From chemotherapy to targeted treatment in metastatic melanoma

Reinhard Dummer, Lea Felderer, Jeannine Rinderknecht, Nina Eggmann, Simone Goldinger, Merlin Guggenheim, Daniela Mihic, Lars French, Joanna Mangana, Mitch Levesque

Department of Dermatology, Zürich, Switzerland

DKG KREBSGESELLSCHAFT
Zertifiziertes Hautkrebszentrum

University Hospital Zurich

Cancer Network zürich

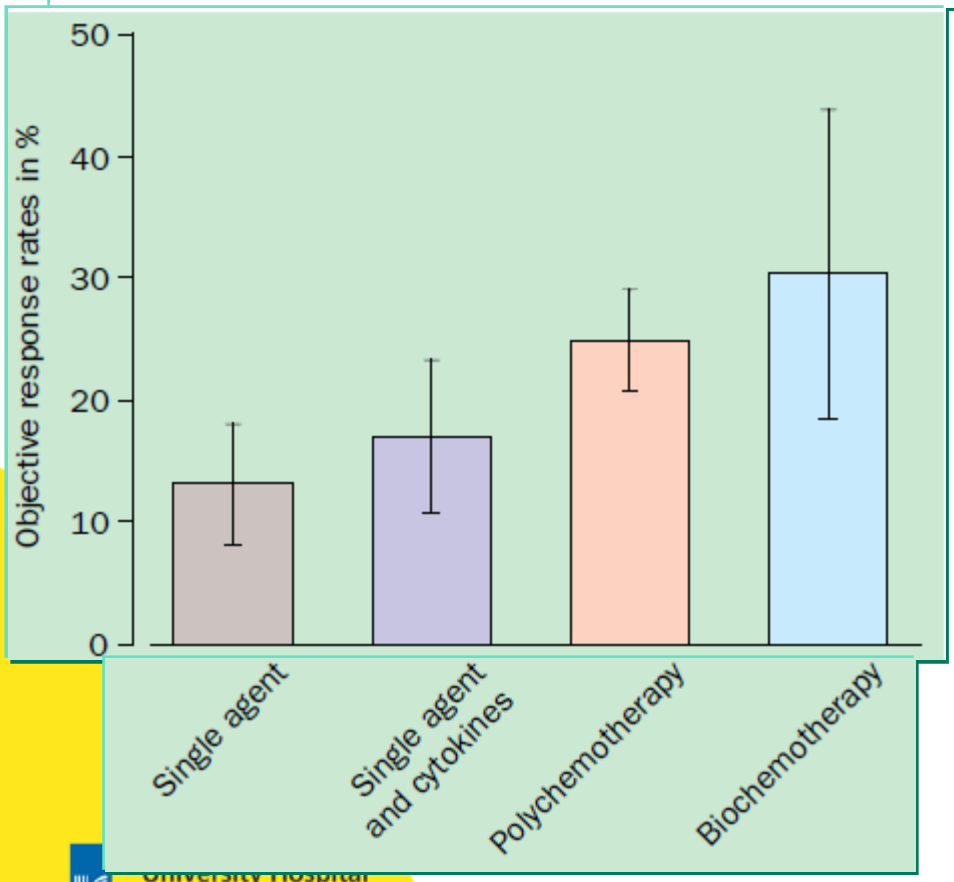
Schwerpunkt Hautkrebs
Dermatologische Klinik
UniverstätsSpital Zürich

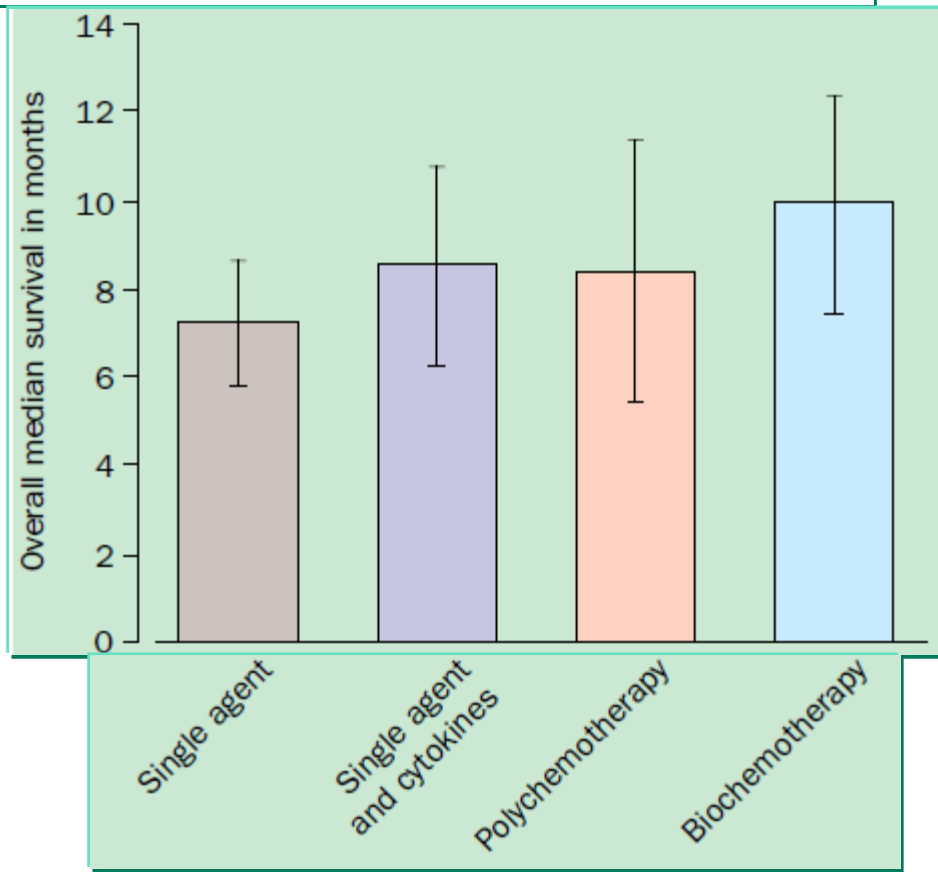
Chemotherapy in melanoma: common drugs

- Dacarbazine, temozolomide
- Vincristine
- Cisplatin and carboplatin
- Paclitaxel, Abraxane
- Lomustine, Fotemustine

Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials

Thomas K Eigentler, Ulrich M Caroli, Peter Radny, and Claus Garbe





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THE LANCET Oncology Vol 4 December 2003

Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV melanoma: Final results of a randomised phase III study (EORTC 18032)

Poulam M. Patel [a,], Stefan Suciu [b], Laurent Mortier [c], Wim H. Kruit [d], Caroline Robert [e], Dirk Schadendorf [f], Uwe Trefzer [g], Cornelis J.A. Punt [h], Reinhard Dummer [i], Neville Davidson [j], Juergen Becker [k], Robert Conry [l], John A. Thompson [m], Wen-Jen Hwu [n], Kristel Engelen [b], Sanjiv S. Agarwala [o], Ulrich Keilholz [p], Alexander M.M. Eggermont [q], Alain Spatz [r], on behalf of the EORTC Melanoma Group*

Eur J Cancer 2011

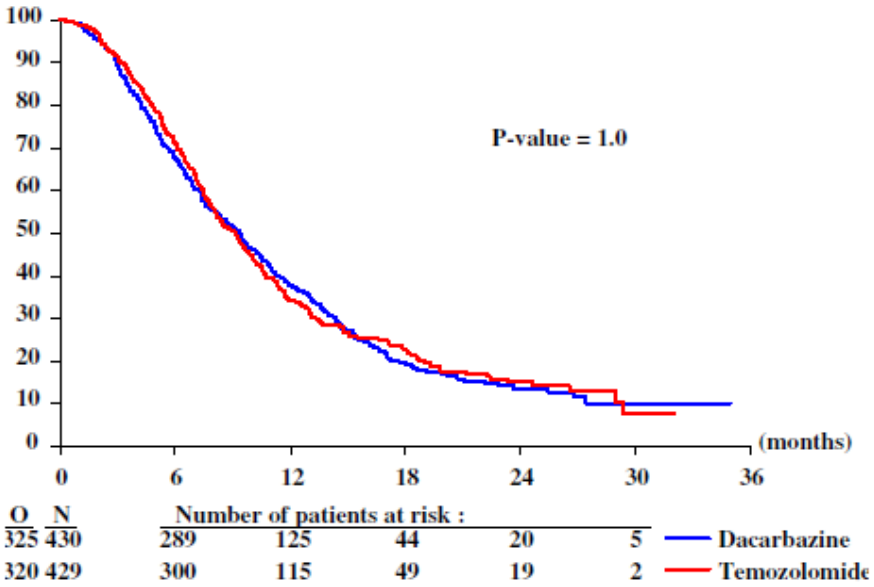


Fig. 3A – Overall survival by treatment group. O, observed

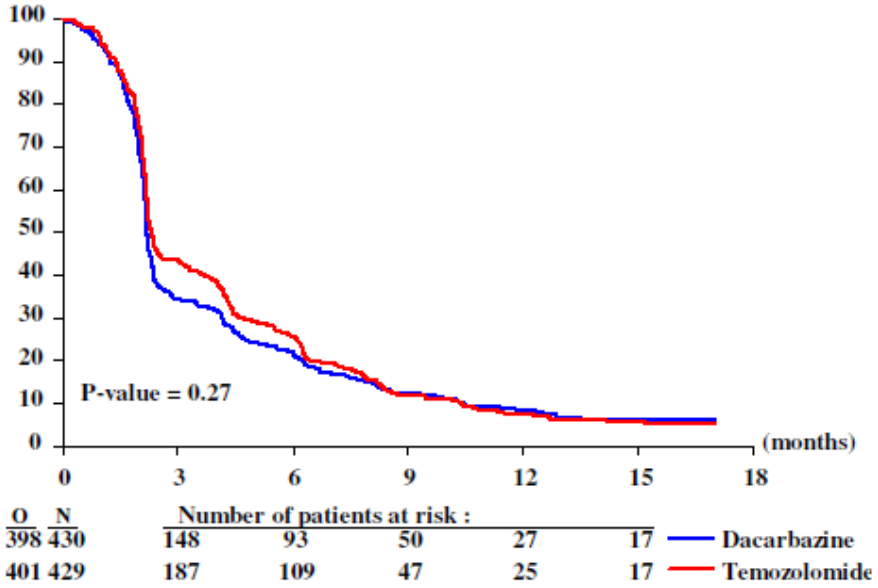
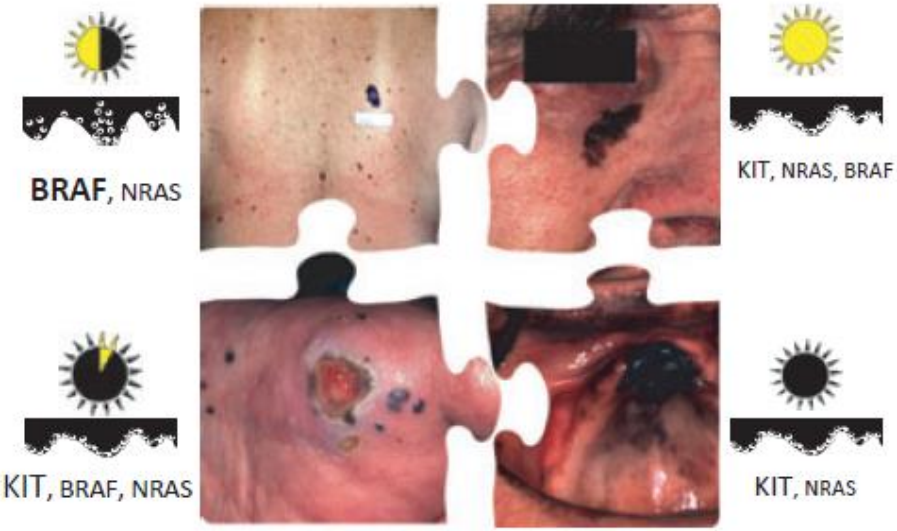


