

# Melanom 2012: Chancenoptimierung durch individualisierte Therapie

*21. Erlanger Mini-Symposium 12-5-2012*

*Melanom 2012: neue Therapien, große Hoffnungen, andere Sorgen !*

*Eckhart Kämpgen*

# Systemtherapie des Melanoms

## bis 2010

- IFN
- IL-2
- DTIC
  
- Polychemo  
+ IFN / IL-2



# Systemtherapie des Melanoms

## bis 2010

- IFN
- IL-2
- DTIC
  
- **Polychemo**  
+ IFN / IL-2

## 2012

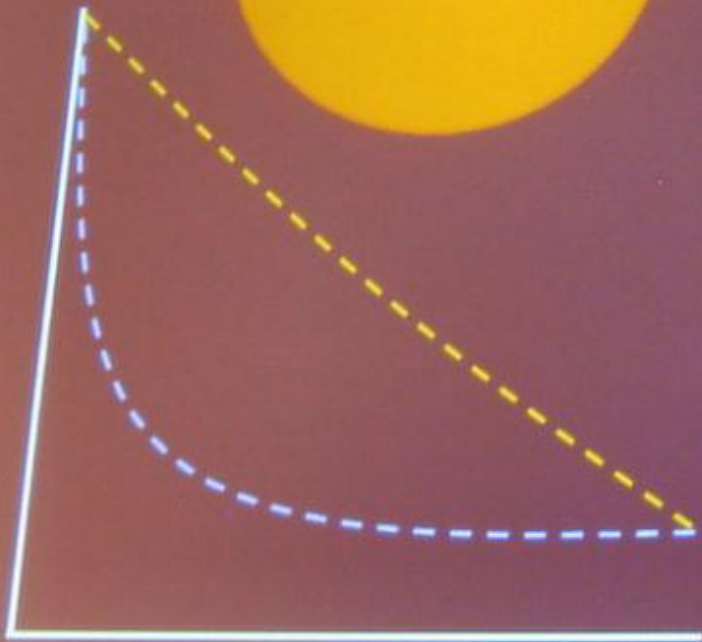
- IFN
- IL-2
- DTIC
  
- Polychemo  
+ IFN / IL-2
  
- **Ipilimumab**
- **Vemurafenib**



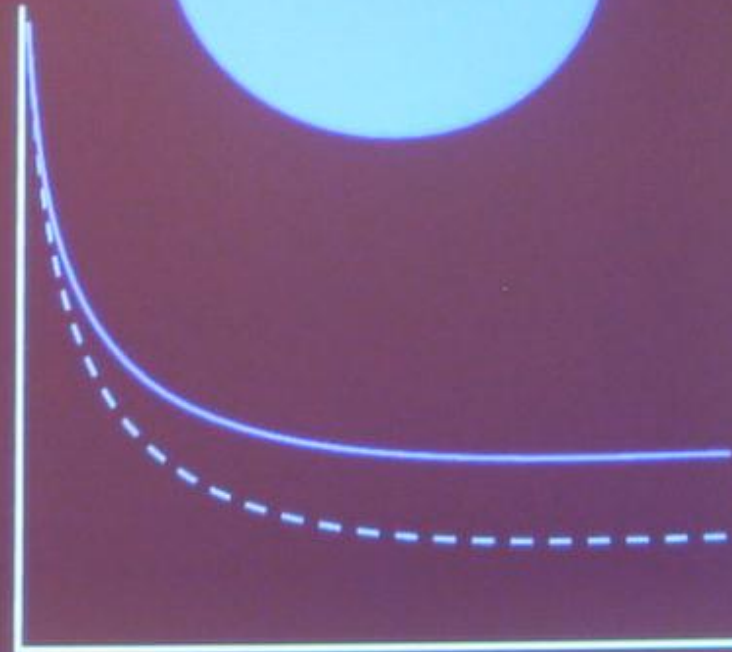
# Überlebenskurven reflektieren Mechanismen und Kinetik

Overall survival

Targeted  
therapy



Immune  
therapy



# Systemtherapie des Melanoms

## bis 2010

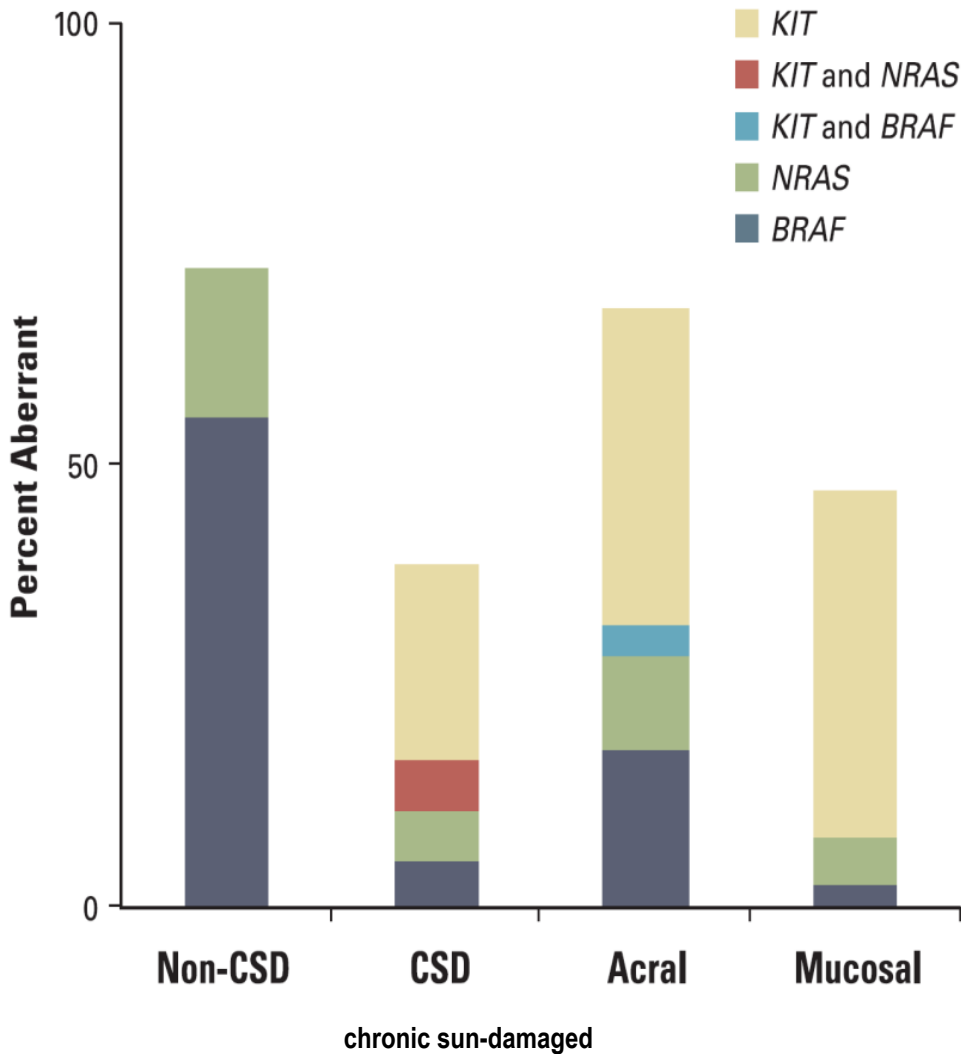
- IFN
- IL-2
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+ IFN / IL-2

## 2012

- IFN
- IL-2
- DTIC
  
- Polychemo  
+ IFN / IL-2
  
- Ipilimumab
- Vemurafenib

**Individualisierung**

# c-KIT und BRAF im Melanom



VOLUME 24 · NUMBER 26 · SEPTEMBER 10 2006

JOURNAL OF CLINICAL ONCOLOGY

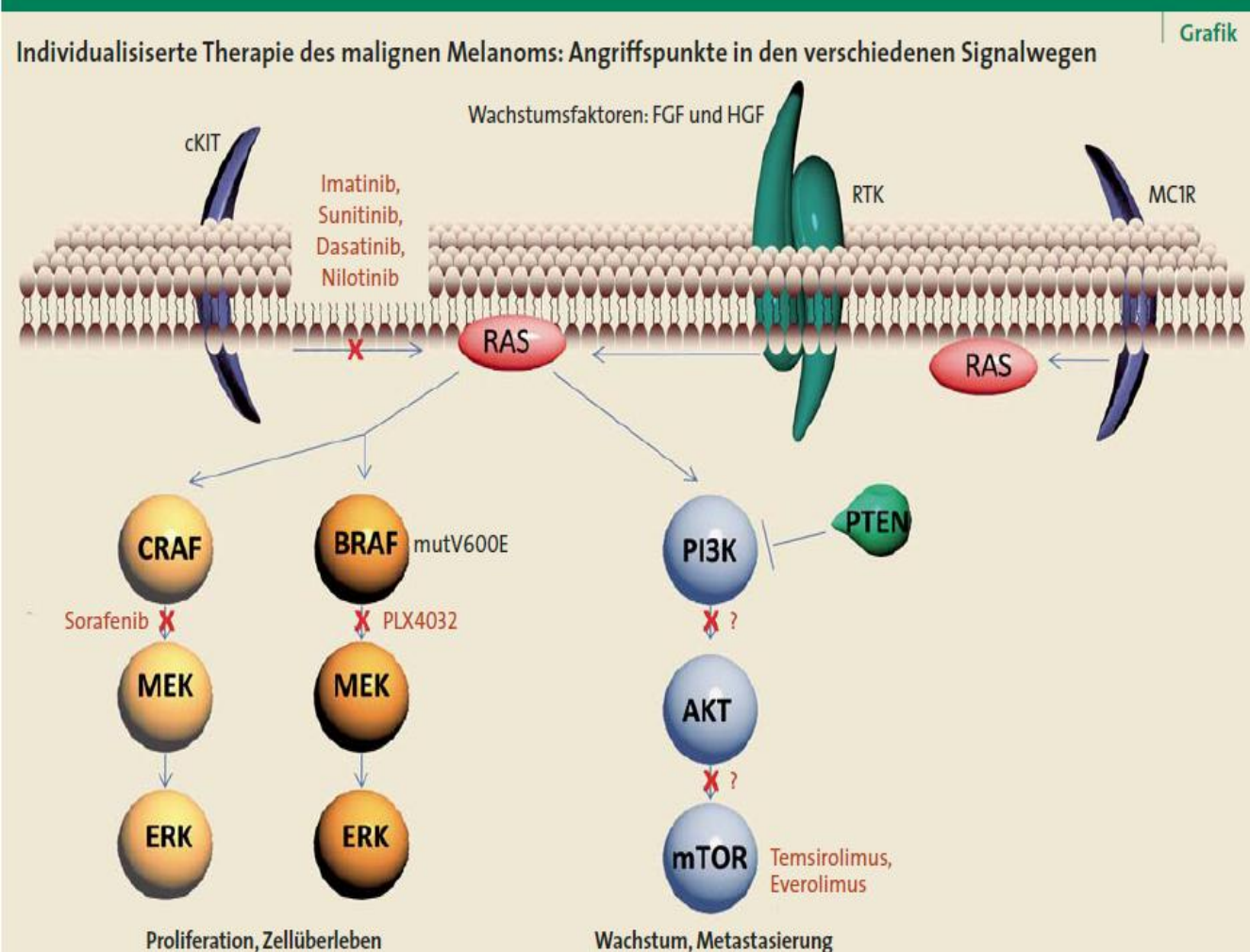
ORIGINAL REPORT

## Somatic Activation of KIT in Distinct Subtypes of Melanoma

*John A. Curtin, Klaus Busam, Daniel Pinkel, and Boris C. Bastian*

Universitätsklinikum  
Erlangen

# Targeted Therapy - Inhibitoren



Bosserhof et al., 2010  
[www.im-focus-onkologie.de](http://www.im-focus-onkologie.de)

Universitätsklinikum  
 Erlangen

FGF = Fibroblasten-Wachstumsfaktor, HGF = Hepatozyten-Wachstumsfaktor, RTK = Rezeptortyrosinkinase, MC1R = Melanocortin-1-Rezeptor, PI3K = Phosphatidylinositol-3,4,5-Triphosphat-Kinase, Akt = Proteinkinase B, mTOR = mammalian target of rapamycin; PTEN = phosphatase and tensin homologue;

# Algorithmus für Stadium IV Melanom

	<b>Tumorlast</b> <b>+++</b> <b>Dynamik</b> <b>+++</b>	<b>Tumorlast</b> <b>+</b> <b>Dynamik</b> <b>+</b>
<b>BRAF +</b>	<b>KI</b>	
<b>BRAF -</b>		





# Kinaseinhibitor PLX4032 (Vemurafenib)

March 3<sup>rd</sup>, 2009  
(baseline)



March 20<sup>th</sup>, 2009  
(day 16)



**Rapides  
Ansprechen**

The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 26, 2010

VOL. 363 NO. 9

Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D.,  
Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D.,  
Joseph F. Grippo, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

