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Universitätsklinikum
Erlangen

Symposium

Highlights vom amerikanischen Krebskongress ASCO

23. Juli 2011

Melanom

Eckhart Kämpgen, Erlangen
Dirk Debus, Nürnberg

CCC Comprehensive Cancer Center
Erlangen-Nürnberg

CCC Erlangen-Nürnberg
Interim Report
2010

CCC Director:
Prof. Dr. med. M. W. Beckmann

CCC Deputy Director
Prof. Dr. med. J. Ficker

CCC Comprehensive Cancer Center
Erlangen-Nürnberg

Deutsche Krebshilfe e. V.
Program for the Development of Interdisciplinary Oncology Centers of Excellence in Germany – 2nd Call – Interim Report

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Appendix No. 10 - Number of all cancer patients treated in the cancer center in 2010

Disease Site	Number of all cancer patients treated in the cancer center in 2010				
	1	2	3	4	5
	total number	inpatients	% inpatients	outpatients	% outpatients
Colorectal cancer***	983	893	90,8%	90	9,2%
Stomach	196	182	92,9%	14	7,1%
Pancreas	145	142	97,9%	3	2,1%
Esophagus	112	107	95,5%	5	4,5%
Thyroid	157	155	98,7%	2	1,3%
Lymphoma***	382	339	88,7%	43	11,3%
Leukemia***	239	188	78,7%	51	21,3%
Breast ***	2284	1299	56,9%	985	43,1%
Cervix***	122	92	75,4%	30	24,6%
Uterus	159	144	90,6%	15	9,4%
Ovary ***	178	153	86,0%	25	14,0%
Melanoma***	715	667	93,3%	48	6,7%
Lung***	791	769	97,2%	22	2,9%
Prostate***	515	264	51,3%	251	48,7%
Testes	39	24	61,5%	15	38,5%
Kidney	197	147	74,6%	50	25,4%
Bladder***	165	108	65,4%	57	34,5%
Stoma/Pharynx***	832	814	97,8%	18	2,2%
Larynx***	195	190	97,4%	5	2,6%
Others* / ***	2272	2102	92,5%	170	7,5%
TOTAL**	**10678**	**8779**	**82,2%**	**1899**	**17,8%**

* Others: incl. 1047cases of non-melanoma skin cancer.

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Appendix 11 A - Number of cancer patients newly diagnosed in 2010

Disease Site	Number of cancer patients newly diagnosed in 2010				
	1	2	3	4	5
	total number	inpatients	% inpatients	outpatients	% outpatients
Colorectal cancer***	577	554	96,0%	23	4,0%
Stomach***	100	97	97,0%	3	3,0%
Pancreas	68	68	100,0%	0	0,0%
Esophagus	56	55	98,2%	1	1,8%
Thyroid	111	110	99,1%	1	0,9%
Lymphoma***	169	155	91,7%	14	8,3%
Leukemia***	88	84	95,5%	4	4,5%
Breast***	656	620	94,5%	36	5,5%
Cervix***	69	62	89,9%	7	10,1%
Uterus	91	89	97,8%	2	2,2%
Ovary	82	80	97,6%	2	2,4%
Melanoma***	448	427	95,3%	21	4,7%
Lung***	462	453	98,1%	9	1,9%
Prostate	284	135	47,5%	149	52,5%
Testes	29	18	62,1%	11	37,9%
Kidney	102	63	61,8%	39	38,2%
Bladder***	84	55	65,5%	29	34,5%
Stoma/Pharynx***	421	416	98,8%	5	1,2%
Larynx***	99	97	98,0%	2	2,0%
Others * / ***	1447	1368	94,5%	79	5,5%
TOTAL**	**5443**	**5006**	**98,0%**	**437**	**8,0%**

* Others incl. 855 cases of non-melanoma skin cancer.

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Erlangen-Nürnberg

FORTGESCHRITTENES MELANOM: YERVOY®

Immunsystem mobilisieren

Leben verlängern[1]

YERVOY® IST ZUR BEHANDLUNG FORTGESCHRITTENER (NICHT RESEZIERBARER ODER METASTASIERTER) MELANOME BEI VORBEHANDELTEN ERWACHSENEN INDIZIERT.[2]

YERVOY®
(Ipilimumab)
Konzentrat zur Herstellung einer Infusionslösung

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WELCOME

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Immuntherapie

- Ipilimumab 020 (ASCO 2010)
- Ipilimumab 024 (ASCO 2011)

Targeted Therapy

- Vemurafenib (ASCO 2011)

CCC Comprehensive Cancer Center Erlangen-Nürnberg

A phase III, randomized, double-blind, multicenter study comparing monotherapy with ipilimumab or gp100 peptide vaccine and the combination in patients with previously treated, unresectable stage III or IV melanoma

Study MDX010-20

Steven O'Day[1], F. Stephen Hodi[2], David McDermott[3], Robert Weber[4], J Zhu[7], Michae

[1]The Angeles Clinic and Resear MA; [3]Beth Israel Deaconess Me CA; [5]Vanderbilt-Ingram Cancer The Netherlands; [7]Medarex Inc., Chiles Research Institute, Portl

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

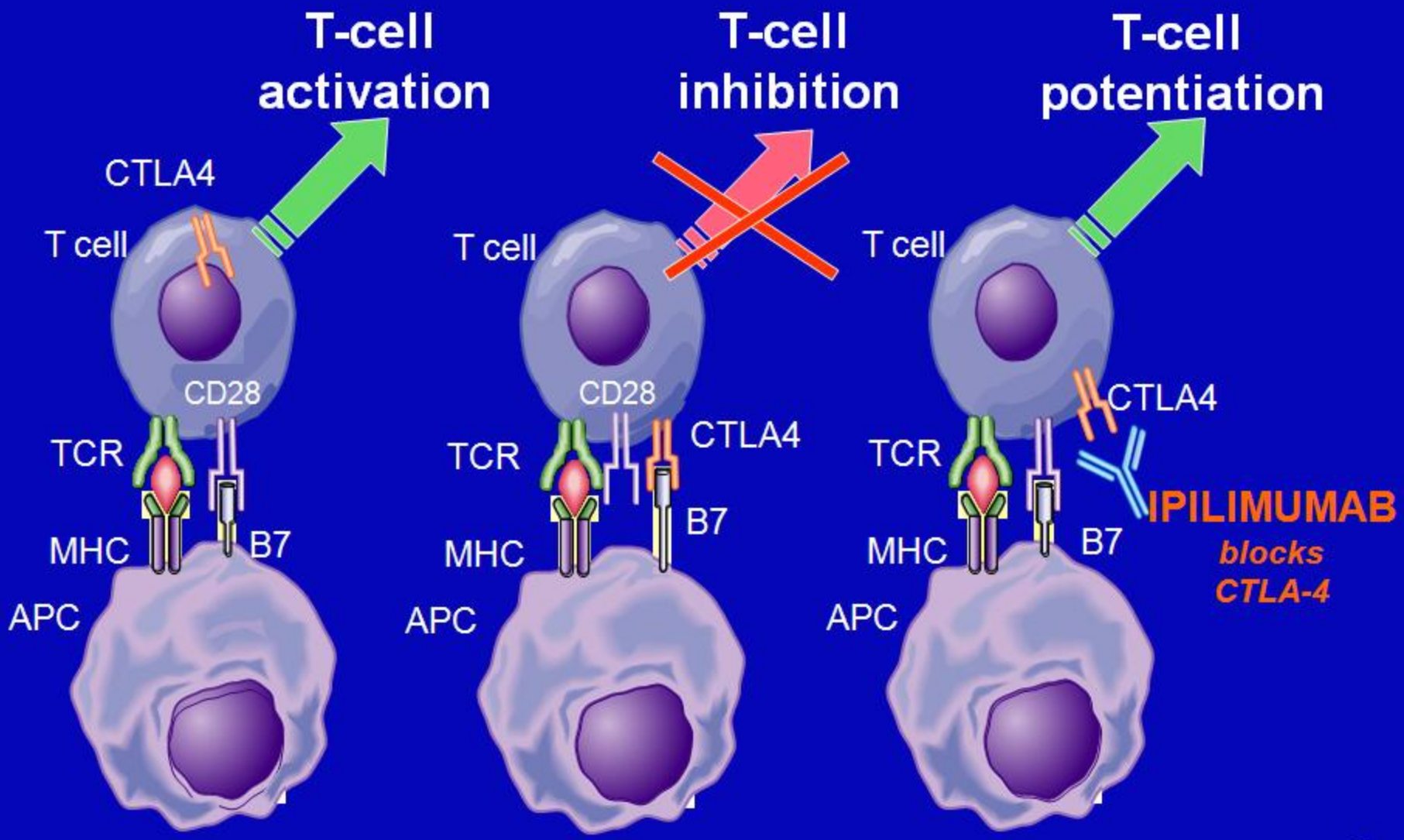
F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D.,

Ipilimumab in Treatment of Cancer

- CTLA-4:
  - Downregulates T-cell activation
- Ipilimumab:
  - Fully human monoclonal antibody
  - Blocks CTLA-4 receptor
  - Potentiates T cell activation

Korman, Peggs and Allison: Adv. In Immunol 2006;90:297-339

Ipilimumab: Mechanism of Action



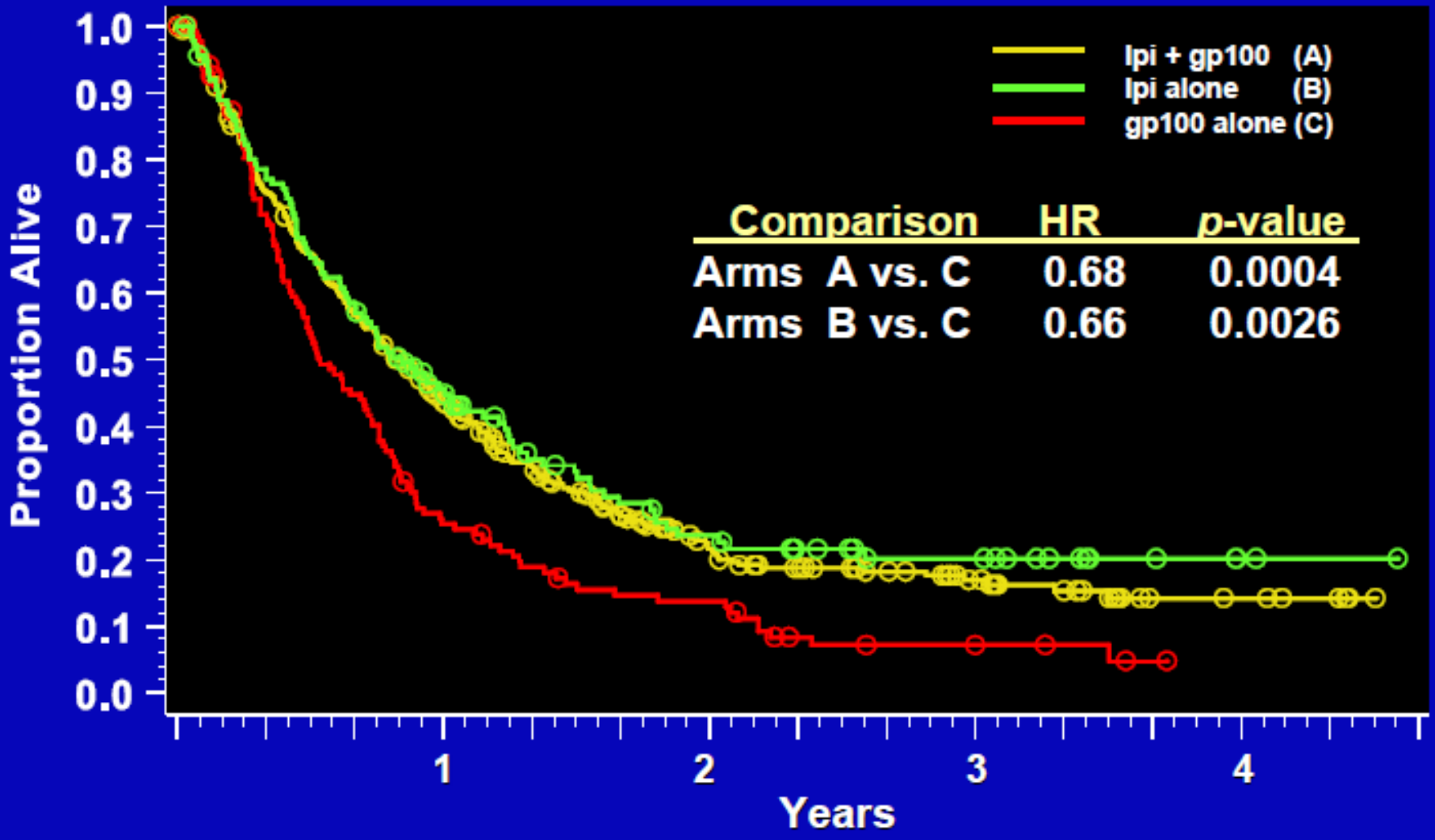
MDX010-20: Patient Eligibility

- Inclusion
  - Pre-treated stage III or IV melanoma
  - HLA-A*0201 positive
  - Pre-treated CNS metastases allowed
  - Any LDH level
- Exclusion
  - No autoimmune disease
  - No prior therapy with anti-CTLA-4 antibody
  - No prior therapy with anti-cancer vaccine

