con il patrocinio di

APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

5ª edizione

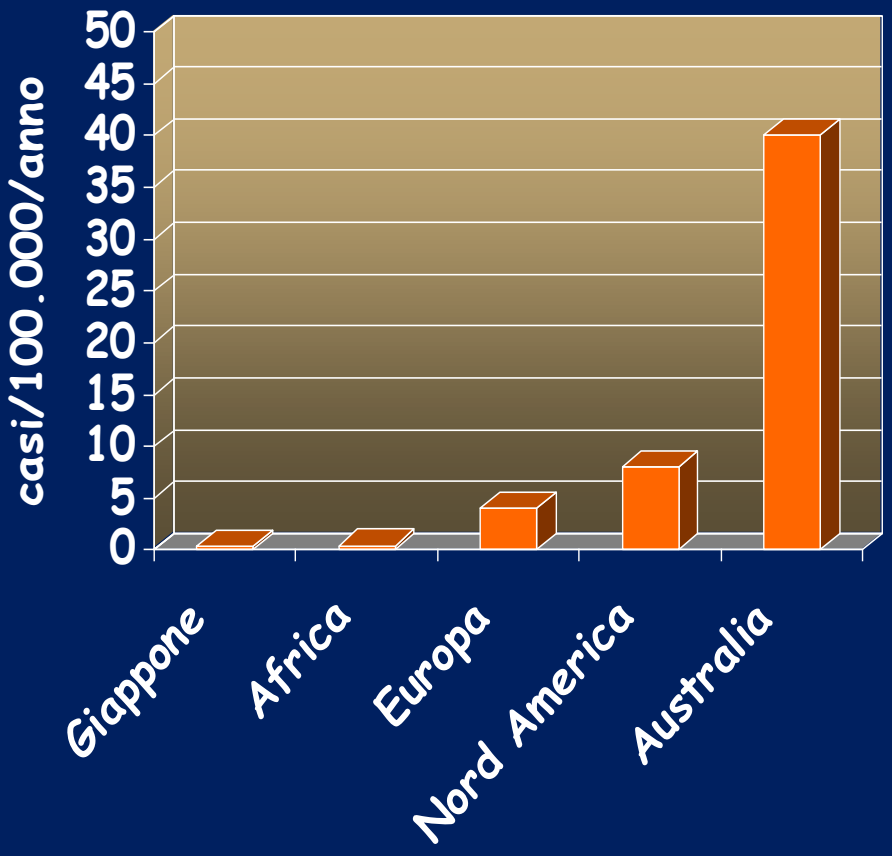
REUMATOLOGIA E MALATTIE NEOPLASTICHE

STATO DELL'ARTE IN TERAPIA ONCOLOGICA: MELANOMA

Prof.ssa MARIA TERESA FIERRO - SC DERMATOLOGIA U

INCIDENZA DEL MELANOMA

in Europa: 20.000 nuovi casi/anno)



1% dei tumori maschili

1,8% dei tumori femminili

Nei paesi occidentali

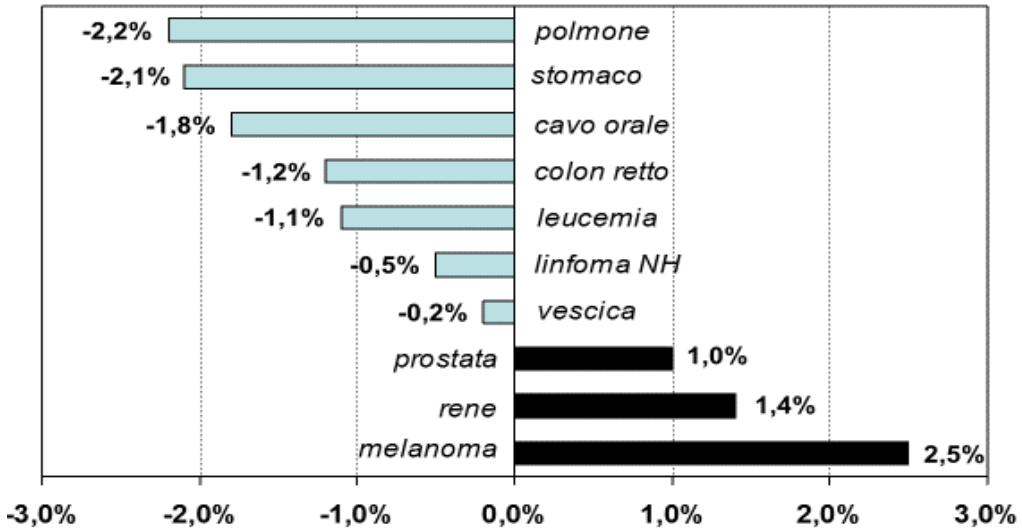
FREQUENZA > 5-7%/ANNO
(x2 OGNI 10 ANNI)

in U.S.A. (30.000 nuovi casi/anno):

rischiano il melanoma nel corso della vita 1/100 abitanti

USA: incidenza dei tumori nei maschi (1995 – 2002)

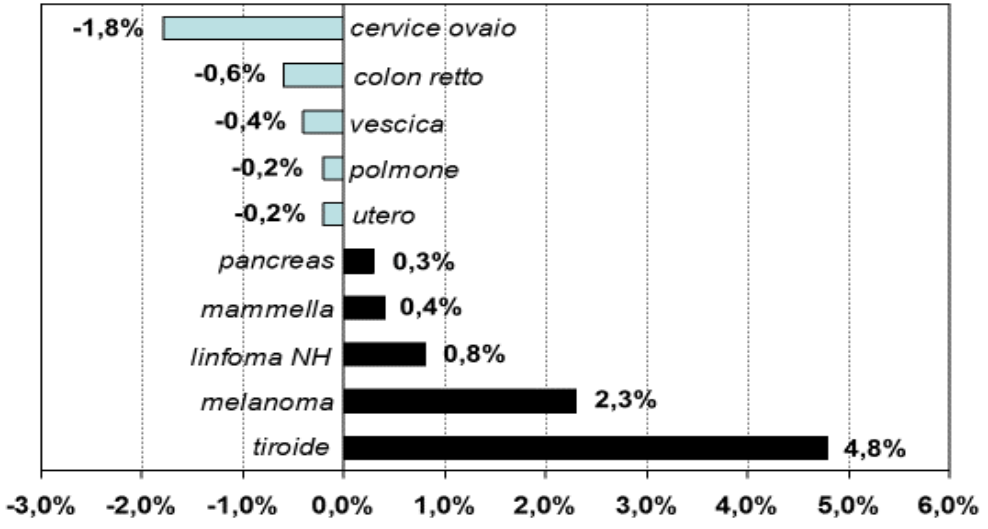
% cambiamento annuo



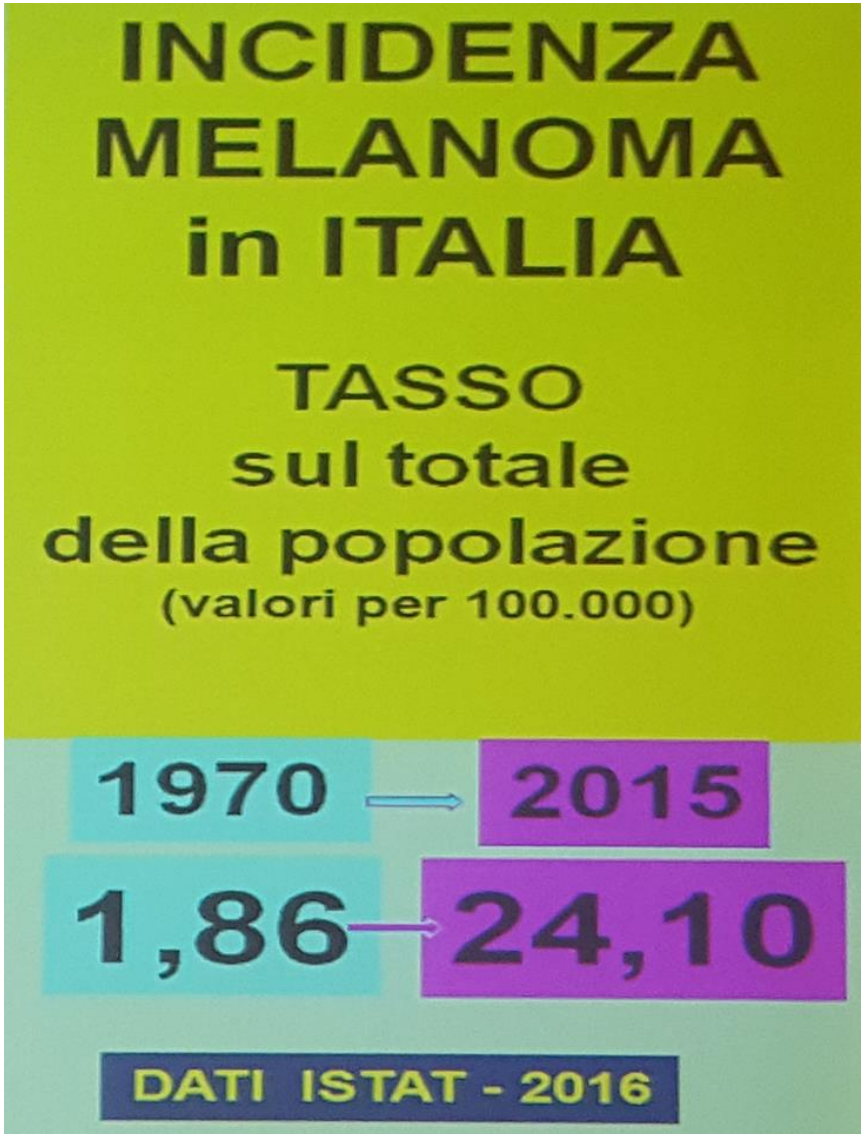
Edwards et al. JNCI, 2005

USA: incidenza dei tumori nelle femmine (1995 – 2002)

% cambiamento annuo



Edwards et al. JNCI, 2005



FATTORI DI RISCHIO ENDOGENI

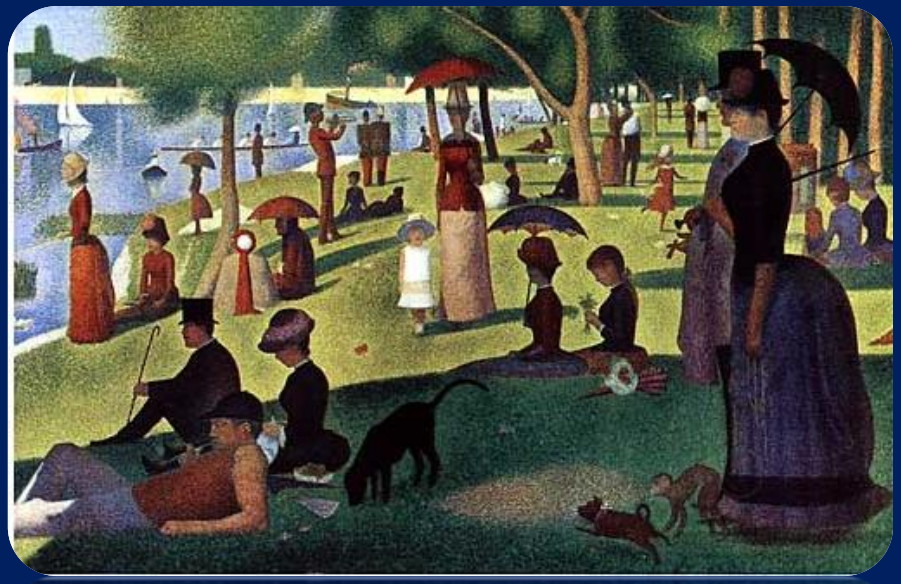
- ✓ **Occhi azzurri, verdi o grigi**: OR 1.99; 95% CI = 1.37-2.89
- ✓ **Capelli castano chiaro**: OR 2.93; 95% CI = 2.01-4.27
- ✓ **Capelli biondi o rossi**: OR 4.40; 95% CI = 2.58-7.52
- ✓ **Cute chiara**: OR 3.81; 95% CI = 2.59-5.61
- ✓ **Fototipo I e II**: OR 2.77; 95% CI = 1.97-3.90

- ✓ **Lentiggini**: OR 3.38; 95% CI = 2.29-4.99
- ✓ **Lentigo solari**: OR 3.59; 95% CI = 1.78-7.24
- ✓ **25-59 nevi**: OR 3.33; 95% CI = 2.09-5.30
- ✓ **> 60 nevi**: OR 8.27; 95% CI = 5.16-13.2
- ✓ **1 o più nevi atipici**: OR 3.50; 95% CI = 2.27-5.40

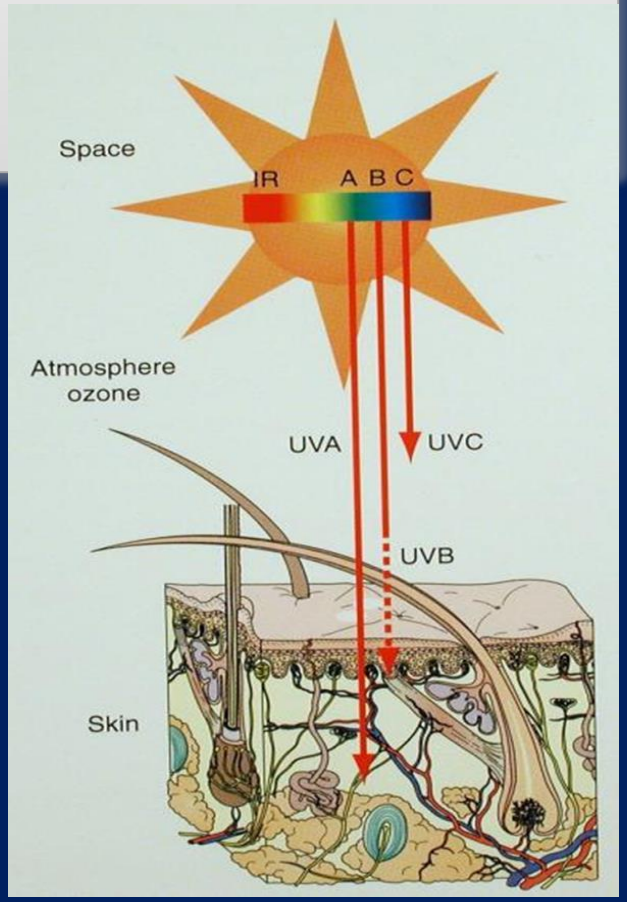
FATTORI DI RISCHIO ESOGENI

- ✓ **6 o più episodi di ustione solare nell'infanzia:** OR 3.89; 95 % CI 2.05 – 7.38
- ✓ **> 6 ore all'aperto durante le vacanze**: OR 1.53; 95% CI = 1.04 – 2.25
- ✓ **uso di lampade abbronzanti** (UVA12 volte più intensi di radiazioni solari) OR 1.30; 95% CI = 0.83-2.04

Lin J. AHRQ 2011



Fortes et al. *Int J Epidemiol* 2008; **37**: 1018-29



Handheld Dermoscopy Devices

Cheap
Fast for screening
Great quality

"... The only chance for benefit depends on the early removal of the black cancer by operation..."

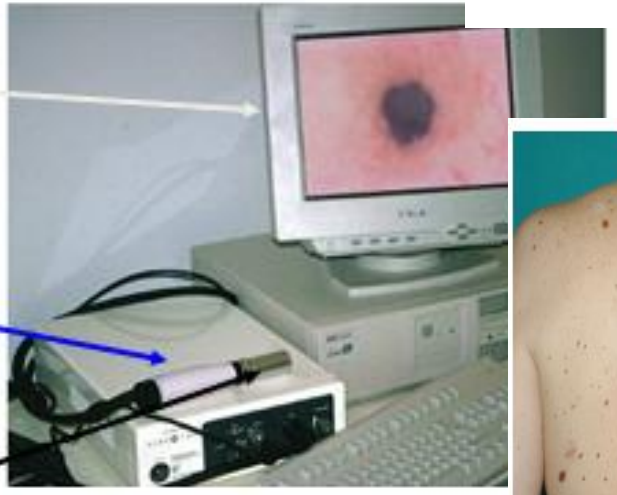
Samuel Cooper, 1840

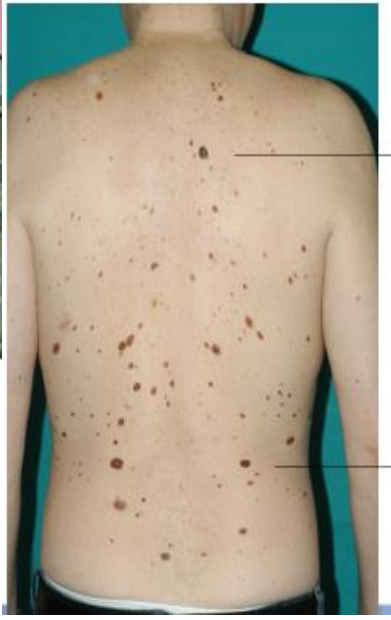
Sir William S. Handley (1872-1962)

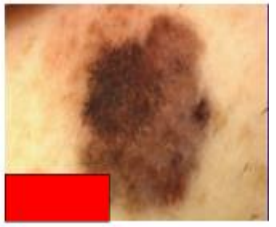
Immagine è digitalizzata da un convertitore di immagini che dà vita ad un segnale poi trasferito al PC

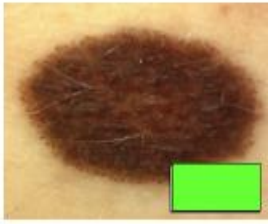
Sonda

Micro-telecamera a colori ad alta risoluzione

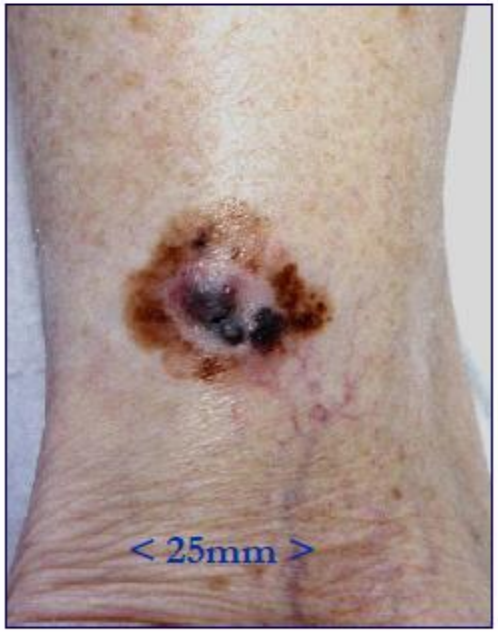


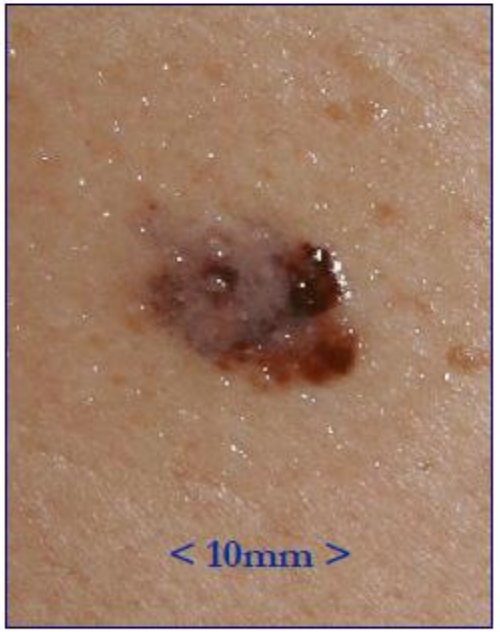






Il melanoma ieri e il melanoma oggi …





< 1970 → 2014

spessore medio del melanoma è diminuito da 1.81 mm nel 1976 a 0.53 mm nel 2000 (P < 0.0001)

ettner PG, Leiter U, Eigentler TK, Garbe C. Development of prognostic factors and survival in cutaneous melanoma over 25 years: An analysis of the Central Ma
lanoma Registry of the German Dermatological Society. Cancer. 2005 Feb 1;103(3):616-24.

La Campagna «Il Sole per Amico»

- Campagna di Awareness sul Melanoma promossa da IMI e AIOM

- Patrocinata da Ministero della Salute e Ministero dell'Istruzione, Università e Ricerca

In partnership con Società Scientifiche GIPMe e Gised e Associazioni Pazienti

Nel 2015-2016 in 143 scuole primarie di 34 provincie di sette Regioni italiane (Lombardia, Liguria, Emilia Romagna, Toscana, Lazio, Puglia, Sardegna) si sono svolte attività educazionali con il coinvolgimento dei bambini, delle loro famiglie e dei docenti, con l'obiettivo di insegnare, fin dall'infanzia, qual è il modo corretto di esporsi al sole, prevenendo rischi futuri. Sono state coinvolte 1252 classi e più di 27000 bambini.

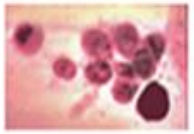
Nel 2016-2017 IMI ha esteso il progetto ad altre 4 regioni italiane: Piemonte, Veneto, Marche e Sicilia.

CLINICA

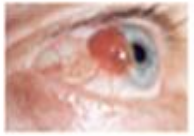
- Insorge su cute sana o su un nevo melanocitico acquisito o congenito preesistente o in contiguità con esso (nel 22-57% dei casi)
- Melanomi multipli: fino al 20% dei casi
- 5-10% insorge in sedi diverse dalla cute (occhio, mucose ano-genitali, mucose oro-nasali)
- Età mediana insorgenza 50 anni

Melanoma epiteliale  CUTE

Melanoma orale  MUCOSA ORALE

Melanoma vulvare  MUCOSA ANO-GENITALE

Melanoma esofageo  ESOFAGO

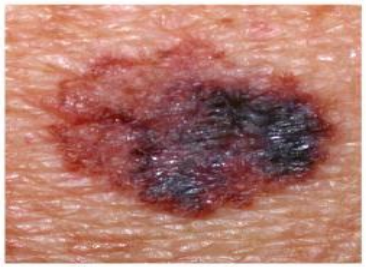
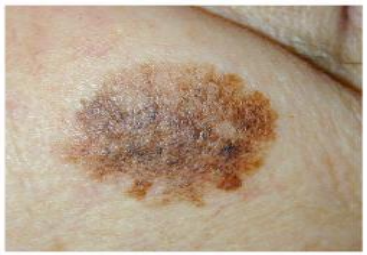
Melanoma uveale  OCCHIO

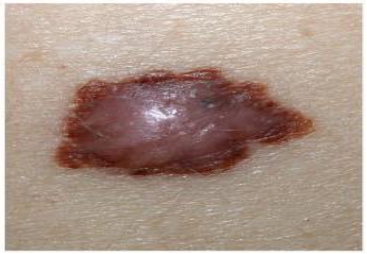
Melanoma primitivo sconosciuto

Classificazione clinico-patologica

Dal punto di vista clinico-patologico, il melanoma cutaneo è stato classificato in diversi sottogruppi che presentano caratteristiche peculiari, soprattutto per quanto riguarda il comportamento nella fase precoce di crescita.