**Universitätsklinikum  
Erlangen**



# BRAF + Tumorlast +++ Dynamik +++

Kinase Inhibitor **Vemurafenib**



October  
2011



January  
2012



# BRAF + Tumorlast +++ Dynamik +++

Kinase Inhibitor **Vemurafenib**



October  
2011



Mai  
2012



January  
2012



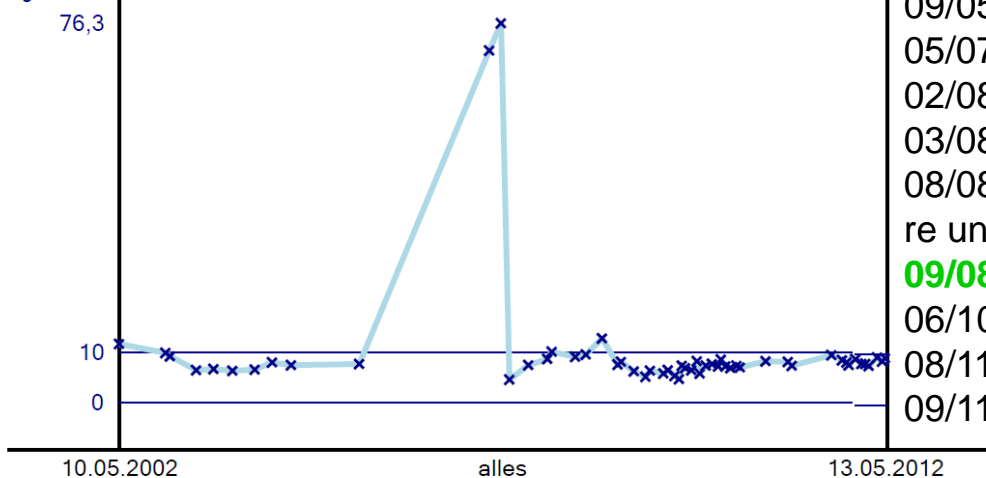
# Algorithmus für Stadium IV Melanom

	<b>Tumorlast</b> <b>+++</b> <b>Dynamik</b> <b>+++</b>	<b>Tumorlast</b> <b>+</b> <b>Dynamik</b> <b>+</b>
<b>BRAF +</b>	<b>KI</b>	<b>(Ipi)</b>
<b>BRAF -</b>		<b>(Ipi)</b>



# Systemtherapie im Stadium IV Melanom

Melanoma Inhibitory Activity (MIA)  
ng/ml



05/02 Z.n. ulz. NM (TD 5.1 mm), US li, SNB neg.

05/03 Z.n. Satellitenfiliae, US li

09/05 Z.n. LK-Diss. ing. li (0/7), 1 WT-Filia

05/07 Z.n. Bauchdeckenfilia

02/08 Z.n. LK-Filia iliakal li., (R1)

03/08 Z.n. RT mit Hyperthermie

08/08 LK-Filiae scapulär u. paravertebral  
re und cervical li

**09/08-06/10 23 Zyklen DTIC**

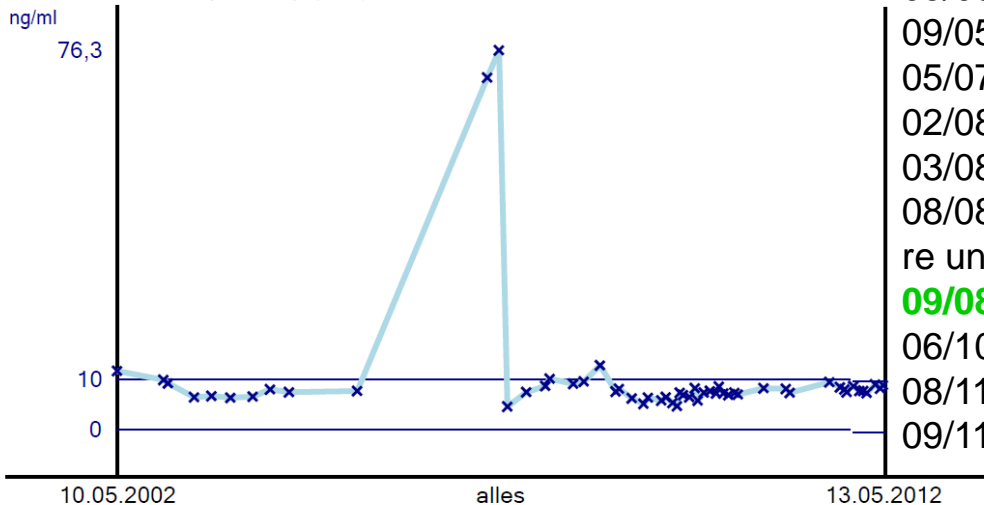
06/10 Ende der Chemotherapie bei Tumorfreiheit

08/11 Filiae am OS li.

09/11 Filiae li. prox. OS, V.a. WT-Filia li. SG,

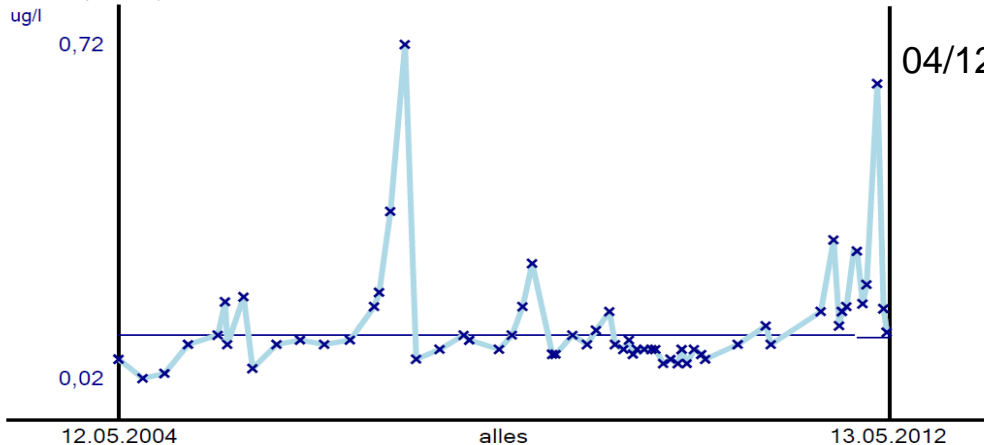
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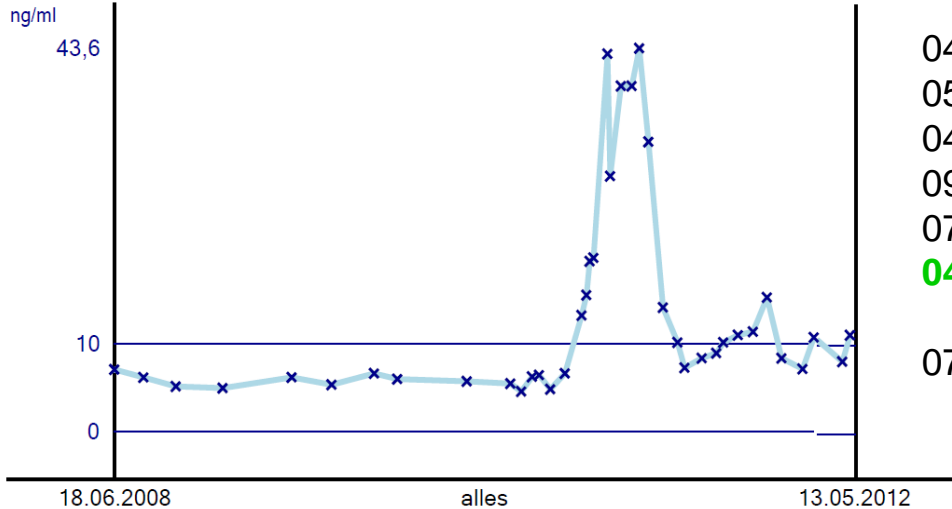
S100 (Roche)  
ug/l



04/12 **Einschluss in dRNA Vakzinestudie**

# Systemtherapie im Stadium IV Melanom

Melanoma Inhibitory Activity (MIA)



04/06 ulz. ALM li Fuß

05/06 LK-Diss. ing. li

04/09 HEP li Bein (CH, FAU)

09/09 ED pul. Filiae, anschließend RT

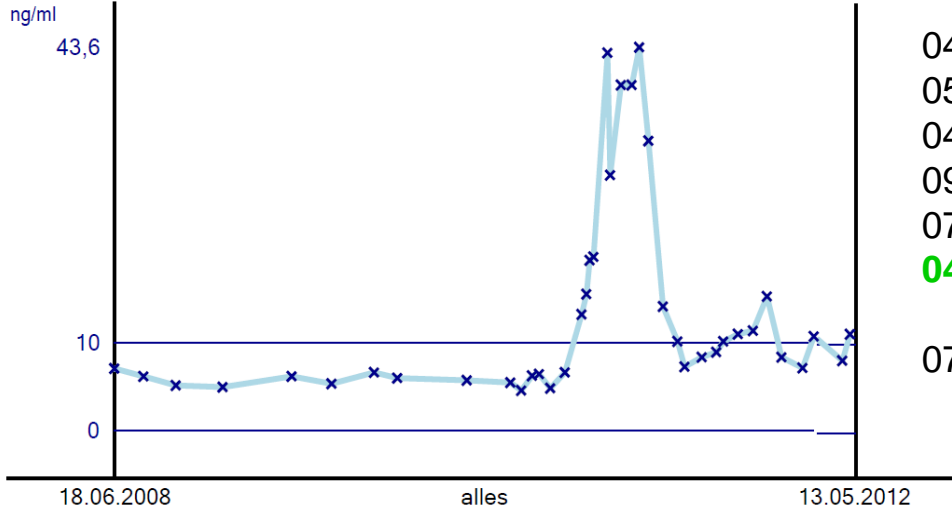
07/10 DTIC only

**04/11 3x Taxol/ Carboplatin**

07/11 4 **DC-Vakzinierungen (dRNAStudie)**

# Systemtherapie im Stadium IV Melanom

Melanoma Inhibitory Activity (MIA)



04/06 ulz. ALM li Fuß

05/06 LK-Diss. ing. li

04/09 HEP li Bein (CH, FAU)

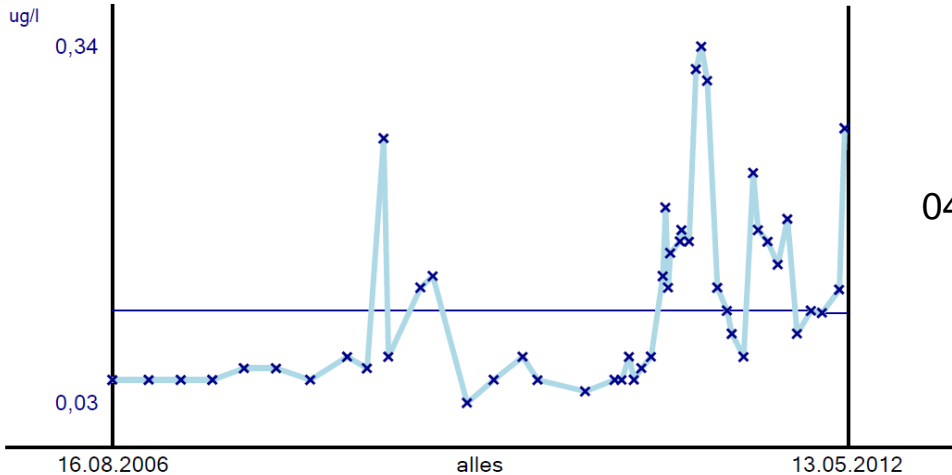
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07/10 DTIC only

**04/11 3x Taxol/ Carboplatin**

07/11 **Einschluss in dRNA Vakzinestudie**

S100 (Roche)

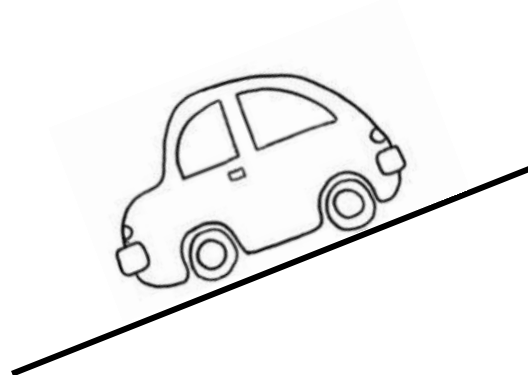
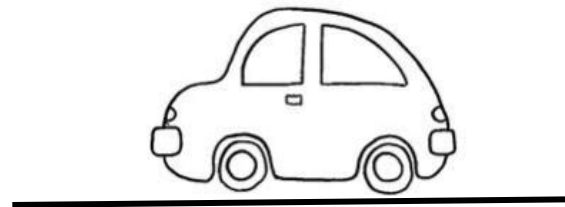


04/12 **Ipilimumab**



# Wirkmechanismus von Ipilimumab

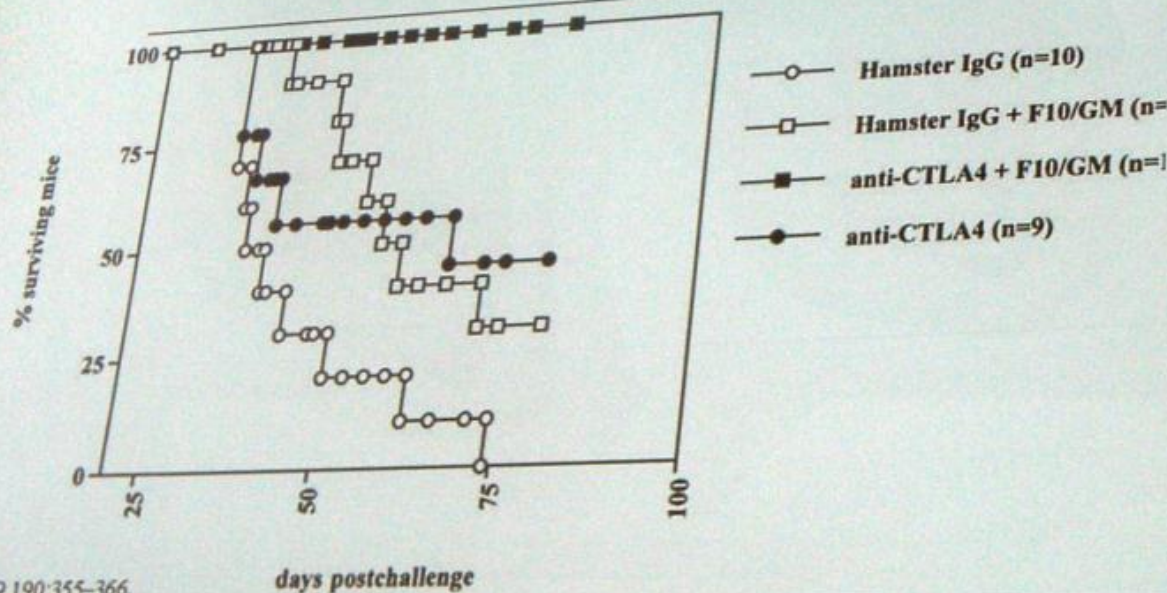
Die Bremse des Immunsystems wegnehmen ?



