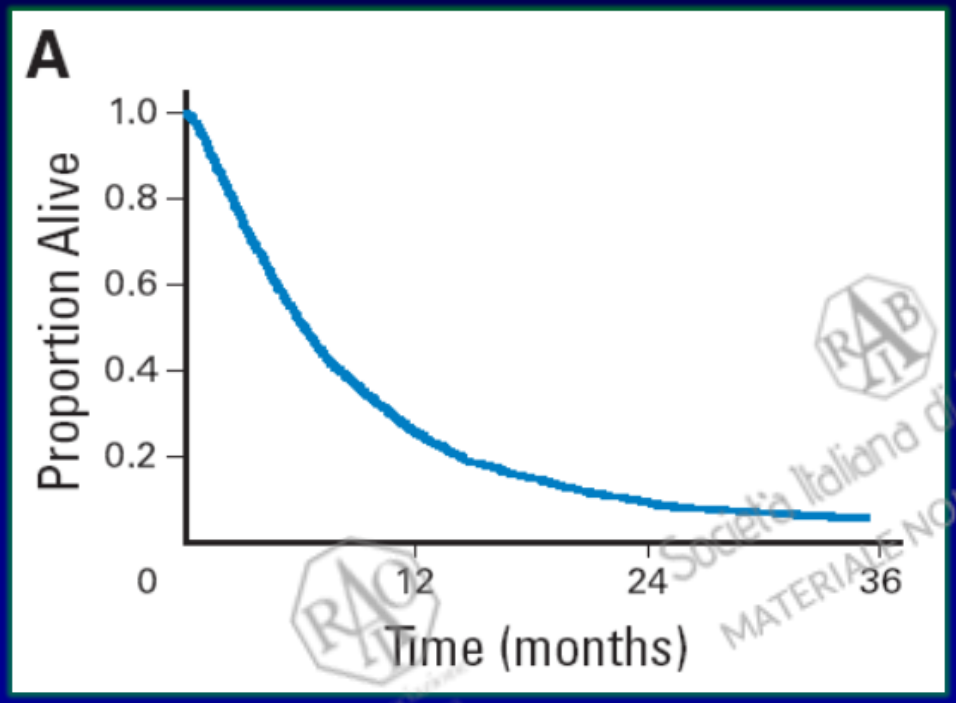
INQUADRAMENTO TERAPEUTICO GENERALE

Terapia medica del melanoma metastatico in fase avanzata

PIETRO QUAGLINO
PAOLO FAVA
MARIA TERESA FIERRO

CLINICA DERMATOLOGICA,
DIPARTIMENTO SCIENZE MEDICHE
UNIVERSITA' DI TORINO

Sopravvivenza globale per il melanoma metastatico

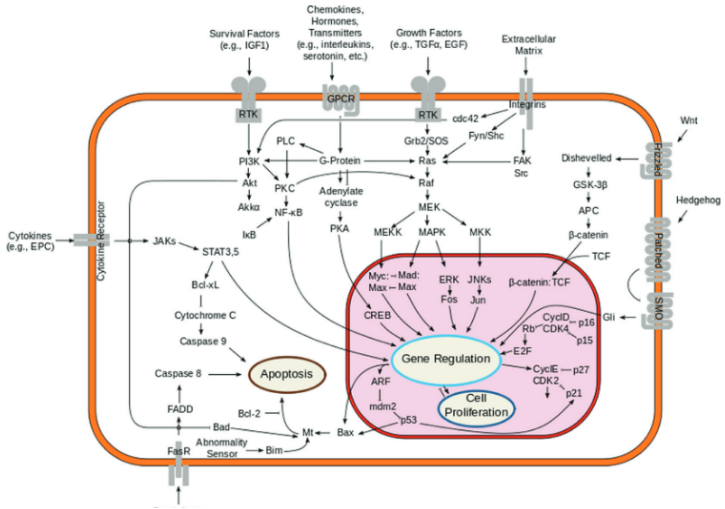


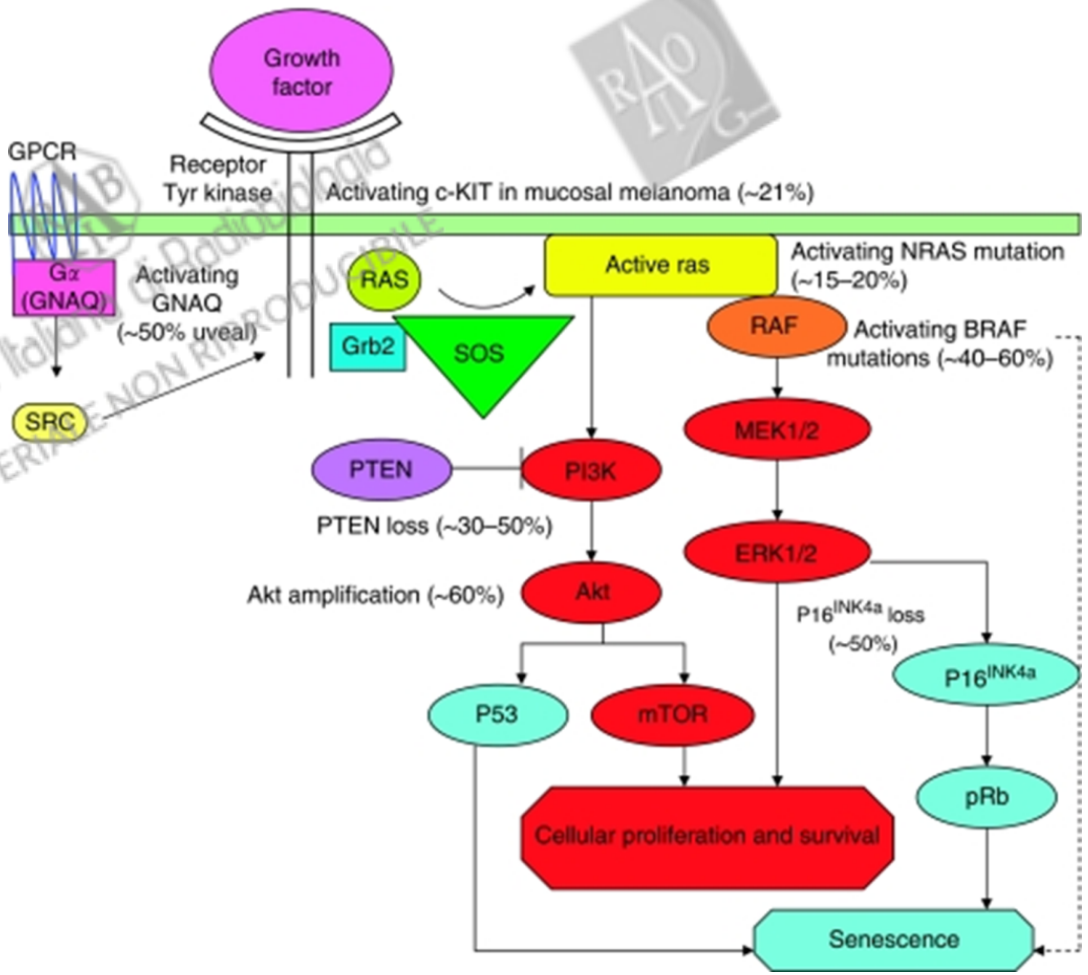
Dati sulla sopravvivenza da 42 studi di Fase II su oltre 2.100 pazienti in stadio IV:

- ✓ OS a 12 mesi: 25,5 %
- ✓ OS mediana: 6,2 mesi

Negli ultimi 30 anni non vi sono stati miglioramenti di rilievo in termini di sopravvivenza globale nel melanoma metastatico

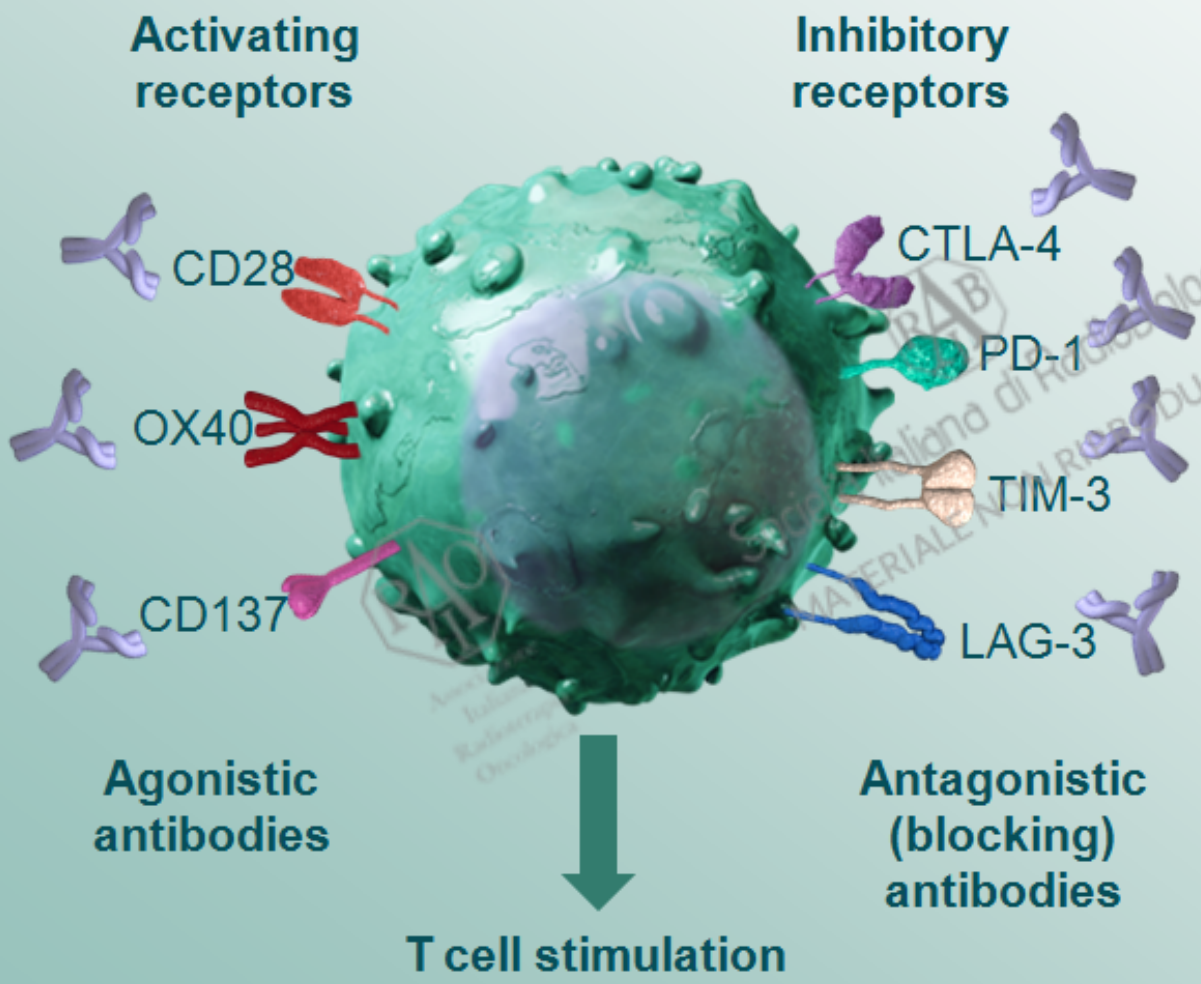
- *Korn EL et al. J Clin Oncol 2008;26(4):527-34.*
- *Dummer R, Hauschild A, Jost L. Cutaneous malignant melanoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19 Suppl 2:ii86-8.*
- *Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline. Eur J Cancer;46(2):270-83.*





Arkenau, BJC 2011

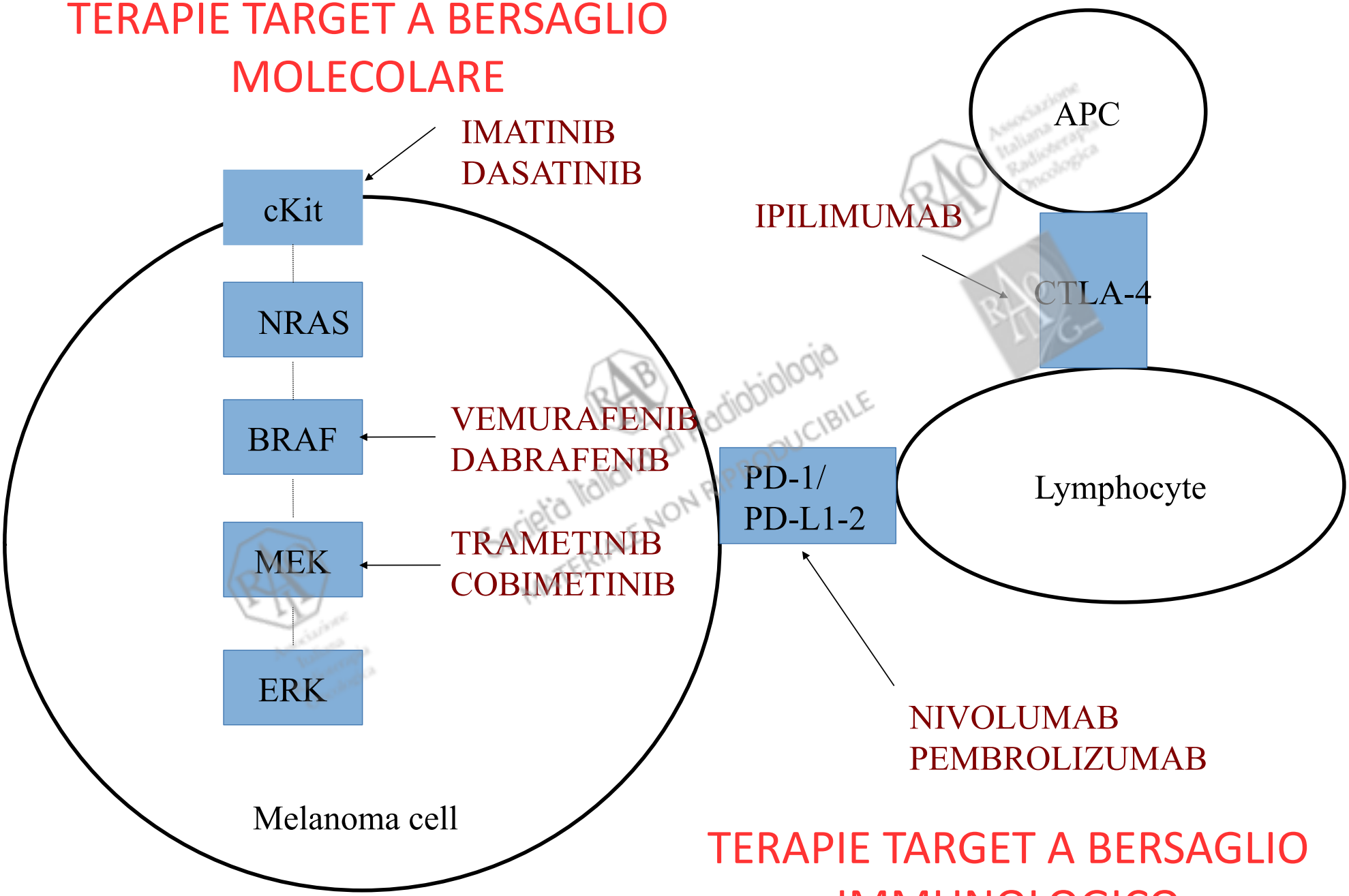
Regulating the T cell immune response[1,2a]



- T cell responses are regulated through a complex balance of inhibitory ('checkpoint') and activating signals
- Tumours can dysregulate checkpoint and activating pathways, and consequently the immune response
- Targeting checkpoint and activating pathways is an evolving approach to cancer therapy, designed to promote an immune response

[a]The image shows only a selection of the receptors/pathways involved
LAG-3 = lymphocyte-activation gene 3

TERAPIE TARGET A BERSAGLIO MOLECOLARE



TERAPIE TARGET A BERSAGLIO IMMUNOLOGICO

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2) Qual è il pattern mutazionale minimo da richiedere?

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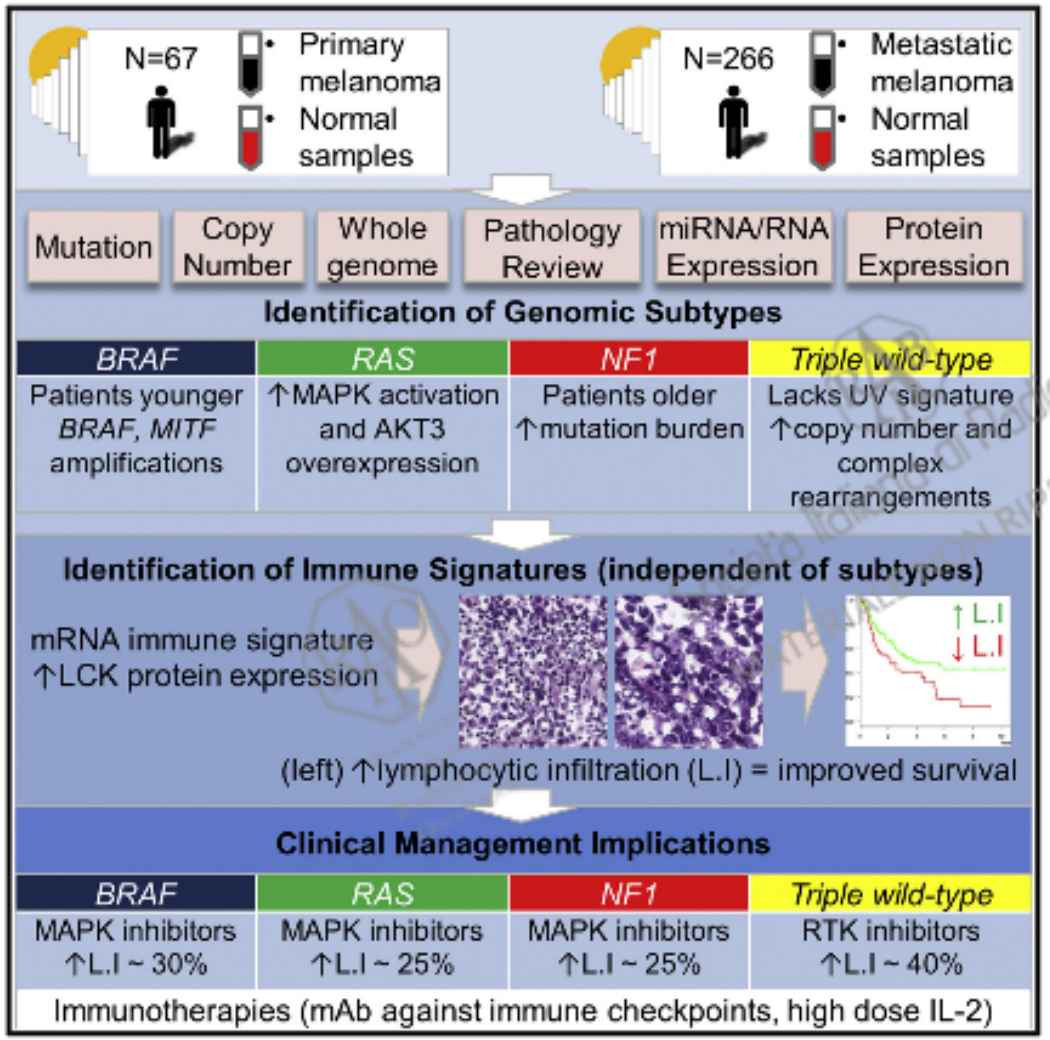
Genomic Classification of Cutaneous Melanoma

Graphical Abstract



Authors

The Cancer Genome Atlas Network

Correspondence

irwatson@mdanderson.org (I.R.W.), jgershen@mdanderson.org (J.E.G.), lchin@mdanderson.org (L.C.)

In Brief

An integrative analysis of cutaneous melanomas establishes a framework for genomic classification into four subtypes that can guide clinical decision-making for targeted therapies. A subset of each of the genomic classes expresses considerable immune infiltration markers that are associated with improved survival, with potential implications for immunotherapy.

Cell 161, 1681–1696, June 18, 2015 a2015

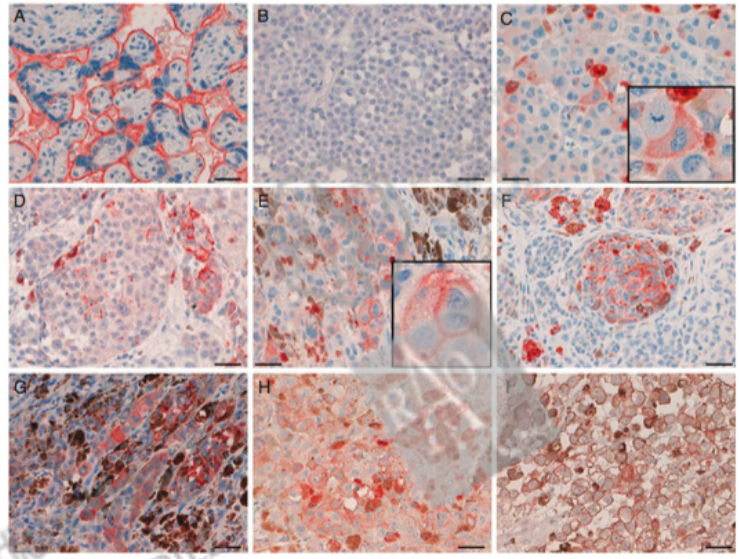
Annals of Oncology 25: 2433–2442, 2014
doi:10.1093/annonc/mdu452
Published online 15 September 2014

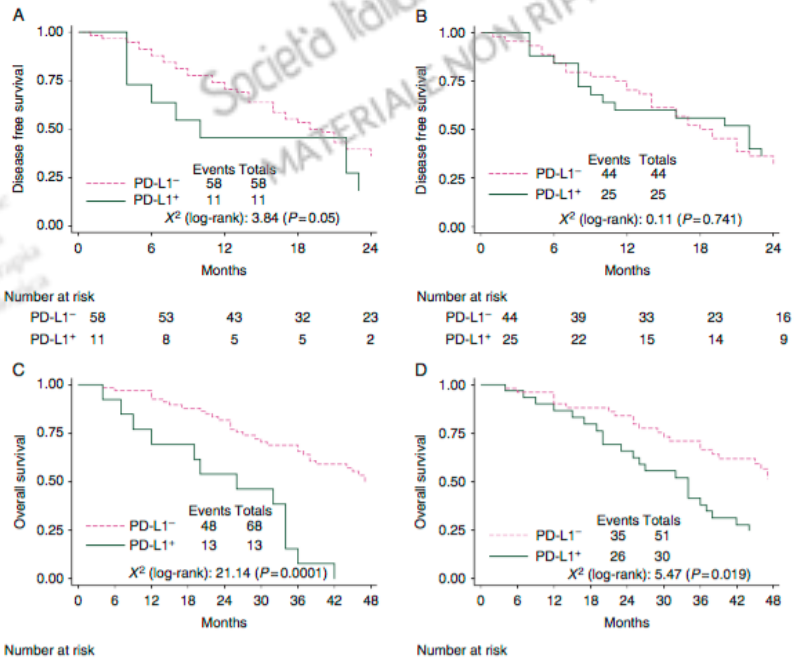
PD-L1 marks a subset of melanomas with a shorter overall survival and distinct genetic and morphological characteristics

D. Massi[1,†], D. Brusa[2,†], B. Merelli[3], M. Ciano[2], V. Audrito[2,4], S. Serra[2,4], R. Buonincontri[2,4], G. Baroni[1], R. Nassini[5], D. Minocci[5], L. Cattaneo[6], E. Tamborini[7], A. Carobbio[8], E. Rulli[9], S. Deaglio[2,4,‡] & M. Mandalà[3,‡*]

[1]*Department of Surgery and Translational Medicine, Division of Pathological Anatomy, University of Florence;* [2]*Human Genetics Foundation (HuGeF), Turin;* [3]*Unit of Medical Oncology, Department of Oncology and Hematology, Papa Giovanni XXIII Hospital, Bergamo;* [4]*Department of Medical Sciences, University of Turin , Turin;* [5]*Unit of Clinical Pharmacology and Oncology, Department of Health Sciences, University of Florence, Firenze;* [6]*Division of Pathological Anatomy, Papa Giovanni XXIII Hospital, Bergamo;* [7]*Department of Pathology, Experimental Molecular Pathology, National Cancer Institute, Milan;* [8]*Research Foundation, Papa Giovanni XXIII Hospital, Bergamo;* [9]*Department of Oncology, Clinical Research Laboratory, Mario Negri Institute IRCCS, Milan, Italy*

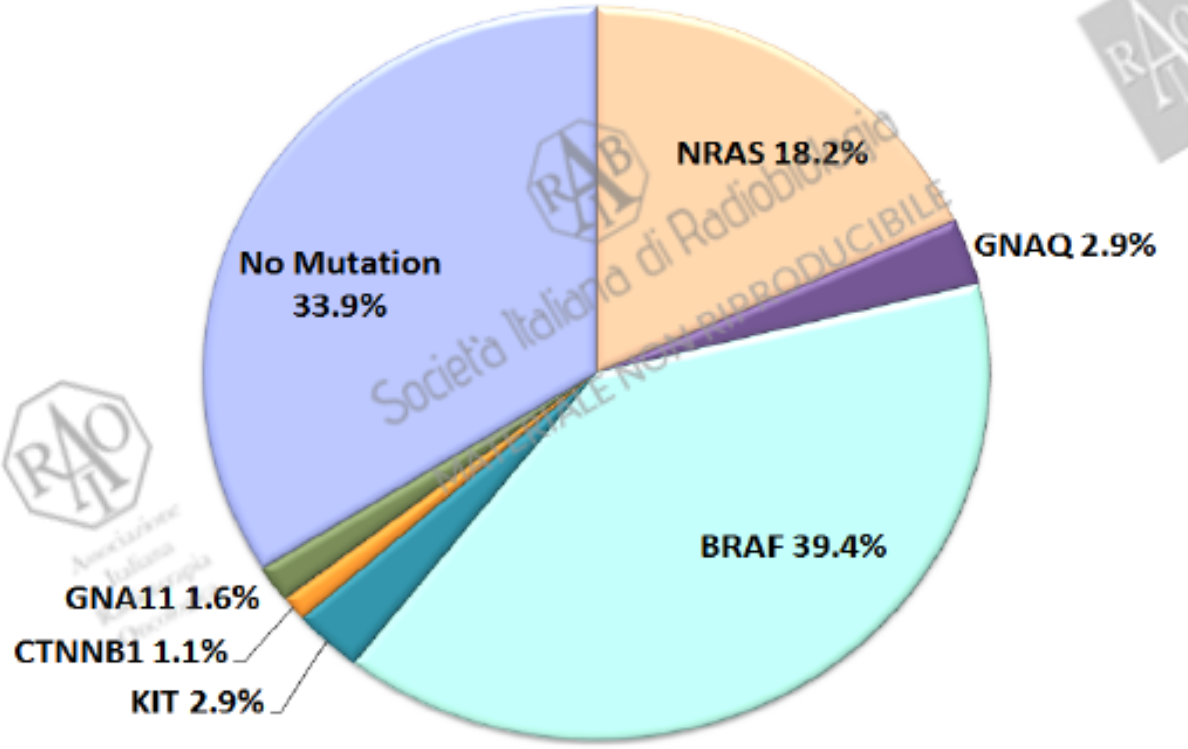
Received 27 April 2014; revised 14 July 2014 and 5 September 2014; accepted 8 September 2014





Melanoma Molecular Profiling

60% BRAF WT



Mutation Distribution

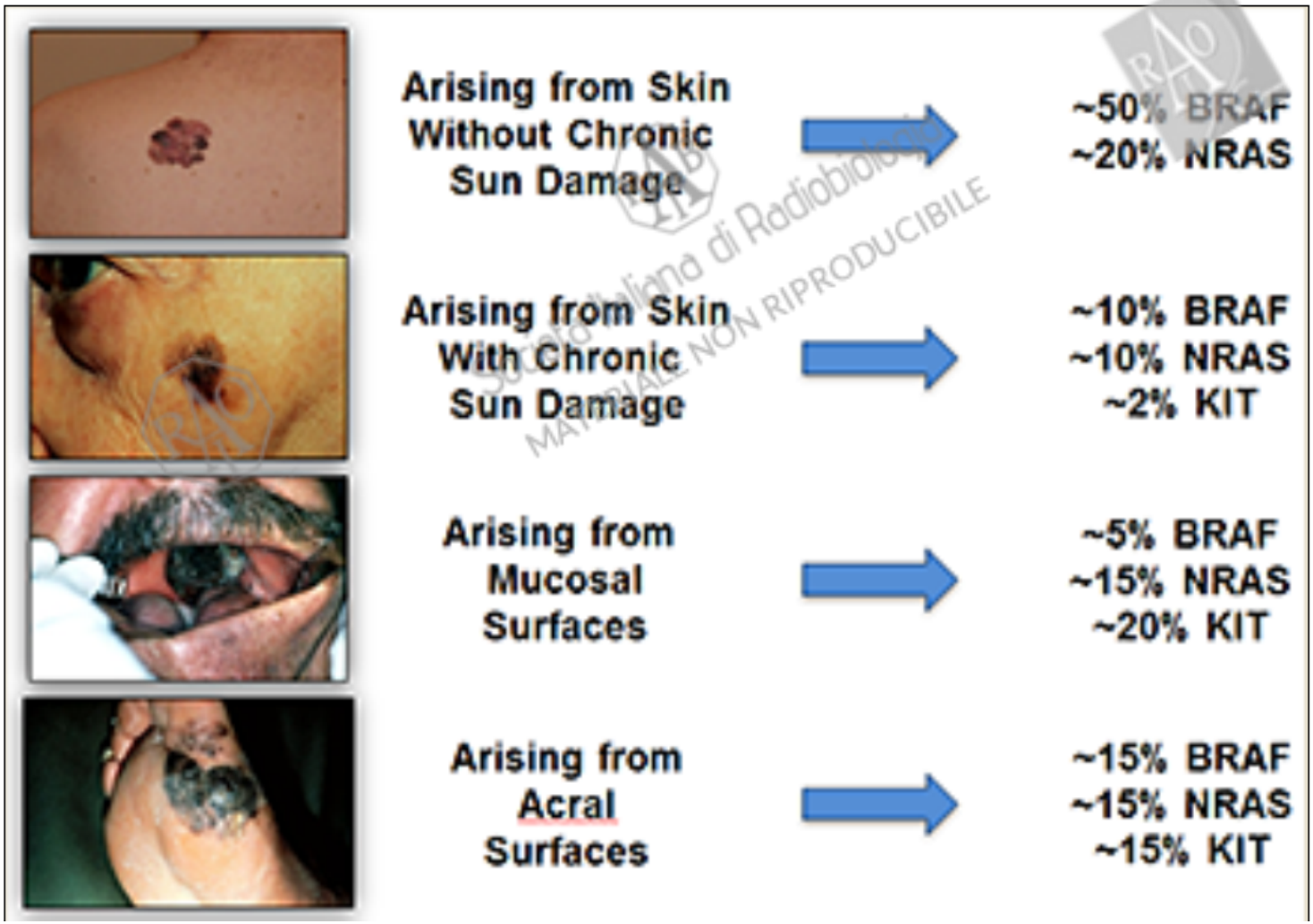
OPEN ACCESS Freely available online

PLoS one

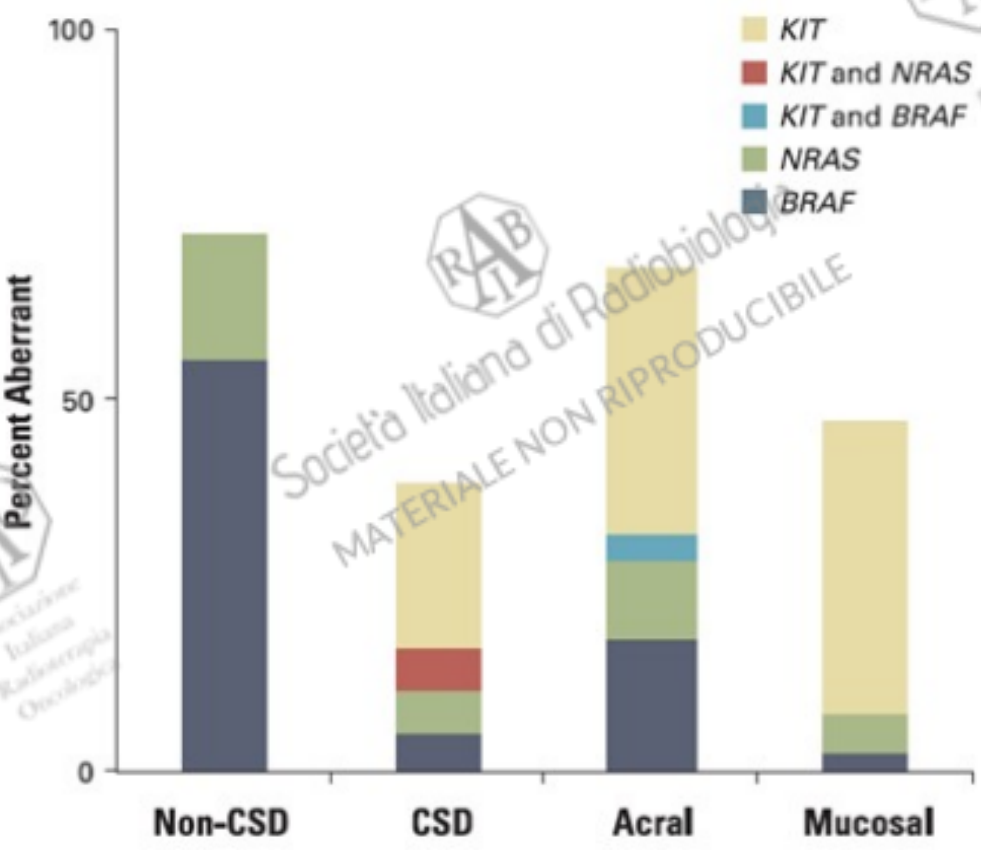
A Melanoma Molecular Disease Model

Smruti J. Vidwans[1], Keith T. Flaherty[2], David E. Fisher[3], Jay M. Tenenbaum[1], Michael D. Travers[1¤], Jeff Shrager[1,4*]

1 CollabRx Inc., Palo Alto, California, United States of America, **2** Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States of America, **3** Department of Dermatology, Cutaneous Biology Research Center and Melanoma Program, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **4** Symbolic Systems Program (Consulting), Stanford University, Stanford, California, United States of America



Frequency distribution of genetic alterations in BRAF, *NRAS*, and *KIT* in melanoma



BRAF e NRAS mutualmente esclusivi

Curtin JCO 2006

CLINICA: DOMANDE E RISPOSTE

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Linee guida

MELANOMA

Edizione 2015

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	E' indicata la determinazione dello stato mutazionale di BRAF nei melanomi in stadio IV e III non operabile (70,71)	**Positiva forte**

IIIB, IIIC disease – free ad alto rischio di recidiva?