MDX010-20: Study Design Details

- Accrual: September 2004 – July, 2008
  - 125 Centers in 13 Countries
- Randomized (3:1:1), Double-Blind
- Stratified for M-Stage and prior IL-2
- Induction
  - Ipilimumab: 3 mg/kg q 3 weeks X 4 doses
  - gp100: 1mg q 3 weeks X 4 doses
- Re-induction (same regimen) in eligible patients

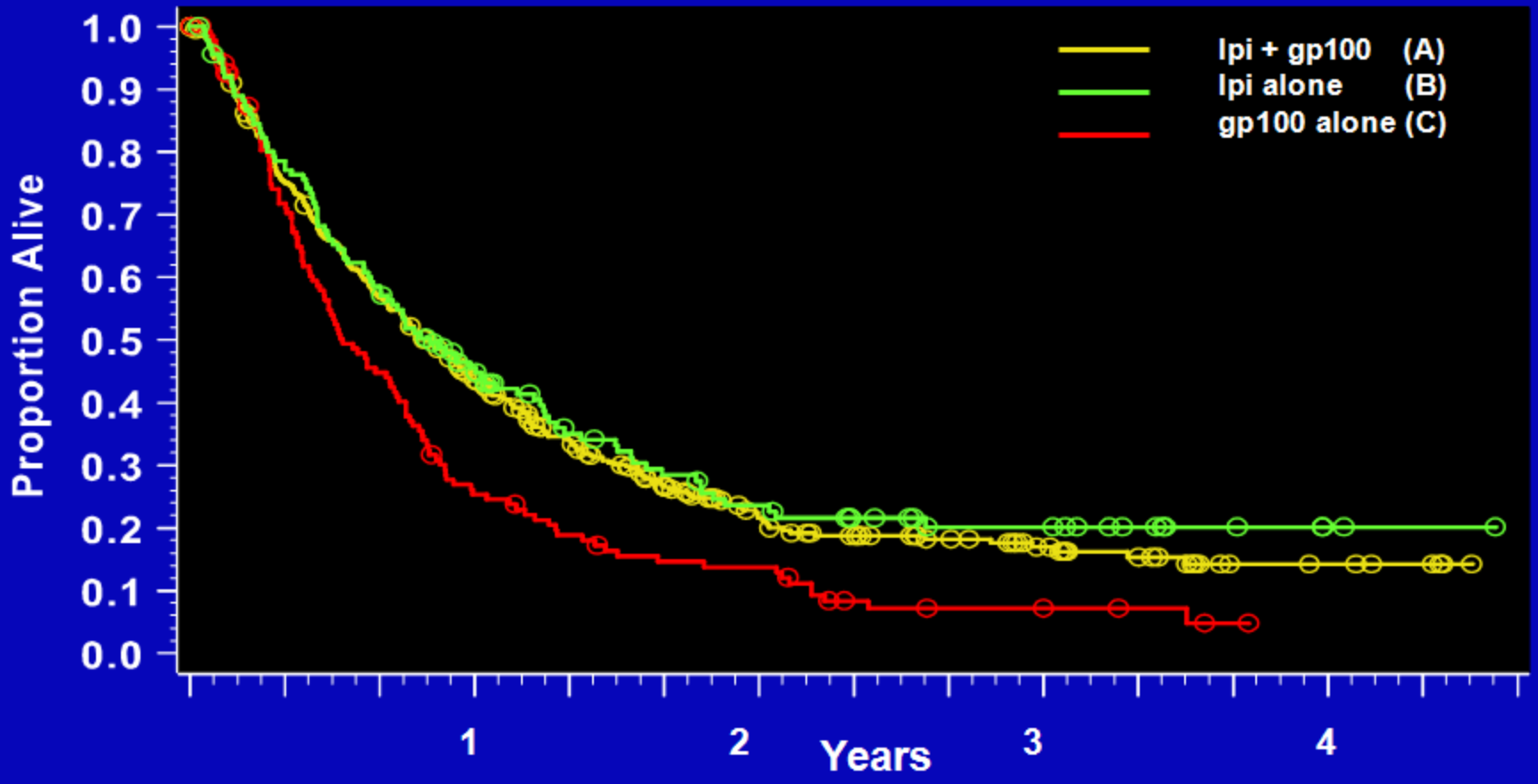
Kaplan-Meier Analysis of Survival



Ipilimumab alone Improves Overall Survival Compared to gp100

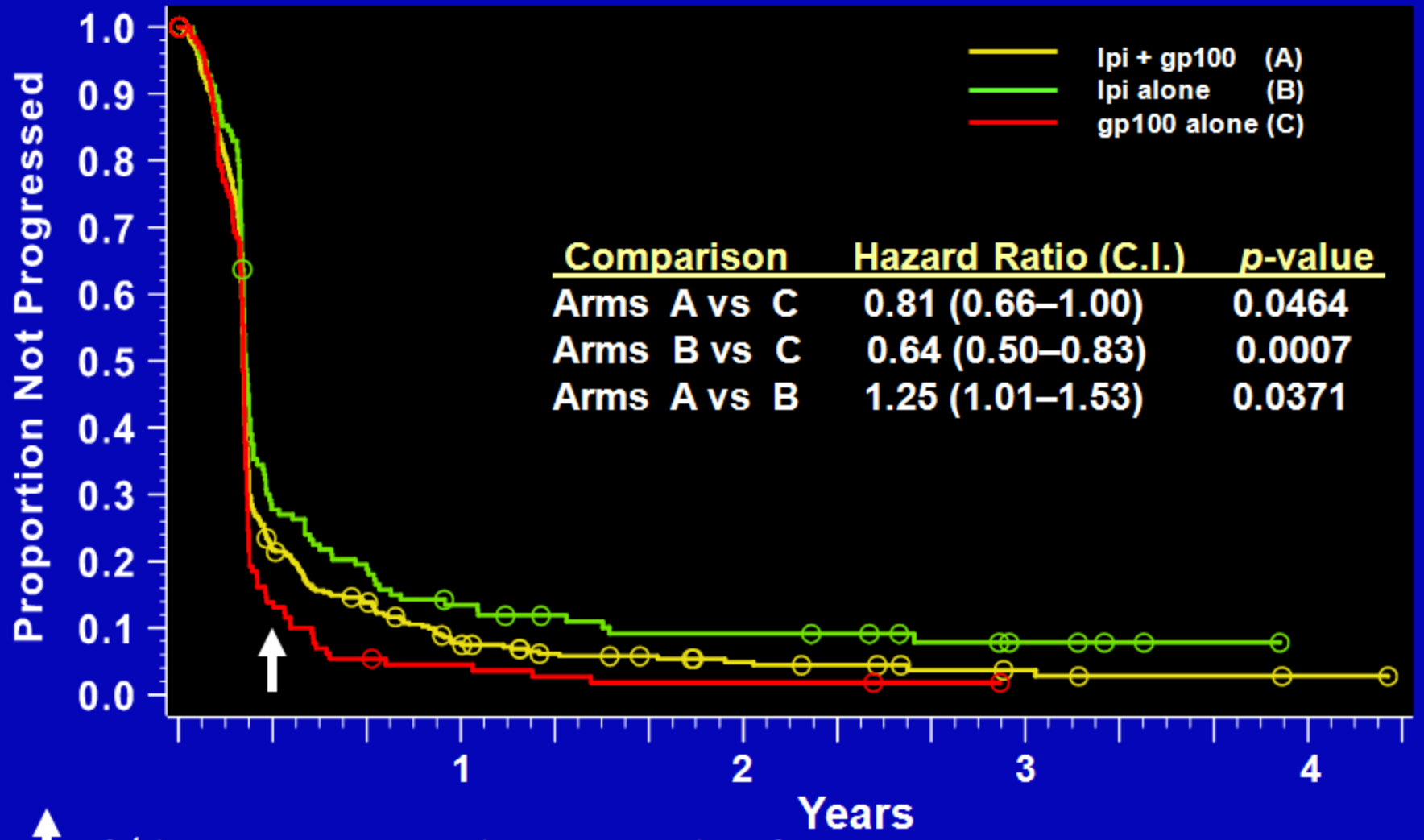
	Ipi + pbo	gp100 + pbo	P-value
Secondary Comparison			
N	137	136	0.0026
Number of deaths	100	119	
Hazard ratio (95% CI)	0.66 (0.51, 0.87)		
Median OS, Month (95% CI)	10.1 (8.0,13.8)	6.4 (5.5, 8.7)	

Kaplan-Meier Analysis of Survival



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

PFS: Impact of Both Ipilimumab Regimens vs gp100



↑ = 1st tumor assessment as per protocol

Most Common Immune-Related Adverse Events* (irAEs; All Grades)

% of Patients			
irAE	Ipi + gp100 N=380	Ipi + pbo N=131	gp100 + pbo N=132
All grades			
Any	58.2	61.1	31.8
Dermatologic	40.0	43.5	16.7
GI	32.1	29.0	14.4
Endocrine	3.9	7.6	1.5
Hepatic	2.1	3.8	4.5

*Across entire study duration

Most Common Immune-Related Adverse Events* (Grades 3, 4 & 5)

% of Patients						
irAE	Ipi + gp100 N=380		Ipi + pbo N=131		gp100 + pbo N=132	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any	9.7	0.5	12.2	2.3	3.0	0
Dermatologic	2.1	0.3	1.5	0	0	0
GI	5.3	0.5	7.6	0	0.8	0
Endocrine	1.1	0	2.3	1.5	0	0
Hepatic	1.1	0	0	0	2.3	0
Death due to irAE	1.3		1.5		0	

*Across entire study duration

Phase 3 randomized study of ipilimumab (IPI) plus dacarbazine (DTIC) vs DTIC alone as first line treatment in patients with unresectable stage III or IV melanoma

Jedd Wolchok[1], Luc Thomas[2], Igor Bondarenko[3], Steven O'Day[4], Jeffr
Francis[7], Ramy Ibrah

[1]Memorial Sloan-Kettering Cancer Ce
Sud, Pierre Benite, France; [3]City Clin
Research Institute, Los Angeles, CA;
Tübingen, Germany; [7]Bristol-Myers S
Wallingford, CT; [9]Institut Gustave Ro

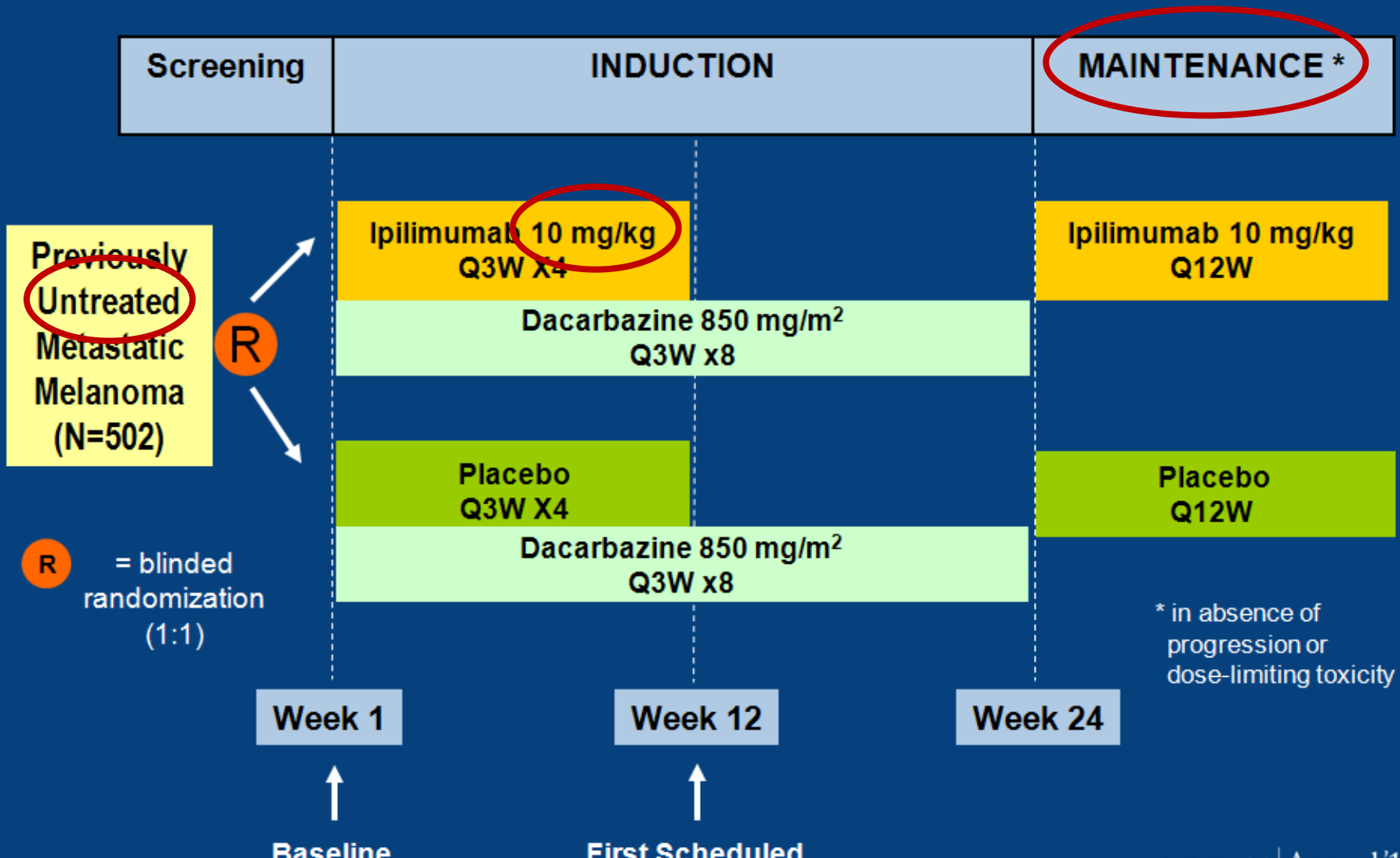
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D.