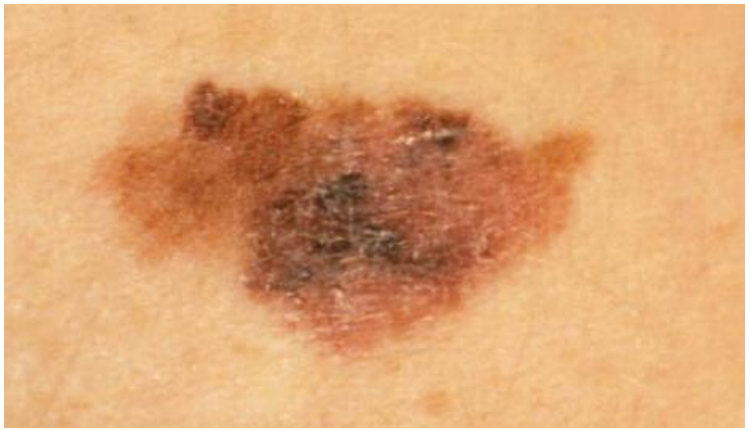
Frequenza	Circa 90%	Circa 10%
Evoluzione	Lenta (mesi-anni)	Rapida
Clinica	Macchia pigmentata asimmetrica, bordi irregolari, colore disomogeneo (melanoma piano) che tende a estendersi in senso radiale (orizzontale). Nel contesto della lesione può successivamente insorgere un elemento papuloso o nodulare (melanoma piano cupoliforme) che caratterizza lo sviluppo di una fase di crescita verticale invasiva nel derma.	Nodulo più o meno rilevato o sessile, pigmentato o acromico, a superficie liscia, spesso ulcerata e ricoperta da squamo-croste (melanoma cupoliforme), in assenza di evidente crescita radiale.
Istotipi	*Superficial spreading* melanoma (70%), lentigo maligna melanoma (10%), melanoma lentigginoso acrale (10%)	Melanoma nodulare
Istogenesi	A partire da melanociti dell'epidermide	A partire da melanociti del derma
Diagnosi	In caso di dubbio diagnostici, si può controllare la lesione in epiluminescenza a distanza di 3-4 mesi	Asportazione immediata in caso di dubbio
Prognosi	Favorevole in caso di asportazione precoce	Generalmente infausta (difficoltà di asportazione precoce)

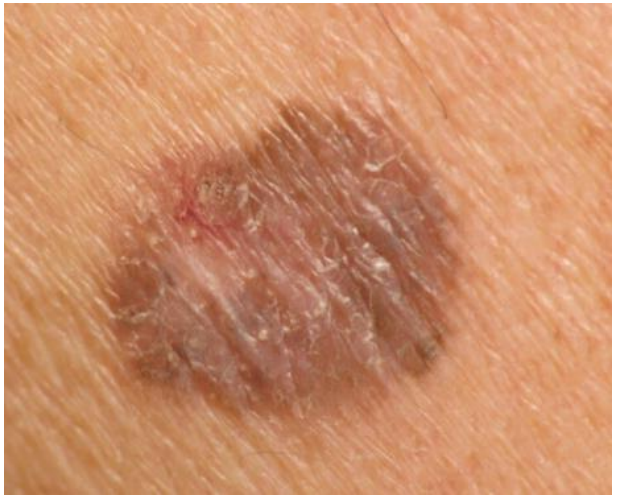



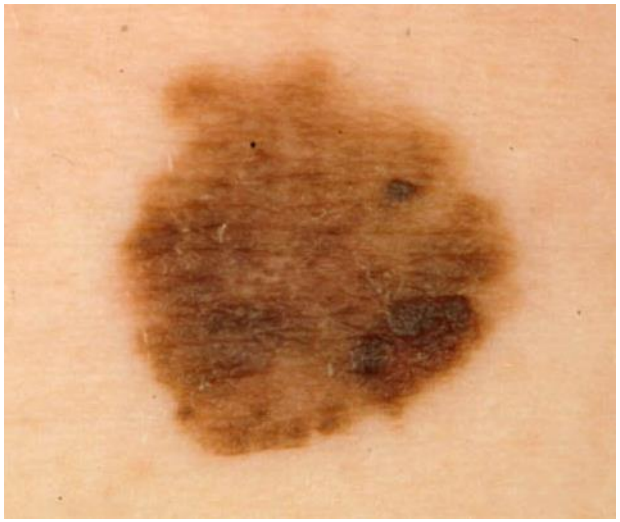


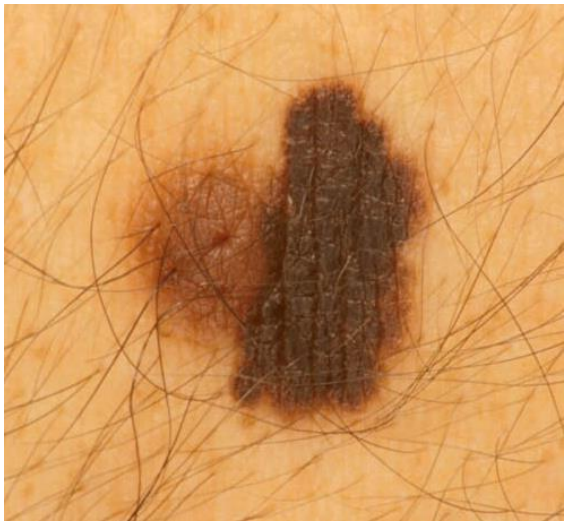
MELANOMA A DIFFUSIONE SUPERFICIALE

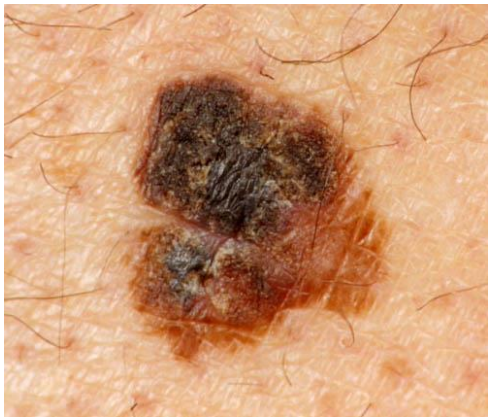
(superficial spreading melanoma)

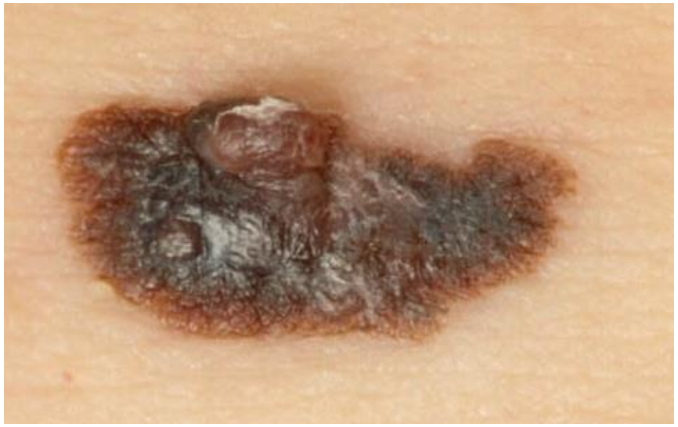


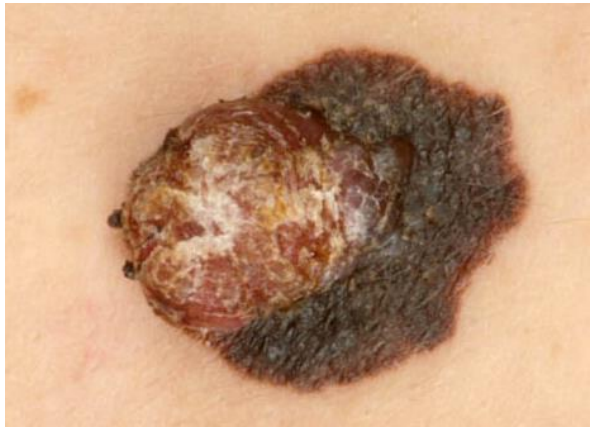




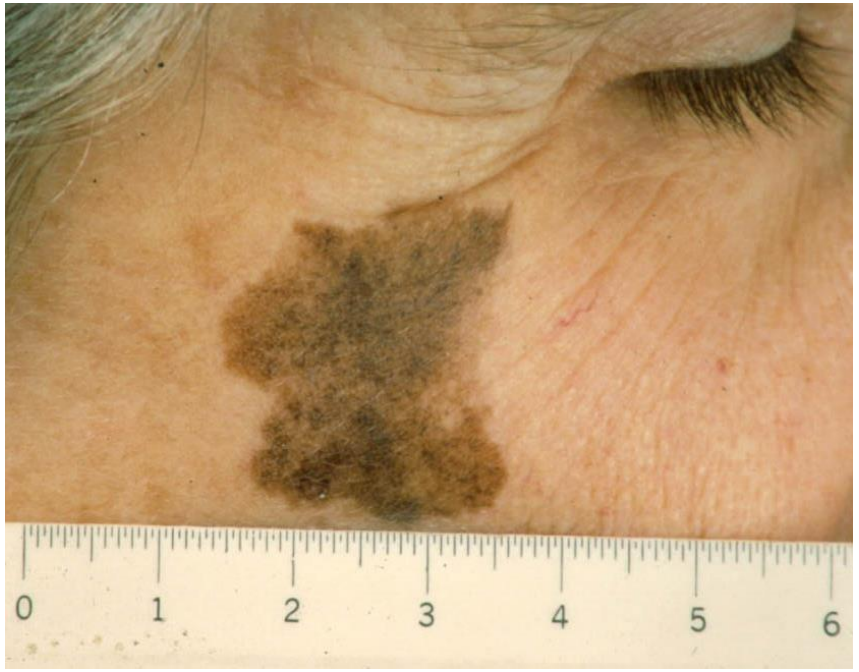


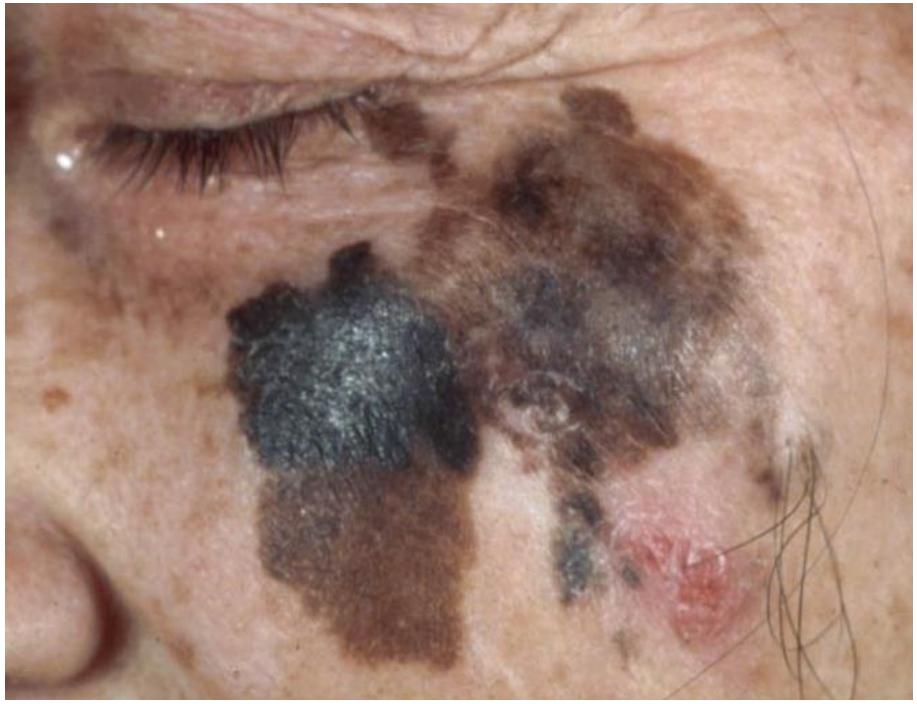






LENTIGO MALIGNA MELANOMA





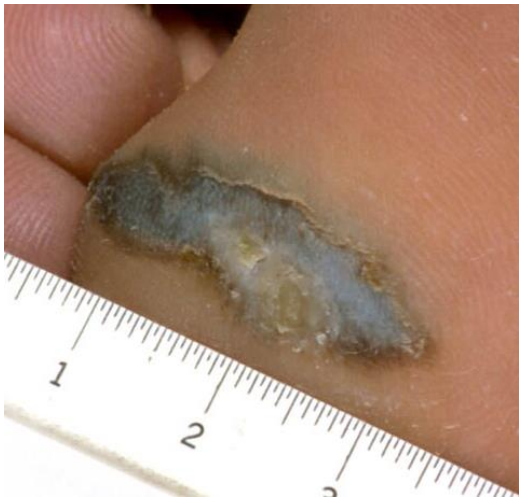
Aree fotoesposte (volto)

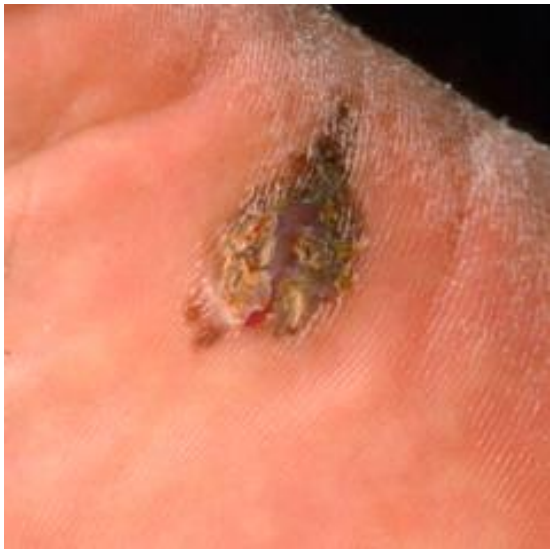
Sesso femminile, età avanzata

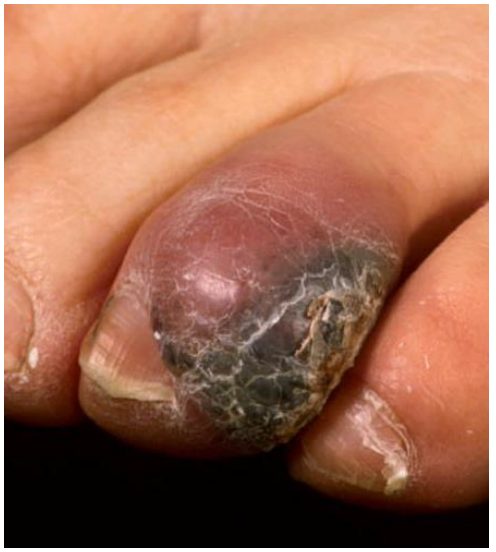
Origina dalla lentigo maligna di Dubreuilh, fase in situ che precede anche di anni la crescita invasiva

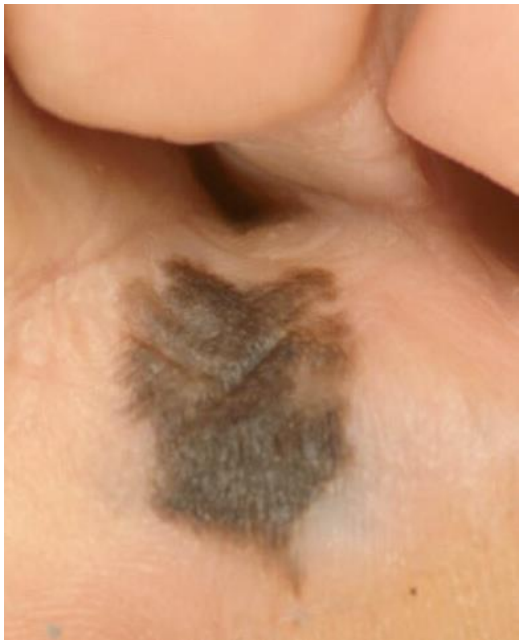
MELANOMA ACRALE LENTIGGINOSO

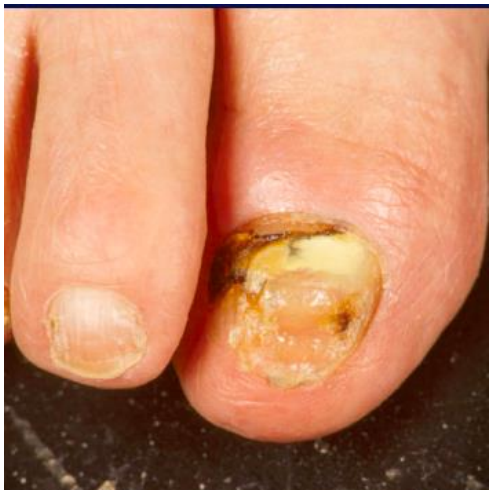
Istotipo più frequente negli asiatici e afroamericani. Colpisce anziani alle estremità degli arti o zona subungueale

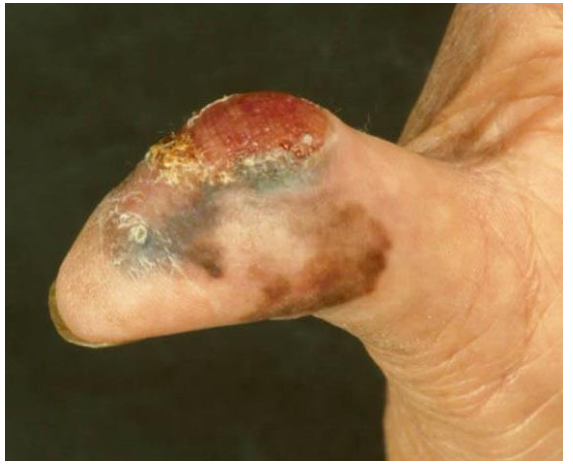






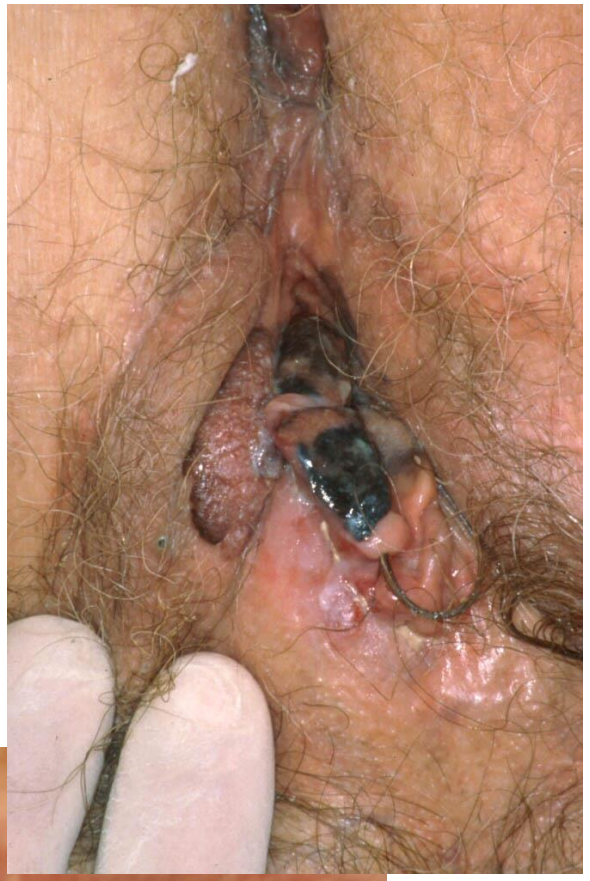


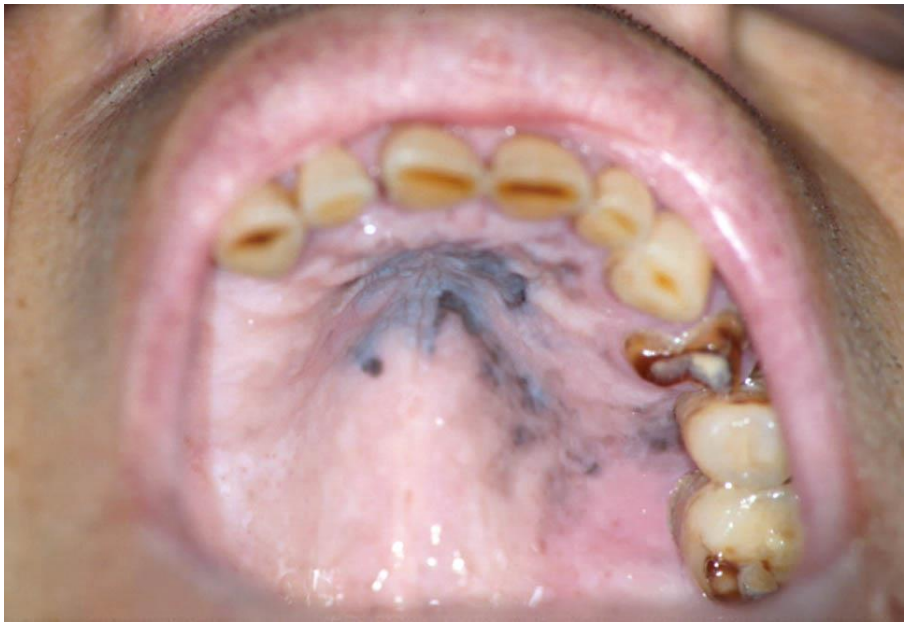


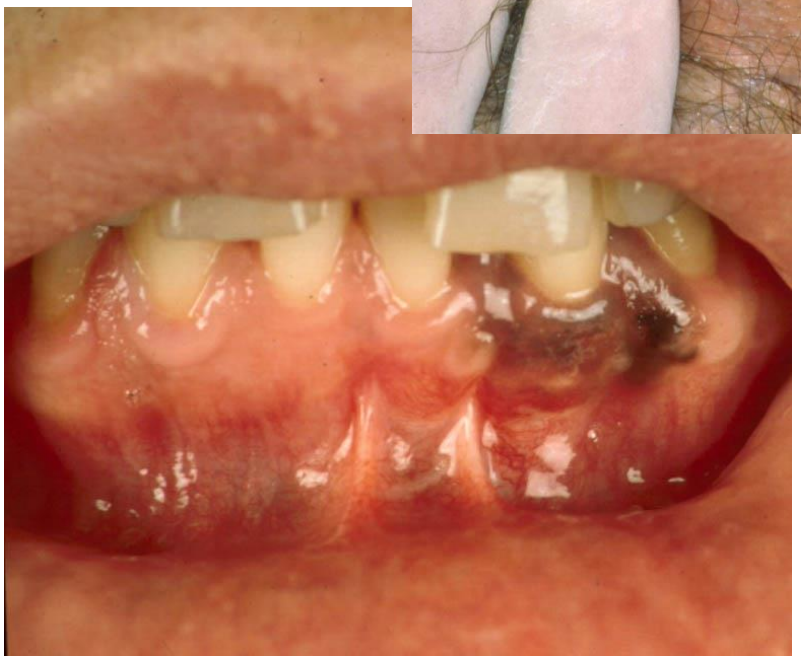


MELANOMA DELLE MUCOSE

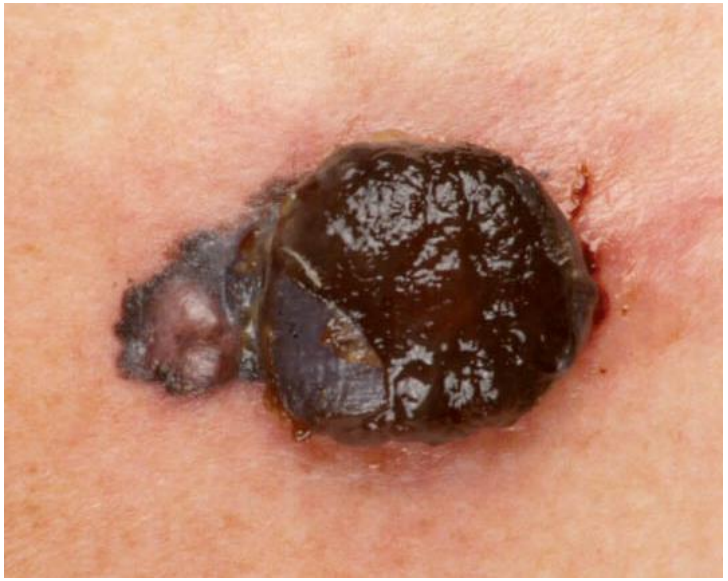
Per lo più istologia simile al melanoma acrale.
I m. della congiuntiva: prognosi legata allo spessore, mentre i m. della coroide hanno una prognosi legata all'estensione alla sclera e al nervo ottico