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Il campione istologico

- Il campione istologico può essere rappresentato da lesioni primitive o metastatiche (cutanee, linfonodali o viscerali).
- E' comunque preferibile un campione di lesioni metastatiche, nelle quali la componente di cellule neoplastiche è in genere maggiormente rappresentata rispetto a quanto osservato nei melanomi primitivi.
- Il tessuto tumorale può essere prelevato mediante una biopsia incisionale o essere costituito da un campione operatorio.
- L'indagine molecolare può essere eseguita: 1) su tessuto fissato in formalina e incluso in paraffina (FFPE); 2) su campione tissutale fresco; 3) su tessuto congelato a -80°C.

VOLUME 30 · NUMBER 20 · JULY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

BRAF/NRAS Mutation Frequencies Among Primary Tumors and Metastases in Patients With Melanoma

Maria Colombino, Mariaelena Capone, Amelia Lissia, Antonio Cossu, Corrado Rubino, Vincenzo De Giorgi, Daniela Massi, Ester Fonsatti, Stefania Staibano, Oscar Nappi, Elena Pagani, Milena Casula, Antonella Manca, MariaCristina Sini, Renato Franco, Gerardo Botti, Corrado Caracò, Nicola Mozzillo, Paolo A. Ascierto, and Giuseppe Palmieri

Maria Colombino, Milena Casula, Antonella Manca, MariaCristina Sini, and Giuseppe Palmieri, Istituto Clinico

A B S T R A C T

Purpose

Table 1. Somatic Mutations Detected in *BRAF* and *NRAS* Genes Among In Vivo (primary and secondary tumor sites from patients with melanoma) and In Vitro (melanoma cell lines) Samples

Sample	No. of Samples	Frequency of Mutations and Subtypes: *BRAF* Mutation Subtype	*BRAF* Mutation No.	*BRAF* Mutation %	*NRAS* Mutation Subtype	*NRAS* Mutation No.	*NRAS* Mutation %	*BRAF* or *NRAS* Mutation No.	*BRAF* or *NRAS* Mutation %
Primary tumor	102		44	43		15	15	59	58
		V600E	40		Q61R	10			
		V600K	3		Q61L	3			
		V600D	1		Q61K	2			
All metastatic sites	189	91		48		28	15	119	63
		V600E	83		Q61R	17			
		V600K	6		Q61L	8			
		V600D	1		Q61K	3			
		L597R	1						
Lymph node metastases	84		40	48		12	14	52	62
		V600E	36		Q61R	9			
		V600K	3		Q61K	2			
		L597R	1		Q61L	1			
Brain metastases	44		21	48		10	23	31	70
		V600E	18		Q61R	4			
		V600K	2		Q61L	6			
		V600D	1						
Skin metastases	36		19	53		3	8	22	61
Locoregional	22		11	50		2	9	13	59
Distant	14		8	57		1	7	9	64
		V600E	19		Q61R	2			
					Q61L	1			
Visceral metastases	25		11	44		3	12	14	56
Liver	20		9	45		2	10	11	55
Lung	5		2	40		1	20	3	60
		V600E	10		Q61R	2			
		V600K	1		Q61K	1			
Cell lines	29	17		59		4	14	21	72
		V600E	13		Q61L	2			
		V600R	3		Q61K	1			
		V600D	1		Q61R	1			

Table 2. Consistency Between *BRAF/NRAS* Mutation Status in Primary and Secondary Lesions in Patients With Melanoma and Mutation Patterns in Those in Whom There Were Discrepancies

Tissue Type	No. of Samples	Patients With Consistent Mutation Patterns (secondary *v* primary melanoma samples) No.	%	Mutation Patterns Among Discrepant Paired Samples: *BRAF* Primary Tumor	*BRAF* Metastasis	*NRAS* Primary Tumor	*NRAS* Metastasis
Lymph node metastases	84	78	93	V600K	wt	wt	wt
				wt	L597R	wt	wt
				wt	V600E	wt	wt
				wt	V600E	wt	wt
				wt	V600E	wt	wt
				V600E	wt	wt	wt
Visceral metastases	25	24	96	V600E	wt	wt	wt
Brain metastases	20	16	80	V600E	wt	wt	wt
				wt	wt	wt	Q61L
				wt	wt	wt	Q61L
				wt	wt	wt	Q61R
Skin metastases	36	27	75	wt	wt	wt	Q61L
				V600E	wt	wt	wt
				V600E	wt	wt	wt
				wt	wt	Q61R	wt
				wt	V600E	Q61R	wt
				wt	V600E	Q61R	wt
				wt	V600E	wt	wt
				wt	V600E	wt	wt
				V600E	wt	wt	wt

Abbreviation: wt, wild-type.

RI-TESTING su nuove lesioni

How do methods compare by performance?

Method	Limit of detection (ie, minimum % of mutant alleles in a wild type background required for reliable mutation detection)	Analytical sensitivity	Range of mutations detected
Sequencing/PCR	Around 20-30%	80-85%	Comprehensive
PLA-LNA clamp	Reportedly below 1%		Limited
ARMS (Therascreen)	Up to 1%	90-95%	Limited
PCR Invader®			Limited
Pyro-sequencing	Reportedly 1-10%	90-95%	Near comprehensive
High-ResolutionMelting (HRM)	10-20%	80-85%	Near comprehensive
SNaPshot®	5–10%		
PCR/flRFLP	5-10%		
Fragment analysis	Approximately 5%	90-95%	Insertions/deletions
CE-SSCP/DHPLC	5-10%	90-95%	Near comprehensive

cobas® BRAF V600 Mutation Test

Specifications and mutation detection cobas 4800 BRAF^{V600} mutation test

Parameter	Requirements
Clinical specimen required	FFPET slide (≥5-µm section)
Limit of detection of FFPET	5% mutant allele[a]
Minimal tumor content within specimen	15%
DNA requirement within specimen	125 ng
Mutation detection	
V600 isoform	**Agreement with Sanger sequencing**
V600E	97.3%
V600K	65.8%
Other V600	Not established[b]

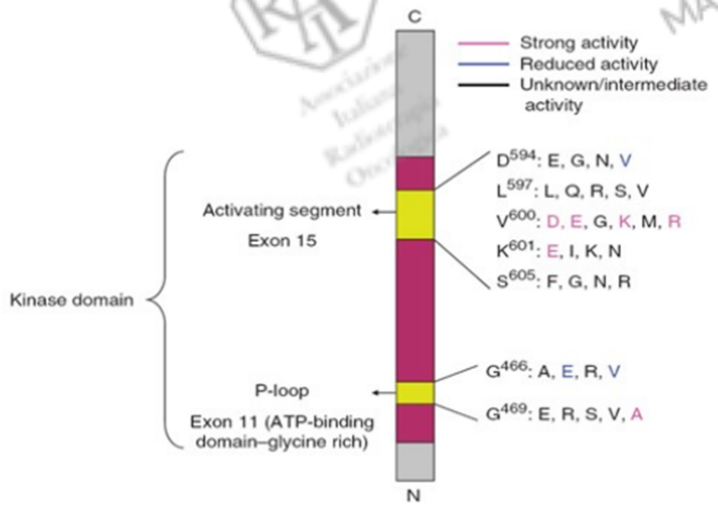
Abbreviation: FFPET, formalin-fixed paraffin-embedded tissue.

[a]Compared with 20% for Sanger sequencing.

[b]Insufficient sample size for assessment of V600D, V600E$_2$, and V600R.

Luke CCR 2012

Types of BRAF mutation



BRAF Mutations Affect Kinase Activity

- Ninety percent of *BRAF* mutations in melanoma result in substitution at position V600[2]
  - All tested mutations at V600 are classified as high-activity mutants when compared with *BRAF*$^{wild\text{-}type\ (WT)}$[3,4]
  - These mutations constitutively stimulate ERK phosphorylation [3]
- A unifying feature of the high- and intermediate-activity *BRAF* mutants is that they disrupt the hydrophobic interaction between the P loop and the activation segment of the kinase domain[4]
  - This results in destabilization of the inactive conformation of BRAF, thus stimulating its kinase activity and leading to increased ERK phosphorylation

BRAF Mutation at Position V600	Melanomas (Total 2,651 V600X)[1]	Relative Frequency (%)[1]
V600E	2,436	91.9
V600K	162	6.1
V600D	35	1.3
V600R	18	0.7

BRAF kinase domain structure. Position 600 is indicated i yellow. The BRAF activation segment is shown in purpl dashes indicate the region that was not resolved. The loop is shown in green (adapted from Garnett MJ).[2]

BRAF = rapidly accelerated fibrosarcoma isoform B; ERK = extracellular signal–regulated kinase; WT = wild-type.

1. Forbes SA, *et al. Nucleic Acids Res* 2010;38:D652–7
2. Garnett MJ, *et al. Cancer Cell* 2004;6:313–9
3. Wan PTC, *et al. Cell* 2004;116:855–67.
4. Pritchard C, *et al. Biochem Soc Trans* 2007;35:1329–33.

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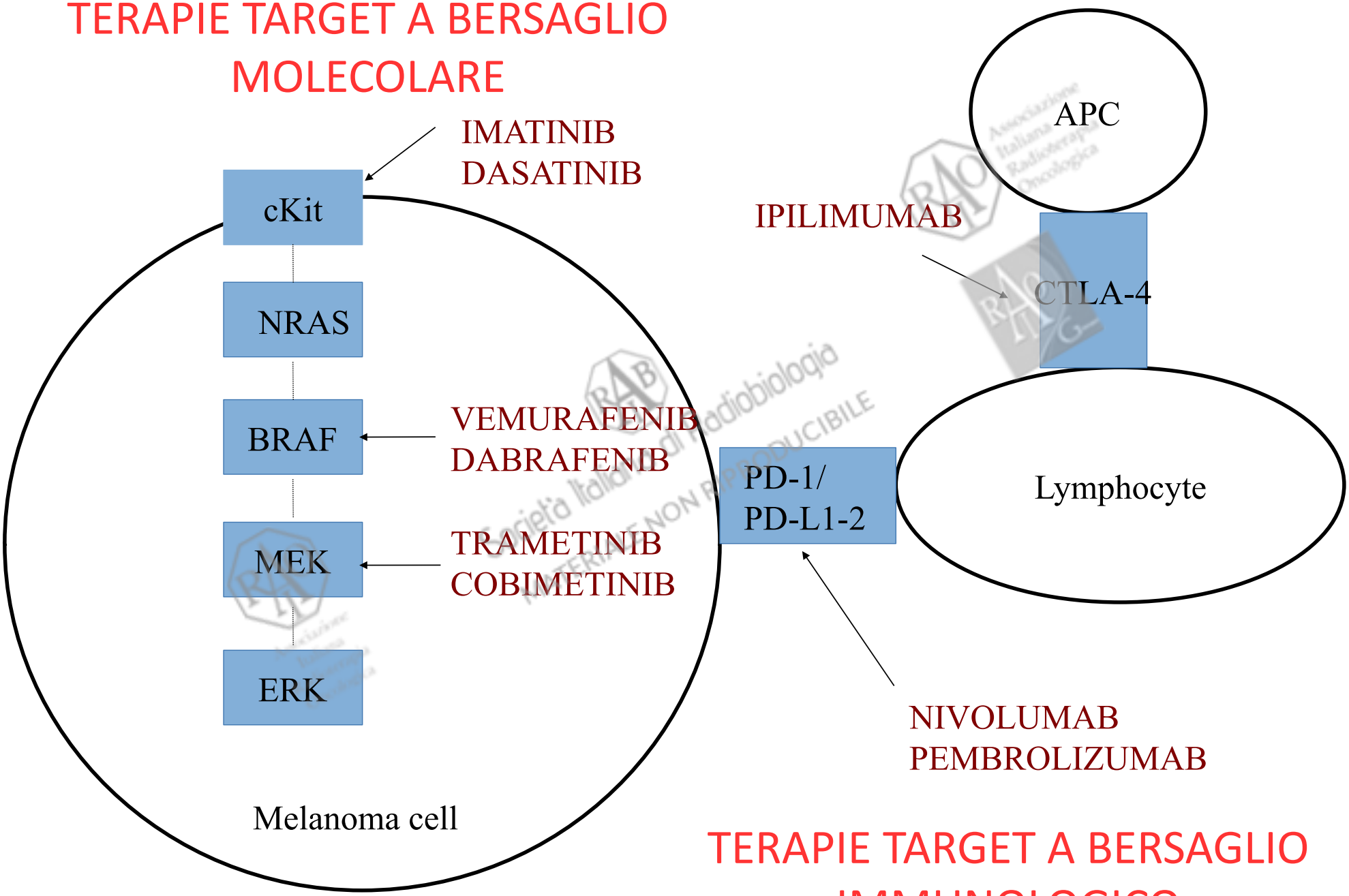


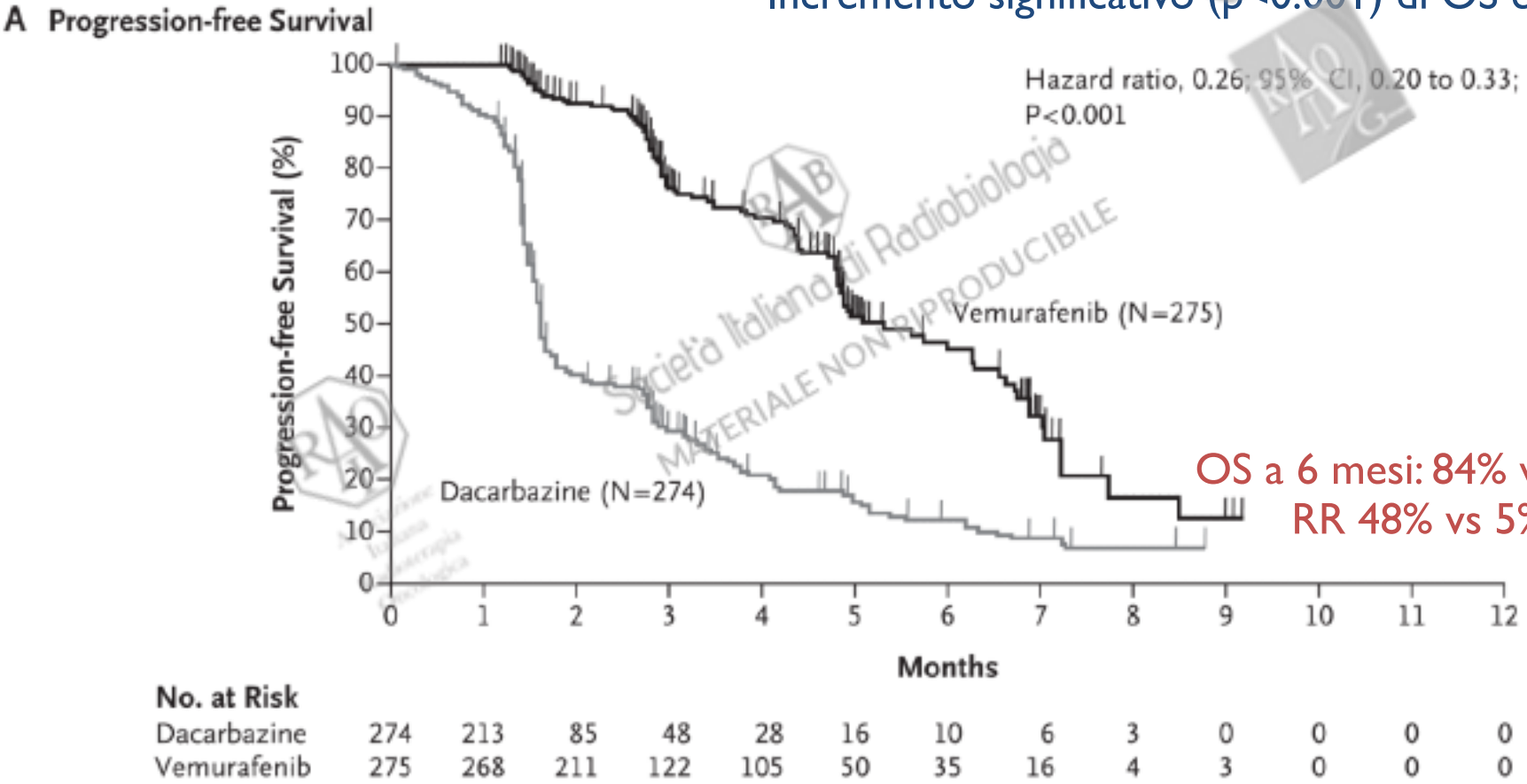
TERAPIE TARGET A BERSAGLIO IMMUNOLOGICO

Published in final edited form as:
N Engl J Med. 2011 June 30; 364(26): 2507–2516. doi:10.1056/NEJMoa1103782.

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., Grant A. McArthur, M.B., B.S., Ph.D., and BRIM-3 Study Group*
The authors' affiliations are listed in the Appendix.

Incremento significativo (p<0.001) di OS e PFS.



OS a 6 mesi: 84% vs 64%
RR 48% vs 5%

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

Lancet 2012; 380: 358–65
Published Online
June 25, 2012
http://dx.doi.org/10.1016/S0140-6736(12)60868-X
See Comment page 320

University Hospital, Schleswig-Holstein, Department of Dermatology, Kiel, Germany (Prof A Hauschild MD); **Aix-Marseille University, Assistance Publique-Hôpitaux de Marseille, Hôpital Timone**

Summary

Background Dabrafenib, an inhibitor of mutated BRAF, has clinical activity with a manageable safety profile in studies of phase 1 and 2 in patients with $BRAF^{V600}$-mutated metastatic melanoma. We studied the efficacy of dabrafenib in patients with $BRAF^{V600E}$-mutated metastatic melanoma.

Methods We enrolled patients in this open-label phase 3 trial between Dec 23, 2010, and Sept 1, 2011. This report is based on a data cutoff date of Dec 19, 2011. Patients aged 18 years or older with previously untreated, stage IV or unresectable stage III $BRAF^{V600E}$ mutation-positive melanoma were randomly assigned (3:1) to receive dabrafenib (150 mg twice daily, orally) or dacarbazine (1000 mg/m² intravenously every 3 weeks). Patients were stratified according to American Joint Committee on Cancer stage (unresectable III+IVM1a+IVM1b *vs* IVM1c). The primary endpoint was investigator-assessed progression-free survival and was analysed by intention to treat; safety was assessed per protocol. This study is registered with ClinicalTrials.gov, number NCT01227889.

	Dabrafenib (n=187)	Dacarbazine (n=63)
Complete response	6 (3%)	1 (2%)
Partial response	87 (47%)	3 (5%)
Stable disease*	78 (42%)	30 (48%)
Progressive disease	10 (5%)	23 (37%)
Not evaluable†	6 (3%)	6 (10%)
Response rate (complete+partial response, n [%, 95% CI])	93 (50%, 42·4–57·1)	4 (6%, 1·8–15·5)

Data are number of patients (%), unless otherwise stated. *Includes cases determined to have non-target disease only by independent review. †Includes two cases determined to have no disease at baseline or post-baseline assessment by independent review.

***Table 2:* Best confirmed response to treatment, by independent review**

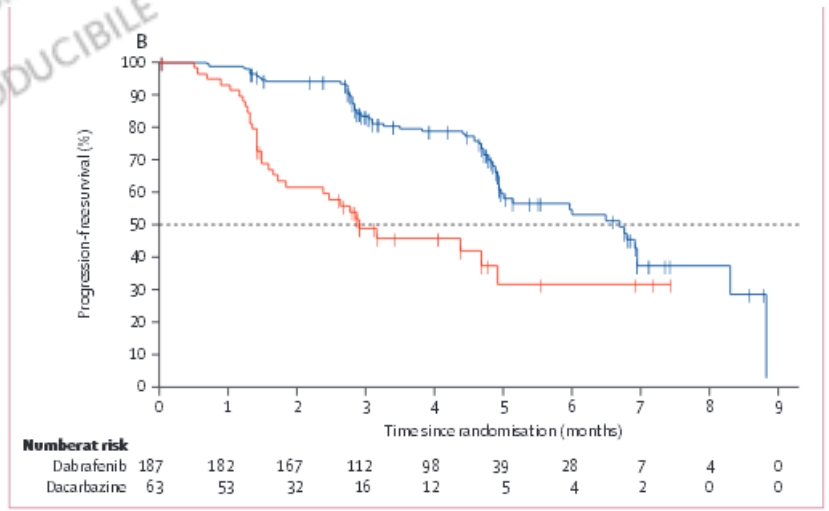


***Figure 2:* Progression-free survival by investigator assessment (A) and independent review (B)**
Progression-free survival (PFS) as assessed by the investigator (A) and by the independent review committee (B). Patients randomised to dabrafenib are shown in blue, patients randomised to dacarbazine in red. Tick marks indicate censored patients.

MECCANISMI DI RESISTENZA ACQUISITA A INIBITORI BRAF

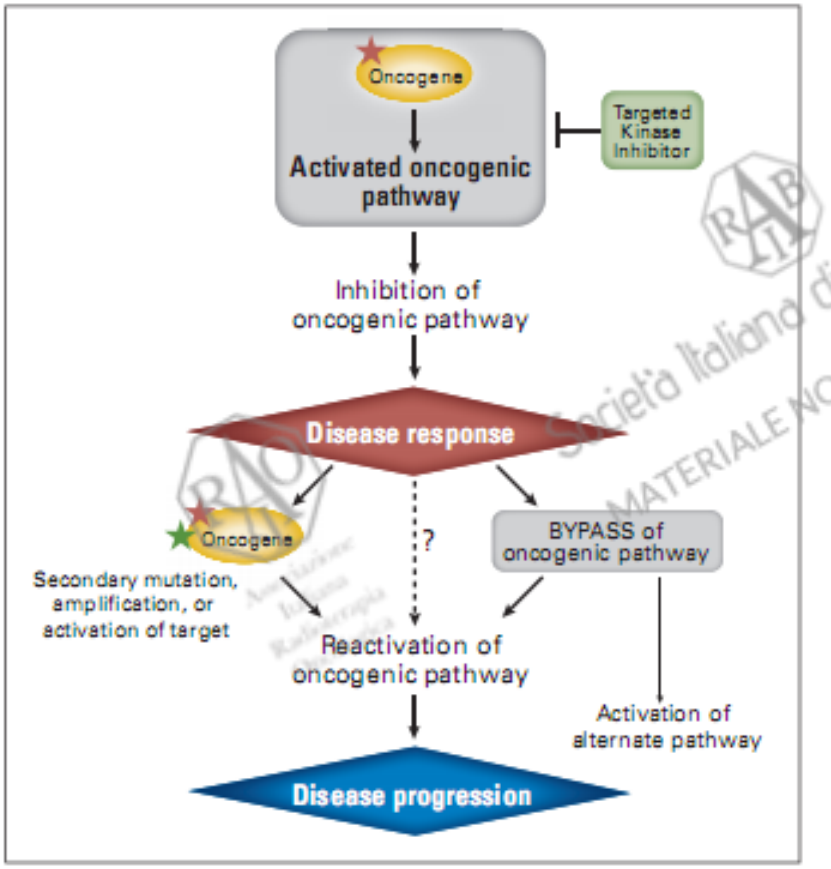


Fig 1. Kinase oncogene dependence and principles of drug resistance. Tumor

- 80% DEI CASI SONO BLOCCATI DA INIBIZIONE DELLA PATHWAY DI MAPK
- OPPURE ATTIVAZIONE VIE DI SEGNALE ALTERNATIVE (P13K/AKT/ mTOR)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma

G.V. Long, D. Stroyakovskiy, H. Gogas, E. Levchenko, F. de Braud, J. Larkin, C. Garbe, T. Jouary, A. Hauschild, J.J. Grob, V. Chiarion Sileni, C. Lebbe, M. Mandalà, M. Millward, A. Arance, I. Bondarenko, J.B.A.G. Haanen, J. Hansson, J. Utikal, V. Ferraresi, N. Kovalenko, P. Mohr, V. Probachai, D. Schadendorf, P. Nathan, C. Robert, A. Ribas, D.J. DeMarini, J.G. Irani, M. Casey, D. Ouellet, A.-M. Martin, N. Le, K. Patel, and K. Flaherty

ABSTRACT

BACKGROUND

Combined BRAF and MEK inhibition, as compared with BRAF inhibition alone, delays the emergence of resistance and reduces toxic effects in patients who have melanoma with *BRAF* V600E or V600K mutations.

METHODS

In this phase 3 trial, we randomly assigned 423 previously untreated patients who had unresectable stage IIIC or stage IV melanoma with a *BRAF* V600E or V600K mutation to receive a combination of dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily) or dabrafenib and placebo. The primary end point was progression-free survival. Secondary end points included overall survival, response rate, response duration, and safety. A preplanned interim overall survival analysis was conducted.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Long at the Melanoma Institute Australia, University of Sydney, and the Mater Hospital, 40 Rocklands Rd., North Sydney, NSW 2060, Australia, or at georgina.long@sydney.edu.au.

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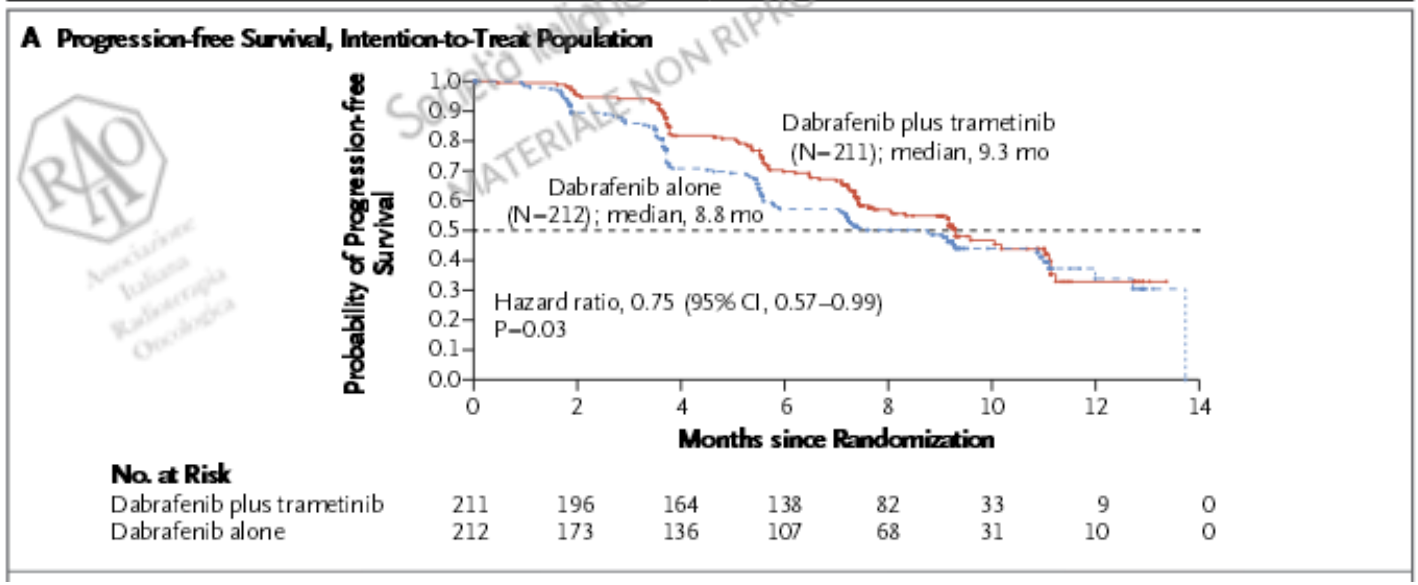
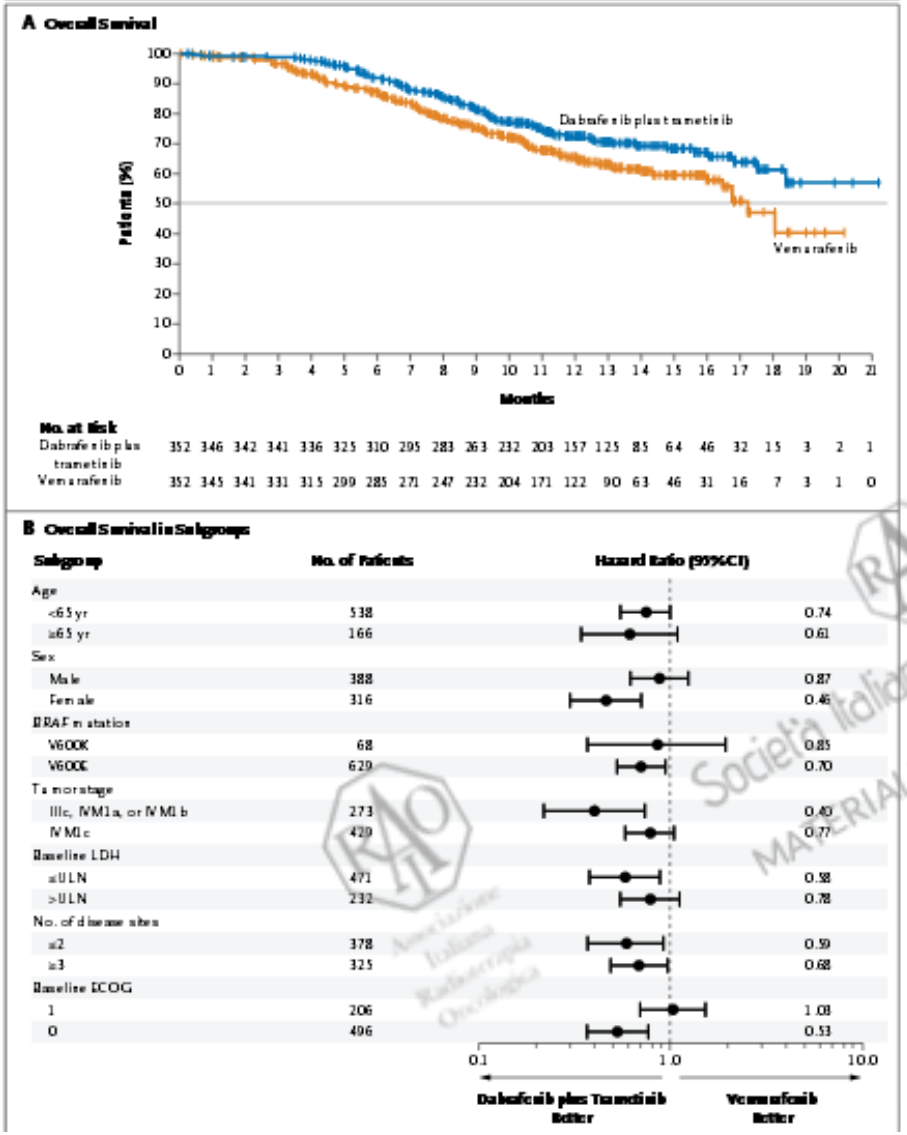
Table 2. Disease Response, According to the Type of *BRAF* Mutation.*

Variable	*BRAF* V600E or V600K		*BRAF* V600E		*BRAF* V600K	
	Dabrafenib plus Trametinib (N=210)	Dabrafenib Alone (N=210)	Dabrafenib plus Trametinib (N=179)	Dabrafenib Alone (N=180)	Dabrafenib plus Trametinib (N=31)	Dabrafenib Alone (N=30)
Best response — no. (%)						
Complete response	22 (10)	18 (9)	19 (11)	16 (9)	3 (10)	2 (7)
Partial response	118 (56)	90 (43)	102 (57)	80 (44)	16 (52)	10 (33)
Stable disease	54 (26)	69 (33)	46 (26)	62 (34)	8 (26)	7 (23)
Progressive disease	13 (6)	19 (9)	10 (6)	11 (6)	3 (10)	8 (27)
Could not be evaluated	3 (1)	14 (7)	2 (1)	11 (6)	1 (3)	3 (10)
Complete or partial response†						
No. of patients with response	140	108	121	96	19	12
Percentage (95% CI)	67 (60–73)	51 (45–58)	68 (60–74)	53 (46–61)	61 (42–78)	40 (23–59)





ORIGINAL ARTICLE

Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib

Caroline Robert, M.D., Ph.D., Boguslawa Karaszewska, M.D., Jacob Schachter, M.D., Piotr Rutkowski, M.D., Ph.D., Andrzej Mackiewicz, M.D., Ph.D., Daniil Stroiakovski, M.D., Michael Lichinitser, M.D., Reinhard Dummer, M.D., Florent Grange, M.D., Ph.D., Laurent Mortier, M.D., Vanna Chiarion-Sileni, M.D., Kamil Drucis, M.D., Ph.D., Ivana Krajsova, M.D., Axel Hauschild, M.D., Ph.D., Paul Lorigan, M.D., Pascal Wolter, M.D., Georgina V. Long, M.D., Ph.D., Keith Flaherty, M.D., Paul Nathan, M.D., Ph.D., Antoni Ribas, M.D., Ph.D., Anne-Marie Martin, Ph.D., Peng Sun, Ph.D., Wendy Crist, B.A., Jeff Legos, Ph.D., Stephen D. Rubin, M.D., Shonda M. Little, M.P.H., and Dirk Schadendorf, M.D.

