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HAUT TUMOR ZENTRUM NÜRNBERG

CCC Comprehensive Cancer Center Erlangen-Nürnberg

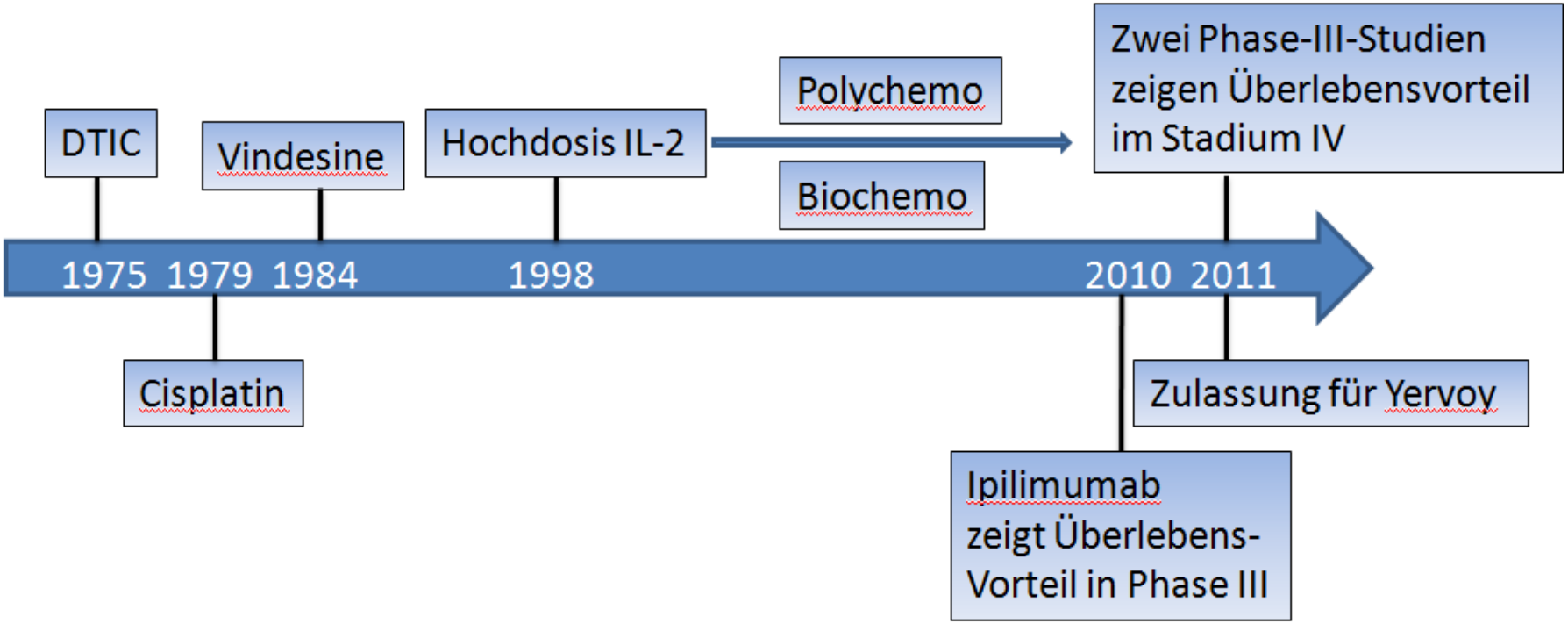
21. Erlanger Minisymposium

Melanom 2012

12. Mai 2012

Vemurafenib – Vorreiter einer neuen Therapie-Ära

Dirk Debus, Nürnberg


DTIC
Vindesine
Hochdosis IL-2
Polychemo
Biochemo
Zwei Phase-III-Studien zeigen Überlebensvorteil im Stadium IV
1975
1979
1984
1998
2010
2011
Cisplatin
Zulassung für Yervoy
Ipilimumab zeigt Überlebens-Vorteil in Phase III

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.

Überlebensvorteil durch Immuntherapie

- Ipilimumab MDX 010-20 (ASCO 2010; NEJM Hodi et al.)
- Ipilimumab CA 184-024 (ASCO 2011; NEJM Robert et al.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

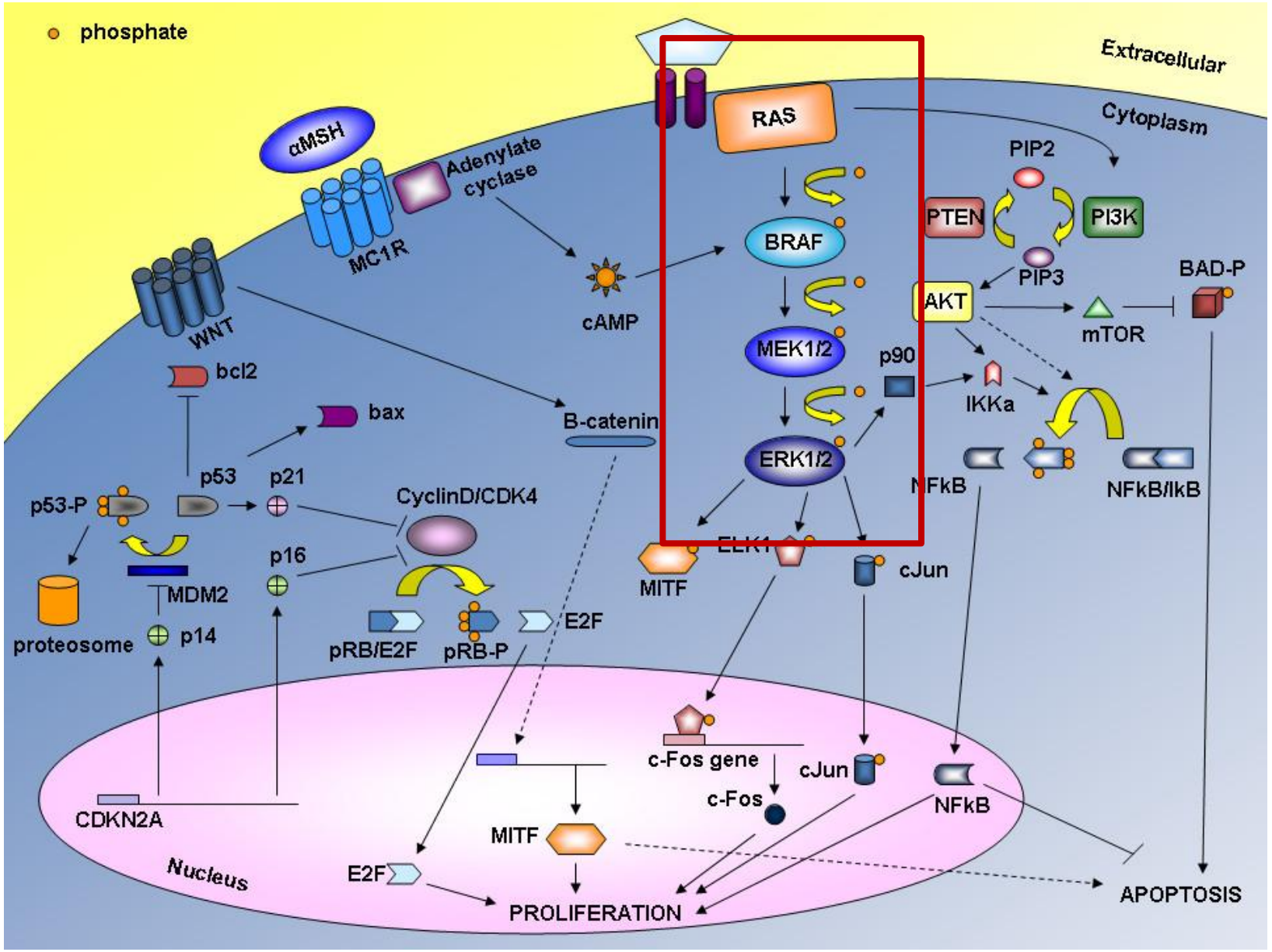
Überlebensvorteil durch Targeted Therapy

- Vemurafenib BRIM 3 (ASCO 2011; NEJM Chapman et al.)

Phase III randomized, open-label, multicenter trial (BRIM3) comparing BRAF inhibitor vemurafenib with dacarbazine in patients with $BRAF^{V600E}$-mutated melanoma (Abstract #LBA4)

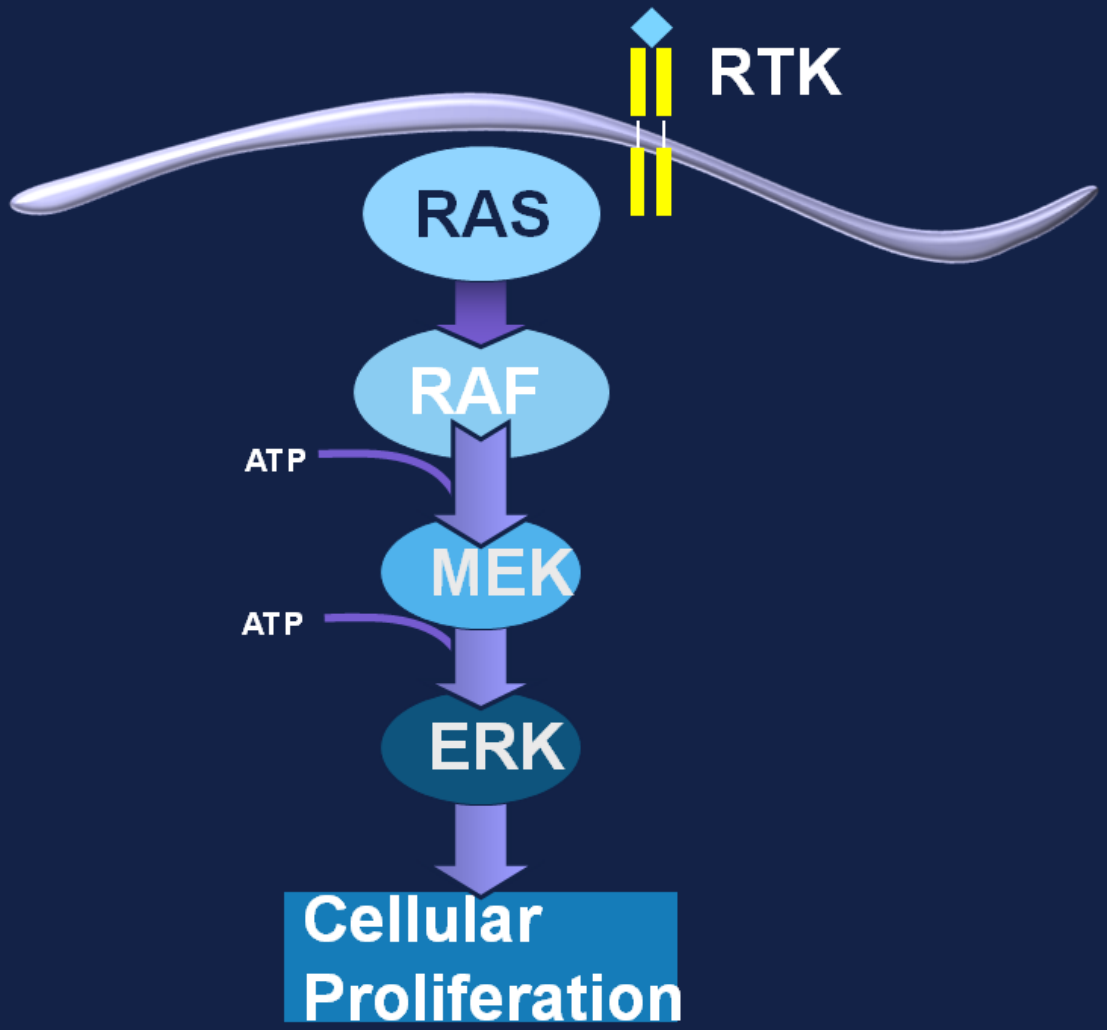
P. Chapman, A. Hauschild, C. Robert, J. Larkin,
J. Haanen, A. Ribas, D Hogg, S. O'Day, P. Ascierto, A. Testori,
P. Lorigan, R. Dummer, J. Sosman, C. Garbe, R. Lee, K. Nolop,
B. Nelson, J. Hou, K. Flaherty, G. McArthur