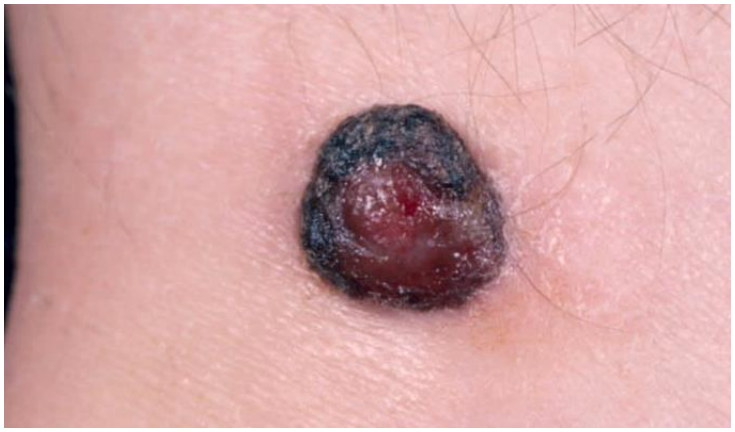


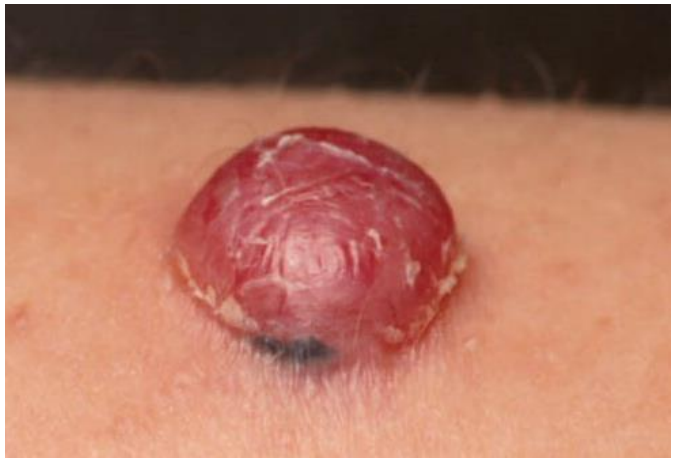




MELANOMA NODULARE

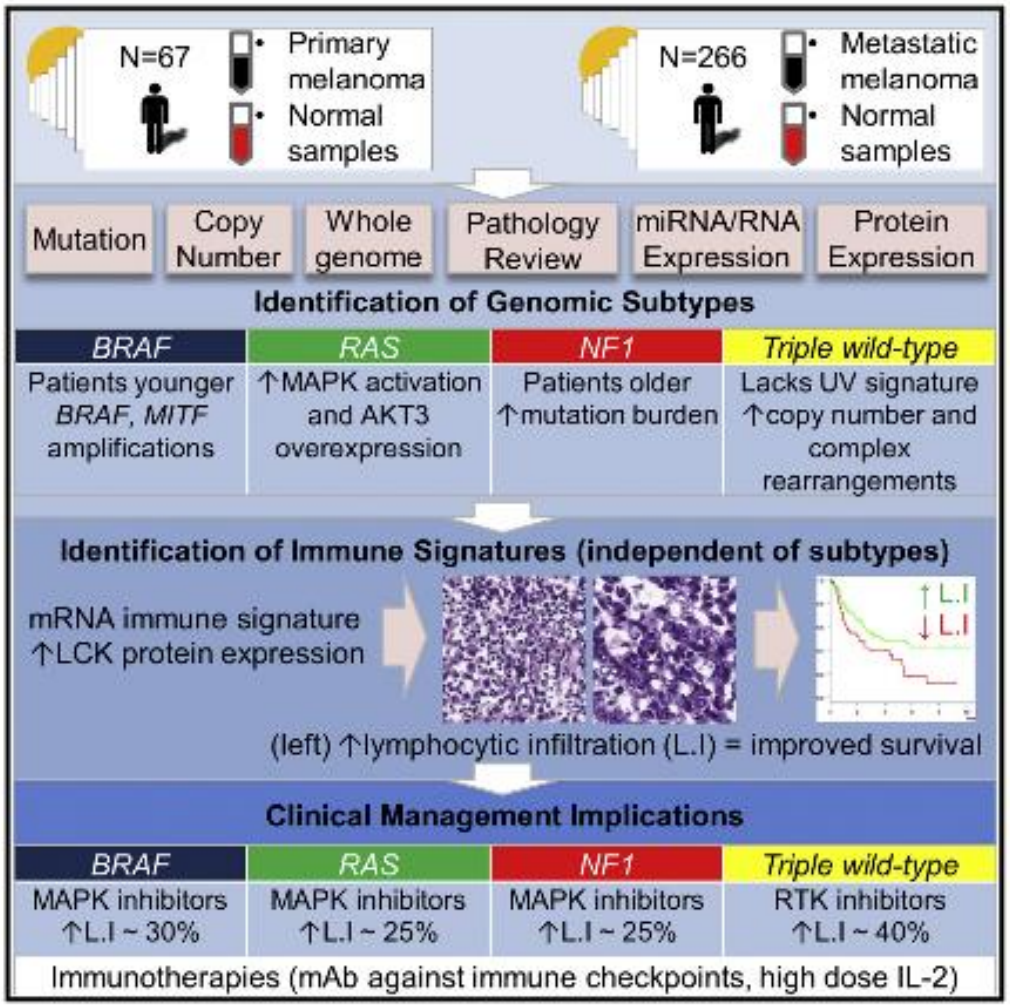






Genomic Classification of Cutaneous Melanoma

Graphical Abstract



Authors

The Cancer Genome Atlas Network

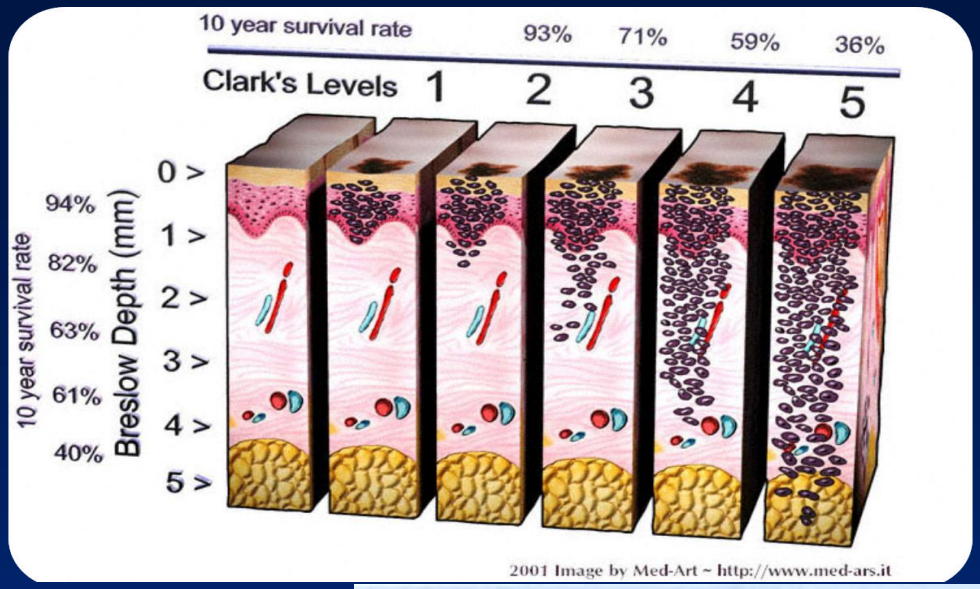
Correspondence

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
Elsevier Inc.



Classificazione T		
T1	Breslow ≤ 1,0 mm	a: senza ulcerazione; b: con ulcerazione o Clark IV-V
T2	Breslow 1,0-2,0 mm	a: senza ulcerazione; b: con ulcerazione
T3	Breslow 2,0-4,0 mm	a: senza ulcerazione; b: con ulcerazione
T4	Breslow > 4,0 mm	a: senza ulcerazione; b: con ulcerazione
Classificazione N		
N1	1 linfonodo	a: micrometastasi[a] ; b: macrometastasi[b]
N2	2-3 linfonodi	a: micrometastasi[a] ; b: macrometastasi[b] c: metastasi in transit/satellitosi senza metastasi linfonodali
N3	> 4 linfonodi o metastasi linfonodali massive o combinazione di metastasi in transit/satellitosi/melanoma ulcerato con metastasi linfonodali	
Classificazione M		
M1	Tessuti molli a distanza	LDH nella norma
M2	Metastasi polmonari	LDH nella norma
M3	Altre metastasi viscerali o ogni metastasi a distanza	LDH nella norma LDH elevato

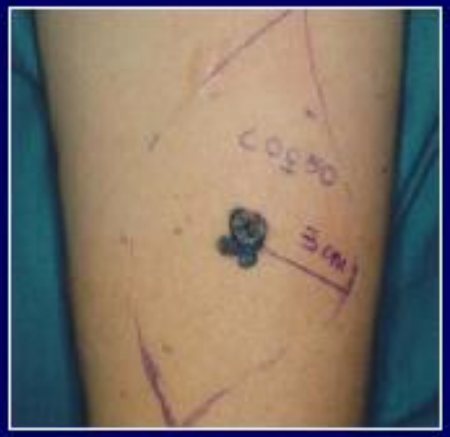
a: dopo biopsia del linfonodo sentinella o linfadenectomia elettiva

b: metastasi linfonodali clinicamente palpabili e confermate dopo linfadenectomia o metastasi linfonodali con superamento capsulare.

Terapia del melanoma primitivo

- **Asportazione chirurgica**

  ampia (1 – 3 cm dal bordo) e profonda (fino alla fascia muscolare esclusa)



- **Biopsia del Linfonodo Sentinella**

  (melanomi di spessore > 1 mm)

  esame di stadiazione

BIOPSIA LINFONODO SENTINELLA

Tecnica specifica e sensibile per individuare pz con micrometastasi da sottoporre a dissezione radicale:

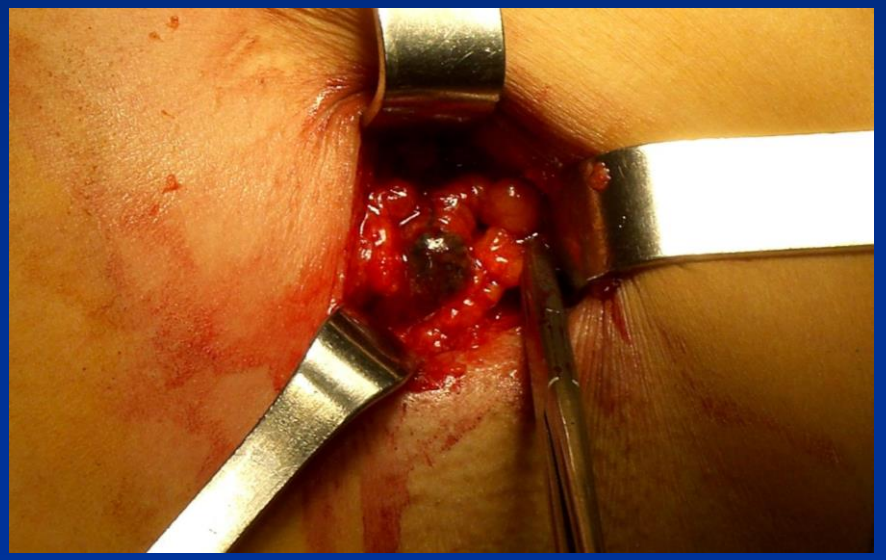
% reperimento linf. sentinella 70-100% a seconda della sede; se sentinella negativo 1-3% positività nei linf. non sentinella)

Indicata nei casi con Breslow > 1 mm o inferiore se ulcerazione o mitosi

Incidenza di metastasi in linf. sentinella 15-30%

↓

Se positivo CLND



Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial

Ulrike Leiter, Rudolf Stadler*, Cornelia Mauch, Werner Hohenberger, Norbert Brockmeyer, Carola Berking, Cord Sunderkötter, Martin Kaatz, Klaus-Werner Schulte, Percy Lehmann, Thomas Vogt, Jens Ulrich, Rudolf Herbst, Wolfgang Gehring, Jan-Christoph Simon, Ulrike Keim, Peter Martus, Claus Garbe, for the German Dermatologic Cooperative Oncology Group (DeCOG)*

Summary

Background Complete lymph node dissection is recommended in patients with positive sentinel lymph node biopsy results. To date, the effect of complete lymph node dissection on prognosis is controversial. In the DeCOG-SLT trial, we assessed whether complete lymph node dissection resulted in increased survival compared with observation.

Methods In this multicentre, randomised, phase 3 trial, we enrolled patients with cutaneous melanoma of the torso, arms, or legs from 41 German skin cancer centres. Patients with positive sentinel lymph node biopsy results were eligible. Patients were randomly assigned (1:1) to undergo complete lymph node dissection or observation with permuted blocks of variable size and stratified by primary tumour thickness, ulceration of primary tumour, and intended adjuvant interferon therapy. Treatment assignment was not masked. The primary endpoint was distant metastasis-free survival and analysed by intention to treat. All patients in the intention-to-treat population of the complete lymph node dissection group were included in the safety analysis. This trial is registered with ClinicalTrials.gov, number NCT02434107. Follow-up is ongoing, but the trial no longer recruiting patients.

Findings Between Jan 1, 2006, and Dec 1, 2014, 5547 patients were screened with sentinel lymph node biopsy and 1269 (23%) patients were positive for micrometastasis. Of these, 483 (39%) agreed to randomisation into the clinical trial; due to difficulties enrolling and a low event rate the trial closed early on Dec 1, 2014. 241 patients were randomly assigned to the observation group and 242 to the complete lymph node dissection group. Ten patients did not meet the inclusion criteria, so 233 patients were analysed in the observation group and 240 patients were analysed in the complete lymph node dissection group, as the intention-to-treat population. 311 (66%) patients (158 in the observation group and 153 in the dissection group) had sentinel lymph node metastases of 1 mm or less. Median follow-up was 35 months (IQR 20–54). Distant metastasis-free survival at 3 years was 77·0% (90% CI 71·9–82·1; 55 events) in the observation group and 74·9% (69·5–80·3; 54 events) in the complete lymph node dissection group. In the complete lymph node dissection group, grade 3 and 4 events occurred in 15 patients (6%) and 19 patients (8%) patients, respectively. Adverse events included lymph oedema (grade 3 in seven patients, grade 4 in 13 patients), lymph fistula (grade 3 in one patient, grade 4 in two patients), seroma (grade 3 in three patients, no grade 4), infection (grade 3 in three patients, no grade 4), and delayed wound healing (grade 3 in one patient, grade 4 in four patients); no serious adverse events were reported.

Interpretation Although we did not achieve the required number of events, leading to the trial being underpowered, our results showed no difference in survival in patients treated with complete lymph node dissection compared with observation only. Consequently, complete lymph node dissection should not be recommended in patients with melanoma with lymph node micrometastases of at least a diameter of 1 mm or smaller.

Funding German Cancer Aid.

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See Comment page 688

*Contributed equally
Centre for Dermatooncology, Department of Dermatology (U Leiter MD, U Keim PhD, Prof C Garbe MD) and Institute of Clinical Epidemiology and Applied Biostatistics (Prof P Martus PhD), Eberhard-Karls-University of Tuebingen, Tuebingen, Germany; Department of Dermatology, Medical Centre Minden, Minden, Germany (R Stadler MD); Department of Dermatology, University of Cologne, Cologne, Germany (Prof C Mauch MD); Department of Surgery, University of Erlangen, Erlangen, Germany (Prof W Hohenberger MD); Department of Dermatology, University of Bochum, Bochum, Germany (Prof N Brockmeyer MD); Department of Dermatology, Ludwig-Maximilians University of Munich, Munich, Germany (Prof C Berking MD); Department of Dermatology, University of Munster, Munster, Germany (Prof C Sunderkötter MD); Department of Dermatology, Gera and University of Jena, Jena, Germany (M Kaatz MD);

No difference in survival!
Not recommended in patients with micrometastases

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 8, 2017 VOL. 376 NO. 23

Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma

M.B. Faries, J.F. Thompson, A.J. Cochran, R.H. Andtbacka, N. Mozzillo, J.S. Zager, T. Jahkola, T.L. Bowles, A. Testori, P.D. Beitsch, H.J. Hoekstra, M. Moncrieff, C. Ingvar, M.W.J.M. Wouters, M.S. Sabel, E.A. Levine, D. Agnese, M. Henderson, R. Dummer, C.R. Rossi, R.I. Neves, S.D. Trocha, F. Wright, D.R. Byrd, M. Matter, E. Hsueh, A. MacKenzie-Ross, D.B. Johnson, P. Terheyden, A.C. Berger, T.L. Huston, J.D. Wayne, B.M. Smithers, H.B. Neuman, S. Schneebaum, J.E. Gershenwald, C.E. Ariyan, D.C. Desai, L. Jacobs, K.M. McMasters, A. Gesierich, P. Hersey, S.D. Bines, J.M. Kane, R.J. Barth, G. McKinnon, J.M. Farma, E. Schultz, S. Vidal-Sicart, R.A. Hoefer, J.M. Lewis, R. Scheri, M.C. Kelley, O.E. Nieweg, R.D. Noyes, D.S.B. Hoon, H.-J. Wang, D.A. Elashoff, and R.M. Elashoff

ABSTRACT

BACKGROUND

Sentinel-lymph-node biopsy is associated with increased melanoma-specific survival (i.e., survival until death from melanoma) among patients with node-positive intermediate-thickness melanomas (1.2 to 3.5 mm). The value of completion lymph-node dissection for patients with sentinel-node metastases is not clear.

METHODS

In an international trial, we randomly assigned patients with sentinel-node metastases detected by means of standard pathological assessment or a multimarker molecular assay to immediate completion lymph-node dissection (dissection group) or nodal observation with ultrasonography (observation group). The primary end point was melanoma-specific survival. Secondary end points included disease-free survival and the cumulative rate of nonsentinel-node metastasis.

RESULTS

Immediate completion lymph-node dissection was not associated with increased melanoma-specific survival among 1934 patients with data that could be evaluated in an intention-to-treat analysis or among 1755 patients in the per-protocol analysis. In the per-protocol analysis, the mean (±SE) 3-year rate of melanoma-specific survival was similar in the dissection group and the observation group (86±1.3% and 86±1.2%, respectively; P=0.42 by the log-rank test) at a median follow-up of 43 months. The rate of disease-free survival was slightly higher in the dissection group than in the observation group (68±1.7% and 63±1.7%, respectively; P=0.05 by the log-rank test) at 3 years, based on an increased rate of disease control in the regional nodes at 3 years (92±1.0% vs. 77±1.5%; P<0.001 by the log-rank test); these results must be interpreted with caution. Nonsentinel-node metastases, identified in 11.5% of the patients in the dissection group, were a strong, independent prognostic factor for recurrence (hazard ratio, 1.78; P=0.005). Lymphedema was observed in 24.1% of the patients in the dissection group and in 6.3% of those in the observation group.