# Wirkmechanismus von Ipilimumab

Combination Immunotherapy of B16 Melanoma Using Anti-Cytotoxic T Lymphocyte-associated Antigen 4 (CTLA-4) and Granulocyte/Macrophage Colony-Stimulating Factor (GM-CSF)-producing Vaccines Induces Rejection of Subcutaneous and Metastatic Tumors Accompanied by Autoimmune Depigmentation

By Andrea van Elsas, Arthur A. Hurwitz, and James P. Allison



Vakzine  
Vak + Ipi  
Ipi

# ASCO 2010 - Immuntherapie

FOCUS Magazin | Nr. 24 (2010)

DOSIERT

## Neues Mittel gegen Hautkrebs

Montag 14.06.2010, 00:00 - von FOCUS-Redakteurin Dr. Regina Albers



Patienten mit einer erblichen Veranlagung für Hautkrebs müssen regelmäßig zum Screening

Colourbox

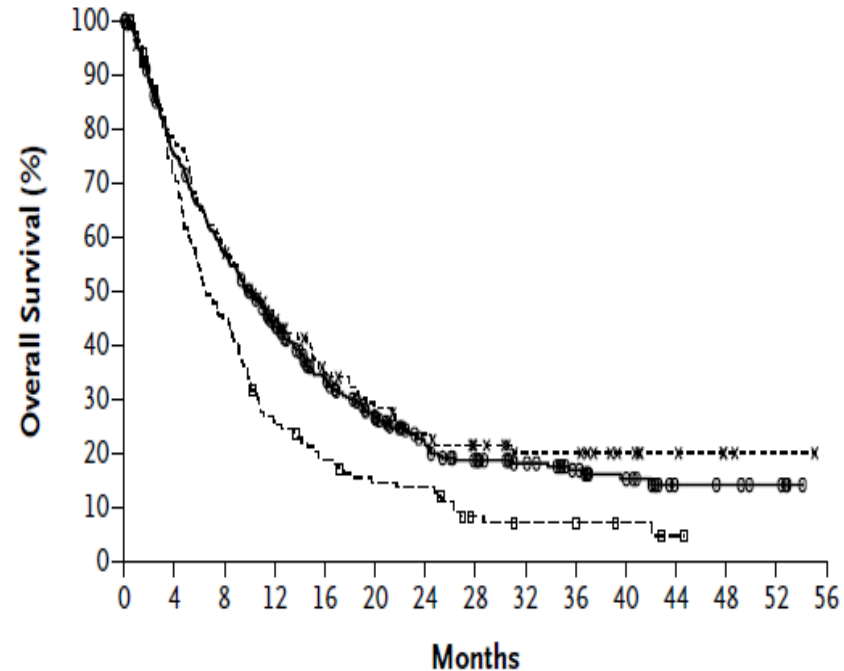
**Hoffnungsschimmer für Patienten mit fortgeschrittenem schwarzem Hautkrebs: Ein neues Mittel soll Tumoren zurückbilden und das Überleben verlängern.**

Patienten mit fortgeschrittenem schwarzem Hautkrebs können künftig von einer neuen Substanz profitieren. In einer internationalen Studie an 576 Patienten, die jetzt auf der Krebsforscherkonferenz ASCO in Chicago vorgestellt wurde, verlängerte ein Wirkstoff aus Antikörpern, Ipilimumab, das Überleben der Behandelten um durchschnittlich zehn Monate.

Ipilimumab habe bei einigen Studienteilnehmern sogar große metastasierte Tumoren lang anhaltend zurückgebildet, erklärt der Leiter des Zentrums für Dermatoonkologie an der Uniklinik Tübingen, Claus Garbe. Er betont: „Angesichts der sehr begrenzten Therapiemöglichkeiten bei fortgeschrittenem Hautkrebs hoffen wir auf eine rasche Zulassung des Präparats.“

In Zusammenarbeit mit jameda

Overall Survival



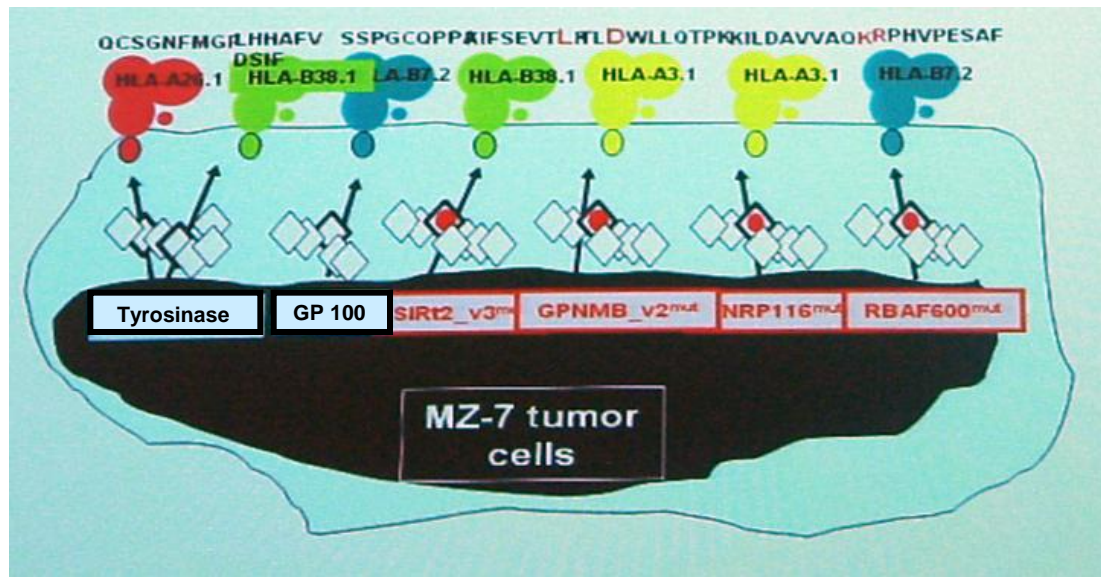
# Langzeitüberleber nach Immuntherapie zeigen Immunantworten gegen **individuelle Mutationen**

## The response of autologous T cells to a human melanoma is dominated by mutated neoantigens

Volker Lennerz<sup>†</sup>, Martina Fatho<sup>†</sup>, Chiara Gentilini<sup>‡</sup>, Roy A. Frye<sup>§</sup>, Alexander Lifke<sup>†</sup>, Dorothea Ferel<sup>†</sup>, Catherine Wölfel<sup>†</sup>, Christoph Huber<sup>†</sup>, and Thomas Wölfel<sup>†1</sup>

<sup>†</sup>Department of Medicine, Hematology/Oncology, Johannes Gutenberg University, Langenbeckstrasse 1, D-55101 Mainz, Germany; <sup>‡</sup>Department of Medicine, Hematology/Oncology, University of Leipzig, Liebigstrasse 22, D-04103 Leipzig, Germany; and <sup>§</sup>Department of Pathology, Veterans Affairs Medical Center, University Drive C, Pittsburgh, PA 15240

Edited by Lloyd J. Old, Ludwig Institute for Cancer Research, New York, NY, and approved September 12, 2005 (received for review January 6, 2005)



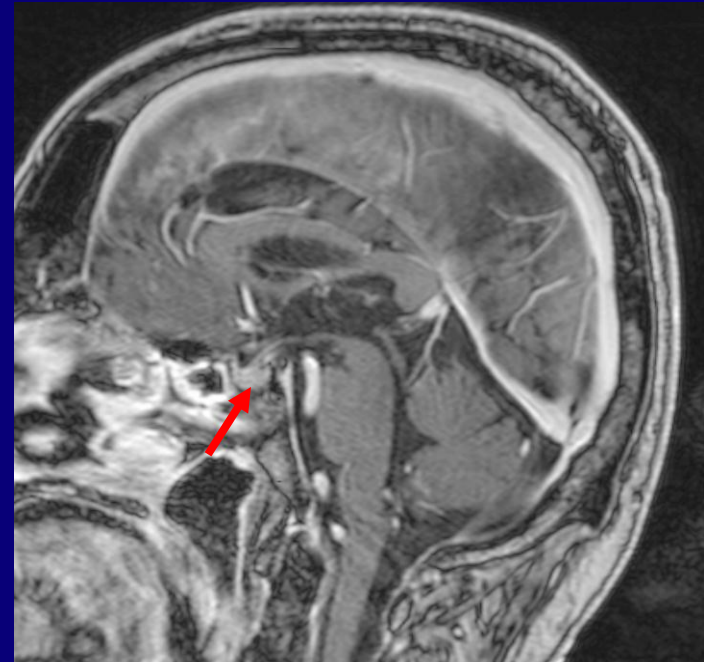


# Case history details

- MRT showing inflammation of pituitary gland



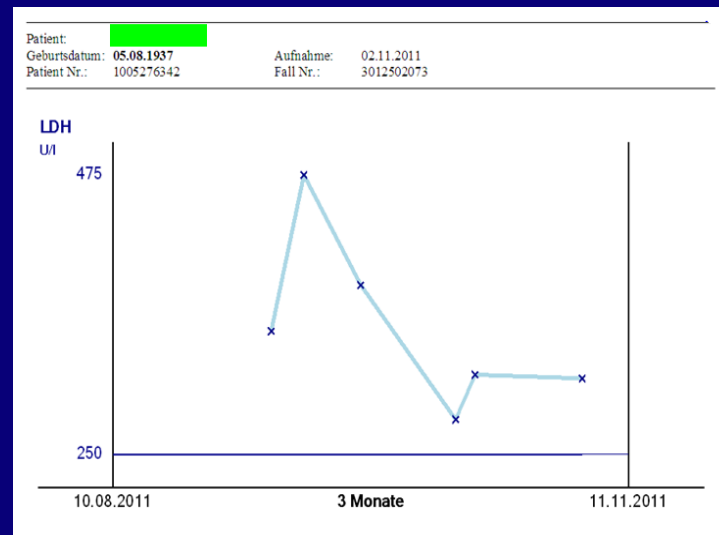
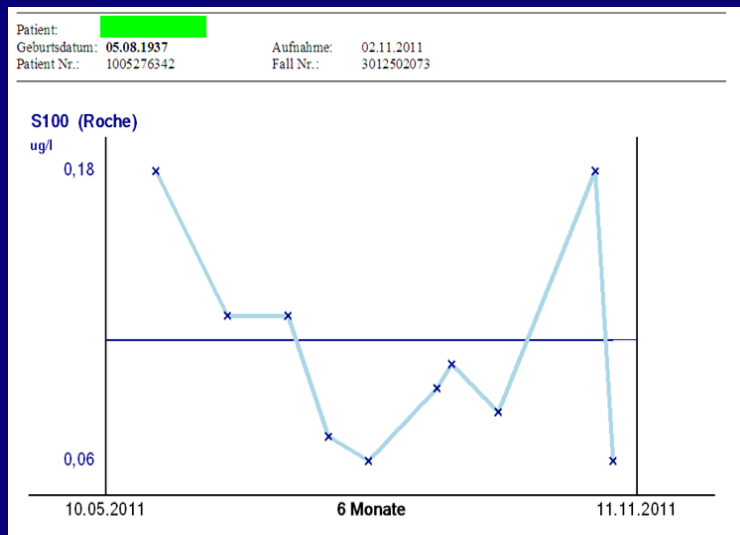
September 13, 2011