ASCO Annual '11 Meeting

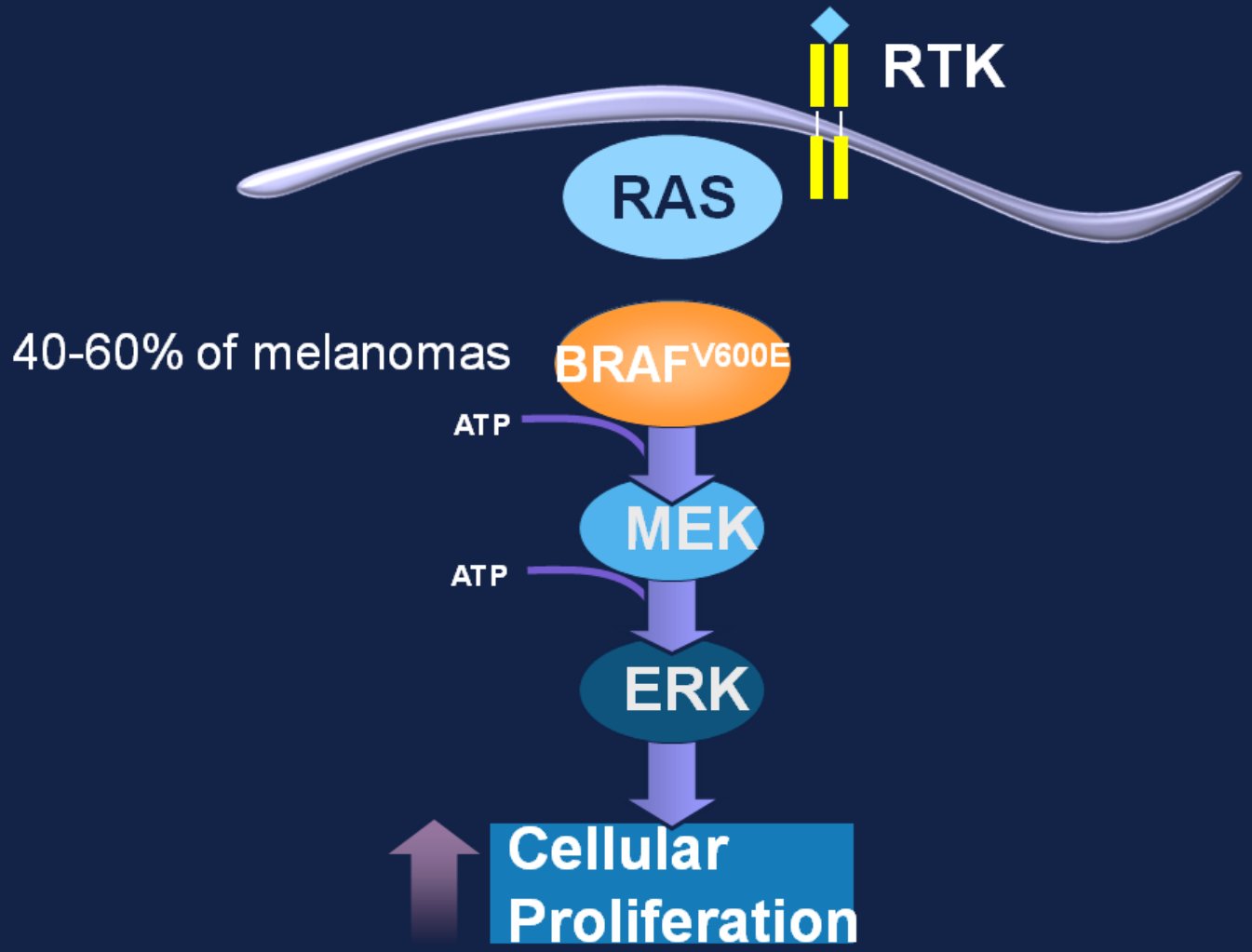


Palmieri et al. Journal of Translational Medicine 2009 7:86

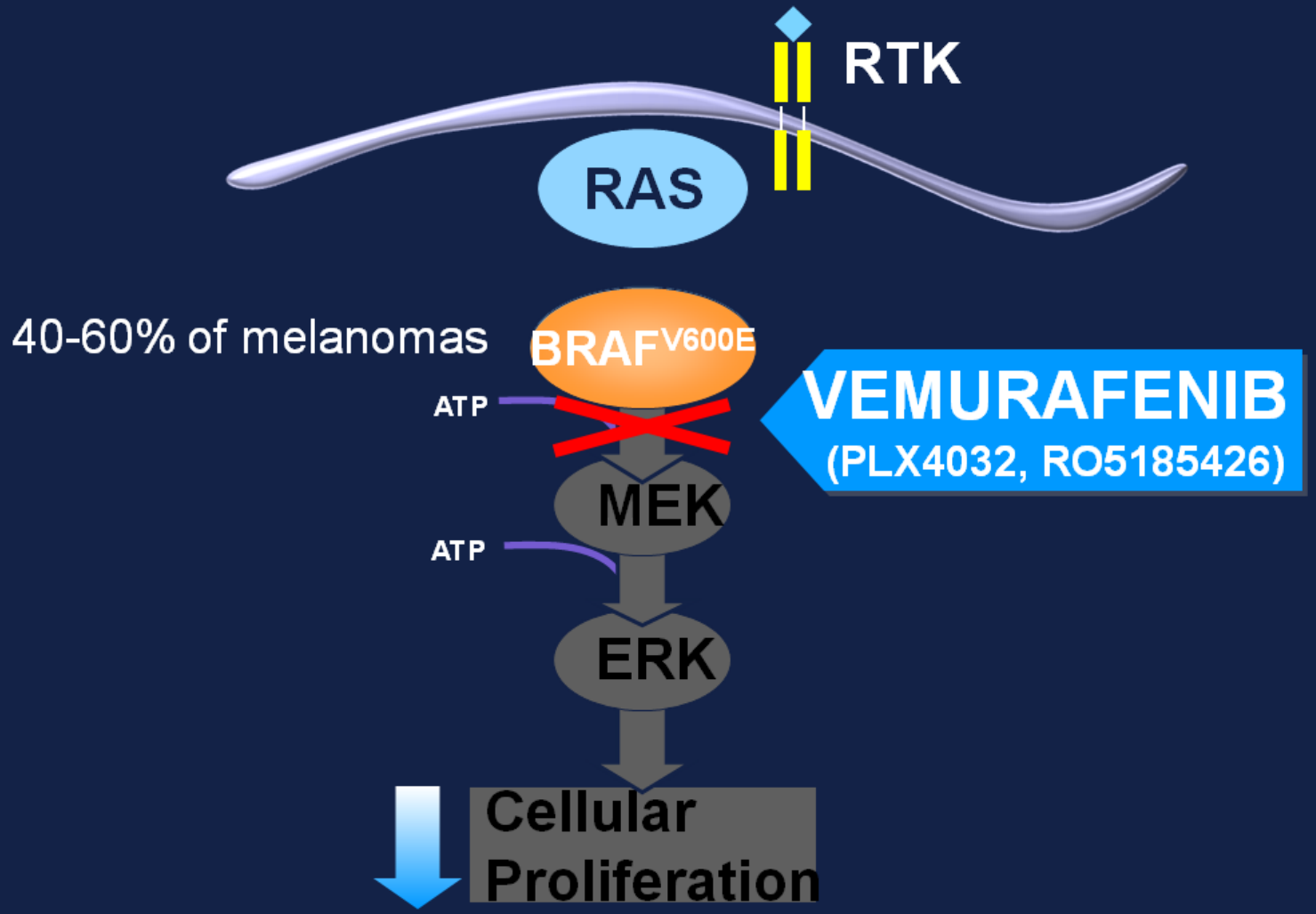
Vemurafenib inhibits $BRAF^{V600E}$ Kinase



Vemurafenib inhibits $BRAF^{V600E}$ Kinase

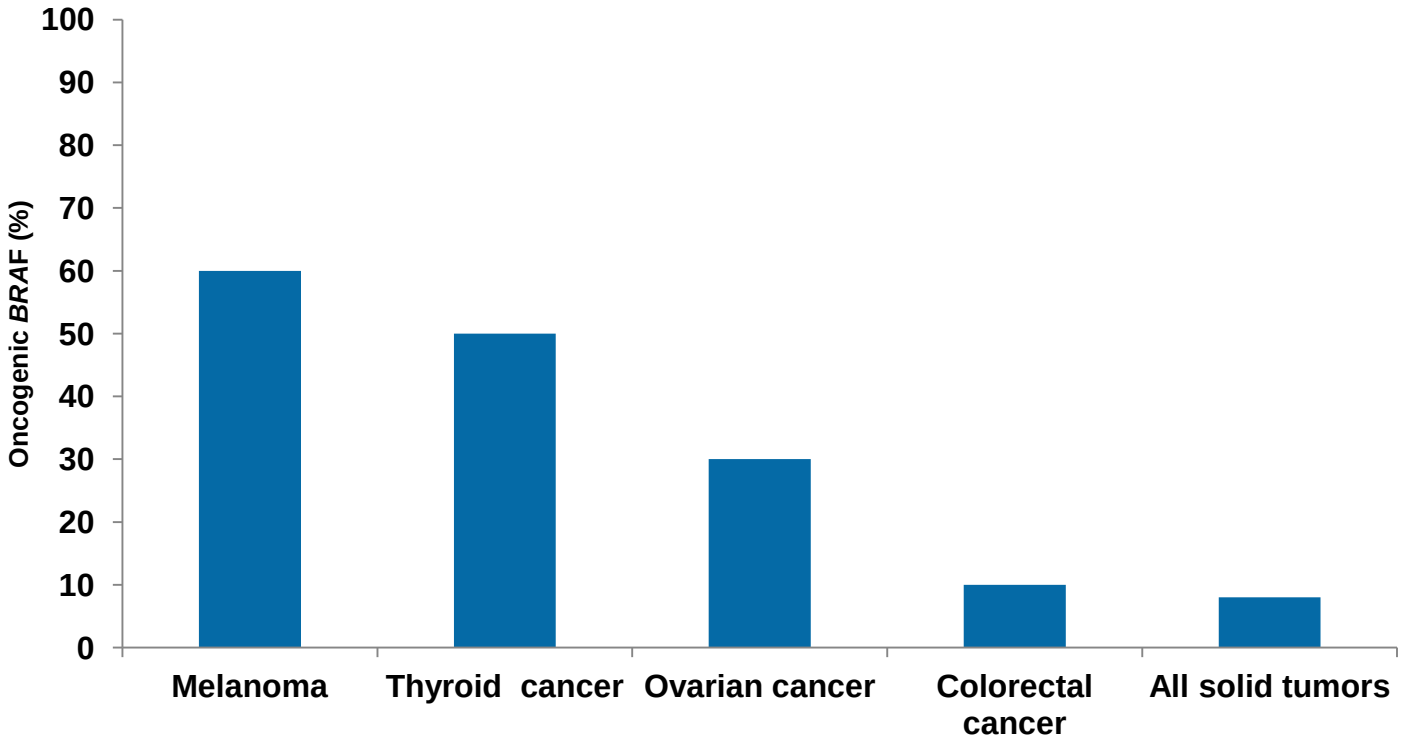


Vemurafenib inhibits $BRAF^{V600E}$ Kinase



BRAF-Onkogen

- Bei Karzinomen wird häufig mutiertes BRAF identifiziert
- Höchste Inzidenz für BRAF-Mutationen beim Melanom



BRAF-Mutation beim Melanom

- V600E 93,2%
- V600K 5,6%
- V600R 1%
- andere <0,1%

Fachinformation Zelboraf® Feb 2012

Phase III randomized, open-label, multicenter trial (BRIM3) comparing BRAF inhibitor vemurafenib with dacarbazine in patients with $BRAF^{V600E}$-mutated melanoma (Abstract #LBA4)

P. Chapman, A. Hauschild, C. Robert, J. Larkin,
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B. Nelson, J. Hou, K. Flaherty, G. McArthur