CONCLUSIONS

Immediate completion lymph-node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases. (Funded by the National Cancer Institute and others; MSLT-II ClinicalTrials.gov number, NCT00297895.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Faries at 11818 Wilshire Blvd., Suite 200, Los Angeles, CA 90025, or at mfaries@theangelesclinic.org.

N Engl J Med 2017;376:2211-22.
DOI: 10.1056/NEJMoa1613210

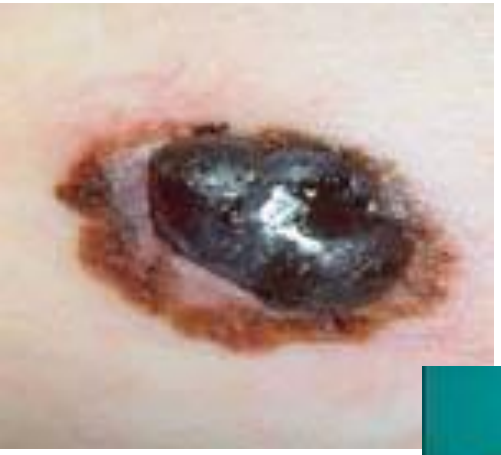
La Dissezione linfonodale
Non incide sulla sopravvivenza!

3 PATHWAYS METASTATICHE

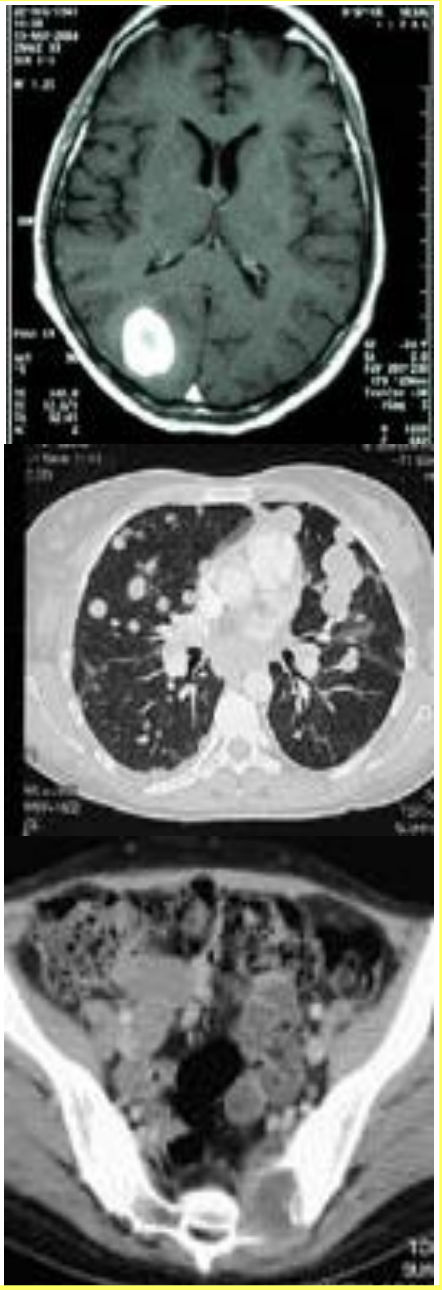
METASTASI LINFONODALI REGIONALI

60-70%

10-20%



20%



Sedi metastatiche

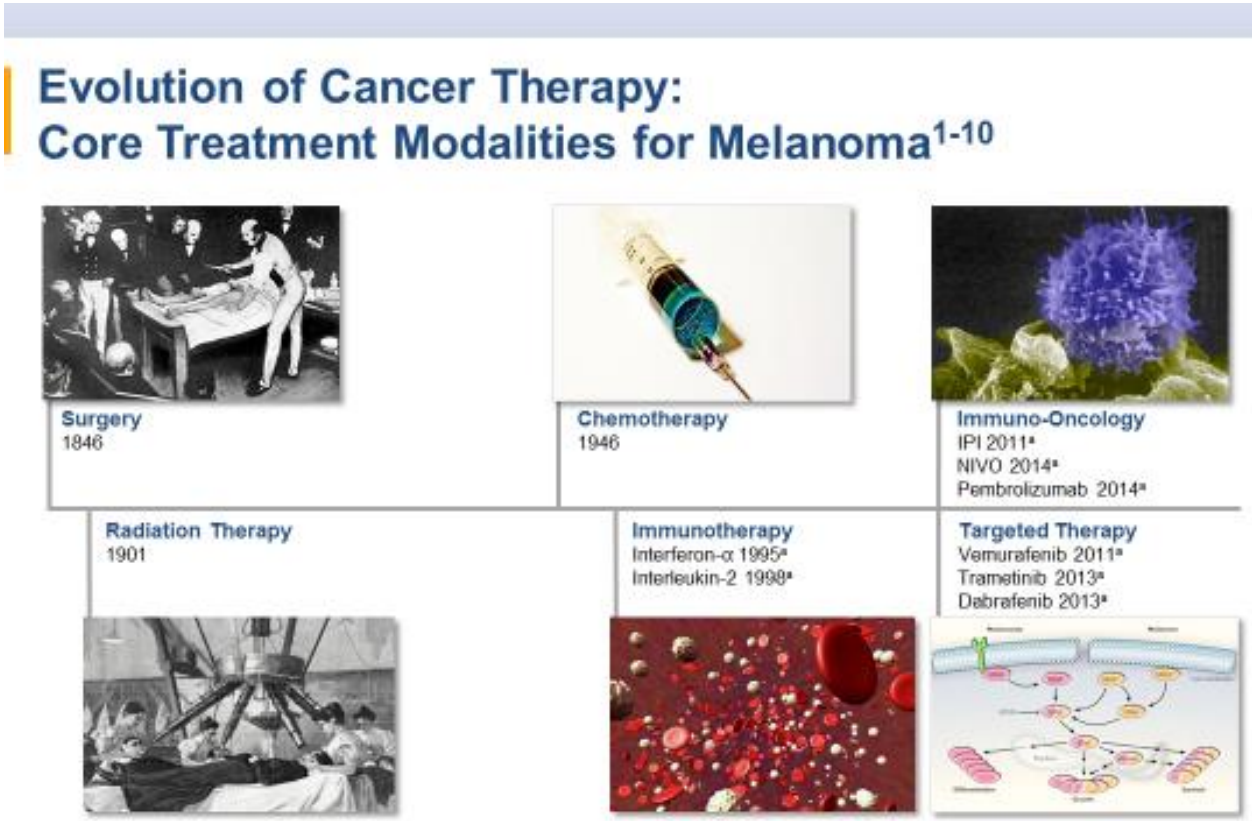
TABLE I. Common Sites of Metastatic Melanoma Detected Clinically or by Imaging Techniques and by Autopsies [13,19,25,34,35,42,65–67]

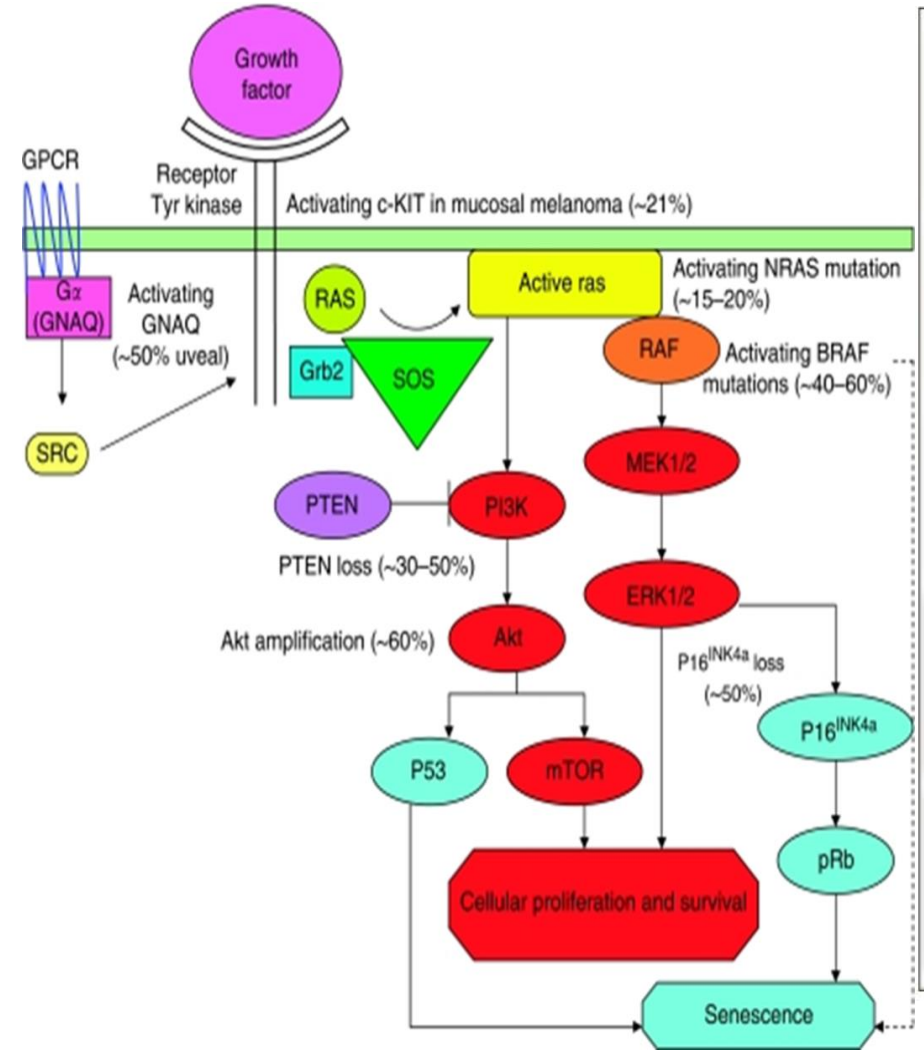
Site	Clinical and imaging techniques	Autopsies
Skin, subcutaneous tissue, and distant lymph node	37–59%	50–75%
Lung	18–36%	70–87%
Liver	14–20%	54–77%
CNS	2–20%	36–54%
Bone	4–17%	23–49%
Gastrointestinal tract	1–8%	26–60%
Small bowel	ca. 2/3	
Colon and anorectum	ca. 1/3	
Heart	<1%	19–45%
Pancreas	3%	38–53%
Adrenal gland	1–11%	36–54%
Kidney	<1%	35–48%
Thyroid gland	<1%	25–39%

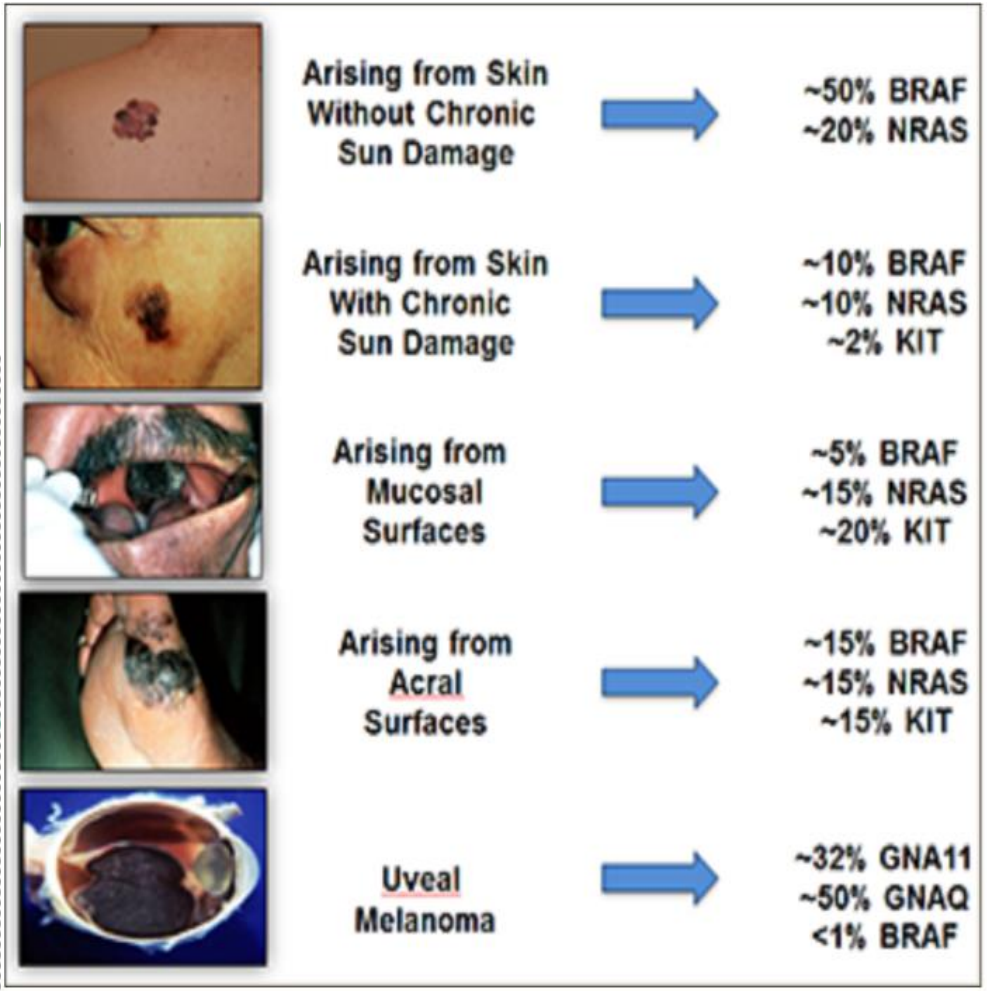
Meta-Analysis of Phase II Cooperative Group Trials in Metastatic Stage IV Melanoma to Determine Progression-Free and Overall Survival Benchmarks for Future Phase II Trials

Edward L. Korn, Ping-Yu Liu, Sandra J. Lee, Judith-Anne W. Chapman, Donna Niedzwiecki, Vera J. Suman, James Moon, Vernon K. Sondak, Michael B. Atkins, Elizabeth A. Eisenhauer, Wendy Parulekar, Svetomir N. Markovic, Scott Saxman, and John M. Kirkwood

Sopravvivenza mediana stadio IV 6.2 mo
PFS mediana 1.7 mo
Sopravvivenza a 12 mo 25.5%







mutazione V600: 40-60% V600E (80%) e V600K (5-30%)

Le mutazioni V600K sembrerebbero essere associate a:

-maggior incidenza di metastasi cerebrali e polmonari

-periodo più breve tra la diagnosi di melanoma e l'insorgenza di metastasi

Raccomandazioni per la determinazione dello stato mutazionale di *BRAF* nel melanoma

A cura del Gruppo di Lavoro di AIOM e SIAPEC-IAP

Quando? Stadio III inoperabile o stadio IV

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/fIRFLP	5-10%		
Fragment analysis	Approximately 5%	90-95%	Insertions/deletions
CE-SSCP/DHPLC	5-10%	90-95%	Near comprehensive

- 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.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 26, 2010 VOL. 363 NO. 9

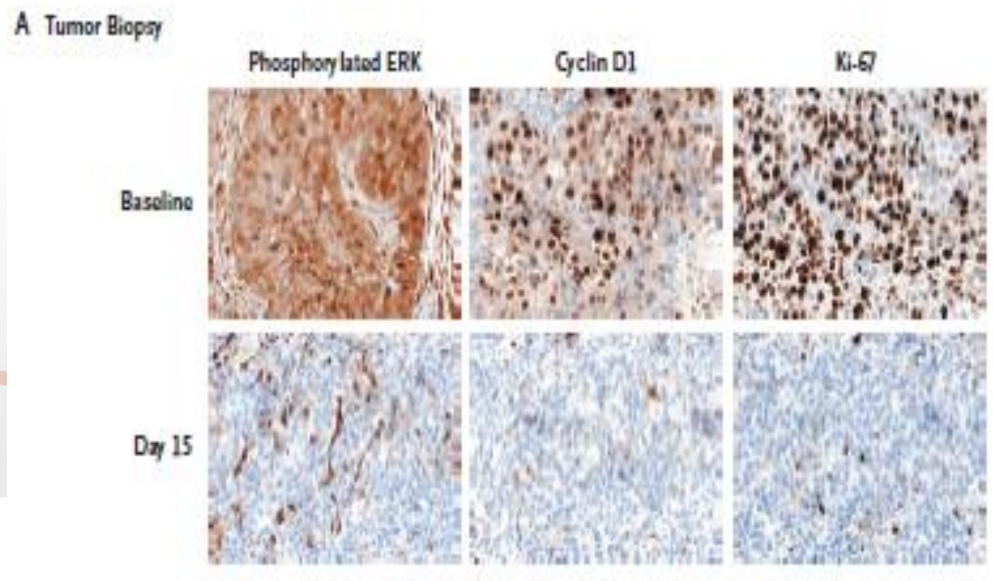
Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

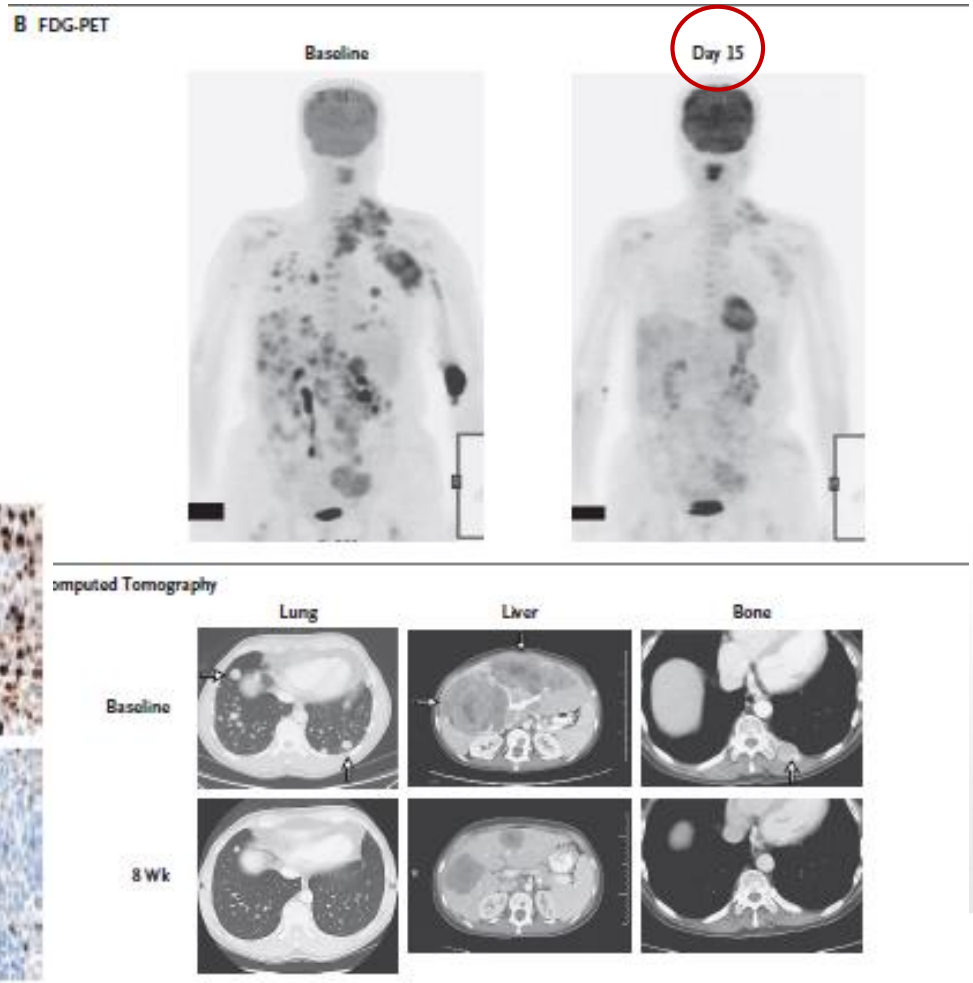
Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D., Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D., Joseph F. Grippo, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

Studio multicentrico di fase I dose-escalation: 55 pz.

Studio di fase II: 32 pz.

per dose di 960 mg x 2
OR 81%



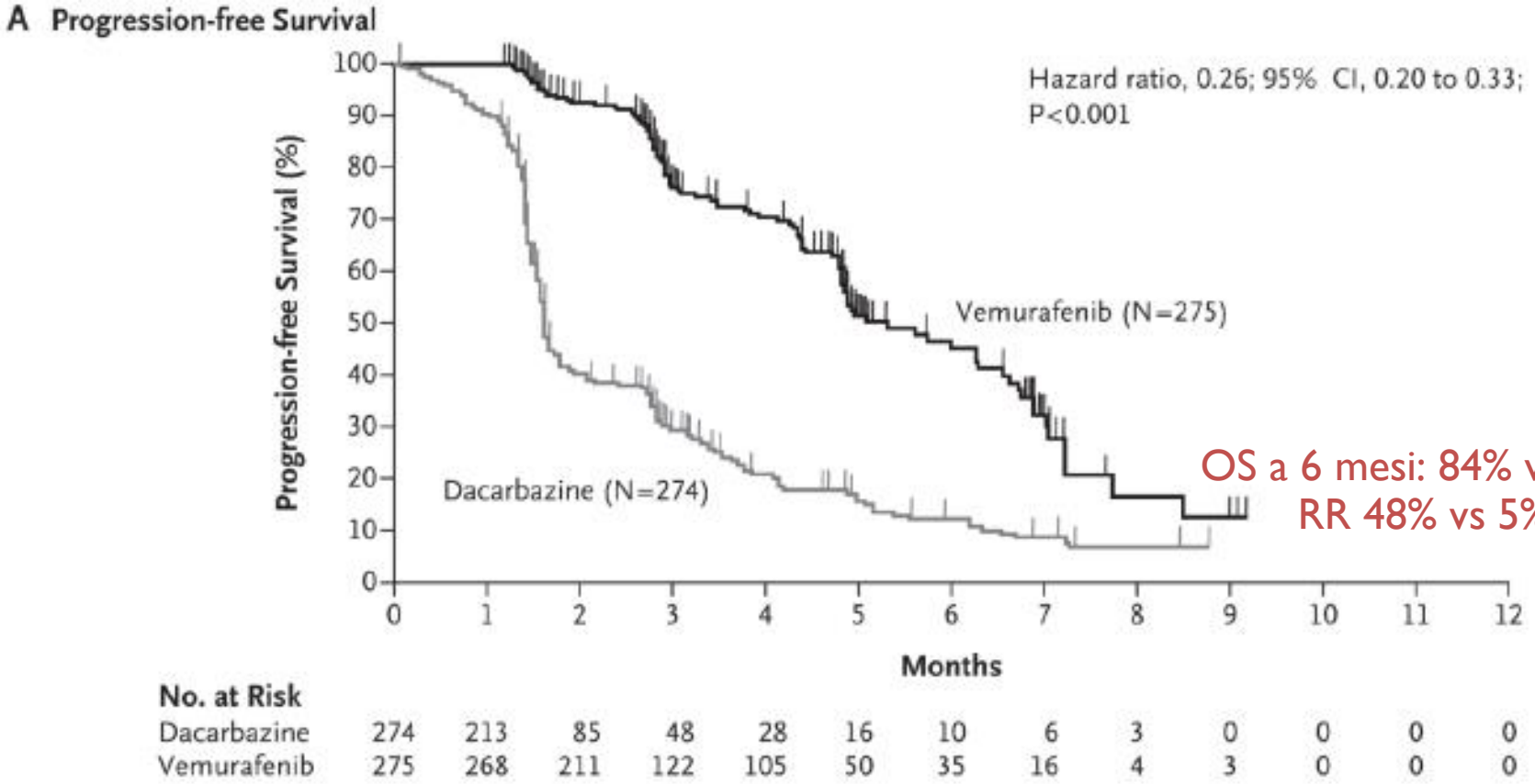


Published in final edited form as:
N Engl J Med. 2011 June 30; 364(26): 2507–2516. doi:10.1056/NEJMoa1103782.