Study 024: Design



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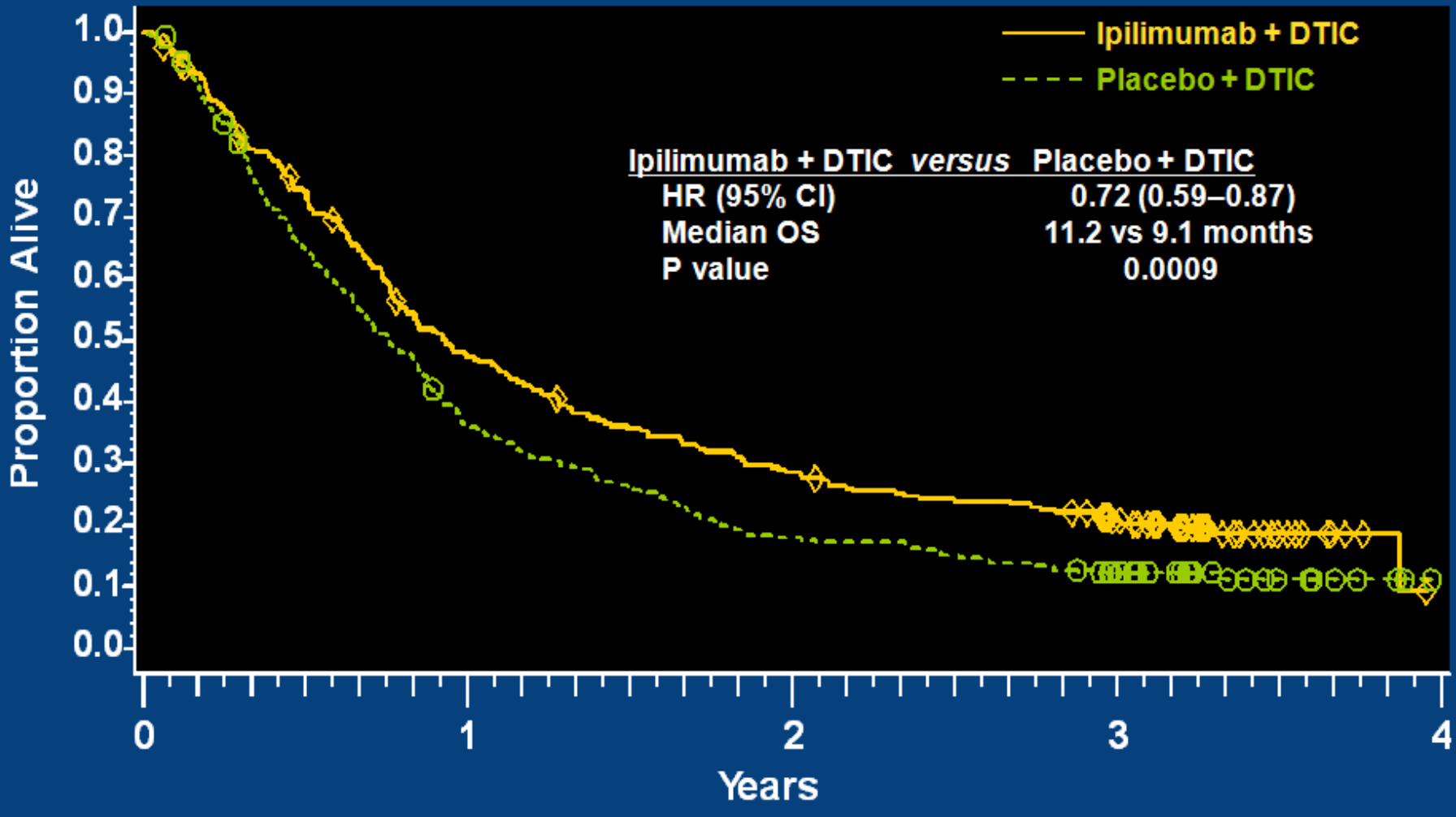
Study 024: Exposure

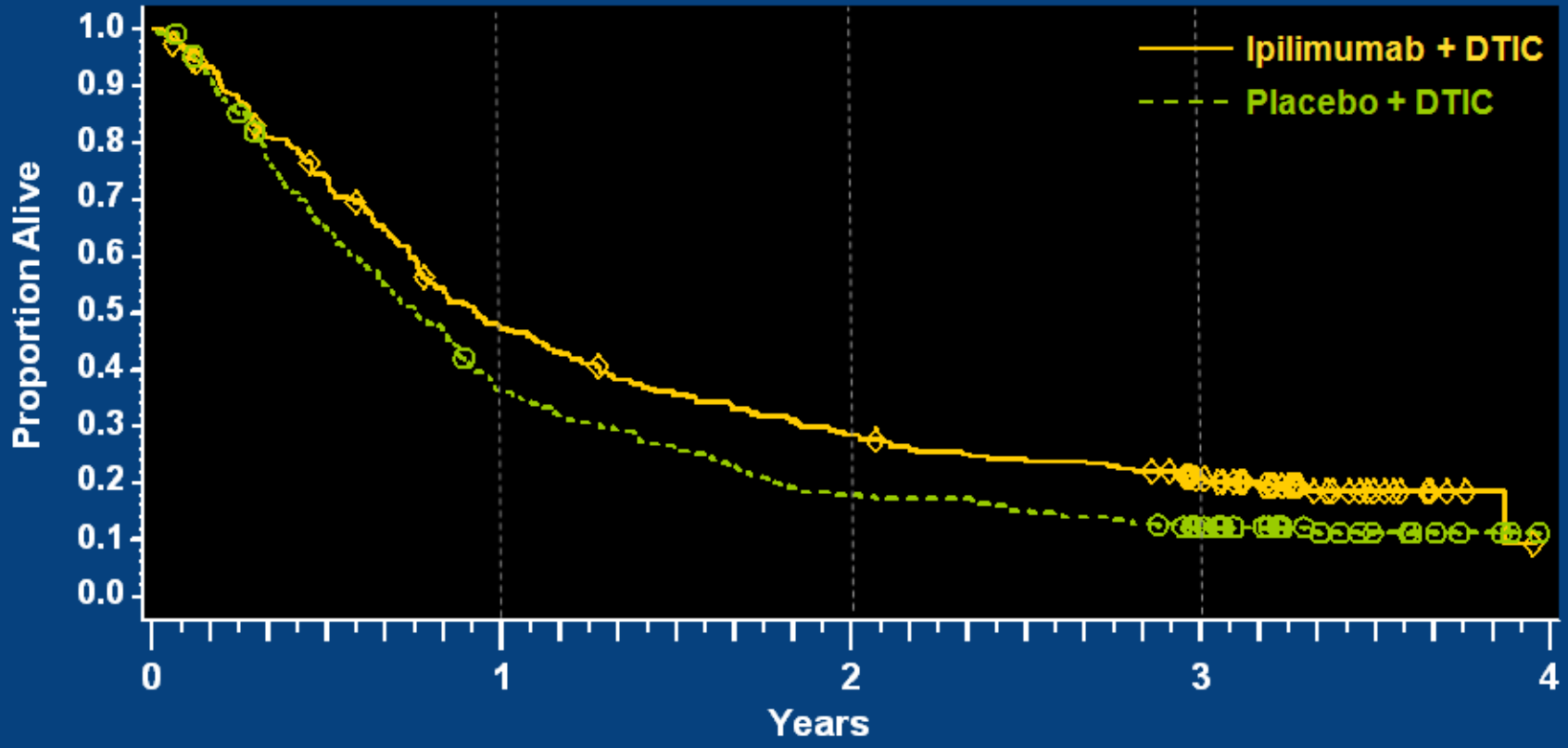
	Ipilimumab + DTIC n=247	Placebo + DTIC n=251
Induction		
Median number of doses	3.0	4.0
4 doses, % patients	37.2	66.0
Maintenance		
≥1 dose, % patients	17.4	21.1

Study 024: Overall Survival



PRESENTED AT: ASCO Annual '11 Meeting

Study 024: Overall Survival



Estimated Survival Rate	1 Year	2 Year	3 Year*
Ipilimumab + DTIC n=250	47.3	28.5	20.8
Placebo + DTIC n=252	36.3	17.9	12.2

*3-year survival was a post-hoc analysis

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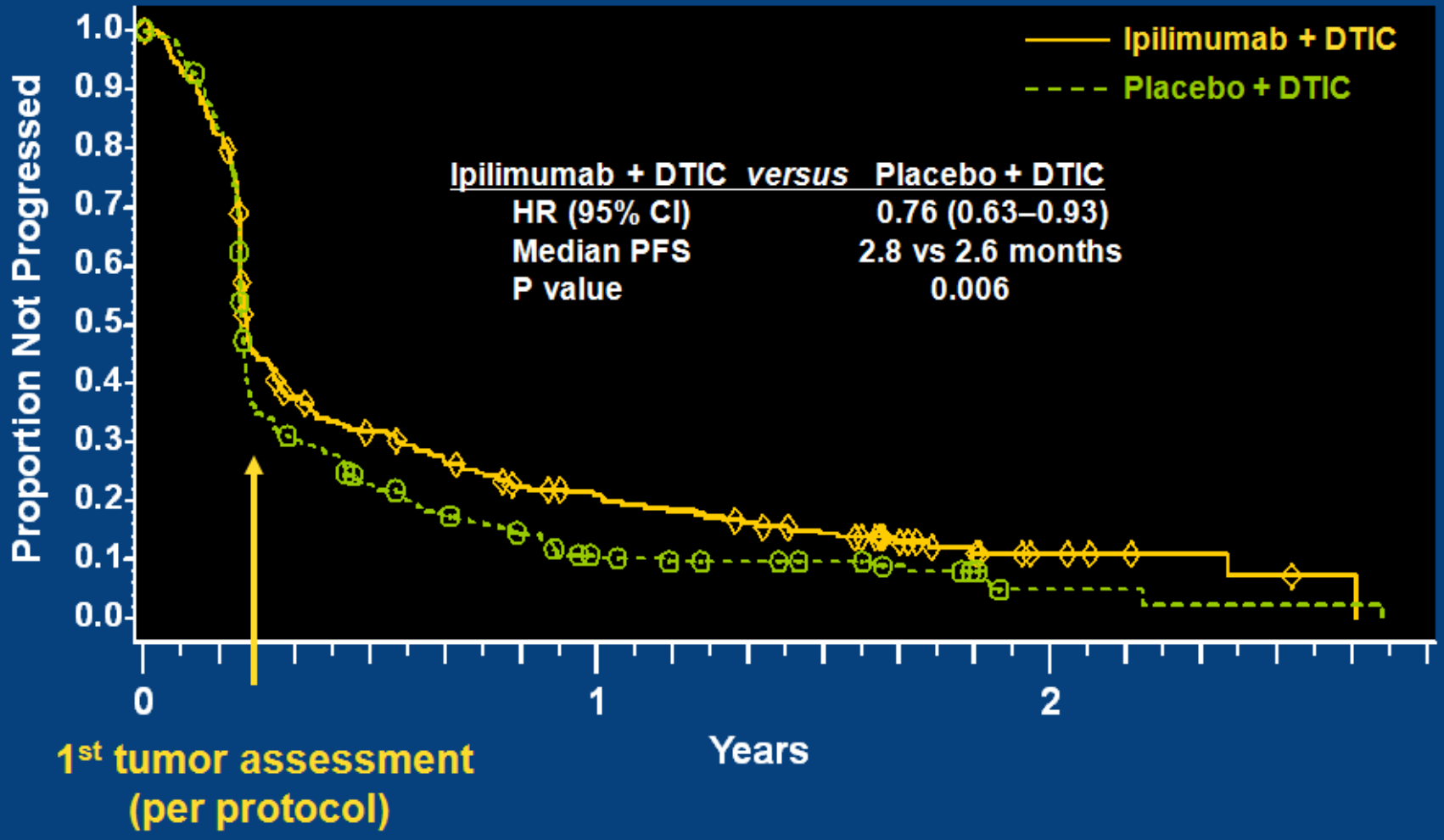
Study 024: Progression-Free Survival



PRESENTED AT: ASCO Annual '11 Meeting

Study 024: Tumor Response

	Ipilimumab + DTIC n=250	Placebo + DTIC n=252
Disease Control Rate, n (%)	83 (33.2)	76 (30.2)
BORR (CR + PR), n (%)	38 (15.2)	26 (10.3)
Complete response	4 (1.6)	2 (0.8)
Partial response	34 (13.6)	24 (9.5)
Stable disease	45 (18.0)	50 (19.8)
Progressive disease	111 (44.4)	131 (52.0)
Duration of response, months	19.3	8.1