Table 2. Investigator-Assessed Best Response (Intention-to-Treat Population).*

Response	Dabrafenib plus Trametinib (N=351)	Vemurafenib (N=350)
Type of response — no. (%)		
Complete	47 (13)	27 (8)
Partial	179 (51)	153 (44)
Stable disease	92 (26)	106 (30)
Progressive disease	22 (6)	38 (11)
Not evaluated	11 (3)	26 (7)
Objective response rate		
No. of patients with response (%)†	226 (64)	180 (51)
95% CI	59.1–69.4	46.1–56.8
Duration of response (95% CI) — mo	13.8 (11.0–NR)	7.5 (7.3–9.3)

* Data are missing for one patient in the combination-therapy group and two patients in the vemurafenib group because these patients did not have measurable disease at baseline. NR denotes not reached.

† Included in the objective response are complete and partial responses. P<0.001 for the between-group difference of 13% (95% CI, 6 to 20).

The NEW ENGLAND JOURNAL of MEDICINE

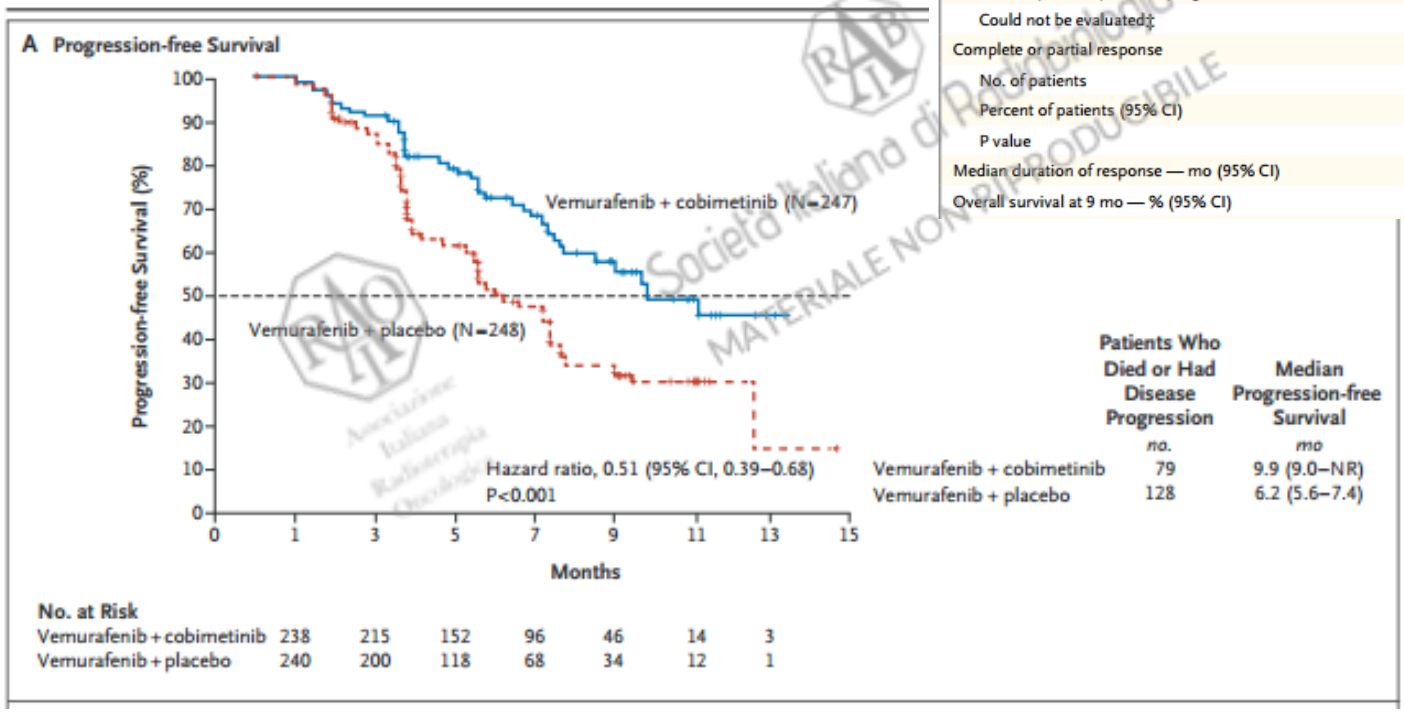
ORIGINAL ARTICLE

Combined Vemurafenib and Cobimetinib in *BRAF*-Mutated Melanoma

James Larkin, M.D., Ph.D., Paolo A. Ascierto, M.D., Brigitte Dréno, M.D., Ph.D., Victoria Atkinson, M.D., Gabriella Liszkay, M.D., Michele Maio, M.D., Mario Mandalà, M.D., Lev Demidov, M.D., Daniil Stroyakovskiy, M.D., Luc Thomas, M.D., Ph.D., Luis de la Cruz-Merino, M.D., Caroline Dutriaux, M.D., Claus Garbe, M.D., Mika A. Sovak, M.D., Ph.D., Ilsung Chang, Ph.D., Nicholas Choong, M.D., Stephen P. Hack, M.D., Ph.D., Grant A. McArthur, M.B., B.S., Ph.D., and Antoni Ribas, M.D., Ph.D.

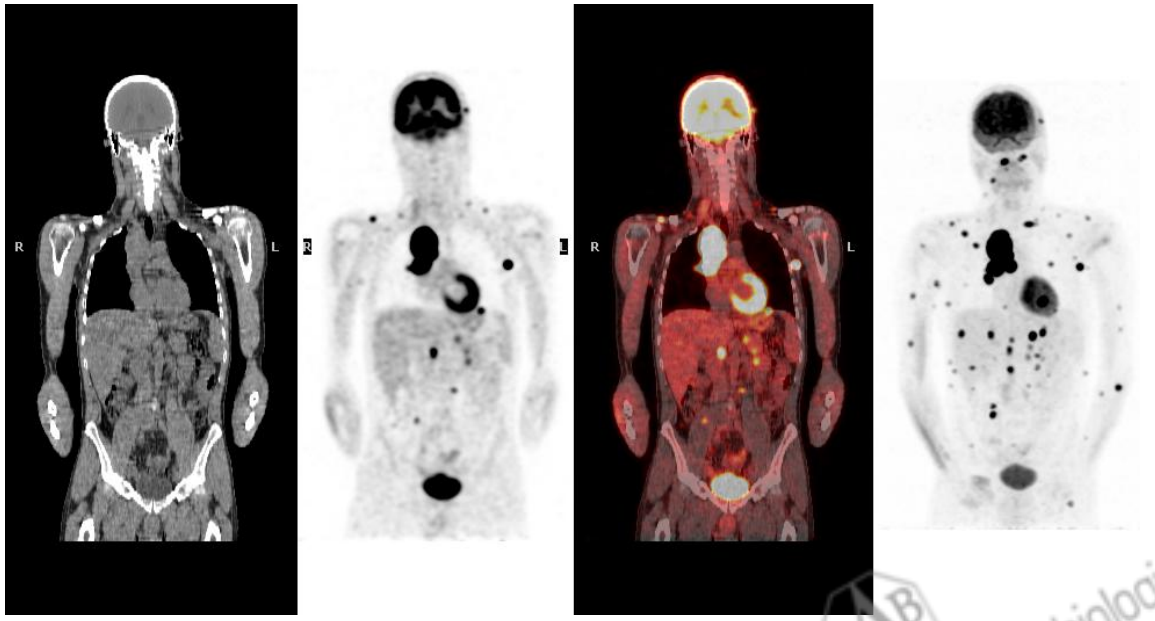
Table 2. Efficacy Summary.*

End Point	Vemurafenib and Placebo (N=248)	Vemurafenib and Cobimetinib (N=247)
Progression-free survival		
According to investigator assessment†		
Median duration — mo (95% CI)	6.2 (5.6–7.4)	9.9 (9.0–NR)
Hazard ratio for death or disease progression (95% CI)	Reference	0.51 (0.39–0.68)
P value	Reference	<0.001
According to assessment by independent review facility†		
Median duration — mo (95% CI)	6.0 (5.6–7.5)	11.3 (8.5–NR)
Hazard ratio for death or disease progression (95% CI)	Reference	0.60 (0.45–0.79)
P value	Reference	<0.001
Best response — no. (%)		
Complete response	11 (4)	25 (10)
Partial response	100 (40)	142 (57)
Stable disease	105 (42)	49 (20)
Progressive disease	25 (10)	19 (8)
No complete response or progressive disease	1 (<1)	0
Could not be evaluated‡	6 (2)	12 (5)
Complete or partial response		
No. of patients	111	167
Percent of patients (95% CI)	45 (38–51)	68 (61–73)
P value	Reference	<0.001
Median duration of response — mo (95% CI)	7.3 (5.8–NR)	NR (9.3–NR)
Overall survival at 9 mo — % (95% CI)	73 (65–80)	81 (75–87)



This article was published on September 29, 2014, at NEJM.org.

TORINO
IL PAZIENTE BRAF MUTATO: DALLA RICERCA ALLA GESTIONE CLINICA
Multidisciplinarità e integrazione
12 Settembre 2016



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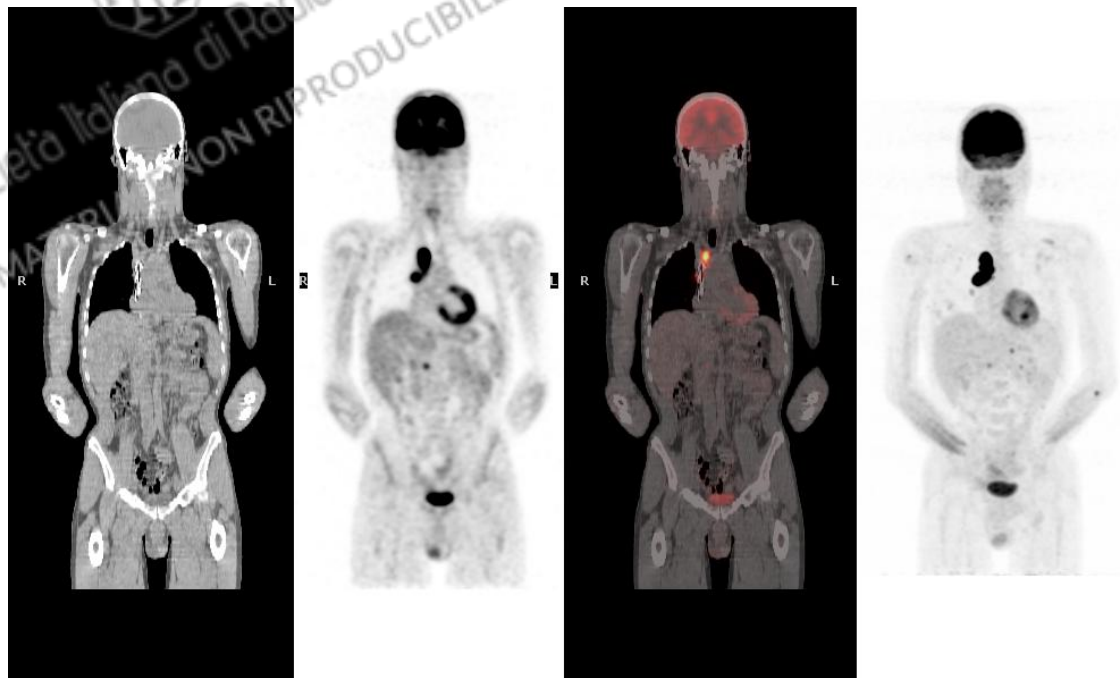

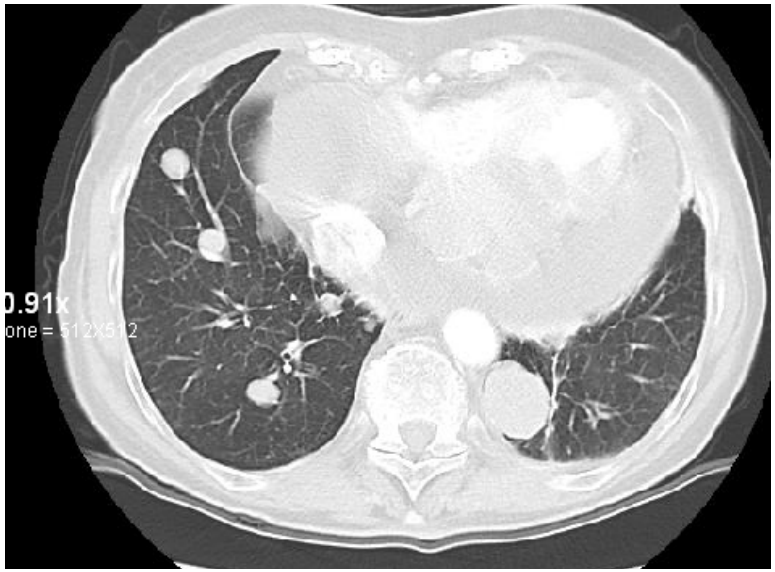

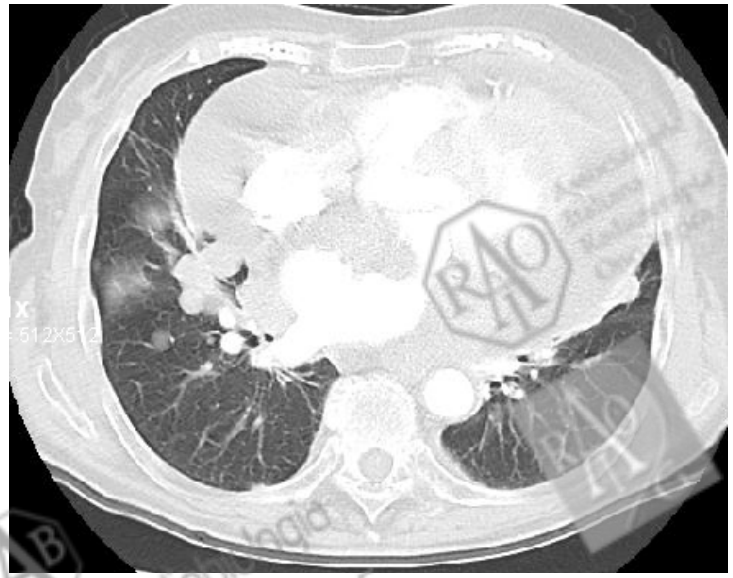

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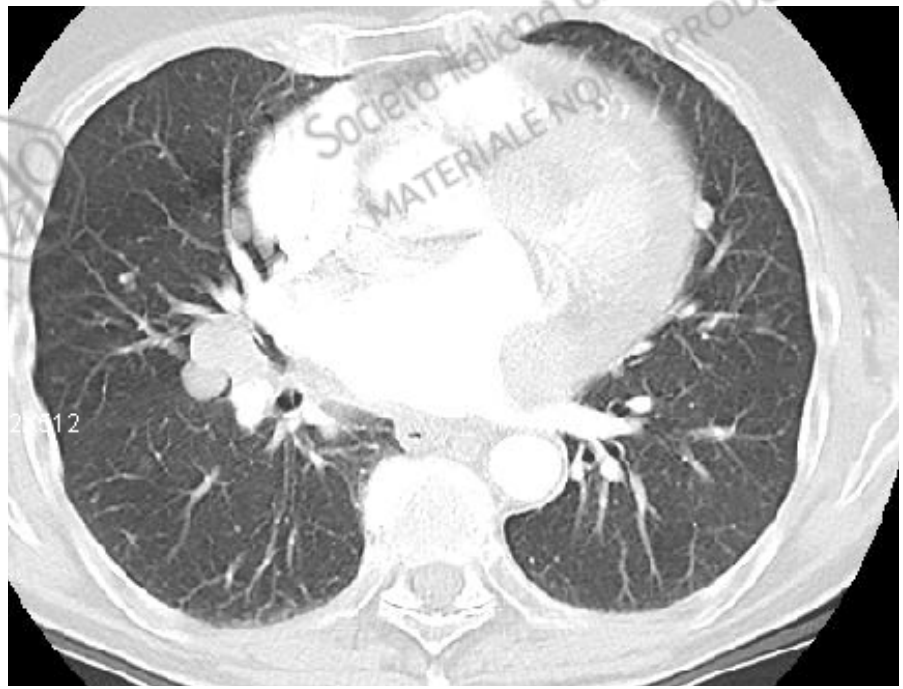

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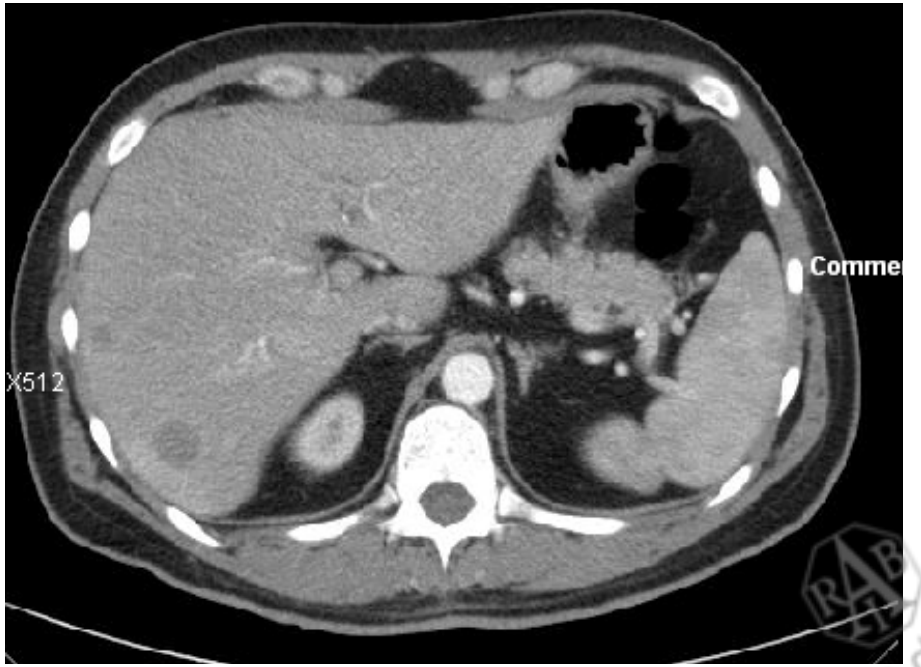
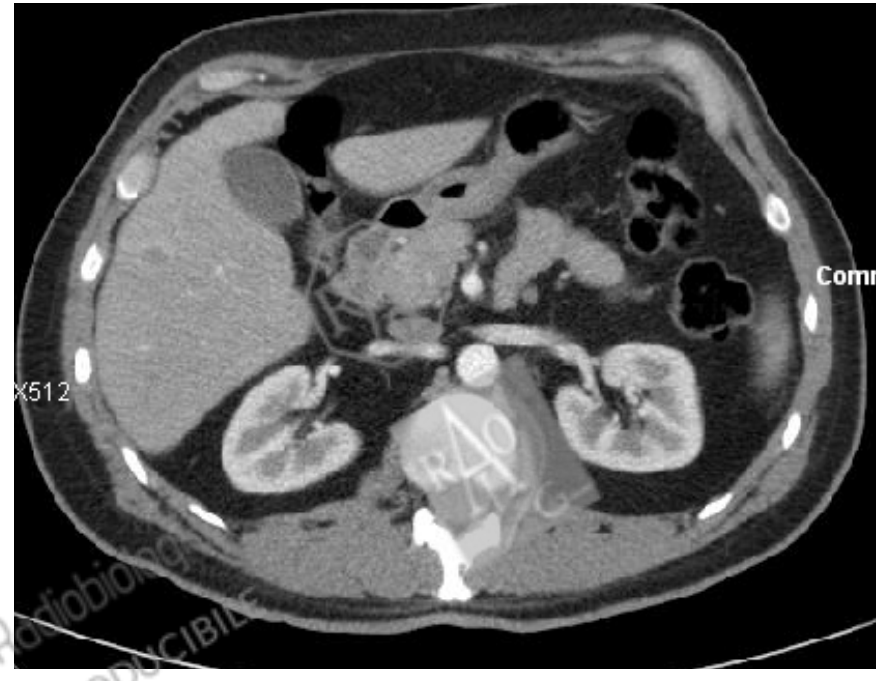
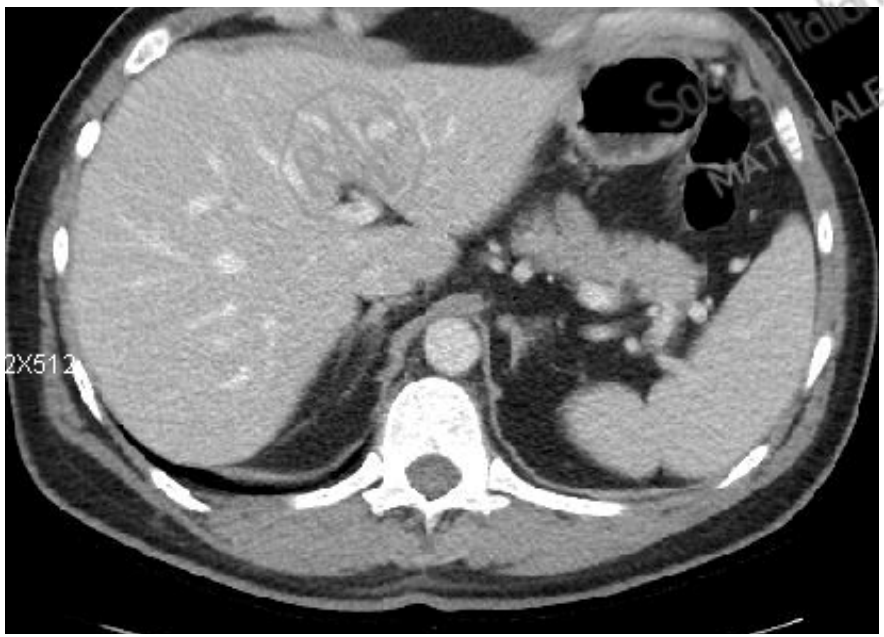
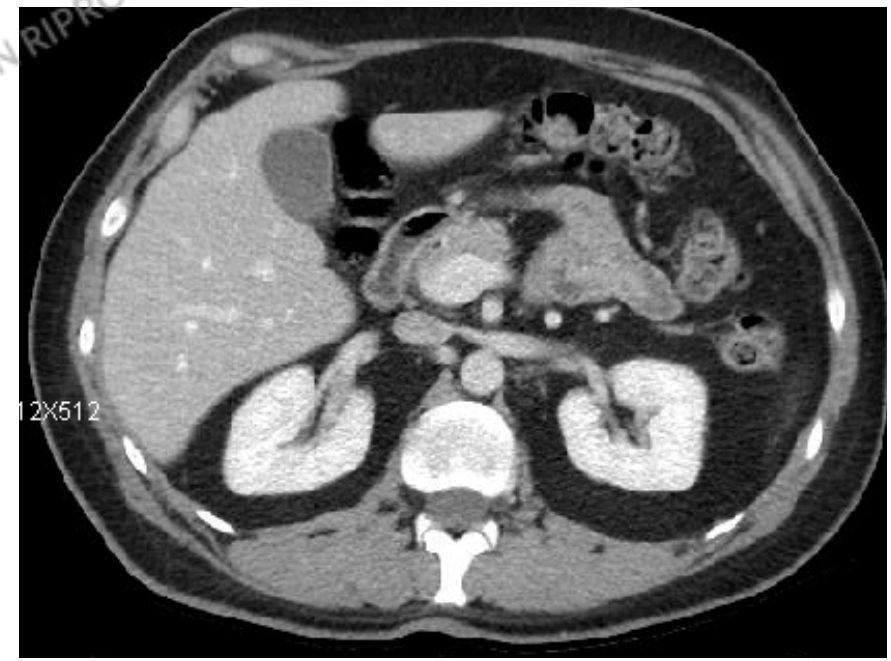








MDX010-20: risultati per endpoint secondari

	Arm A Ipi + gp100 N=403	Arm B Ipi + pbo N=137	Arm C gp100 + pbo N=136
BORR*, %	5.7	10.9	1.5
P-value: A vs C		0.0433	
P-value: B vs C		0.0012	
DCR‡, %	20.1	28.5	11.0
P-value: A vs C		0.0179	
P-value: B vs C		0.0002	

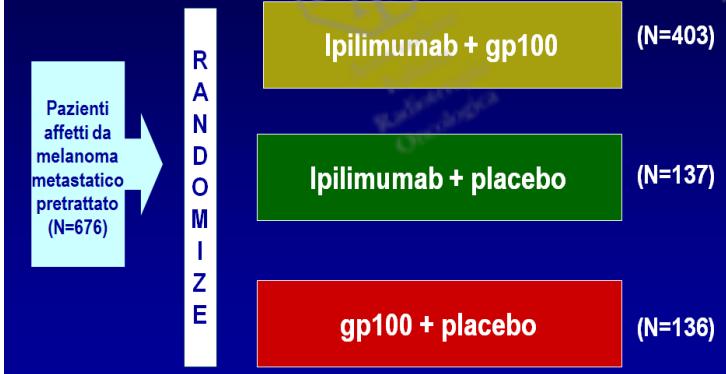
*: Best Overall Response Rate: CR + PR
‡: Disease Control Rate: percentage of patients with CR, PR, or SD

Hodi FS, et al. New Engl J Med 2010;363(8):711-723.

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

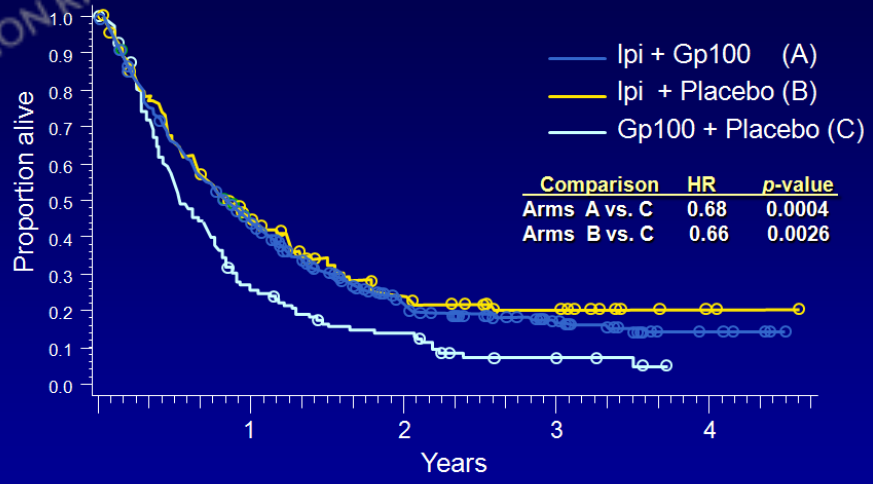
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

MDX010-20: Randomizzazione



Hodi S et al. NEJM 2010;363(8):711-23

MDX010-20: Sopravvivenza globale



Tasso di sopravvivenza	Ipi + gp100 (N=403)	Ipi + pbo (N=137)	Gp100 + pbo (N=136)
1 anno	44%	46%	25%
2 anni	22%	26%	14%
Sopravvivenza globale mediana (range)	10,0 (8,5-11,5)	10,1 (8,0-13,8)	6,4 (5,5-8,7)

Hodi S et al. NEJM 2010;363(8):711-23

3-year survival rate= 22%

VOLUME 33 · NUMBER 17 · JUNE 10 2015

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

Dirk Schadendorf, F. Stephen Hodi, Caroline Robert, Jeffrey S. Weber, Kim Margolin, Omid Hamid, Debra Patt, Tai-Tsang Chen, David M. Berman, and Jedd D. Wolchok

See accompanying editorial on page 1865 and article on page 1873

Dirk Schadendorf, University Hospital Essen, Essen, Germany; F. Stephen Hodi, Dana-Farber Cancer Institute, Boston, MA; Caroline Robert, Institute Gustave Roussy, Villejuif, France; Jeffrey S. Weber, Moffitt Cancer Center, Tampa, FL; Kim Margolin, [illegible] Washington, Seattle, WA; [illegible], The Angeles Clinic and [illegible]stitute, Los Angeles, CA; [illegible] The US Oncology Network, Specialty Health, Houston, [illegible]g Chen, Bristol-Myers [illegible]lingford, CT; David M.

A B S T R A C T

Purpose

To provide a more precise estimate of long-term survival observed for ipilimumab-treated patients with advanced melanoma, we performed a pooled analysis of overall survival (OS) data from multiple studies.

Methods

The primary analysis pooled OS data for 1,861 patients from 10 prospective and two retrospective studies of ipilimumab, including two phase III trials. Patients were previously treated (n = 1,257) or treatment naive (n = 604), and the majority of patients received ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706). We also conducted a secondary analysis of OS data (n = 4,846) with an

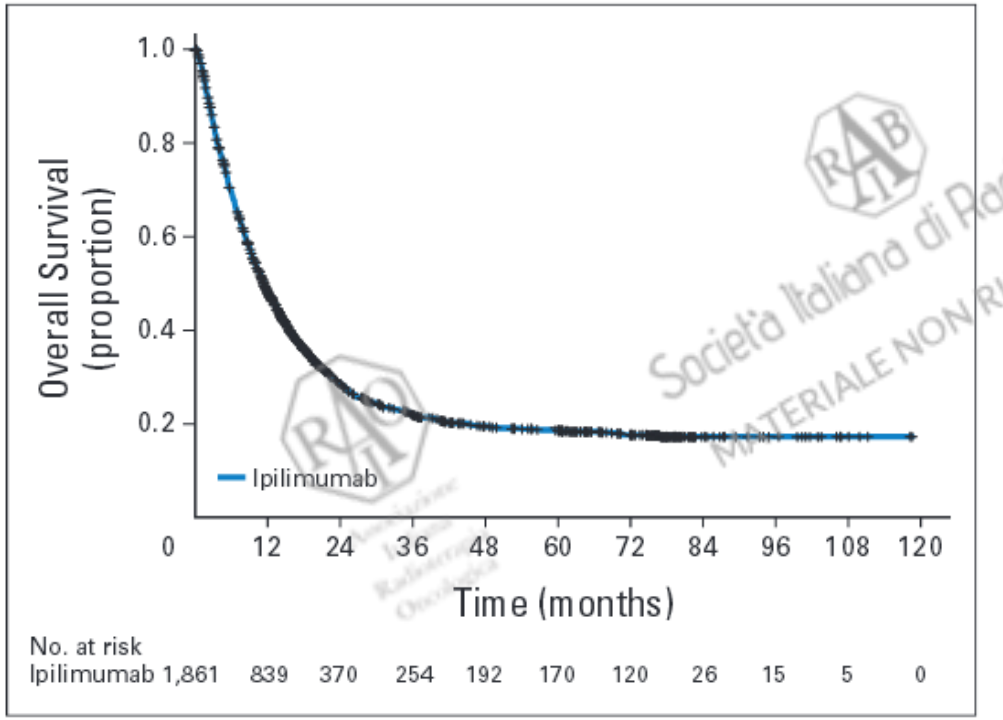


Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.

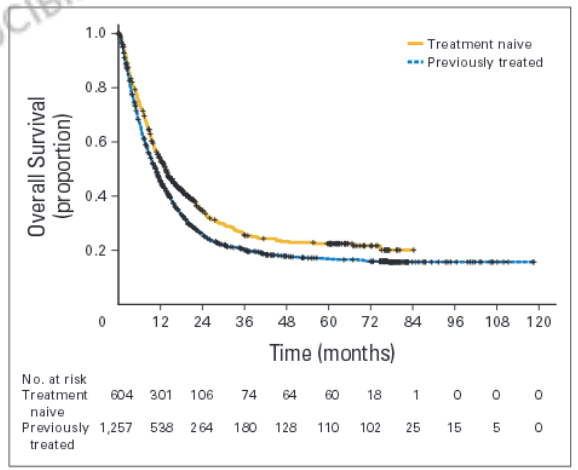


Fig 2 Subset analysis of overall survival (OS) by prior therapy. Nonrandomized subset analysis of OS in treatment-naive (n = 604) and previously treated (n = 1,257) patients with metastatic melanoma who received ipilimumab in 10 prospective trials and two retrospective, observational studies. Median OS was 13.5 months (95% CI, 11.9 to 15.4 months) for treatment-naive patients and 10.7 months (95% CI, 9.6 to 11.4 months) for previously treated patients, with 3-year survival rates of 26% (95% CI, 21% to 30%) and 20% (95% CI, 18% to 23%), respectively. Crosses indicate censored patients.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalcioiu, M.D., Vanna Chiarion-Sileni, M.D., Cornelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.

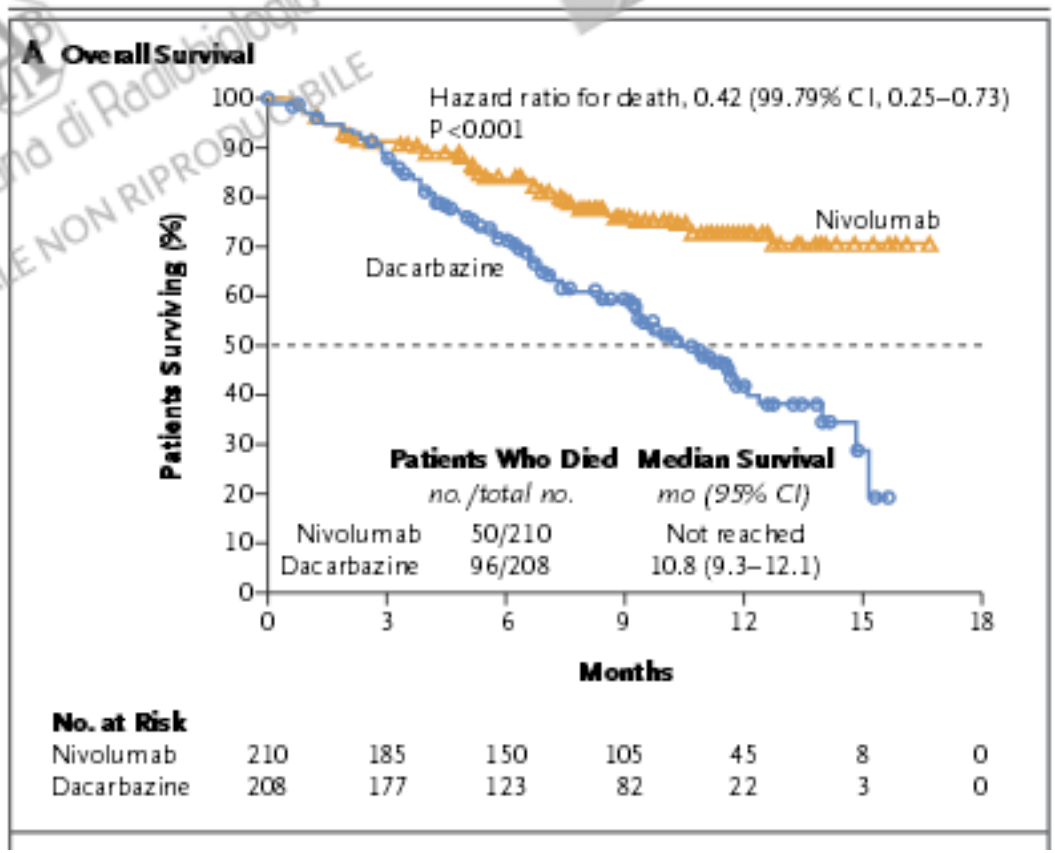
N Engl J Med. 2015 Jan 22;372(4):320-30.