July 26, 2011

# Case history details

- Current staging: stable disease, drop of S100 and LDH



# Case history details

---

- **Melanoma Stage IV**
- 03/06 NMM, TD 4,5 mm, CL IV, right thigh – surgery, negative SLN
- 08/06 in transit metastasis, right thigh - surgery
- 09/06 novel in-transit metastases in skin and regional lymph nodes  
lymph node dissection, hyperthermic perfusion of right leg with melphalan
- 07/08 novel in-transit metastases in skin  
immunochemotherapy with local DNCB and systemic DTIC (7 x)
- 04/11 novel metastases in skin, lymph nodes and both adrenal glands  
systemic DTIC (3 x) → progression at all sites
- 07/11 immunotherapy with Yervoy (Ipilimumab) 2x
- 09/11 inflammation of pituitary gland with siADH syndrome
- 10/11 steroid induced psychosis

# DNCB / DTIC Immunchemotherapie



**16.09.09**



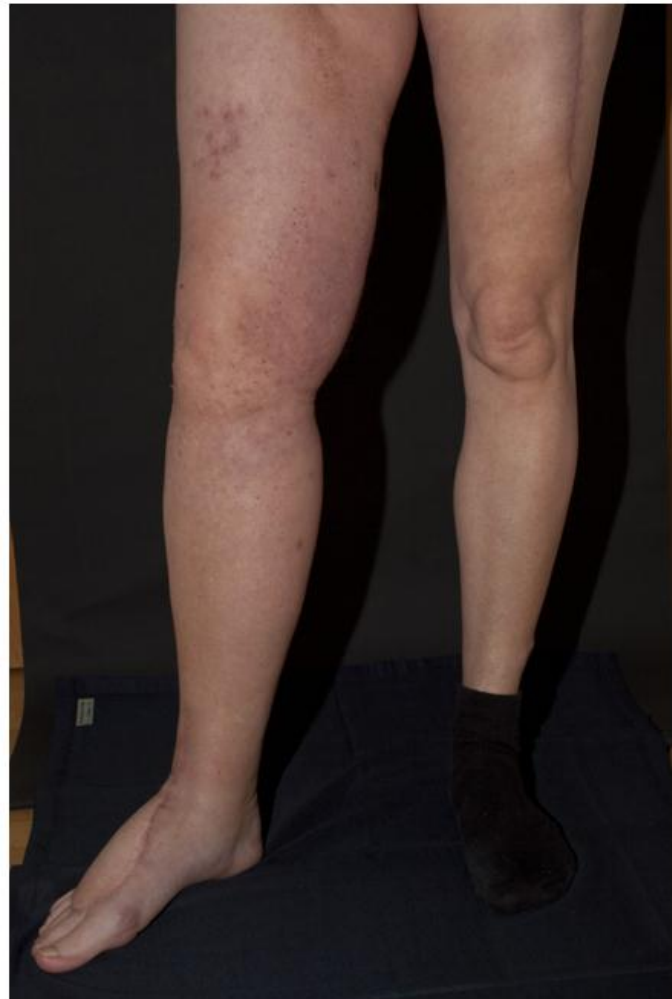
**30.09.09**

**Universitätsklinikum  
Erlangen**

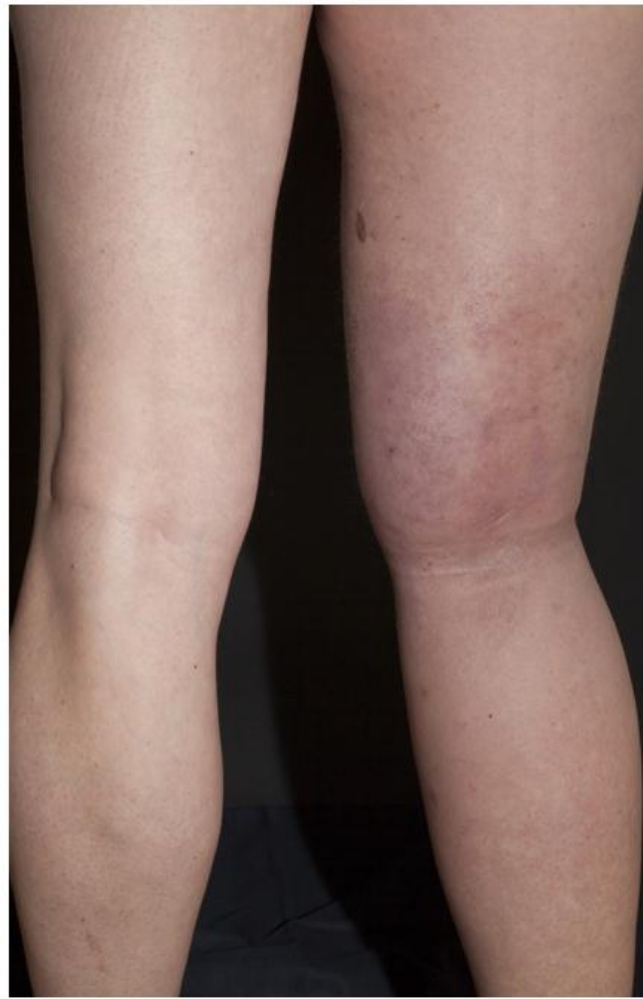




# DNCB / DTIC Immunchemotherapie



25.11.09



25.11.09

CR

7x  
DNCB lokal

3x  
DTIC systemisch

Universitätsklinikum  
Erlangen



# Algorithmus für Stadium IV Melanom

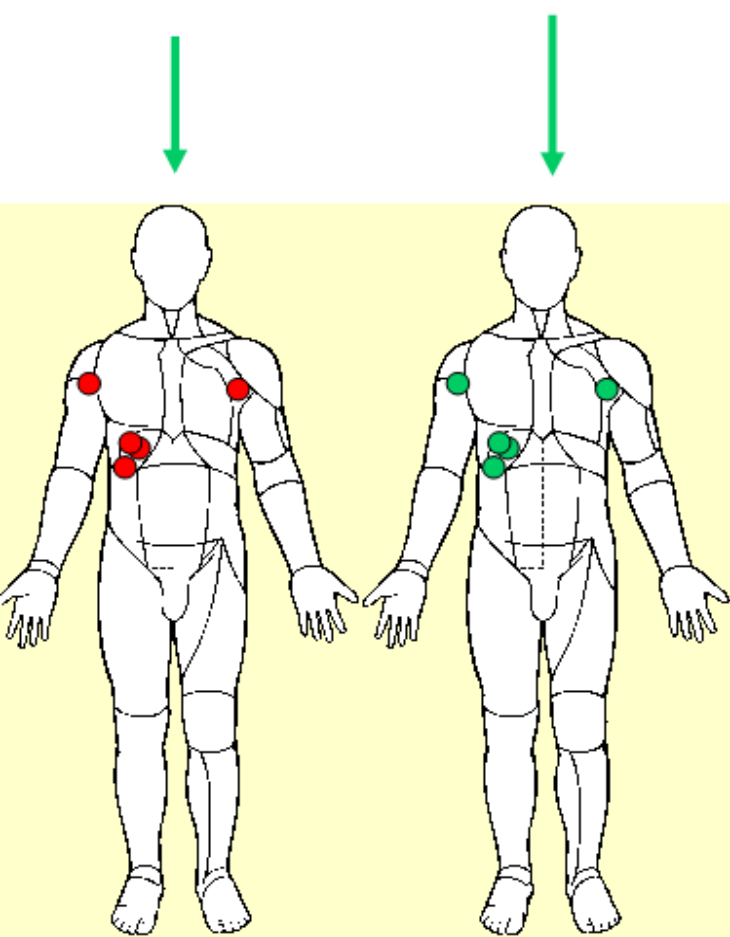
	<b>Tumorlast</b> <b>+++</b> <b>Dynamik</b> <b>+++</b>	<b>Tumorlast</b> <b>+</b> <b>Dynamik</b> <b>+</b>
<b>BRAF +</b>	<b>KI</b> →	<b>(Ipi)</b>
<b>BRAF -</b>	<b>?</b> →	<b>(Ipi)</b>

**DTIC**  
**C/T**  
**Vakzine**



# Systemtherapie Stadium IV Melanom BRAF-

**DTIC 01/07 – 03/07**  
**+ Sorafenib 4/07: CR**

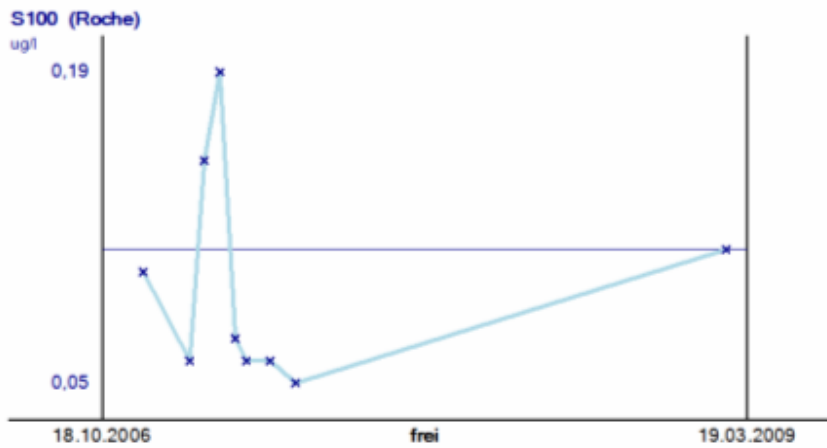


**2 yrs**  
**Sorafenib**  
**only**

Patient: [redacted]  
Geburtsdatum: 03.11.1923 Aufnahme: 18.02.2009  
Patient Nr.: 1006745005 Fall Nr.: 3003519141



Patient: [redacted]  
Geburtsdatum: 03.11.1923 Aufnahme: 18.02.2009  
Patient Nr.: 1006745005 Fall Nr.: 3003519141



# Clinical remission by Sorafenib followed by surgery and RNA-DC vaccination

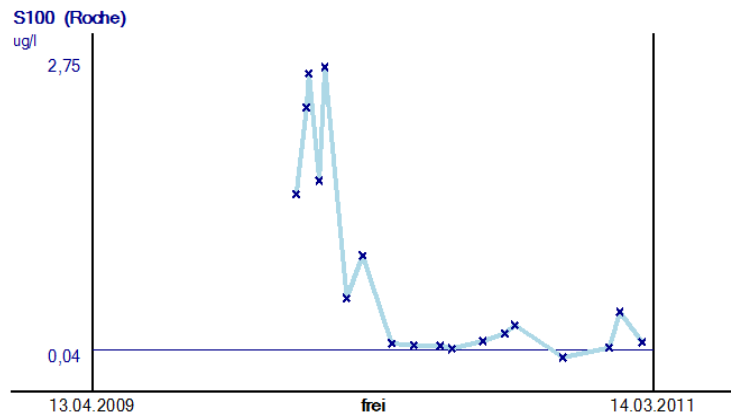
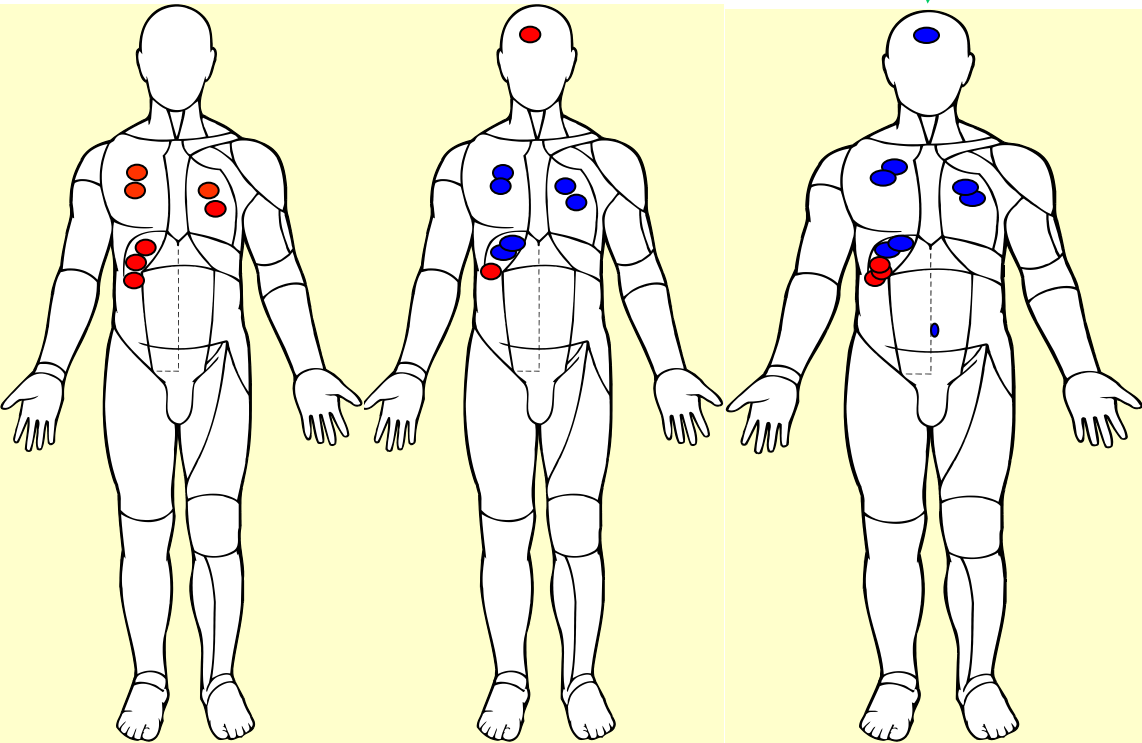
DTIC 10/09 – 12/09