Fig. 3B – Progression-free survival. O, observed number of

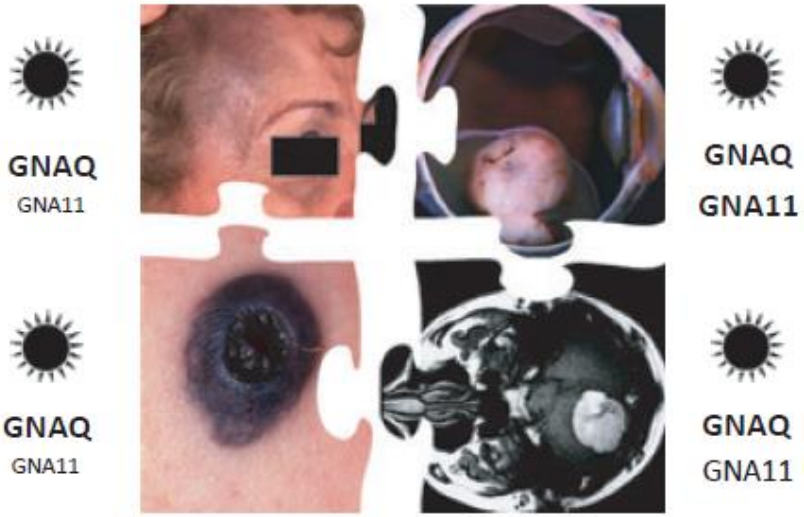
The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin

David C. Whiteman[1], William J. Pavan[2] and Boris C. Bastian[3]

Melanomas arising from melanocytes associated with epithelia



Melanomas arising from melanocytes not associated with epithelia



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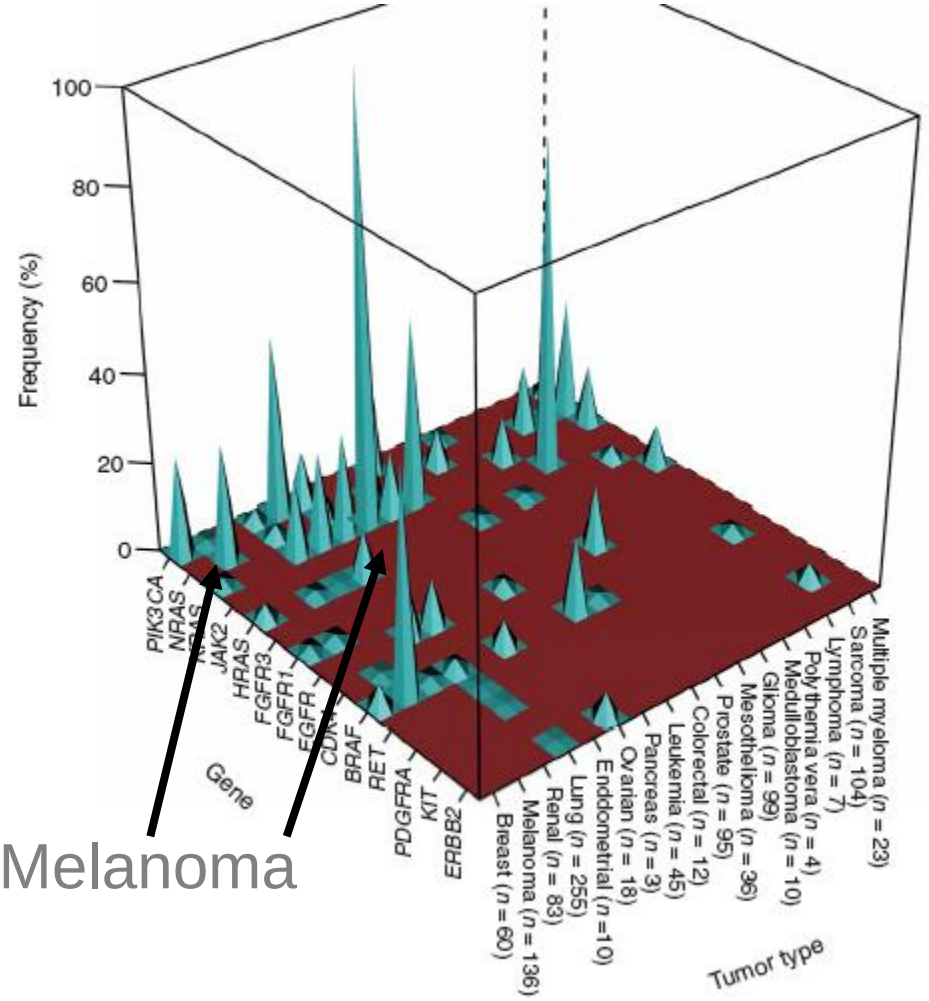
Pigment Cell Melanoma Res. **24**; 879–897

High-throughput oncogene mutation profiling in human cancer



Melanoma

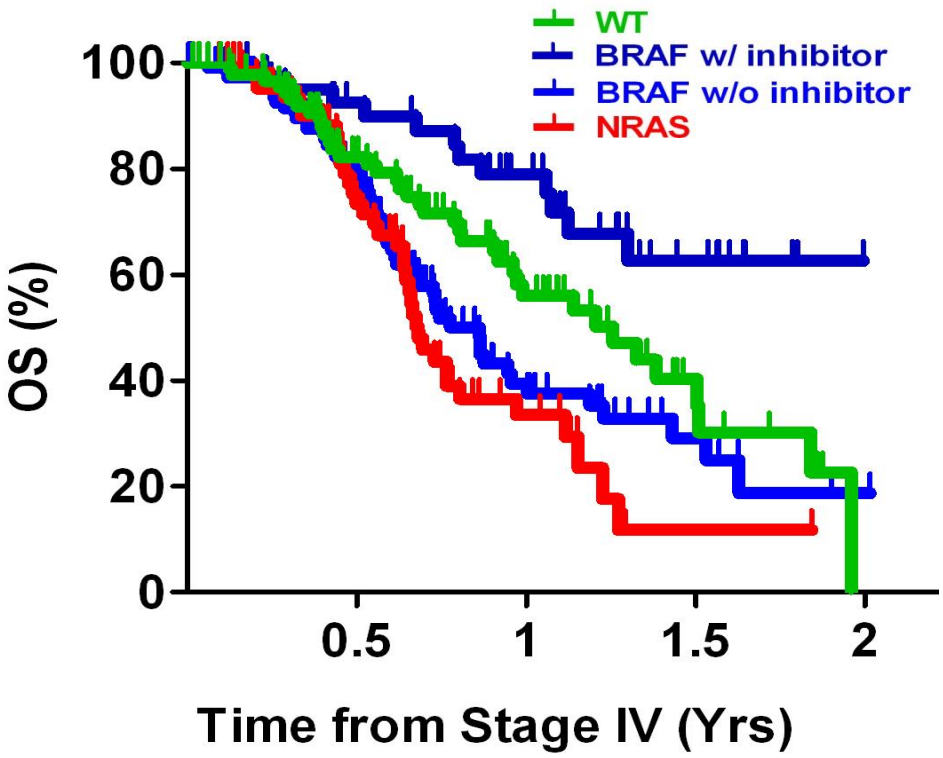
b

RAS^{mt} +	RAS^{mt} −	
0	77	$BRAF^{600–601}$
4	3	$BRAF^{non600–601}$

$P = 1.8 \times 10^{-5}$

Figure 1 Frequencies of oncogene mutations across human tumor types.

Survival of Patients With B-RAF- or N-RAS-Mutant Melanoma (N = 313)



	N	Median OS (y)	*P*
WT	94	1.3	------
B-RAF with inhibitor	41	NR	.02
B-RAF without inhibitor	112	0.9	.10
N-RAS	66	0.7	.003

Inhibitors: PLX-4032;GSK-2118436;GSK-1120212;AZD-6244.

OS for N-RAS vs WT

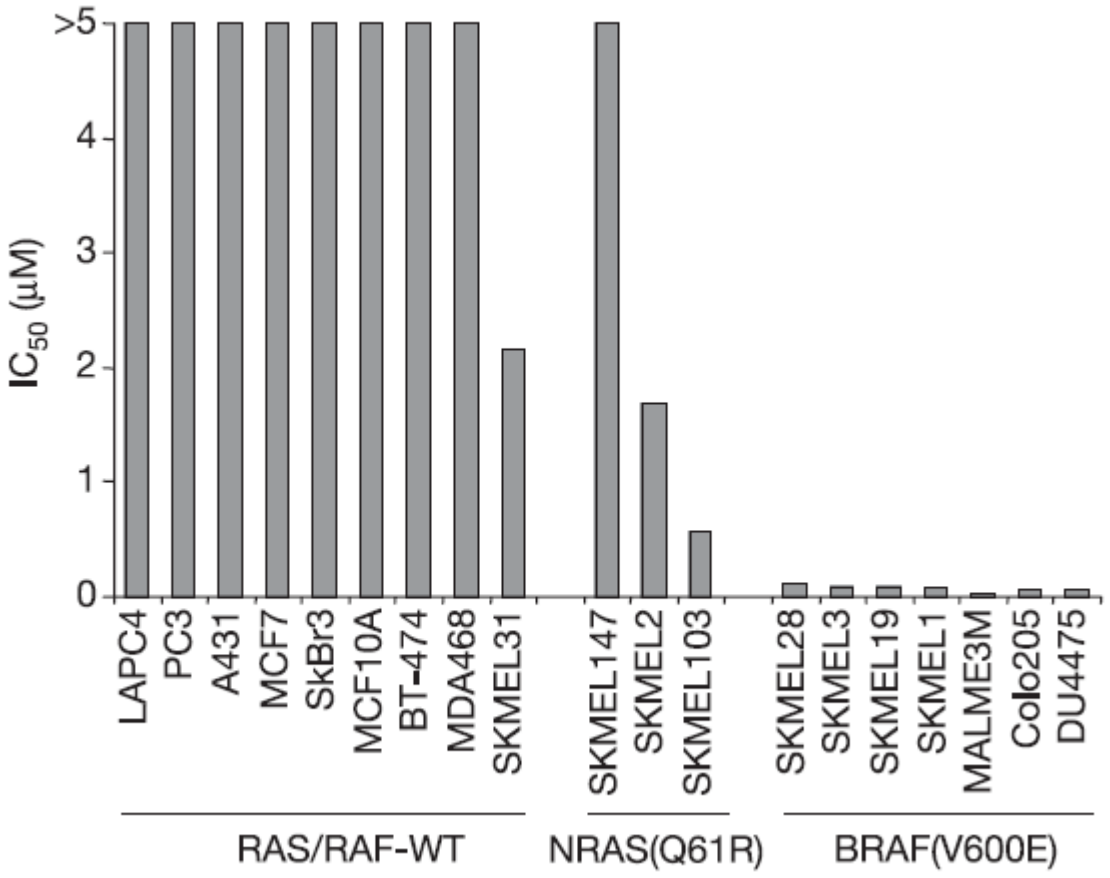
N-RAS: Candidate as a new prognostic marker for stage IV?

Jakob JA, et al. *Cancer* 2012

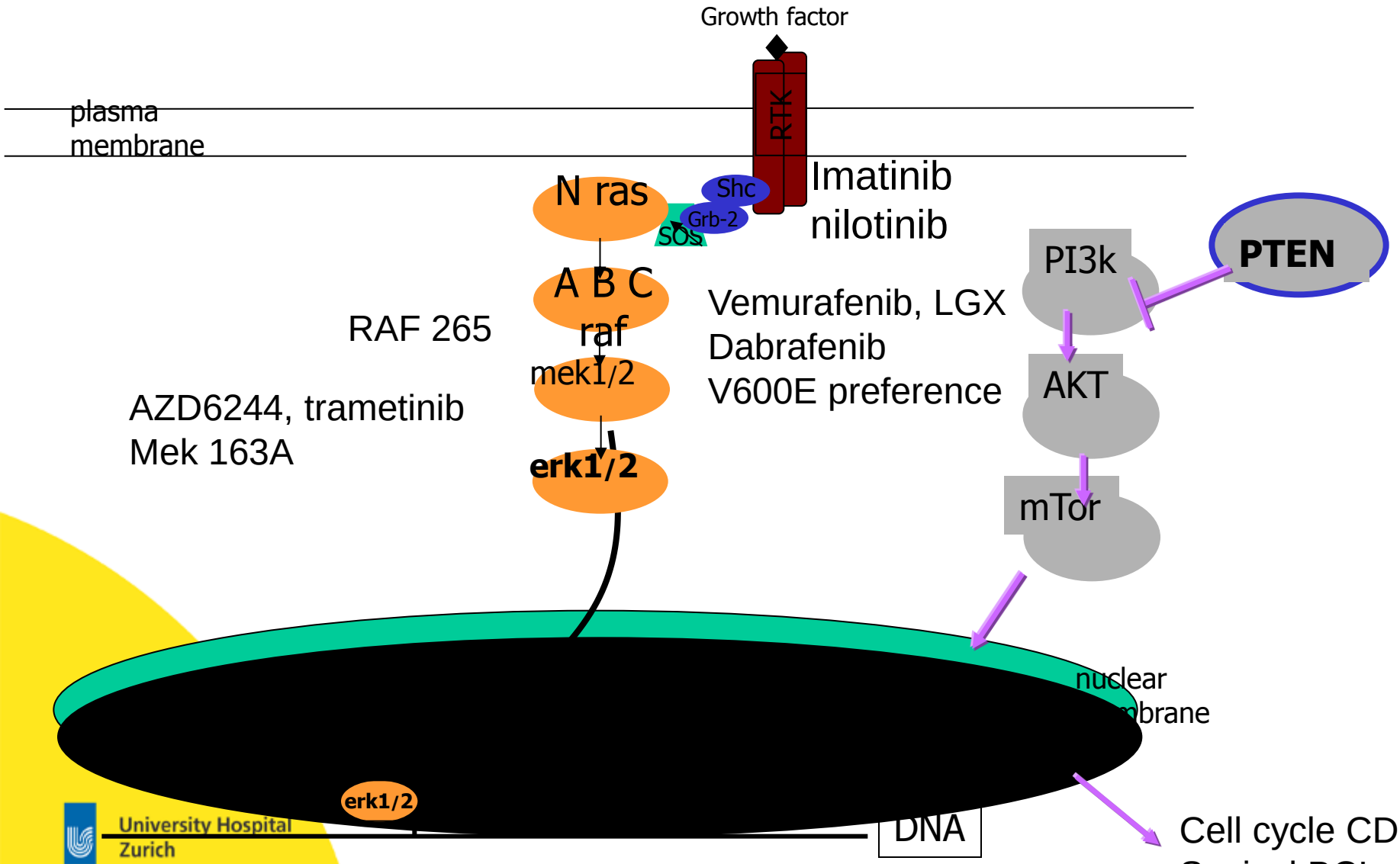
BRAF mutation predicts sensitivity to MEK inhibition