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%

MECCANISMI DI RESISTENZA ACQUISITI A INIBITORI BRAF

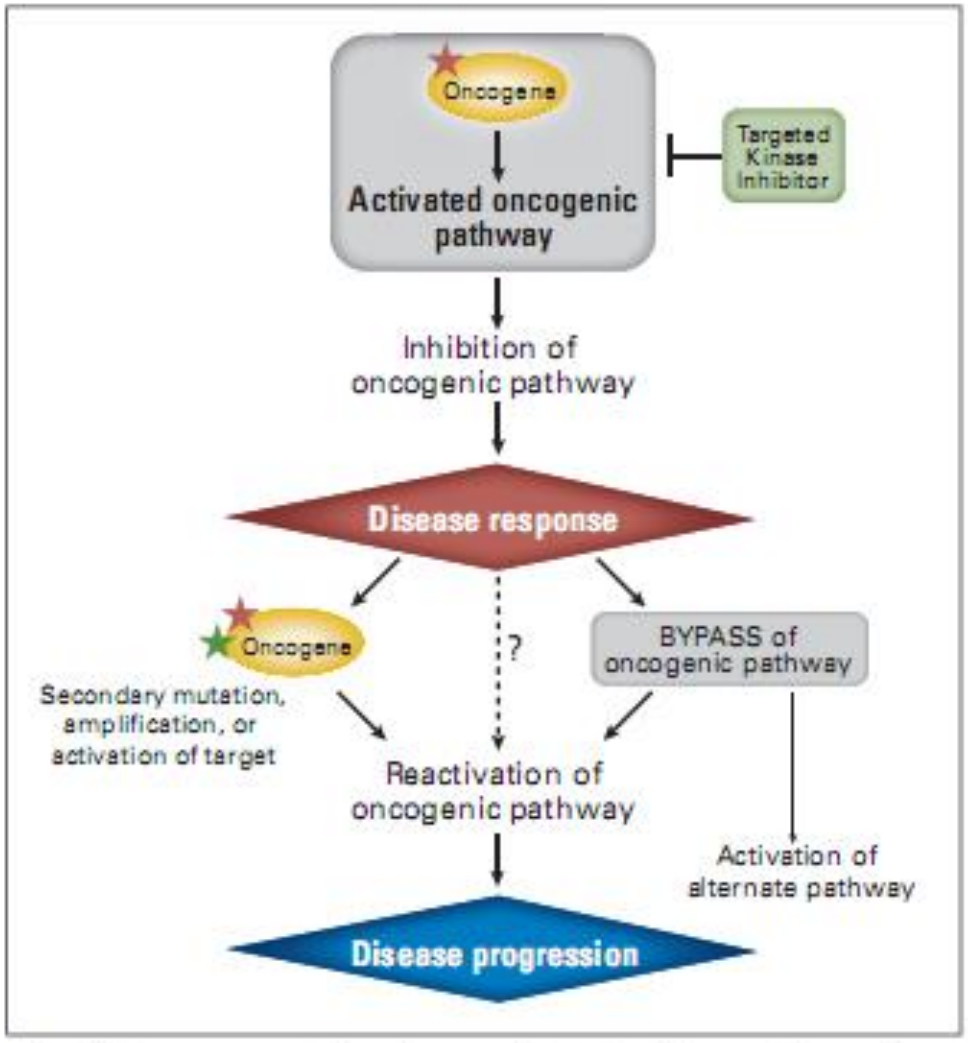
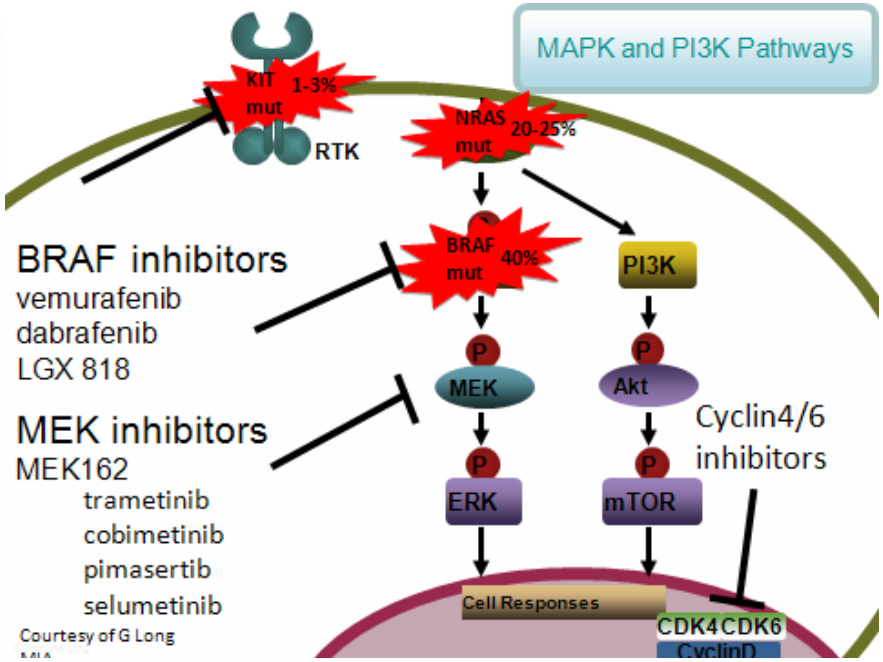
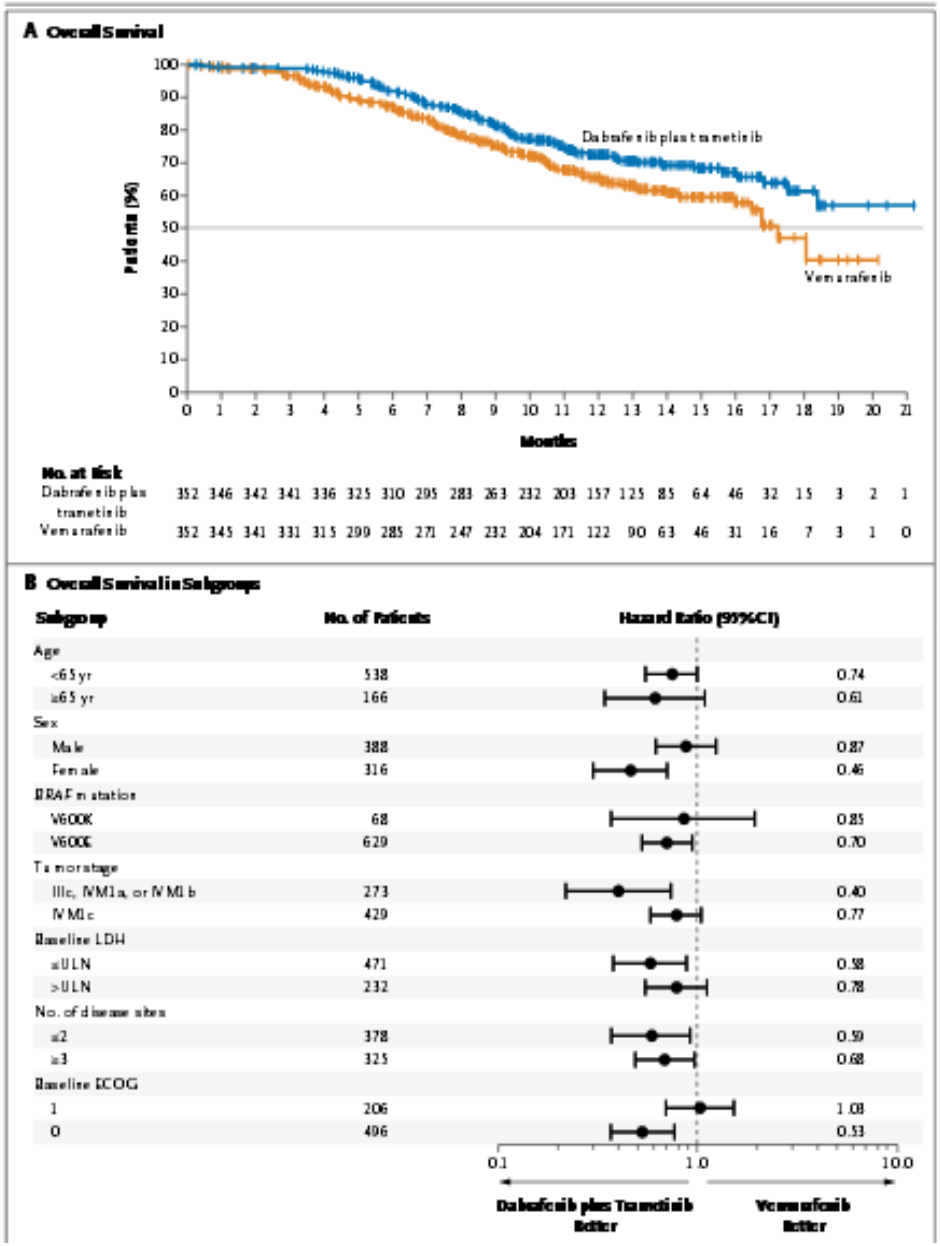


Fig 1. Kinase oncogene dependence and principles of drug resistance. Tumor



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



ORIGINAL ARTICLE

Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib

ıroline 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., ɔrent Grange, M.D., Ph.D., Laurent Mortier, M.D., Vanna Chiarion-Sileni, M.D., Camil 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., ıne-Marie Martin, Ph.D., Peng Sun, Ph.D., Wendy Crist, B.A., Jeff Legos, Ph.D., tephen 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).

RECIST RESPONSE: BRAFi + MEKi

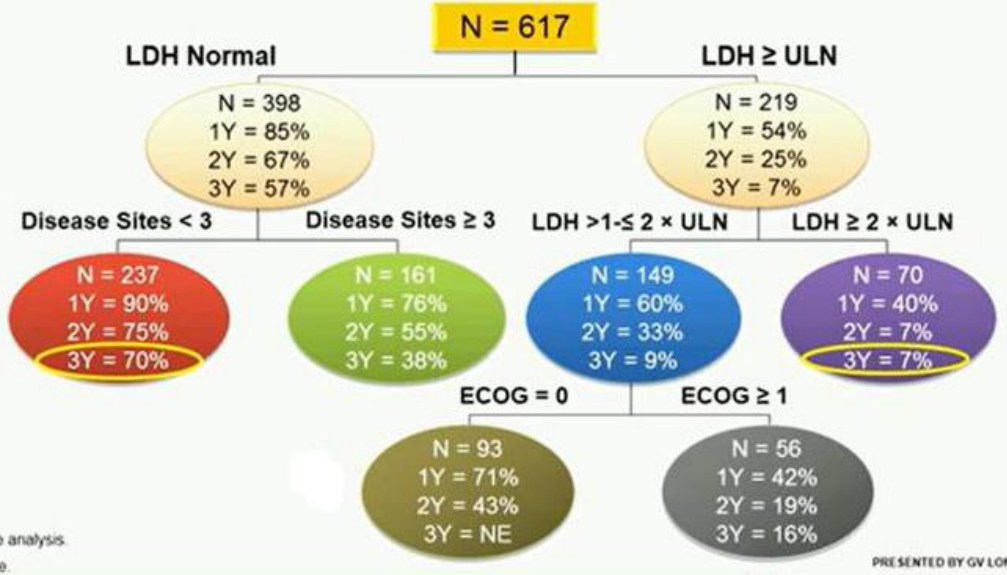
BRAFi+MEKi	ORR	CR	DoR	Med PFS	Med OS
COMBI-d	69%	16%	12.9mo	11.0mo	25.1mo
COMBI-v	66%	17%	13.8mo	11.4mo	25.6mo
COBRIM	70%	16%	12.98mo	12.25mo	NR
Encoraf + Binimet*	75%	13%	-	11.3mo	-

* Phase 1 and all doses.

No other therapy in melanoma has shown a better ORR

Long GV et al Lancet 2015; Robert et al ECC 2015; Larkin ASCO 2015; Sullivan ASCO 2015

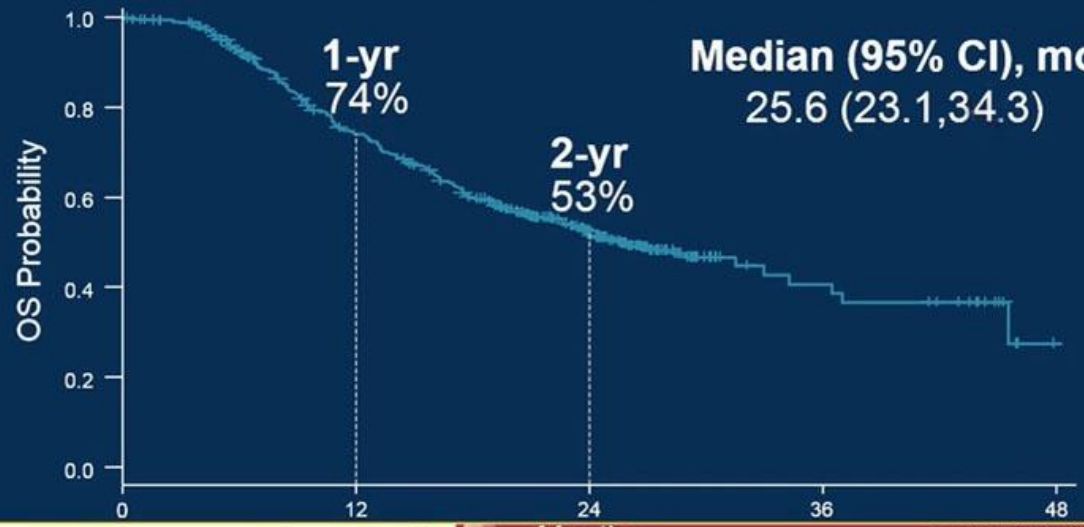
Five Baseline Factors Influenced OS[a]



[a] Regression tree analysis.
NE, not estimable.

Pooled Overall Survival: Dabrafenib + Trametinib

Three Randomised Trials (N = 617)

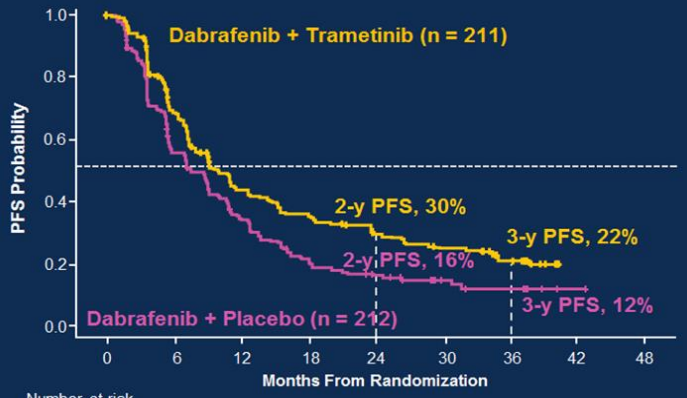


1. Long GV, *et al*. JCO 2016; 34:871;

COMBI-d: PFS and OS[a]

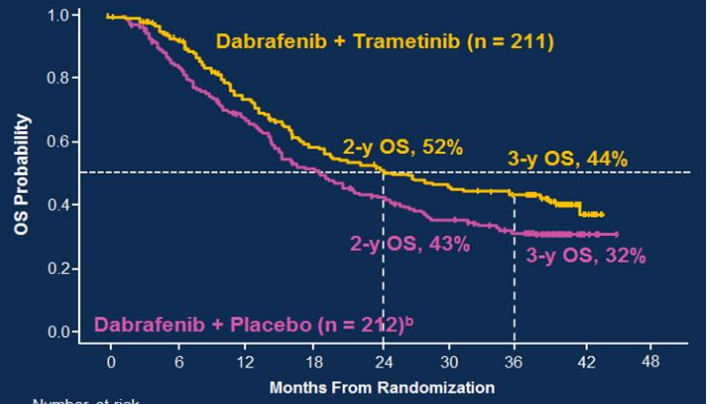
58% of D+T patients alive at 3 years still on D+T

Progression-Free Survival



Number at risk									
D+T	211	137	84	69	54	45	31	0	
D+Pbo	212	110	67	41	29	11	7	1	0

Overall Survival



Number at risk									
D+T	211	187	143	111	96	86	76	13	0
D+Pbo	212	175	138	104	84	69	57	7	0

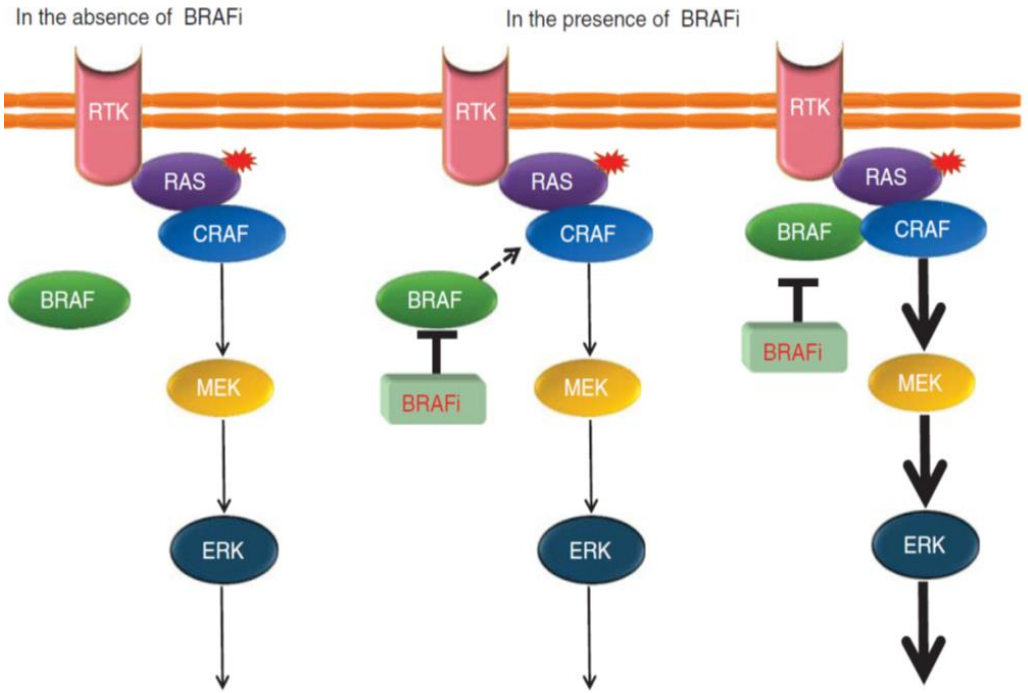
[a] Intent-to-treat population; [b] Dabrafenib + placebo includes 26 patients who crossed over to combination arm; +, censored.