DTIC + Sorafenib 12/09 – 06/10

Surg. brain, Fote + S 07/10 – 01/11

Surg. liver, 03/11

+ start DC vaccination



# Targeted Therapy: Sorafenib

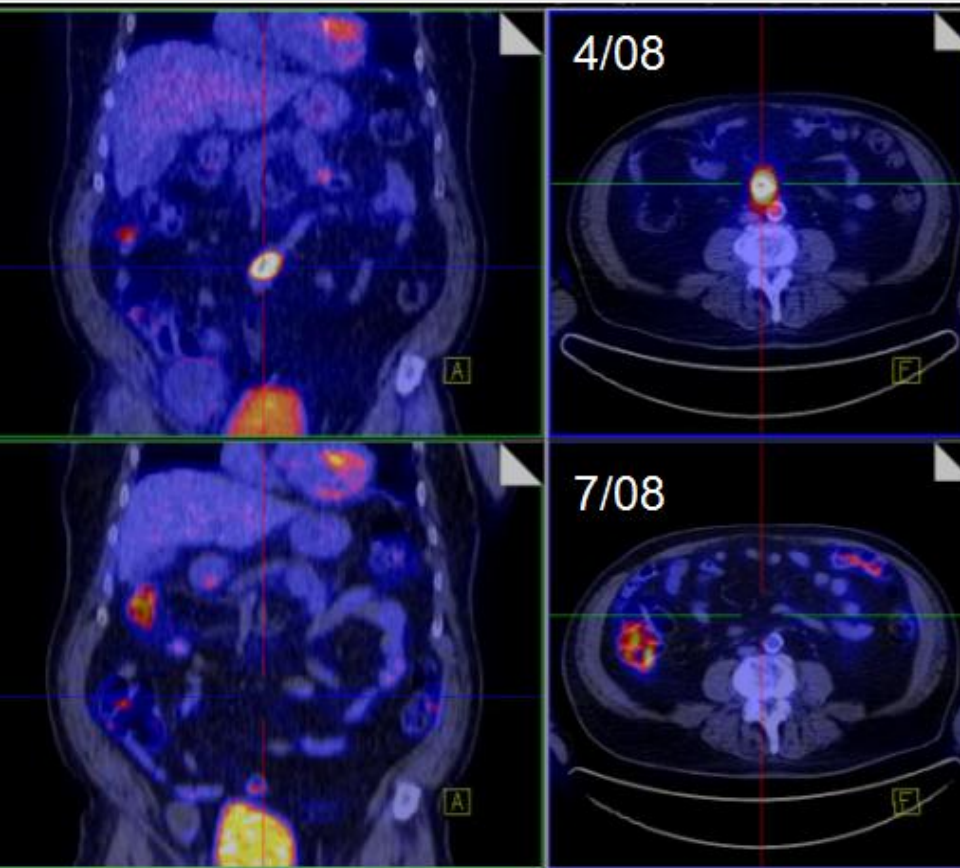


**12.01.2009**

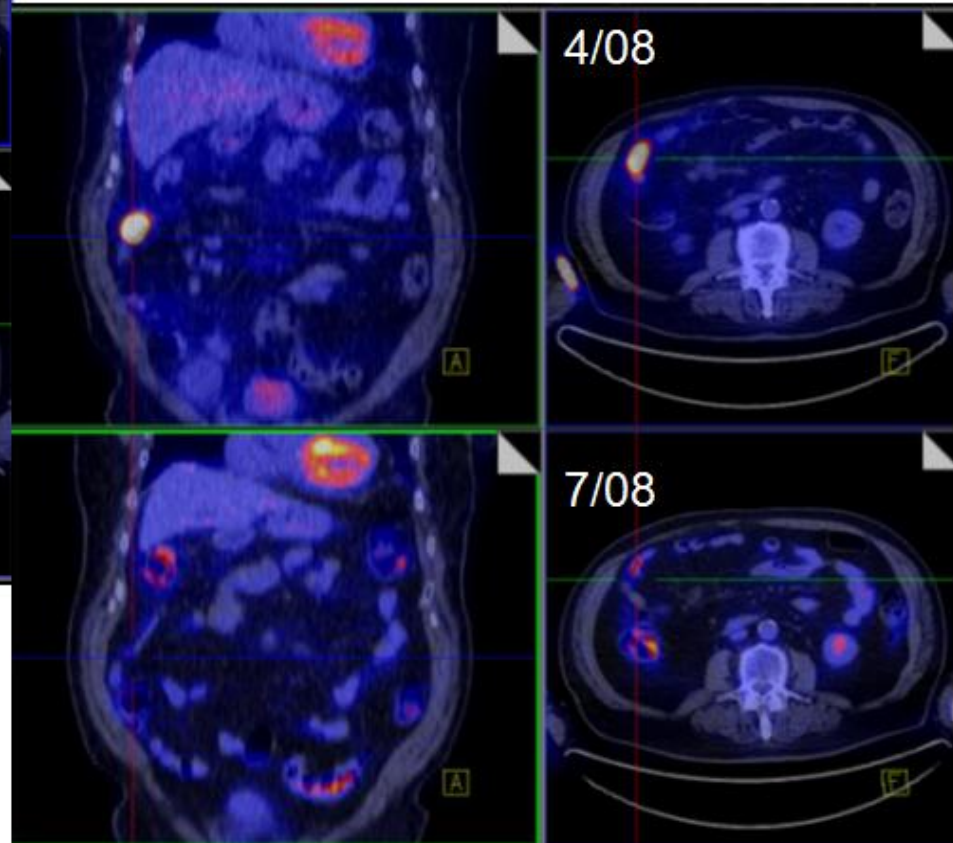
**28.01.2009**



# MM Stadium IV: Therapieoptionen für BRAF - Melanome

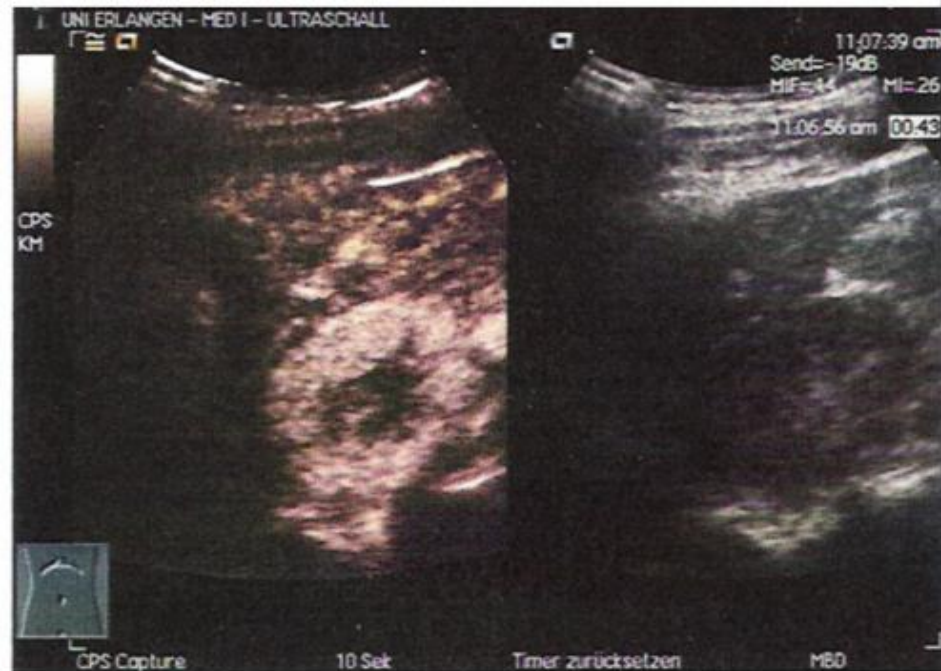


7/04 ALM pT4a,N2a  
81y male, B.G.  
BRAF -

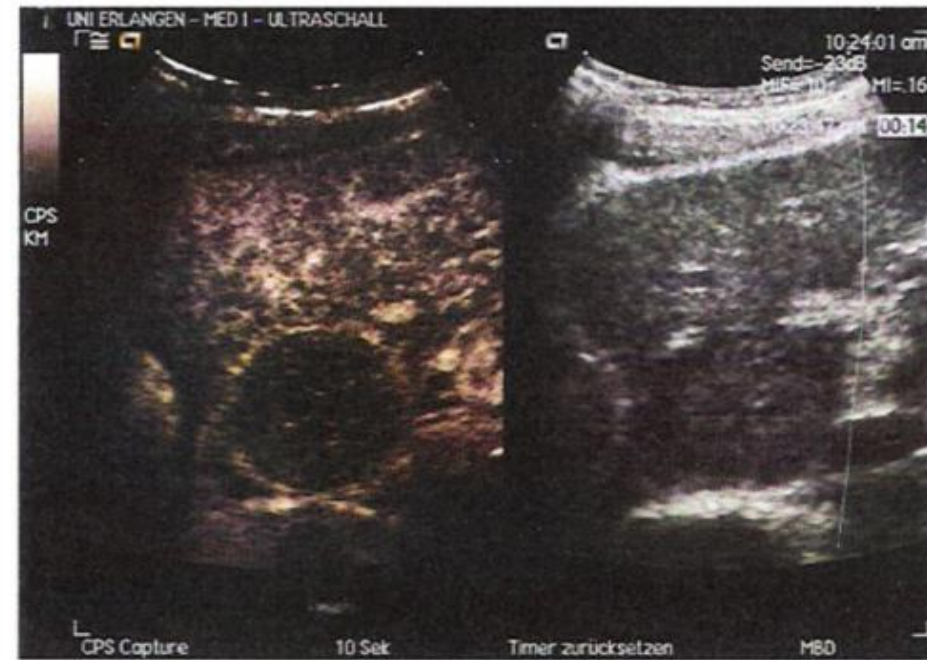


drop in FDG uptake  
already after 2 weeks !

# MM Stadium IV: Therapieoptionen für BRAF - Melanome



Arterielle Phase VOR Sorafenib!



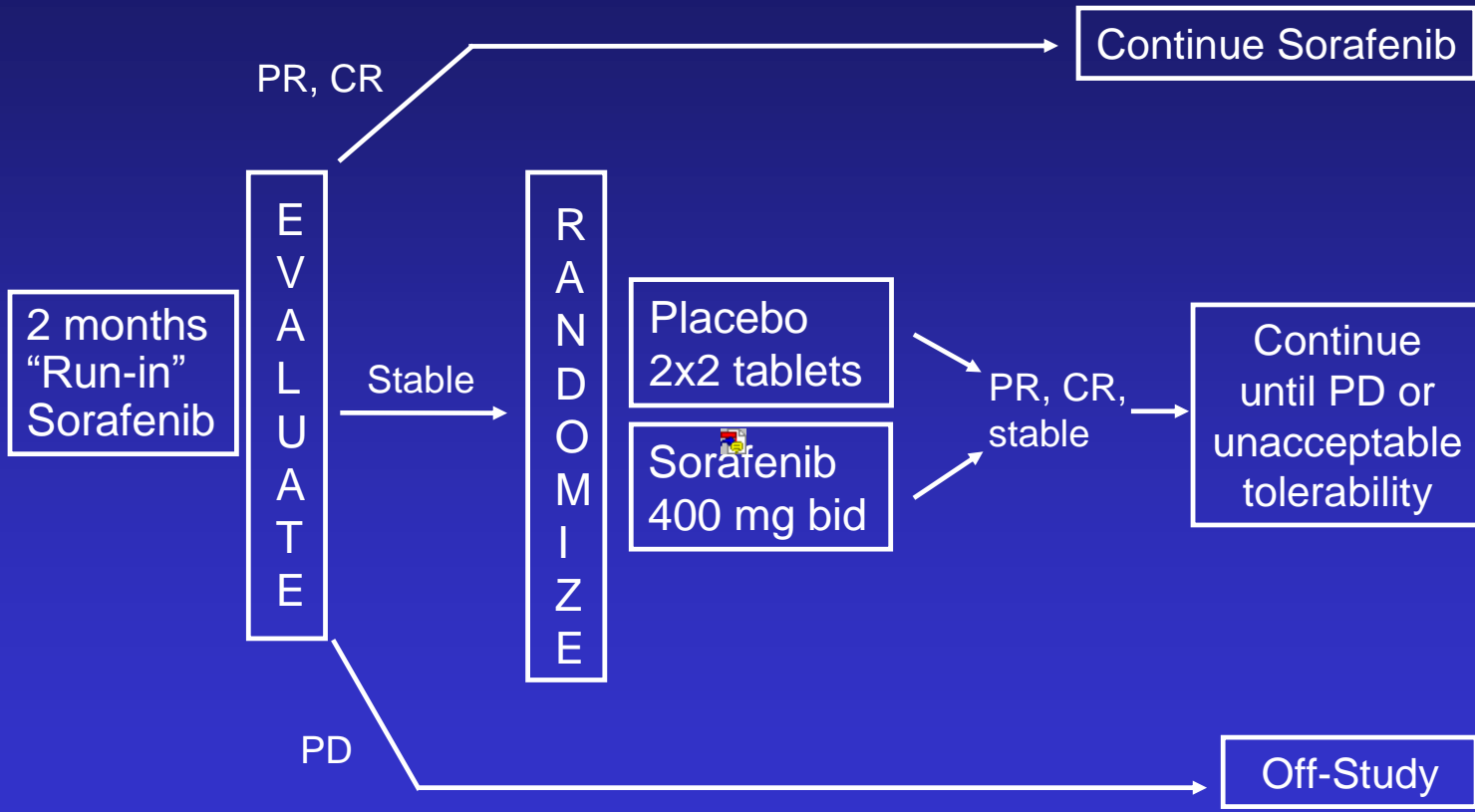
Arterielle Phase hypovaskularisiert nach Sorafenib