CheckMate 066 ClinicalTrials.gov number, NCT01721772.

ABSTRACT

Table 2. Response to Treatment.*

Response	Nivolumab (N=210)	Dacarbazine (N=208)
Best overall response — no. (%)†		
Complete response	16 (7.6)	2 (1.0)
Partial response	68 (32.4)	27 (13.0)
Stable disease	35 (16.7)	46 (22.1)
Progressive disease	69 (32.9)	101 (48.6)
Could not be determined	22 (10.5)	32 (15.4)
Objective response‡		
No. of patients (% [95% CI])	84 (40.0 [33.3–47.0])	29 (13.9 [9.5–19.4])
Difference — percentage points (95% CI)	26.1 (18.0–34.1)	
Estimated odds ratio (95% CI)	4.06 (2.52–6.54)	
P value	<0.001	
Time to objective response — mo		
Median	2.1	2.1
Range	1.2–7.6	1.8–3.6
Mean	2.6±1.3	2.5±0.7
Duration of response — mo§		
Median (95% CI)	Not reached	6.0 (3.0–not reached)
Range	0.0–12.5	1.1–10.0



Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial

Jeffrey S Weber, Sandra P D'Angelo, David Minor, F Stephen Hodi, Ralf Gutzmer, Bart Neyns, Christoph Hoeller, Nikhil I Khushalani, Wilson H Miller Jr, Christopher D Lao, Gerald P Linette, Luc Thomas, Paul Lorigan, Kenneth F Grossmann, Jessica C Hassel, Michele Maio, Mario Sznol, Paolo A Ascierto, Peter Mohr, Bartosz Chmielowski, Alain Bryce, Inge M Svane, Jean-Jacques Grob, Angela M Krackhardt, Christine Horak, Alexandre Lambert, Arvin S Yang, James Lorigan

Summary

Background Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, can result in durable responses in patients with melanoma who have progressed after ipilimumab and BRAF inhibitors. We assessed the efficacy and safety of nivolumab compared with investigator's choice of chemotherapy (ICC) as a second-line or later-line treatment in patients with advanced melanoma.

Methods In this randomised, controlled, open-label, phase 3 trial, we recruited patients at 90 sites in 14 countries. Eligible patients were 18 years or older, had unresectable or metastatic melanoma and progressed after ipilimumab or

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See Comment page 350
See Online for interview with

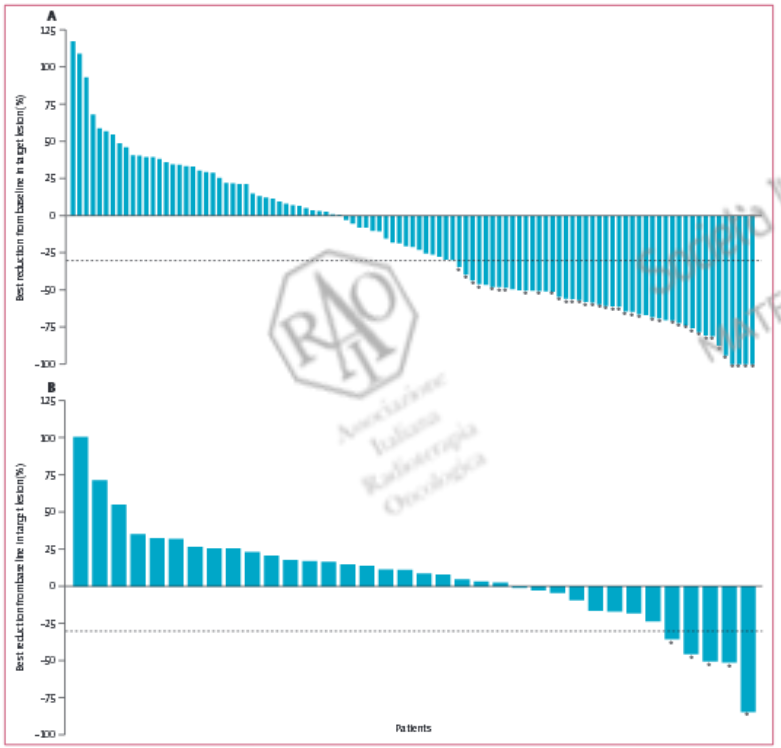


Figure 2: Best tumour burden change from baseline in target lesions in patients who received nivolumab (A) and patients who received investigator's choice of chemotherapy (B)
Waterfall plots show tumour response, which measure the change from baseline in the sum of the longest diameters of target lesions, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Asterisks denote confirmed responders, defined as those who had a repeat scan at least 4 weeks after the first scan that confirmed a response.

	Nivolumab (n=120)	ICC (n=47)
Objective response	38 (31·7% [23·5–40·8])	5 (10·6% [3·5–23·1])
Best overall response		
Complete response	4 (3·3%)	0
Partial response	34 (28·3%)	5 (10·6%)
Stable disease	28 (23·3%)	16 (34·0%)
Progressive disease	42 (35·0%)	15 (31·9%)
Unable to establish†	12 (10·0%)	11 (23·4%)

Data are n (% [95% CI]) or n (%). *Confirmed response by independent radiology review committee per Response Evaluation Criteria in Solid Tumors version 1.1. †Patients who did not have a protocol-specified scan at 9 months, most commonly because of clinical progression, consent withdrawal, or receiving of subsequent treatment. ICC=investigator's choice of chemotherapy.

Table 2: Response* to treatment in the per-protocol objective response population

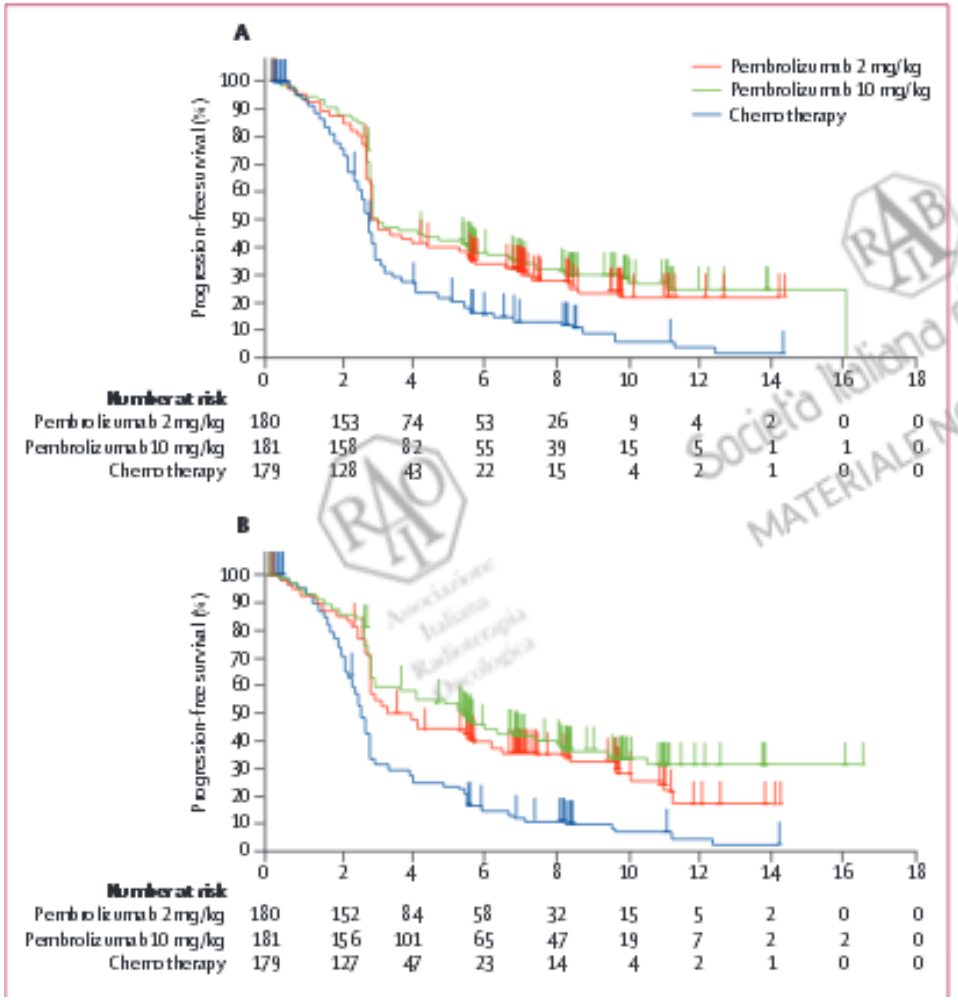
Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial

Antoni Ribas, Igor Puzanov, Reinhard Dummer, Dirk Schadendorf, Omid Hamid, Caroline Robert, F Stephen Hodi, Jacob Schachter, Anna C Pavlick, Karl D Lewis, Lee D Cranmer, Christian U Blank, Steven J O'Day, Paolo A Ascierto, April K S Salama, Kim A Margolin, Carmen Loquai, Thomas K Eigentler, Tara C Gangadhar, Matteo S Carlino, Sanjiv S Agarwala, Stergios J Moschos, Jeffrey A Sosman, Simone M Goldinger, Ronnie Shapira-Frommer, Rene Gonzalez, John M Kirkwood, Jedd D Wolchok, Alexander Eggermont, Xiaoyun Nicole Li, Wei Zhou, Adriane M Zernhelt, Joy Lis, Scot Ebbinghaus, S Peter Kang, Adil Daud

Lancet Oncol 2015; 16: 908–18
Published Online
June 24, 2015
http://dx.doi.org/10.1016/

Summary

Background Patients with melanoma that progresses on ipilimumab and, if *BRAF*^{V600} mutant-positive, a BRAF or MEK inhibitor or both, have few treatment options. We assessed the efficacy and safety of two pembrolizumab doses versus investigator-choice chemotherapy in patients with ipilimumab-refractory melanoma.



	Pembrolizumab 2 mg/kg (n=180)	Pembrolizumab 10 mg/kg (n=181)	Chemotherapy control (n=179)
Progression-free survival assessed per RECIST v1.1, by independent central review			
Number of events*	129 (72%)	126 (70%)	155 (87%)
Median duration (months)	2·9 (2·8–3·8)	2·9 (2·8–4·7)	2·7 (2·5–2·8)
Proportion progression free at 6 months	34% (27–41)	38% (31–45)	16% (10–22)
Proportion progression free at 9 months	24% (17–31)	29% (23–37)	8% (4–14)
Restricted mean duration based on 12 months of follow-up (months; post-hoc analysis)	5·4 (4·7–6·0)	5·8 (5·1–6·4)	3·6 (3·2–4·1)
HR for death or disease progression,† pembrolizumab vs chemotherapy	0·57 (0·45–0·73); p<0·0001‡	0·50 (0·39–0·64); p<0·0001‡	Ref
HR for death or disease progression,† pembrolizumab 10 mg/kg vs 2 mg/kg	Ref	0·91 (0·71–1·16)§	..
Progression-free survival assessed per RECIST v1.1, by investigator review			
Number of events*	122 (68%)	112 (62%)	157 (88%)
Median duration (months)	3·7 (2·9–5·4)	5·4 (3·8–6·8)	2·6 (2·4–2·8)
Proportion progression free at 6 months	39% (32–46)	45% (37–52)	15% (10–21)
Proportion progression free at 9 months	32% (25–40)	36% (29–44)	10% (6–15)
Restricted mean duration based on 12 months of follow-up (months; post-hoc analysis)	5·8 (5·2–6·4)	6·5 (5·8–7·1)	3·7 (3·2–4·1)
HR for death or disease progression,† pembrolizumab vs chemotherapy	0·49 (0·38–0·62); p<0·0001‡	0·41 (0·32–0·52); p<0·0001‡	Ref
HR for death or disease progression,† pembrolizumab 10 mg/kg vs 2 mg/kg	Ref	0·81 (0·63–1·05); p=0·12¶	..
Progression-free survival assessed per modified RECIST v1.1, by investigator review			
Number of events	117 (65%)	108 (60%)	154 (86%)
Median duration (months)	4·2 (3·1–6·2)	5·6 (4·2–7·7)	2·6 (2·5–2·8)
Proportion progression free at 6 months	43% (35–50)	48% (40–55)	17% (12–23)
Proportion progression free at 9 months	35% (27–43)	38% (30–46)	10% (6–16)
HR for death or disease progression,† pembrolizumab vs chemotherapy	0·45 (0·35–0·57); p<0·0001‡	0·39 (0·30–0·51); p<0·0001‡	Ref
HR for death or disease progression,† pembrolizumab 10 mg/kg vs 2 mg/kg	Ref	0·82 (0·63–1·07); p=0·15¶	..
Best overall response assessed per RECIST v1.1, by independent central review			
Complete response	4 (2%)	5 (3%)	0
Partial response	34 (19%)	41 (23%)	8 (4%)
Stable disease	32 (18%)	31 (17%)	33 (18%)
Progressive disease	84 (47%)	86 (48%)	111 (62%)
Not evaluable‖	26** (14%)	18 (10%)	27 (15%)
Overall response assessed per RECIST v1.1, by independent central review			
Number of patients who responded (% [95% CI])	38 (21% [15–28])	46 (25% [19–32])	8 (4% [2–9])
Difference in overall response,†† pembrolizumab vs control	13% (7–21); p<0·0001	18% (11–27); p<0·0001	Ref
Difference in overall response,†† pembrolizumab 10 mg/kg vs 2 mg/kg	Ref	6% (−3 to 14); p=0·21¶	..
Duration of response			

KEYNOTE-006

ORIGINAL ARTICLE

Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*

ABSTRACT

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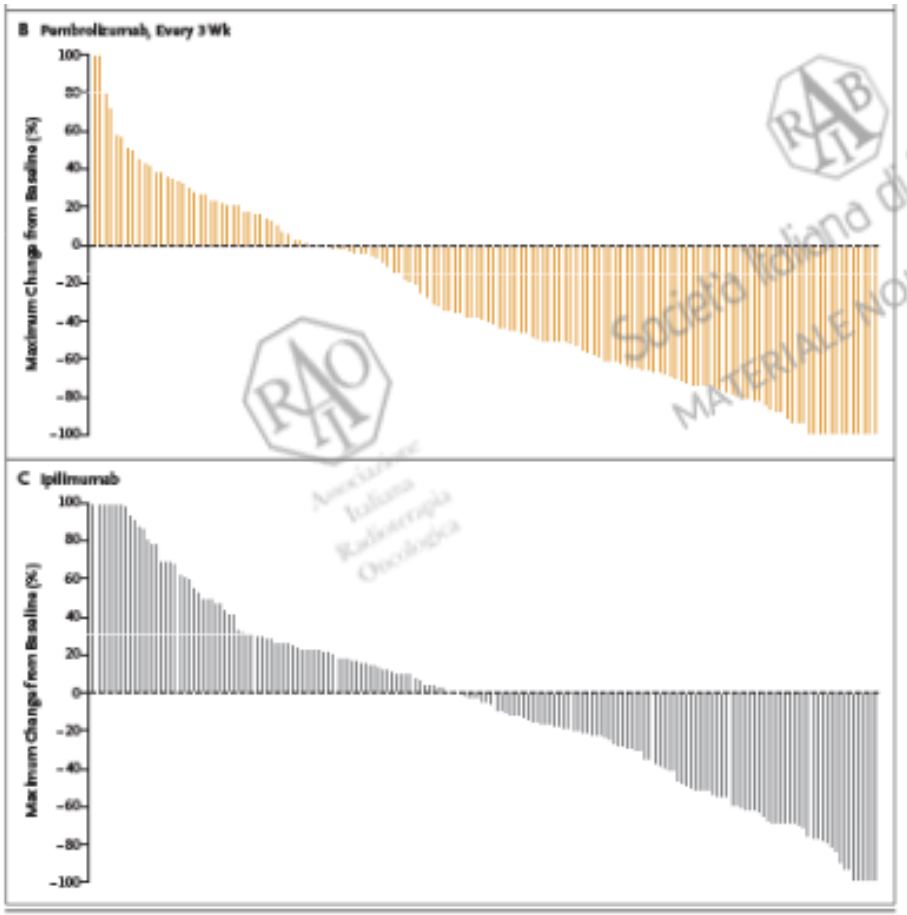

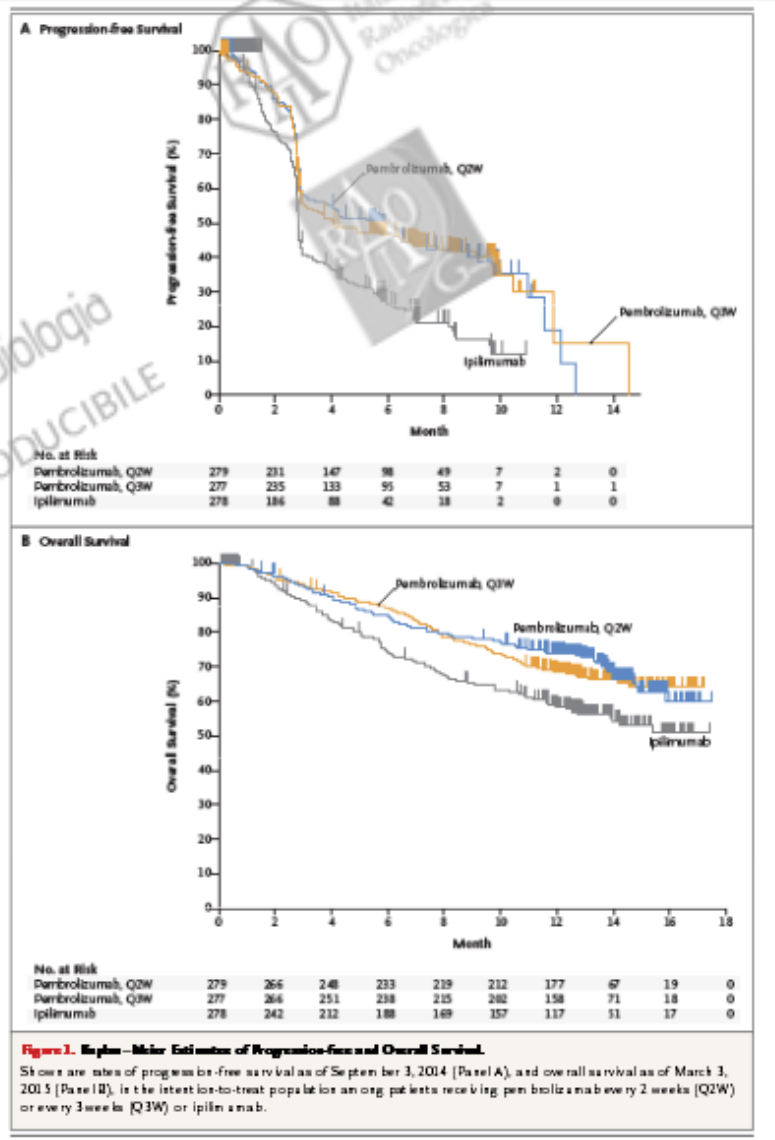

Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival.

Shown are rates of progression-free survival as of September 3, 2014 (Panel A), and overall survival as of March 3, 2015 (Panel B), in the intention-to-treat population among patients receiving pembrolizumab every 2 weeks (Q2W) or every 3 weeks (Q3W) or ipilimumab.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

Michael A. Postow, M.D., Jason Chesney, M.D., Ph.D., Anna C. Pavlick, D.O., Caroline Robert, M.D., Ph.D., Kenneth Grossmann, M.D., Ph.D., David McDermott, M.D., Gerald P. Linette, M.D., Ph.D., Nicolas Meyer, M.D., Jeffrey K. Giguere, M.D., Sanjiv S. Agarwala, M.D., Montaser Shaheen, M.D., Marc S. Ernstoff, M.D., David Minor, M.D., April K. Salama, M.D., Matthew Taylor, M.D., Patrick A. Ott, M.D., Ph.D., Linda M. Rollin, Ph.D., Christine Horak, Ph.D., Paul Gagnier, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and F. Stephen Hodi, M.D.

ABSTRACT

BACKGROUND

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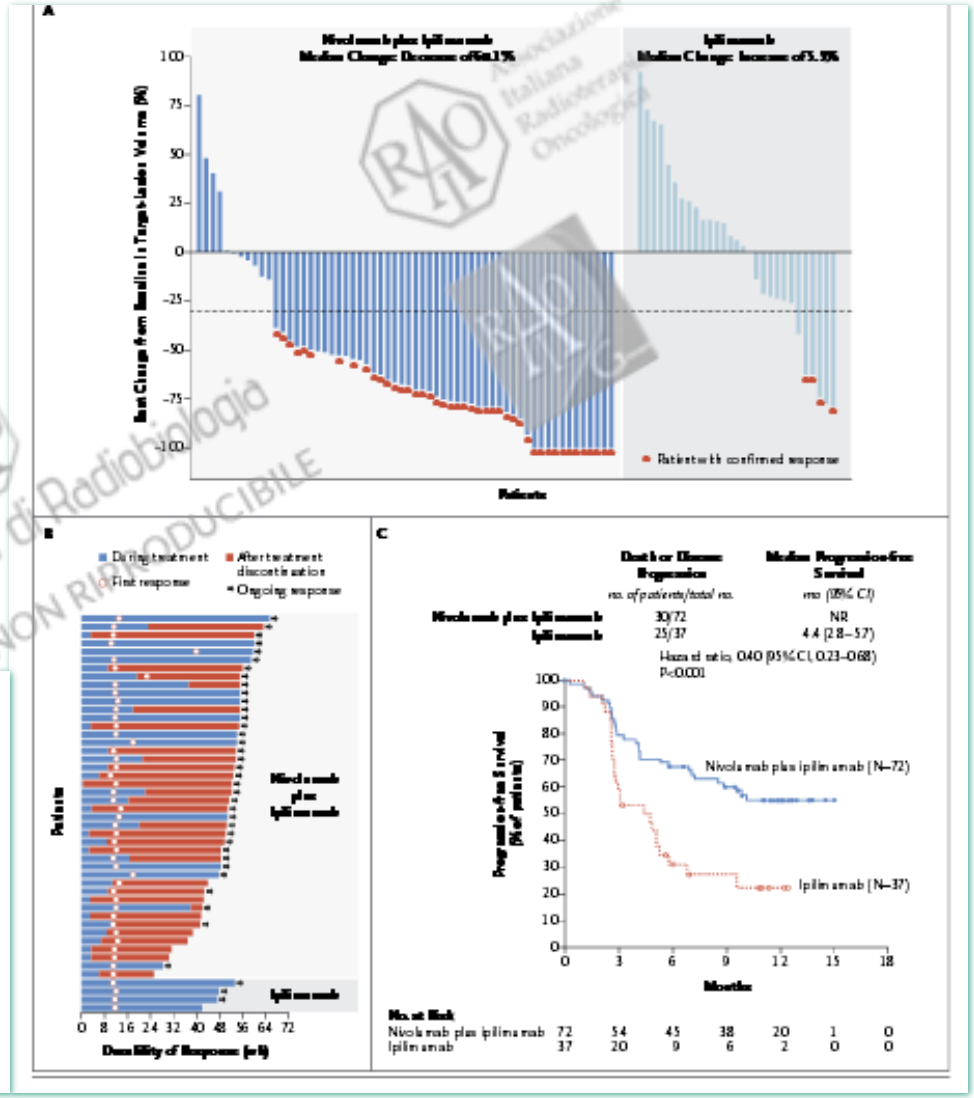

Table 2. Response to Treatment.

Variable	Patients with *BRAF* Wild-Type Tumors		Patients with *BRAF* V600 Mutation–Positive Tumors	
	Nivolumab plus Ipilimumab (N=72)	Ipilimumab (N=37)	Nivolumab plus Ipilimumab (N=23)	Ipilimumab (N=10)
Best overall response — no. (%)*				
Complete response	16 (22)	0	5 (22)	0
Partial response	28 (39)	4 (11)	7 (30)	1 (10)
Stable disease	9 (12)	13 (35)	3 (13)	1 (10)
Progressive disease	10 (14)	15 (41)	5 (22)	7 (70)
Could not be determined	9 (12)	5 (14)	3 (13)	1 (10)
Patients with objective response — no. (% [95% CI])†	44 (61 [49–72])	4 (11 [3–25])	12 (52 [31–73])	1 (10 [0–45])

n engl j med 372;21, 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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ABSTRACT

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ClinicalTrials.gov
NCT01844505.

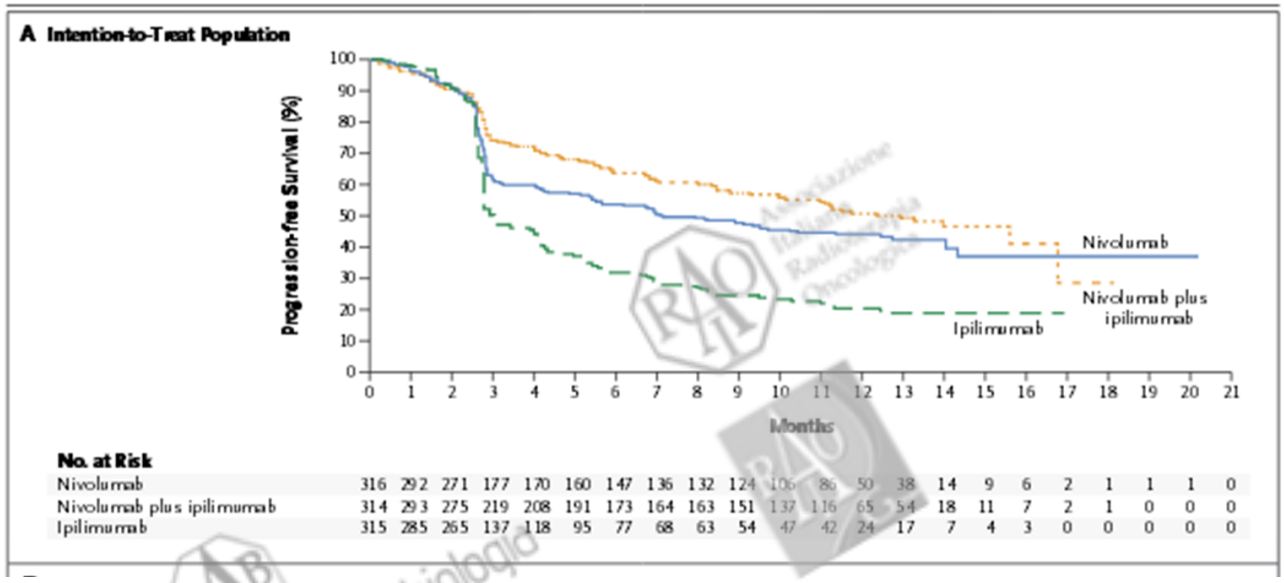
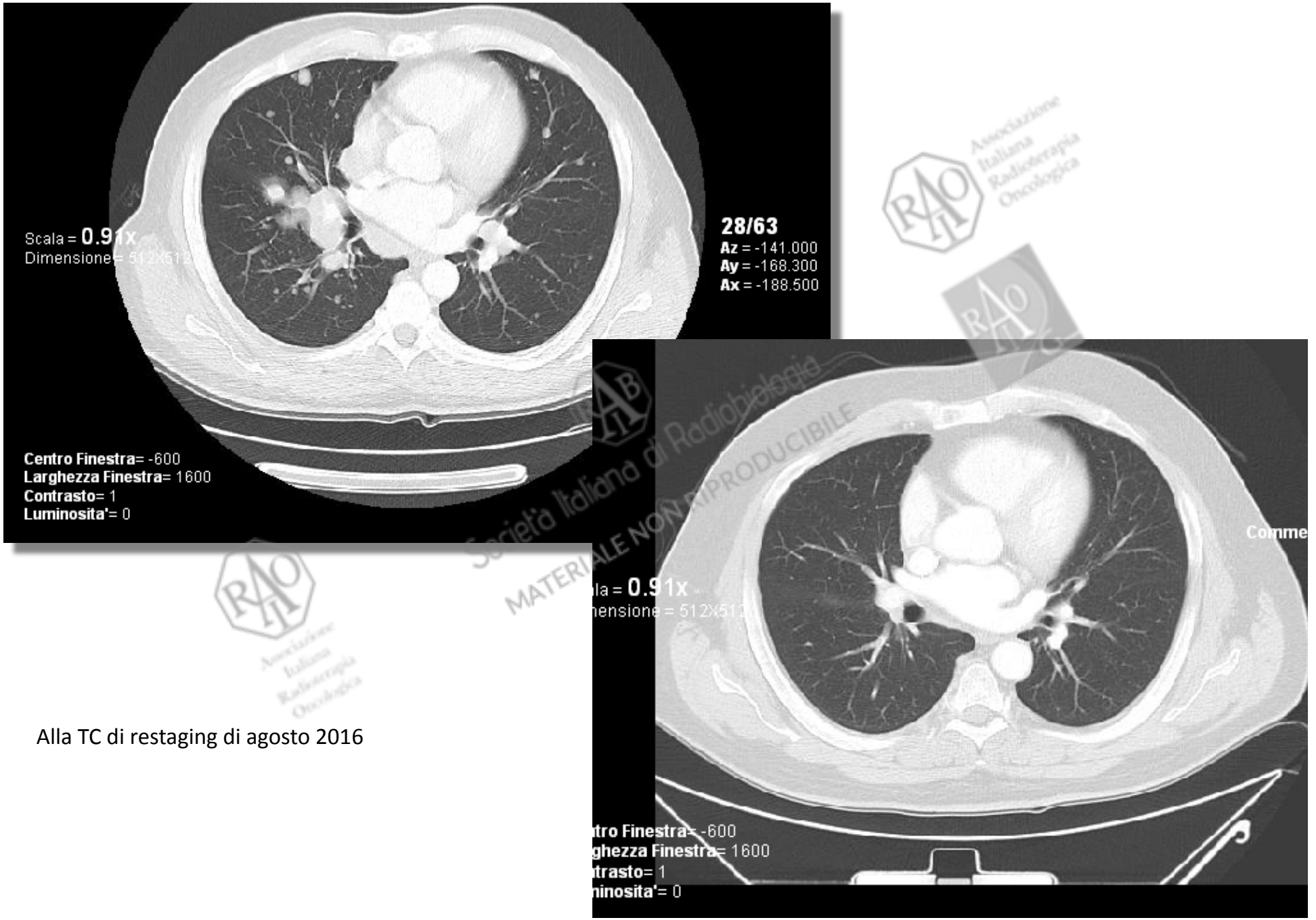


Table 2. Response to Treatment.