Eventi avversi: Vemurafenib

- Dose dipendenti (compaiono per dosi >720 mg x2 die)
- Alla dose attualmente autorizzata gli effetti avversi più comuni sono stati:

  - Artralgia 31%
  - Tossicità cutanea 22%
  - Carcinomi squamocellulari 18-25%
  - Nausea 12%
  - Fotosensibilità 12%

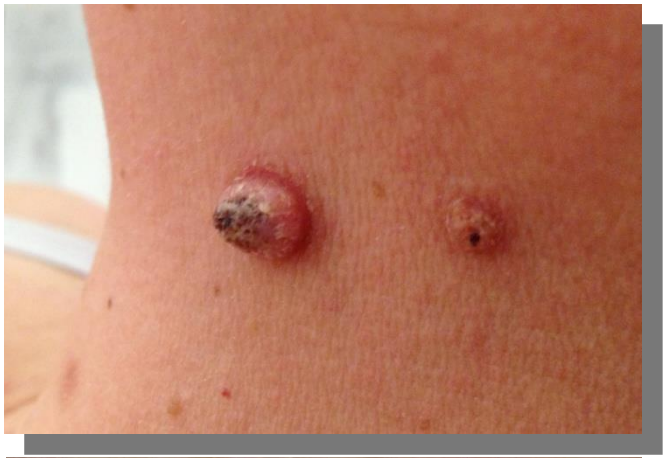
Attivazione paradossa di ERK:

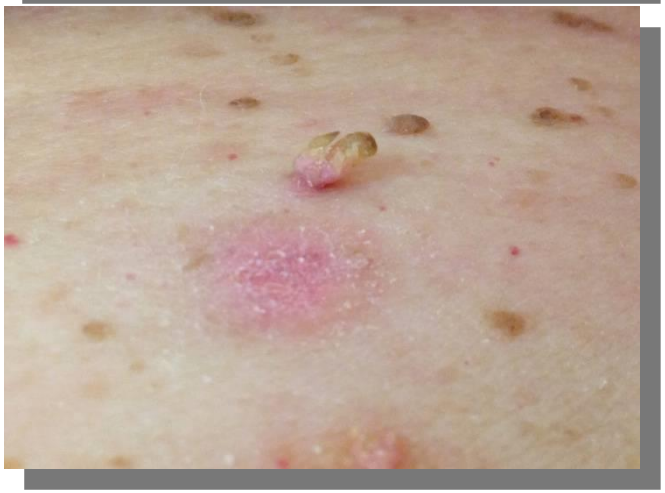


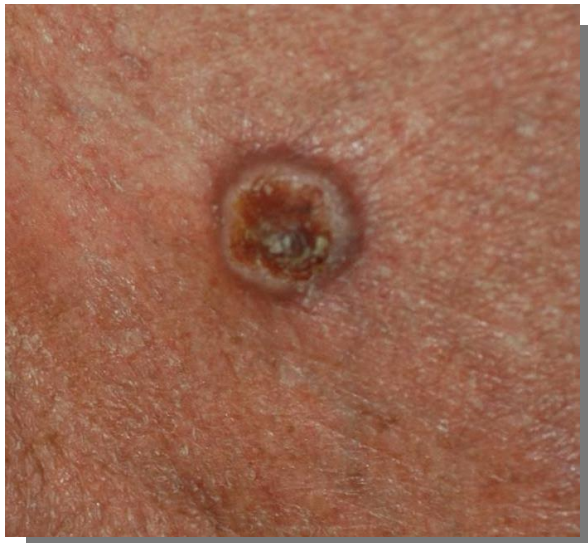
Tsai K et al. Expert Opin Drug Saf 2013; 12: 767-775

Vemurafenib tossicità cutanea:

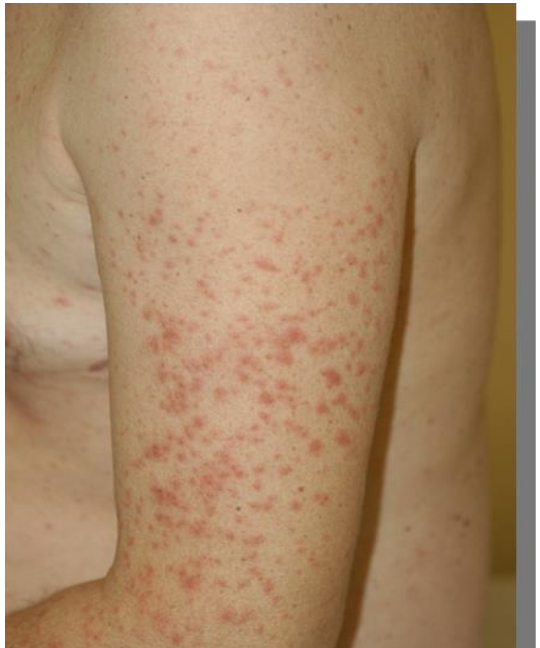
Les. Verrucose-fibropapillomi

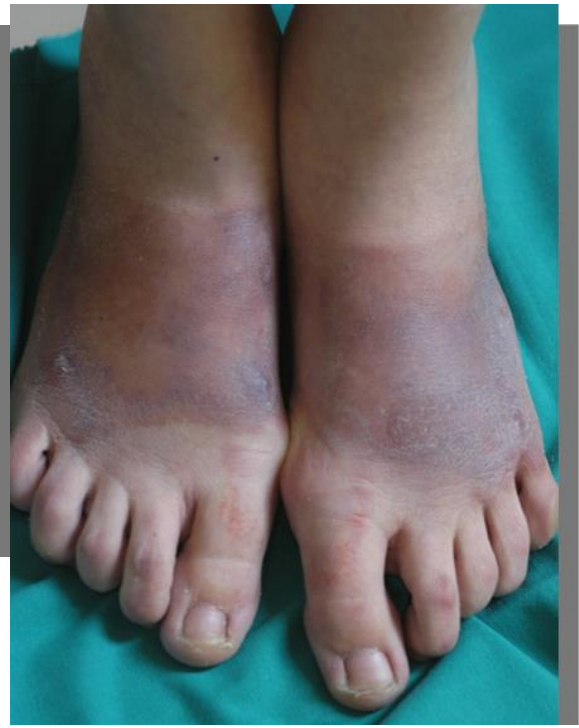






Cheratoacantoma





Fototossicità

Esantema maculo papulare

VOLUME 31 · NUMBER 26 · SEPTEMBER 10 2013

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

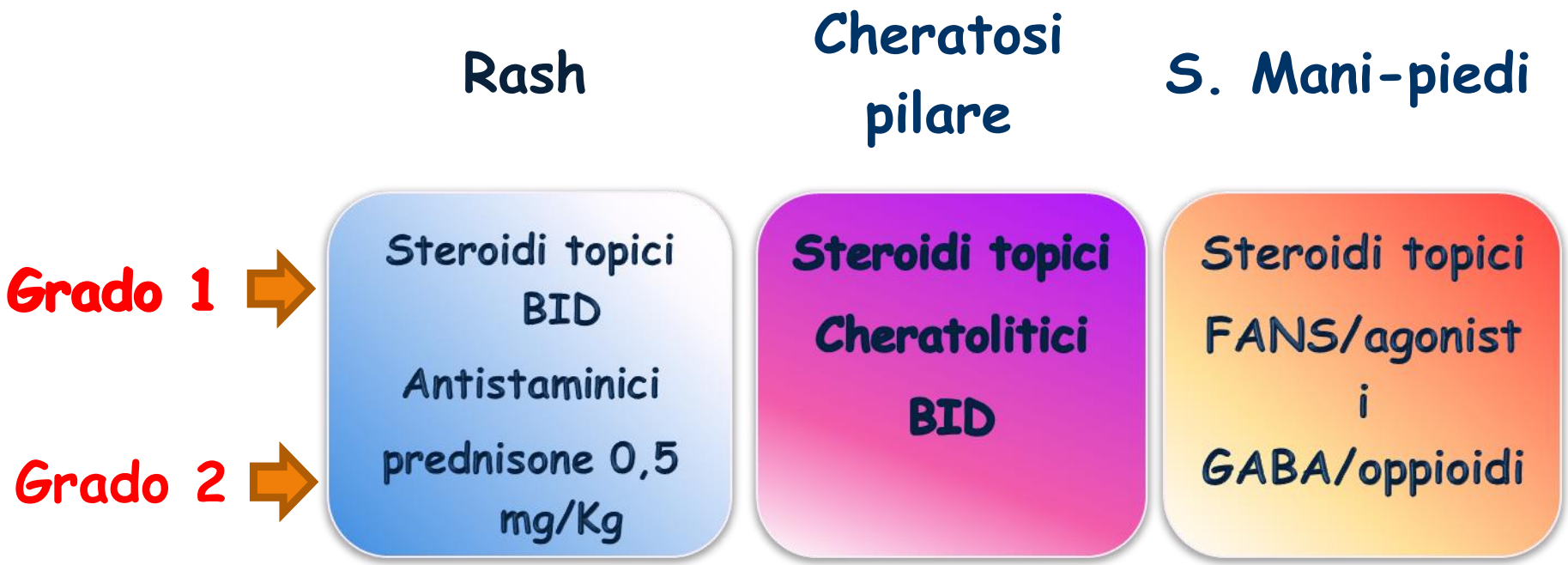
RASH DA FOTOSENSIBILIZZAZIONE MOLTO PIU' RARI

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

	Grade 3		Grade 4		Total	
Preferred Term	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)

Gestione degli eventi avversi cutanei



Proseguire il trattamento senza modificazioni della dose

Controllo a 2 settimane se non vi è miglioramento

Lacouture M.E. et al. 2013

Gestione degli eventi avversi cutanei

	Rash	Cheratosi pilare	S. Mani-piedi
Grado 3	Steroidi topici BID Antistaminici prednisone 0,5 mg/Kg	Steroidi topici Cheratolitici BID	Steroidi topici FANS/agonisti GABA/oppioidi

Proseguire il trattamento a dose ridotta

Controllo a 2 settimane se non vi è miglioramento

Sospendere il trattamento

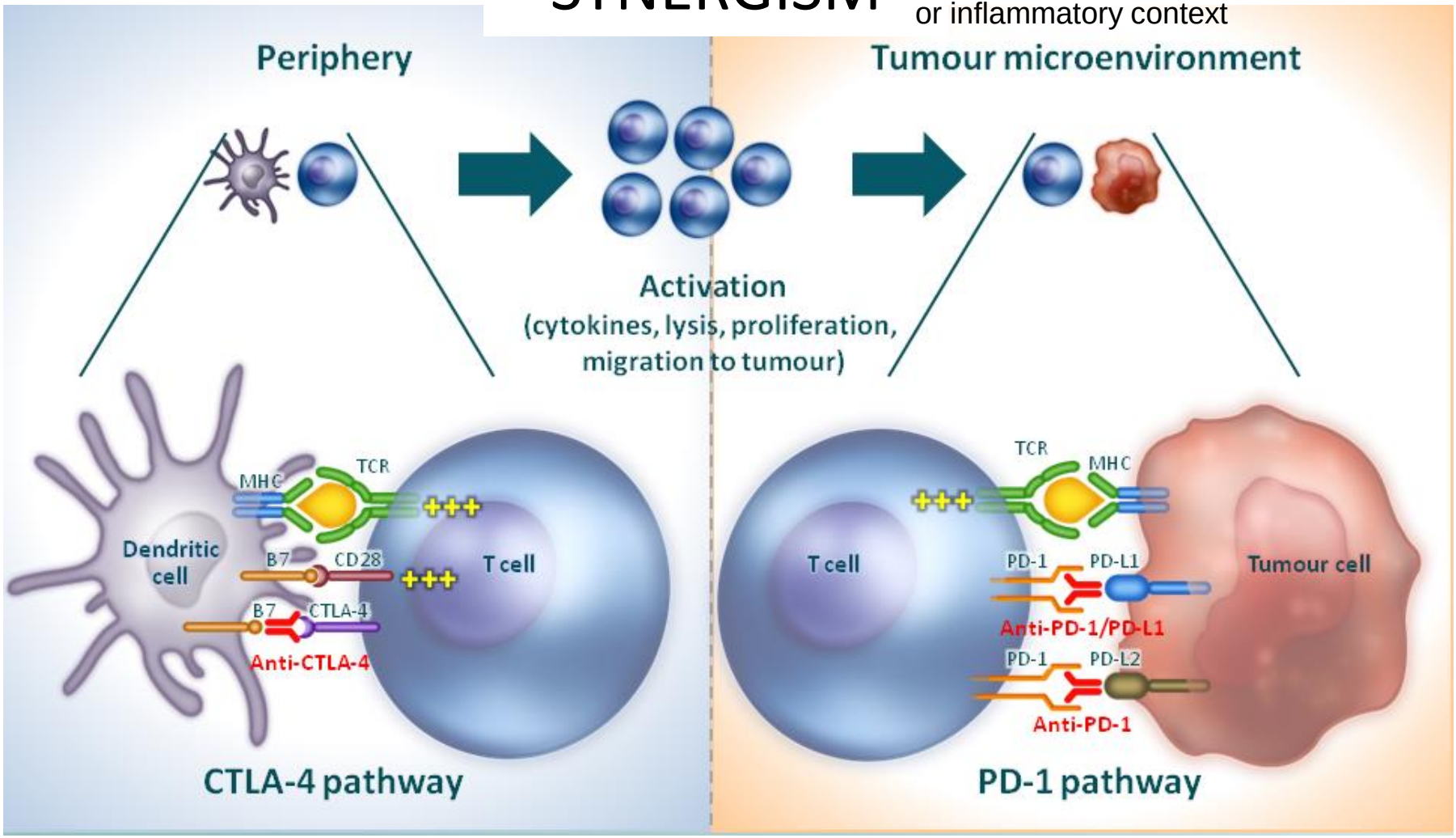
Lacouture M.E. et al. 2013

TARGETING CTLA-4 AND PD-1 PATHWAYS

Broad T cell repertoire activation

SYNERGISM

More specific for tumor-specific T cells or inflammatory context



WOLCHOK J. ET AL. JCO 2013

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

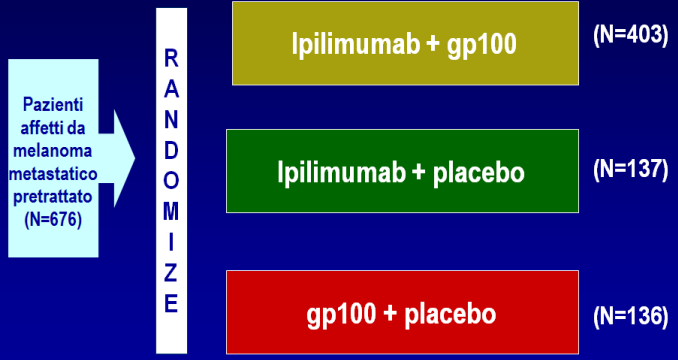
Hodi FS, et al. New Engl J Med 2010;363(8):711-723.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

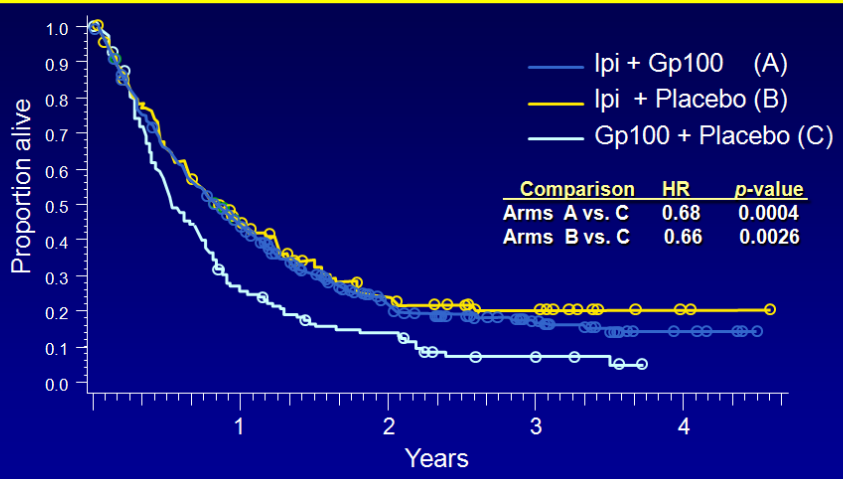
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

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)

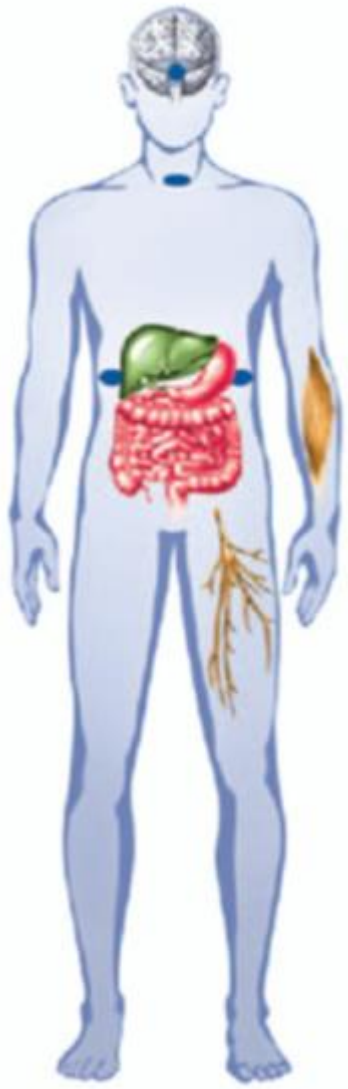
Hodi S et al. NEJM 2010;363(8):711-23

Ipilimumab/Nivolumab: immune-related Adverse Reactions

Gastrointestinal:
- Diarrhoea
- Abdominal pain
- Blood or mucus in stool
- Dry mouth
- Peritoneal signs
- Vomiting

General and musculoskeletal disorders:
- Fatigue- Pyrexia
- Pain
- Arthralgia- Myalgia

Liver:
- Abnormal liver function tests (e.g. AST, ALT or total bilirubin)



Skin:
- Pruritus- Rash
- Dermatitis acneiform
- Vitiligo-like lesions

Endocrine:
- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unsual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

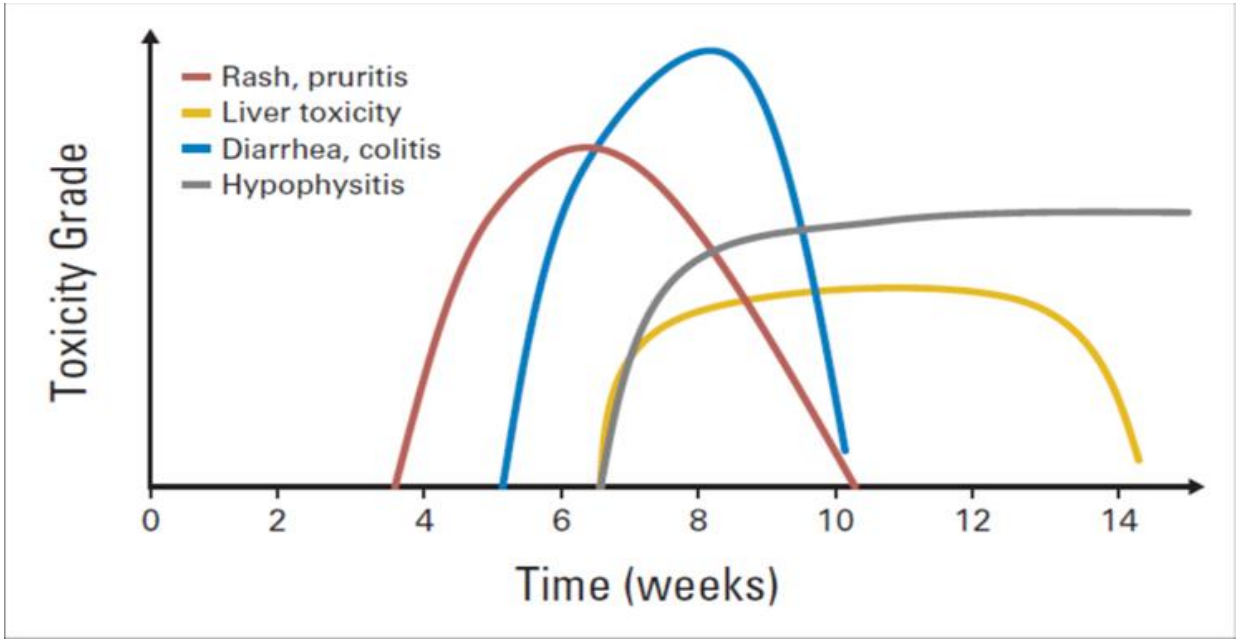
Pneumonia: Dyspnea- cough

Neurologic:
- Weakness, paresthesia
- Sensory alterations

Treatment Guidelines for the management of immune-related adverse events (irAEs) - Ipilimumab

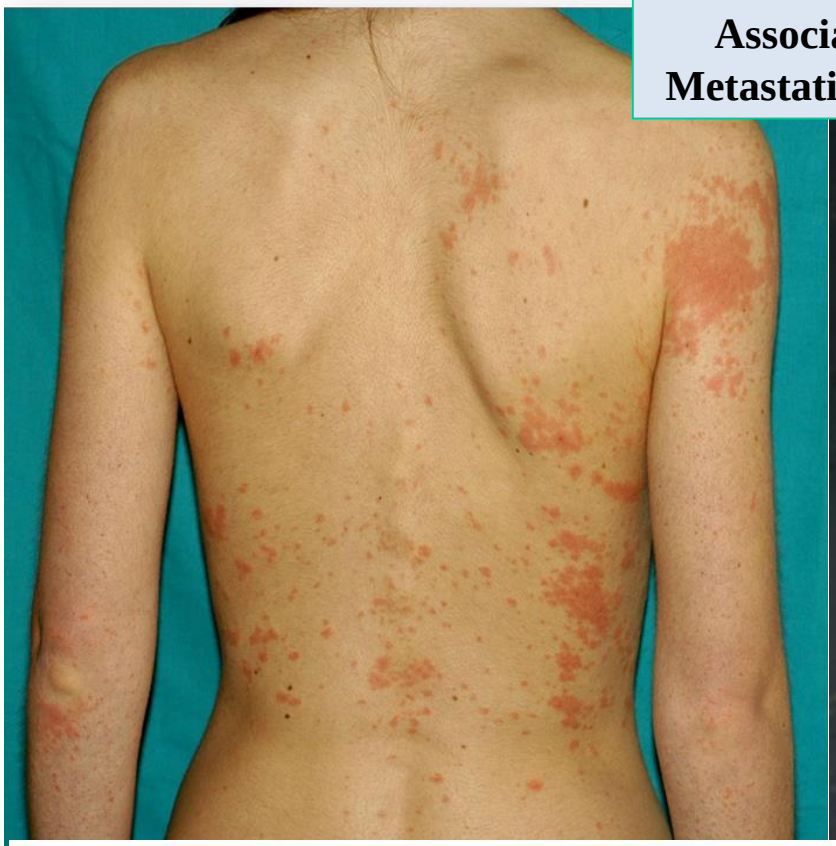
- Specific to management of irAEs involving skin toxicities, GI toxicities, hepatotoxicities, and endocrinopathies
- Developed in cooperation with external experts and implemented in clinical trials
- Physician/patient education
- Rule out other etiologies
- Treatment dependent on irAE grade:
  - Low-grade (grade 1/2) treated symptomatically.
  - Persistent low-grade irAEs managed as high-grade irAEs.
  - High grade (grade 3/4) treated with corticosteroids, tapered over 4 or more weeks. Ipilimumab discontinued
  - Steroid-refractory, high-grade irAEs: secondary immunosuppressive regimens

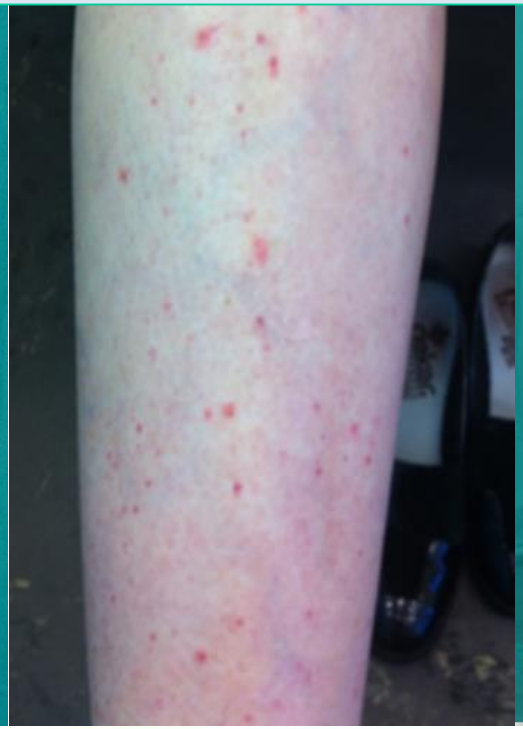
Chin K et al. ESMO 2008, poster presentation Abstract #787P

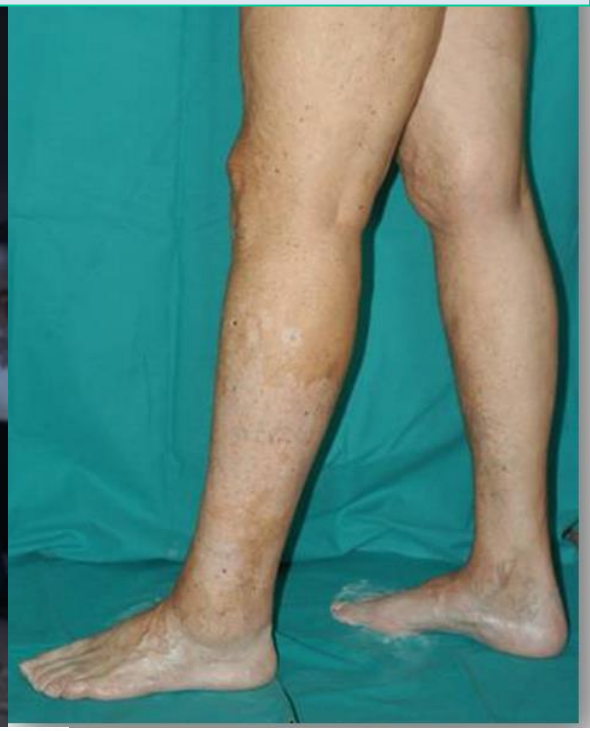


JAMA Dermatol. 2016

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







Gestione del rash immunocorrelato[1]

Grado del rash (NCI CTCAE v4)	Rash di grado 3	Rash di grado 4
Trattamento con nivolumab e monitoraggio	Il trattamento con nivolumab deve essere sospeso fino a quando i sintomi si risolvono e il trattamento con i corticosteroidi è completato	Interrompere definitivamente nivolumab
Corticosteroidi	Un rash severo deve essere trattato con corticosteroidi ad alte dosi equivalenti a una dose di 1-2 mg/kg/die di prednisone	

NCI-CTCAE v4 – Criteri Comuni di Terminologia per gli Eventi Avversi del National Cancer Institute, Versione 4.0

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.