BORR=Best Overall Response Rate

Patients (%) not evaluable for response (no follow-up scans): 56 (22.4) vs 45 (17.9)

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Study 024: Safety Overview

	Adverse Events		Drug-related Adverse Events		Treatment-related Deaths
	Total	Grade 3-4	Total	Grade 3-4	
	% Patients				
Ipilimumab + DTIC n=247	98.8	56.3	89.5	50.6	0
Placebo + DTIC n=251	94.0	27.5	76.5	11.6	0.4*

* 1 death due to gastrointestinal hemorrhage in placebo + DTIC group

Study 024: Select Adverse Events

	Ipilimumab + DTIC n=247		Placebo + DTIC n=251	
	Total	Grade 3-4	Total	Grade 3-4
	% Patients			
Dermatologic				
Pruritus	29.6	2.0	8.8	0
Rash	24.7	1.2	6.8	0
Gastrointestinal (GI)				
Diarrhea	36.4	4.0	24.7	0
Colitis	4.5	2.0	0.4	0
GI perforation	0	0	0	0

Select adverse events are shown, regardless of attribution

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Study 024: Select Adverse Events

	Ipilimumab + DTIC n=247		Placebo + DTIC n=251	
	Total	Grade 3-4	Total	Grade 3-4
	% Patients			
Hepatic				
Increased ALT	33.2	21.9	5.6	0.8
Increased AST	29.1	18.2	5.6	1.2
Endocrine				
Hypothyroidism	1.6	0	0.4	0
Thyroiditis	0.8	0	0	0
Hyperthyroidism	0.4	0	0.4	0
Hypophysitis*	0	0	0	0

*1 (0.4%) hypophysitis in a patient on maintenance was reported on Day 364

Select adverse events are shown, regardless of attribution

PRESENTED AT: ASCO Annual '11 Meeting

Study 024: Efficacy Summary

- Ipilimumab (10 mg/kg) + DTIC prolongs survival vs. DTIC in previously untreated metastatic melanoma (HR= 0.72; P=0.0009)
- Estimated 1, 2 and 3 year survival rates:
  - 1 year: 47.3% vs 36.3%
  - 2 year: 28.5% vs 17.9%
  - 3 year: 20.8% vs 12.2%
- Durable responses:
  - Median of 19.3 months vs 8.1 months

YERVOY™ (ipilimumab)
Injection for Intravenous Infusion

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- FDA-Zulassung seit 25.3.2011
- EMA-Zulassung seit 13.7.2011

- Indikation: vorbehandeltes malignes Melanom
- Dosierung: 3mg/kg alle 3 Wochen, 4 Gaben

- Kosten: ca. 80-120.000 Euro für 4 Gaben

CCC Comprehensive Cancer Center Erlangen-Nürnberg

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
P. Lorigan, R. Dummer,
B. Nelson, J.

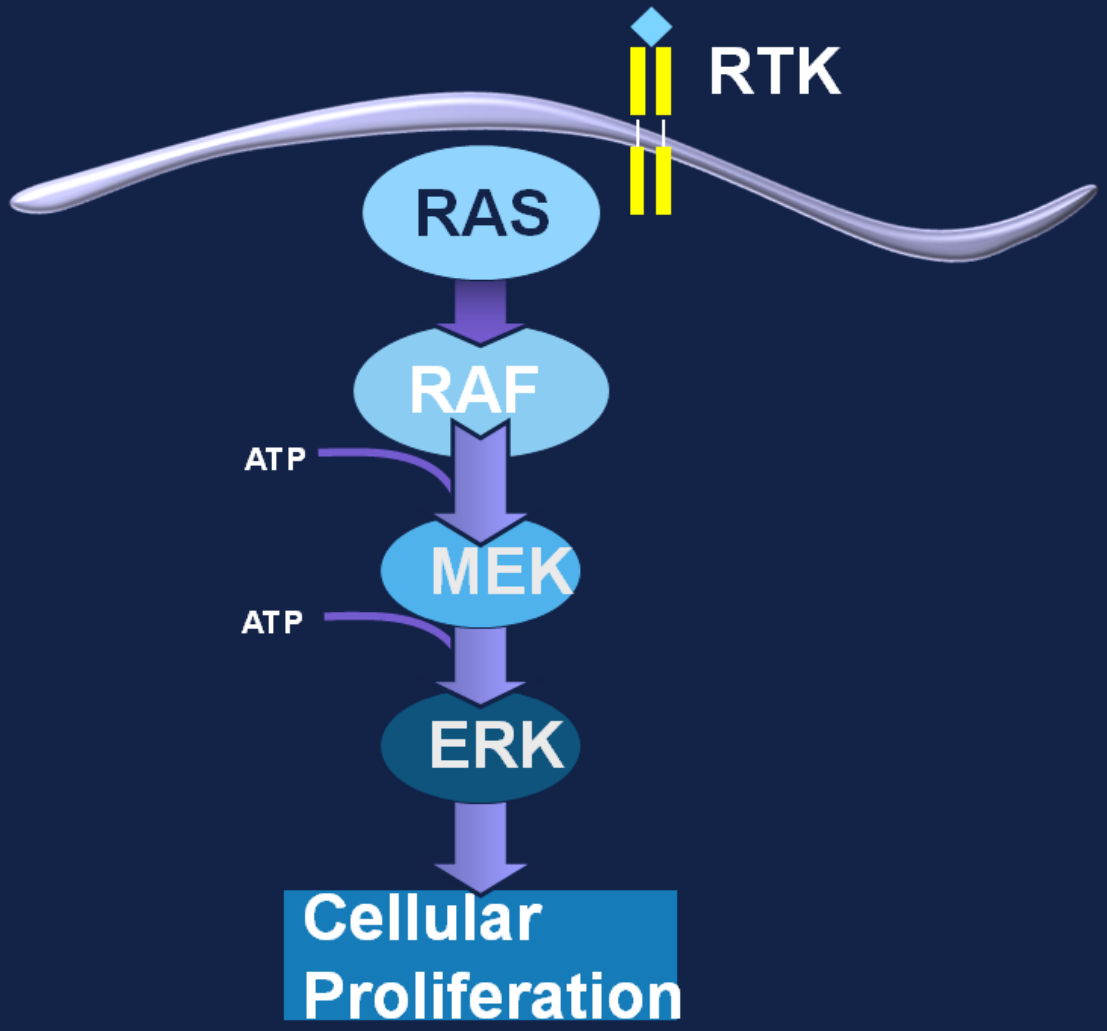
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

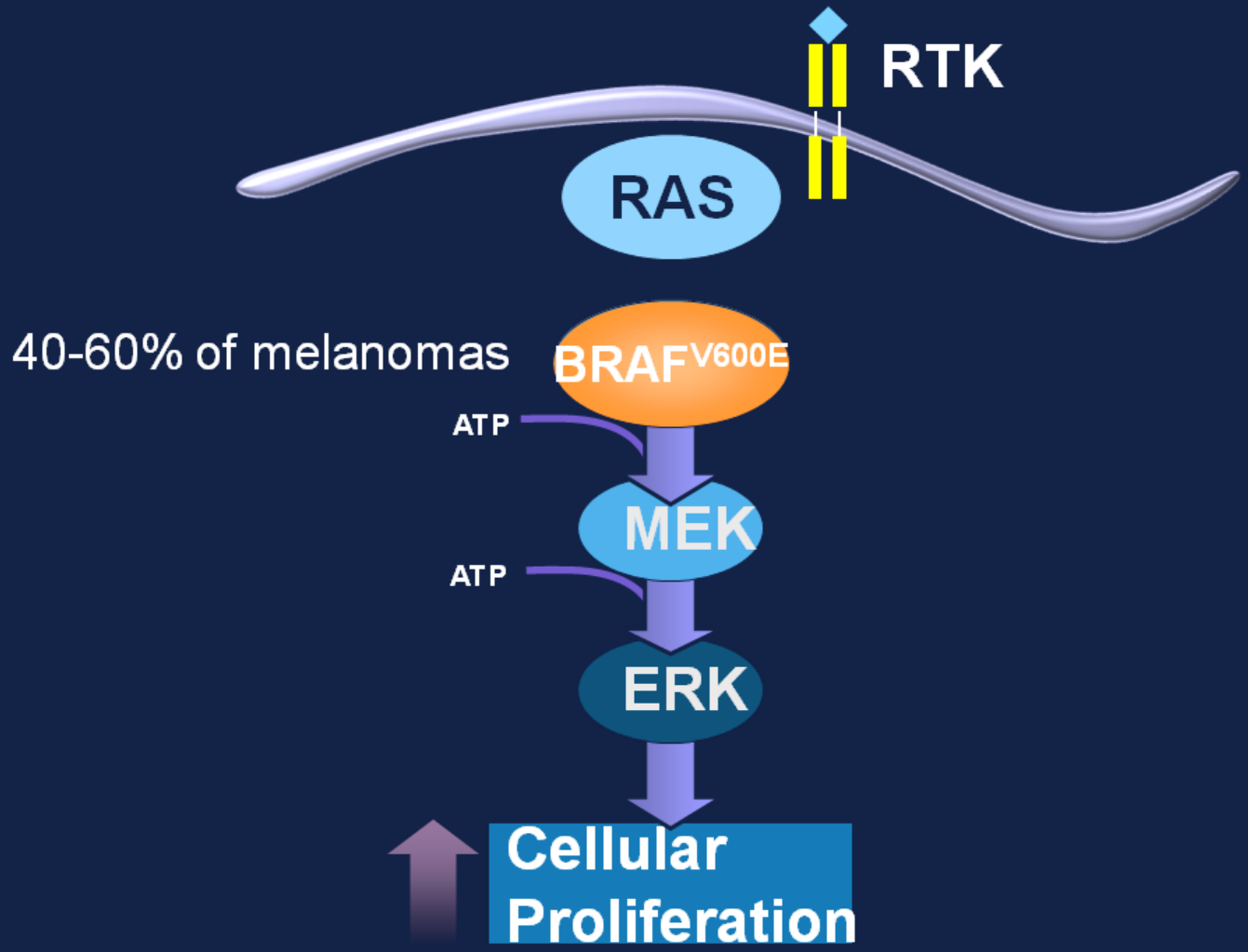
Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

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.,

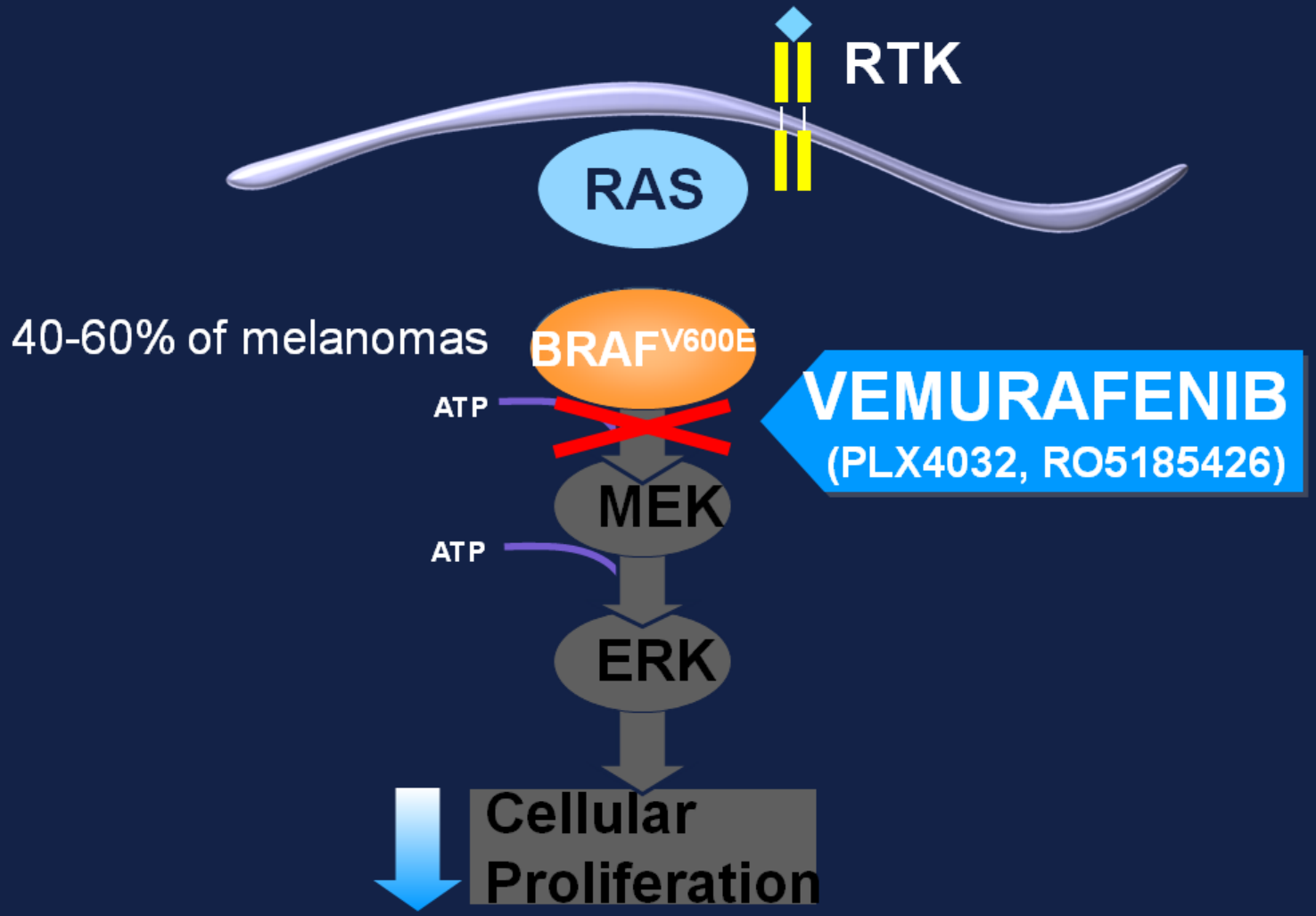
Vemurafenib inhibits $BRAF^{V600E}$ Kinase