**Rapid drop in perfusion  
of liver metastases !**

**14d treatment with sorafenib  
200mg 2x daily**

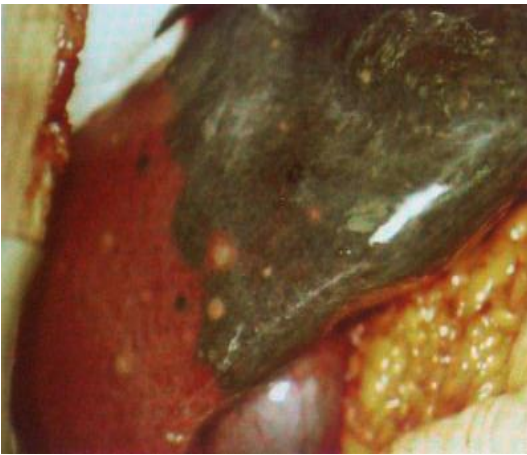
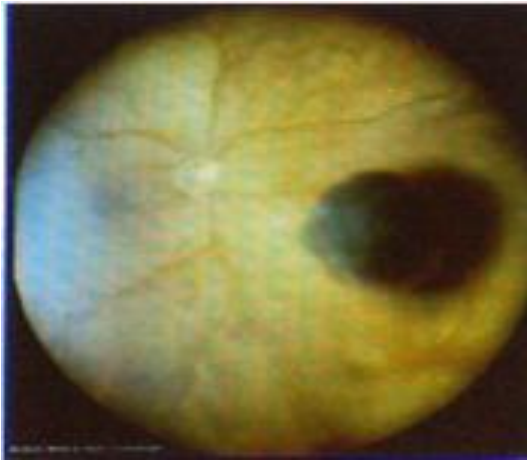
# STREAM: phase II trial in metastatic uveal melanoma –Sorafenib 1<sup>st</sup> line

A Randomized Discontinuation, Blinded, Placebo-Controlled, Phase II Study of Sorafenib in patients with Chemonaïve Metastatic Uveal Melanoma (Sorafenib Treatment of Metastatic Uveal Melanoma) (EudraCT-No.: 2010-022687-12) Start 02/2011





# Therapieoptionen des Uvea Melanoms



Adjuvant **DC Vaccination trial**  
In High Risk  
Monosomy 3  
Uveal melanoma



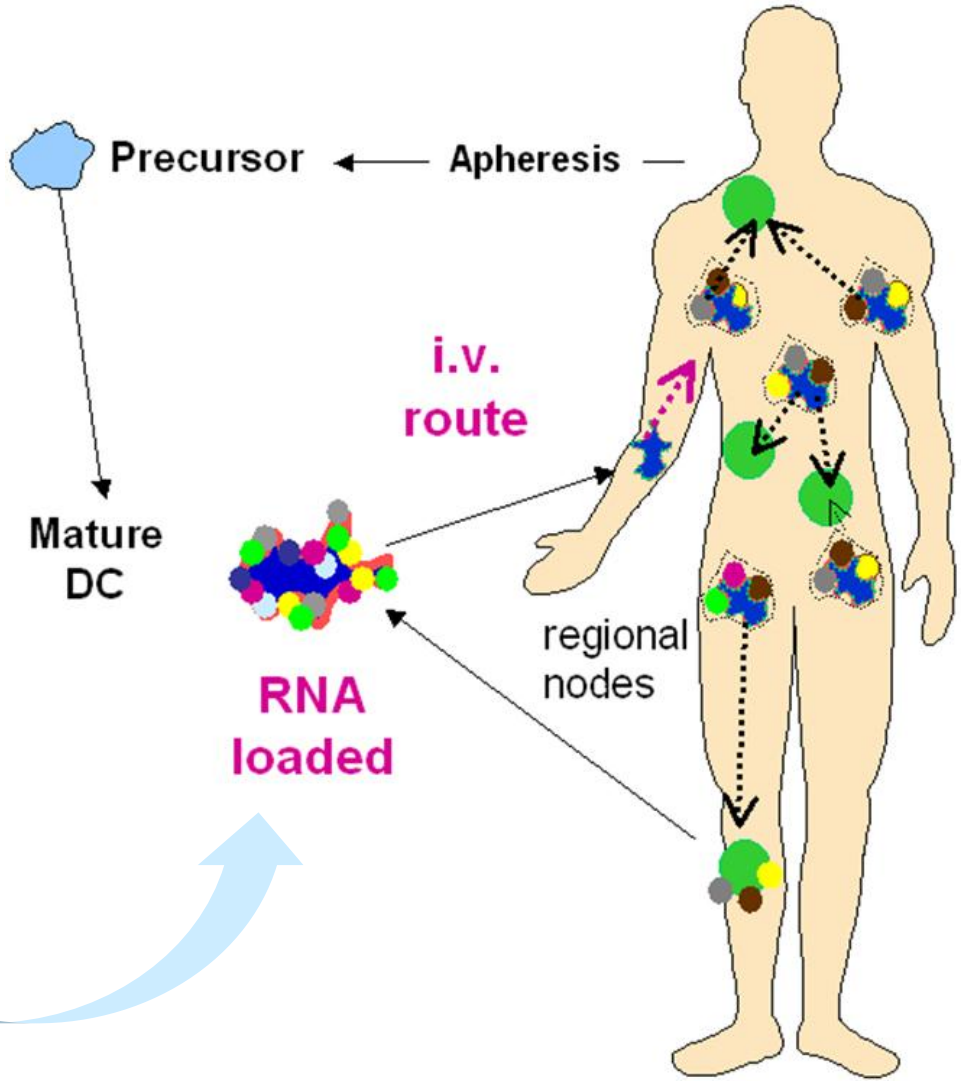
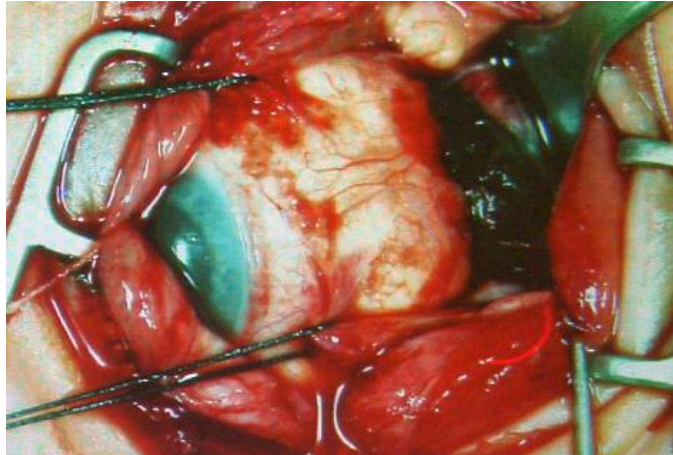
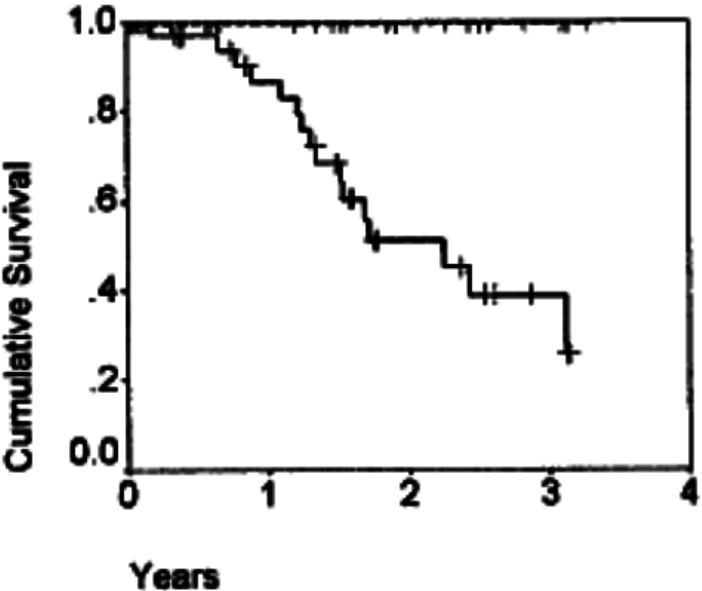
**STREAM trial**  
Sorafenib 1st line  
therapy in stage IV  
Uveal melanoma



 Weltweit einmaliges Zentrum zur  
Systemtherapie von Uvea Melanomen



# Adjuvante Vakzinierung von **Monosomie 3** Hochrisiko Patienten mit Uvea Melanom



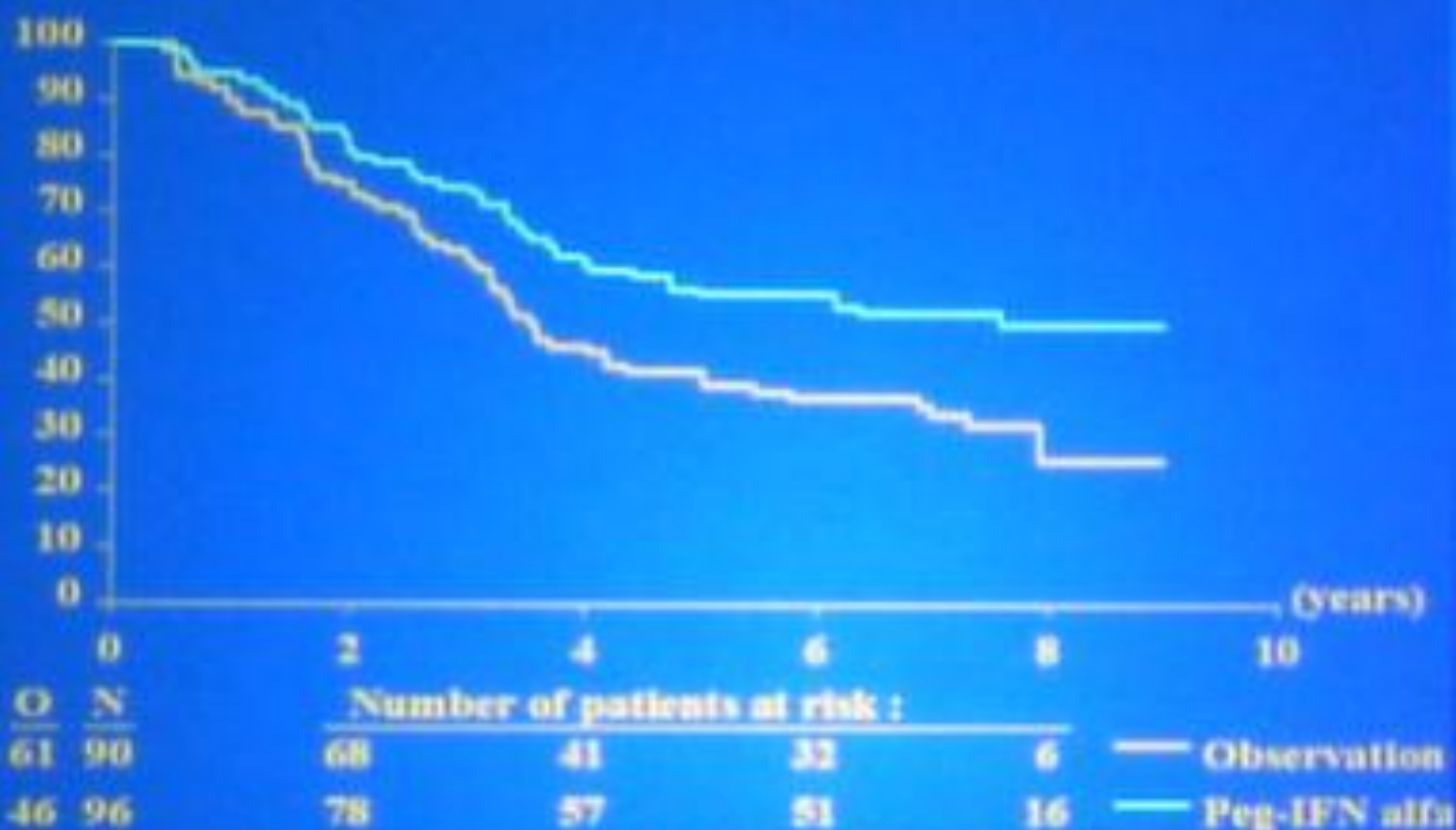
# Melanom: Prognostische Faktoren





# 18991 & III-N1 & Ulceration:

## 2011 OVERALL SURVIVAL



$p=0.006$  HR=0.59 (99% CI 0.35 , 0.97)

