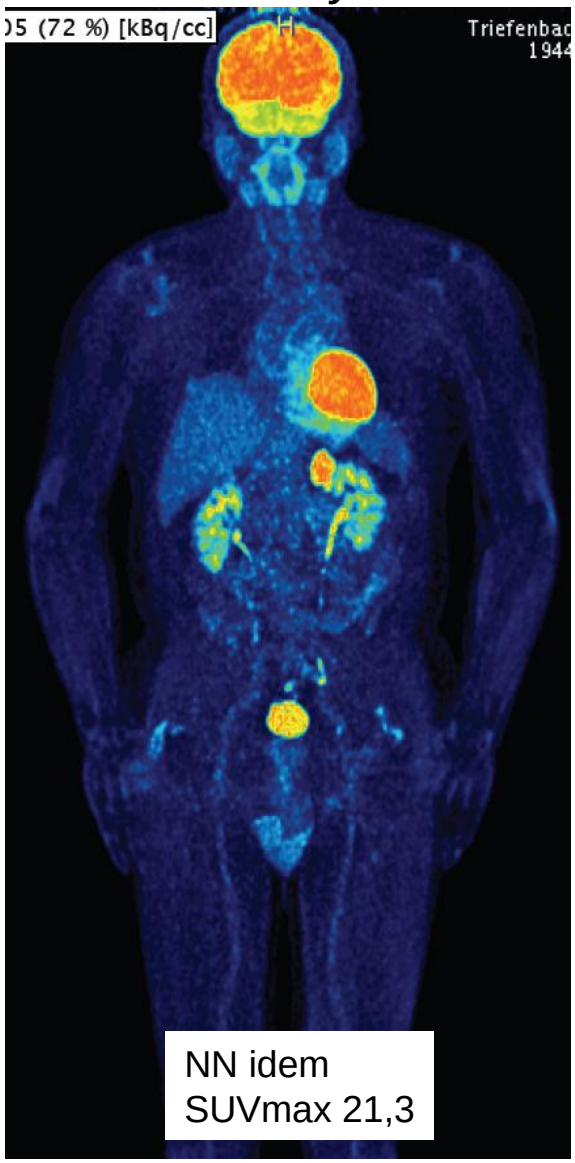
Lunge 13x6
SUVmax 24

67j. Patient

vor Ipi

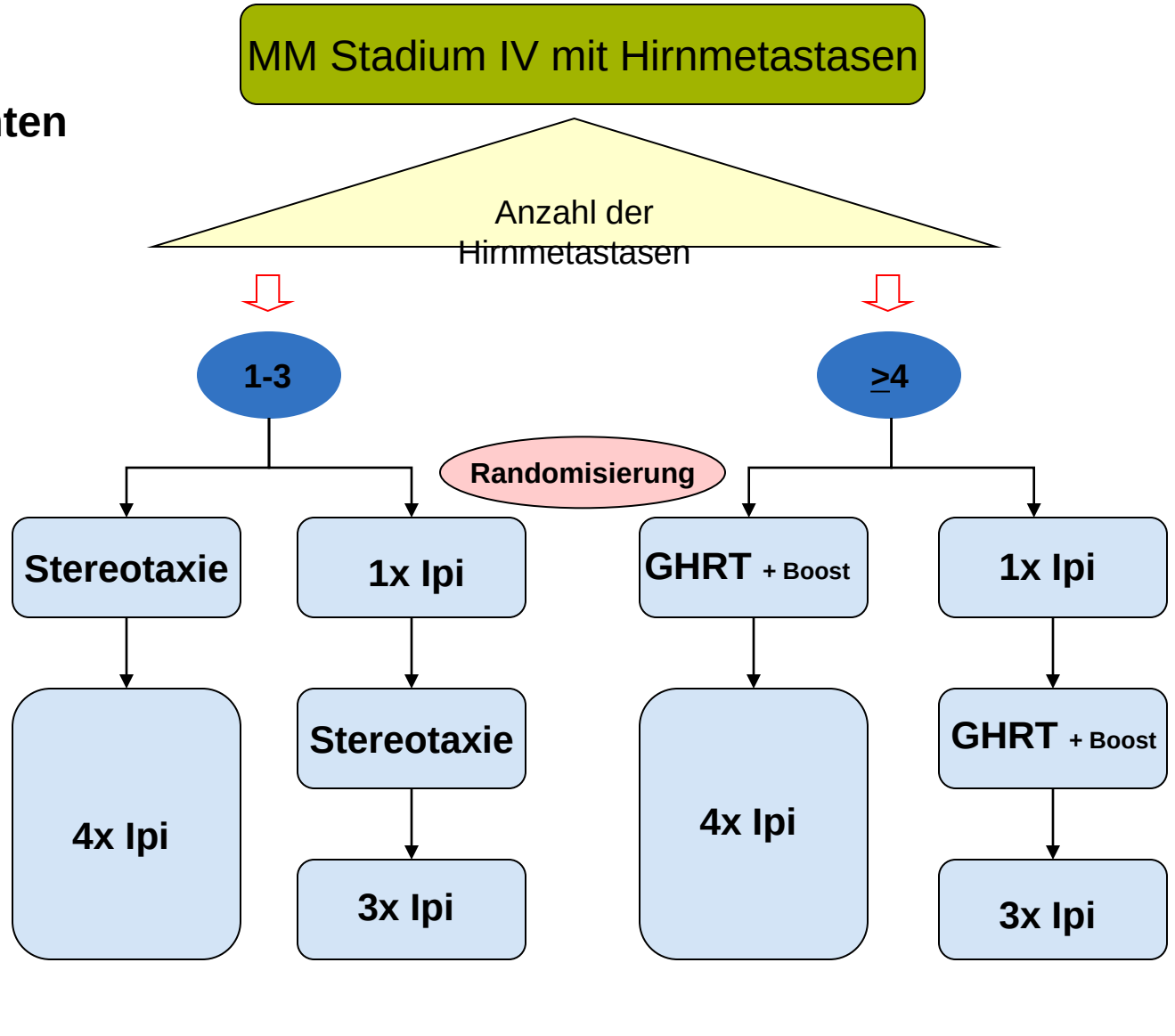


nach 2 Zyklen



ELEKTRA-Studie

pro Arm:
10 Patienten



Dankeschön!