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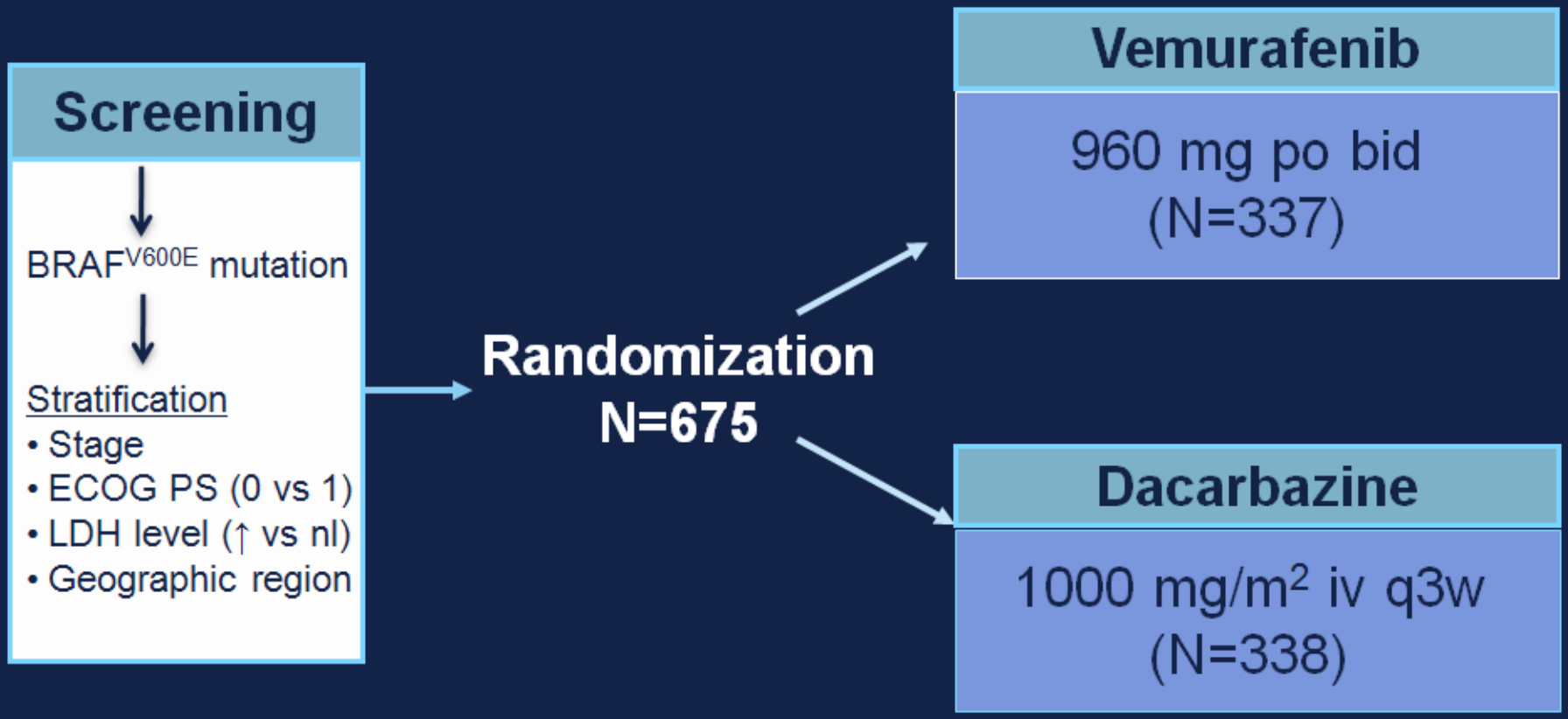
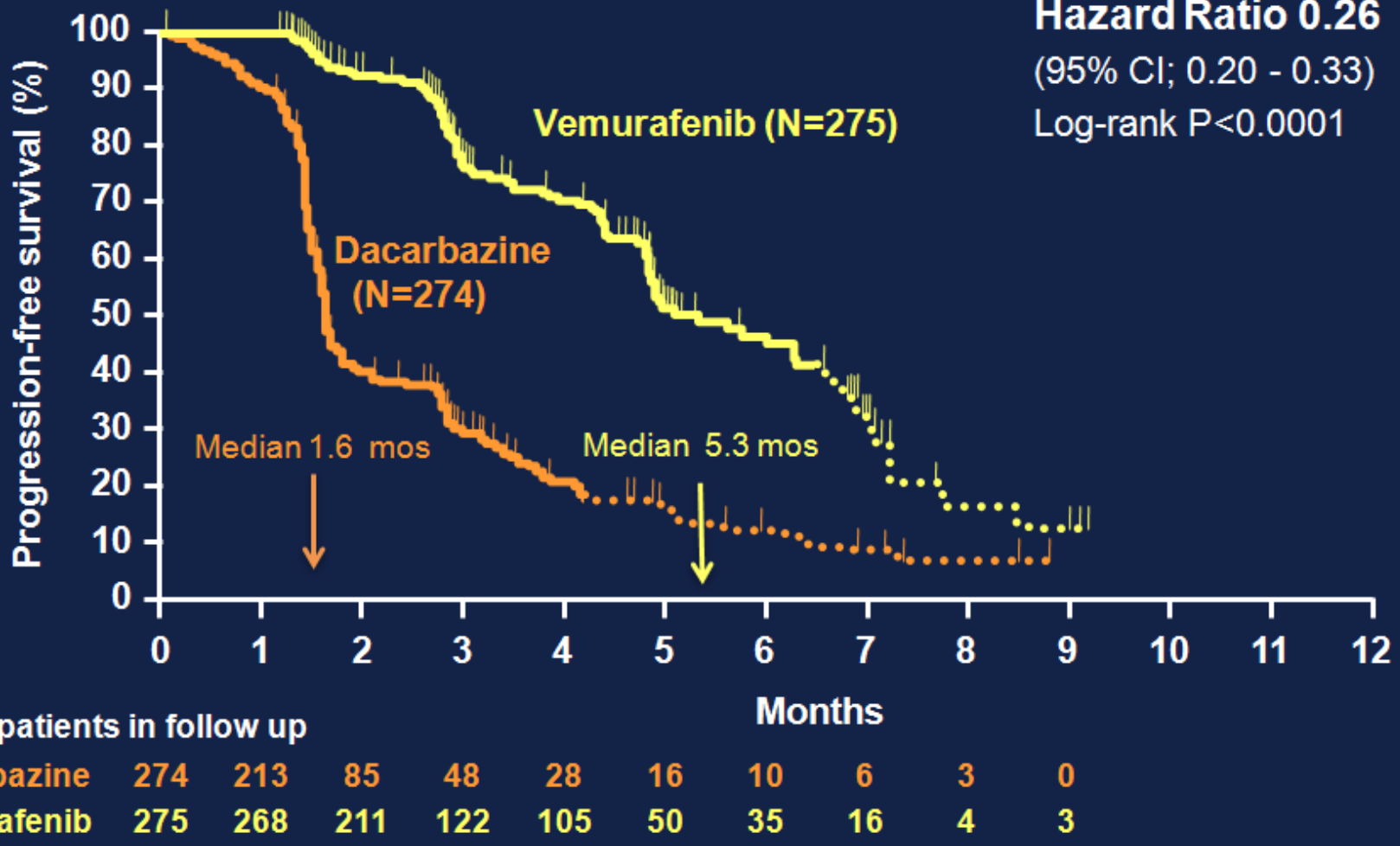
Phase III BRIM3 Study design



Progression-free survival (Dec 30, 2010 cutoff)



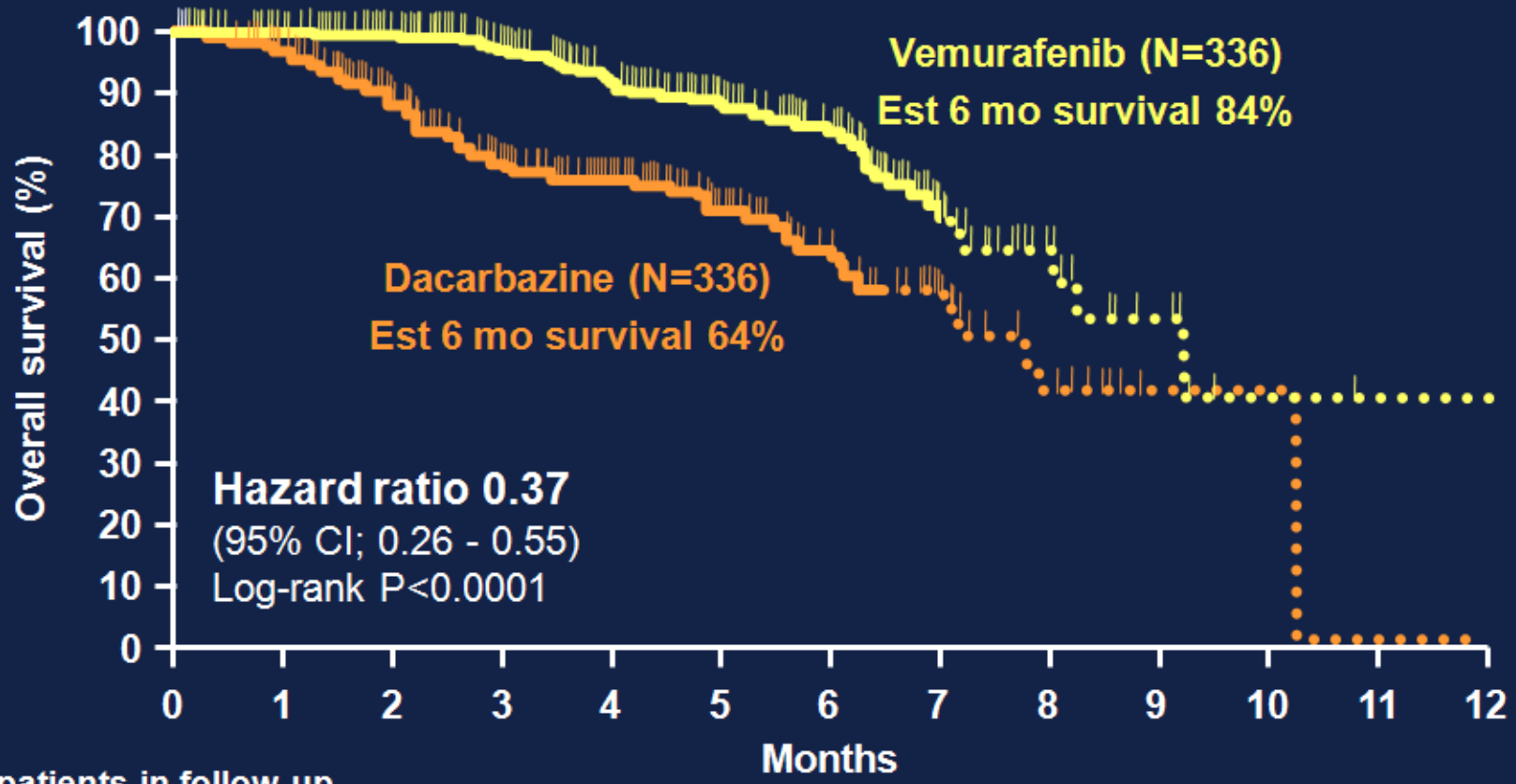
No. of patients in follow up

Dacarbazine	274	213	85	48	28	16	10	6	3	0
Vemurafenib	275	268	211	122	105	50	35	16	4	3

„early termination due to compelling efficacy“

ASCO Annual '11 Meeting

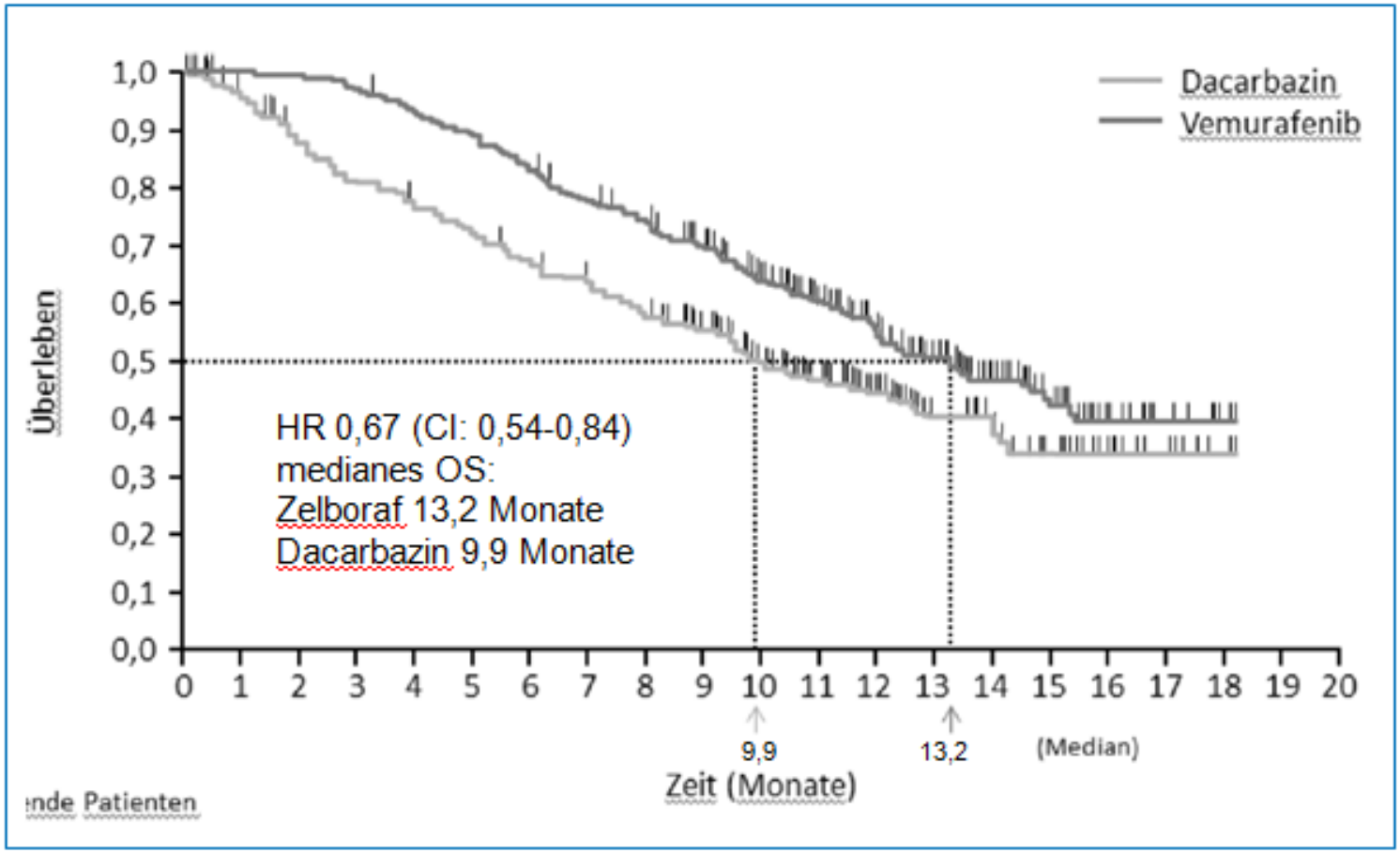
Overall survival (Dec 30, 2010 cutoff)



No. of patients in follow up

Dacarbazine	336	283	192	137	98	64	39	20	9	1	1
Vemurafenib	336	320	266	210	162	111	80	35	14	6	1