Median OS: 3.7 yrs vs > 9 yrs

# Individualisierte Melanomtherapie

Schleimhautmelanome  
**cKIT**

Uveamelanome  
**Monosomie 3**



Kutane Melanome  
**BRAF**

Adjuvante Situation  
**Ulzeration**



# Individualisierte Melanomtherapie

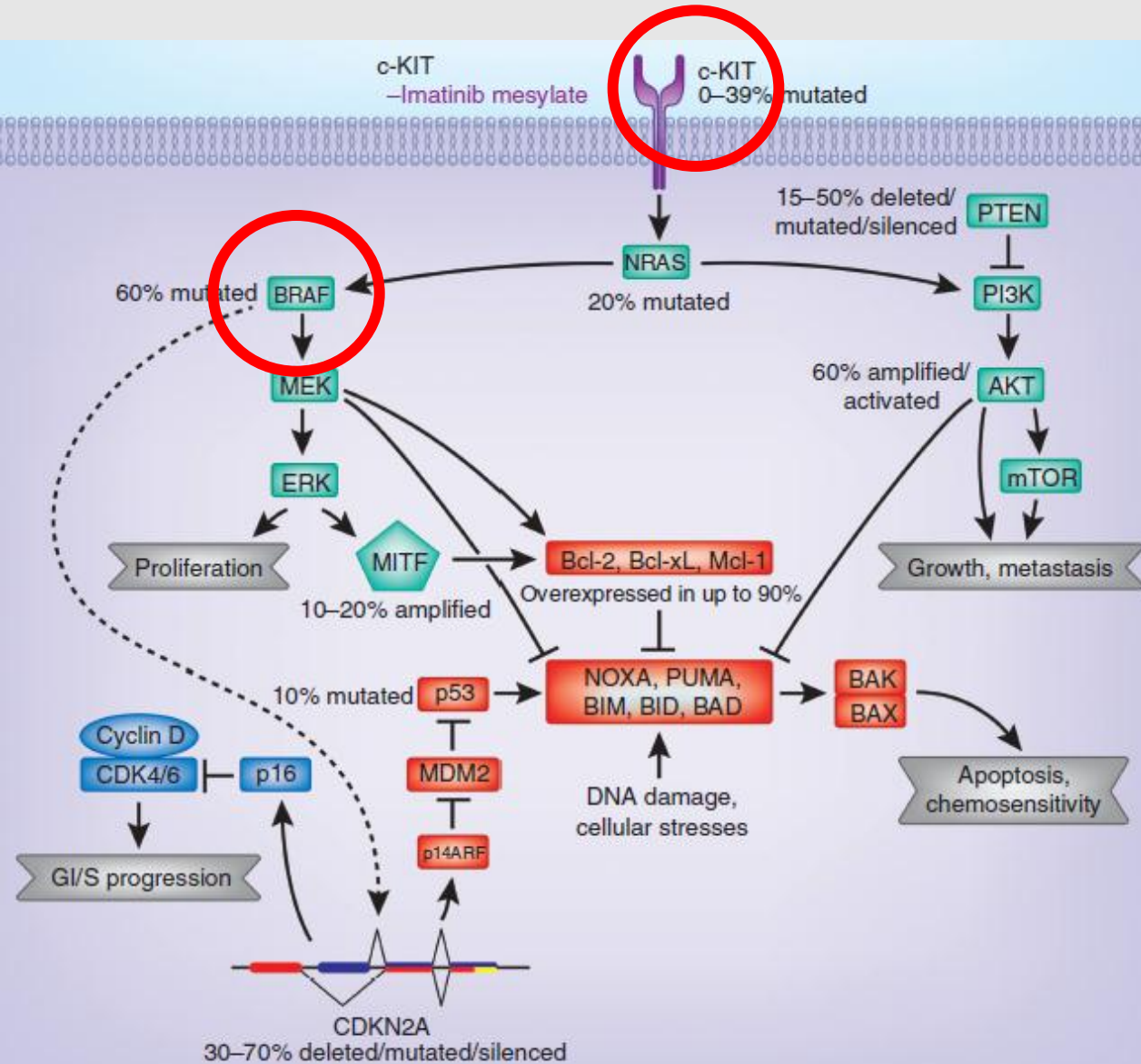
Geburtsdatum: 02.02.1982

05/01	Z.n. LK-Filia re. Kieferwinkel bei MUP
06/01	Z.n. Neck re. (1/9)
07/01	Z.n. RT Hals re.
07/01	20 x Vacc (Peptid-belad.)
04/07	Z.n. Leberfiliae
05/08	Vacc mit alpha-Gal-Cer DC
12/08	DTIC + Sorafenib
09/09	RT v. paraaort. LK-Filiae
10/10	4 x Ipi
05/11	Z.n. Exzision Samenblasenfilia
07/11	3x Ipi
11/11	3x T/C

BRAF wt  
c-KIT negativ



# Targeted Therapy



TL Hocker et al.  
Melanoma Genetics  
and Therapeutic Approaches  
JID (2008) 128, 2575-2595;

Universitätsklinikum  
Erlangen

# Systemtherapie des Melanoms

## bis 2010

- IFN
- IL-2
- DTIC
  
- Polychemo  
+ IFN / IL-2

## 2012

- IFN
- IL-2
- DTIC
  
- Polychemo  
+ IFN / IL-2
  
- Ipilimumab
- Vemurafenib

## Laufend / geplant

**Studien mit KI gegen**  
cKIT  
BRAF + MEK  
NRAS  
PI3K  
Protein Kinase C (GNAQ / GNA11)

**Vemurafenib plus  
Ipilimumab**

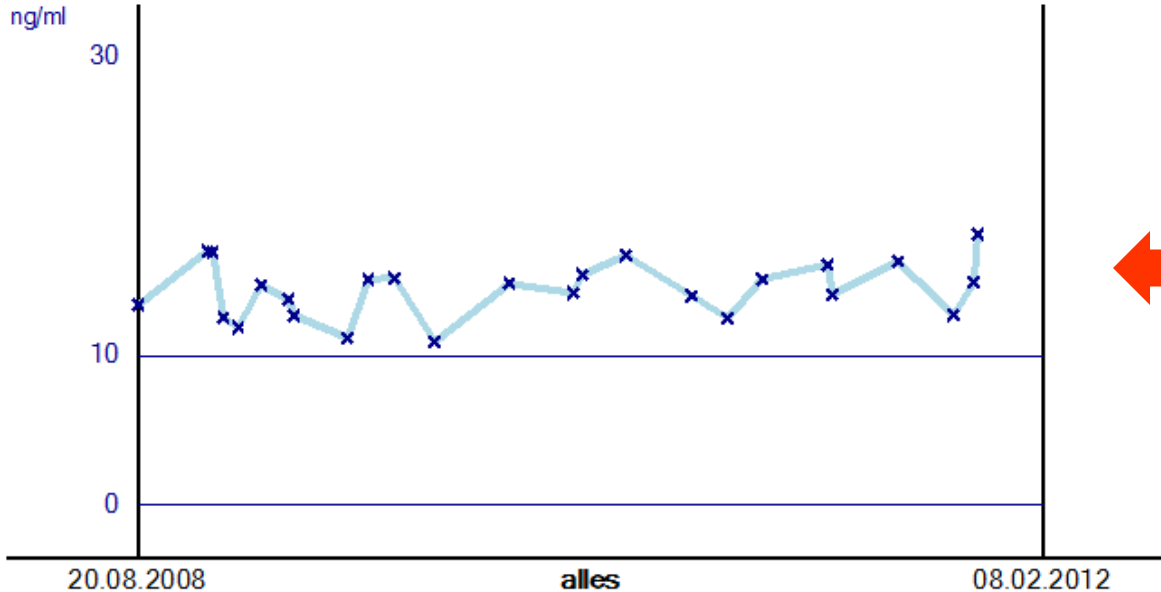




# Melanom - Zukunft

## Mutationsanalyse von zirkulierenden Tumorzellen

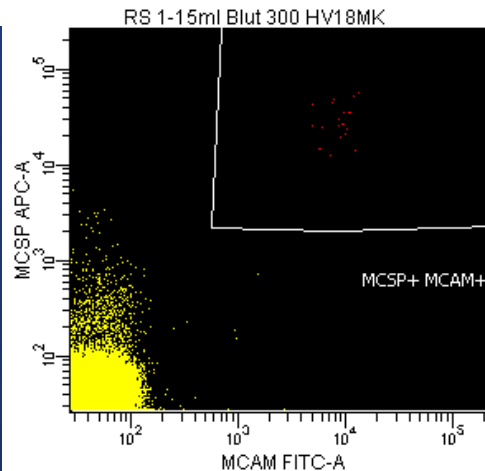
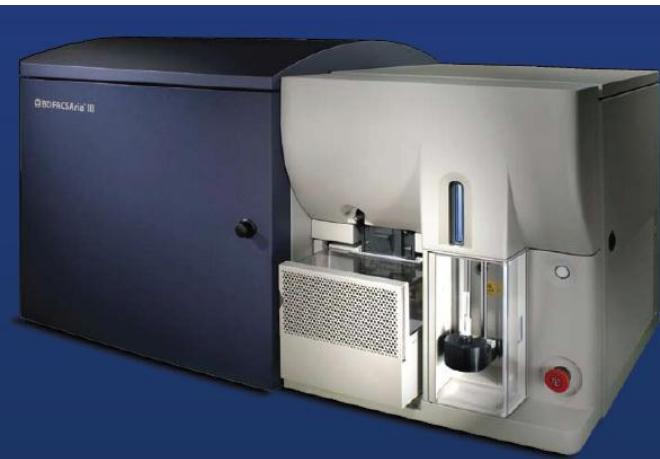
Melanoma Inhibitory Activity (MIA)