Variable	Nivolumab (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab (N=315)
Best overall response — no. (%)*			
Complete response	28 (8.9)	36 (11.5)	7 (2.2)
Partial response	110 (34.8)	145 (46.2)	53 (16.8)
Stable disease	34 (10.8)	41 (13.1)	69 (21.9)
Progressive disease	119 (37.7)	71 (22.6)	154 (48.9)
Could not be determined	25 (7.9)	21 (6.7)	32 (10.2)
Objective response†			
No. of patients with response	138	181	60
% of patients (95% CI)	43.7 (38.1–49.3)	57.6 (52.0–63.2)	19.0 (14.9–23.8)
Estimated odds ratio (95% CI)‡	3.40 (2.02–5.72)	6.11 (3.59–10.38)	—
Two-sided P value	<0.001	<0.001	—
Time to objective response — mo			
Median	2.78	2.76	2.79
Range	2.3–12.5	1.1–11.6	2.5–12.4



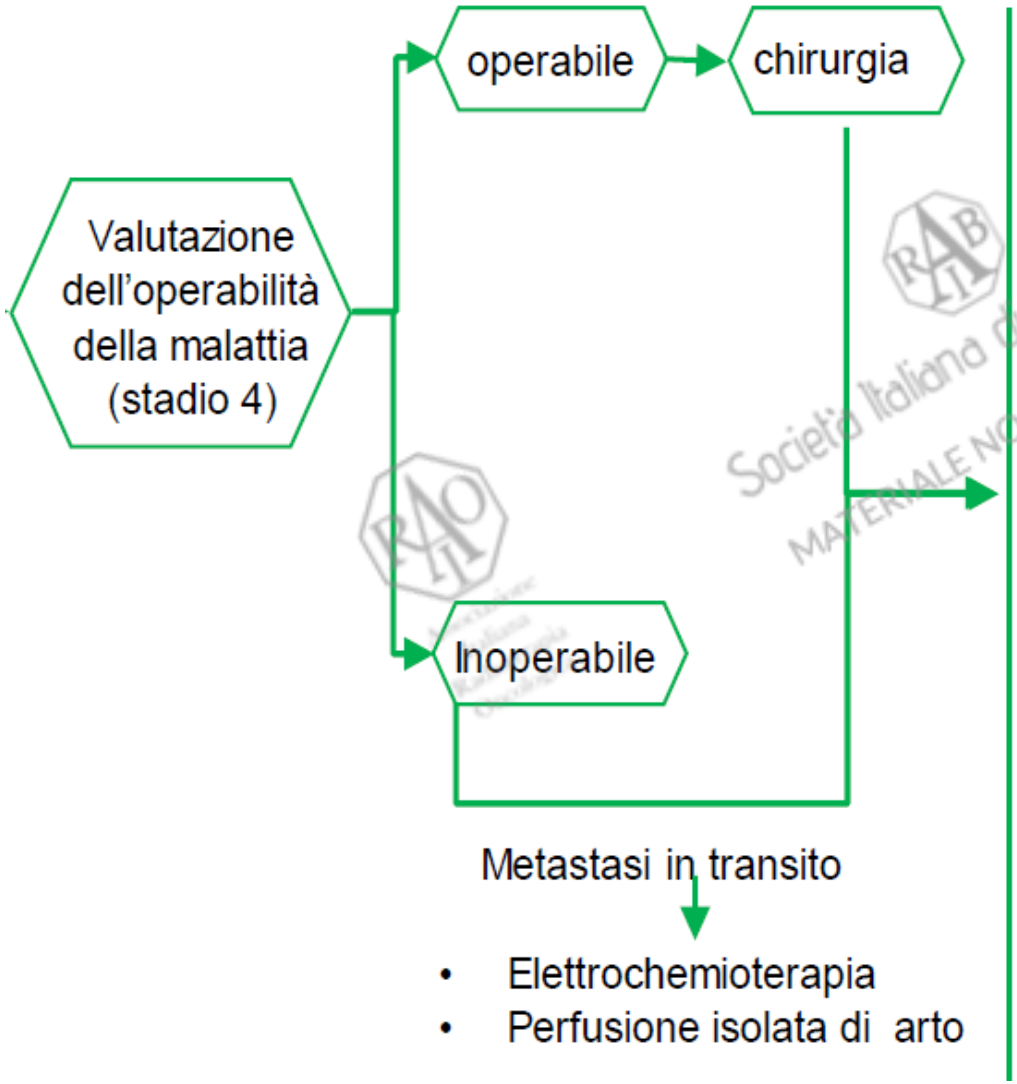
Alla TC di restaging di agosto 2016

2015

Linee guida

MELANOMA

Edizione 2015



1. Trial clinico
2. Nei pazienti non arruolabili in trial clinici:

Valutazione mutazione BRAF+/-NRAS e c-KIT (c-KIT limitatamente per m. mucosali, acrali o di aree cutanee cronicamente esposte al sole)

- pz con mutazione V600 di BRAF

a) I linea BRAF +/- MEK inibitore o ipilimumab
b) II linea BRAF +/- MEK inibitore o ipilimumab
c) III linea CT

- pz con mutazione di c-KIT o NRAS

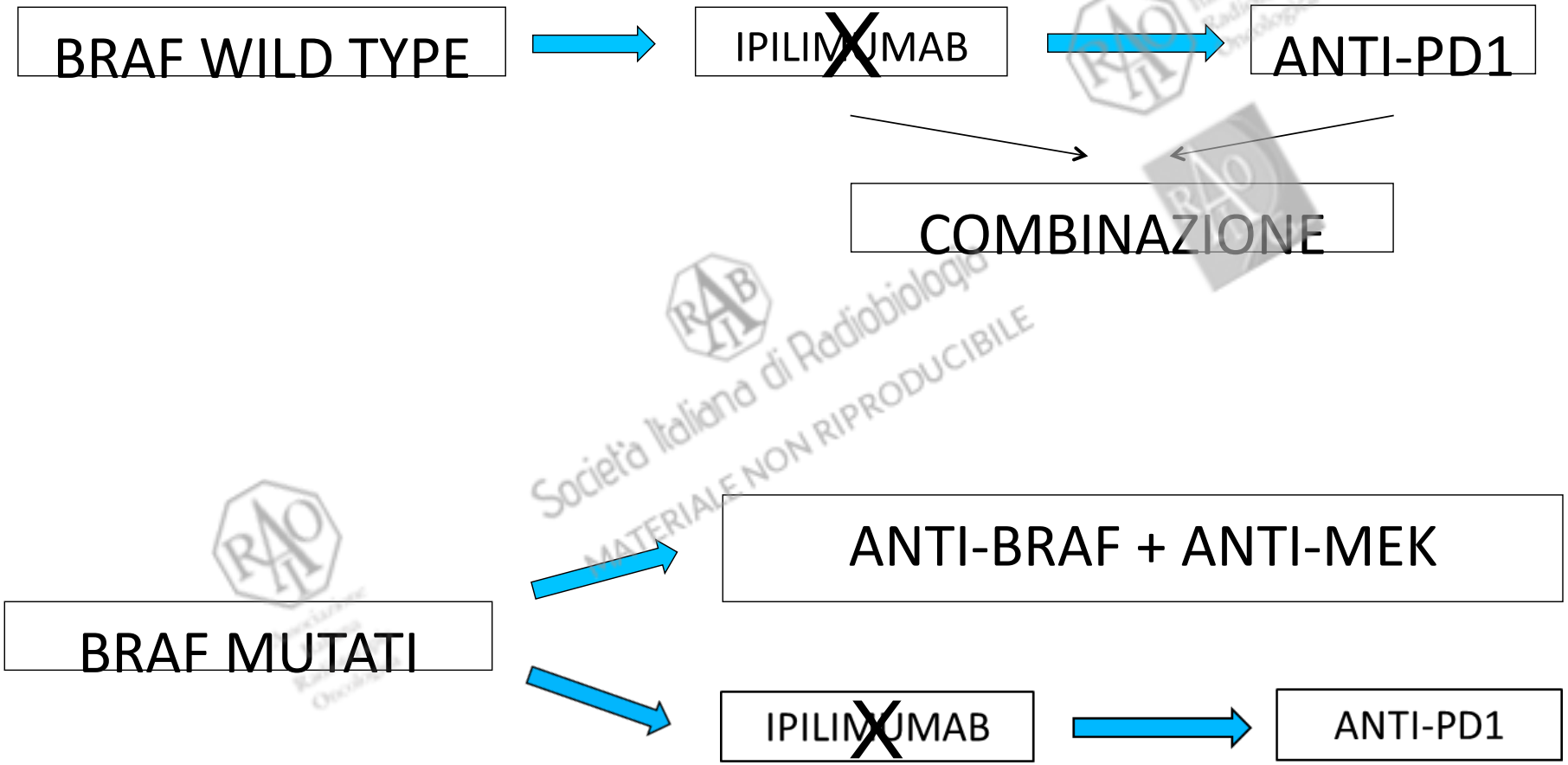
a) I linea ipilimumab
b) II linea CT
c) III linea (solo per c-KIT mutati): inibitori C-KIT (off-label)

-pz senza mutazioni

a) I linea ipilimumab
b) II linea CT

3. Trattamento RT (mts cerebrali/ossee)

METASTATIC MELANOMA TREATMENT SCENARIO 2015- 2016



TARGET THERAPIES & IMMUNOTHERAPIES

Combining a *BRAF* inhibitor with an immune-checkpoint inhibitor offers the potential of inducing a rapid response from the targeted agent and durable, long-term survival from immunotherapy

Tempo di induzione della risposta

Drug	Median
Ipilimumab (Hodi, 2010)	3.18 – 3.32 mo
BRIM-3 (Chapman, 2011)	1.45
BREAK-3 (Hauschild, 2012)	6.2 weeks
CheckMate 066 – Nivo (Robert, 2015)	2.1 mo
CHeckMate 067 – Nivo (Postow, 2015)	2.78

Author	Drug(s)	RR%
Wolchock, 2010	ipilimumab10 mg/kg ipilimumab 3 mg/kg ipilimumab 0.3 mg/kg	**11.1%** **4.2%** **0**
Hodi, 2010	ipilimumab+gp100 ipilimumab alone gp100 alone	**5.7%** **10.9%** **1.5%**
Robert, 2011	ipilimumab+dacarbazine dacarbazine+placebo	**15.2%** **10.3%**
Robert, 2014	Nivolumab Dacarbazine	**40%** **13.9%**
Robert, 2015	Pembrolizumab Q2W Pembrolizumab Q3W Ipilimumab	**33.7%** **32.9%** **11.9%**
Wolchock, 2013	Ipi-Nivo Sequenced Ipi-Nivo Combined	**40%** **40%**
Larkin, 2015	Nivolumab+Ipilimumab Ipilimumab Nivolumab	**57.6%** **19%** **43.7%**
Hodi, 2015	Nivolumab + Ipilimumab Ipilimumab	**60%** **11%**
Chapman, 2011 BRIM-3	Dacarbazine Vemurafenib	**5%** **48%**
Hauschild, 2012 BREAK-3	Dacarbazine Dabrafenib	**6%** **50%**
Long, 2015 Combi-D	Dabrafenib+Trametinib Dabrafenib + placebo	**67%** **51%**
Robert, 2015 Combi-V	Dabrafenib+Trametinib Vemurafenib + placebo	**64%** **51%**
Larkin, 2014 Co-BRIM	Vemurafenib+Cobimetinib Vemurafenib + placebo	**68%** **45%**

% di risposta

Ipi: 4.2%- 19%

Nivo: 40%-43.7%

Ipi+Nivo: 40%-60%

Vemu: 48%

Dabra: 50%

D + T: 64%-67%

V+ C : 68%

Original Investigation

Efficacy and Safety of Nivolumab in Patients With *BRAF* V600 Mutant and *BRAF* Wild-Type Advanced Melanoma

A Pooled Analysis of 4 Clinical Trials

James Larkin, MD, PhD; Christopher D. Lao, MD, MPH; Walter J. Urba, MD, PhD; David F. McDermott, MD; Christine Horak, PhD; Joel Jiang, PhD; Jedd D. Wolchok, MD, PhD

IMPORTANCE The anti–PD-1 therapeutic antibody, nivolumab, has demonstrated clinical activity in patients with advanced melanoma. The activity of nivolumab in subgroups of patients with tumors which have wild-type *BRAF* kinase vs patients with tumors having

Editorial page 427

Supplemental content at jamaoncology.com

Studies that contributed data to the current analysis included a dose-ranging phase 1 study (CA209-003 [NCT00730639]),19 a phase 1 biomarker study (CA209-038 [NCT01621490]),20 a phase 1 study of concurrent ipilimumab and nivolumab or ipilimumab sequenced with nivolumab (CA209-004 [NCT01024231]),21 and a phase 3 trial of nivolumab monotherapy vs chemotherapy (CA209-037 [CheckMate037] [NCT01721746])

Table 2. Summary of Efficacy Data

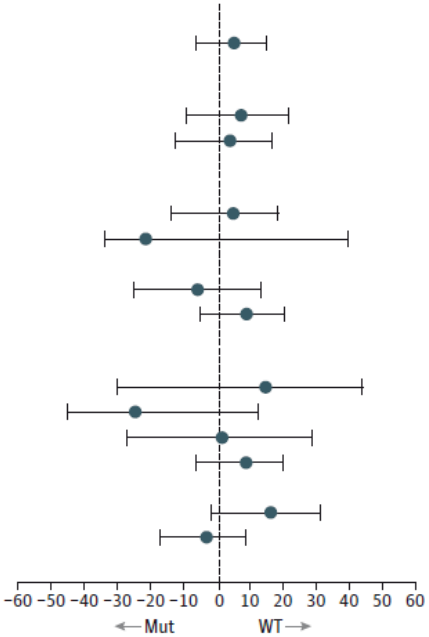
Variable	*BRAF* WT (n = 217)	*BRAF* Mut (n = 74)
Best overall response, No. (%)		
Complete	9 (4.1)	2 (2.7)
Partial	66 (30.4)	20 (27.0)
Stable disease	53 (24.4)	13 (17.6)
Progressive disease	74 (34.1)	33 (44.6)
Unknown	15 (6.9)	6 (8.1)
Objective response rate, % (95% CI)[a]	34.6 (28.3-41.3)	29.7 (19.7-41.5)
Mut over WT, OR (95% CI)	0.8 (0.5-1.4)	
Time to objective response, mo		
Median (range)	2.2 (1.6-14.8)	2.2 (1.7-7.9)
Mean (SD)	3.3 (2.2)	3.0 (1.7)
Duration of objective response, median (95% CI) [range], mo[b]	14.8 (11.1-24.0) [1.4-30.5]	11.1 (7.3-22.9) [2.8-27.6]

Abbreviations: Mut, mutation; OR, odds ratio; WT, wild-type.

[a] Proportion of patients with a complete response or a partial response. 95% Confidence interval based on the Clopper and Pearson method.

[b] Median calculated using the Kaplan-Meier method.

Source	*BRAF* WT n/N	*BRAF* WT ORR (95% CI)	*BRAF* Mut n/N	*BRAF* Mut ORR (95% CI)
Overall	57/164	34.8 (27.5-42.6)	16/54	29.6 (18.0-43.6)
Baseline LDH level,				
≤ULN	37/81	45.7 (34.6-57.1)	11/29	37.9 (20.7-57.7)
>ULN	20/80	25.0 (16.0-35.9)	5/24	20.8 (7.1-42.2)
Prior *BRAF* inhibitor				
No	57/163	35.0 (27.7-42.8)	5/17	29.4 (10.3-56.0)
Yes	0/1	0.0 (0.0-97.5)	11/37	29.7 (15.9-47.0)
Prior IPI				
No	12/39	30.8 (17.0-47.6)	7/18	38.9 (17.3-64.3)
Yes	45/125	36.0 (27.6-45.1)	9/36	25.0 (12.1-42.2)
M stage at study entry				
M0	1/6	16.7 (0.4-64.1)	0/3	0.0 (0.0-70.8)
M1A	7/15	46.7 (21.3-73.4)	4/5	80.0 (28.4-99.5)
M1B	12/24	50.0 (29.1-70.9)	3/6	50.0 (11.8-88.2)
M1C	29/92	31.5 (22.2-42.0)	7/32	21.9 (9.3-40.0)
PD-L1 status				
Positive	35/65	53.8 (41.0-66.3)	7/21	33.3 (14.6-57.0)
Negative/ indeterminate	22/99	22.2 (14.5-31.7)	9/33	27.3 (13.3-45.5)



Critical Reviews in Oncology/Hematology 100 (2016) 88–98

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journal homepage: www.elsevier.com/locate/critrevonc

PD-L1 expression in cancer patients receiving anti PD-1/PD-L1 antibodies: A systematic review and meta-analysis

Sara Gandini[a], Daniela Massi[b], Mario Mandalà[c,*]

[a] Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy
[b] Division of Pathological Anatomy, Department of Surgery and Translational Medicine, University of Florence, Italy
[c] Unit of Medical Oncology, Department of Oncology and Hematology, Papa Giovanni XXIII Hospital, Bergamo, Italy

Contents

Table 2
Summary estimates according to PD-L1 status for clinical objective response and deaths by possible heterogeneity factors.

Heterogeneity factors	MM					P-value
Anti-PD-1 concomitant to Ipi¥		4 (3)	Objective Response Rate	Positive	62% (34, 86)	0.21
				Negative	48% (18, 79)	0.18
No Ipi concomitant¥		8 (8)	Objective Response Rate	Positive	43% (32, 54)	
				Negative	23% (14, 34)	
Anti-PD-1 in first line		2 (2)	Objective Response Rate	Positive	55% (21, 86)	0.34
				Negative	38% (10, 71)	0.07
Anti-PD-1 as second line and no Ipi		6 (6)	Objective Response Rate	Positive	37% (25, 50)	
				Negative	15% (10, 21)	

I^2% Percentage of heterogeneity; Odd Ratio: Odd Ratio for positive objective response and PD-L1 status (positive *vs.* negative); Ipi = Ipilimumab; MM = Metastatic melanoma; NSCLC = Non-Small Cell Lung Cancer. RCC = Renal Cell Cancer. §P-value of heterogeneity factors in meta-regression random effect model. ¥ The total number of trials is 9 because one study (Wolchok et al., 2015; Gibney et al., 2015) presented one estimate for patients with Ipi concomitant and one with no Ipi.

OVERALL SURVIVAL

				% OS				
Author	Study design	Drug(s)	No patients	1-year	2-yr	3-yr %	4-yr	5-yr
Wolchock, 2010	Randomized, double-blind, phase 2 trial	ipilimumab10 mg/kg ipilimumab 3 mg/kg ipilimumab 0.3 mg/kg	73 72 72	48.6% 39.3% 39.6%	29.8% 24.2% 18.4%			
Hodi, 2010	Randomized, double-blind phase III	ipilimumab+gp100 ipilimumab alone gp100 alone	403 137 136	43.6% 45.6% 25.3%	21.6% 23.5% 13.7%			
Robert, 2011	Randomized, double-blind phase II	ipilimumab+dacarbazine dacarbazine+placebo	250 252	47.3% 36.3%	28.5% 17.9%	20.8% 12.2%		
Schadendorf, 2015	Pooled analysis	Ipilimumab	1,861	-	-	22%	~22%	~22%
Robert, 2014	Randomized, double-blind Phase III	Nivolumab Dacarbazine	210 208	72.9% 42.1%	-	-		
Robert, 2015	Randomized, double-blind Phase III	Pembrolizumab Q2W Pembrolizumab Q3W Ipilimumab	279 277 278	74.1% 68.4% 58.2%	-	-		
Sznol, 2015	Long –term CA209-004 Phase I	Ipilimumab + nivolumab	114	81%	73%			
Hodi, 2016 (AACR)	CA209-003 phase I update	Nivolumab	107	63%	48%	42%	35%	34%
Postow, 2016 (AACR)	CheckMate 069 phase II update	Ipilimumab + Nivolumab Ipilimumab	95 47	73% 65%	64% 54%			
Long GV, 2015	Randomised, double-blind phase III	Dabrafenib + trametinib Dabrafenib	211 212	74% 68%	51% 42%			
Long, 2016	Phase I Phase II	Dabrafenib + trametinib	78	72% 80%	60% 51%	47% 38%		
Robert, 2015	Combi-V ESMO update	Dabrafenib + trametinib Vemurafenib	352 352	73% 64%	51% 38%			
Daud, 2015	Phase I-II ASCO 2015	Dabrafenib + trametinib	108	80%	51%	38%		

TARGET THERAPIES & IMMUNOTHERAPIES

Combining a *BRAF* inhibitor with an immune-checkpoint inhibitor offers the potential of inducing a rapid response from the targeted agent and durable, long-term survival from immunotherapy

AUMENTO % RISPOSTE CON ANTI-PD1 (E COMBO), AUMENTO % OS A LUNGO TERMINE CON COMBO-TARGET

Decision-making factors in advanced metastatic melanoma: pre-treatment parameters to be evaluated (modified from an oral communication by prof Axel Hauschild at ASCO 2014)

Parameter	Significance	Marker
Mutation pattern	- Possibility to prescribe a molecular target therapy	**BRAF, NRAS, cKIT**
Performance status (PS)	- Candidate for active therapy or only palliation - Need to obtain a quick response	**ECOG**
High/low tumour load	- Responsiveness to systemic treatment	**LDH** **Blood chemistry** **CT/MRI images**
Brain mets	- Risk of CNS symptoms	**CT/MRI images**
Progression pattern (low/ fast)	- responsiveness to systemic treatment - need to obtain a quick response	**LDH** **CT/MRI images**
Clinical trials	- availability of clinical trials	**NA**

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journal homepage: www.ejcancer.com

Original Research

Prognostic score for patients with advanced melanoma treated with ipilimumab

Stefan Diem [a,1], Benjamin Kasenda [a,1], Juan Martin-Liberal [a,b], Alexander Lee [a], Dharmisha Chauhan [a], Martin Gore [a], James Larkin [a,*]

[a] Department of Medical Oncology, Royal Marsden Hospital NHS Foundation Trust, Fulham Road, London SW36JJ, United Kingdom
[b] Department of Medical Oncology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Pg Vall d'Hebron, 119-129, 08035 Barcelona, Spain

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Available online 18 November 2015

Table 4
Selected multivariable model after backward elimination based on 128 patients, 6 patients were excluded because of missing data.

Parameter	Parameter estimate	SE	HR	95% CI	*p*-value
ECOG performance status, 0 versus >0	0.646	0.280	1.91	1.10–3.30	0.021
LDH in steps of 10 (continuous)	0.029	0.007	1.03	1.02–1.04	<0.001
NOI (continuous)	0.412	0.106	1.51	1.22–1.86	<0.001

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; LDH = serum lactate dehydrogenase; NOI = number of involved organs; SE = standard error.

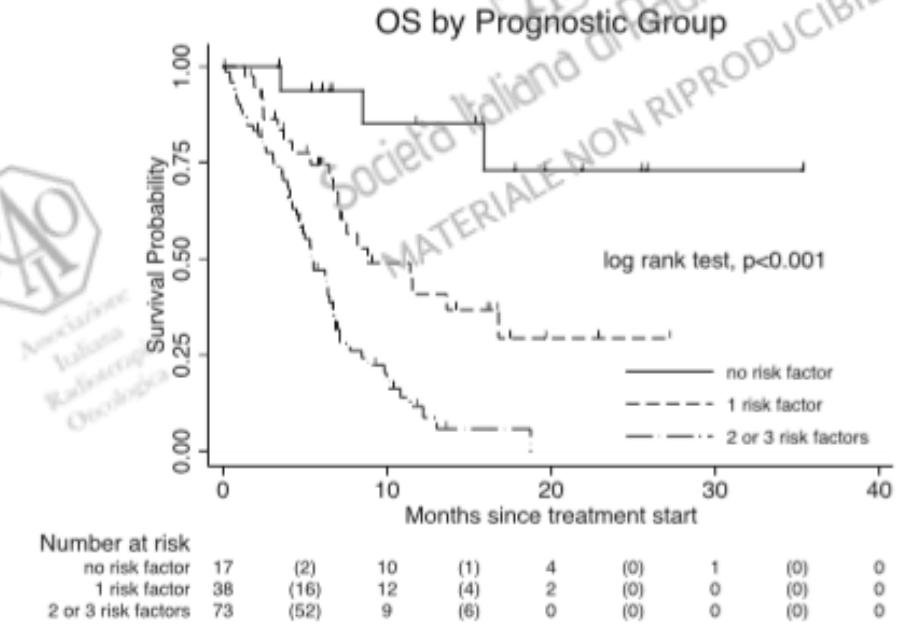


Fig. 1. Overall survival according to the proposed prognostic score (favourable, intermediate, poor). Prognostic factors include: ECOG performance status >0, LDH > ULN, and NOI > 2. Numbers in brackets denote the number of events. Abbreviations: ECOG = Eastern Cooperative Oncology group; LDH = serum lactate dehydrogenase; NOI = number of organs involved; ULN = upper limit of normal.

I tumori a rapida crescita presentano spesso ridotta vascolarizzazione

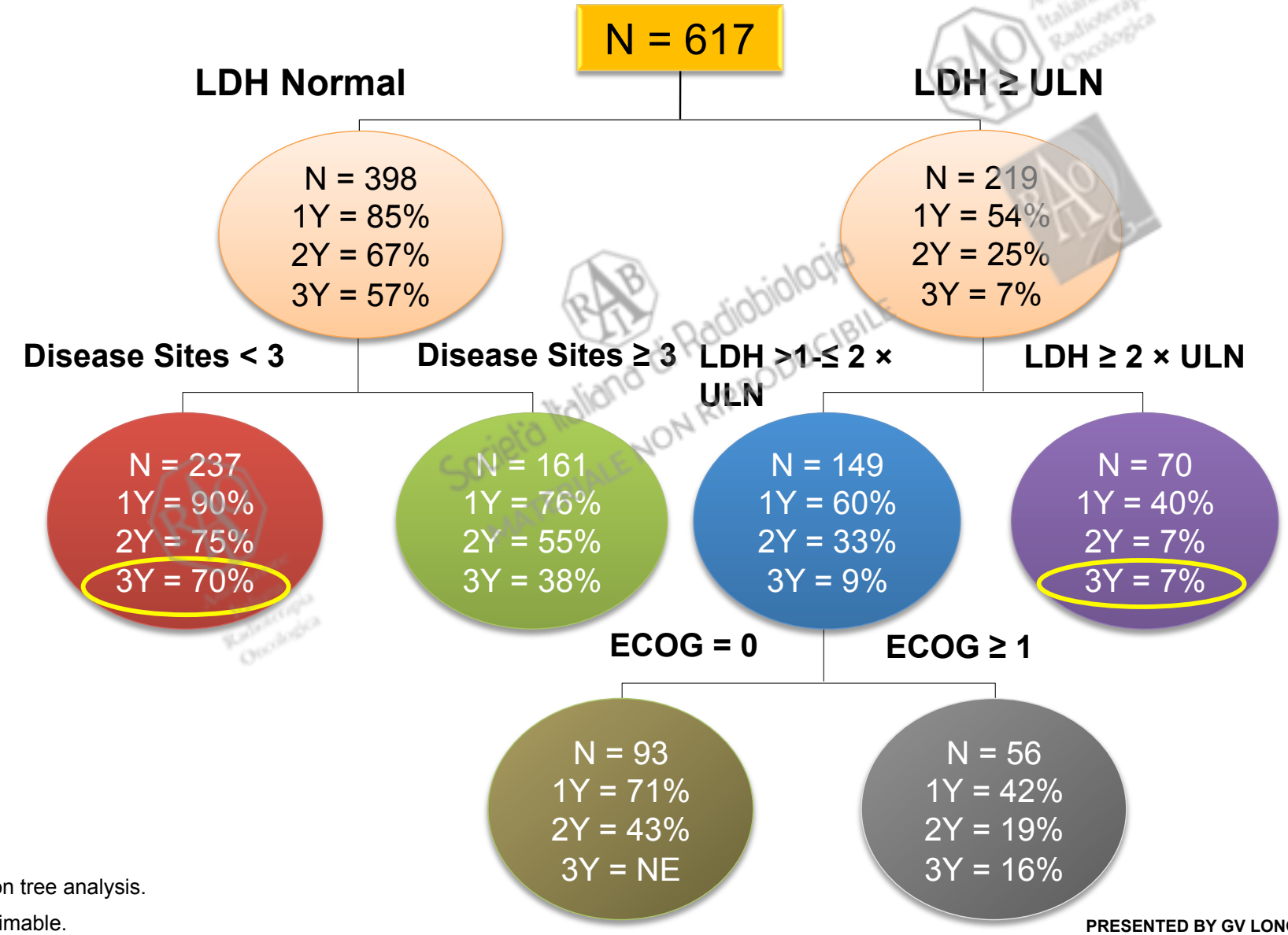
Glicolisi anaerobia come fonte di energia (ATP)

Incremento LDH come misura di crescita del tumore

Riduzione del ph extracellulare

Inibizione linfocitaria

Five Baseline Factors Influenced OS[a]



[a] Regression tree analysis.

NE, not estimable.

PRESENTED BY GV LONG AT SMR 2015

SEQUENCING?

ALTO TUMOUR LOAD

ELEVATO LDH ?

TERAPIA FUTURA ..


Target therapies
immunoterapia

NCT01767454

Ipilimumab + Dabrafenib +/- Trametinib Combination Trial (NCT01767454)

- Phase 1 dose escalation study; N = 78 max
- Primary endpoint: safety

- Design:

–Doublet arm: dabrafenib + ipilimumab combo

- Dabrafenib 150 mg (Cohort 1A) or 100 mg (Cohort -1A) BID for 2 week run-in followed by ipilimumab 3 mg/kg Q3W for 4 doses
- Dabrafenib is continued through combo with ipilimumab and post-ipilimumab until PD or toxicity

Dabrafenib

Ipilimumab

–Triplet arm: dabrafenib + trametinib + ipilimumab combo

- Dabrafenib for 2 week run-in followed by ipilimumab 3 mg/kg Q3W for 4 doses
- Dabrafenib is continued through combo dabrafenib + trametinib for 1 week run-in followed by ipilimumab 3 mg/kg Q3W for 4 doses
- Dabrafenib and trametinib continued though combo with ipilimumab and post-ipilimumab until PD or toxicity
- Arm will be started using dabrafenib and ipilimumab dose from the double arm
  - Cohort 1B: Dabrafenib 150 mg BID + trametinib 1 mg QD + ipilimumab
  - Cohort -1B: Dabrafenib 100 mg BID + trametinib 1 mg QD + ipilimumab
  - Cohort 2B: Dabrafenib 150 mg BID + trametinib 2 mg QD + ipilimumab

Dabrafenib

Trametinib

Ipilimumab

Dabrafenib 150 mg bid + ipilimumab 3 mg/kg q3w × 4 doses was well tolerated (ASCO 2014)

Sponsor: CTEP & GSK
NCT01767454

https://clinicaltrials.gov/ct2/show/NCT01767454?term=NCT01767454&rank=1 Accessed Jan 2015

A Study of the Safety and Efficacy of Pembrolizumab (MK-3475) in Combination With Trametinib and Dabrafenib in Participants With Advanced Melanoma (MK-3475-022/KEYNOTE-022)

Sponsor:Merck Sharp & Dohme Corp. Collaborator: Novartis

Experimental: Pembro+D+T (Parts 1, 2, and 3)
Participants receive pembrolizumab intravenously (IV) on Days 1 and 22 of each 6-week cycle; dabrafenib capsules, 150 mg/day total, orally, in a divided dose (twice per day, or BID) starting on Day 1, through study treatment discontinuation; and trametinib tablets, 2 mg, orally, once daily (QD) starting on Day 1, through study treatment discontinuation.

Placebo Comparator: Placebo+D+T (Part 3)
Participants receive placebo IV on Days 1 and 22 of each 6-week cycle; dabrafenib capsules, 150 mg/day total, orally, in a divided dose BID starting on Day 1, through study treatment discontinuation; and trametinib tablets, 2 mg, orally, QD starting on Day 1, through study treatment discontinuation.

Sequential Combo Immuno and Target Therapy (SECOMBIT) Study (SECOMBIT)

This study is not yet open for participant recruitment.

Sponsor: Fondazione Melanoma Onlus

A Three Arms Prospective, Randomized Phase II Study to Evaluate the Best Sequential Approach With Combo Immunotherapy (Ipilimumab/Nivolumab) and Combo Target Therapy (LGX818/MEK162) in Patients With Metastatic Melanoma and BRAF Mutation

Experimental: Arm A: Combo Target/Combo Immuno
Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) until PD; then Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until PD

Experimental: Arm B: Como immuno/Combo Target
Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until PD; then Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) until PD

Experimental: Arm C: Sandwich
Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) for 8 weeks followed by Combo Immuno (nivolumab 1 mg/kg solution IV combined with ipilimumab 3 mg/kg solution IV every 3 weeks for 4 doses then nivolumab 3 mg/kg solution IV every 2 weeks) until PD; then Combo Target (LGX818 450 mg p.o. od + MEK162 45 mg p.o. bid) until PD

CLINICA: DOMANDE E RISPOSTE

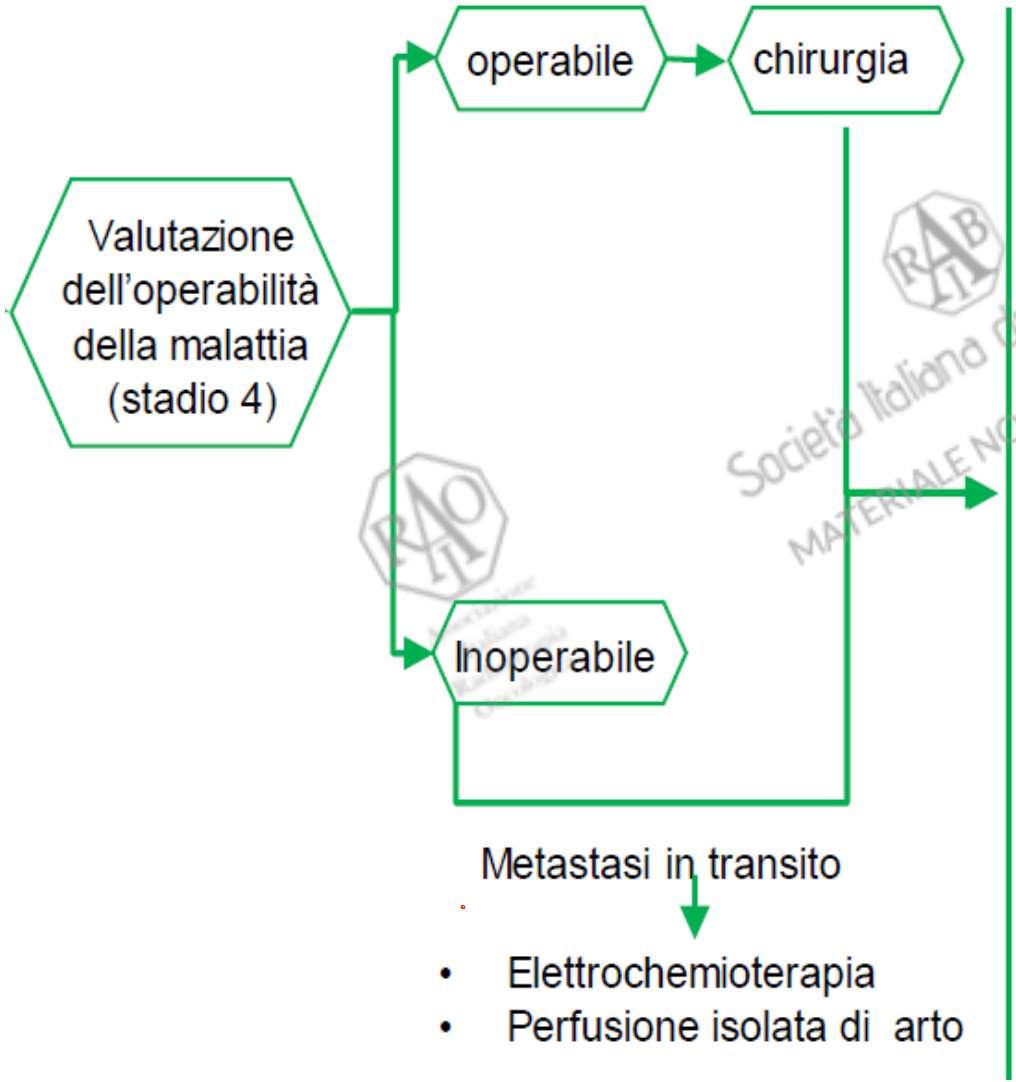
1) Quali farmaci possiamo utilizzare? Anti-BRAF, anti-MEK, c-Kit inhibitors, anti-CTLA4, anti-PD1
2) Qual è il pattern mutazionale minimo da richiedere? BRAF (NRAS), cKIT (sede e dopo terapie di prima linea)
3) Quando dobbiamo richiedere la mutazione e in quali pazienti? Stadio III non operabile, stadio IV
4) Su quali campioni dobbiamo chiedere la mutazione? Metastasi preferibile, ri-testing
5) Quale terapia in base alla mutazione? Combo-target o (combo)-immuno in base alle caratteristiche del paziente

2015

Linee guida

MELANOMA

Edizione 2015



1. Trial clinico
2. Nei pazienti non arruolabili in trial clinici:

Valutazione mutazione BRAF+/-NRAS e c-KIT (c-KIT limitatamente per m. mucosali, acrali o di aree cutanee cronicamente esposte al sole)

- pz con mutazione V600 di BRAF

a) I linea BRAF +/- MEK inibitore o ipilimumab
b) II linea BRAF +/- MEK inibitore o ipilimumab
c) III linea CT

- pz con mutazione di c-KIT o NRAS

a) I linea ipilimumab
b) II linea CT
c) III linea (solo per c-KIT mutati): inibitori C-KIT (off-label)

-pz senza mutazioni

a) I linea ipilimumab
b) II linea CT

3. Trattamento RT (mts cerebrali/ossee)

ASSOCIATION OF LOCAL AND SYSTEMIC THERAPIES: WHY, WHEN AND IN WHICH PATIENTS

BEFORE..