Vemurafenib Phase III Studie BRIM3 (Datenschnitt Okt 2011)

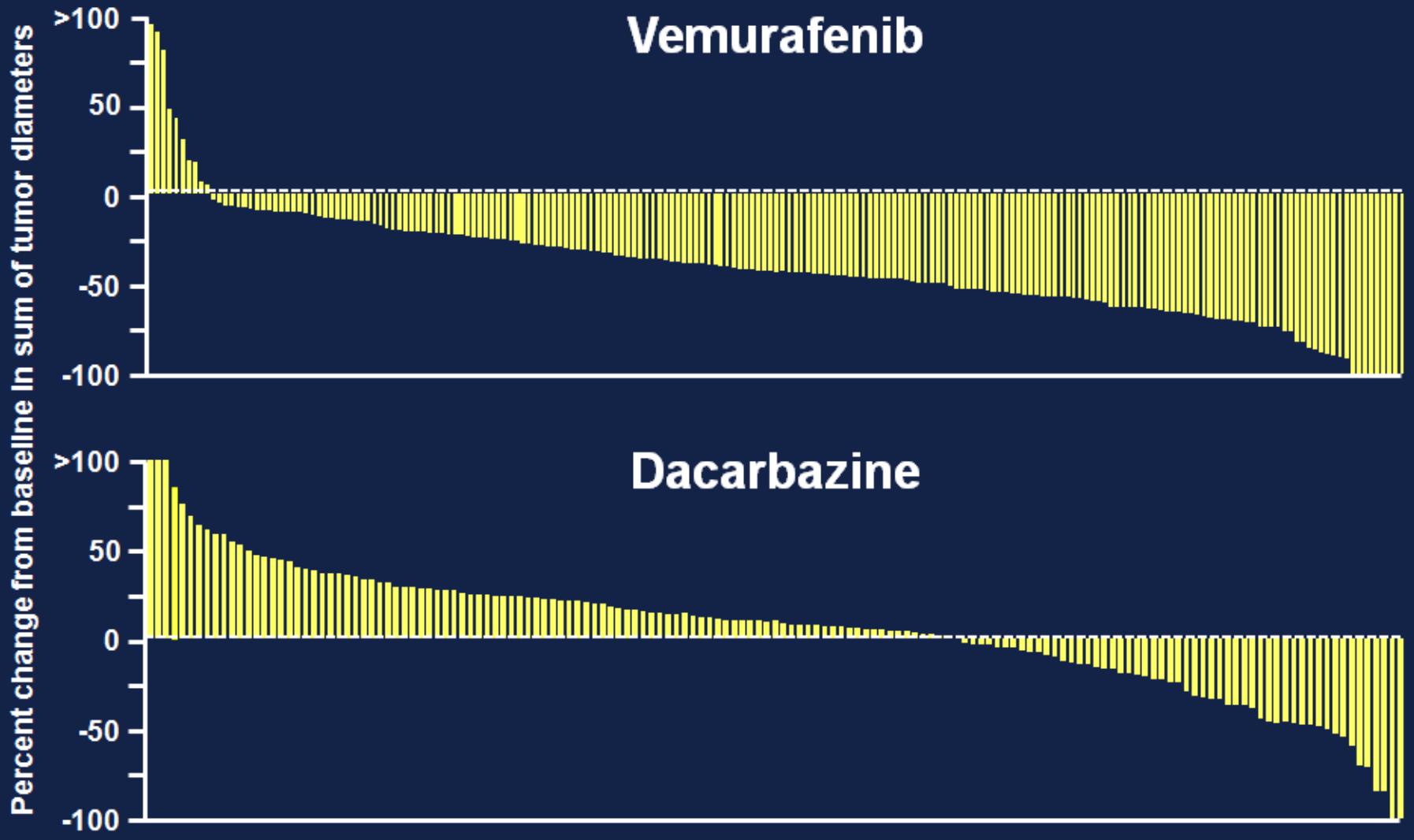


Modifiziert aus der Fachinformation Zelboraf Feb 2012

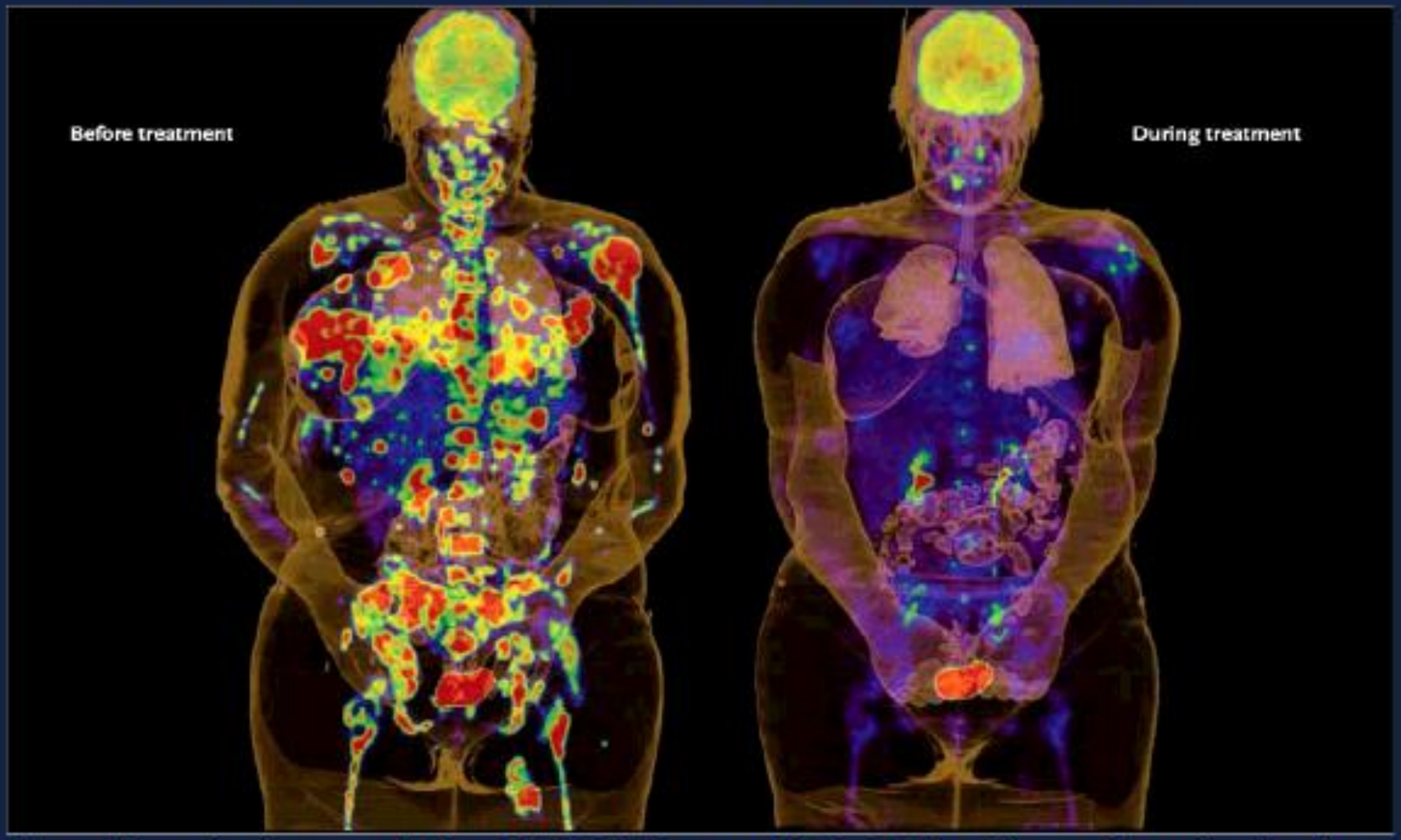
Objective response rates (RECIST 1.1)

	CR	PR	Overall response rate
Vemurafenib	**0.9%**	**47.5%**	**48.4%**
Dacarbazine	**0**	**5.5%**	**5.5%**

Maximal tumor shrinkage by individual patient



FDG-PET Scans of a patient showing response to vemurafenib* after 2 weeks treatment[1]

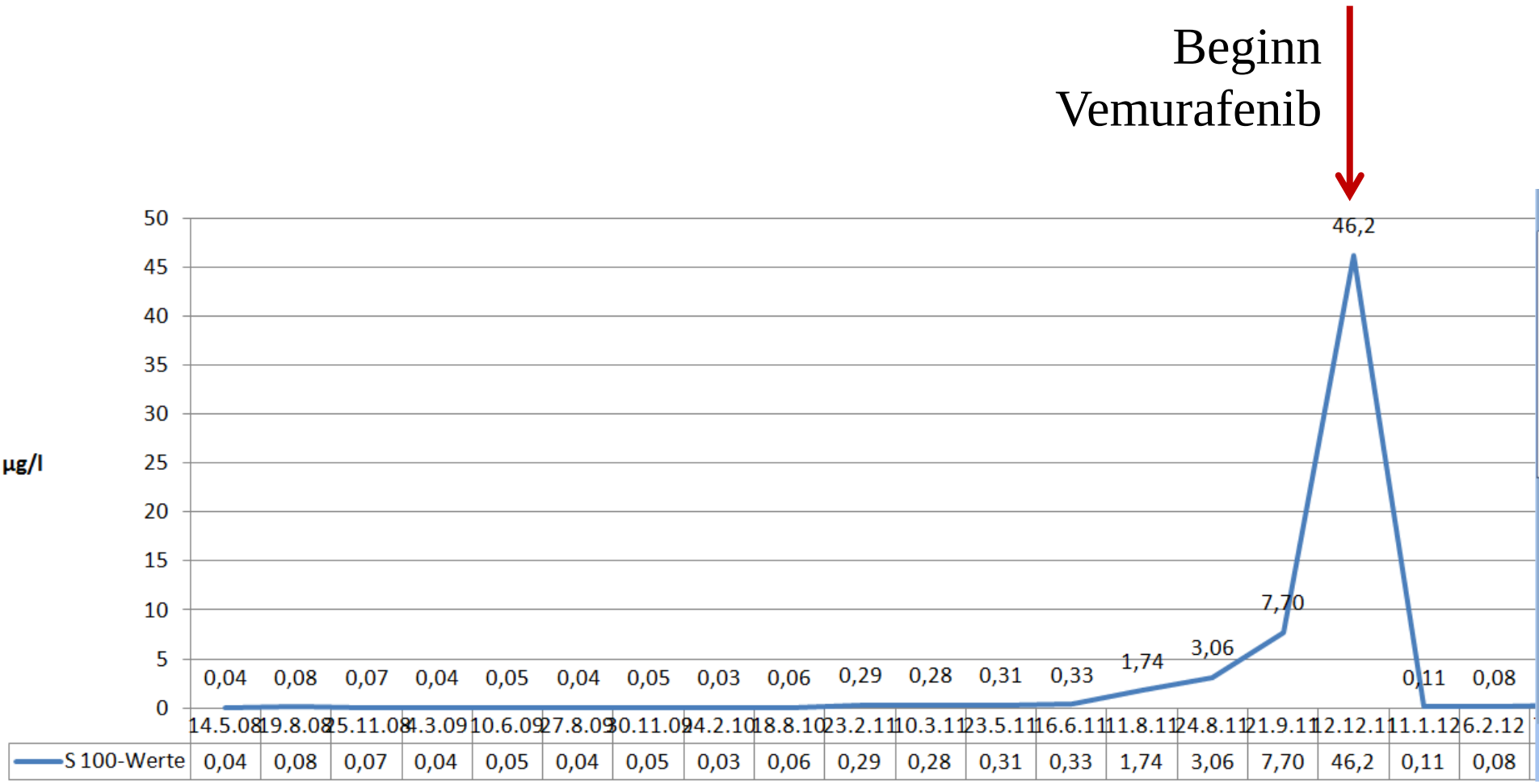


Three-dimensional representation of FDG–PET scans obtained at baseline and 2 weeks after the initiation of treatment with vemurafenib* in a melanoma patient carrying the V600E BRAF mutation[1].