David B. Solit[1,3], Levi A. Garraway[4,6], Christine A. Pratilas[2,3], Ayana Sawai[3], Gad Getz[6], Andrea Basso[3]†, Qing Ye[3], Jose M. Lobo[3], Yuhong She[3], Iman Osman[7], Todd R. Golub[5,6], Judith Sebolt-Leopold[8], William R. Sellers[4,6] & Neal Rosen[1,3]

a



Targeting signaling pathways



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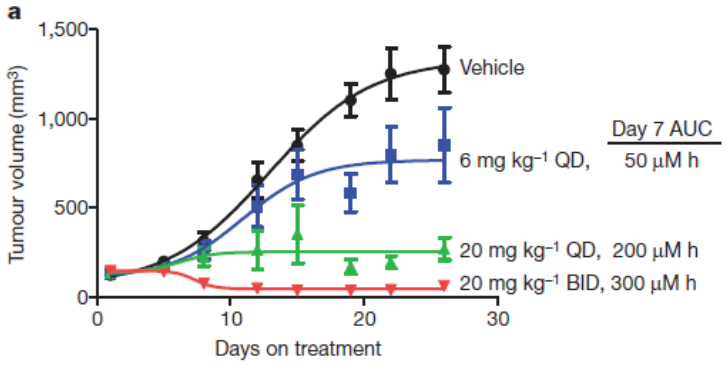
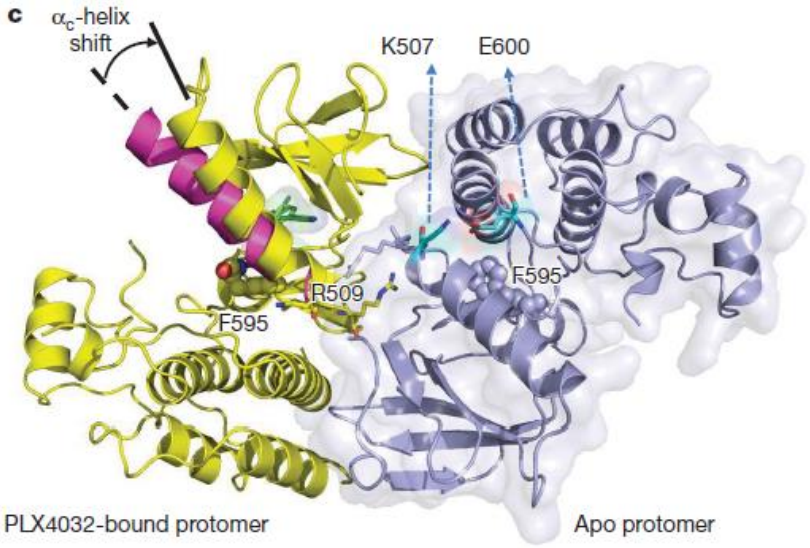
Clinical efficacy of a RAF inhibitor needs broad target blockade in *BRAF*–mutant melanoma

Gideon Bollag[1], Peter Hirth[1], James Tsai[1], Jiazhong Zhang[1], Prabha N. Ibrahim[1], Hanna Cho[1], Wayne Spevak[1], Chao Zhang[1], Ying Zhang[1], Gaston Habets[1], Elizabeth A. Burton[1], Bernice Wong[1], Garson Tsang[1], Brian L. West[1], Ben Powell[1], Rafe Shellooe[1], Adhirai Marimuthu[1], Hoa Nguyen[1], Kam Y. J. Zhang[1], Dean R. Artis[1], Joseph Schlessinger[2], Fei Su[3], Brian Higgins[3], Raman Iyer[3], Kurt D'Andrea[4], Astrid Koehler[3], Michael Stumm[3], Paul S. Lin[1], Richard J. Lee[3], Joseph Grippo[3], Igor Puzanov[5], Kevin B. Kim[6], Antoni Ribas[7], Grant A. McArthur[8], Jeffrey A. Sosman[5], Paul B. Chapman[9], Keith T. Flaherty[4]†, Xiaowei Xu[4], Katherine L. Nathanson[4] & Keith Nolop[1]





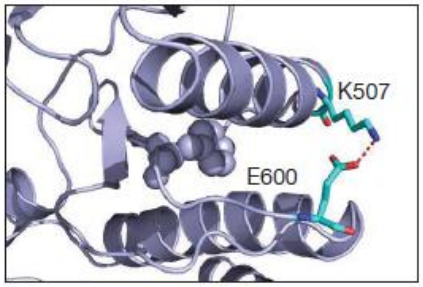


Figure 1 | Three-dimensional structure of PLX4032 binding to B-RAF(V600E). a, Chemical structure of PLX4032. b, Structure highlights the

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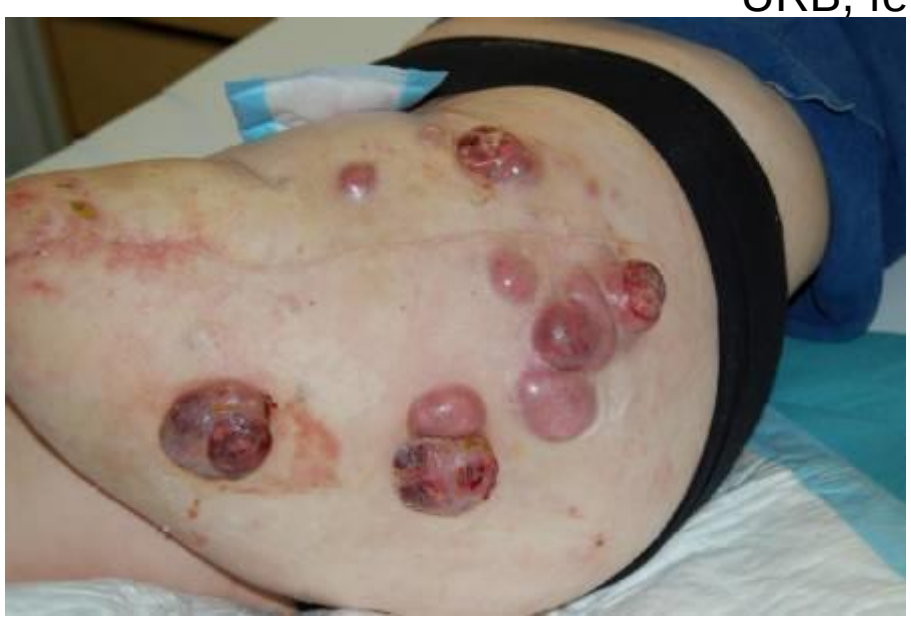
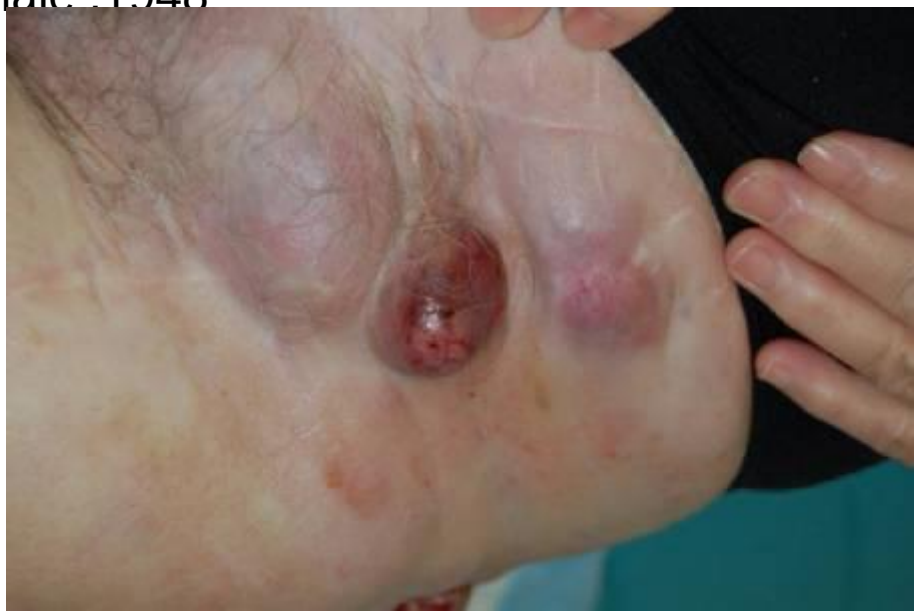
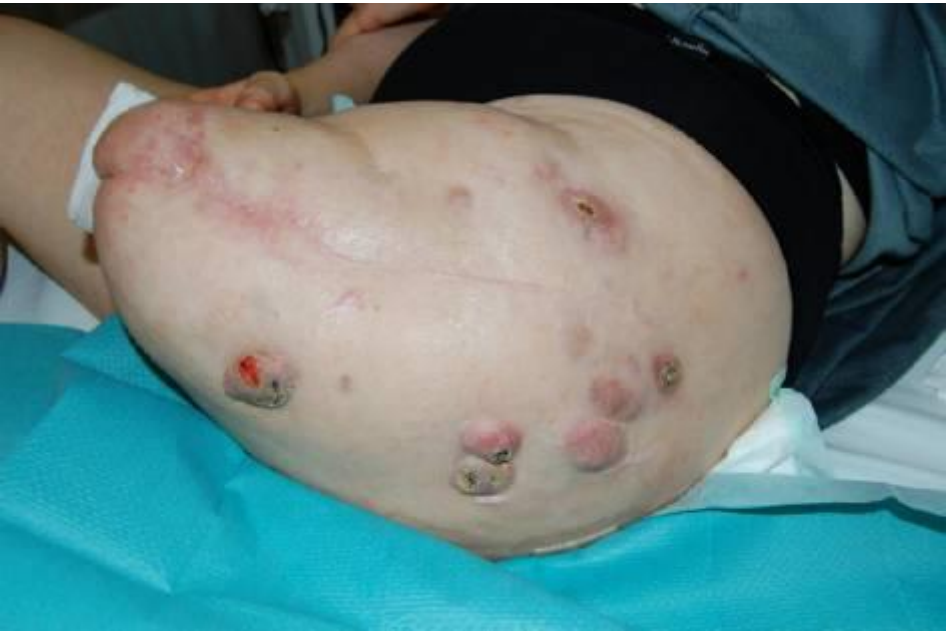
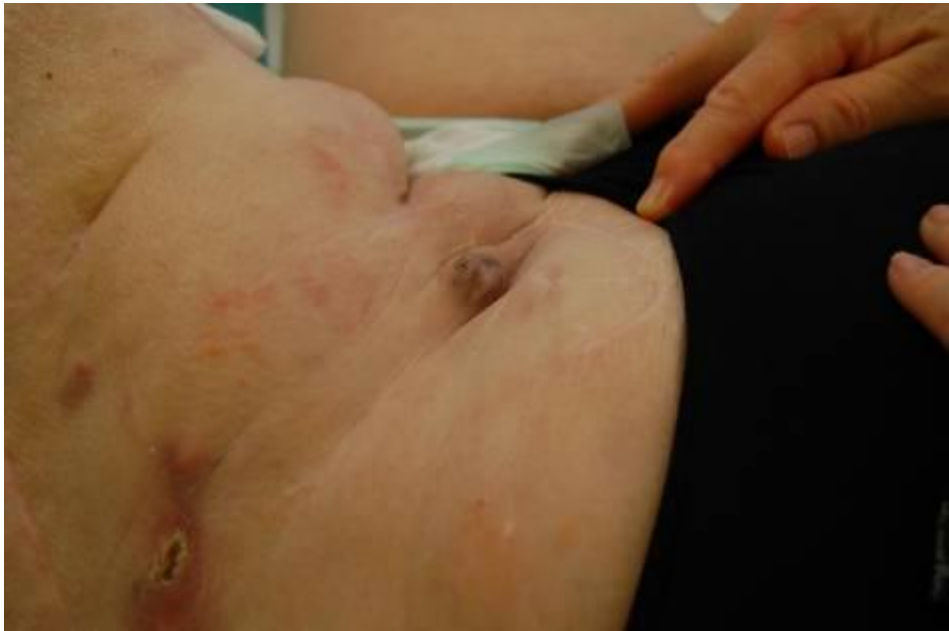
Vemurafenib – B-Raf Inhibition: Comparison Day 0 – Day 17

