# Nuove terapie del melanoma cutaneo avanzato

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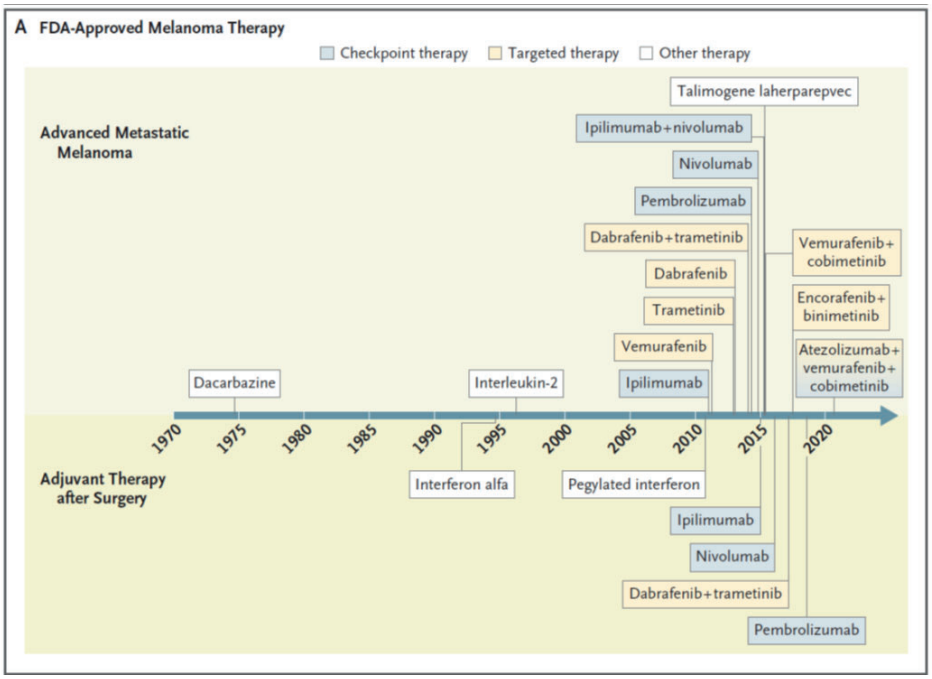
## Sommario

- Introduzione
- La rivoluzione del trattamento a bersaglio molecolare («targeted therapy»)
- Immunoterapia e melanoma
- La rivoluzione delle immunoterapie moderne («checkpoint inhibitors»)
- Dati recenti di terapia sequenziale e combinata
- Conclusioni

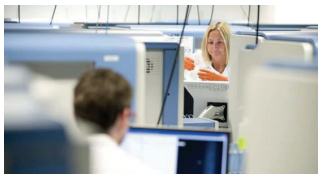
# Espansione delle terapie mediche dopo il 2012




# La rivoluzione della terapia a bersaglio molecolare

Successo della ricerca di base e del «Cancer genome project»

# Cancer genome project



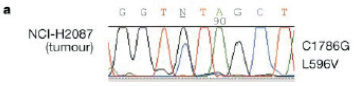
**letters to nature**

## Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[4], Rebecca Wilson[4], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14], Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]

[1]*Cancer Genome Project, The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, CB10 1SA, UK*

phoblastoid cell lines from the same individuals were screened for sequence variants through the coding exons and intron–exon junctions of the *BRAF* gene using a capillary-based modified heteroduplex method followed by direct sequencing of polymerase chain reaction products. (Exon 1, containing 135 base pairs (bp) of coding sequence, failed to amplify despite the use of five different primer sets.) Three single-base substitutions were detected. Two were in *BRAF* exon 15: T1796A leading to a substitution of valine by glutamic acid at position 599 (V599E) in the melanoma cell line Colo-829, and C1786G leading to L596V in the NSCLC cell line NCI-H2087 (Fig. 1). A further mutation was found in exon 11: G1403C leading to G468A in the NSCLC cell line NCI-H1395. None of the three changes were present in the lymphoblastoid cell lines from the same individuals, indicating that the variants were somatically acquired mutations.