1 McDermott U. et al. Genomics and the Continuum of Cancer Care. N Engl J Med 2011;364:340-50.

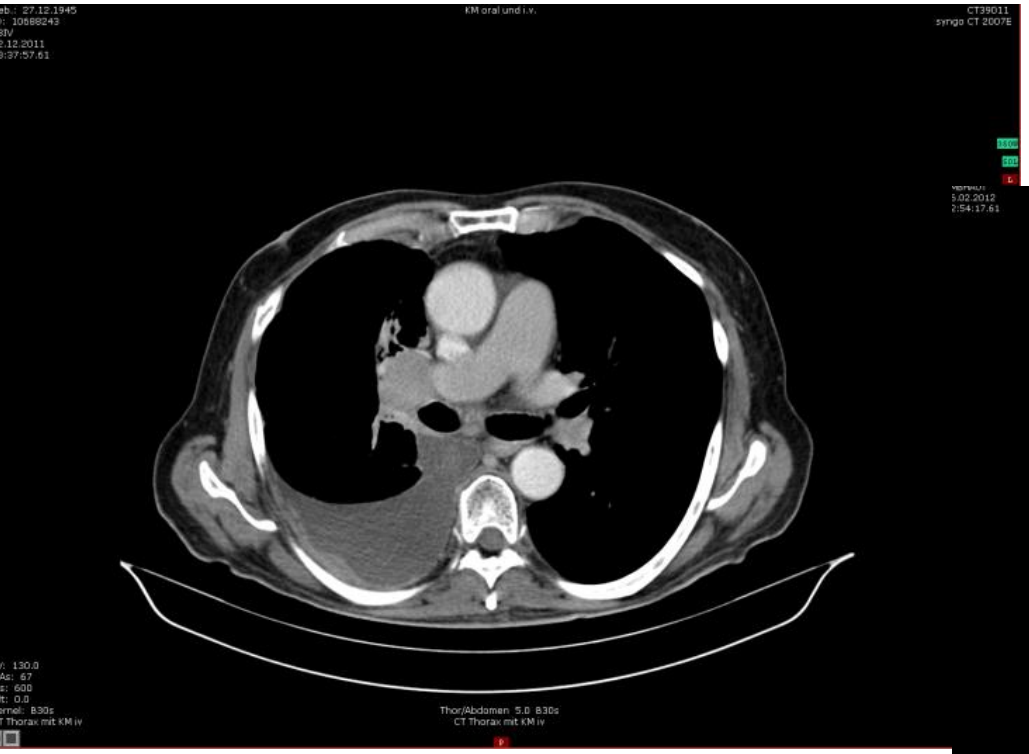
* vemurafenib is not yet approved in Switzerland

Verlauf Tumormarker S100

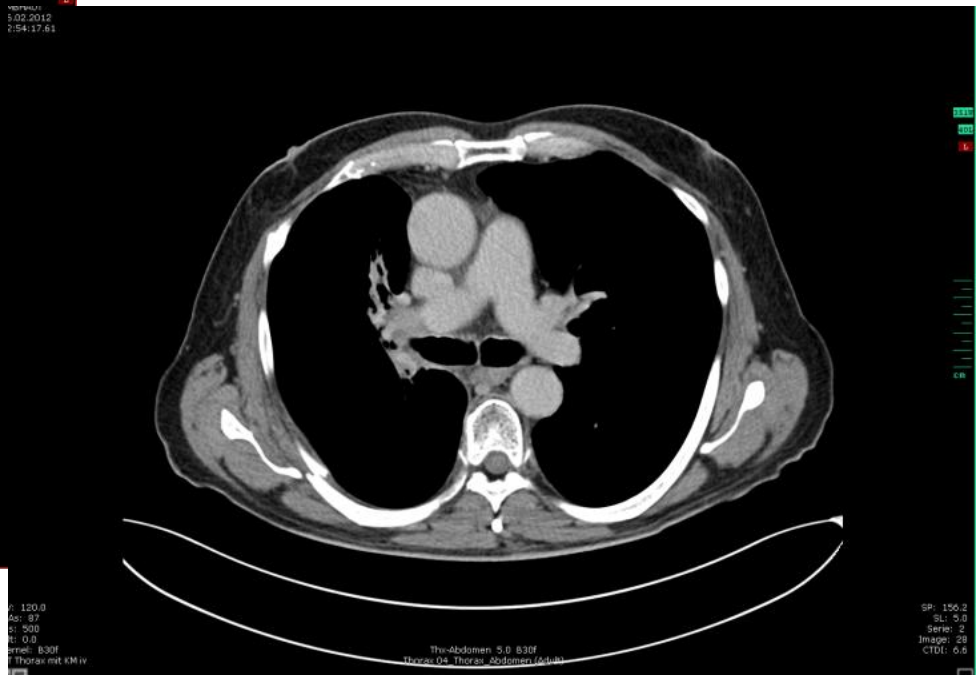


Verlauf CT Thorax

Baseline 12/2011

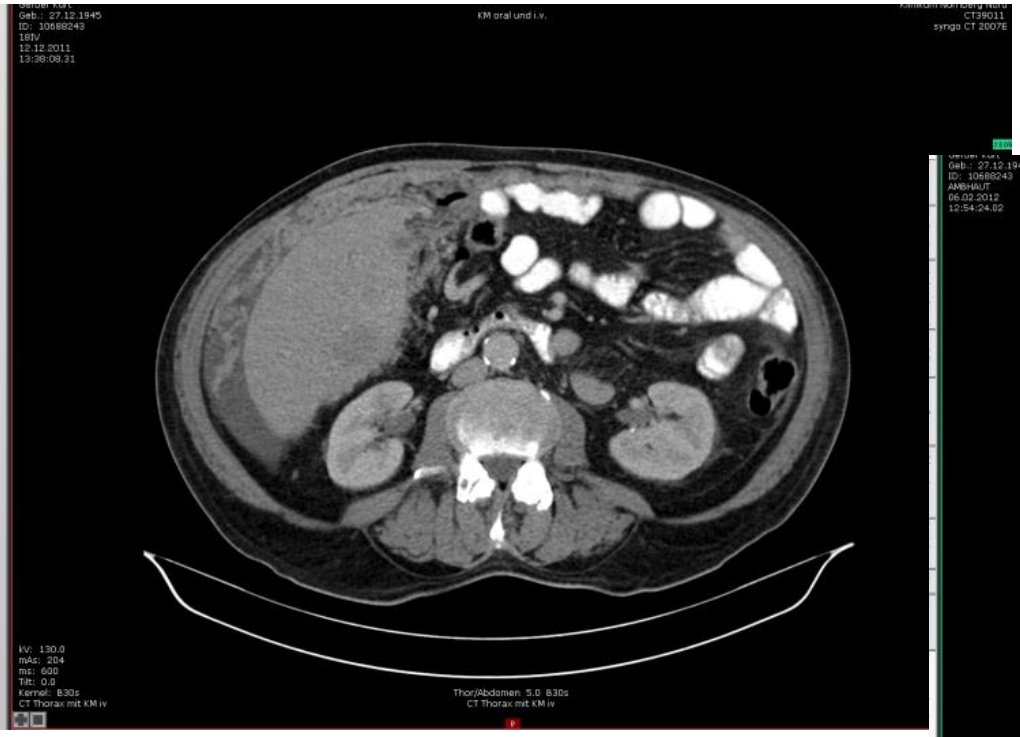


Nach 8 Wochen Vemurafenib

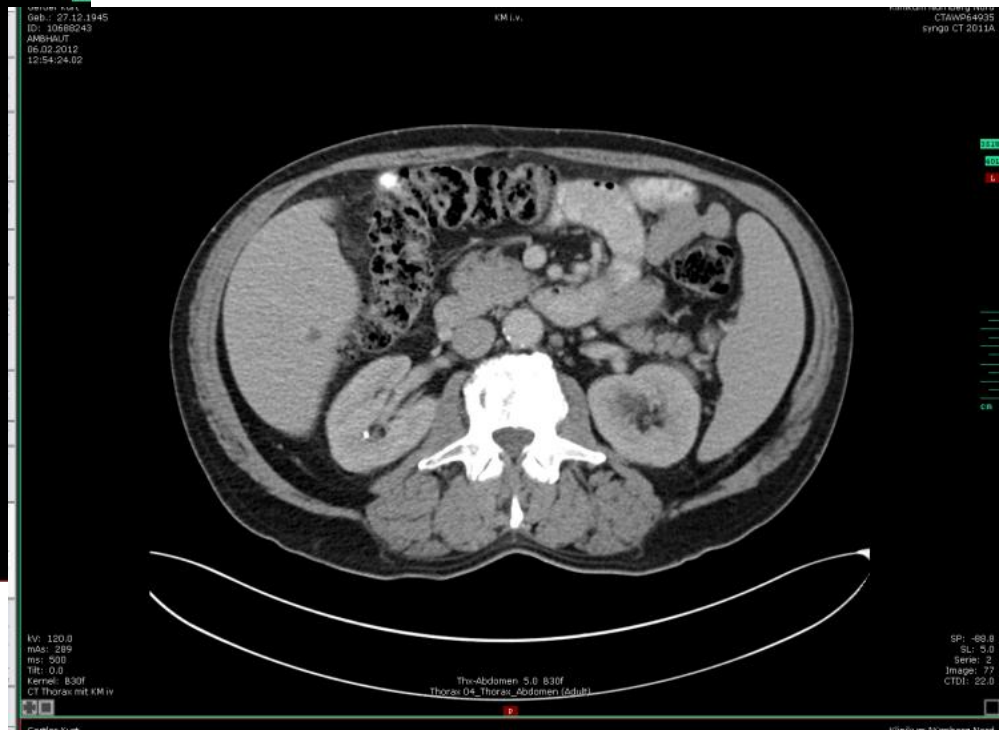


Verlauf CT Abdomen

Baseline 12/2011



Nach 8 Wochen Vemurafenib

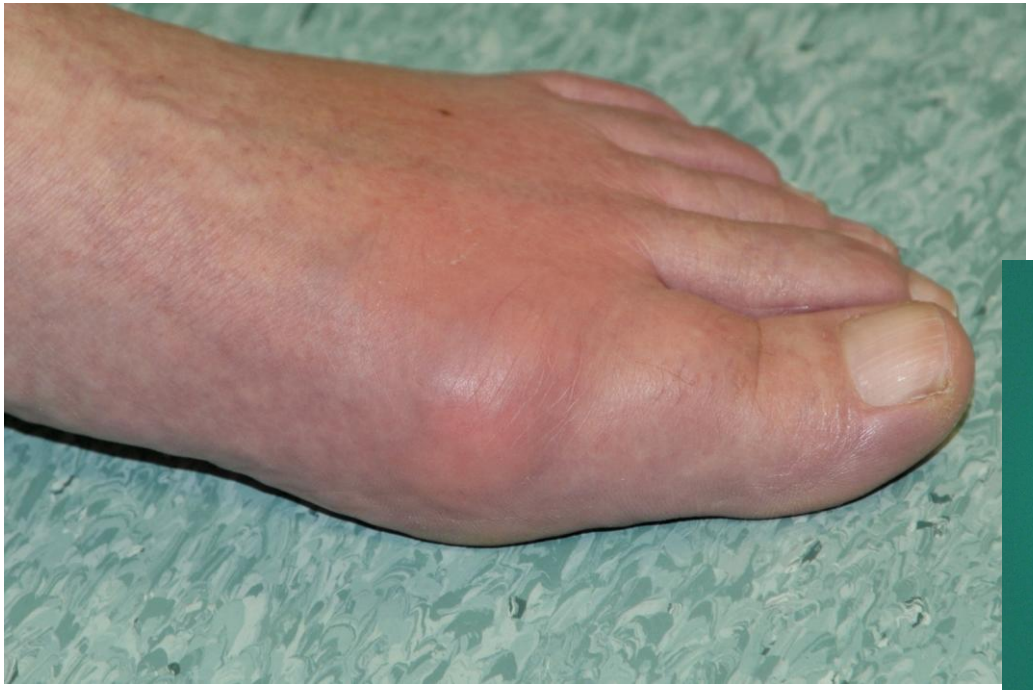


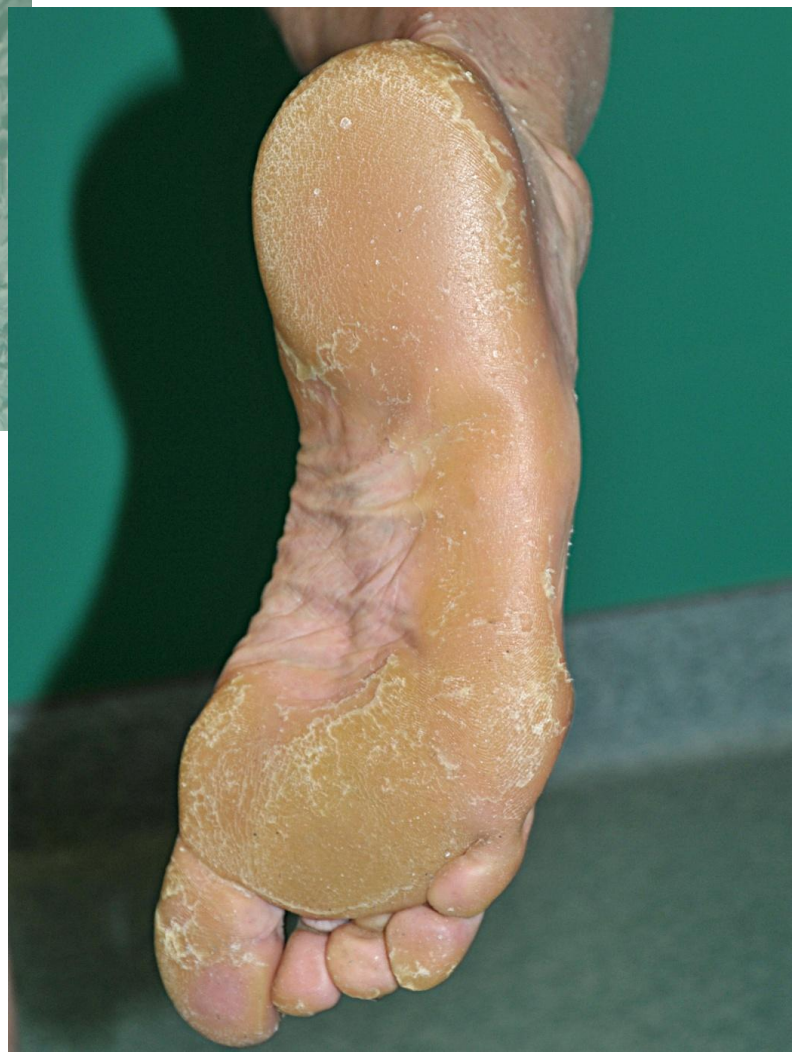
Symptomkontrolle!!!