URB, female, 1948









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*

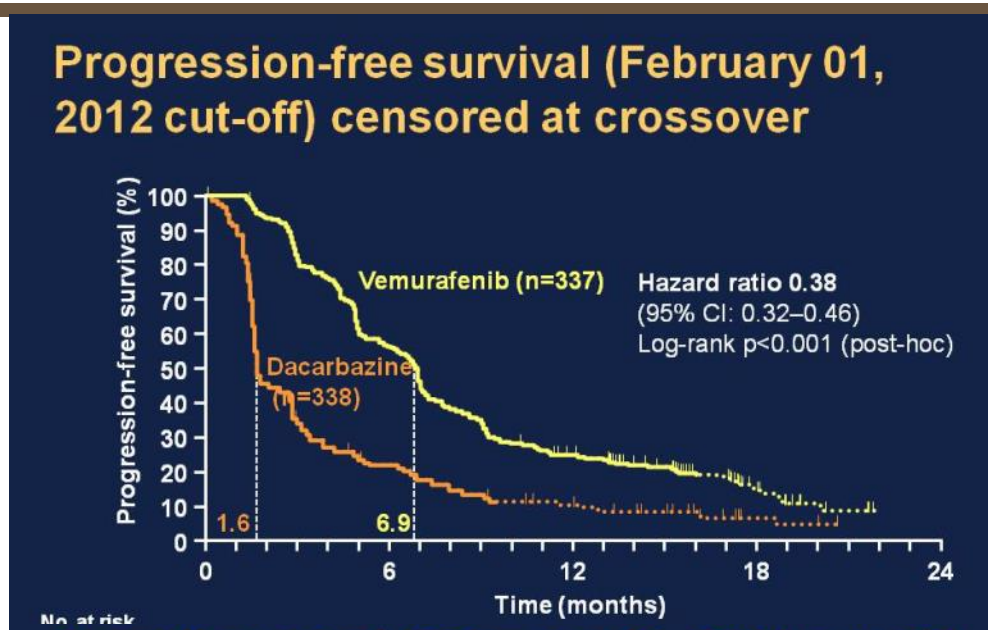
This article (10.1056/NEJMoa1103782) was published on June 5, 2011, at NEJM.org.

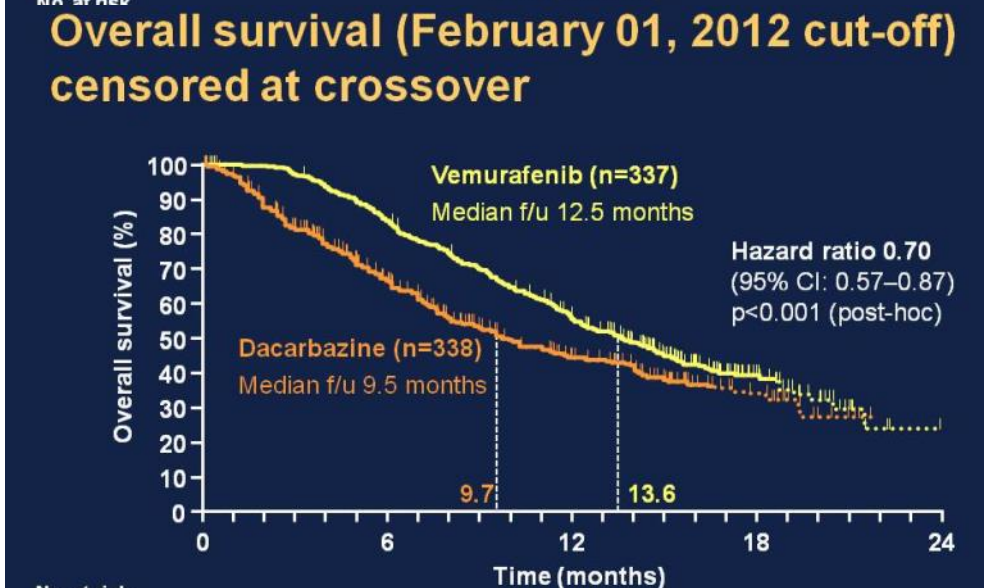
N Engl J Med 2011.

BRIM-3 Phase III study

Vemurafenib (BRAF inhibitor) in BRAF^{V600E}-mutant melanoma: results

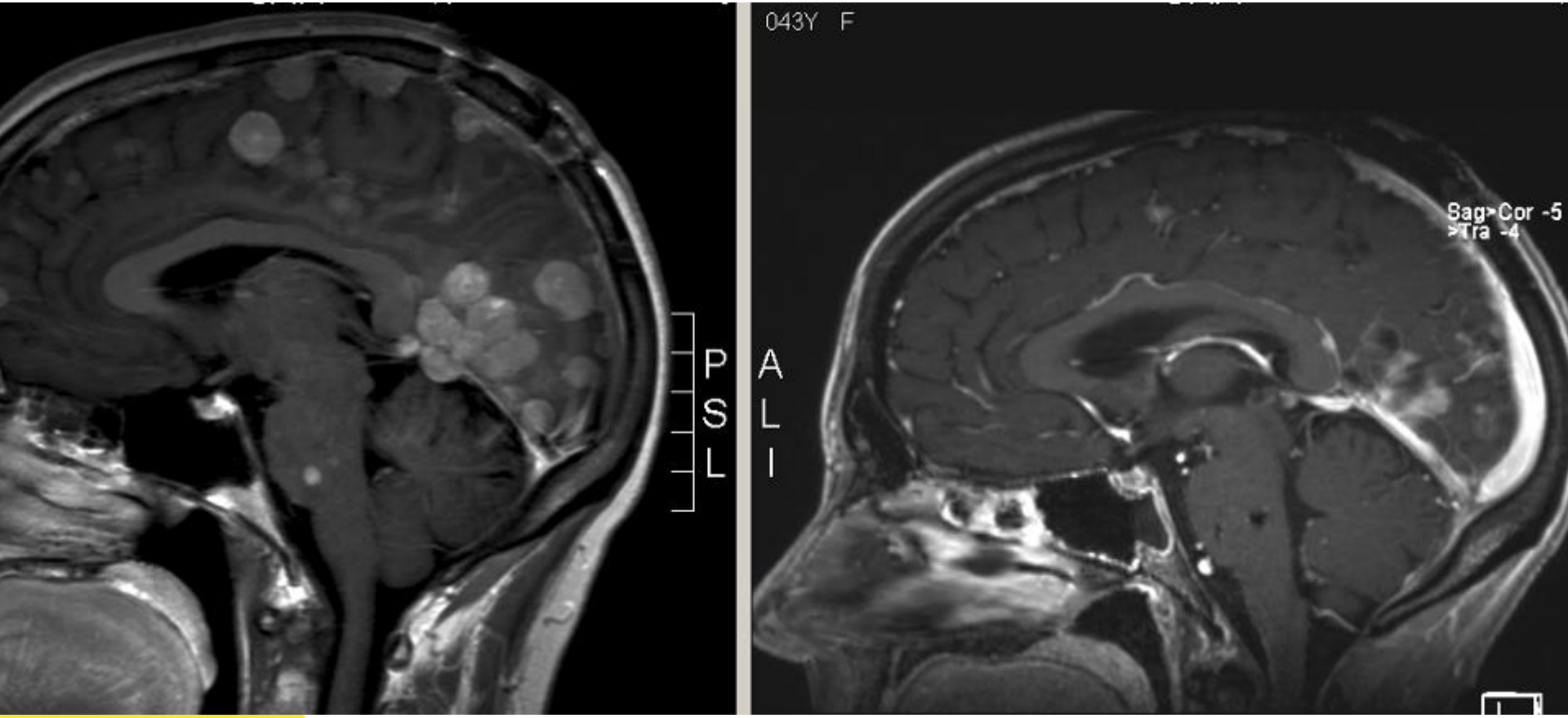
- PFS and OS
  - Median PFS was 6.9 and 1.6 months for vemurafenib and DTIC, respectively (*P*<0.001)
  - PFS advantage remains after considering baseline characteristics
  - Median OS was 13.6 and 9.7 months for vemurafenib and DTIC, respectively (*P*<0.001); HR 0.7 in favor of vemurafenib
  - OS still highly significant when accounting for crossover to vemurafenib
  - OS not significantly improved in patients with Stage IIIc, M1a, and M1b disease
- ORR 57% (6% CR) vs 9% for vemurafenib vs DTIC





Chapman P *et al*. *J Clin Oncol* 2012;30(15s): abstract 8502.