# Mutations of the BRAF gene in human cancer

(Nature, 2002)

- Sequenziamento dei geni della RAS/RAF/MEK/ERK pathway in tumori solidi noti per possibili mutazioni di *RAS* (linee cellulari e tumori primitivi)
- Mutazioni somatiche di *BRAF* in 66% dei melanomi, ma molto più rare in altri tumori solidi
- *BRAF*-V600E è una mutazione attivatrice ed è oncogenica

# Validazione di BRAF$^{V600E}$ quale potenziale bersaglio terapeutico (studi preclinici)

- BRAF$^{V600E}$ è oncogenico in melanociti in cultura (*in vitro* e *in vivo*)
- L'espressione regolata di BRAF$^{V600E}$ nel topo transgenico induce melanoma, se combinata con *knock-out* di PTEN in forma metastatica nel 100% dei casi e con breve latenza
- Inibitori di BRAF e MEK sono attivi nei modelli animali di melanoma

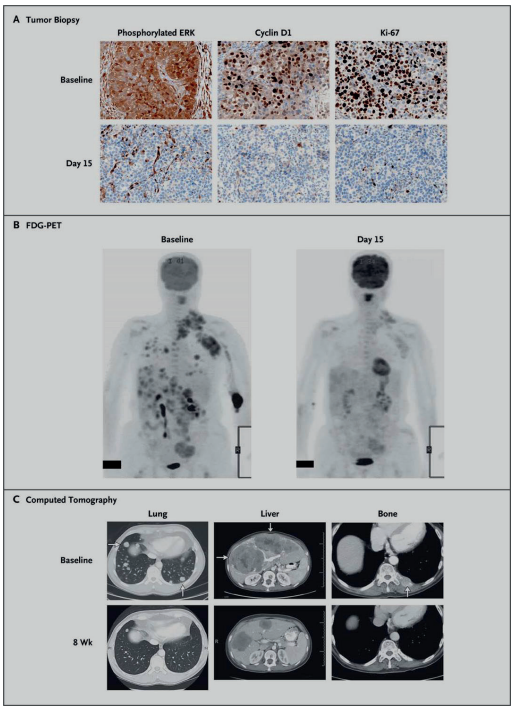
The NEW ENGLAND JOURNAL of MEDICINE

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.

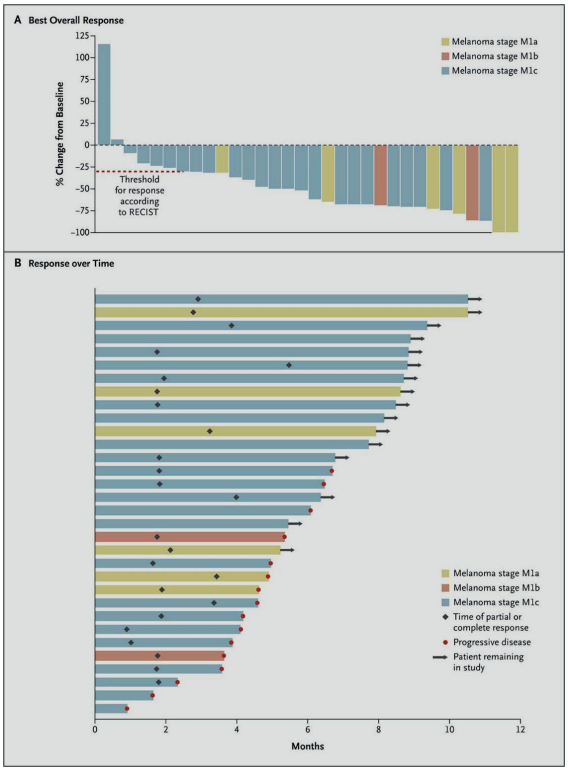
Flaherty, NEJM, 2010




# Farmacodinamica

- Per 7 pazienti a 960 mg biopsia a d.1 e d.15
- Riduzione di pERK, ciclina D1 e Ki-67 in tutti i pazienti al d.15 (prova dell'inibizione della MAPK *pathway* e della proliferazione)
- Riduzione marcata dell'uptake di FDG al d.15

Flaherty, NEJM, 2010



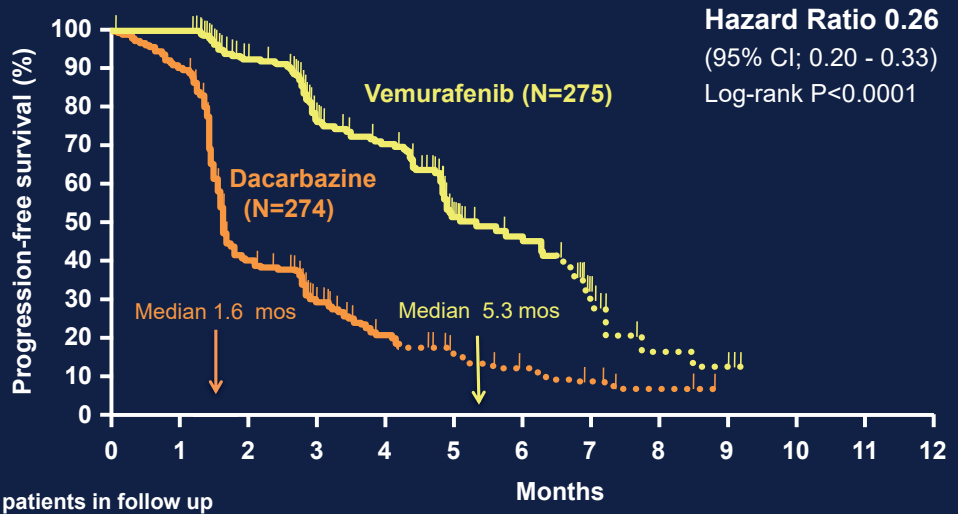

# Tumor response

(extension cohort)