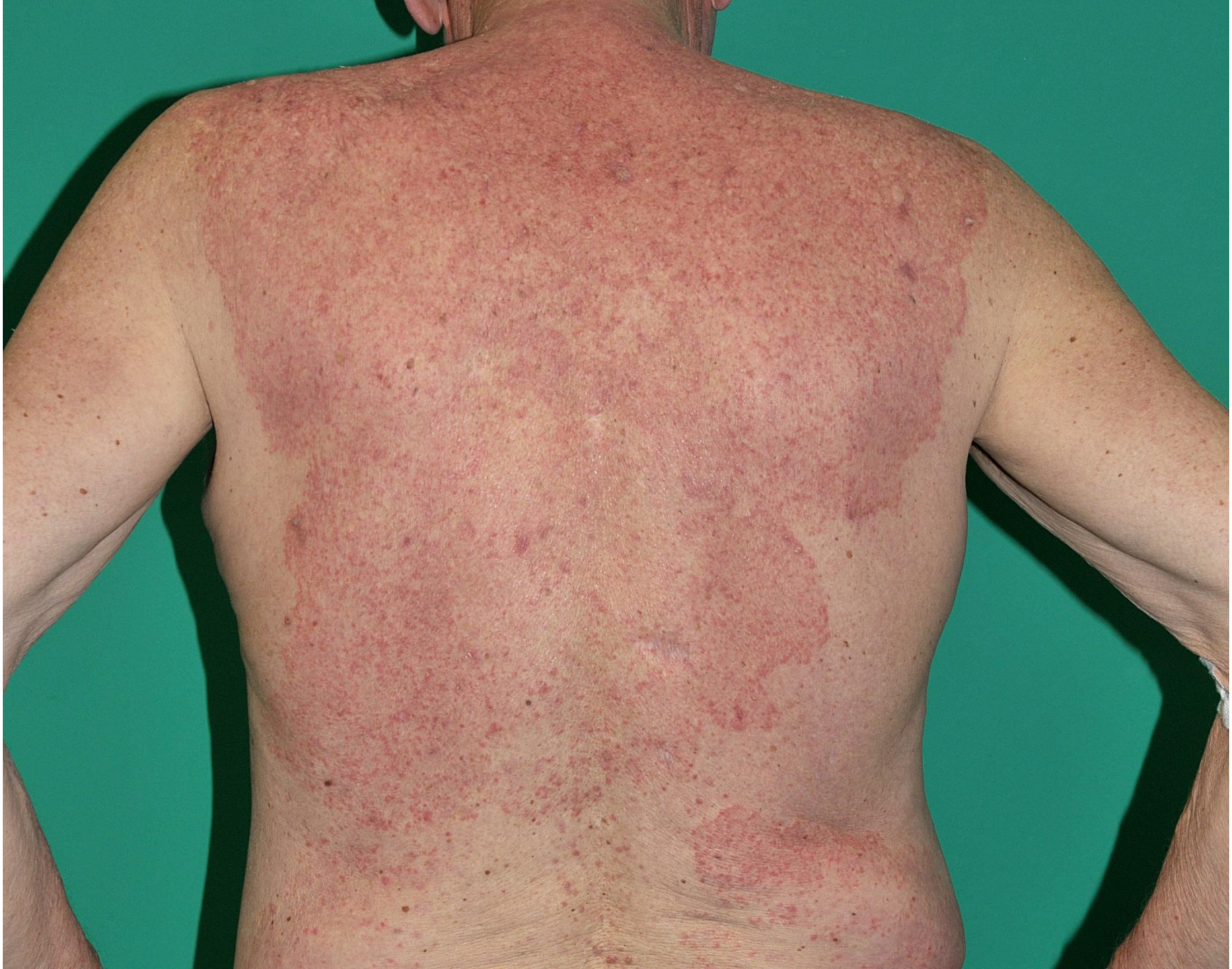
Selected adverse events (% of patients)

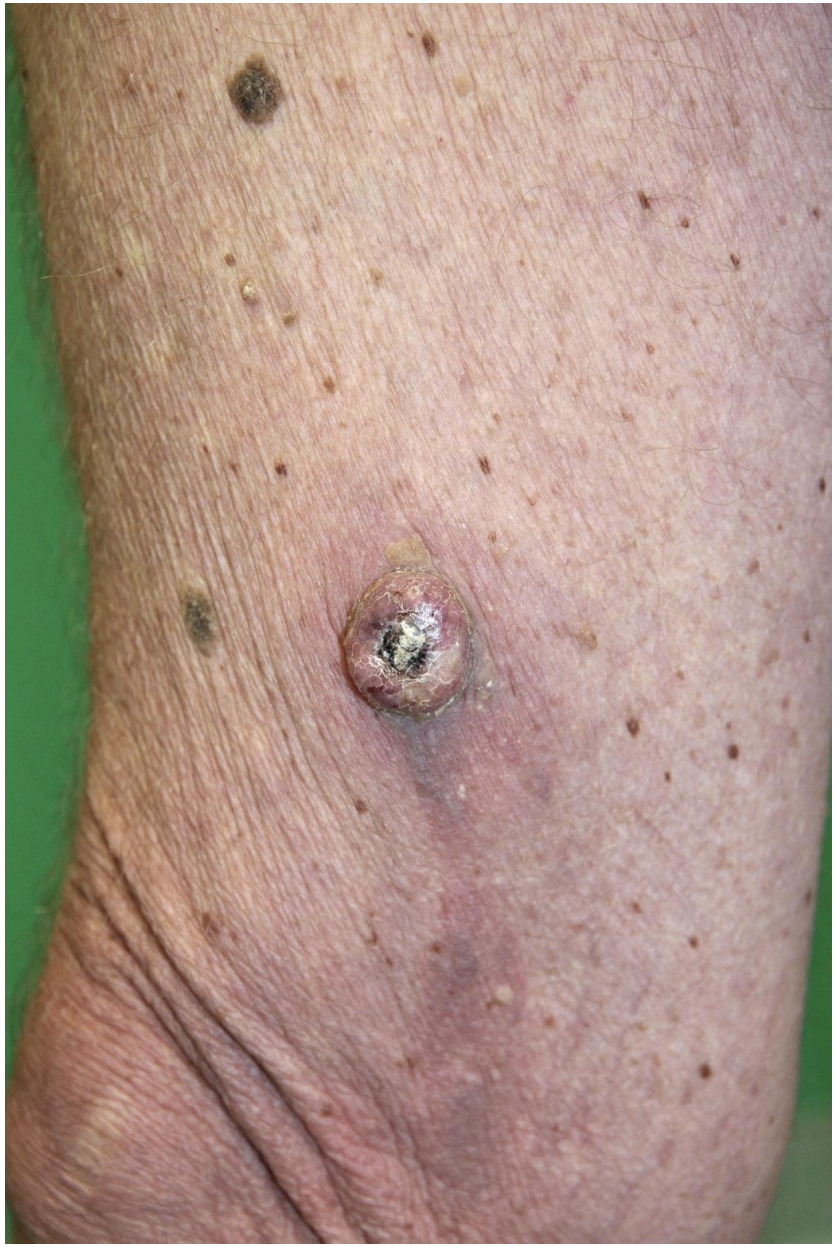
	Vemurafenib, n= 336			Dacarbazine, n= 282		
Adverse events	All	Grade 3	Grade≥ 4	All	Grade 3	Grade ≥4
Arthralgia	49	3	-	3	<1	-
Rash	36	8	-	1	-	-
Fatigue	33	2	-	31	2	-
Photosensitivity	30	3	-	4	-	-
↑LFTs	18	7	<1	5	1	-
Cutaneous SCC	12	12	-	<1	<1	-
Keratoacanthoma	8	6	-	-	-	-
Skin papilloma	18	<1	-	-	-	-
Nausea	30	1	-	41	2	-
Neutropenia	<1	-	<1	11	5	3

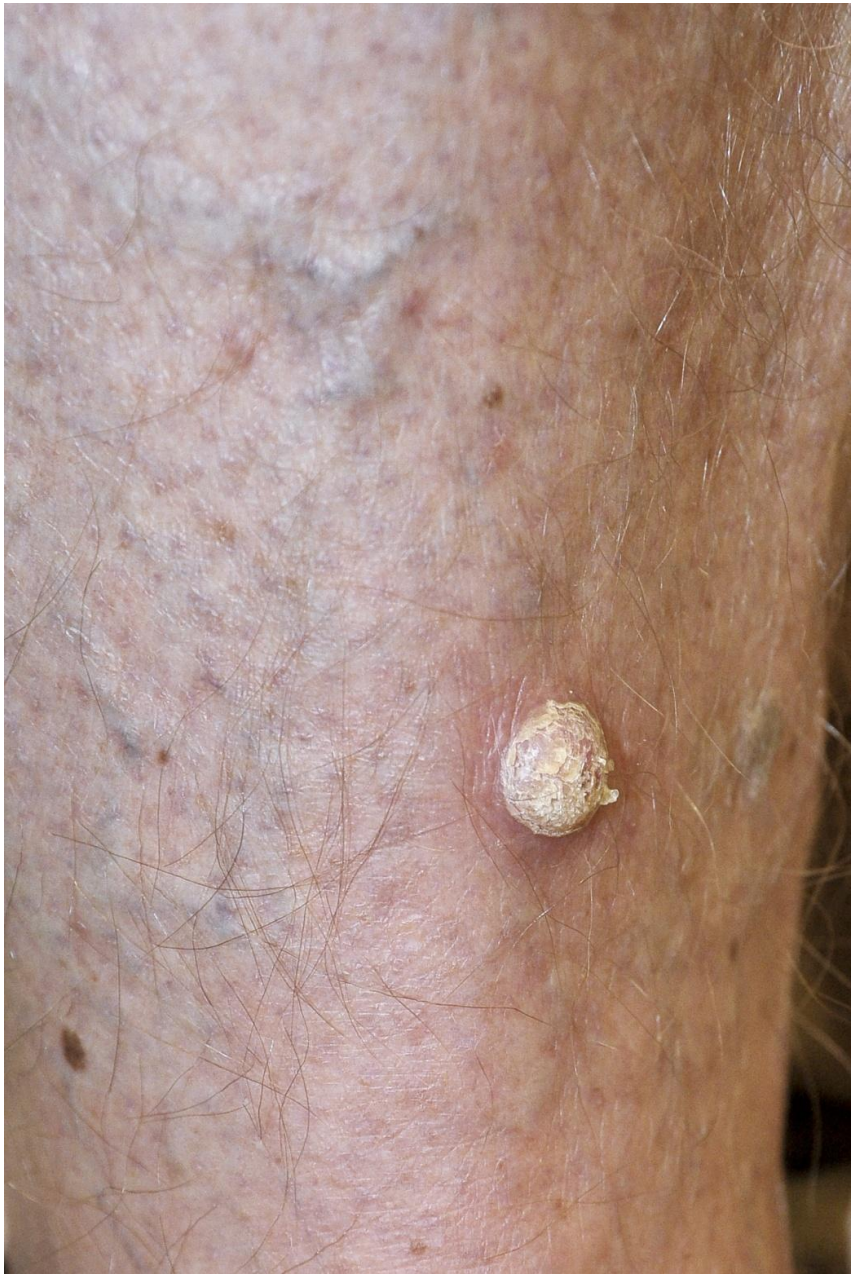
Discontinuations due to AE: 6% Vemurafenib; 4% Dacarbazine











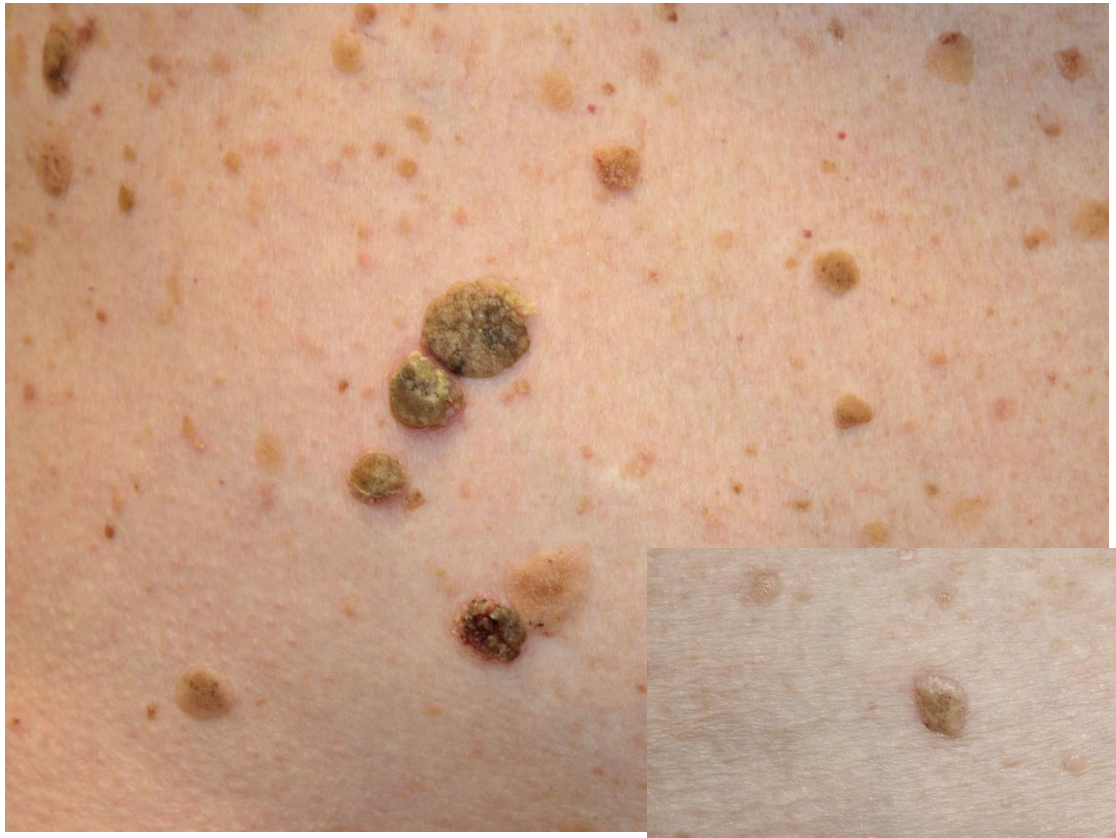
Vemurafenib (Zelboraf®, Roche)