Vemurafenib : efficacy in the brain



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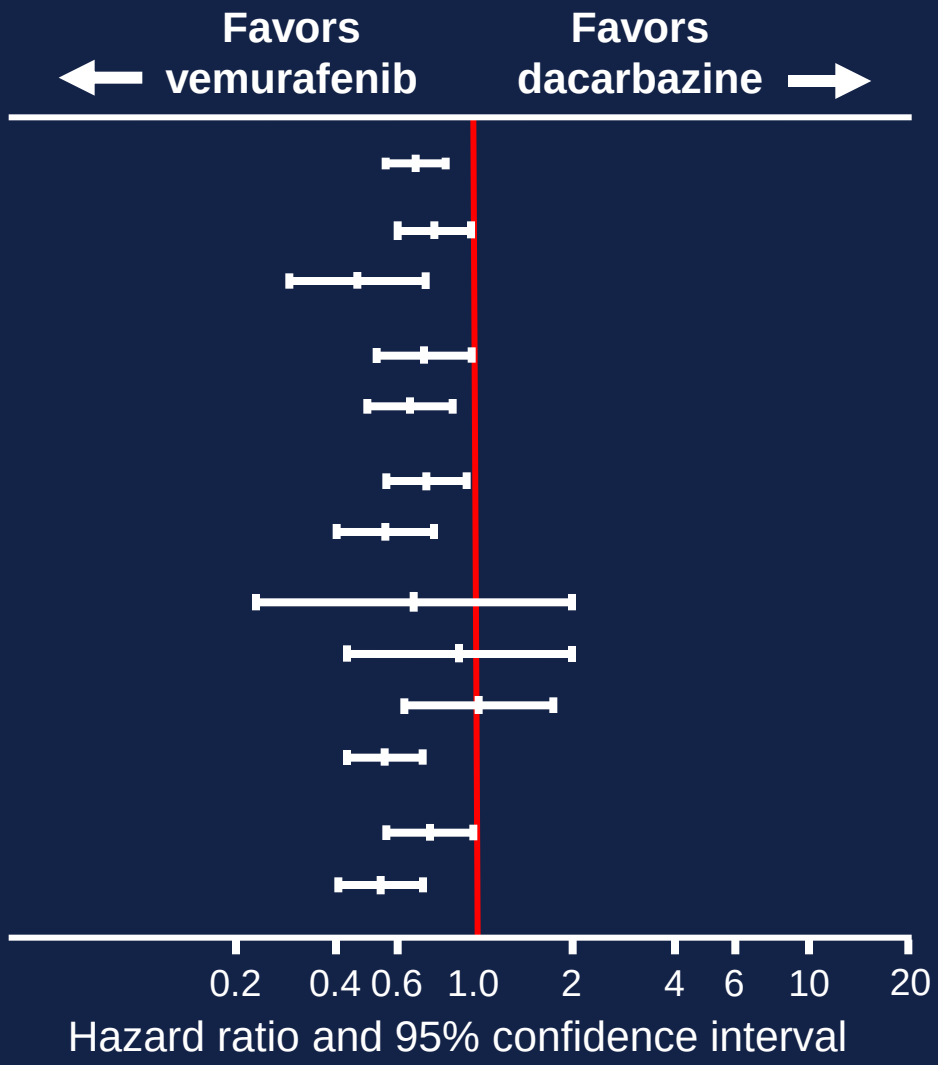
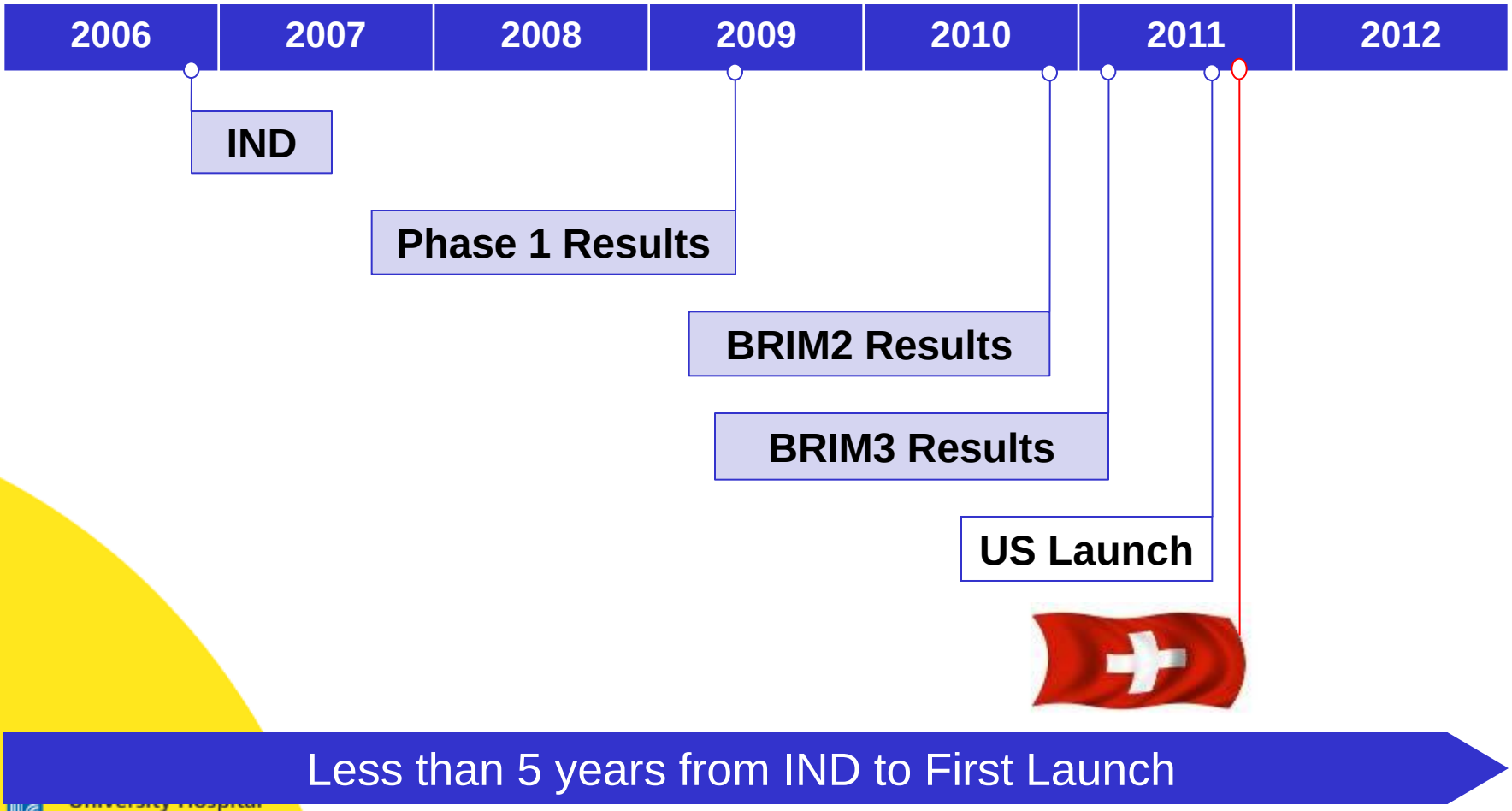
Dummer et al: A pilot study in symptomatic brain mets, ESMO 2012

Overall survival by baseline characteristic (February 01, 2012 cut-off) censored at crossover

Factor		Number of patients
All patients		675
Age:	<65 years	514
	≥65 years	161
Sex:	Female	294
	Male	381
ECOG status:	0	459
	1	216
Disease stage:	IIIc	33
	M1a	74
	M1b	127
	M1c	441
LDH:	Normal	391
	Elevated	284



Bringing Zelboraf to Patients in Record Time



Zurich

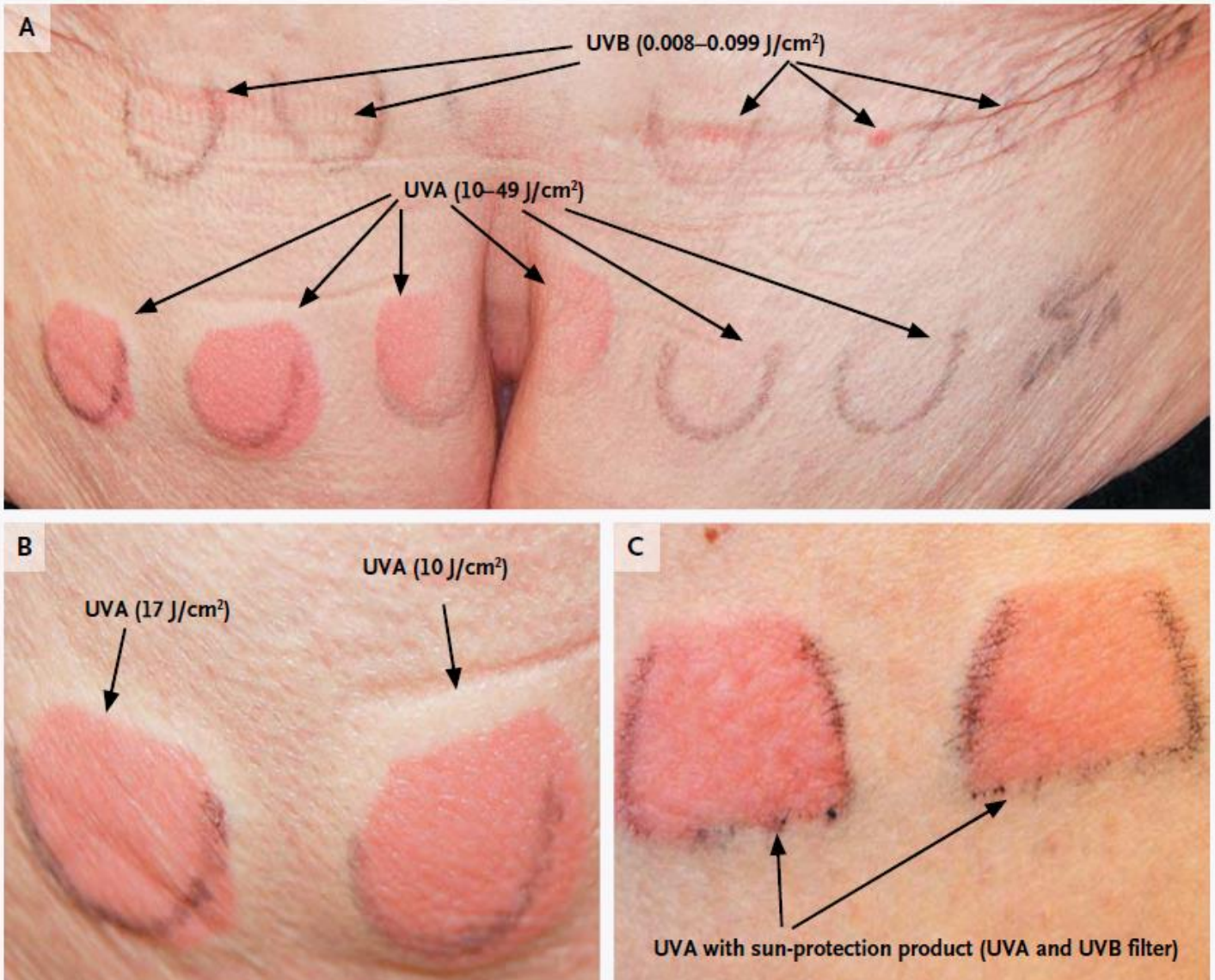
Selected adverse events (% of patients)