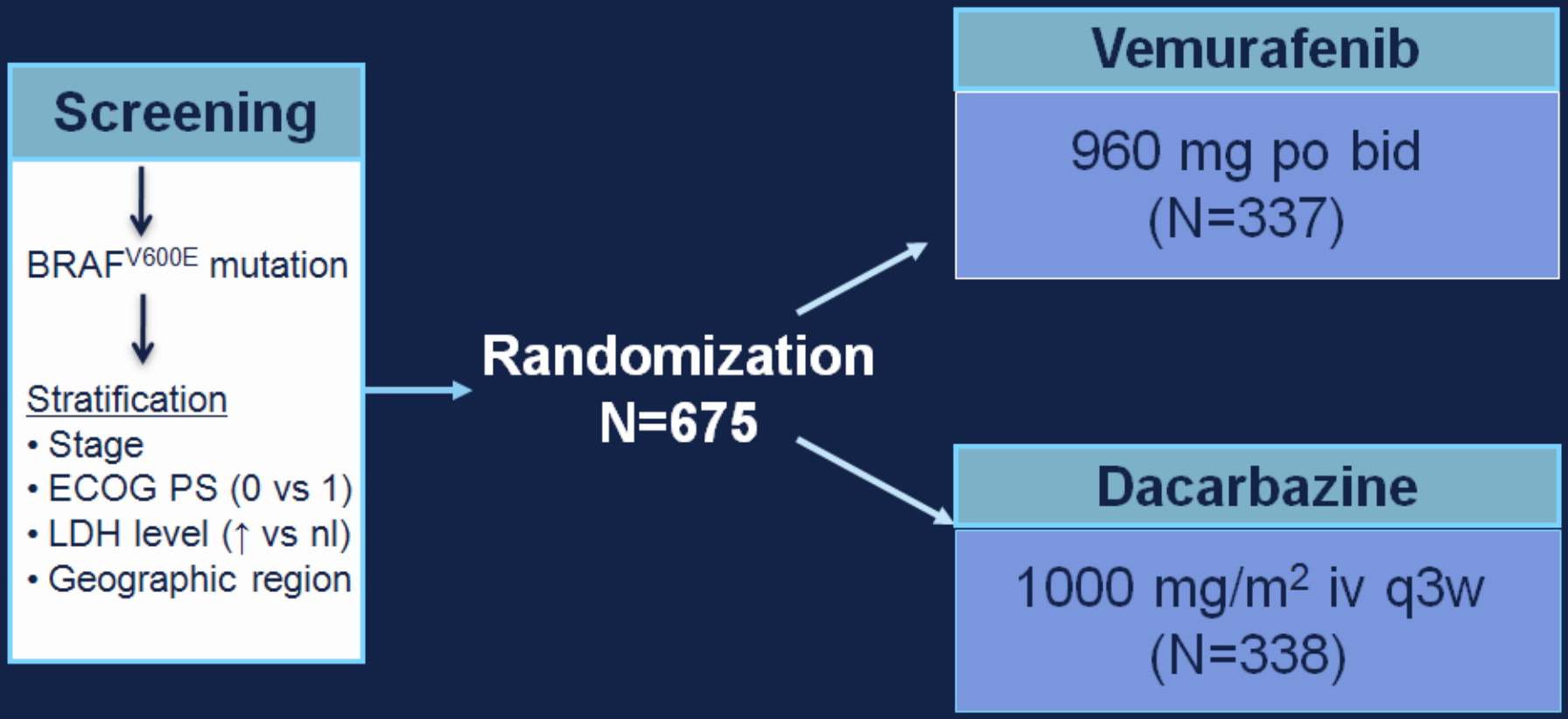
Vemurafenib inhibits BRAF^{V600E} Kinase



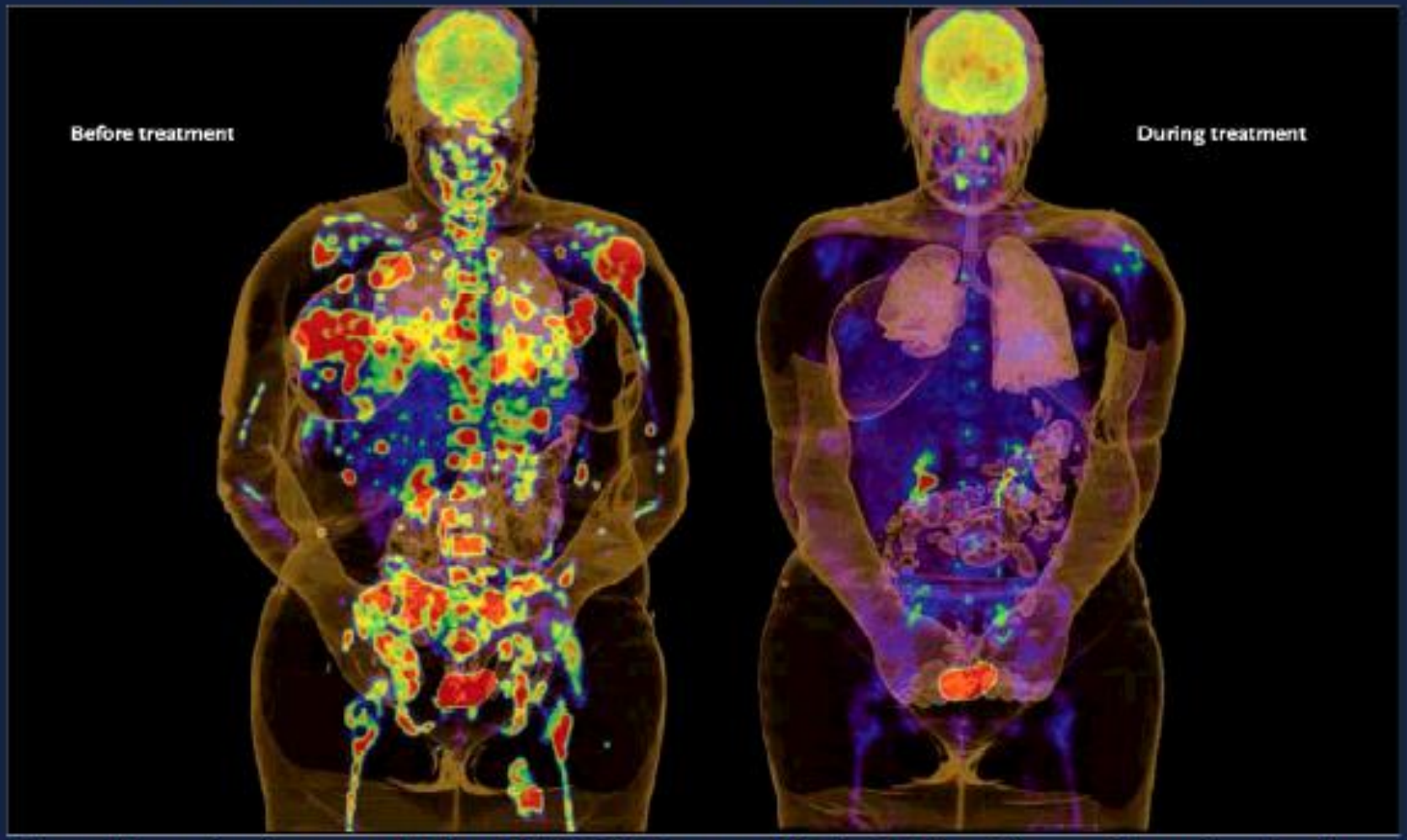
Vemurafenib inhibits $BRAF^{V600E}$ Kinase



Phase III BRIM3 Study design



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

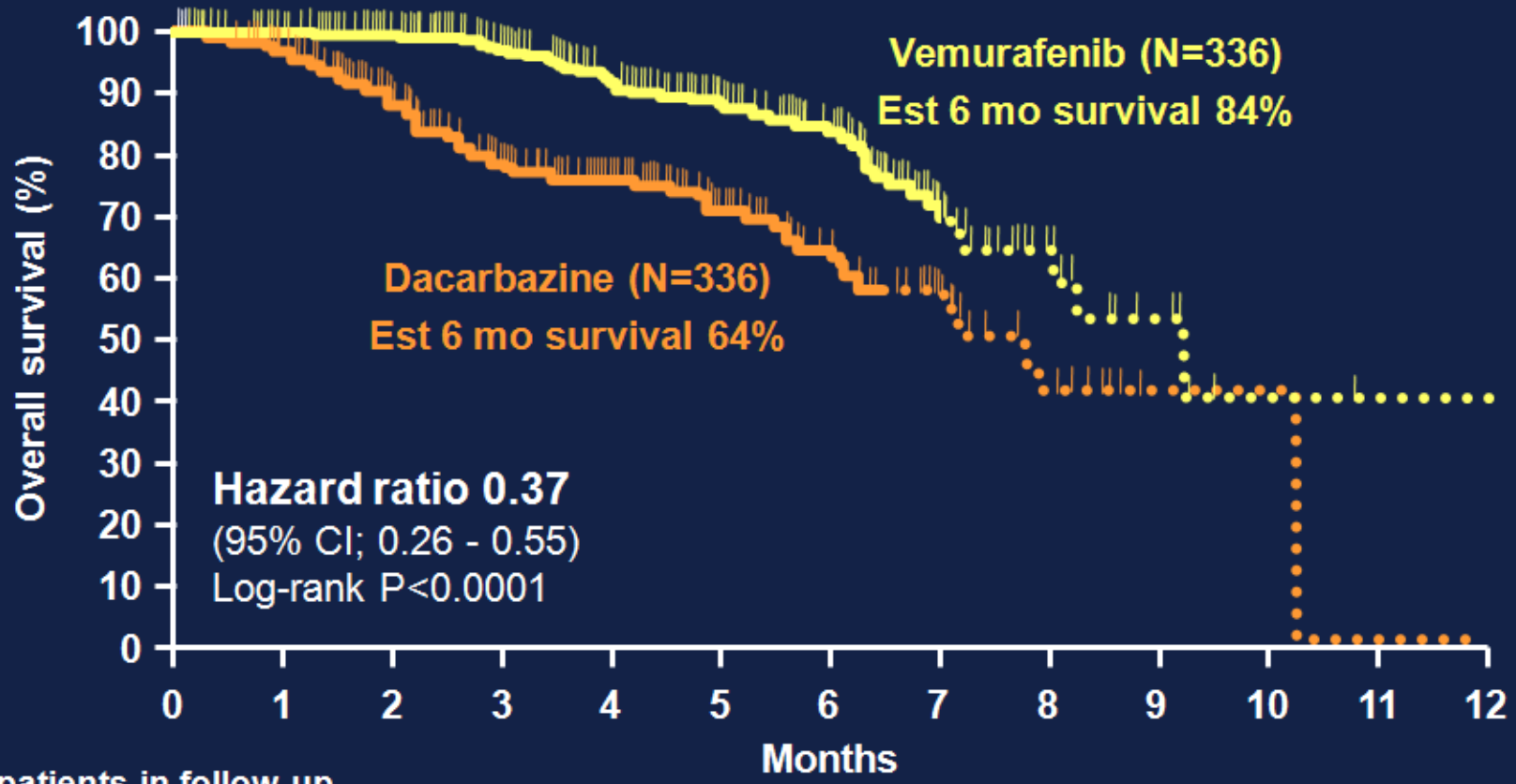


Three-dimensional representation of FDG–PET scans obtained at baseline and 2 weeks after the initiation of treatment with vemurafenib* in a melanoma patient carrying the V600E BRAF mutation[1].