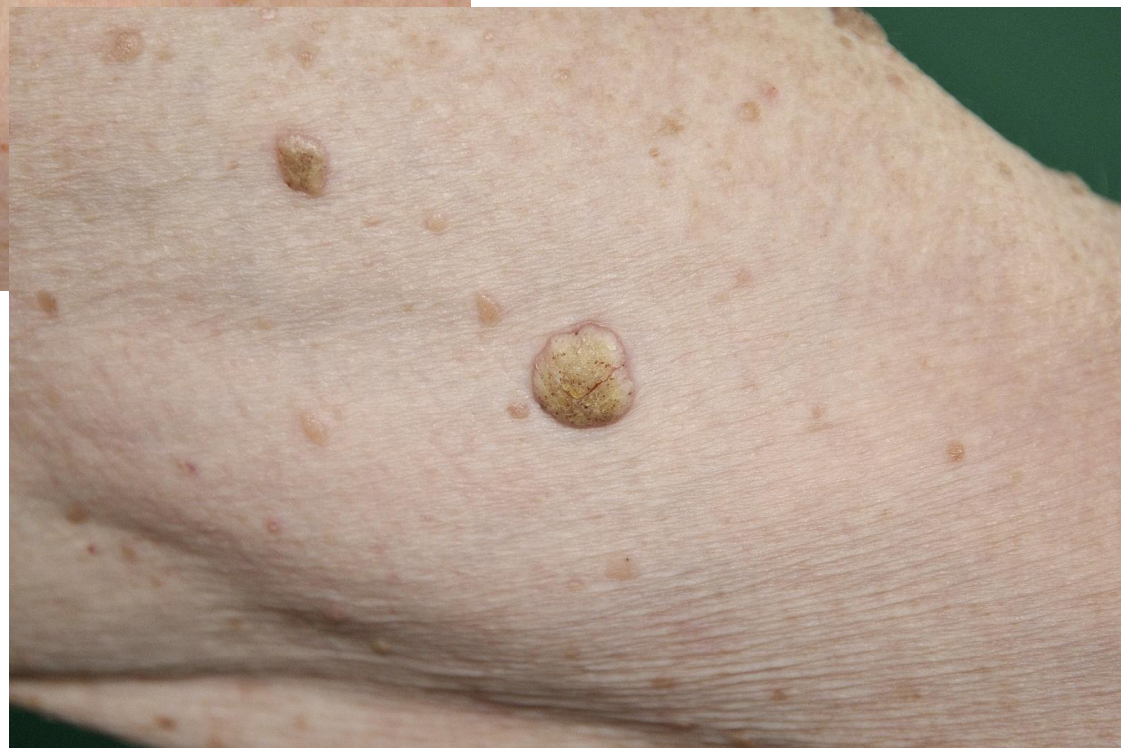
- Zulassung in Europa im Februar 2012 für das fortgeschrittene Melanom nach Nachweis einer V600-BRAF-Mutation

Dabrafenib (GSK2118436, GSK)

- Daten der Phase-III-Studie (BREAK-3) werden bei der ASCO-Tagung 2012 vorgestellt

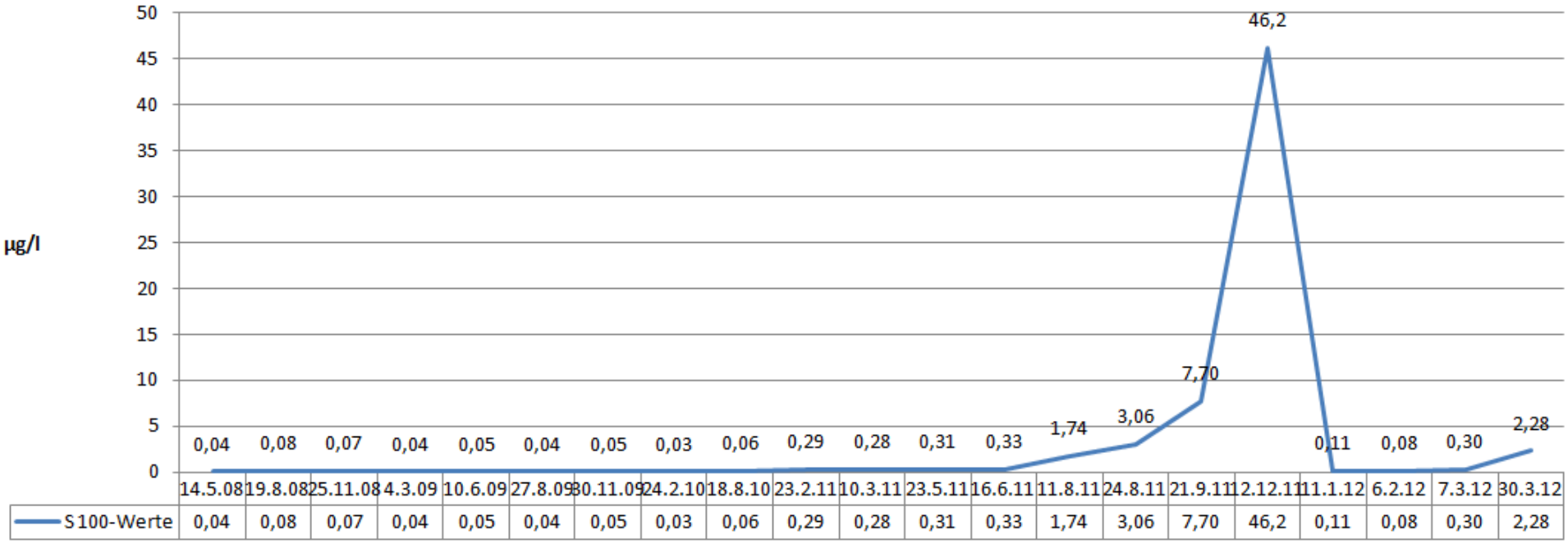
- Weitere (B)RAF-Inhibitoren sind in Entwicklung



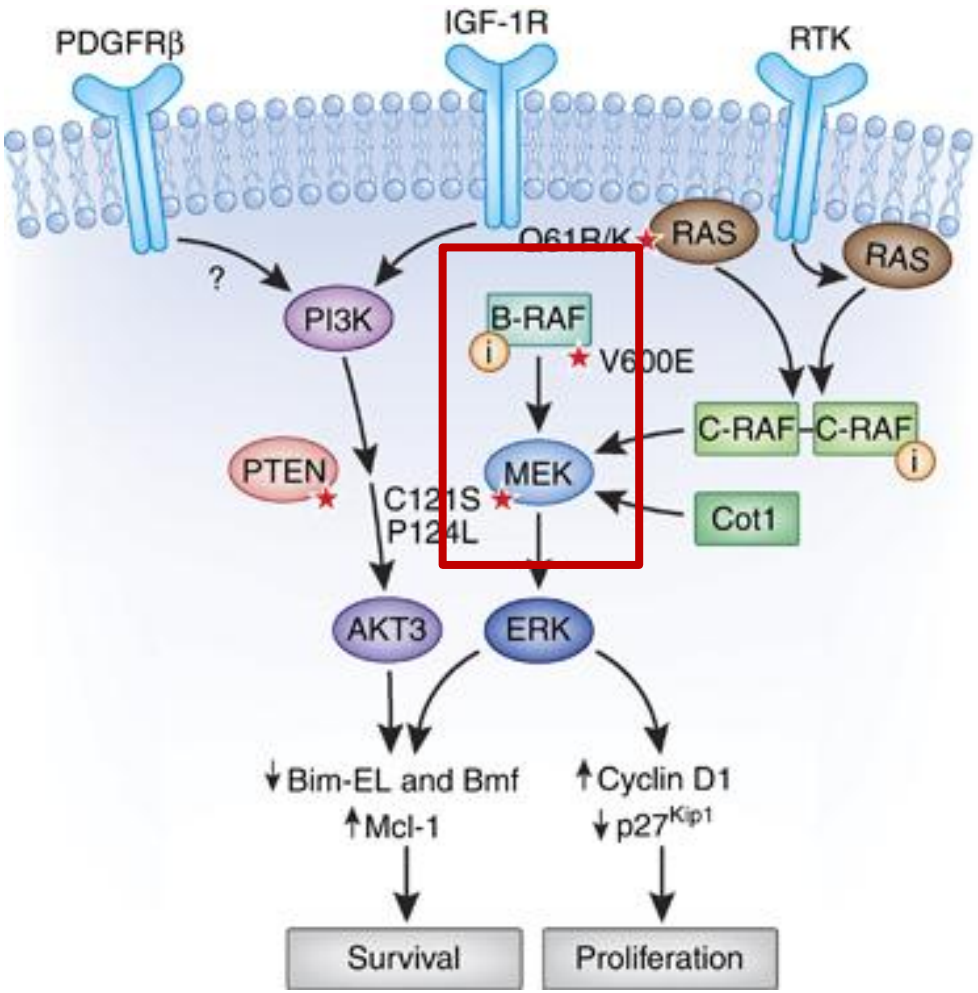


Nebenwirkungen
überwiegend kutan

Resistenzmechanismen

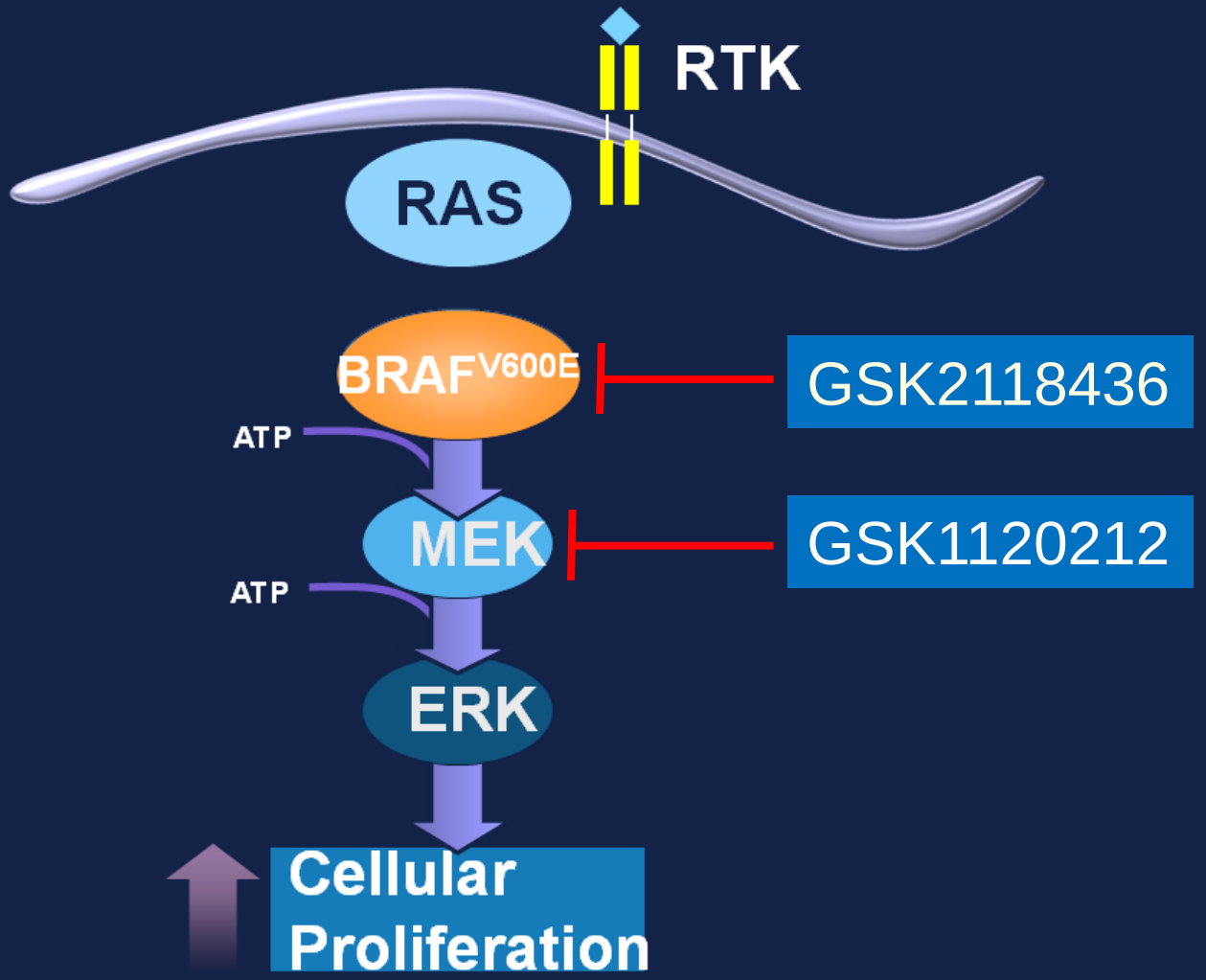


Resistenzmechanismen



Aplin AE et al. Mechanisms of Resistance to RAF Inhibitors in Melanoma.
Journal of Investigative Dermatology 131, 1817-1820 (September 2011)