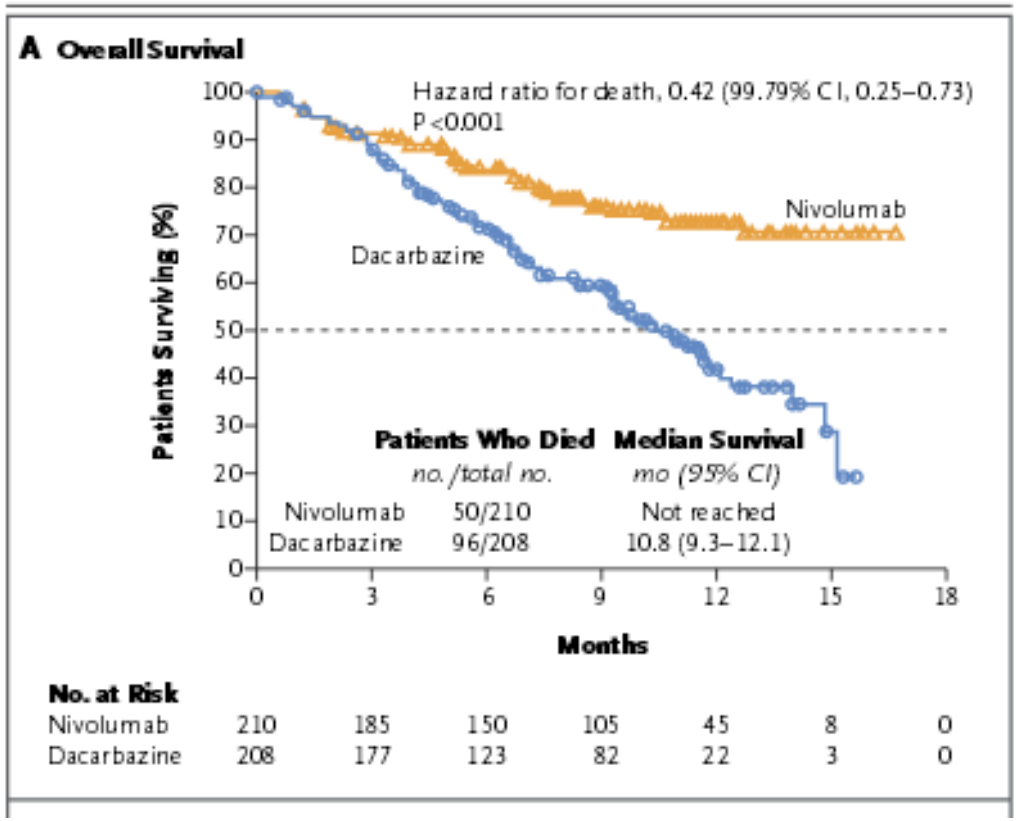
N Engl J Med. 2015 Jan 22;372(4):320-30.

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



KEYNOTE-006 : International, Randomized, Phase III Study

Patients

- Unresectable, stage III or IV melanoma
- ≤1 prior therapy, excluding anti–CTLA-4, PD-1, or PD-L1 agents
- Known *BRAF* status[a]
- ECOG PS 0-1
- No active brain metastases
- No serious autoimmune disease

R 1:1:1

- Pembrolizumab 10 mg/kg IV Q2W
- Pembrolizumab 10 mg/kg IV Q3W
- Ipilimumab 3 mg/kg IV Q3W x 4 doses

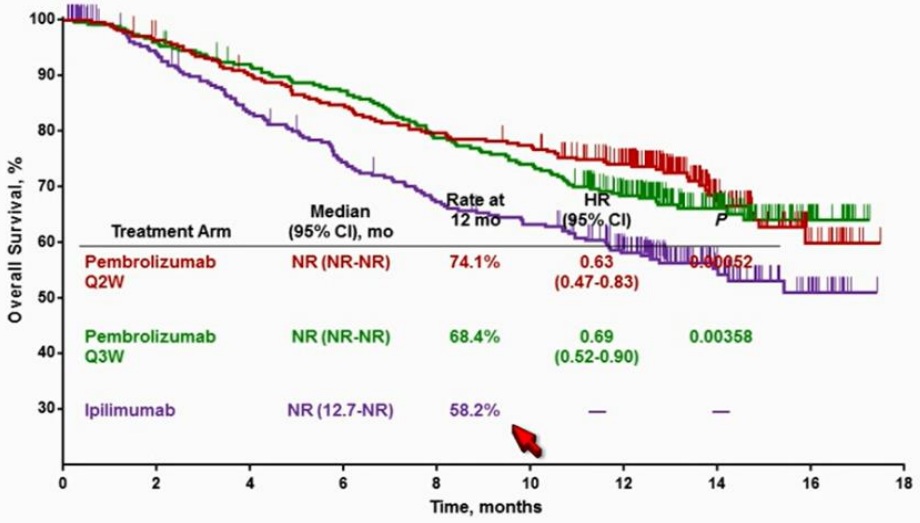
Stratification factors:
- ECOG PS (0 vs 1)
- Line of therapy (first vs second)
- PD-L1 status (positive[b] vs negative)

- Primary end points: PFS and OS
- Secondary end points: ORR, duration of response, safety

Pembrolizumab as First-Line Therapy

- Results from KEYNOTE-001 support use of pembrolizumab as first-line therapy
  - 45% ORR (confirmed RECIST v1.1, central review), including 14% CR rate
  - High ORR in both $BRAF^{V600}$ mutant (50%) and wild type (45%) melanoma
  - Median duration of response not reached
  - 60% survival at 2 years
- KEYNOTE-006: superior OS and safety compared with IPI
- Overall, results from KEYNOTE-001 support the use of pembrolizumab for advanced melanoma, regardless of prior therapy

OS at the Second Interim Analysis



Treatment Arm	Median (95% CI), mo	Rate at 12 mo	HR (95% CI)	P
Pembrolizumab Q2W	NR (NR-NR)	74.1%	0.63 (0.47-0.83)	0.00052
Pembrolizumab Q3W	NR (NR-NR)	68.4%	0.69 (0.52-0.90)	0.00358
Ipilimumab	NR (12.7-NR)	58.2%	—	—

NEJM, Robert et al 2015

Analysis cut-off date: March 3, 2015.

PEMBROLIZUMAB:

Over 2000 melanoma patients evaluated in KN-001, 002 and 006

Approved dose: 2 mg/kg IV over 30 minutes every 3 weeks.

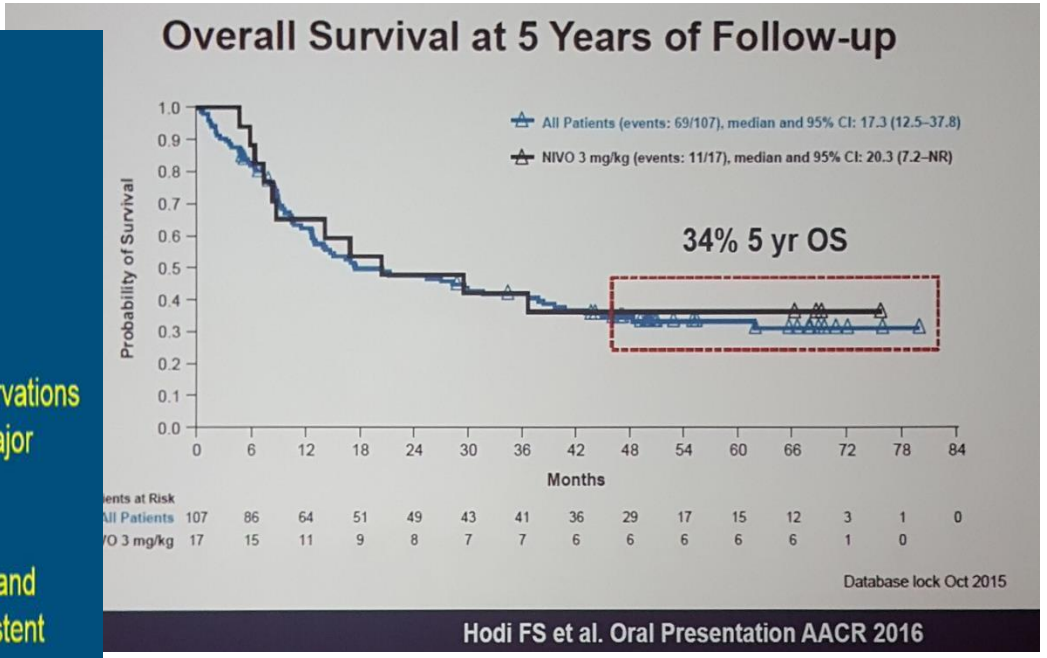
Single Agent Anti-PD1 vs. Anti-CTLA4

- Keynote -006 (P vs. I)
  - OS 55% vs. 43% at 24 mo
  - PFS ~30% vs. 14% at 24 mo
  - ORR ~37% vs. 13%
  - CR ~13% vs. 5%
  - Median duration of response not met for all groups
- Checkmate 067 (N vs. I)
  - OS not reported
  - PFS ~35% vs. ~14% at 24 mo
  - ORR ~44% vs. 19%
  - CR ~12% vs. 2%
  - Median duration of response not reported

No studies compare P to N

The slight differences in observations between N & P suggest no major differences in outcomes.

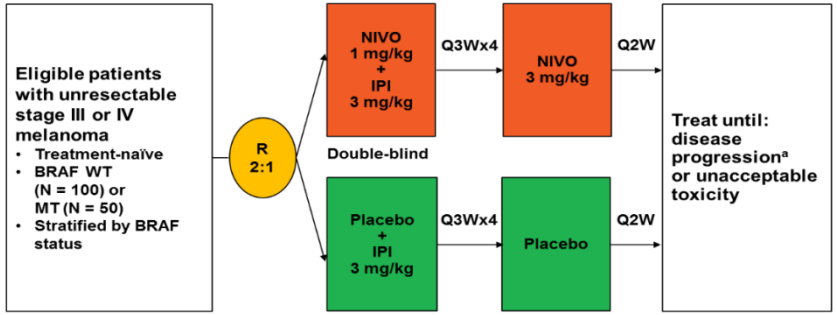
Outcomes between anti-PD1 and anti-CTLA4 remarkably consistent across studies



Truth: PD-1 Blockade

- 3-5 year Overall Survival 35-40%
- Superior OS to Ipilimumab
- DCR >50%, Better Kinetics
- Low Immune RelatedToxicity 10-15%
- Up to 2 years of Continuous Treatment
- Retreatment Appears Successful
- PDL-1 Biomarker Sub-Optimal

Phase II CA209-069: Study Design



[a]Treatment beyond initial investigator-assessed RECIST v1.1- defined progression is permitted in patients experiencing clinical benefit and tolerating study therapy. IPI patients have an option to receive nivolumab monotherapy after progression. Upon confirmed progression and change of treatment, all patients are unblinded.

MT = mutation; PFS = progression-free survival; Q3W = every 3 weeks; WT = wild type

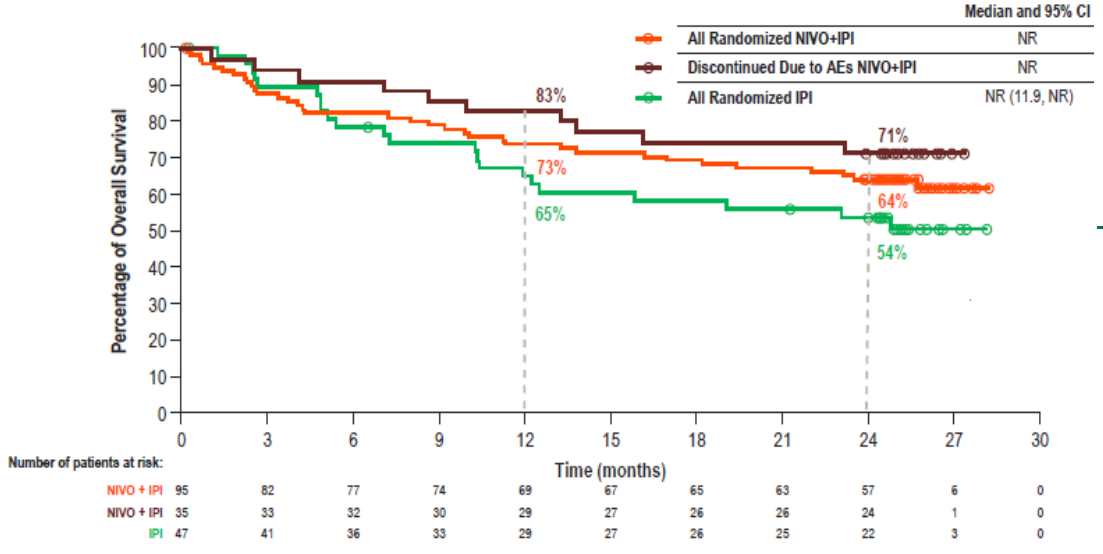
PRESENTED AT: ASCO Annual '15 Meeting

Conclusions

- At a minimum follow-up of 2 years, the OS rate in patients who discontinued NIVO+IPI due to treatment-related AEs was similar to the overall population
- Median progression-free survival and median duration of response were not reached at a minimum follow-up of 2 years, indicating durability of NIVO+IPI efficacy even in patients who discontinued
- Patients who discontinued NIVO+IPI had a similar pattern of treatment-related AEs as the overall population, albeit with a greater frequency
  - The majority of treatment-related select AEs resolved with the use of immune-modulating medications and at a similar rate when patients discontinued due to AEs
- In this post-hoc analysis, patients who experienced a treatment-related AE leading to discontinuation appeared to derive similar benefit from NIVO+IPI, despite discontinuing therapy early

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

Overall survival at 2 years of follow-up



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

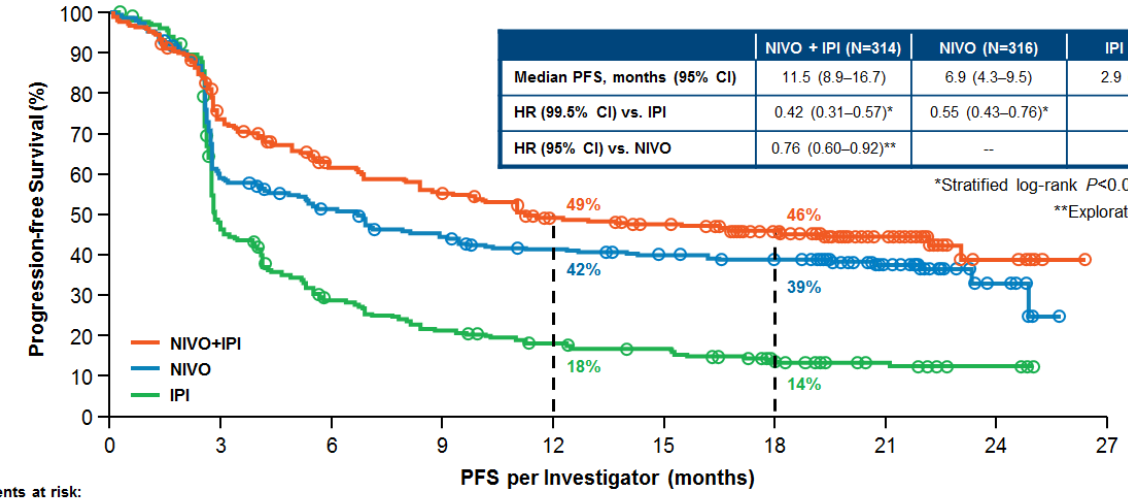
Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

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

Progression-Free Survival (Intent-to-Treat Population)



	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.55 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.76 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI

**Exploratory endpoint

Number of patients at risk:

Nivolumab + Ipilimumab	314	210	174	156	123	126	103	48	8	0
					4	104	94	46	8	0
						40	25	15	3	0

Database lock Nov 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

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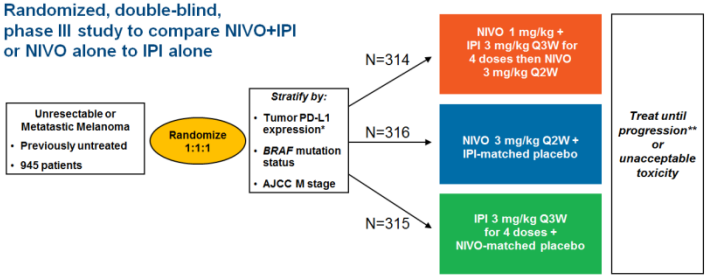
ABSTRACT

CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone



*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

Response To Treatment

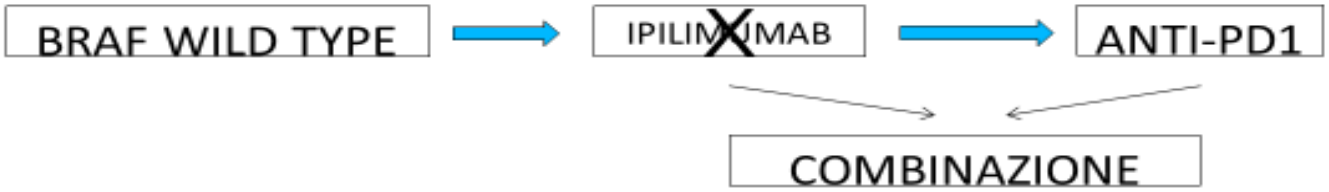
	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	**57.6** (52.0–63.2)	**43.7** (38.1–49.3)	**19.0** (14.9–23.8)
Two-sided *P* value vs IPI	<0.001	<0.001	--
Best overall response — %			
Complete response	12.1	9.8	2.2
Partial response	45.5	33.9	16.8
Stable disease	13.1	10.4	21.9
Progressive disease	22.6	38.0	48.9
Unknown	6.7	7.9	10.2
Median duration of response, months (95% CI)	**NR** (20.5–NR)	**22.3** (20.7–NR)	**14.4** (8.3–NR)
Ongoing response among responders, %	**72.5**	**72.4**	**51.7**

*By RECIST v1.1. NR = not reached.