	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

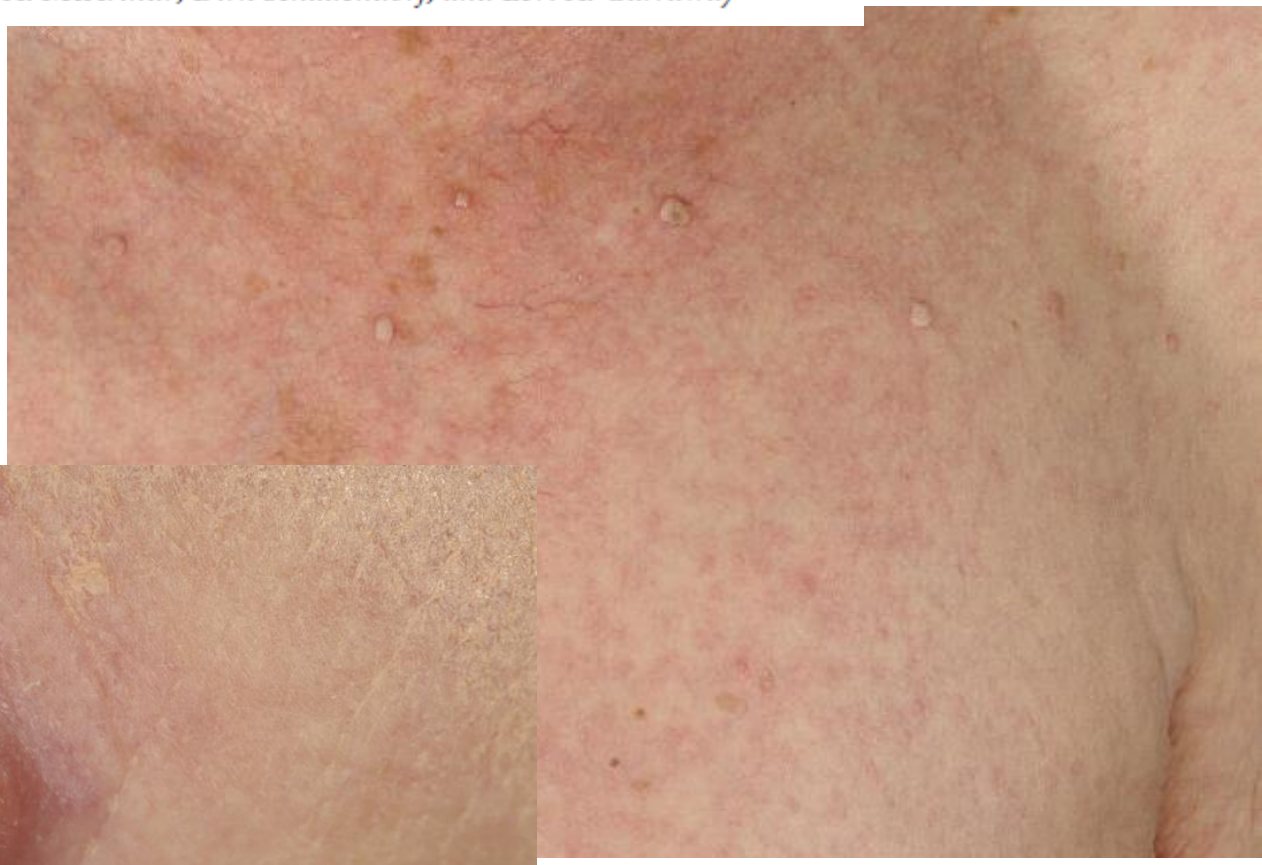
The NEW ENGLAND JOURNAL of MEDICINE

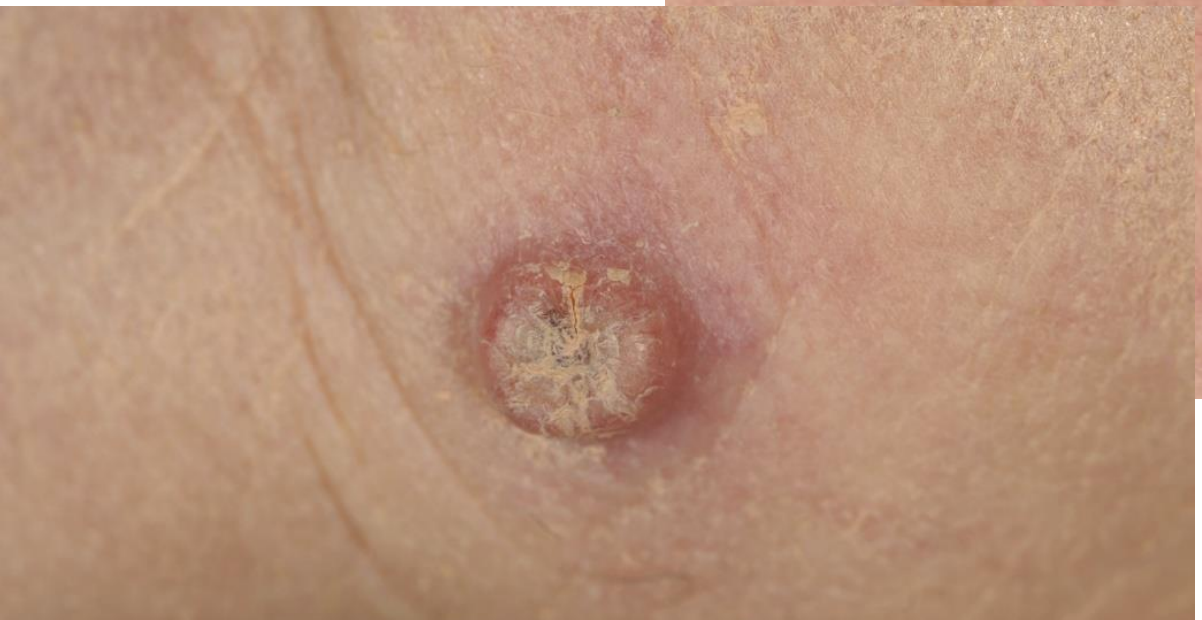
Ultraviolet A and Photosensitivity during Vemurafenib Therapy



RAS Mutations Are Associated With the Development of Cutaneous Squamous Cell Tumors in Patients Treated With RAF Inhibitors

Patrick A. Oberholzer, Damien Kee, Piotr Dziunycz, Antje Sucker, Nyam Kamsukom, Robert Jones, Christine Roden, Clinton J. Chalk, Kristin Ardlie, Emanuele Palescandolo, Adriano Piris, Laura E. MacConaill, Caroline Robert, Günther F.L. Hofbauer, Grant A. McArthur, Dirk Schadendorf, and Levi A. Garraway



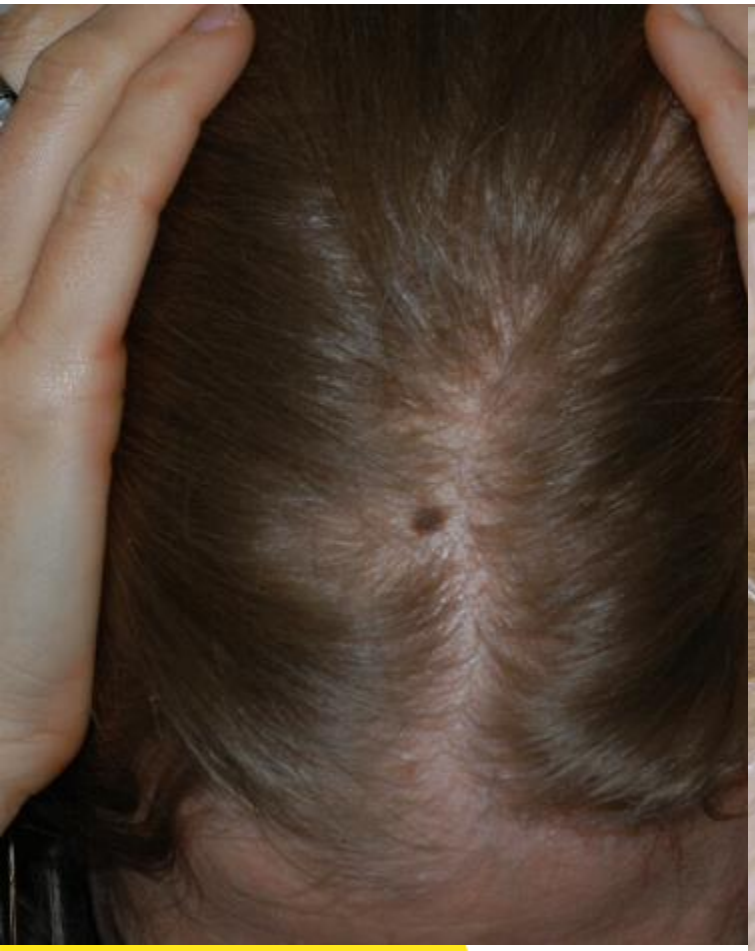


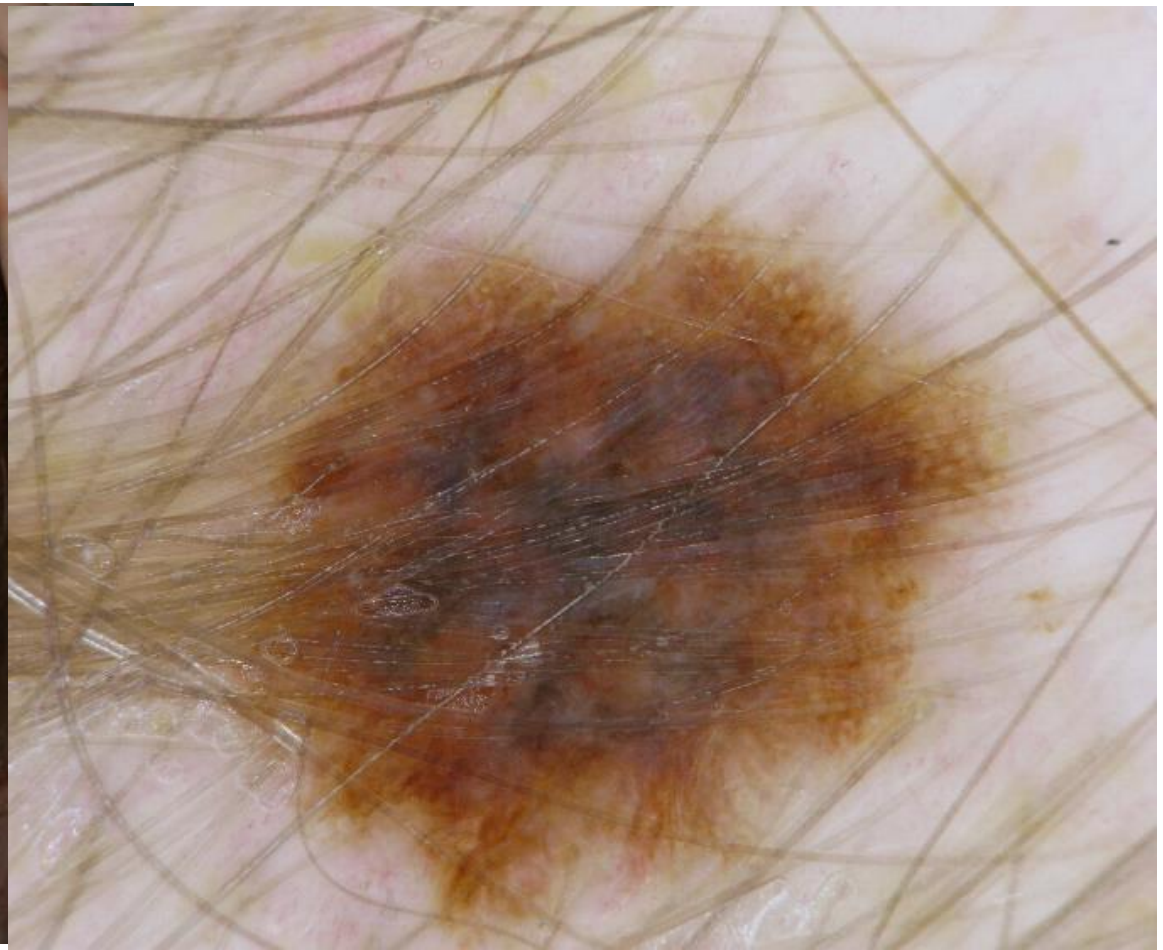
JCO.2011.

Atypical Melanocytic Proliferations and New Primary Melanomas in Patients With Advanced Melanoma Undergoing Selective *BRAF* Inhibition

J Clin Oncol 30. © 2012

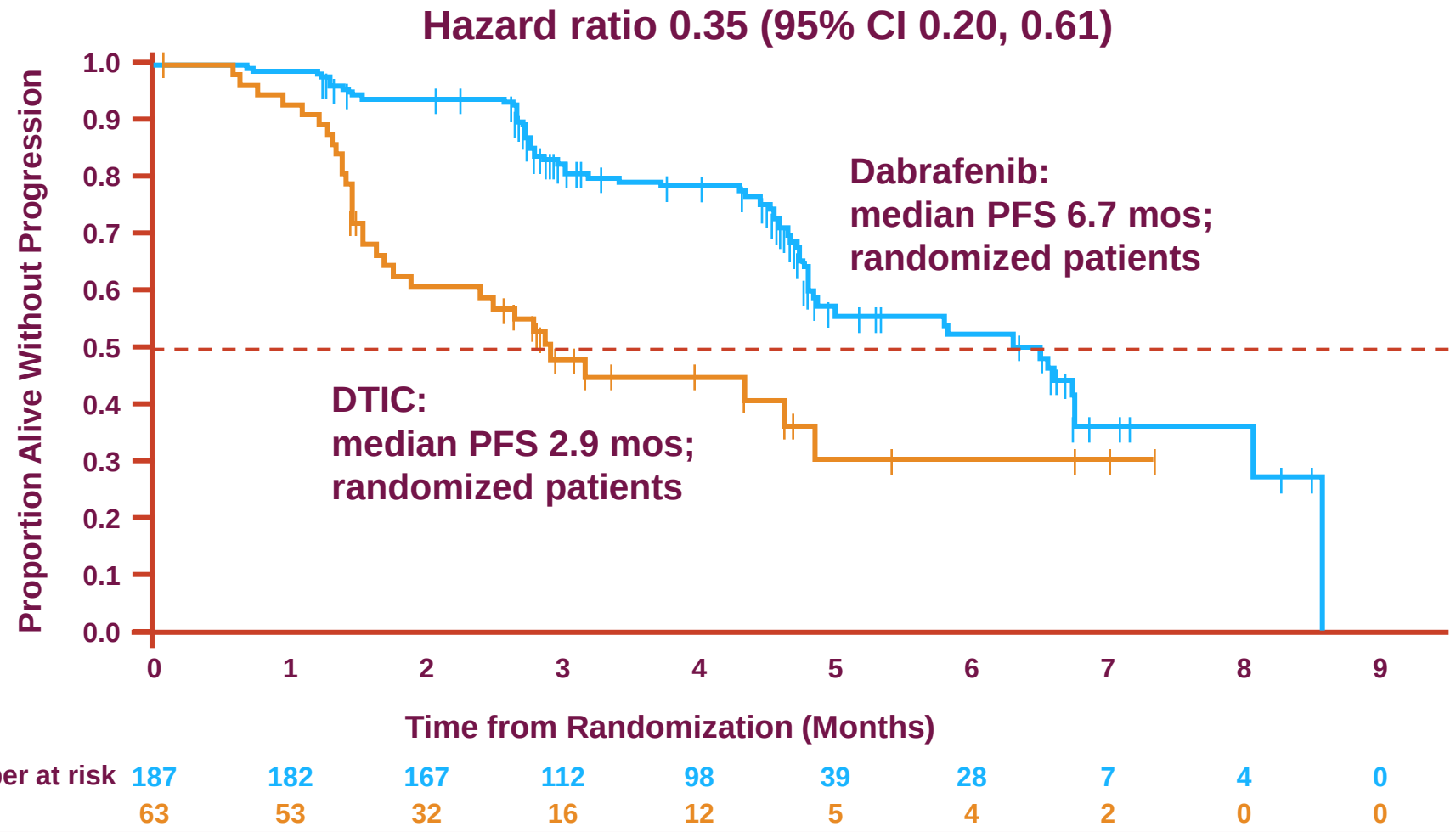
Lisa Zimmer, Uwe Hillen, Elisabeth Livingstone, Mario E. Lacouture, Klaus Busam, Richard D. Carvajal, Friederike Egberts, Axel Hauschild, Mohammed Kashani-Sabet, Simone M. Goldinger, Reinhard Dummer, Georgina V. Long, Grant McArthur, André Scherag, Antje Sucker, and Dirk Schadendorf





Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial

Axel Hauschild, Jean-Jacques Grob, Lev V Demidov, Thomas Jouary, Ralf Gutzmer, Michael Millward, Piotr Rutkowski, Christian U Blank, Wilson H Miller Jr, Eckhart Kaempgen, Salvador Martín-Algarra, Boguslawa Karaszewska, Cornelia Mauch, Vanna Chiarion-Sileni, Anne-Marie Martin, Suzanne Swann, Patricia Haney, Beloo Mirakhur, Mary E Guckert, Vicki Goodman, Paul B Chapman

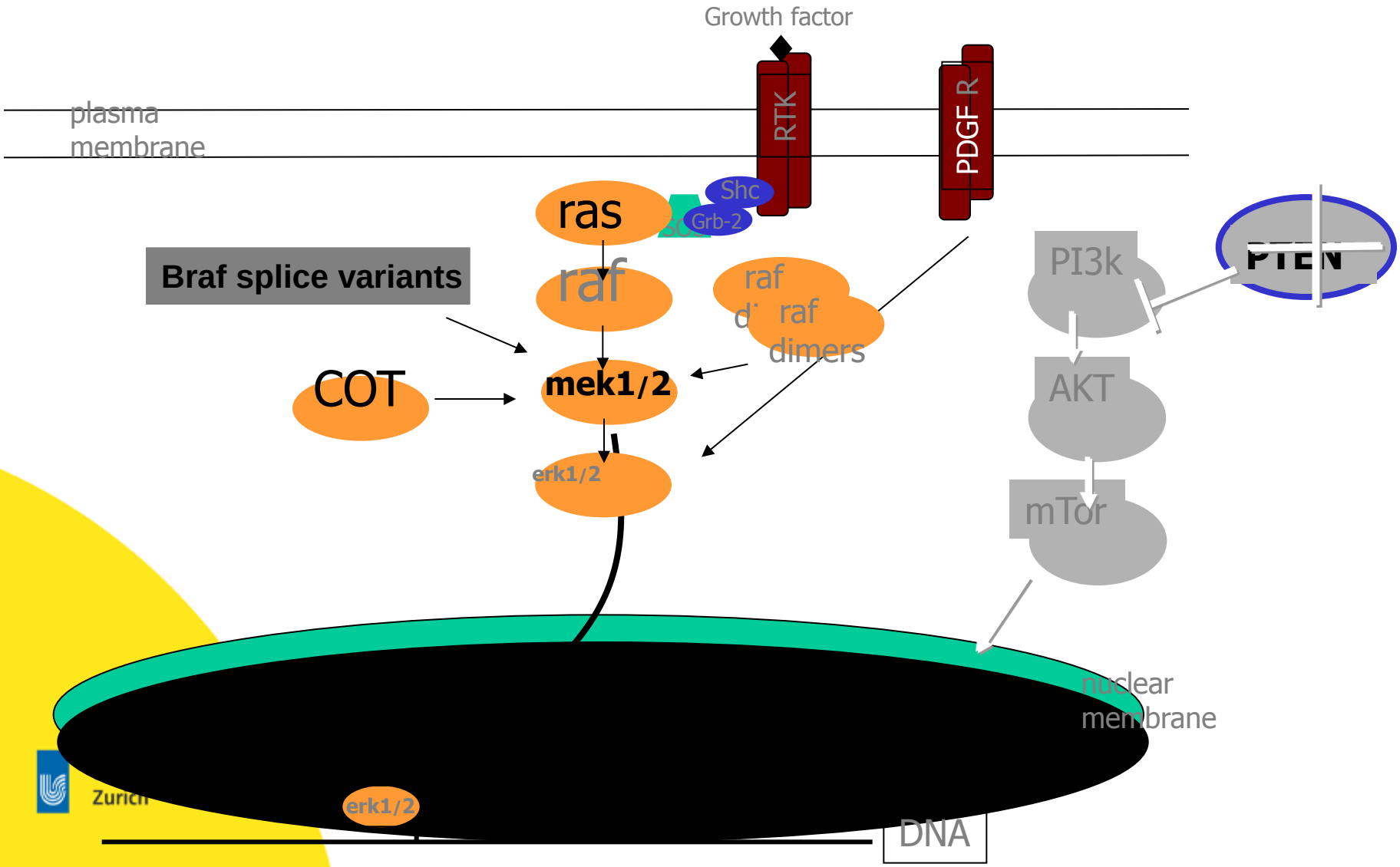


CURRENT OPINION

2012

Resistance patterns with tyrosine kinase inhibitors in melanoma: new insights

Reinhard Dummer[a] and Keith T. Flaherty[b]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

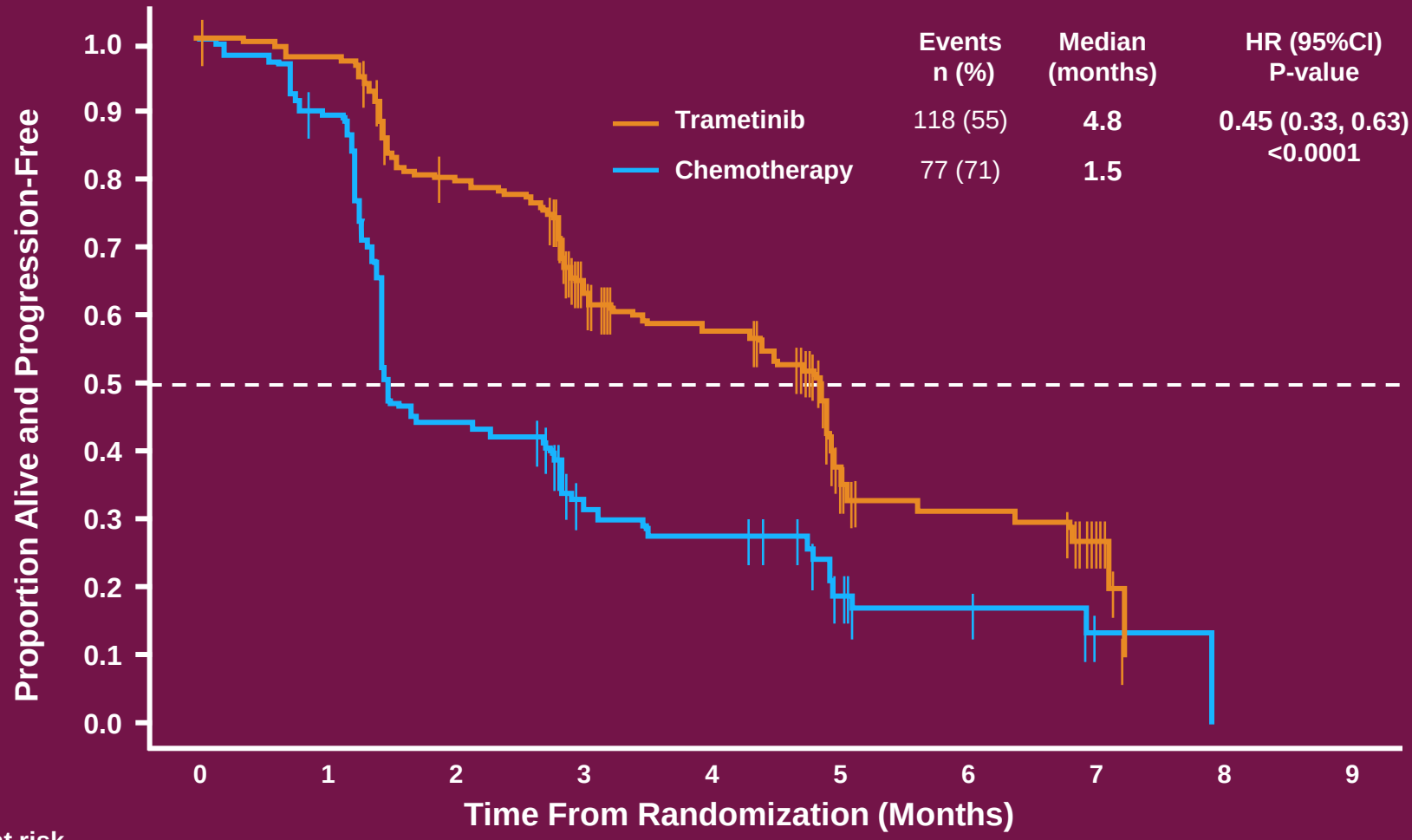
Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma

Keith T. Flaherty, M.D., Caroline Robert, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Paul Nathan, M.D., Ph.D., Claus Garbe, M.D., Mohammed Milhem, M.B., Lev V. Demidov, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Peter Mohr, M.D., Reinhard Dummer, M.D., Uwe Trefzer, M.D., James M.G. Larkin, M.D., Jochen Utikal, M.D., Brigitte Dreno, M.D., Marta Nyakas, M.D., Mark R. Middleton, Ph.D., Jürgen C. Becker, M.D., Ph.D., Michelle Casey, Ph.D., Laurie J. Sherman, R.N., Frank S. Wu, M.D., Ph.D., Daniele Ouellet, Ph.D., Anne-Marie Martin, Ph.D., Kiran Patel, M.D., and Dirk Schadendorf, M.D., for the METRIC Study Group*

This article (10.1056/NEJMoa1203421) was published on June 4, 2012, at NEJM.org.

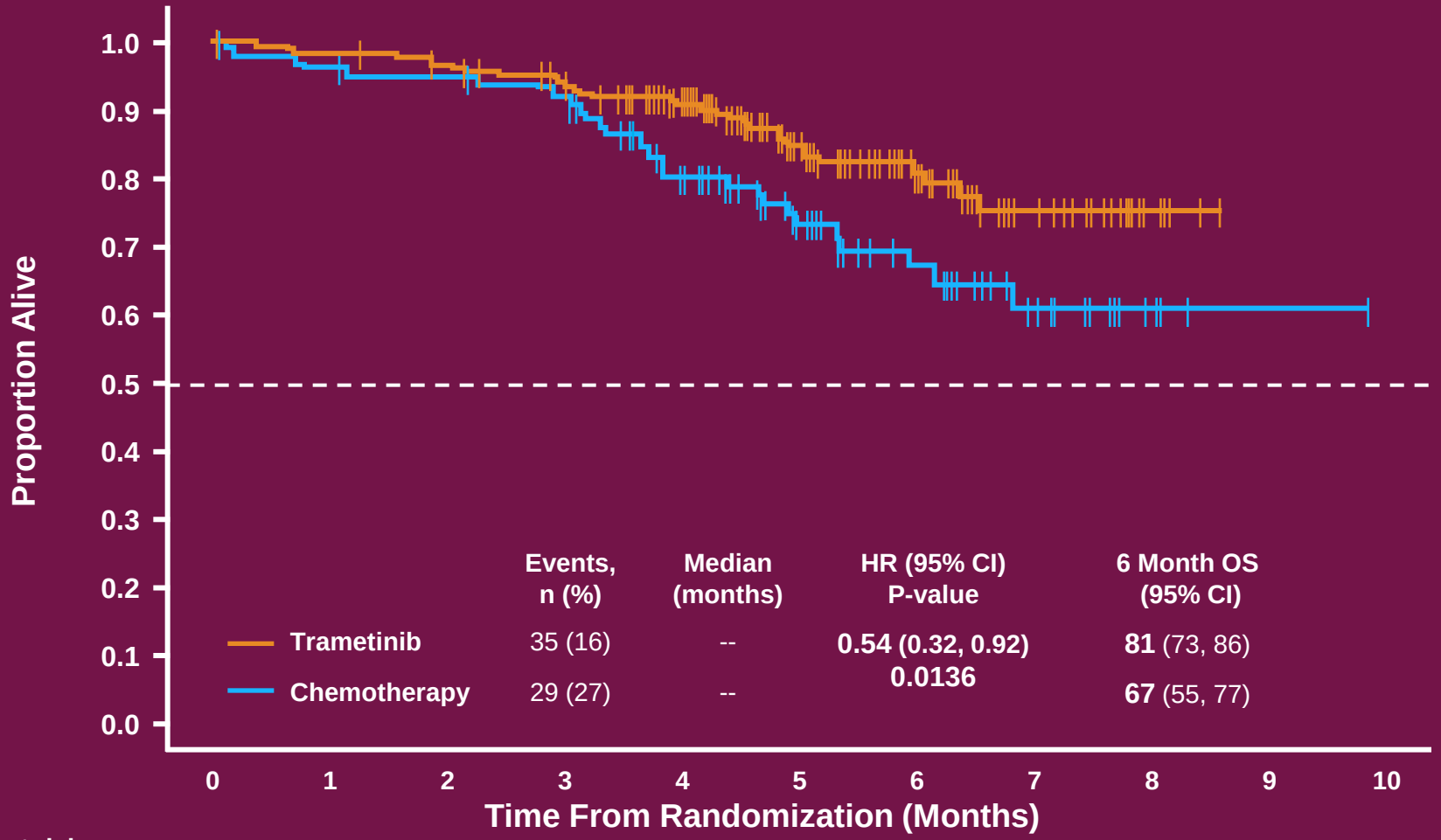
N Engl J Med 2012.