RESPONSE INDUCTION TIME

symptomatic patients, mainly for immunotherapy

Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial

Georgina V Long, Uwe Trefzer, Michael A Davies, Richard F Kefford, Paolo A Ascierto, Paul B Chapman, Igor Puzanov, Axel Hauschild, Caroline Robert, Alain Algazi, Laurent Mortier, Hussein Tawbi, Tabea Wilhelm, Lisa Zimmer, Julie Switzky, Suzanne Swann, Anne-Marie Martin, Mary Guckert, Vicki Goodman, Michael Streit, John M Kirkwood, Dirk Schadendorf**

Summary

Background Brain metastases are common in patients with metastatic melanoma and median overall survival from their diagnosis is typically 17–22 weeks. We assessed dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain.

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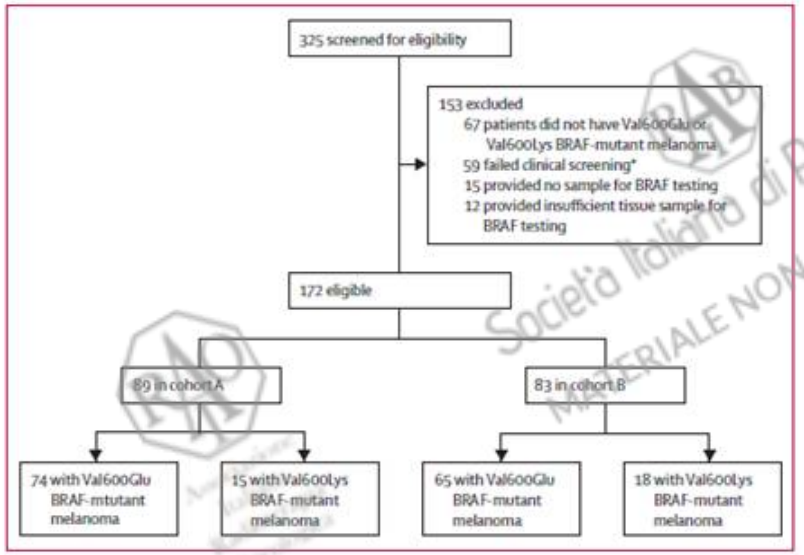


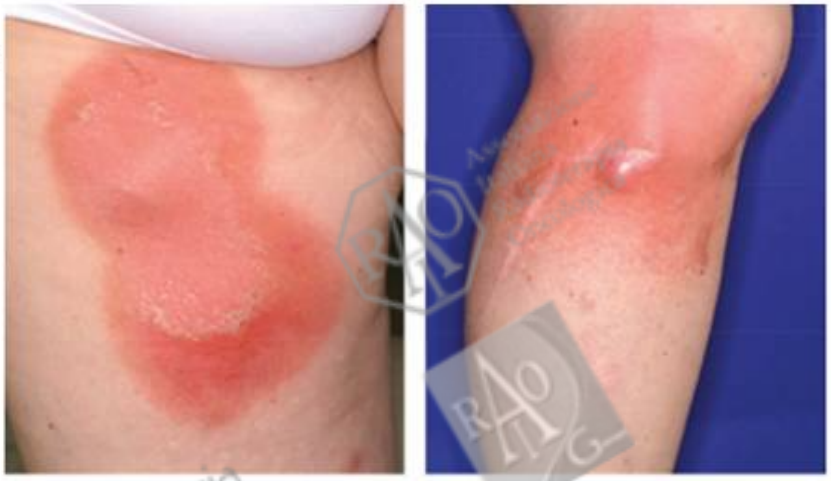
DOPO CHIRURGIA, WBRT O STEREOTASSI

	Cohort A	Cohort B
Val600Glu BRAF mutant	74	65
Overall intracranial response (CR+PR)	29 (39·2%, 28·0–51·2%)	20 (30·8%, 19·9–43·4%)
Intracranial disease control (CR+PR+SD)*	60 (81·1%, 70·3–89·3%)	58 (89·2%, 79·1–95·6%)
Intracranial CR	2 (3%)	0
Intracranial PR	27 (36%)	20 (31%)
Intracranial SD	31 (42%)	38 (58%)
Intracranial PD	9 (12%)	5 (8%)
Not assessable	5 (7%)†	2 (3%)‡
Overall response (CR+PR)§	28 (37·8%, 26·8–49·9%)	20 (30·8%, 19·9–43·5%)
Overall disease control (CR+PR+SD)	59 (79·7%, 68·8–88·2%)	54 (83·1%, 71·7–91·2%)
6-month survival estimate (%)	61% (46·7–73·2%)	61% (46·3–72·7%)
Val600Lys BRAF mutant	15	18
Overall intracranial response (CR+PR)	1 (6·7%, 0–31·9%)	4 (22·2%, 6·4–47·6%)
Intracranial disease control (CR+PR+SD)*	5 (33·3%, 11·8–61·6%)	9 (50·0%, 26·0–74·0%)
Intracranial CR	0	0
Intracranial PR	1 (7%)	4 (22%)
Intracranial SD	4 (27%)	5 (28%)
Intracranial PD	6 (40%)	6 (33%)
Not assessable	4 (27%)¶	3 (17%)‖
Overall response (CR+PR)§	0 (0%, 0–21·8%)	5 (27·8%, 9·7–53·5)
Overall disease control (CR+PR+SD)	7 (46·7%, 21·3–73·4%)	9 (50·0%, 26·0–74·0%)
6-month survival estimate (%)	27% (8·3–49·6%)	41% (16·5–64·0%)

Imke Satzger, Annette Degen, Hiba Asper Alexander Kapp (Hannover Medical School)

Axel Hauschild (University Hospital Schleswig-Holstein, Kiel, Germany)

Ralf Gutzmer (Hannover Medical School)



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Serious Skin Toxicity With the Combination of BRAF Inhibitors and Radiotherapy

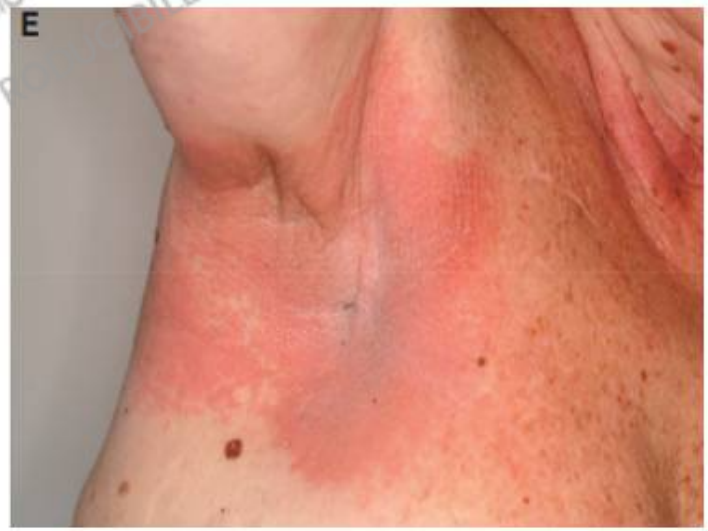
Introduction

Newly introduced BRAF inhibitors like vemurafenib and dabrafenib are effective in patients with metastatic melanoma who harbor *BRAF* V600 mutations, but after a median time of approximately 6 months disease progression occurs.[1,2] In the event of a localized

therapy was applied to this region. After a dose of only 12 Gy, the irradiation had to be interrupted because of painful grade 2 radiodermatitis (Fig 1E). The administration of a cumulative dose of 60 Gy required a prolonged time period of 10 weeks because of multiple skin toxicity–induced interruptions, after which the metastasis progressed to 7.0 × 4.8 cm.

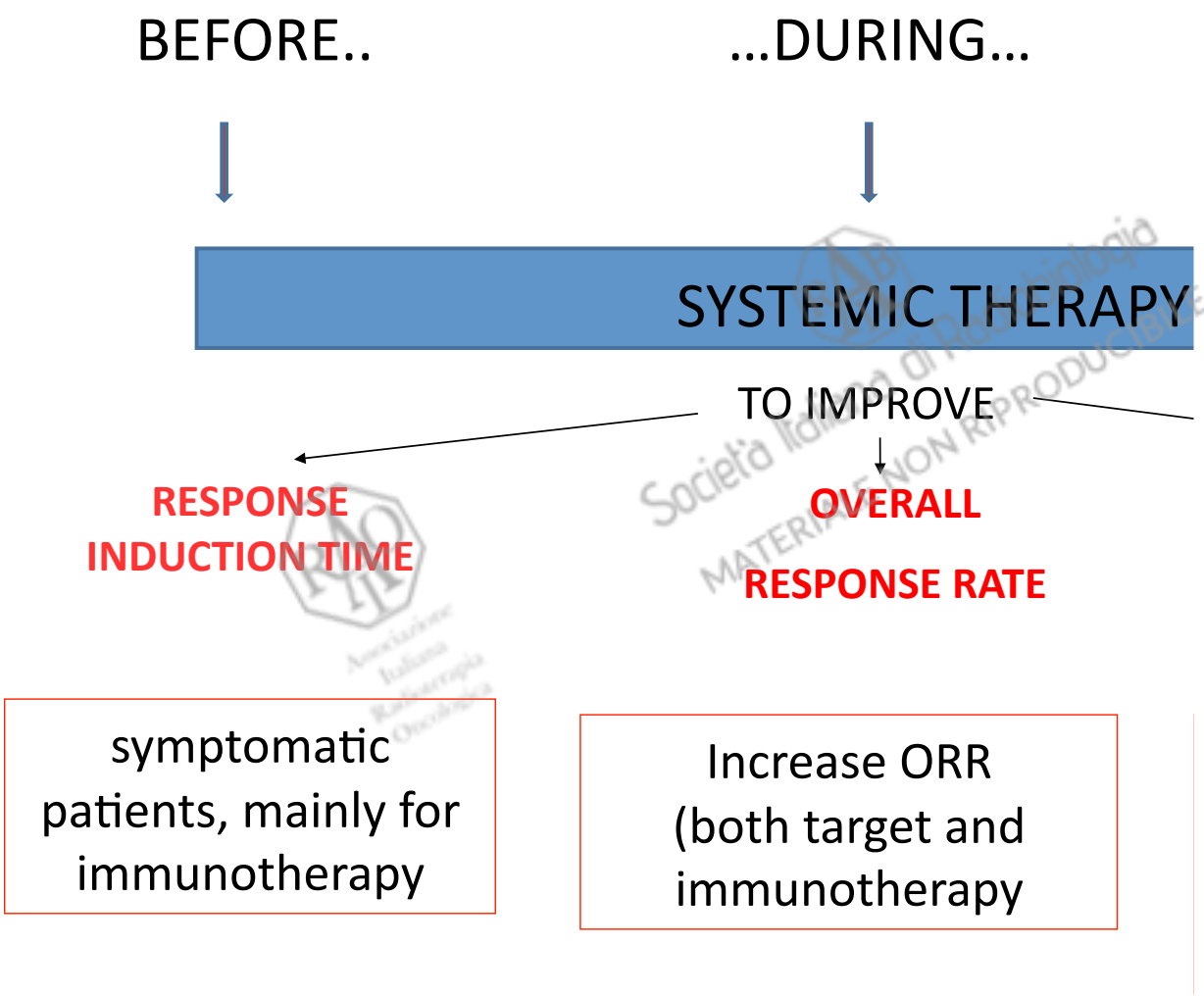
Case Report 4

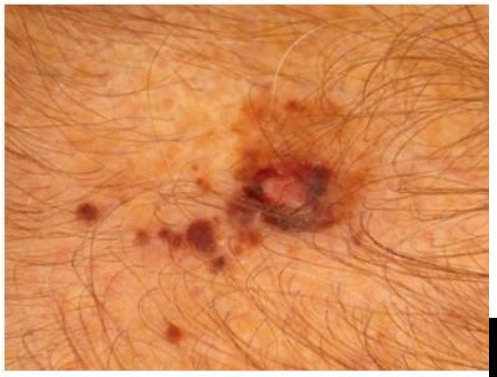
A 63-year-old woman experienced growing cutaneous metas-

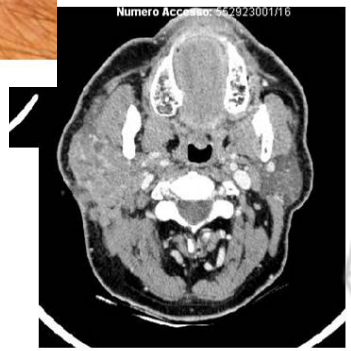


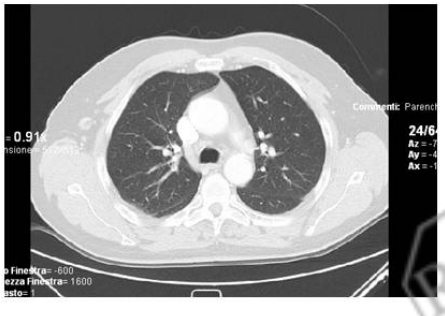
Dose usata: 30-60Gy

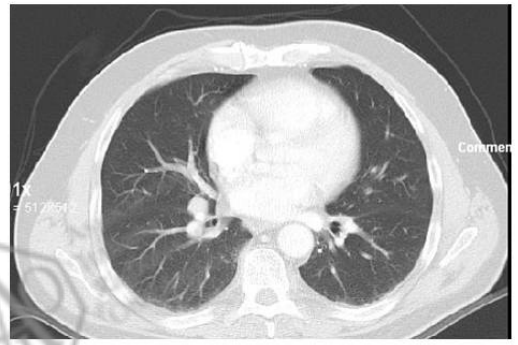
ASSOCIATION OF LOCAL AND SYSTEMIC THERAPIES: WHY, WHEN AND IN WHICH PATIENTS

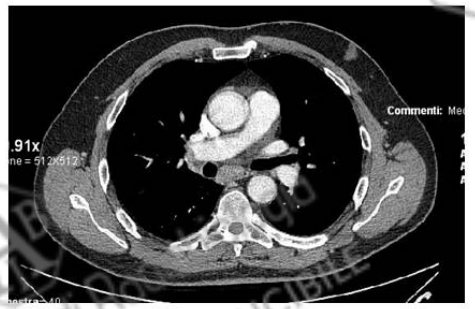




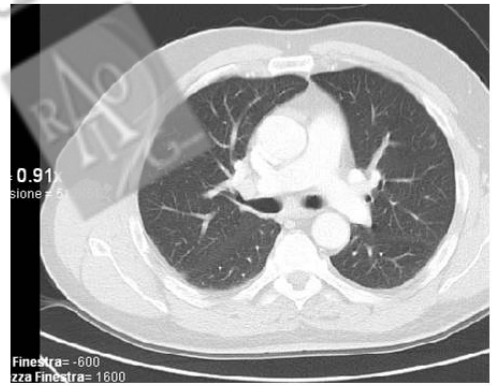








Sub-carinal adenopathy (7 pos)



CLINICAL CASE 2

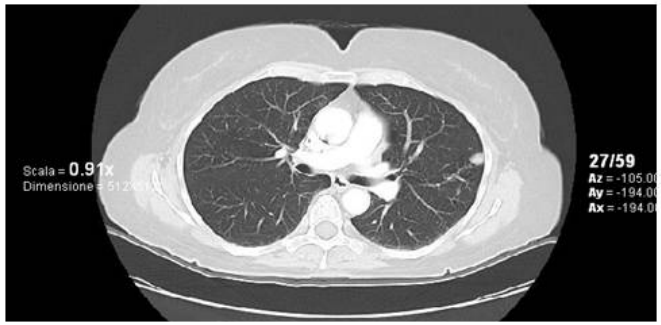
- Ipilimumab (anti-CTLA4) 4 infusions 3 mg/kg october- december 2014
- Cyto-reductive radiotherapy 30 Gy in 10 fractions

April 2014 → September 2014 → December 2014

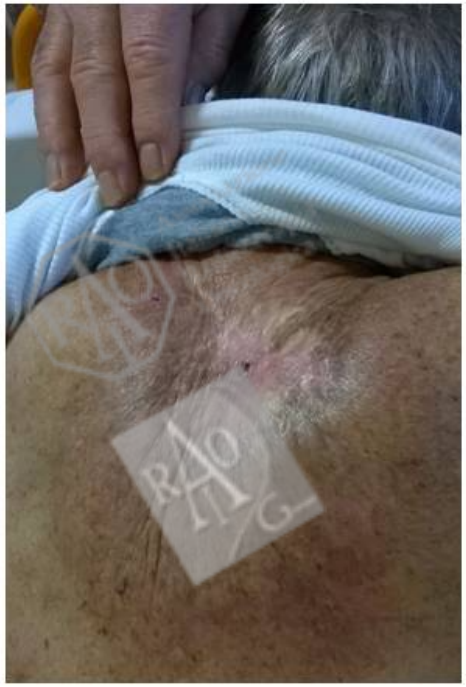
after anti-CTLA4+RT

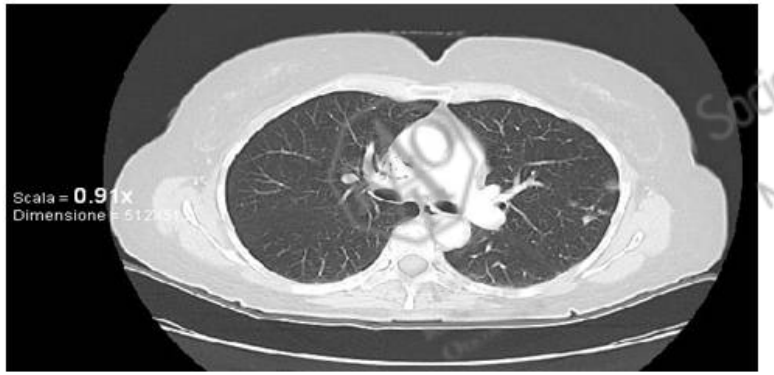
- Clearance of mediastinal adenopathies, PR of neck lymph nodes
- March 2015: complete neck dissection

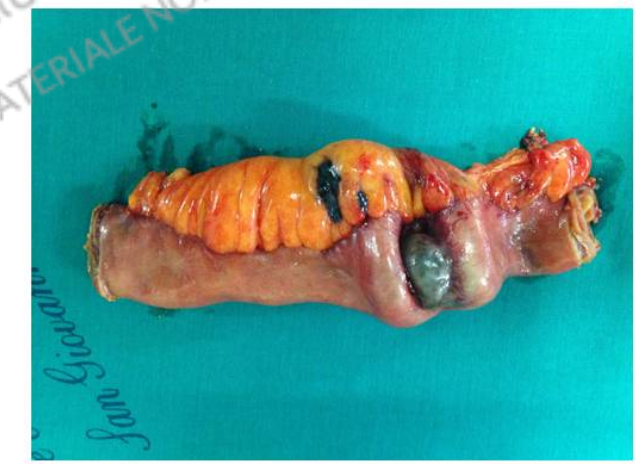
April 2014 → September 2014 → December 2014 → March 2015



Anti-PD1 + RT



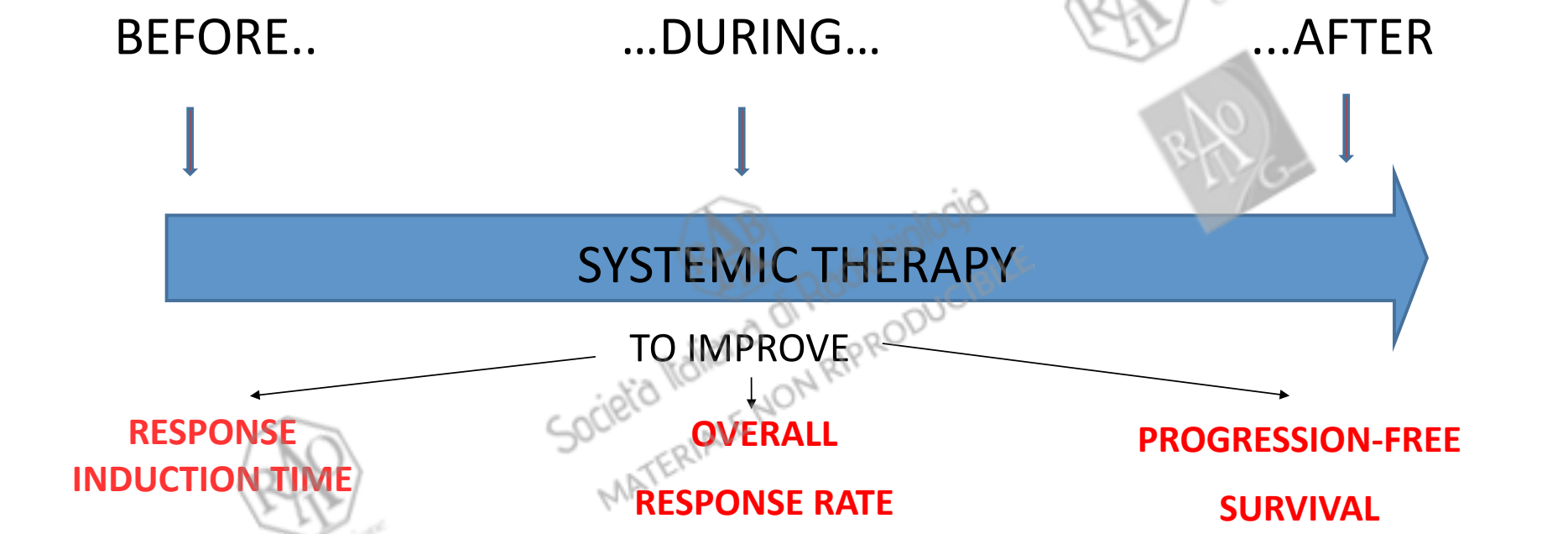




RESEZIONE SEGMENTARIA MULTIPLA DELL'INTESTINO TENUE

Pattern mutazionale :
BRAF mutato V600K

ASSOCIATION OF LOCAL AND SYSTEMIC THERAPIES: WHY, WHEN AND IN WHICH PATIENTS



symptomatic patients, mainly for immunotherapy	Increase ORR (both target and immunotherapy	"BEYOND PROGRESSION" for target therapies "ABSCOPAL EFFECT" for immunotherapy

BEYOND PROGRESSION

BRAFi PD

N=95

48% existing lesions

18% new lesions

23% new and existing

31% isolated

69% generalised

LOCAL TREATMENTS in

29% with extracranial progression

66% with intracranial progression

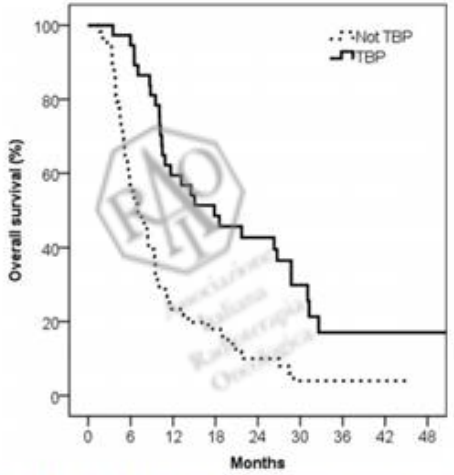


Figure 3. This chart illustrates the survival of patients with melanoma who did and did not receive v-raf murine sarcoma viral oncogene homolog B (BRAF) inhibitor treatment

Original Article

Cancer Jul 2014

The Nature and Management of Metastatic Melanoma After Progression on BRAF Inhibitors: Effects of Extended BRAF Inhibition

Matthew M. K. Chan, MBBS, MClinT(R)[1,2,3]; Lauren E. Haydu, MPH[1,3]; Alexander M. Menzies, MBBS[1,3]; Mary W. F. Azer, MB ChB[2]; Oliver Klein, MD[2]; Megan Lyle, B Med[1,3]; Arthur Clements, MBBS[2,3]; Alexander Guminski, MBBS, PhD[1,3,4]; Richard F. Kefford, MBBS, PhD[1,2,3,5]; and Georgina V. Long, MBBS, PhD[1,3,5]

BACKGROUND: The v-raf murine sarcoma viral oncogene homolog B (BRAF) inhibitor (BRAFi) drugs dabrafenib and vemurafenib have high response rates in *BRAF*-mutant, metastatic melanoma; however, 50% of patients progress by 7 months. In this study, the

Radiotherapy and Oncology 120 (2016) 1–12

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Radiotherapy and immune checkpoints inhibitors for advanced melanoma

Andrea Riccardo Filippi [a,*], Paolo Fava [b], Serena Badellino [a], Chiara Astrua [b], Umberto Ricardi [a], Pietro Quaglino [b]

[a] Department of Oncology, Radiation Oncology; and [b] Department of Medical Sciences, Dermatology/Oncology, University of Torino, Italy

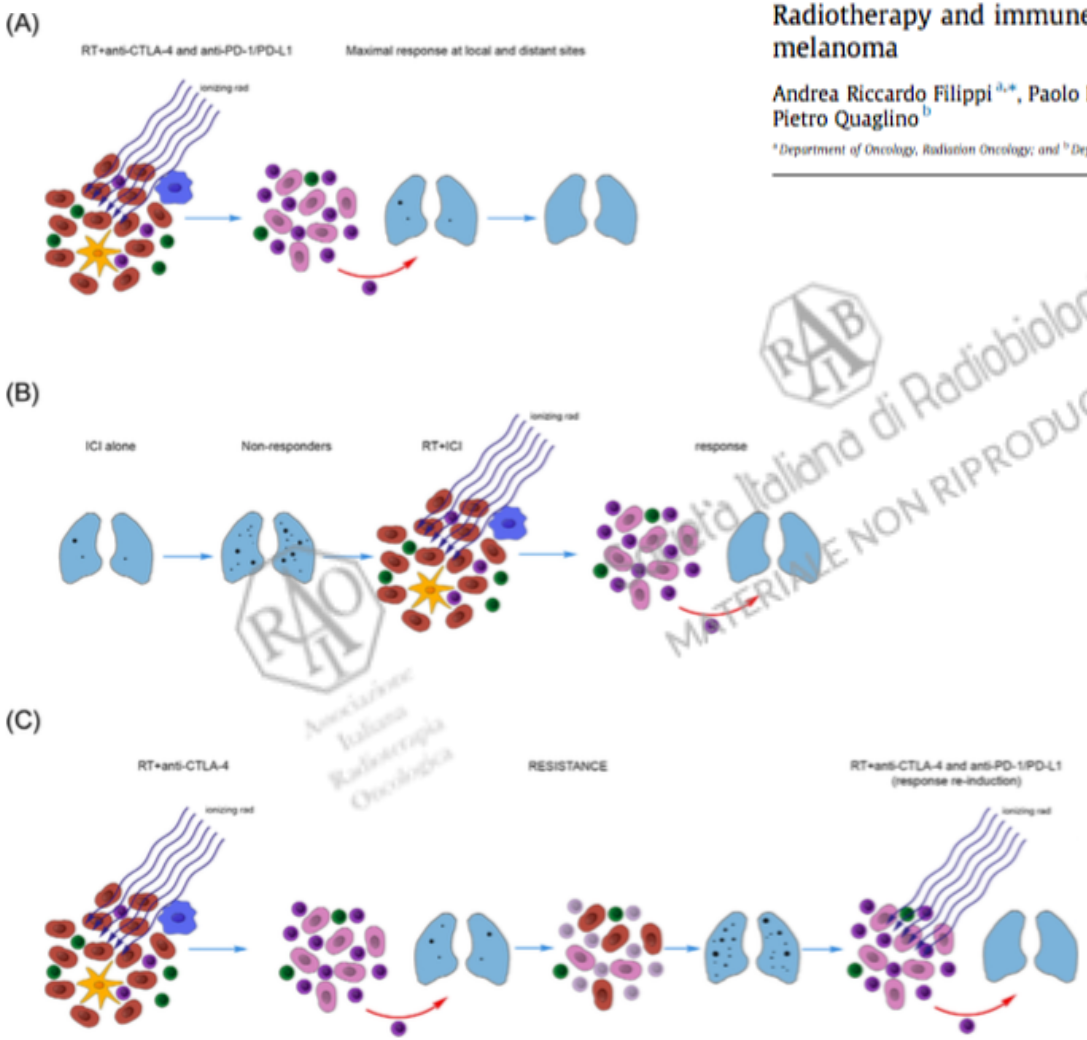


Fig. 2. Different possible therapeutic combinations between RT and ICI for advanced melanoma, with the aim of: (A) maximizing response upfront (concomitant approach, higher toxicity) (B) overcoming resistance in poor responders (sequential approach) and (C) triggering the restoration of immune response and overcoming acquired resistance after initial response (sequential/concomitant approach) [Refs. 52,16]. For cells' shapes and colours see Fig. 1. ICI: immune checkpoint inhibitors.