1400 sorted  
Tumorcells  
[MCSP+] from  
peripheral blood



PET-CT: negativ



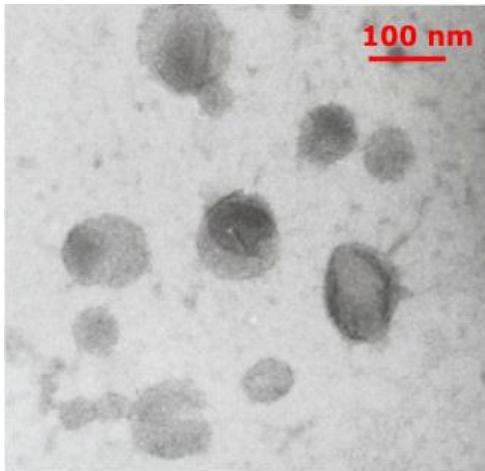
Universitätsklinikum  
Erlangen



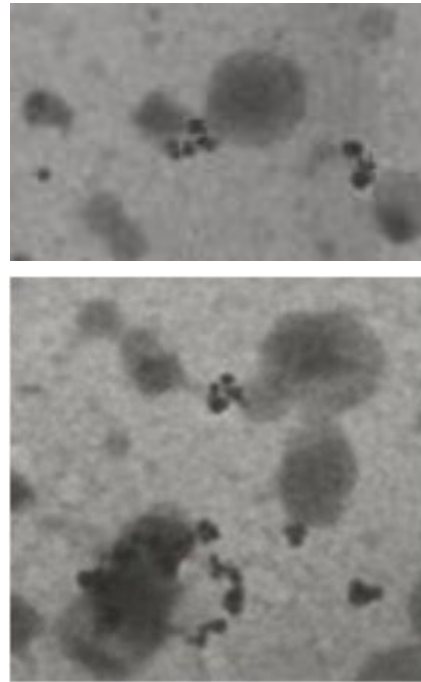
# Melanom - Zukunft

## Protein und RNA Analyse von Exosomen (A. Baur)

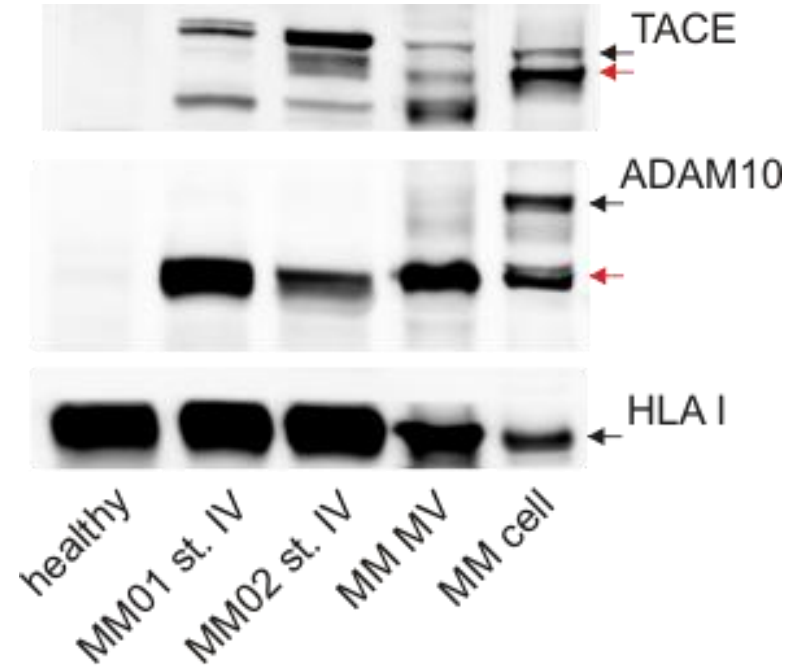
Exosomes



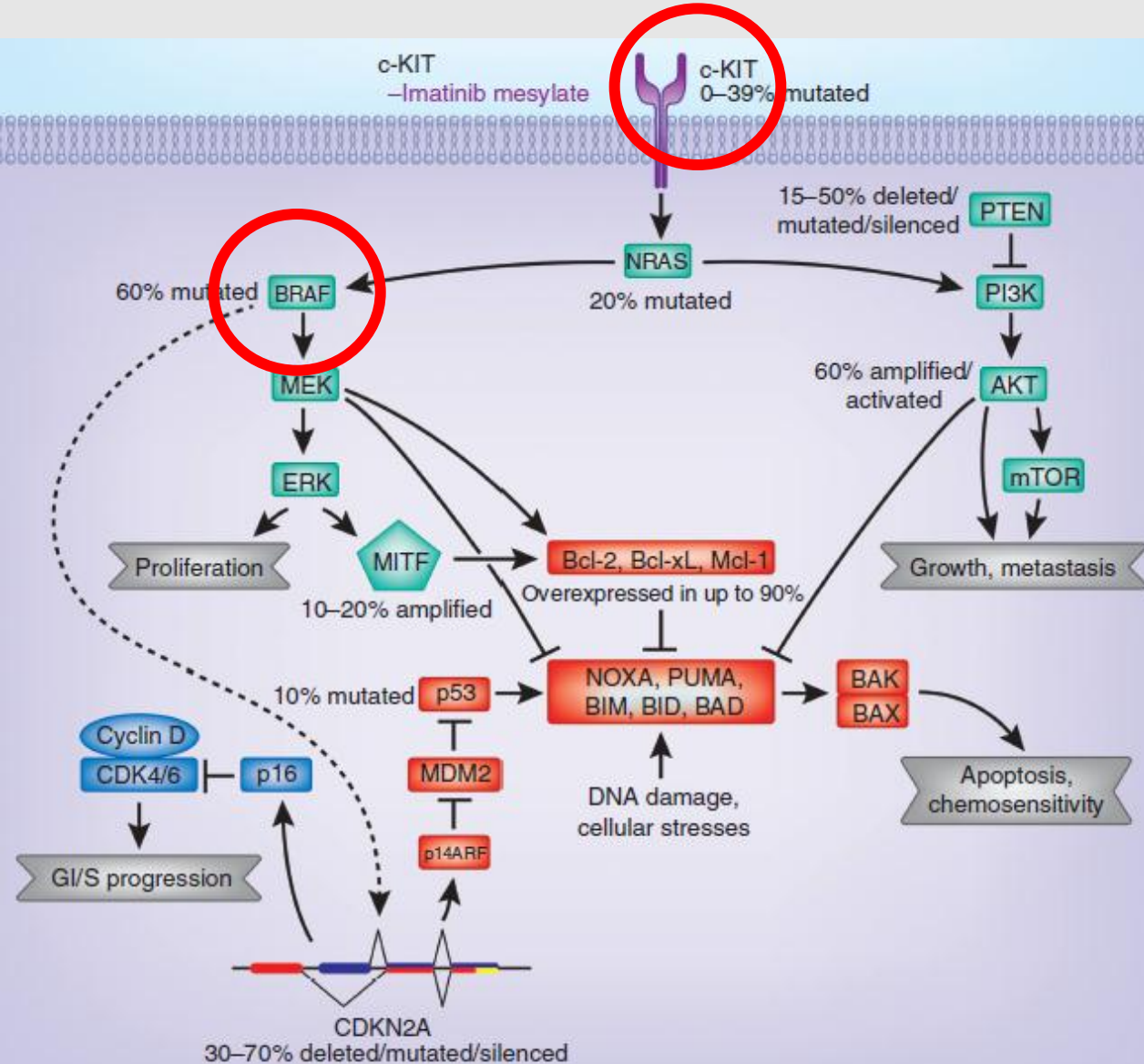
Beads and Exosomes



Melanoma Exosomes



# TARGETS: „known mutated antigens“



=> pathway analysis

**Kinase Inhibition  
in Kombination  
mit Impfung  
gegen die  
Mutationen in  
den „Escape“  
Varianten**

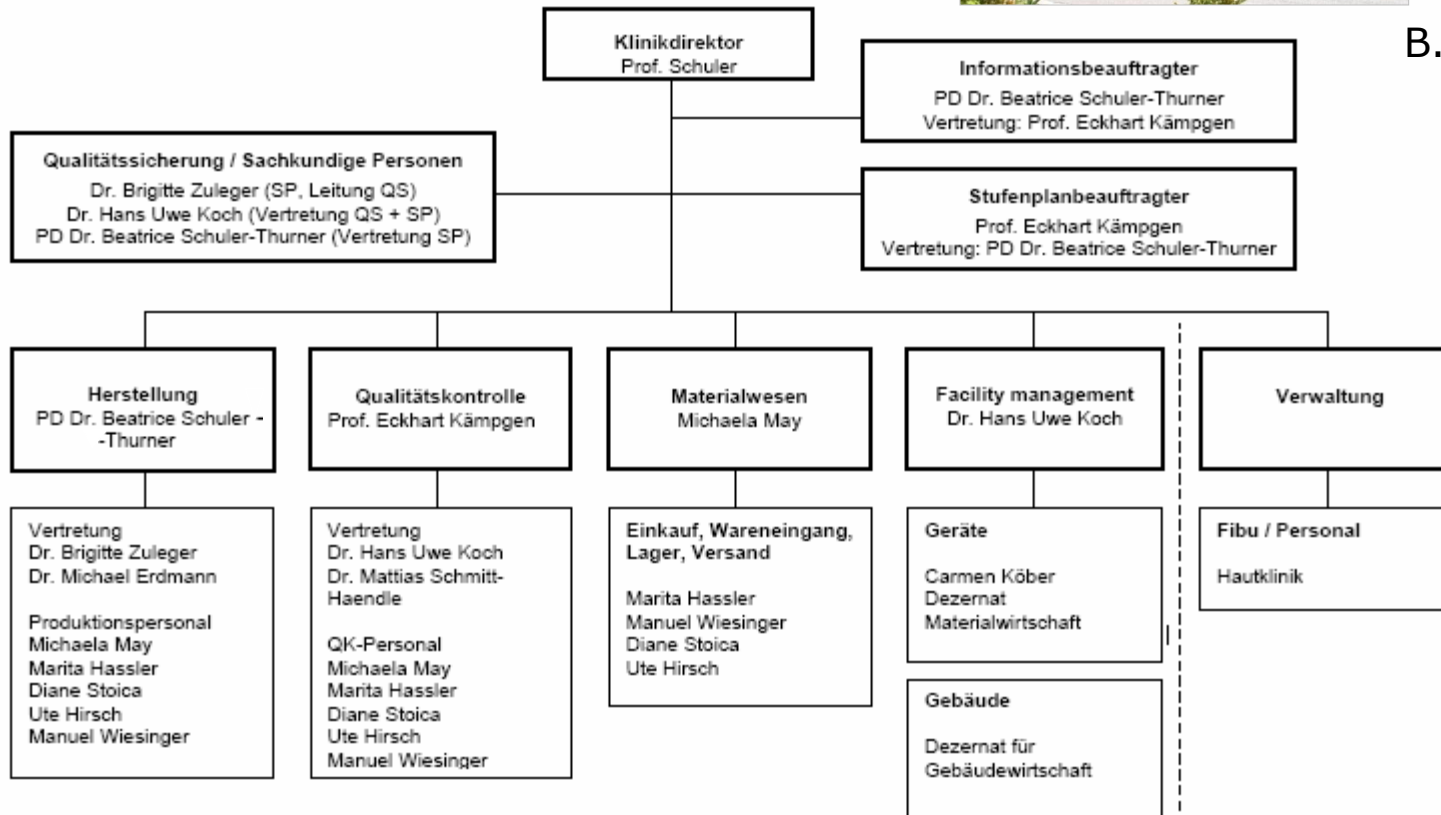
**„be ahead of  
the tumor“**

# Dank – dem GMP Team

<b>HAUTKLINIK</b>	 Universitätsklinikum Erlangen	Version 01
<b>DC-Produktion</b>		
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## 12.1 Organigramm DC-Produktion



B. Schuler-Thurner



U. Koch

# **Dank – allen Mitarbeitern der MM Ambulanz + Station**

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Ulrike Leonhart  
Stephanie Friedel**



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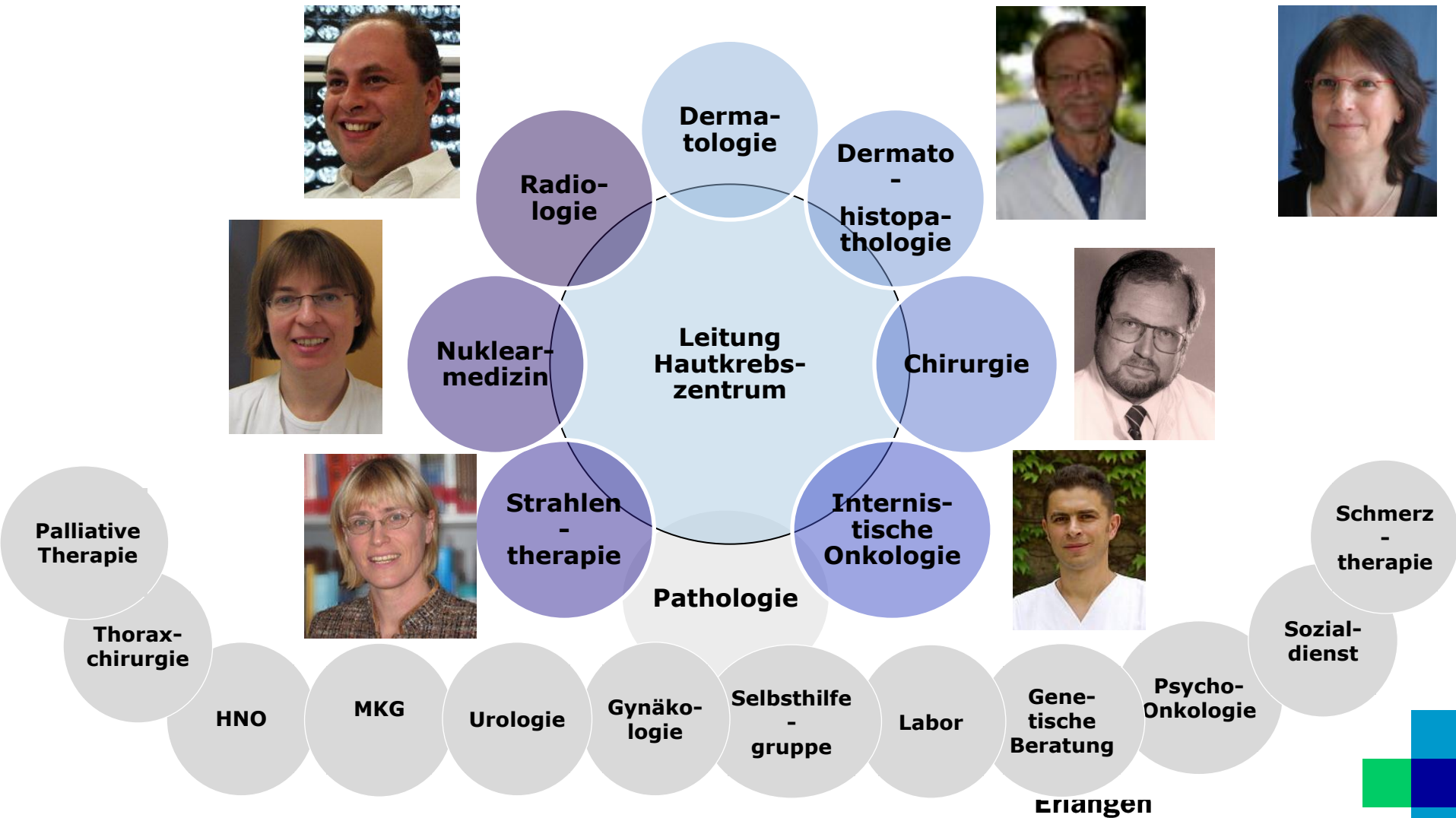


es



# Dank – an die Disziplinen

Tumor  
zentrum



erlangen