Database lock Nov 2015

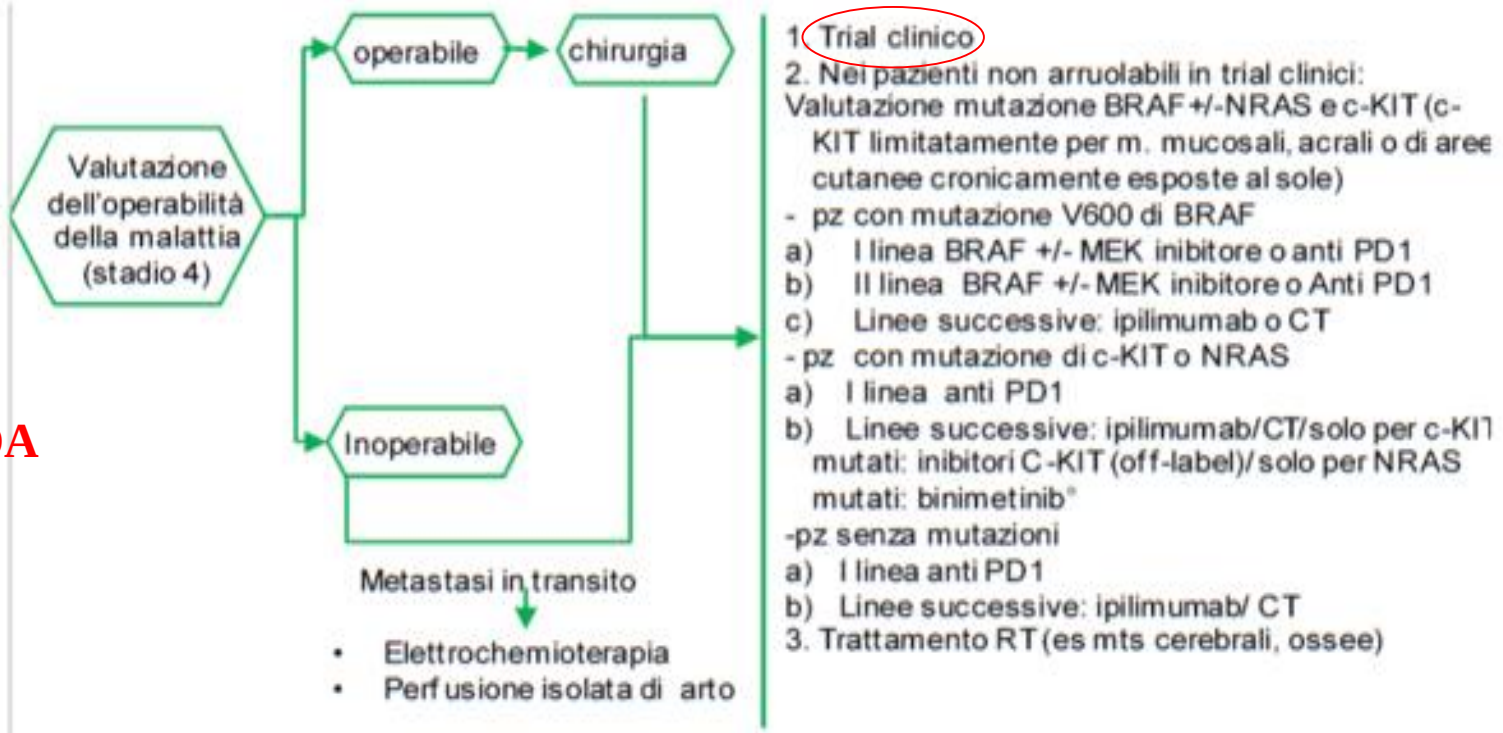
Results from pivotal phase III clinical trials

	Immune checkpoint Inhibitors				BRAF V600 mut	Chemio
	CTLA-4	**Anti PD-1**		**Anti PD-1 + CTLA-4**	**BRAF/MEK inhibition**	**DTIC**
	Ipilimumab	Pembro	Nivo	Nivo + Ipi	Dabra/Trame Vemu/Cobi	
ORR (%)	11-19	42	40-44	58	64-68	9.5
mPFS (mo)	2.8-3.3	8.3	5.1-6.9	11.7	12.6	2.2
mOS (mo)	13.5-16	32.3	NR	NR	25.6	10.8
1yr OS	58%	68-74%	74%	73%	73%	42%
2yrs OS	30%	55%	59%	64%	52-53%	17%
3 yrs OS	26%	50%	(41%)	NA	44-45%	12%
Gr 3-4 AE	19-27%	17%	11-20%	54-58%	48-62%	17%



MELANOMA TREATMENT SCENARIO 2016-17

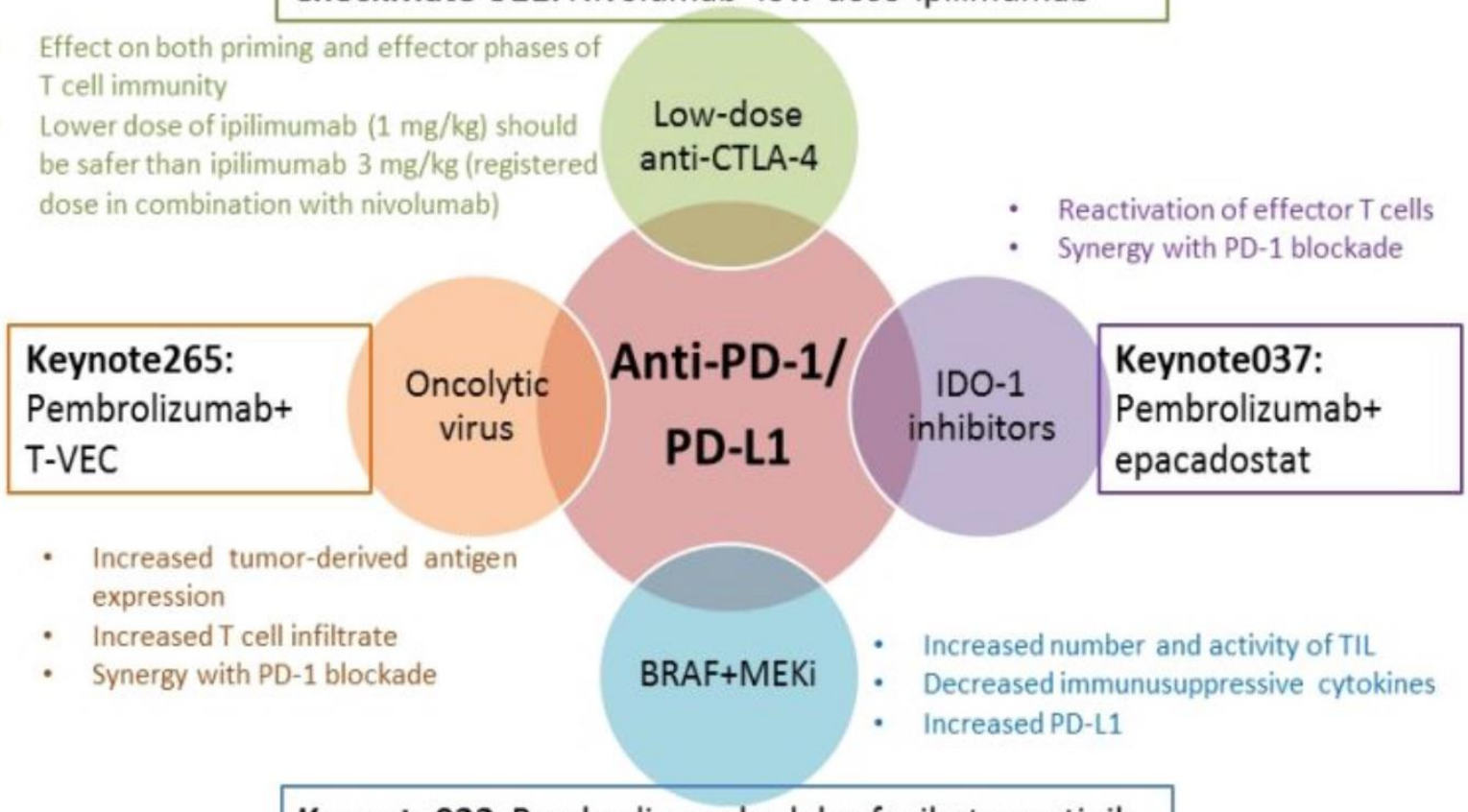
LINEE GUIDA AIOM 2016



Future Perspectives: combination therapy

Keynote029: Pembrolizumab+low-dose ipilimumab
CheckMate-511: Nivolumab+low-dose ipilimumab

- Effect on both priming and effector phases of T cell immunity
- Lower dose of ipilimumab (1 mg/kg) should be safer than ipilimumab 3 mg/kg (registered dose in combination with nivolumab)



- Reactivation of effector T cells
- Synergy with PD-1 blockade

Keynote265: Pembrolizumab+ T-VEC

Keynote037: Pembrolizumab+ epacadostat

- Increased tumor-derived antigen expression
- Increased T cell infiltrate
- Synergy with PD-1 blockade

- Increased number and activity of TIL
- Decreased immunusuppressive cytokines
- Increased PD-L1

Keynote022: Pembrolizumab+dabrafenib+trametinib
Trilogy: Atezolizumab+vemurafenib+cobimetinib
Anti-PD-1+BRAFi+MEKi in elevated LDH patients

SEQUENCING ?

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

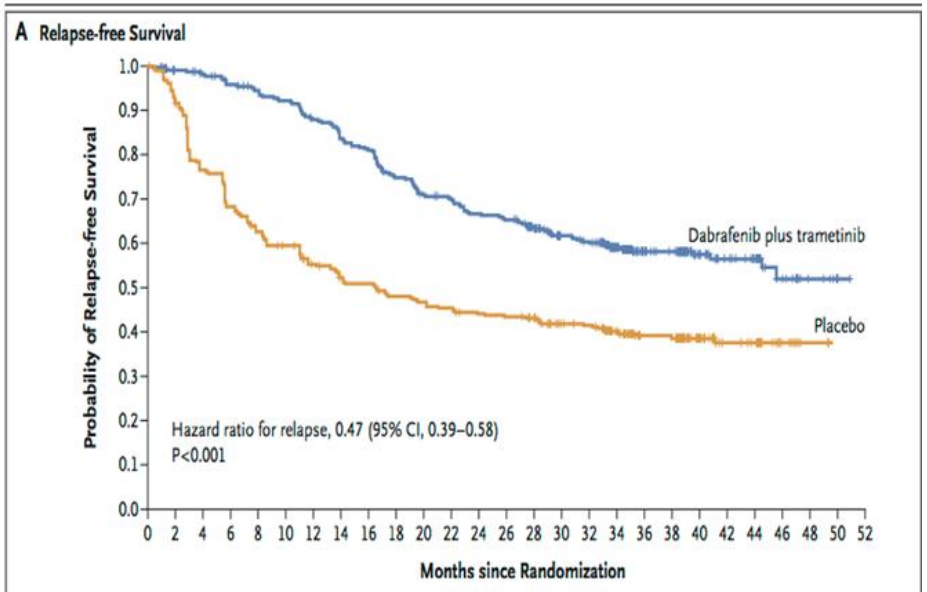
Prospettive future: setting adiuvante MELANOMA STADIO III

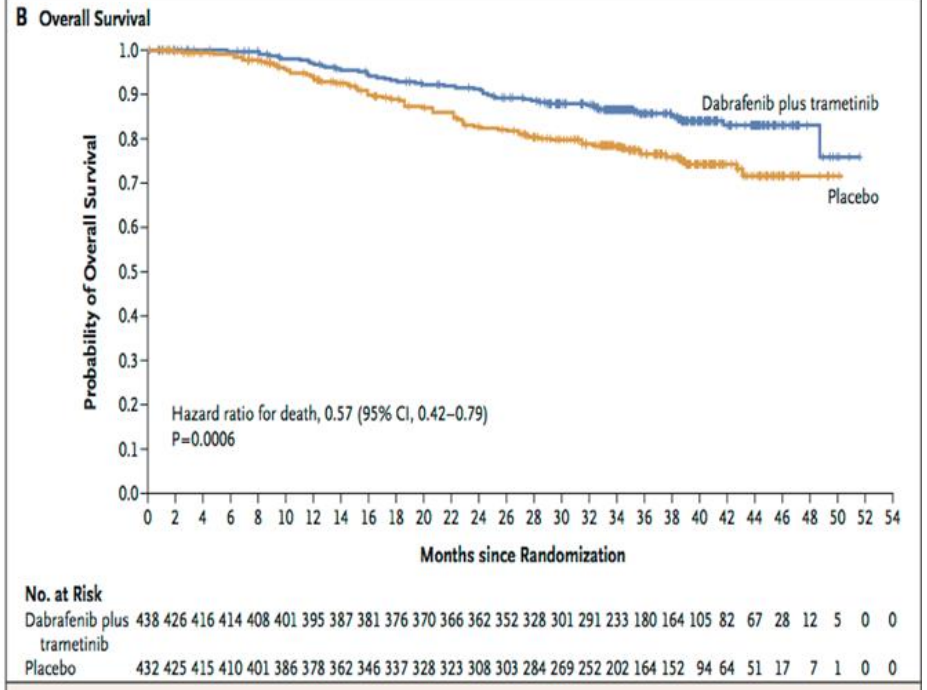
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang B. Mookerjee, J. Legos, R. Kefford, R. Dummer, and J.M. Kirkwood



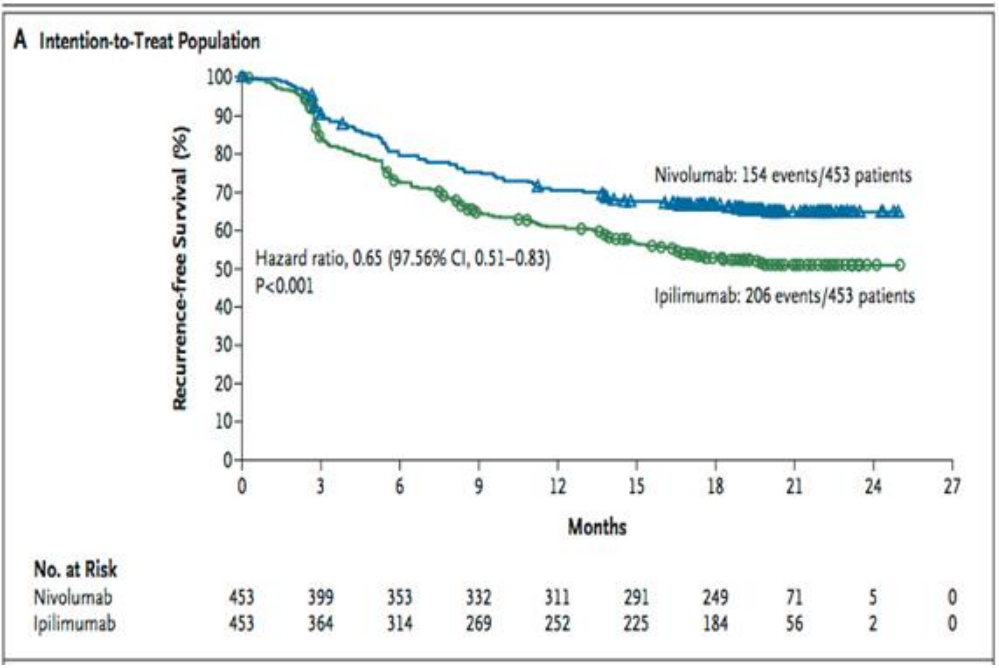


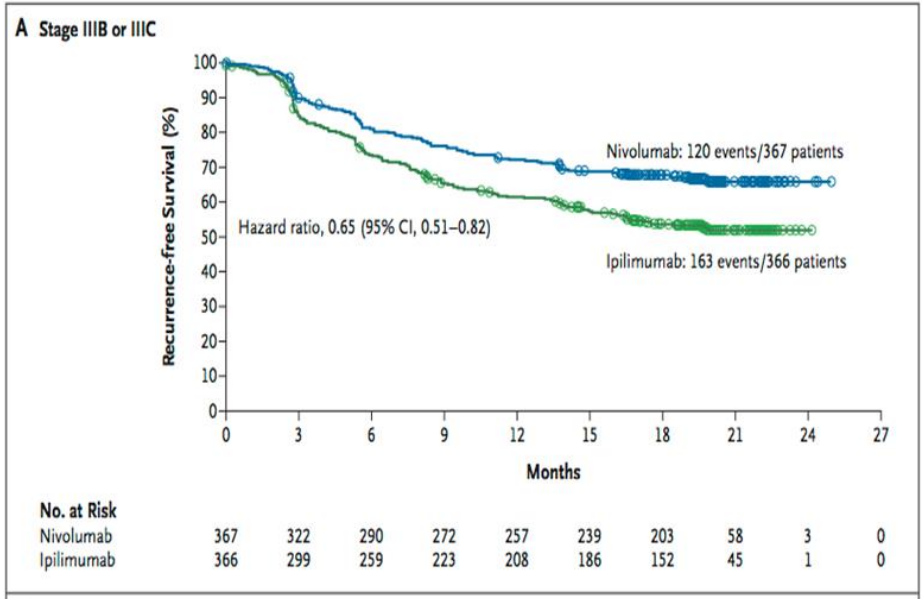
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, and P.A. Ascierto, for the CheckMate 238 Collaborators*





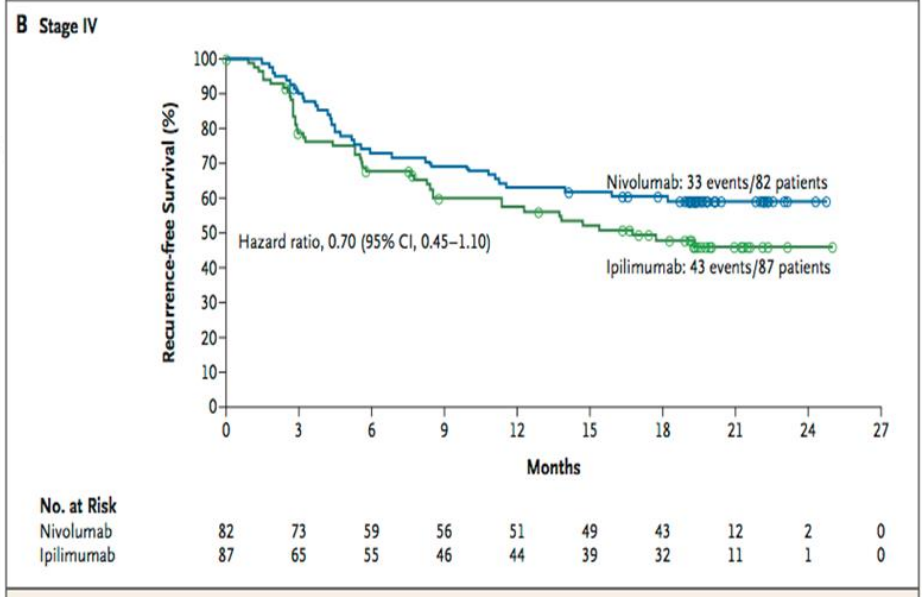
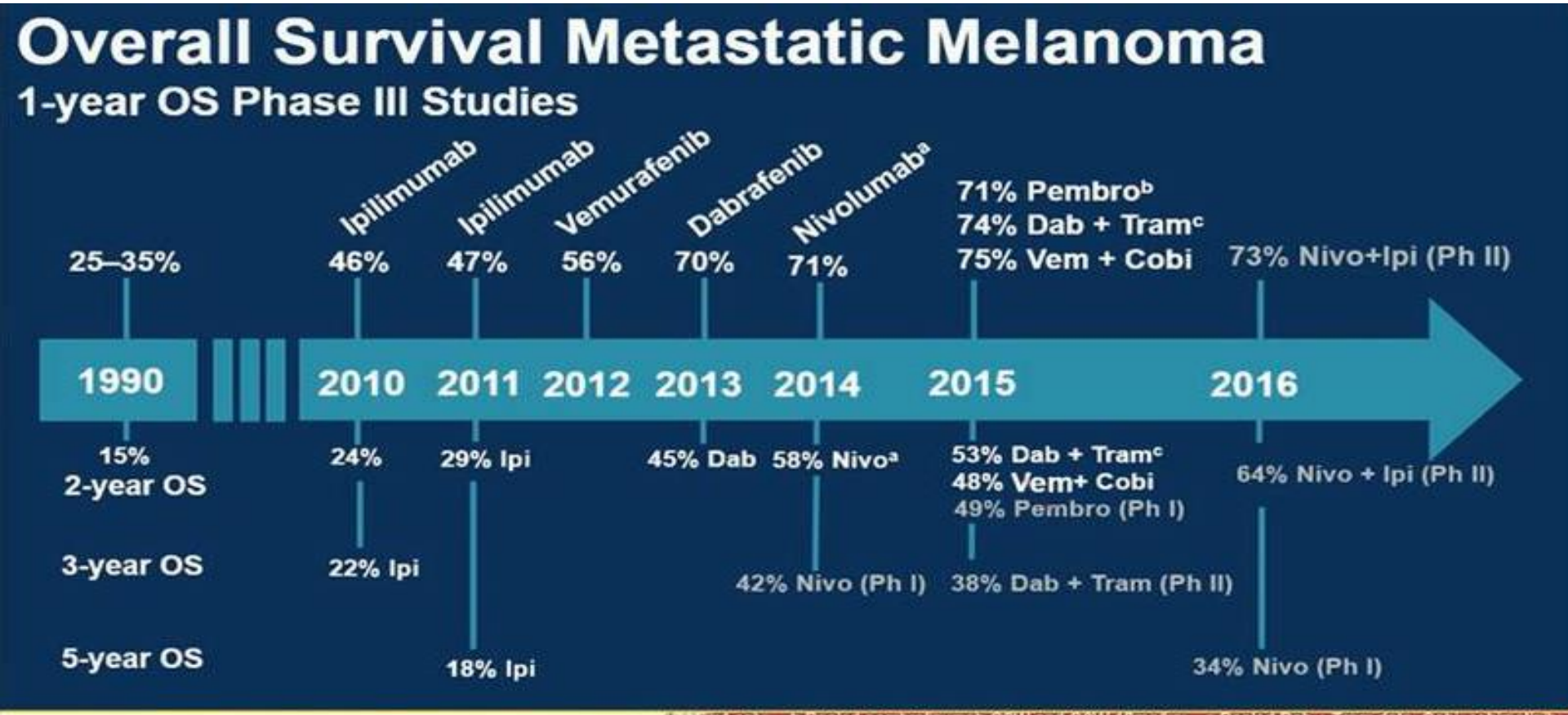


Figure 2. Recurrence-free Survival, According to Disease Stage.

Shown are Kaplan–Meier 12-month estimates of recurrence-free survival in patients with stage IIIB or IIIC disease (72.3% in the nivolumab group and 61.6% in the ipilimumab group) (Panel A) and stage IV disease (63.0% and 57.5%, respectively) (Panel B).

Overall Survival Metastatic Melanoma

1-year OS Phase III Studies



[a] Pooled pembrolizumab Q2W and Q3W 10mg/kg; [c] Pooled Dab + Tram data; Cobi=cobimetinib; Ipi=ipilimumab; Nivo=nivolumab; Pembro=pembrolizumab; Tram=trametinib; Vem=vemurafenib.

sented by Georgina V. Long