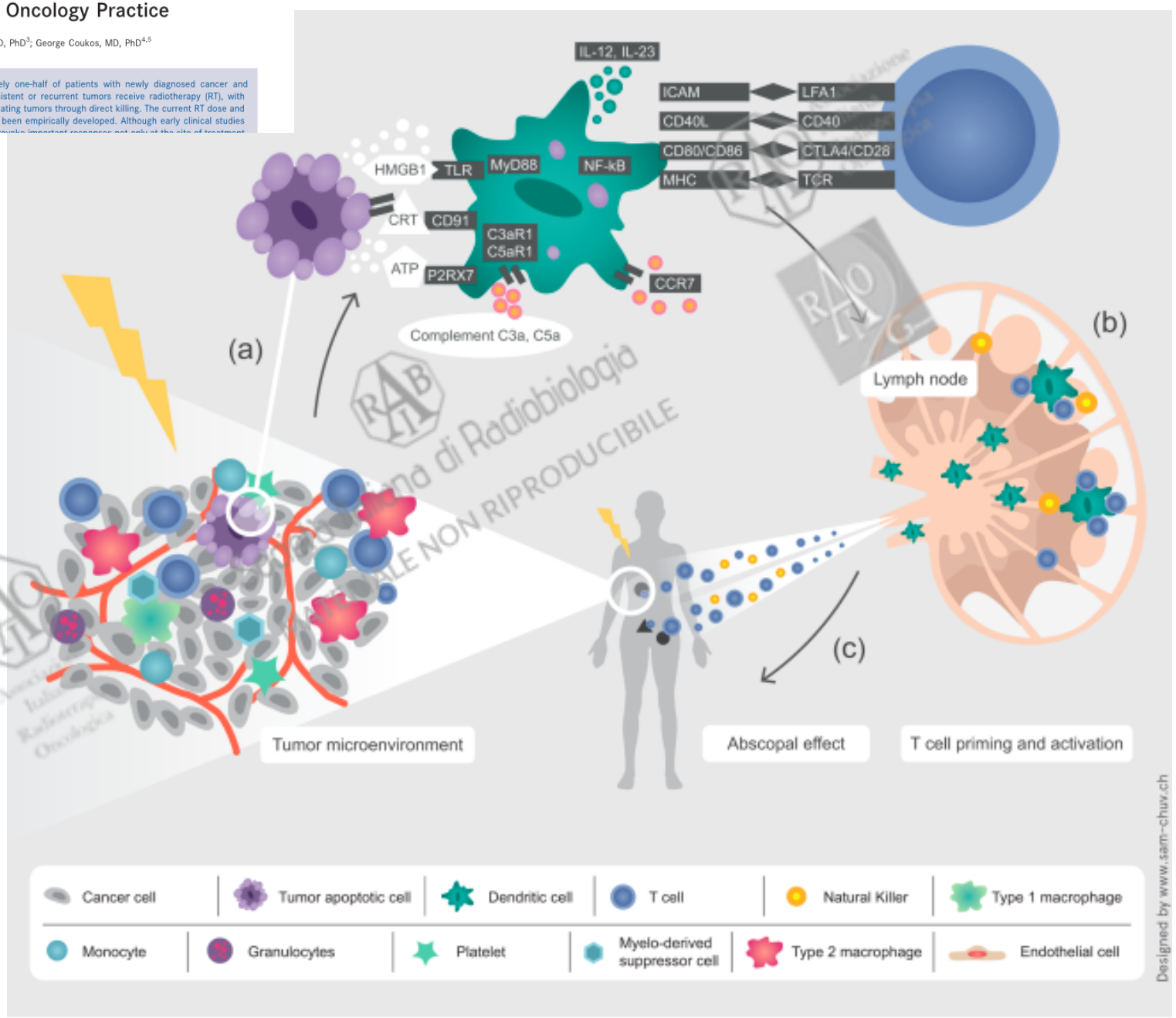
CA CANCER J CLIN 2016;00:00–00

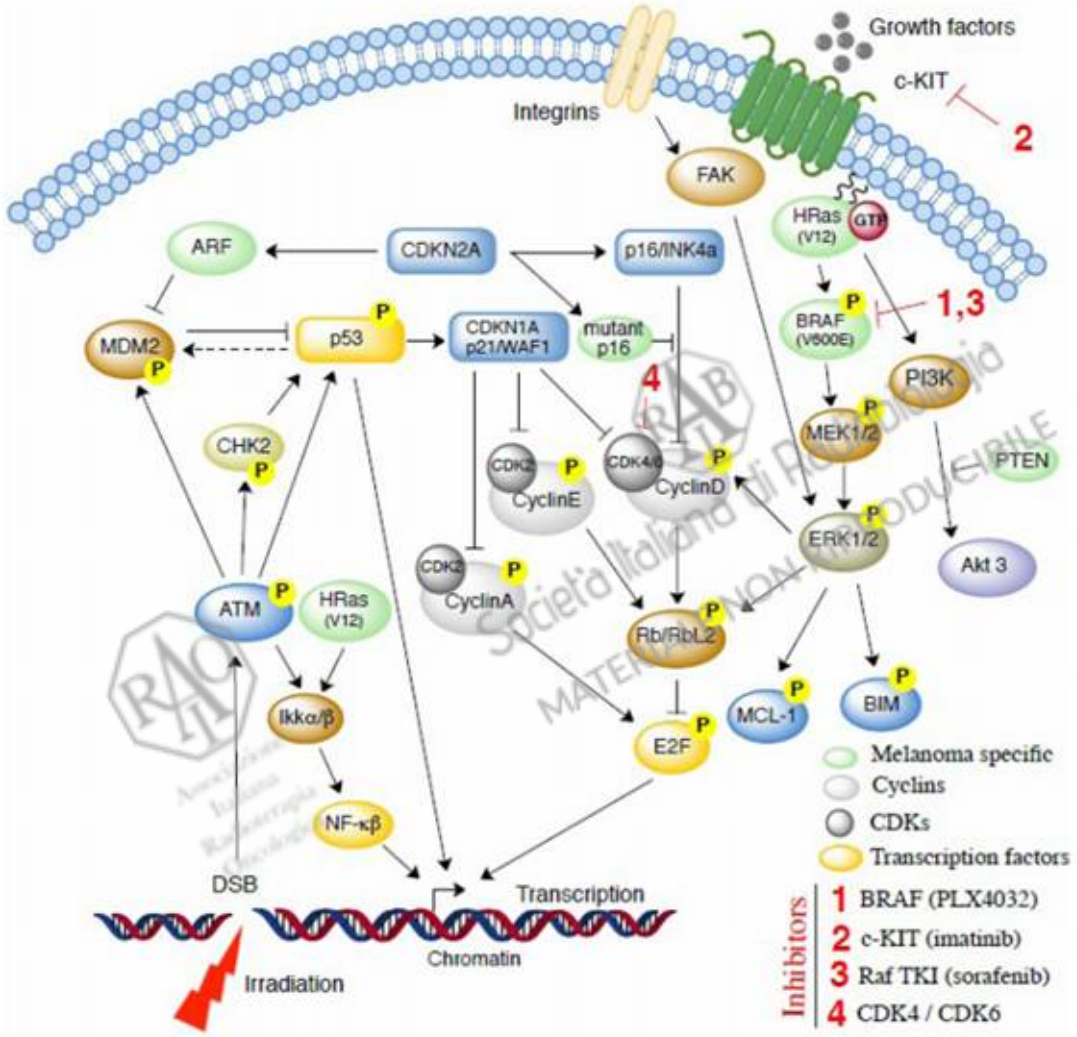
Radiotherapy Combination Opportunities Leveraging Immunity for the Next Oncology Practice

Fernanda G. Herrera, MD[1,2]; Jean Bourhis, MD, PhD[3]; George Coukos, MD, PhD[4,5]

[1]Radiation Oncologist, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [2]Instructor, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; [3]Professor, Chief of Radiation Oncology Service, University Hospital of

ABSTRACT: Approximately one-half of patients with newly diagnosed cancer and many patients with persistent or recurrent tumors receive radiotherapy (RT), with the explicit goal of eliminating tumors through direct killing. The current RT dose and schedule regimens have been empirically developed. Although early clinical studies





Khan K,
Oncotargets &
Therapy, 2014

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Critical Review

Combinations of Radiation Therapy and Immunotherapy for Melanoma: A Review of Clinical Outcomes

Christopher A. Barker, MD,* and Michael A. Postow, MD†

*Department of Radiation Oncology and †Department of Medicine, Melanoma and Sarcoma Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, New York

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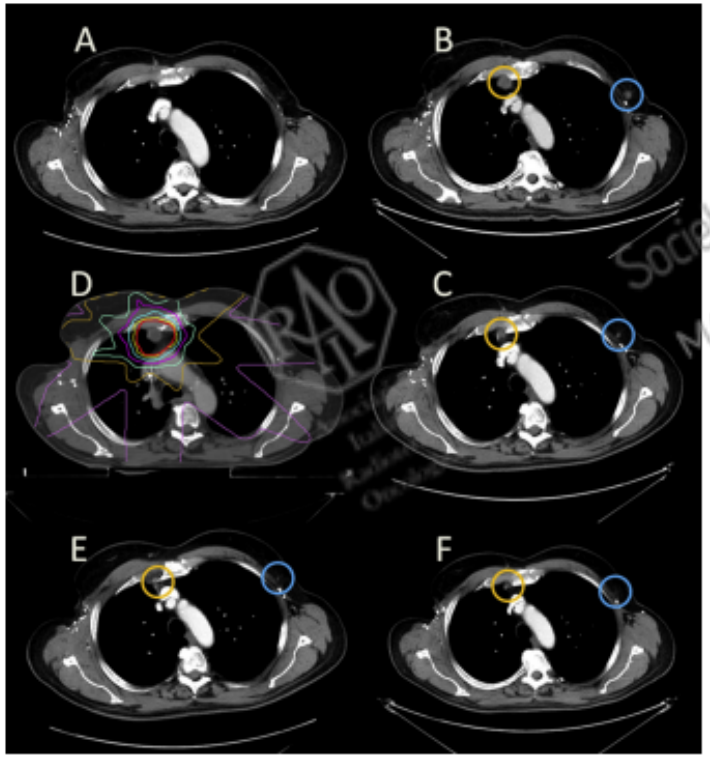

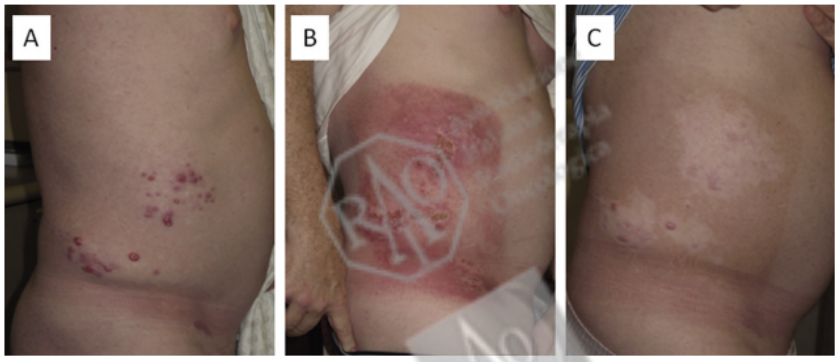

Fig. 1. Halo depigmentation surrounding irradiated dermal metastases from cutaneous melanoma in a 53-year-old man limumab. (A) Recurrent unresectable dermal metastases of melanoma on the right flank present after 2 doses of ipilimu weeks after completing 36 Gy in 6 fractions to the right flank and 4 doses of ipilimumab erythema is noted in the treatment p months after completion of radiation therapy and ipilimumab, hyperpigmentation of the irradiated skin and halo surrounding the irradiated metastases are seen.

ABSCOPAL EFFECT:
regression of metastatic lesions distant from the primary site of RT

Grimaldi *et al. Journal of Translational Medicine* 2014, **12**(Suppl 1):O6
http://www.translational-medicine.com/content/12/S1/O6

JOURNAL OF TRANSLATIONAL MEDICINE

ORAL PRESENTATION Open Access

Efficacy of radiotherapy in patients on progression after treatment with ipilimumab 3 mg/kg

Antonio M Grimaldi*, Ester Simeone, Diana Giannarelli, Paolo Muto, Sara Falivene, Fabio Sandomenico, Antonella Petrillo, Marcello Curvietto, Assunta Esposito, Miriam Paone, Marco Palla, Corrado Caracò, Gennaro Ciliberto, Nicola Mozzillo, Paolo A Ascierto

From Melanoma Bridge meeting 2013
Naples, Italy. 5-8 December 2013

Background

Ipilimumab, a fully human monoclonal antibody (IgG1) that promote antitumor immunity by blocking CTLA4, was the first agent which showed a long-term survival benefit, about the 20% of patients, for the treatment of metastatic melanoma. The combination of ipilimumab with other therapies might improve its efficacy.

The term "abscopal effect" refers to a regression of metastatic lesions distant from the primary site of radiotherapy (RT). This new phenomenon represent the systemic response observed in patients who received ipilimumab.

metastatis. The median doses of radiation was of 30 Gy (range 30-50). A local response to RT was detected in 13 patients (62%) while 8 patients (38%) did not show any local regression. The abscopal response has been detected in 11/21 (52%) patients: in details, we observed 9 abscopal partial response (42,8%), 2 abscopal stable disease (9,6%), and 10 progression (47,6%). The median of occurrence of the abscopal response was of 1 month (range 1-4). The median overall survival (OS) for all the 21 patients was of 13 months (range 6-26). The median OS for patients with and without abscopal responses was respectively of

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Systematic review

Radiotherapy and immune checkpoints inhibitors for advanced melanoma

Andrea Riccardo Filippi [a,*], Paolo Fava [b], Serena Badellino [a], Chiara Astrua [b], Umberto Ricardi [a], Pietro Quaglino [b]

[a] Department of Oncology, Radiation Oncology; and [b] Department of Medical Sciences, Dermatology/Oncology, University of Torino, Italy

Table 4
Clinical outcomes following the combination of radiotherapy and ipilimumab for advanced melanoma.

Study	No patients	Radiotherapy dose/ fractionation (Type)	Ipilimumab schedule (sequence)	Targeted site	Target site response (%)	Abscopal response* (%)
Postow et al., 2012 [12	1	28.5 Gy/3 fr (palliative)	10 mg/kg (sequential)	Para-spinal metastasis	PR 100	PR 100
Hiniker et al., 2012 [67]	1	54 Gy/3 fr (SBRT)	3 mg/kg (concurrent)	Liver metastasis	CR 100	CR 100
Barker et al., 2013 [14]	29	30 Gy/10 fr (median) (SBRT/palliative)	3–10 mg/kg (concurrent/ maintenance)	Non-brain lesions	Symptoms relief 77	NR
Grimaldi et al., 2014 [13]	21	20–24/1; 20 Gy/ 5fr; 30 Gy/10fr; 50 Gy/25 fr (SBRT/SRS/palliative/ WBRT)	3 mg/kg (sequential)	Brain, bone, lymph-node, cutaneous lesions	PR 62	PR 43 SD 10
Chandra et al., 2015 [68]	47	26 Gy (median) (SBRT/SRS/palliative/ WBRT)	3–10 mg/kg (sequential)	Brain, soft tissue, bone, intrathoracic, abdominovisceral	NR	PR 36
Stamell et al., 2013 [69]	1	NR (SRS)	NR	Brain	NR	CR 100
Muller-Brenne et al., 2003 [71]	1	30 Gy/10 fr WBRT	3 mg/kg (sequential)	Brain	CR 100	NR
Bot et al., 2012 [72]	1	20 Gy/5fr WBRT	3 mg/kg (sequential)	Brain	CR 100	NR
Gerber et al. [73]	13	30 Gy/10 fr (median) WBRT	3–10 mg/kg (concurrent)	Brain	PR/ SD 56%	NR
Schoenfeld et al., 2015 [74]	16	22 Gy; 36 Gy (SRS/WBRT)	3–10 mg/kg (sequential/concurrent)	Brain	NR	PR 35
Silk et al., 2013 [75]	33	14–24 Gy/1–5 fr; 30–37.5 Gy/10–13 fr (SRS/WBRT)	3 mg/kg (sequential)	Brain	PR 56.7	NR
Knisely et al., 2012 [76]	27	NR (SRS)	NR (sequential)	Brain	NR	NR
Mathew et al., 2013 [77]	25	20 Gy/1 fr (median) (SRS)	3 mg/kg (sequential/concurrent)	Brain	6-months LC 63%	NR
Tazi et al., 2015 [78]	10	NR (SRS)	3 mg/kg (sequential/concurrent)	Brain	NR	NR
Kiess et al., 2015 [79]	46	15–24 Gy/1 fr (SRS)	3–10 mg/kg (sequential/concurrent)	Brain	NR	NR
Du-Four et al., 2012 [80]	3	20 Gy/1 fr (SRS)	3 mg/kg (sequential)	Brain	CR 100	NR

Table 5
Prospective clinical trials combining either anti-CTLA-4 or anti-PD-1 agents and radiotherapy for advanced melanoma (from www.clinicaltrials.gov, December 2015, in order of estimated completion date).

Registration number	Study design	Eligibility criteria	Intervention	Primary endpoint	Estimated enrolment	Estimated study completion date
NCT01689974	Phase II	Locally unresectable, metastatic melanoma, with at least 2 distinct measurable metastatic sites, one of at least 1 cm or larger	Arm A: IPI alone Arm B: IPI and RT	Response rate	10	Completed in March 2015
NCT01497808	Phase I/II	Metastatic melanoma	IPI and SBRT	Dose- limiting toxicity	40	June 2015 (ongoing, not recruiting)
NCT01557114	Phase I	Unresectable locally advanced or metastatic melanoma with at least one melanoma metastasis accessible to radiation therapy	Induction IPI (4 courses), →RT→ Maintenance IPI	Maximum Tolerated Dose of RT in combination with IPI	30	March 2016
NCT01449279	Single institution, open-label, pilot study	Stage IV melanoma	IPI and palliative radiation therapy	Percentage of patients experiencing serious adverse events in the first 4 months of treatment	20	June 2016
NCT01996202	Phase I	Resected patients at high risk of recurrence/ Neoadjuvant- definitive approach for locally advanced patients	RT and IPI	Incidence of immune related adverse events associated with IPI, acute and late radiation toxicities	24	June 2016
NCT01970527	Phase II	Recurrent/stage IV Melanoma Index lesion between 1 and 5 cm	SBRT (3 fractions) between days 1 and 13 →IPI every 3 weeks (4 courses)	Late toxicity, immune- related clinical response, immune-related PFS, OS	40	September 2016
NCT02115139	Phase II	Melanoma brain metastases	Whole brain RT with concurrent IPI	1-year OS	66	October 2016
NCT02097732	Phase II	Melanoma brain metastases	Standard arm: SRS → IPI (4 cycles) Experimental arm: IPI (2 cycles) → SRS → IPI (2 cycles)	Local control rate	40	May 2017
NCT02107755	Phase II	Oligo-metastatic melanoma	SBRT with concurrent IPI	PFS	32	June 2017
NCT02406183	Phase I	Metastatic melanoma with at least 3 extra-cranial measurable lesions	SBRT with concurrent IPI	Maximum Tolerated dose, with dose-limiting toxicity in 25% of patient	21	July 2017
NCT01565837	Phase II	Oligo-metastatic but unresectable melanoma	SBRT with concurrent IPI	OS, safety and tolerability (acute and subacute toxicity)	50	November 2017
NCT02407171	Phase IIa (expansion cohort)	Metastatic melanoma (with at least one site of measurable disease suitable for SBRT)	SBRT (at maximum tolerated dose discovered in phase I) and Pembro (200 mg every 2 weeks)	Overall response rate	60	December 2018
NCT02562625	Phase II	Unresectable or stage IV melanoma with 1-3 lesions targets for high dose radiotherapy and at least one other lesion which will not be irradiated to assess the abscopal effect of the treatment	Arm 1: Pembro alone Arm 2: Pembro and RT (24 Gy/ 3 fr)	Abscopal effect	234	October 2019
NCT01703507	Phase I	Melanoma brain metastases	Arm A: IPI and WBRT Arm B: IPI and SRS	Maximum tolerated dose of IPI	24	November 2019
NCT02318771	Phase I	Metastatic melanoma (among other tumour types)	• RT (8 Gy/1 fr–20 Gy/5 fr) → re-biopsy → Pembro • Pembro → RT → Pembro	Change in PD-L1 levels	40	January 2020

Abbreviations: SRS: stereotactic radiosurgery; SBRT: stereotactic body radiation therapy; PFS: progression-free survival; OS: overall survival; IPI: ipilimumab; Pembro: pembrolizumab; NA: not applicable; NR: not reported.

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Research Article

Cancer Immunology Research

Local Tumor Treatment in Combination with Systemic Ipilimumab Immunotherapy Prolongs Overall Survival in Patients with Advanced Malignant Melanoma

Sebastian Theurich[1,2,3,4], Sacha I. Rothschild[2,5], Michael Hoffmann[6], Mario Fabri[6], Andrea Sommer[6], Maria Garcia-Marquez[2], Martin Thelen[2], Catherine Schil, Ramona Merki[7], Thomas Schmid[8], Dieter Koeberle[8], Alfred Zippelius[5], Christian Baues[4,9], Cornelia Mauch[6], Christian Tigges[10], Alexander Kreute, Jan Borggrefe[11], Michael von Bergwelt-Baildon[1,2,4], and Max Schlaak[4,6]

Abstract

Immune checkpoint inhibition with ipilimumab has revolutionized cancer immunotherapy and significantly improved outcomes of patients with advanced malignant melanoma. Local peripheral treatments (LPT), such as radiotherapy or electrochemotherapy, have been shown to modulate systemic immune responses, and preliminary data have raised the hypothesis that the combination of LPT with systemic immune checkpoint blockade might be beneficial. Clinical data from 127 consecutively treated melanoma patients at four cancer centers in Germany and Switzerland were analyzed. Patients received either ipilimumab

42 weeks, unadjusted HR, 0.4
related events were not increas
and LPT-induced local toxiciti
multivariable Cox regression a
added LPT on OS remained sta
for BRAF status, tumor stage, t
system metastases (adjusted H
0.31–1.01, $P = 0.05$). Our dat
to ipilimumab is safe and eff
melanoma irrespective of cli

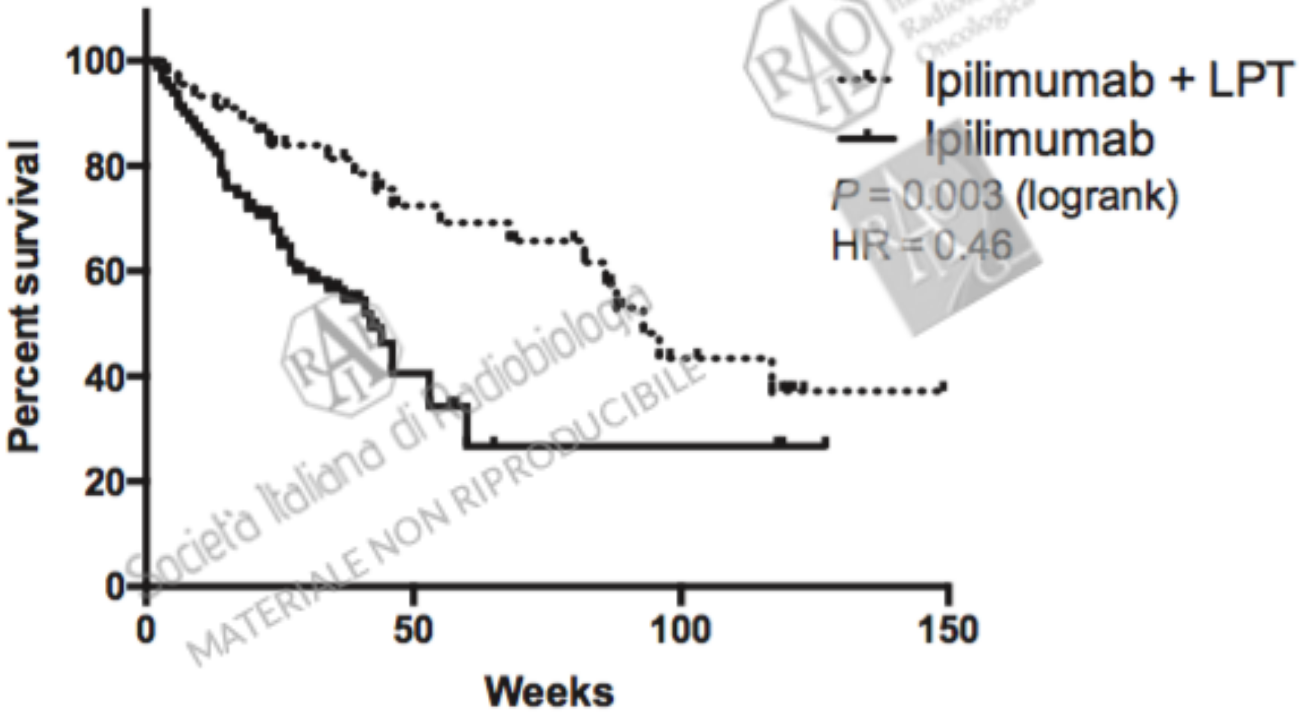
Table 1. Patient characteristics

Parameters	
Age at diagnosis (mean)	61.7 (range, 23–89)
Sex (*n*, patients)	
Males	69 (54.3%)
Females	58 (45.7%)
Stages (*n*, patients)	
IIIc	14 (11.0%)
IV	113 (89.0%)
M_{1a}	9 (7.1%)
M_{1b}	23 (18.1%)
M_{1c}	81 (63.8%)
Sites of metastases[a] (*n*, patients)	
CNS	49 (38.6%)
Bone or soft tissue	36 (23.8%)
Visceral	95 (74.8%)
Lymph nodes	96 (75.6%)
Skin	59 (46.5%)
BRAF mutation status (*n*, patients)	
Mutated	42 (33.1%)
Wild-type	85 (66.9%)
Ipilimumab cycles (mean)	3.34 (range, 1–8)
≤2 cycles (*n*, patients)	31 (24.4%)
≥3 cycles (*n*, patients)	95 (74.8%)
n.a.[b]	1 (0.8%)
Treatments during time of study (*n*, patients)	
Ipilimumab + LPT	39 (30.7%)
Ipilimumab + LPT + brain irradiation	6 (4.7%)
Ipilimumab only	42 (33.1%)
Ipilimumab + LBI	17 (13.4%)
Ipilimumab + WBI	15 (11.8%)
Ipilimumab + combination of LBI and WBI	8 (7.1%)
Timing of LPT to ipilimumab (*n*, patients)	
Pre	9 (20.0%)
During	19 (42.2%)
Post	17 (37.8%)

NOTE: Local brain irradiation (LBI) included stereotactic radiosurgery and cyberknife irradiation. WBI was conventionally performed. LPTs were defined as non-CNS-directed therapies and included the following: local irradiation (of lymph node, bone, visceral, or skin metastases) or skin-directed ECT or SIRT of liver metastases.

[a]Patients with more than one metastatic site were counted in every respective group. Timing of LPT referred to the entire ipilimumab treatment.

Overall survival (all patients)

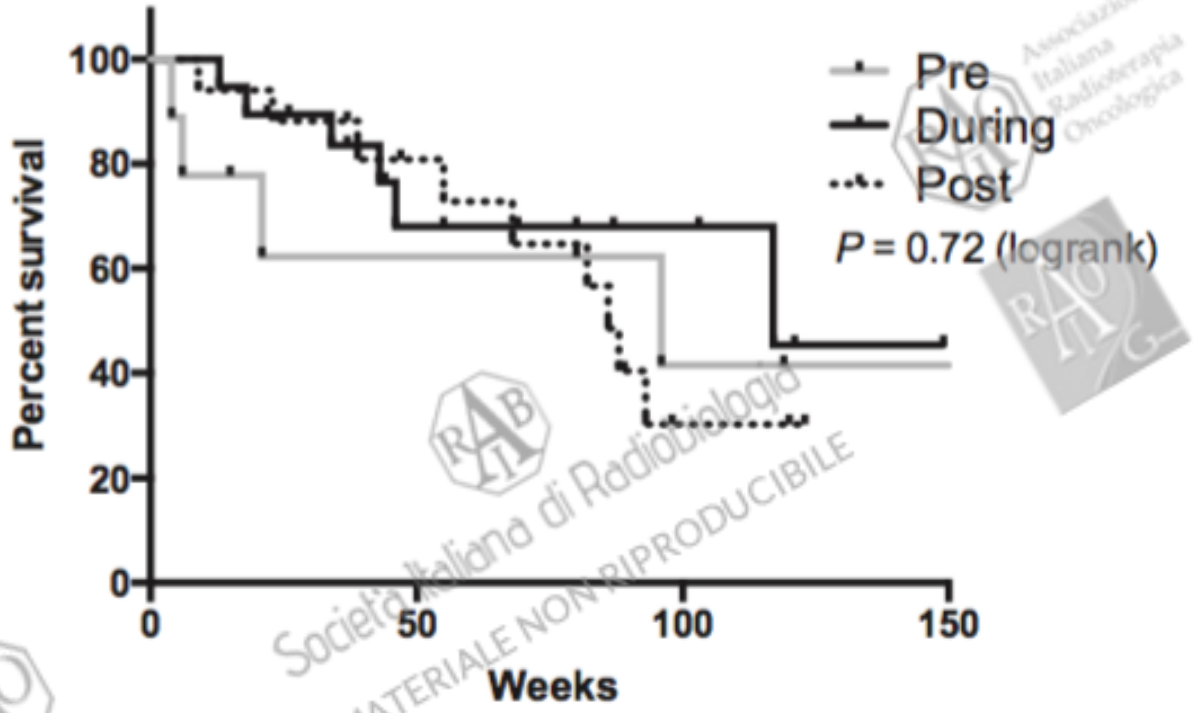


Patients at risk

Week:	*0*	*25*	*50*	*75*	*100*	*125*	*150*
Ipilimumab + LPT:	45	35	23	19	9	3	2
mab:	82	47	16	5	5	2	

Overall survival depending on LPT & CNS radiotherapy

Overall survival depending on LPT timing



Patients at risk

Week:	*0*	*25*	*50*	*75*	*100*	*125*	*150*
Pre:	9	5	5	5	3	2	2
During:	19	17	9	7	5	2	1
Post:	17	15	11	9	3	1	

MULTIMODALITY APPROACH

Terapia medica del melanoma metastatico: la Safety

Ipilimumab: eventi avversi immunorelati irAE

Apparato gastrointestinale:
- Diarrea
- Dolore addominale
- Sangue o muco nelle feci
- Perforazione intestinale
- Peritonismo
- Ileo

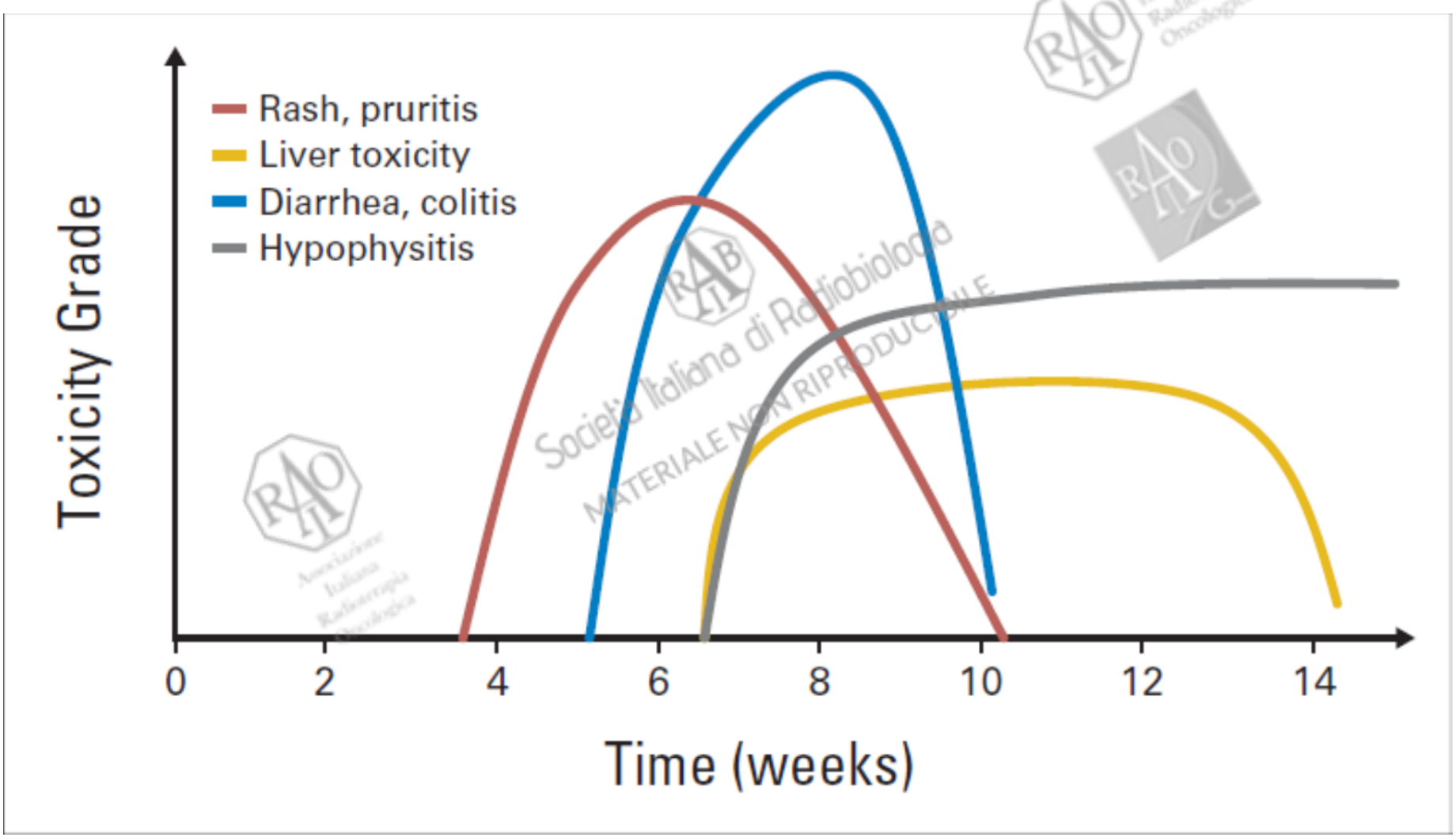
Fegato:
- Elevazione degli enzimi di funzionalità epatica (AST, ALT), Bil tot.