Kombination BRAF- und MEK-Inhibitor



Phase I/II Study of the Oral MEK 1/2 Inhibitor GSK1120212 Dosed in Combination with the Oral BRAF Inhibitor GSK2118436

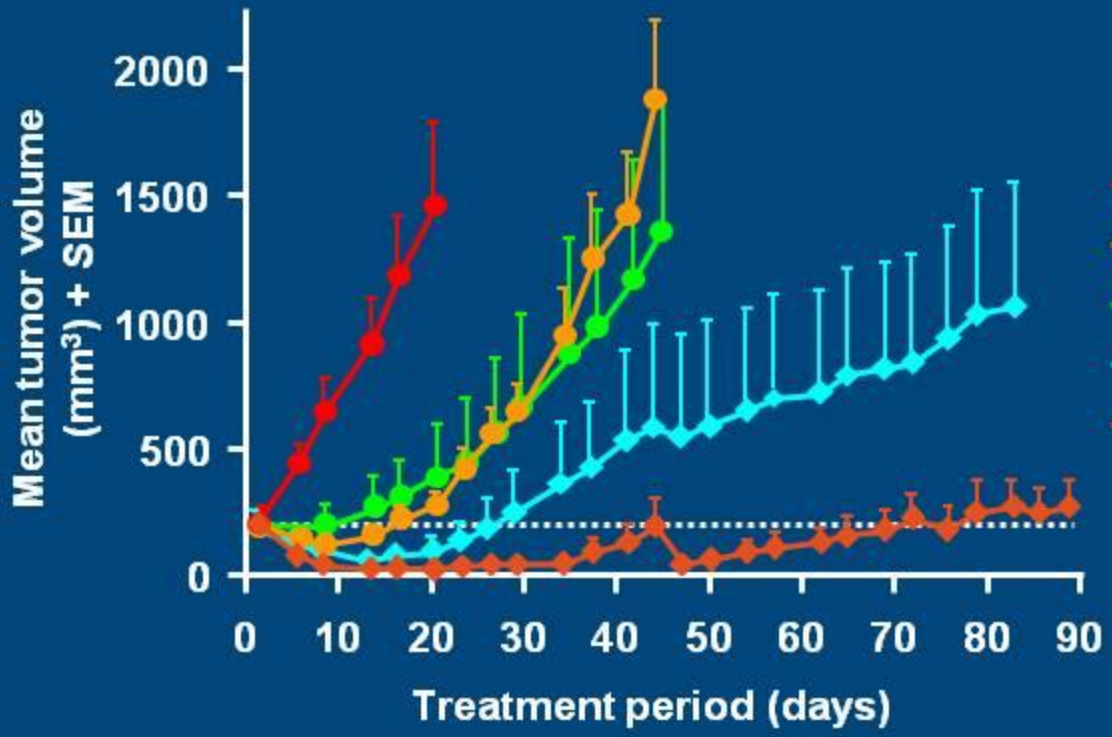
Jeffrey Infante[1], Gerald Falchook[2], Donald Lawrence[3], Jeff Weber[4], Richard Kefford[5] , Johanna Bendell[1], Razelle Kurzrock[2], Geoffrey Shapiro[3], Ragini Kudchadkar[4], Georgina Long[5], Howard Burris[1], Kevin Kim[2], Arthur Clements[5], Peng Sun[6], Bingming Yi[6], Alicia Allred[6], Daniele Ouellet[6], Kiran Patel[6], Peter Lebowitz[6], Keith Flaherty[3]

[1]Sarah Cannon Research Institute, Nashville, TN, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]MGH/DFCI, Boston, MA, USA; [4]Moffitt Cancer Center, Tampa, FL, USA; [5] Melanoma Institute of Australia and Westmead Hospital, University of Sydney, Australia; [6]GlaxoSmithKline Research and Development, Philadelphia, PA and RTP, NC, USA

Presented at the 2011 ASCO Annual Meeting. Presented data is the property of the author.

ASCO | Annual '11 Meeting

Enhanced Antitumor Activity with Combination in BRAF^{V600E} Human Melanoma Xenograft



A375PF11

- Untreated control
- GSK212 (0.3 mg/kg)
- GSK436 (30 mg/kg)
- GSK436 (300 mg/kg)
- GSK436+GSK212 (30/0.3 mg/kg)

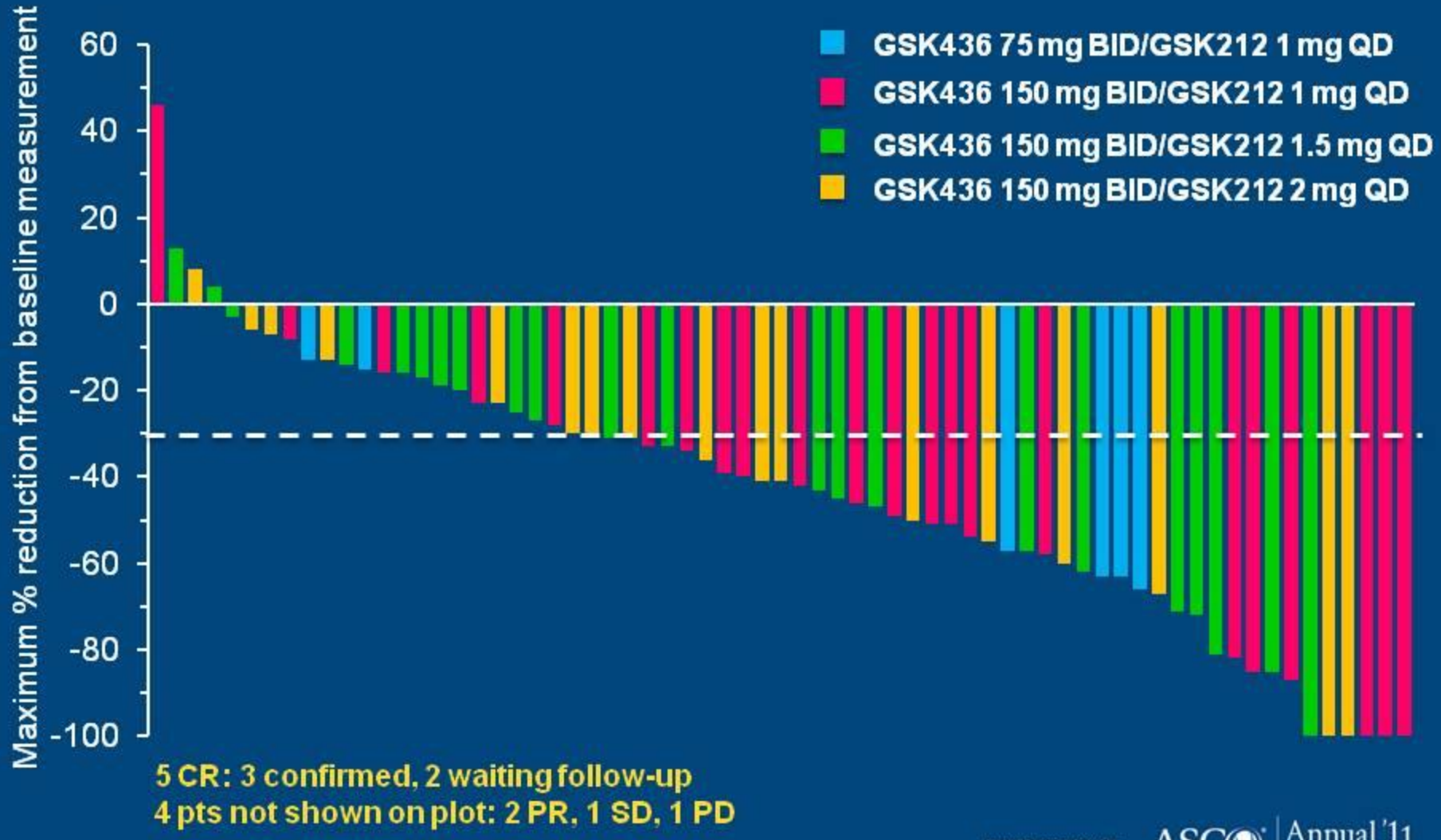
Reduced tumor volume greater than either single agent

$p \leq 0.05$ vs. GSK436 (30 mg/kg) or GSK212 (0.3 mg/kg) at Day 19

GSK unpublished data

PRESENTED AT: ASCO Annual '11 Meeting

Waterfall Plot for Melanoma Patients without Prior BRAFi (n=71)



5 CR: 3 confirmed, 2 waiting follow-up
4 pts not shown on plot: 2 PR, 1 SD, 1 PD

Best Unconfirmed Response Rate for Melanoma Patients without Prior BRAFi (n=71)

Dose Level BRAFi (GSK436)/ MEKi (GSK212)	n, evaluable	Complete Response, n (%)	Objective Response CR + PR, n (%)	CR + PR + SD, n (%)
75/1	6		4 (67%)	6 (100%)
150/1	22	3 (14%)	17 (77%)	21 (95%)
150/1.5	24		12 (50%)	23 (96%)
150/2	19	2 (11%)	14 (74%)	19 (100%)

CR= complete response
PR= partial response
SD= stable disease

Waterfall Plot for Melanoma Patients with Prior BRAFi (n=24)

PRESENTED AT: ASCO Annual '11 Meeting

Treatment-Related AEs Occurring in ≥10% of Patients

	Dose level (BRAFi GSK436/ MEKi GSK212)				
Preferred Term	**75/1 (n=6)**	**150/1 (n=23)**	**150/1.5 (n=27)**	**150/2 (n=53)**	**Total (n=109)**
Any event, n (%)	**5 (83%)**	**21 (91%)**	**23 (85%)**	**37 (70%)**	**86 (79%)**
Pyrexia	2 (33%)	6 (26%)	8 (30%)	18 (34%)	34 (31%)
Rash	2 (33%)	9 (39%)	5 (19%)	11 (21%)	27 (25%)
Chills	2 (33%)	7 (30%)	7 (26%)	8 (15%)	24 (22%)
Nausea	1 (17%)	5 (22%)	6 (22%)	10 (19%)	22 (20%)
Diarrhea	0	5 (22%)	5 (19%)	9 (17%)	19 (17%)
Fatigue	2 (33%)	1 (4%)	6 (22%)	8 (15%)	17 (16%)
Vomiting	1 (17%)	1 (4%)	3 (11%)	6 (11%)	11 (10%)

Treatment-related AEs ≥ Grade 3 occurred in 19% of all patients; events occurring in more than 1 patient: neutropenia (3), leukopenia (2), diarrhea (2), pyrexia (2).

Key Treatment-Related Skin Toxicities

	Combination BRAFi (GSK436) + MEKi (GSK212) n=109[1]	
	Grade ≥ 3, n (%)	Any grade event, n (%)
Rash[2]	2 (2%)	27 (25%)
Skin papilloma	0	1 (<1%)
Squamous cell carcinoma	1 (<1%)	1 (<1%)
Actinic keratosis	0	1 (<1%)
Hyperkeratosis	0	0

[1] GSK436 + GSK212 includes all dose levels from dose escalation
[2] Rash includes all rash-related terms

Conclusions

- MEKi (GSK212) at 2 mg QD (monotherapy dose) combines safely with BRAFi (GSK436) at 150 mg BID (monotherapy dose)
- Lower incidence of rash and BRAFi-induced hyperproliferative skin lesions
  - 1 (< 1%) patient with squamous cell carcinoma
- Clinical activity in BRAF V600-mutant melanoma
  - Awaiting long-term durability data

Ausblick für Targeted Therapy

- Weitere RAF- und MEK-Inhibitoren, duale Inhibitoren und Kombinationen
- Kombinationen mit AKT- und PI3K- bzw. mTOR-Inhibitoren
- Kombination zwischen Targeted Therapy und Immuntherapie
- BRAF-Mutationsanalyse diagnostischer Standard

Klinikum Nürnberg
wir sind für Sie da!

HAUT TUMOR ZENTRUM NÜRNBERG

CCC Comprehensive Cancer Center Erlangen-Nürnberg

Vielen Dank für Ihre Aufmerksamkeit!