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

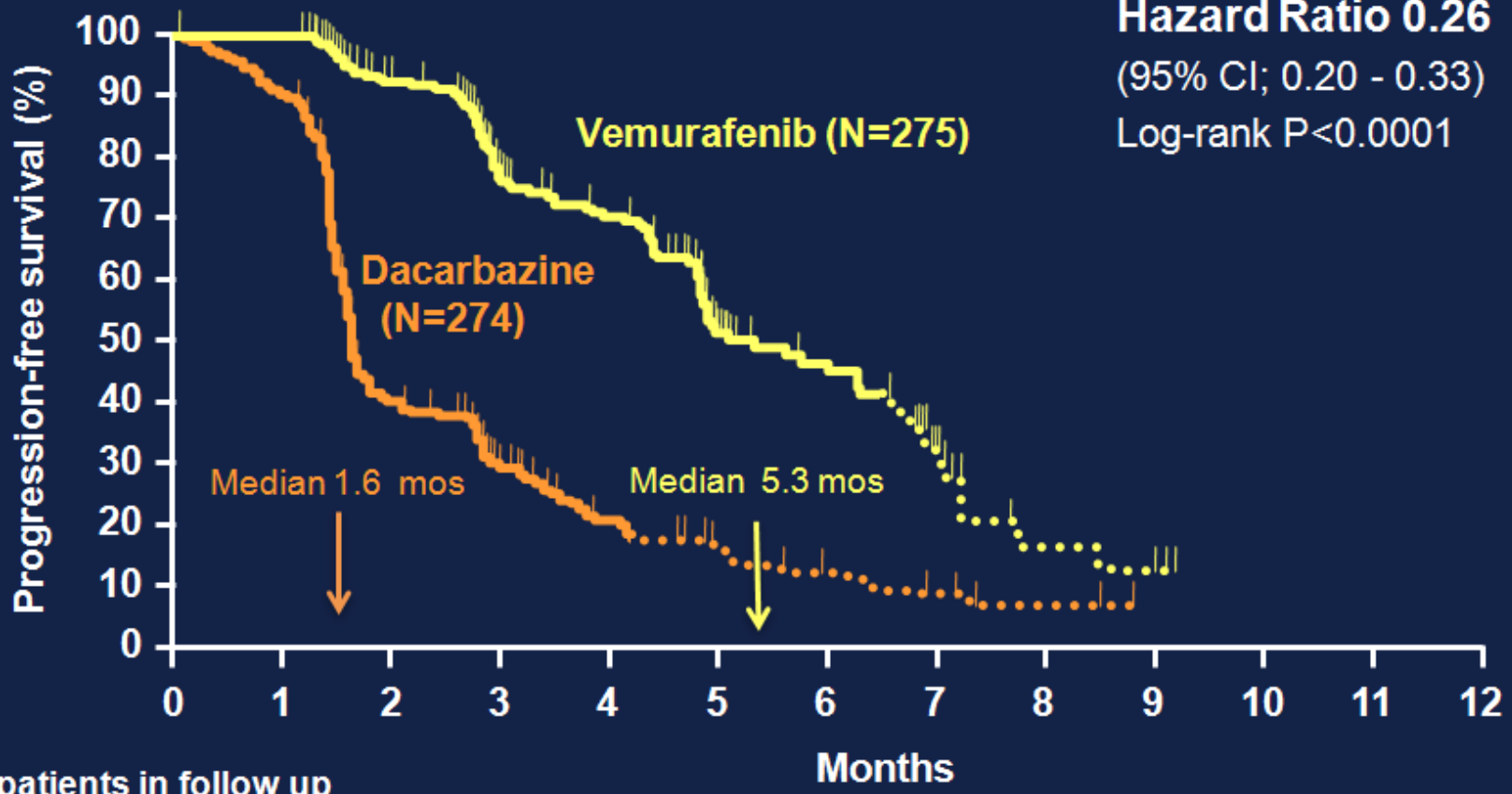
Overall survival (Dec 30, 2010 cutoff)



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

Progression-free survival (Dec 30, 2010 cutoff)



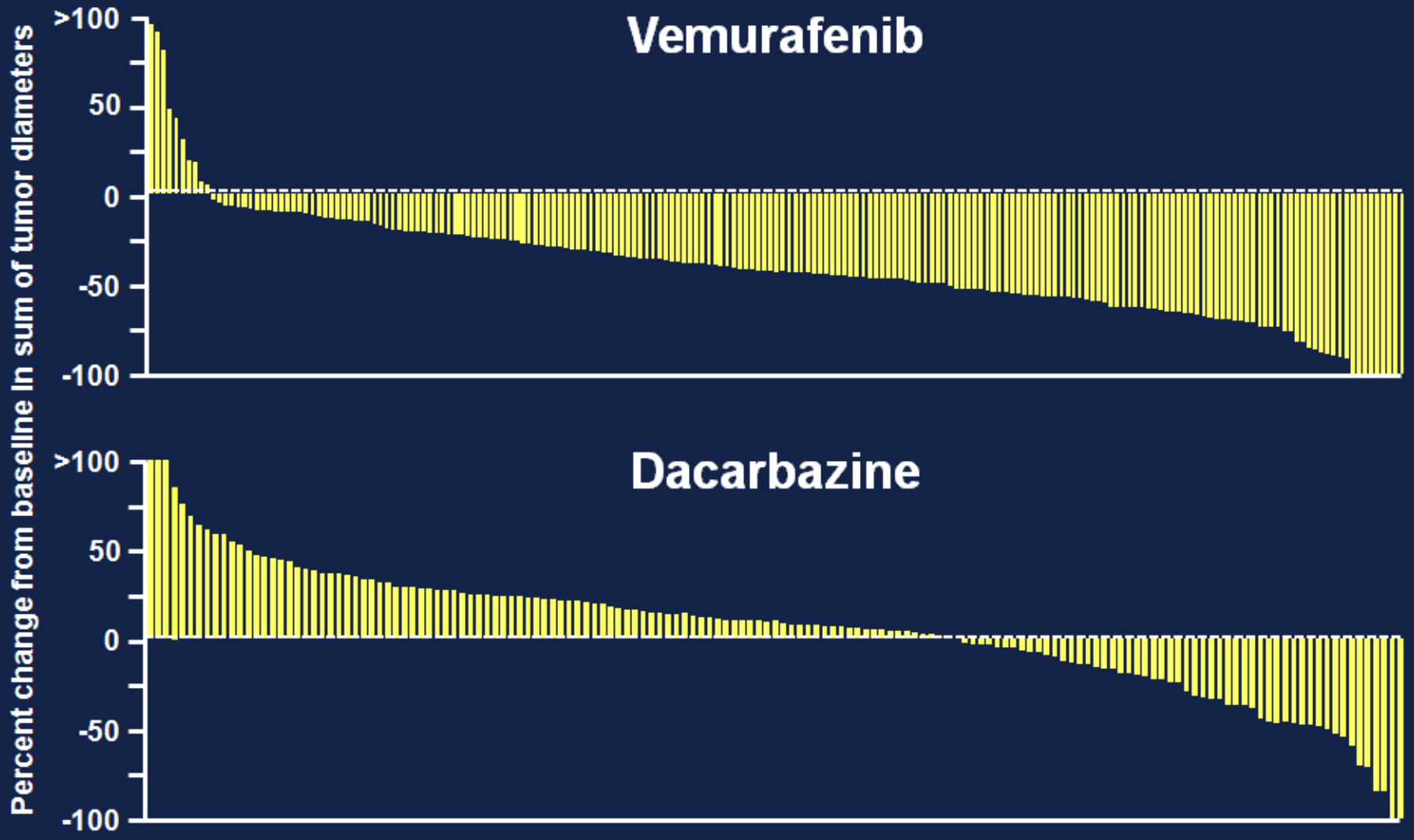
No. of patients in follow up

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

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



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

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Vemurafenib (Zelboraf®, Roche)

- Zulassungsgesuche eingereicht
- Vorrangige Prüfung der FDA
- Aktuell Early Access Programm (EAP)

- Weitere BRAF-Inhibitoren in Entwicklung
- z.B. GSK2118436 (aktuell Phase-III-Studie)

CCC Comprehensive Cancer Center
Erlangen-Nürnberg

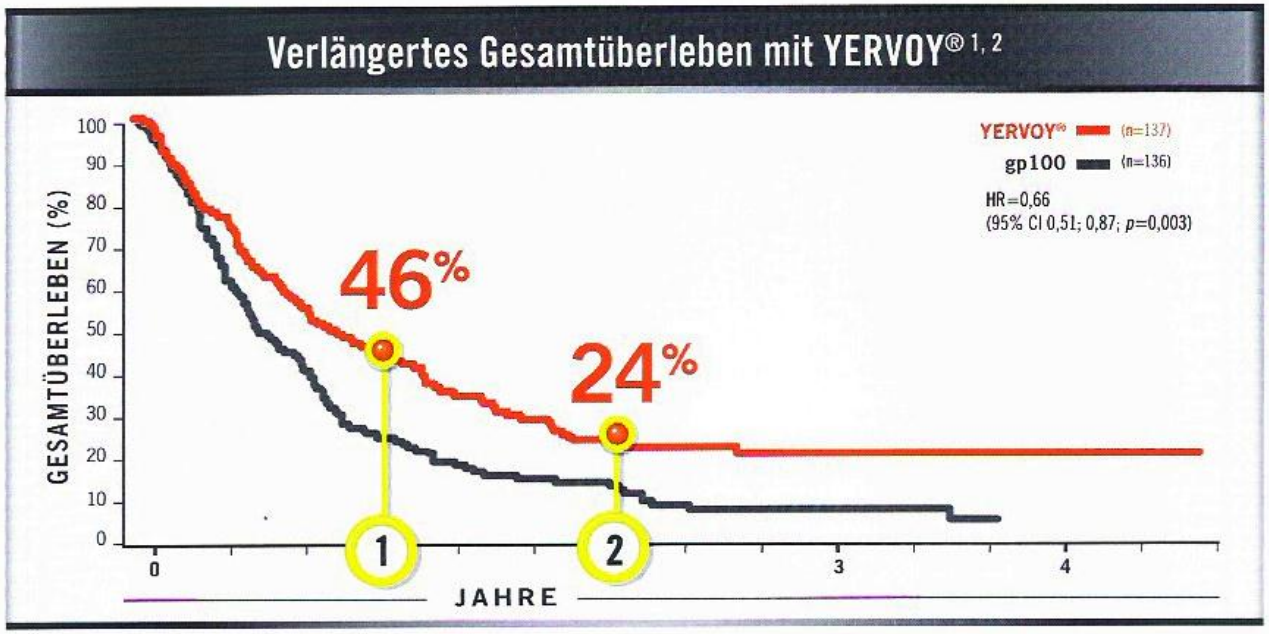
Immunotherapy: The **Message** is **not** the Median

- Ipilimumab phase III second line trial MDX020 median OS
  - 6.4→10 months HR.68 (Hodi et al. 2010)
- Ipilimumab+Dacarbazine phase III first-line trial median OS
  - 9.1→11.2 mos HR .72 (Wolchok et al., 2011)
- Impact upon the **tail of the curve** past 2 years is ultimate goal….?'cure' for >10%?

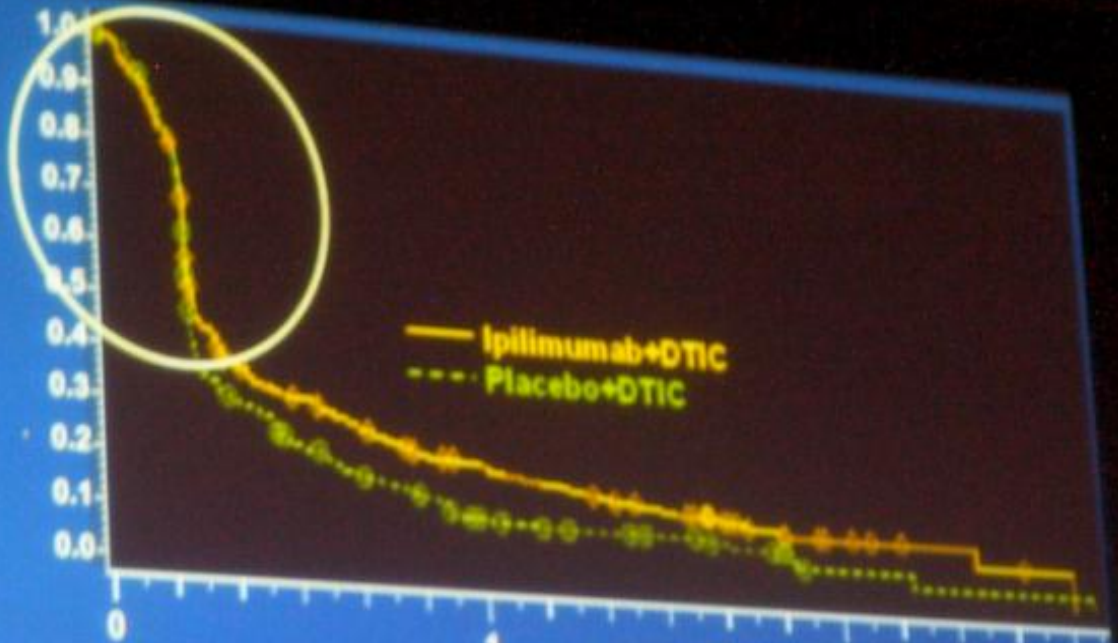
Immunotherapy: The Message is not the Median