Cute:
- Esantema maculo-papuloso
- Prurito
- Vitiligo-like lesions
- Reazioni simil vasculitiche

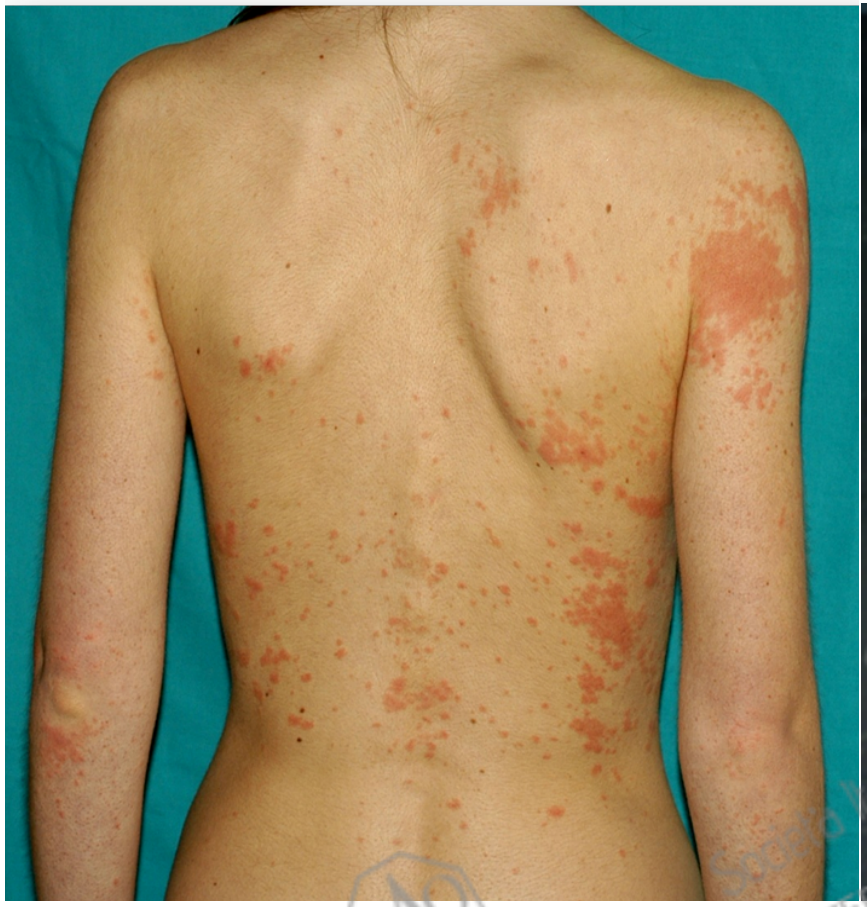
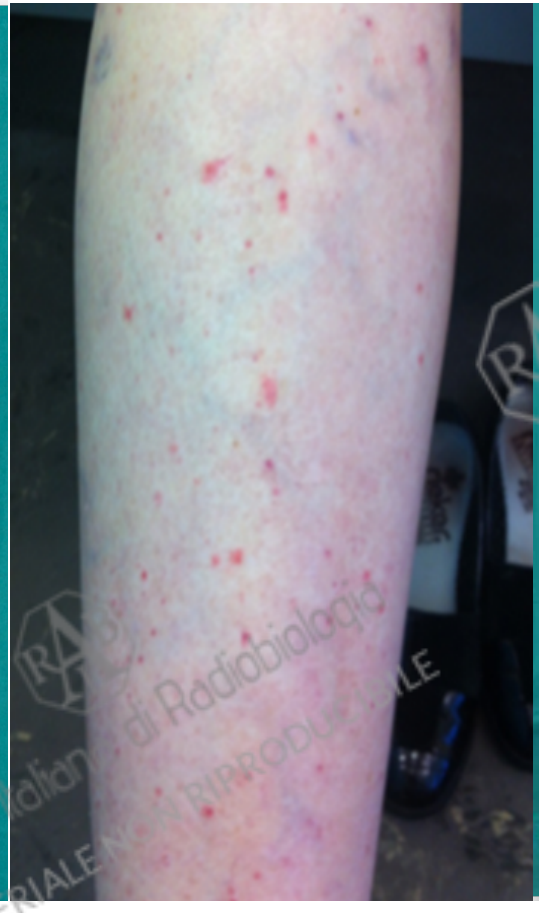
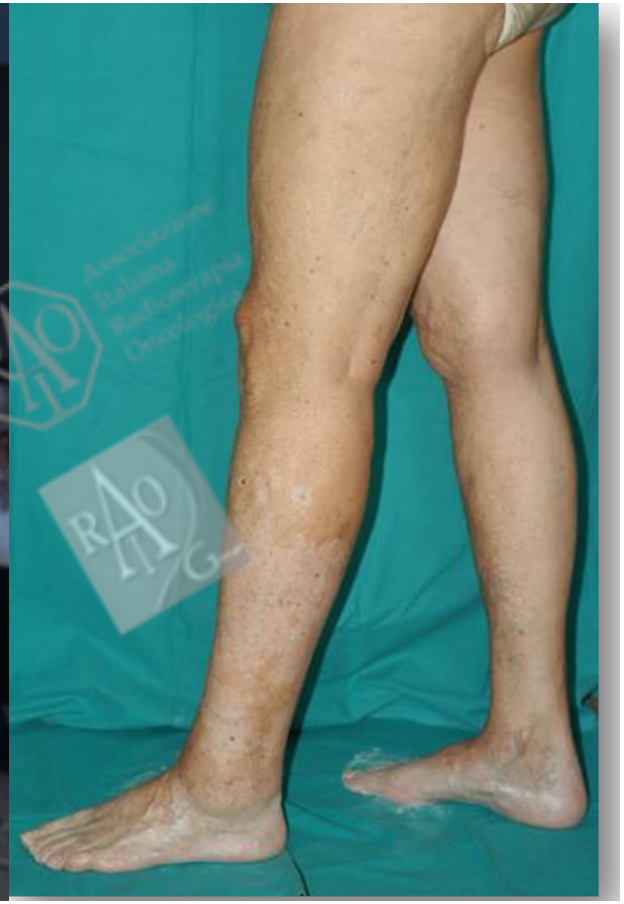
Sistema Endocrino:
- Astenia
- Cefalea
- Alterazioni dello stato mentale
- Alterazioni tiroidee
- Turbe dell'alvo
- Ipotensione

Nervi periferici:
- Ipostenia mono/bilaterale
- Alterazioni sensoriali
- Parestesie

Cinetica degli irAE:



Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol*. 2012 Jul 20;30(21):2691-7

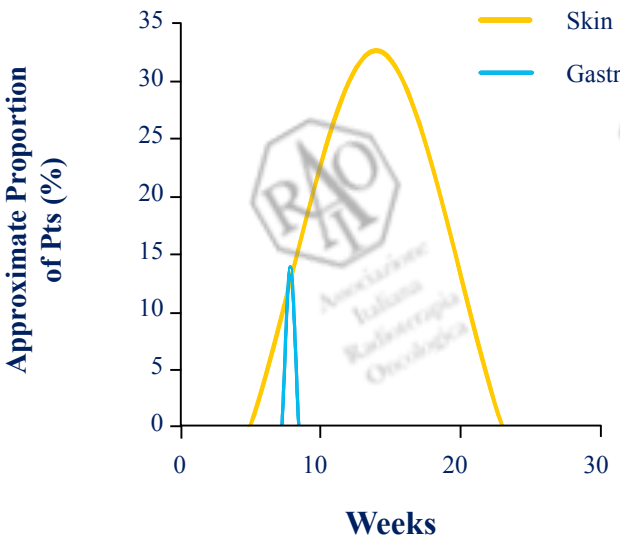
NIVOLUMAB Cinetica di comparsa degli eventi avversi immuno-correlati

Jeffrey S. Weber,[1] Scott J. Antonia,[1] Suzanne Topalian,[2] Dirk Schadendorf,[3] James Larkin,[4] Mario Sznol,[5] Helen Liu,[6] Ian M. Waxman,[7] Caroline Robert[8]

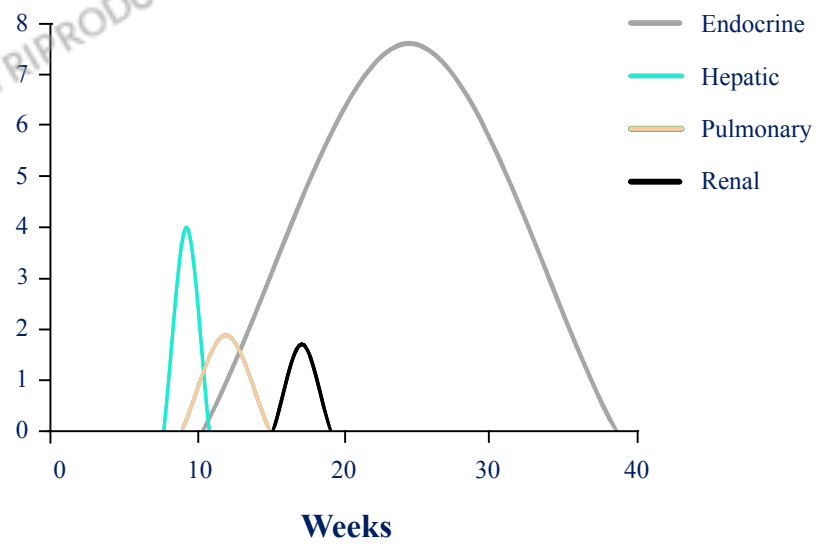
[1]Moffitt Cancer Center, Tampa, FL, USA; [2]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [3]University of Essen, Essen, Germany; [4]Royal Marsden Hospital, London, UK; [5]Yale University School of Medicine and Smilow Cancer Center, Yale-New Haven Hospital, New Haven, CT, USA; [6]Bristol-Myers Squibb, Wallingford, CT, USA; [7]Bristol-Myers Squibb, Lawrenceville, NJ, USA; [8]Gustave Roussy and INSERM Unité 981, Villejuif–Paris Sud, France

Kinetics of onset and resolution of select treatment-related AEs (any grade).

A. Most common select AEs (≥10%)



B. Less common select AEs (<10%)



Tossicità Ipi vs Nivo/Pembro vs Combo

Drug	%Any grade	% 3-4
Ipilimumab (Hodi, 2010)	80.2% - 88.9%	17.4%-22.9%
CheckMate 037 – Nivo (Weber, 2015)	Grade 1-2 59%	9%
KeyNote 002 – Pembro (Ribas, 2015)	Grade 1-2 57%-60%	11%-14%
Ipi + Nivo (Postow, 2015) Ipilimumab	91% 93%	54% 24%

Vitiligo come fattore predittivo di risposta?

JAMA Dermatol. 2016

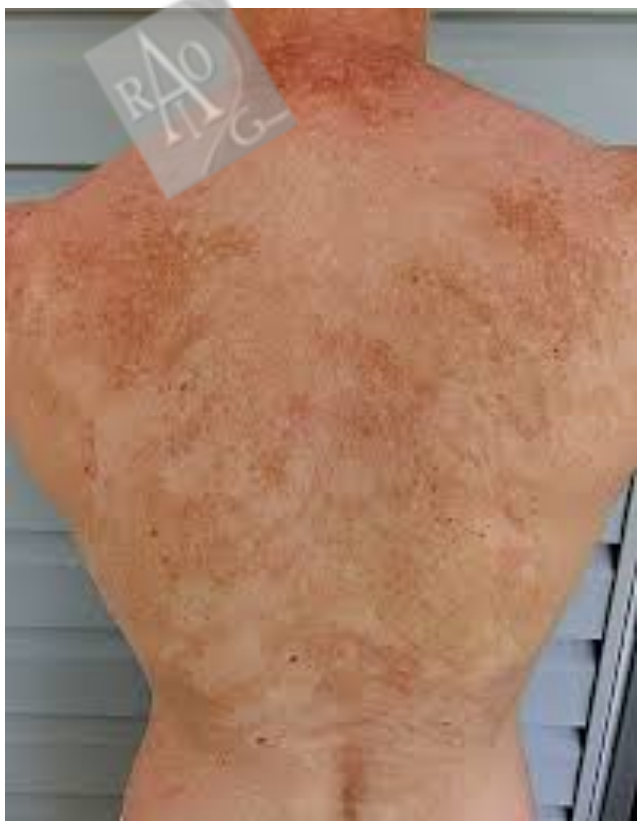
Association of Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab. Hua C1, et al.

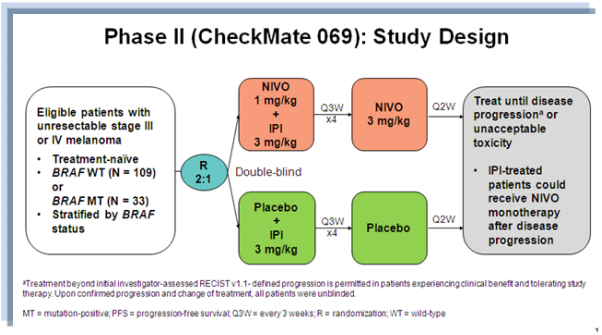
DESIGN, SETTING, AND RESULTS:

Of the 67 patients included in the study, 17 (25%) developed vitiligo during pembrolizumab treatment and 50 (75%) did not. An objective (complete or partial) response to treatment was associated with a higher occurrence of vitiligo (12 of 17 [71%] vs 14 of 50 [28%]; P = .002). The time to onset of vitiligo ranged from 52 to 453 (median, 126) days from the start of treatment. Of the 17 patients with vitiligo, 3 (18%) had a complete response, 9 (53%) had a partial response, 3 (18%) had stable disease, and 2 (12%) had progressive disease at the final follow-up. All the patients treated with pembrolizumab who developed vitiligo were alive at the time of analysis, with a median follow-up of 441 days.

CONCLUSIONS AND RELEVANCE:

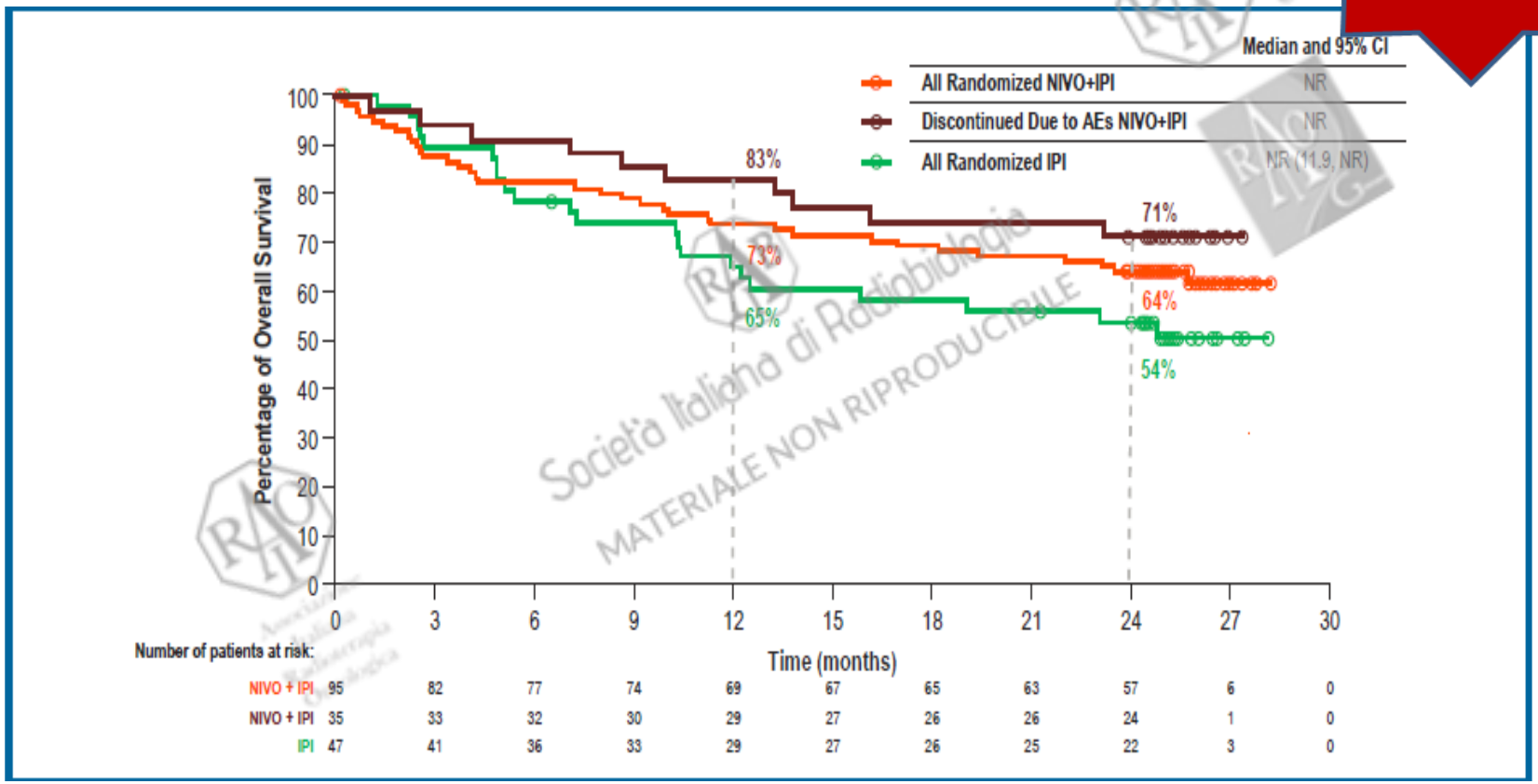
Vitiligo, a clinically visible immune-related adverse event could be associated with clinical benefit in the context of pembrolizumab treatment.



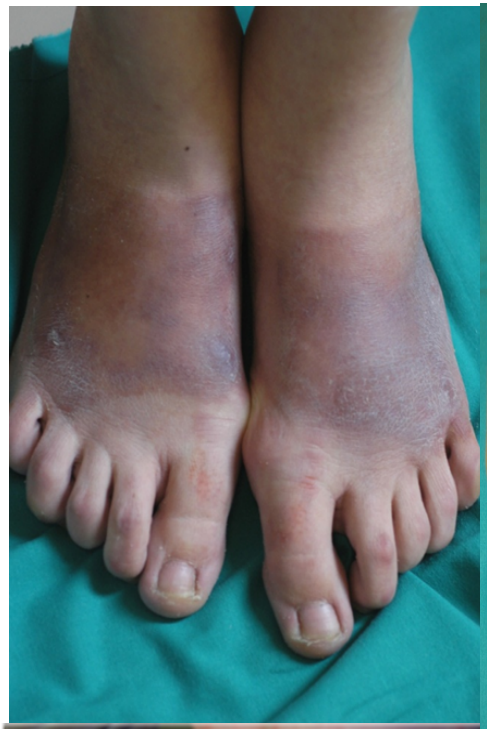
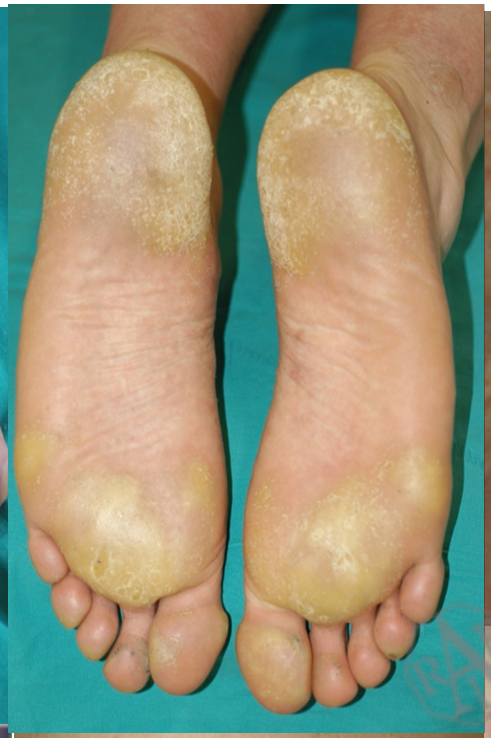
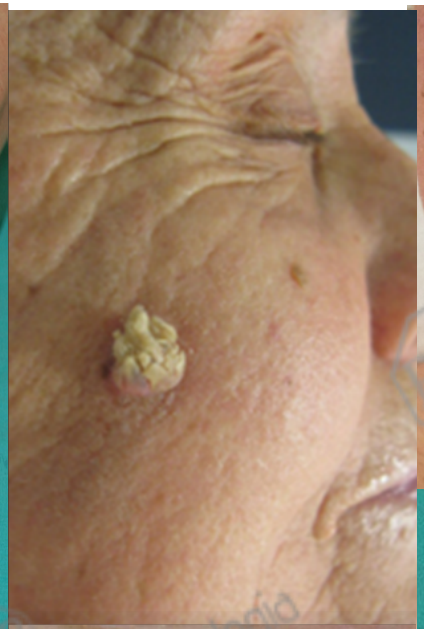
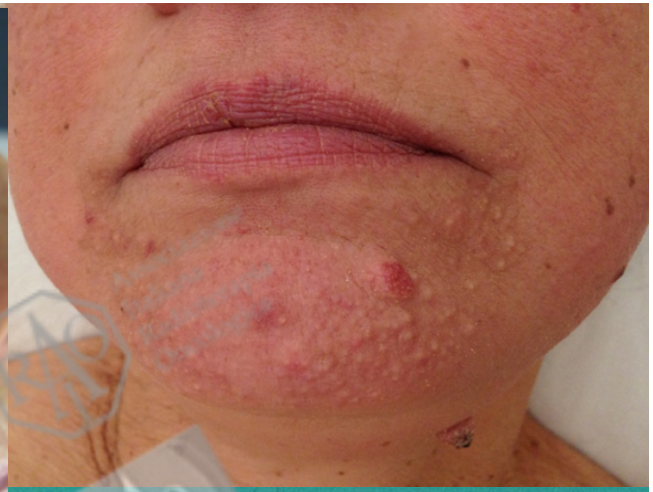
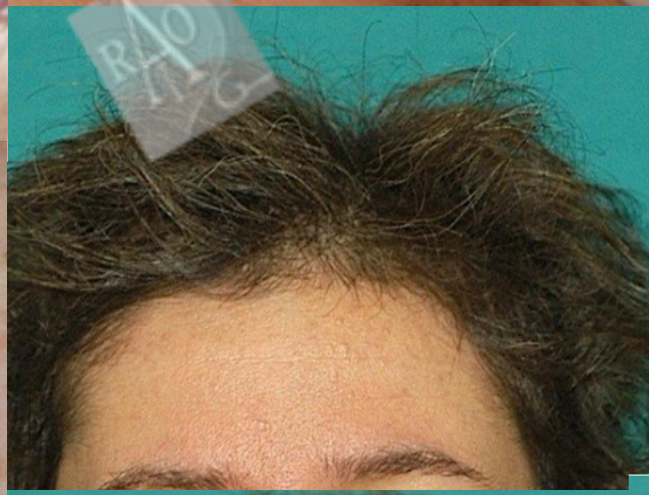
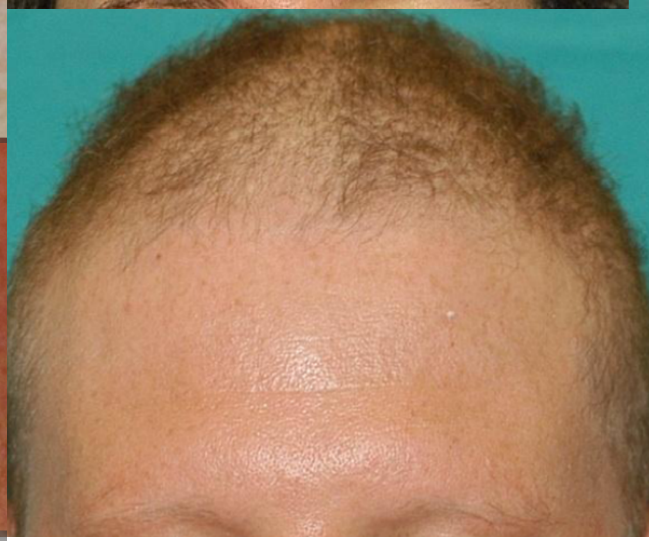
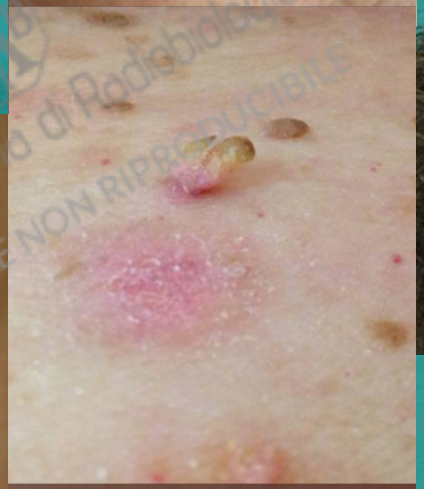
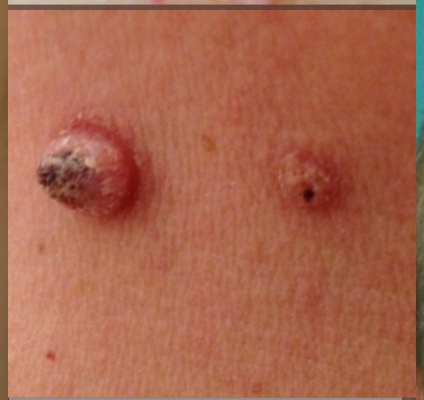
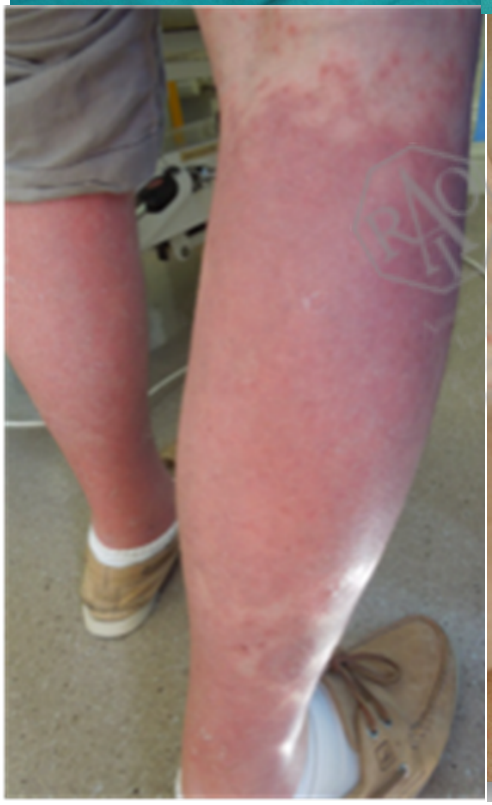
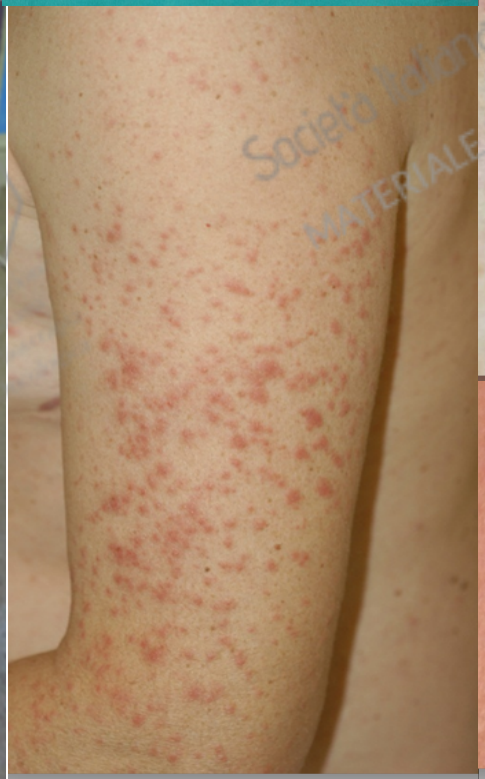


Overall survival at 2 years of follow-up

ASCO 2016



In the 35 patients who discontinued NIVO+IPI due to treatment-related AEs, overall survival was similar to the all randomized population

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Trial (BREAK-2) of the BRAF Inhibitor Dabrafenib (GSK2118436) in Patients With Metastatic Melanoma

Paolo A. Ascierto, David Minor, Antoni Ribas, Celeste Lebbe, Anne O'Hagan, Niki Arya, M Dirk Schadendorf, Richard F. Kefford, Jean-Jacques Grob, Omid Hamid, Ravi Amaravadi, I Tabea Wilhelm, Kevin B. Kim, Georgina V. Long, Anne-Marie Martin, Jolly Mazumdar, Vi and Uwe Trefzer

Paolo A. Ascierto, Ester Simeone, Instituto Nazionale Tumori Fondazione "G. Pascale," Napoli, Italy; David Minor, California Pacific Center for Melanoma Research and Treatment, San Francisco; Antoni Ribas, Jonsson Comprehensive Cancer Center, University of California, Los Angeles; Omid

A B S T R A C T

Purpose

Dabrafenib (GSK2118436) is a potent inhibitor of mutated BRAF kinase.

PATTERN DI TOSSICITA' IN PARTE SOVRAPPONIBILE ANCHE SE CON DIFFERENZE QUALI E QUANTITATIVE

RASH DA FOTOSENSIBILIZZAZIONE MOLTO PIU' RARI

Table 3. Summary of All Adverse Events Experienced by at Least 10% of Patients by Maximum Grade and Preferred Term (all treated patients)

Preferred Term	Grade 3		Grade 4		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Any event	25	27	8	9*	86	93
Arthralgia	1	1	0		30	33
Hyperkeratosis	1	1	0		25	27
Pyrexia	0		0		22	24
Fatigue	1	1	0		20	22
Headache	2	2	0		19	21
Nausea	1	1	0		18	20
Skin papilloma	0		0		14	15
Vomiting	1	1	0		14	15
Pain in extremity	1	1	0		13	14
Cough	0		0		12	13
Decreased appetite	1	1	0		12	13
Alopecia	0		0		11	12
Anemia	4	4	0		11	12
Chills	0		0		11	12
Diarrhea	1	1	0		10	11
Back pain	1	1	0		9	10
Cutaneous squamous cell carcinoma†	7	8	0		9	10
Hypophosphatemia	4	4	0		9	10
Pruritus	0		0		9	10

NOTE. The majority of adverse events were Grade 1 or Grade 2 (data not shown)

COMBI-V TOXICITY PROFILE

Table 3. Adverse Events.*

Event	Dabrafenib plus Trametinib (N=350)		Vemurafenib (N=349)	
	Any Grade†	Grade 3	Any Grade†	Grade 3
	number of patients (percent)			
Clinically significant adverse events occurring in ≥10% of patients				
Any event	343 (98)	167 (48)	345 (99)	198 (57)
Pyrexia‡	184 (53)	15 (4)	73 (21)	2 (1)
Nausea	121 (35)	1 (<1)	125 (36)	2 (1)
Diarrhea	112 (32)	4 (1)	131 (38)	1 (<1)
Chills	110 (31)	3 (1)	27 (8)	0
Vomiting	101 (29)	4 (1)	53 (15)	3 (1)
Arthralgia	84 (24)	3 (1)	178 (51)	15 (4)
Rash	76 (22)	4 (1)	149 (43)	30 (9)
Alopecia	20 (6)	0	137 (39)	1 (<1)
Hand–foot syndrome§	14 (4)	0	87 (25)	1 (<1)
Hyperkeratosis	15 (4)	0	86 (25)	2 (1)
Skin papilloma	6 (2)	0	80 (23)	2 (1)
Photosensitivity reaction	13 (4)	0	78 (22)	1 (<1)
Adverse events of interest occurring in <10% of patients				
Cutaneous squamous-cell carcinoma (including keratoacanthoma)	5 (1)	5 (1)	63 (18)	60 (17)
Decrease in ejection fraction	29 (8)	13 (4)	0	0
Chorioretinopathy	2 (1)	0	1 (<1)	0
Dermatitis acneiform	22 (6)	0	20 (6)	4 (1)

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Characteristics of pyrexia in *BRAF*$^{V600E/K}$ metastatic melanoma patients treated with combined dabrafenib and trametinib in a phase I/II clinical trial

A. M. Menzies[1*], M. T. Ashworth[2], S. Swann[3], R. F. Kefford[1,4,5], K. Flaherty[6], J. Weber[7], J. R. Infante[8], K. B. Kim[9], R. Gonzalez[10], O. Hamid[11], L. Schuchter[12], J. Cebon[13], J. A. Sosman[14], S. Little[3], P. Sun[3], G. Aktan[3], D. Ouellet[3], F. Jin[3], G. V. Long[1,5,†] & A. Daud[2,†]

[1]Melanoma Institute Australia and The University of Sydney, Sydney, Australia; [2]University of California San Francisco, San Francisco; [3]Clinical Statistics, GlaxoSmithKline, Collegeville, USA; [4]Westmead Hospital, University of Sydney, Sydney; [5]Westmead Millennium Institute, University of Sydney, Sydney, Australia; [6]Massachusetts General Hospital Center, Boston; [7]Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa; [8]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville; [9]California Pacific Medical Center, San Francisco; [10]Department of Medical Oncology, The University of Colorado Cancer Center, Aurora; [11]Department of Oncology, The Angeles Clinic and Research Institute, Santa Monica; [12]Penn Medicine, The University of Pennsylvania, Philadelphia, USA; [13]Oncology Unit, Ludwig Institute for Cancer Research, Heidelberg, Australia; [14]Department of Oncology, Vanderbilt University Medical Centre, Nashville, USA

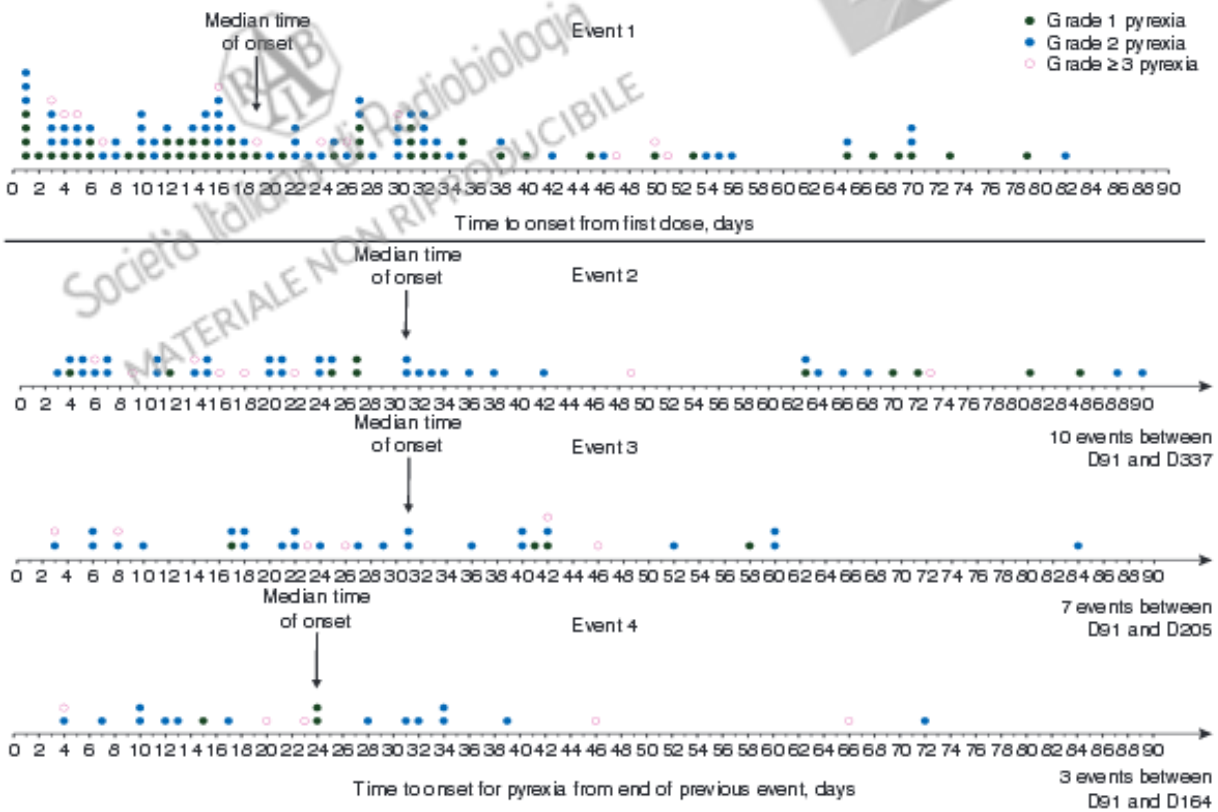

Figure 1. Timing and grade of events of pyrexia.

Drug/regimen	More frequently reported adverse events (%)				
Ipilimumab (Hodi, 2010)	Dermatologic (43%)	Fatigue (42%)	Diarrhea (32.8%)	Nausea, vomiting (23.7%)	Endocrine (7.6%)
Pembrolizumab (KEYNOTE-002)	Fatigue (21%)	Pruritus (21%)	Rash (12%)	Diarrhea (8%)	Arthralgia (7%)
Nivolumab + Ipi (Hodi, 2015)	Diarrhea (45%)	Rash (41%)	Fatigue (39%)	Pruritus (35%)	Nausea, liver (22%)
Vemurafenib (BRIM-3)	Rash (49%)	SCC (14%) Papilloma (15%) Iperkeratosis(19%)	Arthralgia (39%)	Fatigue (34%)	Photosensitivity (31%)
Dabrafenib (BREAK-2)	Iperkeratosis(27%) Papilloma (15%) SCC (10%)	Arthralgia (33%)	Fever (24%%)	Fatigue (22%)	Headache (21%%)
Dabrafenib+ trametinib (Combi D)	Fever (51%)	Fatigue (35%)	Headache (30%)	Nausea (30%)	Chills (30%)
Vemurafenib + cobimetinib (CoBrim)	Diarrhea (56%)	Nausea (40%)	Vomiting (21%)	Rash (38%)	Photosensitivity (28%)

MULTIDISCIPLINARIETA'


obrigado
Dank U
Merci
mahalo
Köszi
спасибо
Grazie
Thank you
arigatoo
Takk
Gracias
Dziękuję
Děkuju
danke
Kiitos