METRIC Investigator-Assessed PFS – ITT



Number at risk										
Trametinib	214	205	163	100	88	28	22	5	0	0
Chemotherapy	108	87	43	24	21	10	6	1	0	0

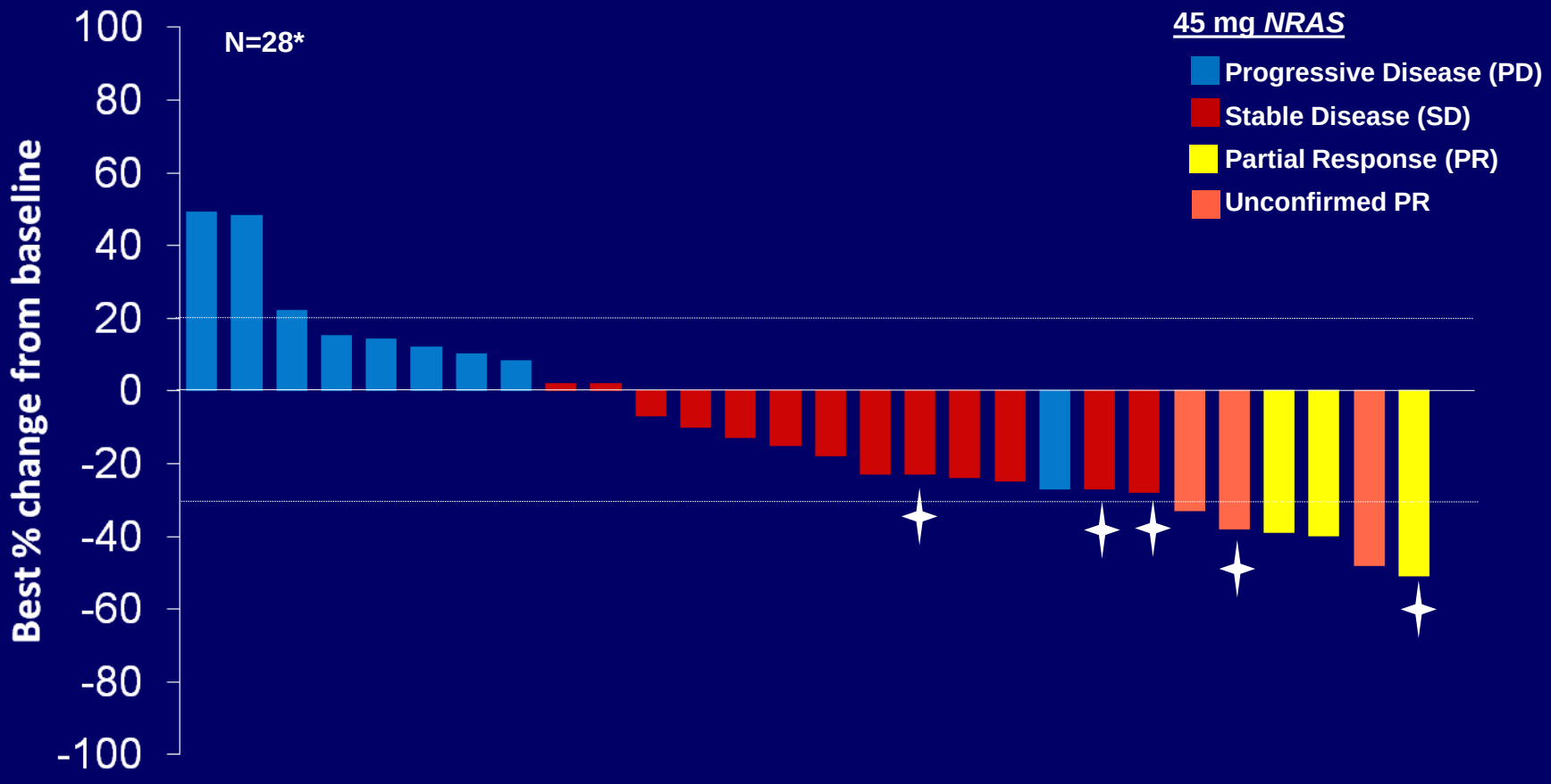
METRIC Overall Survival – ITT



Number at risk											
Trametinib	214	208	203	192	170	105	53	24	5	0	0
Chemotherapy	108	96	94	90	72	47	28	15	4	1	0

47% of the patients in the chemotherapy arm crossed over to trametinib

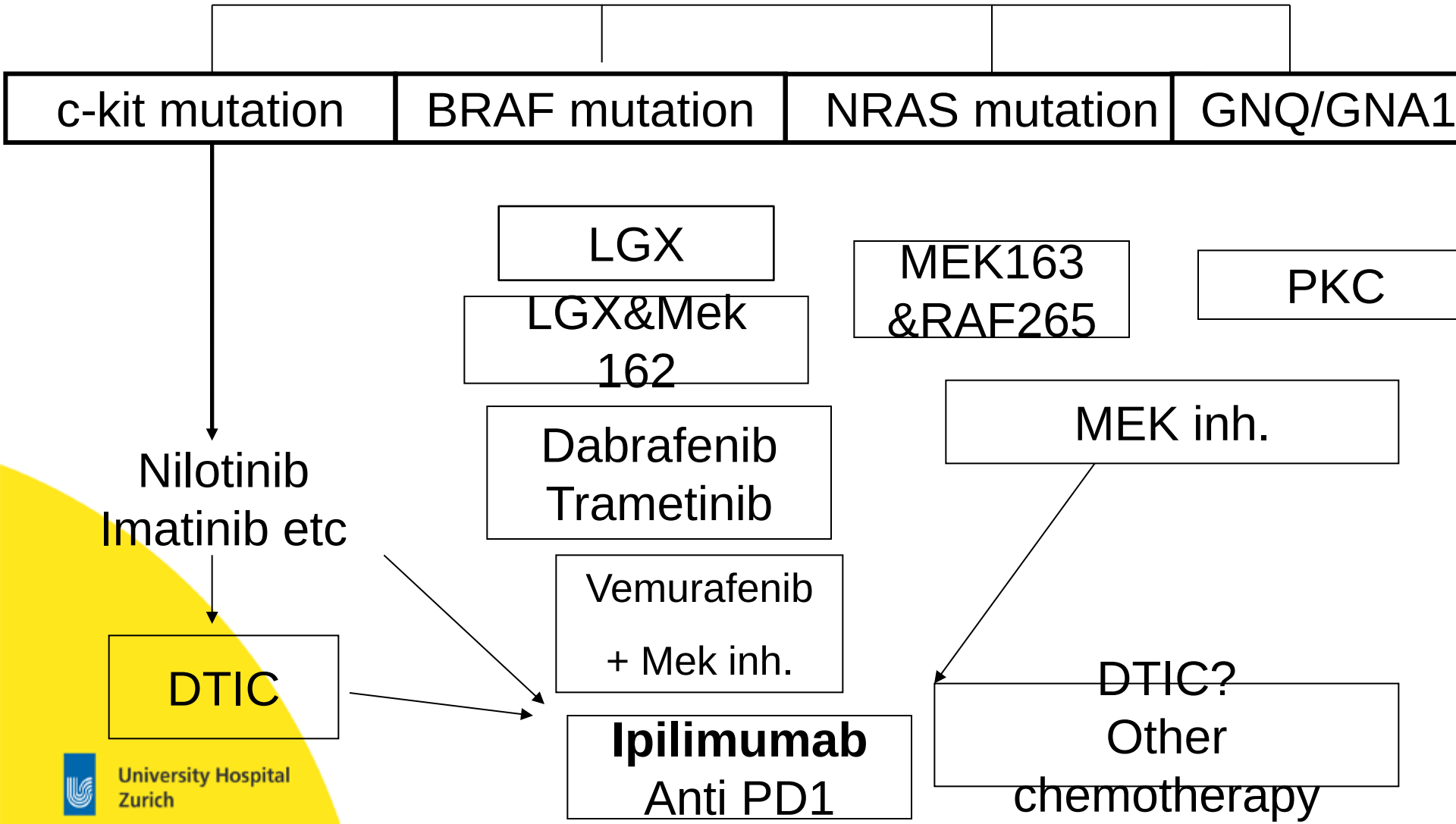
Best percentage change from baseline and best overall response (*NRAS mutated*) after Mek163



*Patients with missing best % change from baseline and unknown overall response are not included.

Ongoing pts

Molecular subtyping and trial landscape



University Hospital Zurich

Monitoring longitudinal personalized cancer evolution

Molecular work- up:

B RAF, N ras, c kit

Tumor antigens

Molecular work- up:

COT, RAS, IGF-R
pten

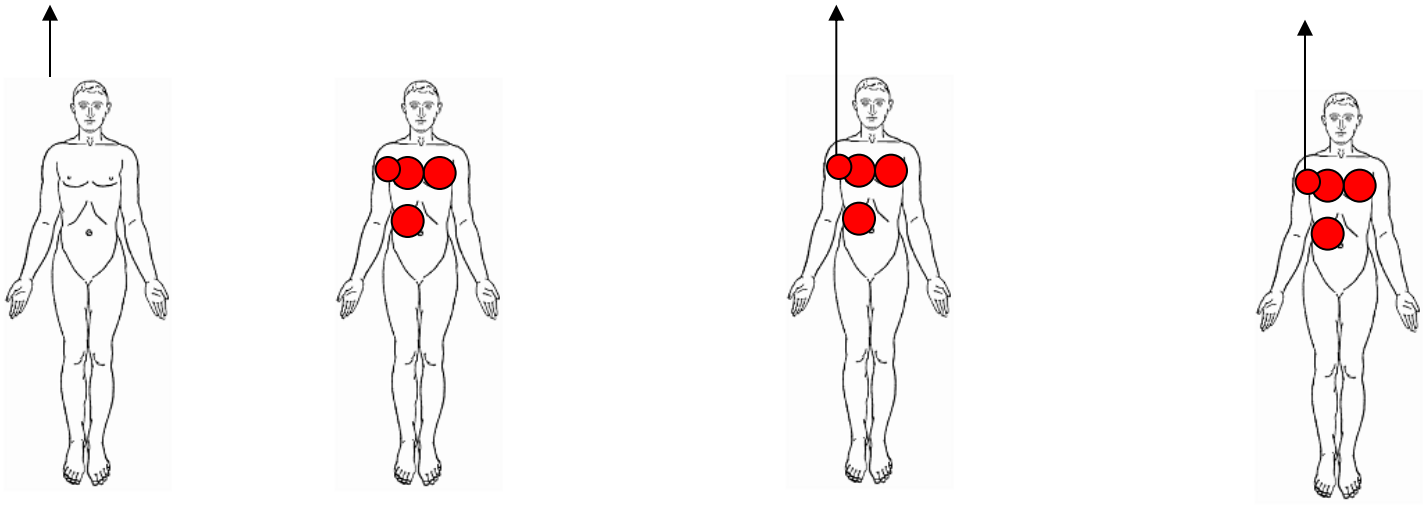
Molecular work- up:

COT, RAS, IGF-R
pten

Excisions

Biopsies

Fine needle aspirates



immunotherapy

raf inhibitor + Mek

RAF Inhibitor + mtor inhibitor

LN surgery

SD

University Hospital Zurich