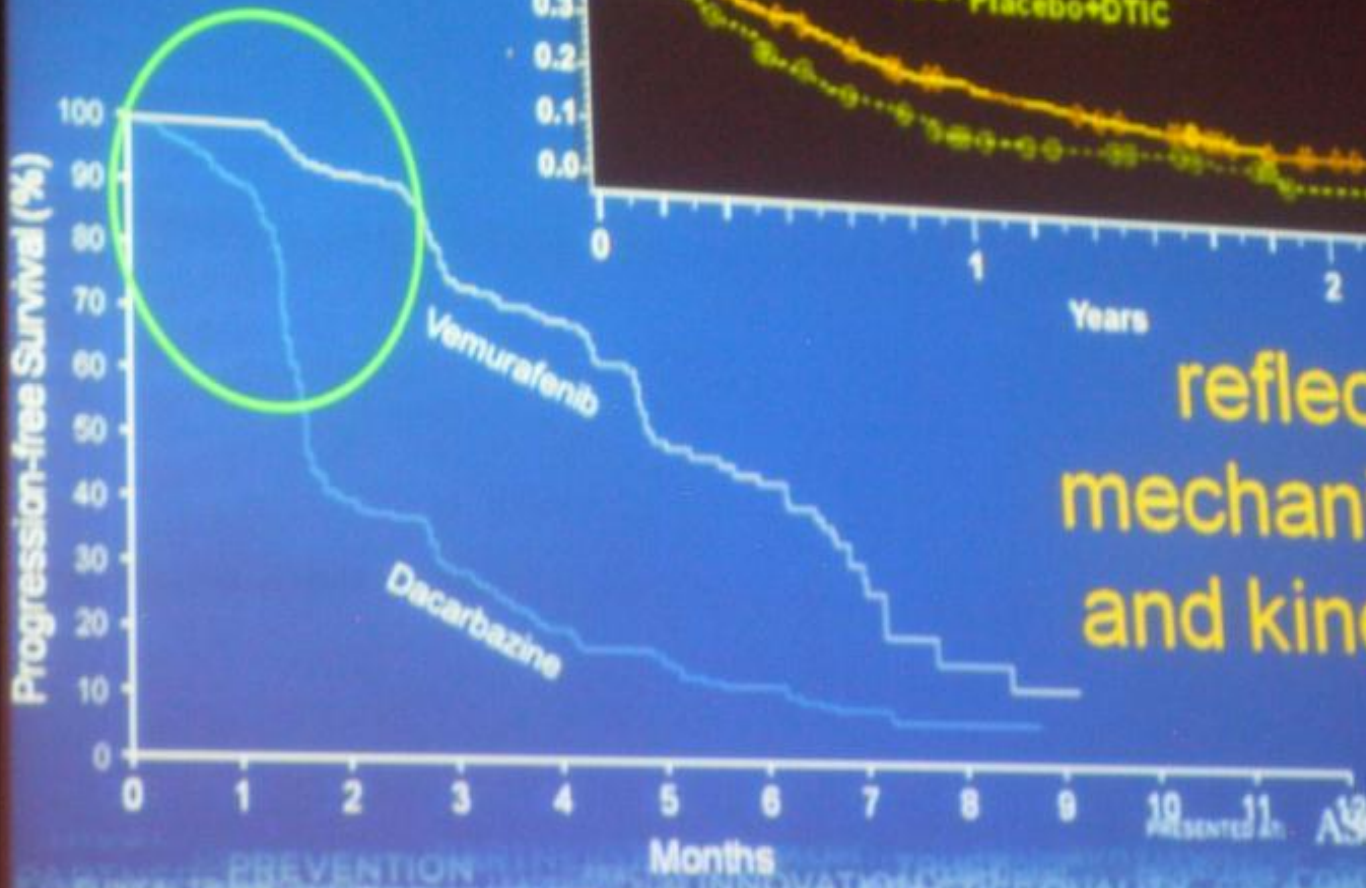
... second line trial

Studie MDX010-20: Gesamtüberleben[1]



PFS curves





reflect mechanisms and kinetics

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Behandlungsalgorythmus für Stadium IV Melanom

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	Tumorlast +++ Dynamik +++	**Tumorlast + Dynamik +**
BRAF +	**KI**	**?**
BRAF -	**?**	**Ipi**

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Behandlungsalgorythmus für Stadium IV Melanom

Universitätsklinikum Erlangen

	Tumorlast +++ Dynamik +++	**Tumorlast + Dynamik +**
BRAF +	**KI** **KI -> Ipi**	**Ipi -> KI**
BRAF -	**?**	**Ipi**

Kosten ??

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MM Stadium IV: Therapieoptionen für BRAF -

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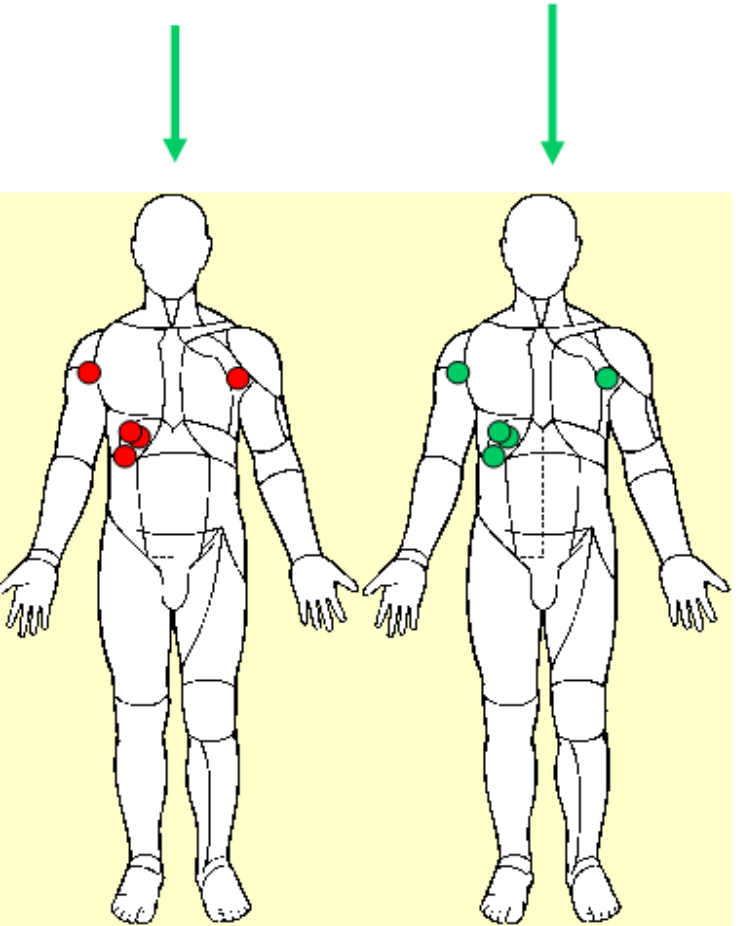
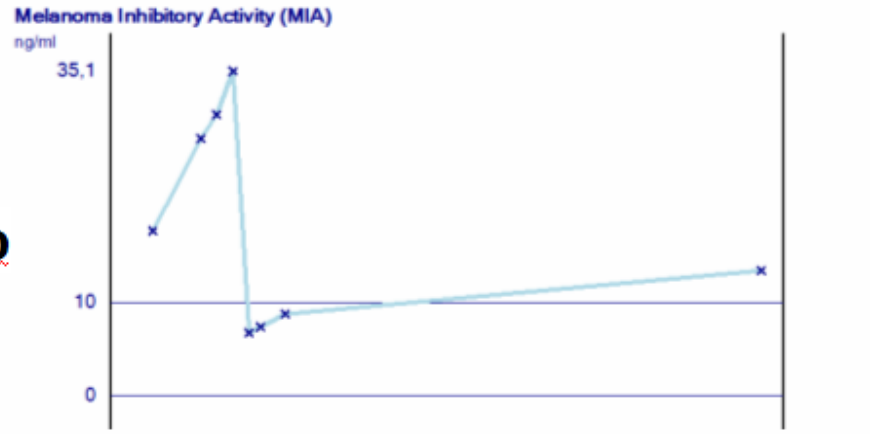
DTIC 01/07 – 03/07
+ Sorafenib 4/07: CR



2 yrs Sorafenib only

Patient:
Geburtsdatum: 03.11.1923 Aufnahme: 18.02.2009
Patient Nr.: 1006745005 Fall Nr.: 3003519141



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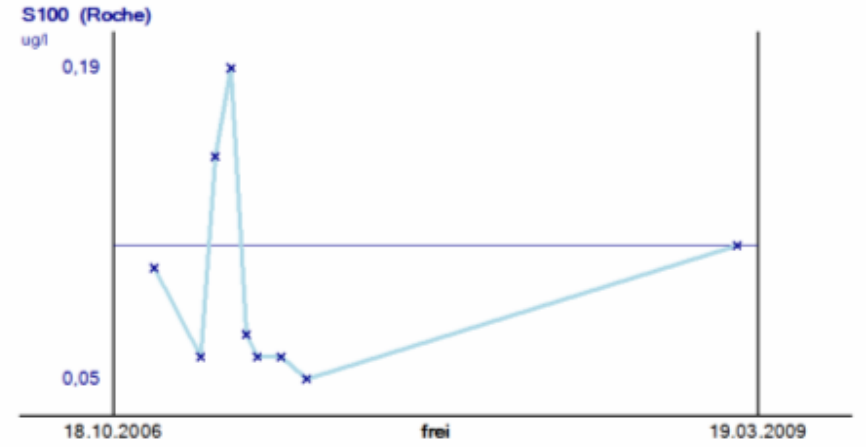

MM Stadium IV: Therapieoptionen für BRAF -

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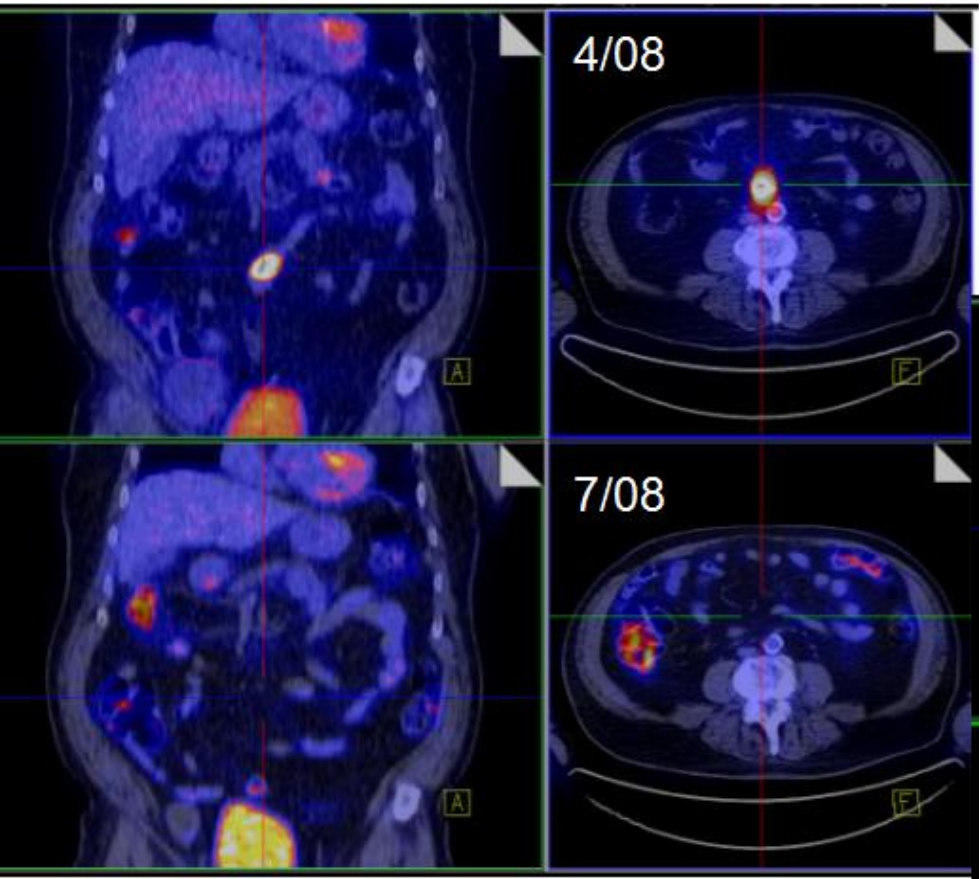
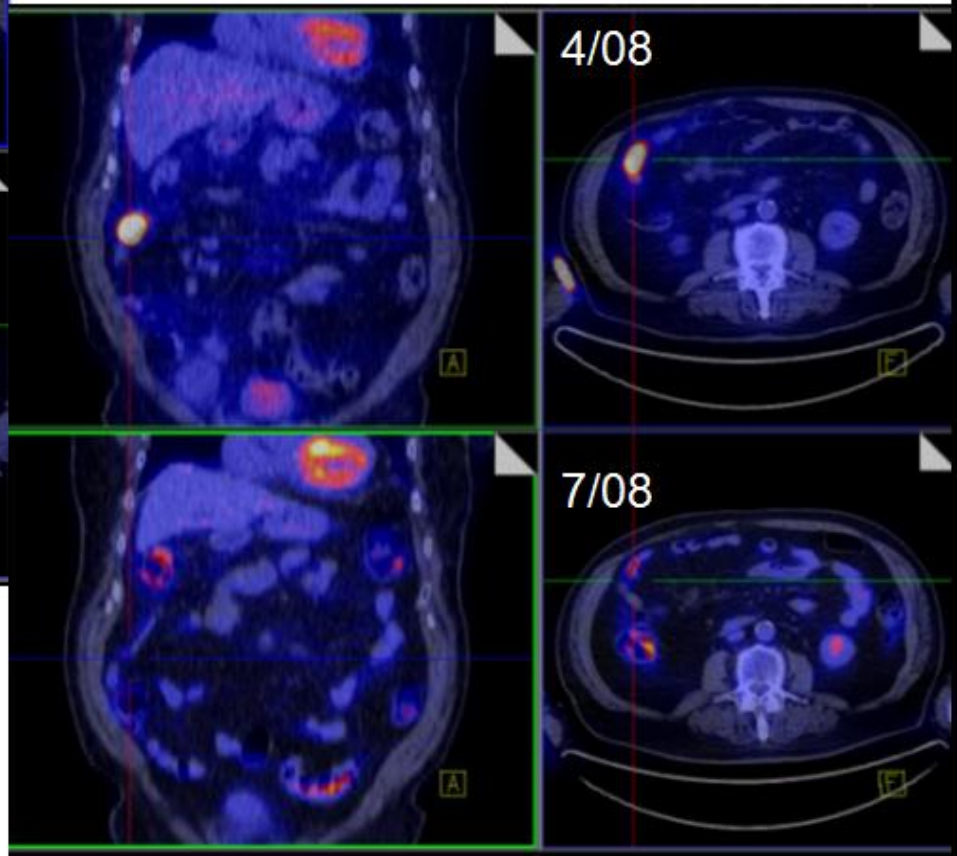
7/04 ALM pT4a,N2a
81y male, B.G.
BRAF -





drop in FDG uptake
already after 2 weeks !

MM Stadium IV: Therapieoptionen für Aderhautmelanom

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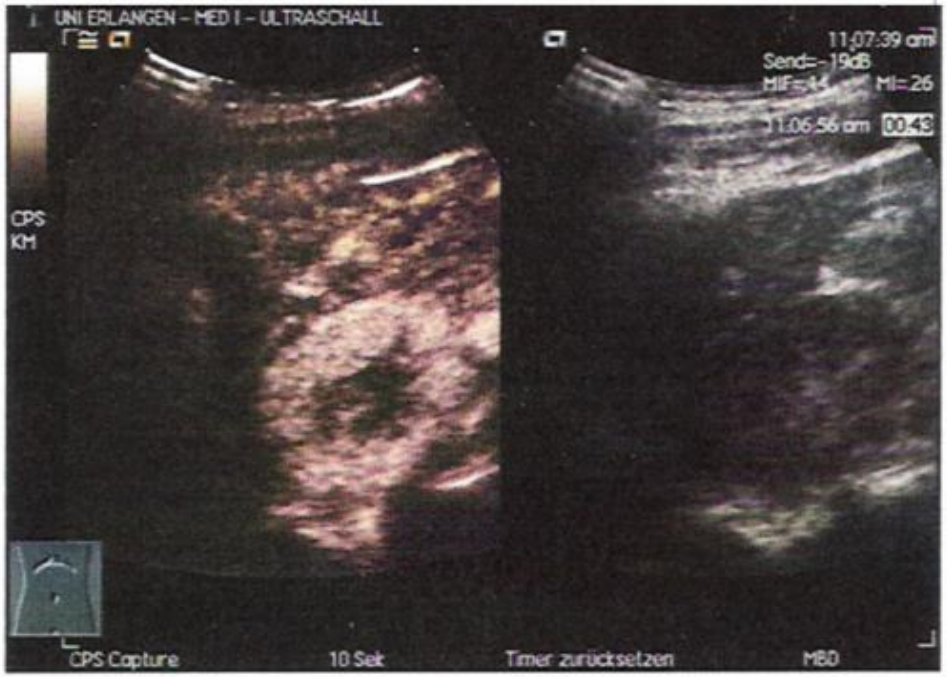
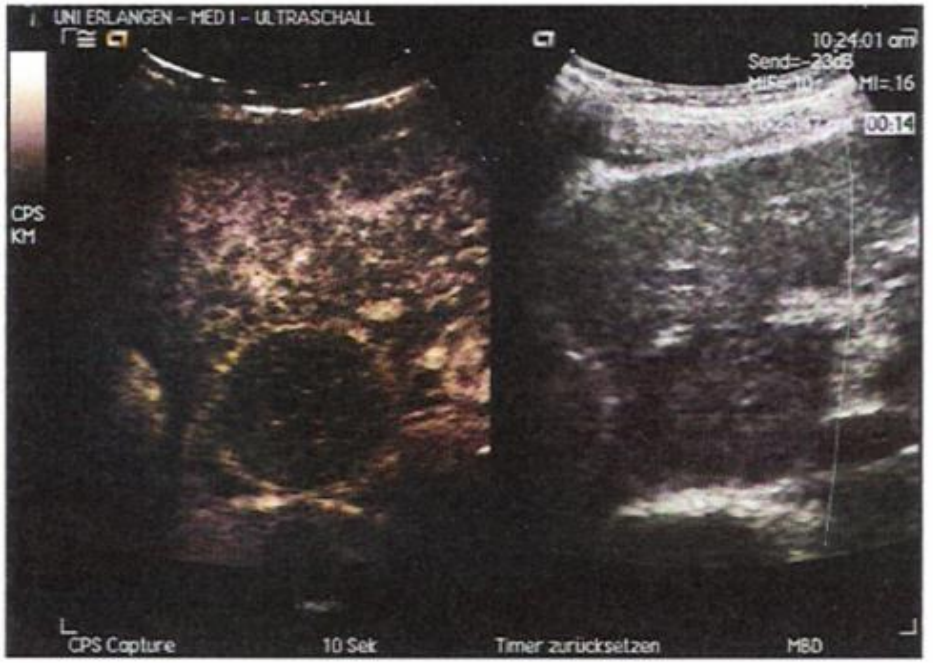


Arterielle Phase VOR Sorafenib!



Arterielle Phase hypovaskularisiert nach Sorafenib

Rapid drop in perfusion of liver metastases !

14d treatment with sorafenib 200mg 2x daily

Ongoing Trials

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Flaherty et al.
MEKi (GSK 212)
+ BRAFi (GSK436

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Ongoing Trials

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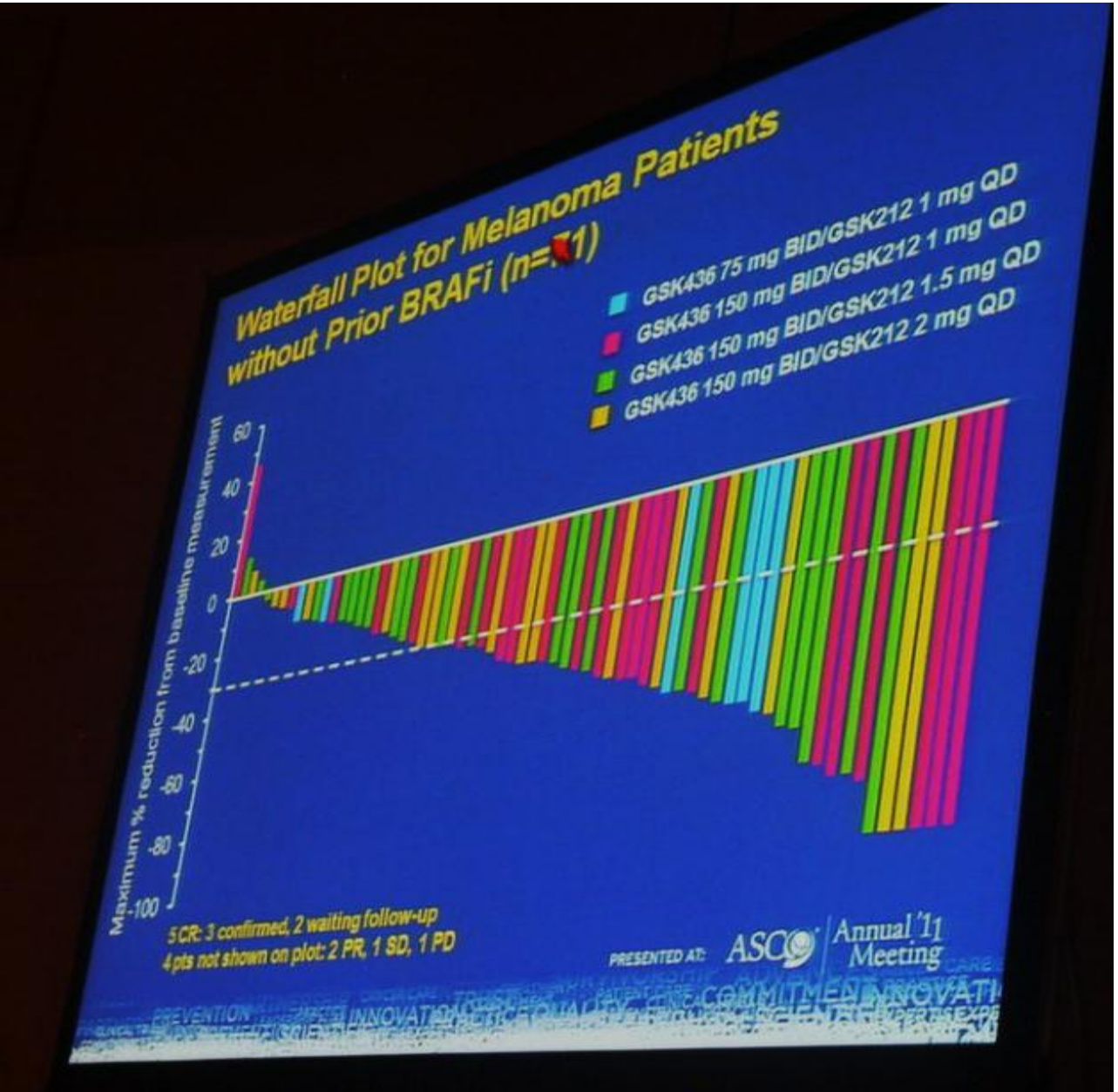

Flaherty et al.
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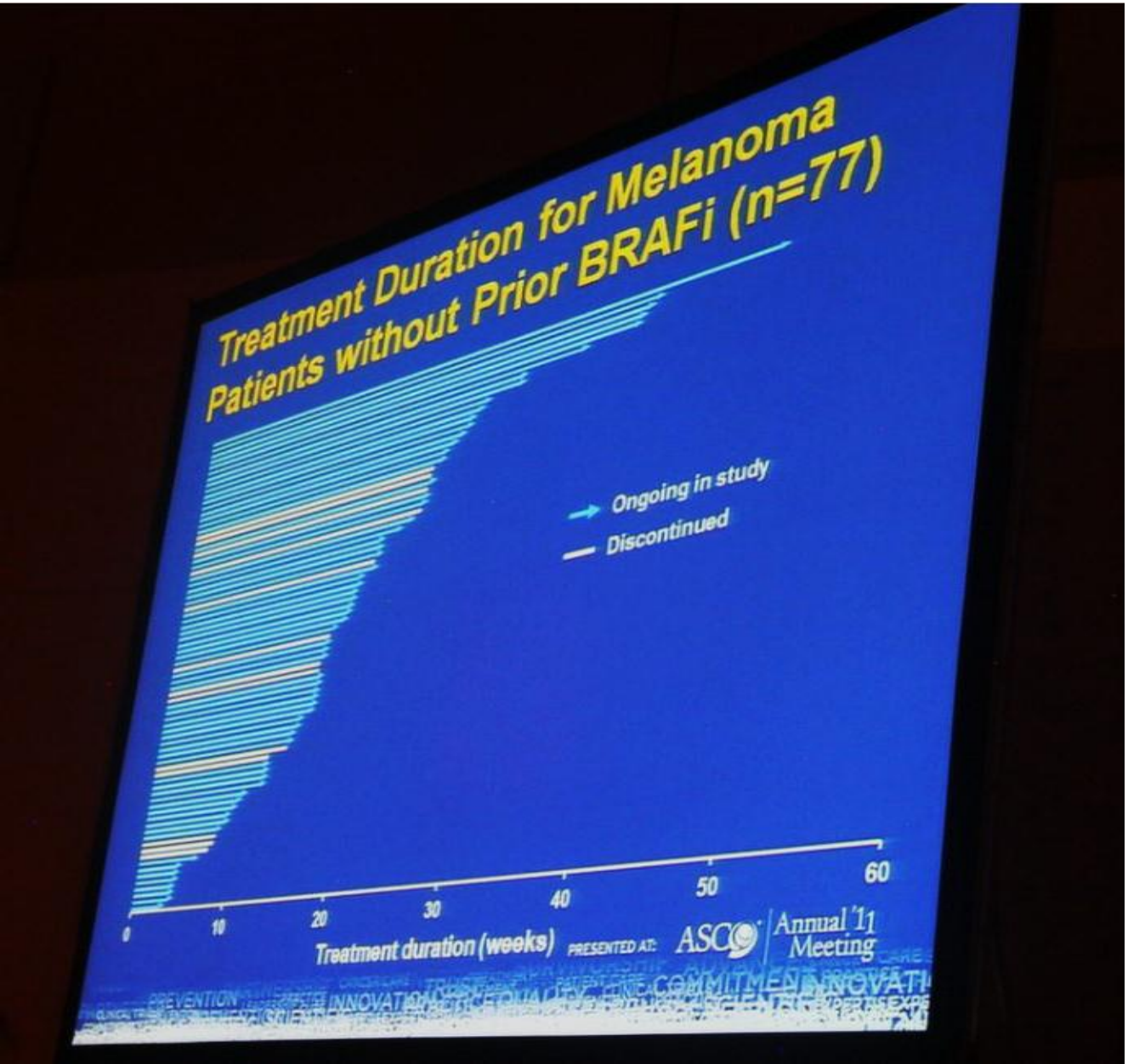

Flaherty et al.
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See you at ASCO 2012

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