- Solo melanoma *BRAF*-V600E (n=32) trattati a 960 mg x 2
- 26/32 (81%), 2CR, 24PR
- Risposte anche in p. con > 1 linea di terapia precedente (11PR)
- PFS$_{mediana}$ > 7mesi, OS$_{mediana}$ non raggiunta

Flaherty, NEJM, 2010

# Progression-free survival (Dec 30, 2010 cutoff)

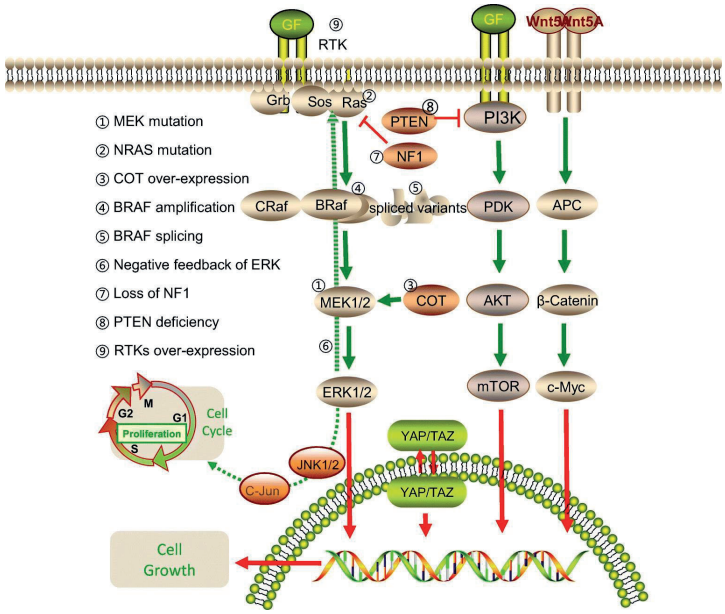



**Hazard Ratio 0.26**
(95% CI; 0.20 - 0.33)
Log-rank P<0.0001

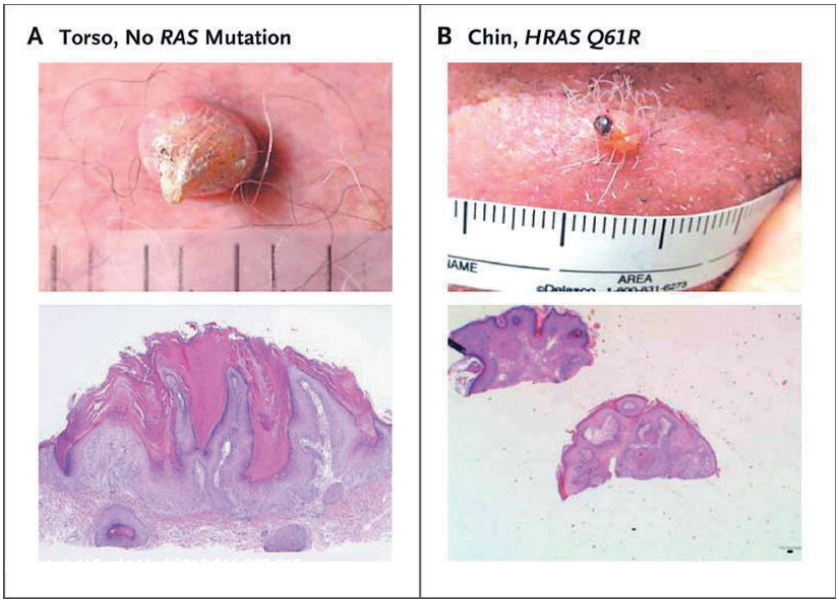
| No. of patients in follow up | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dacarbazine | 274 | 213 | 85 | 48 | 28 | 16 | 10 | 6 | 3 | 0 |
| Vemurafenib | 275 | 268 | 211 | 122 | 105 | 50 | 35 | 16 | 4 | 3 |

ASCO Annual '11 Meeting

# Multipli meccanismi di resistenza a BRAF-inibitori



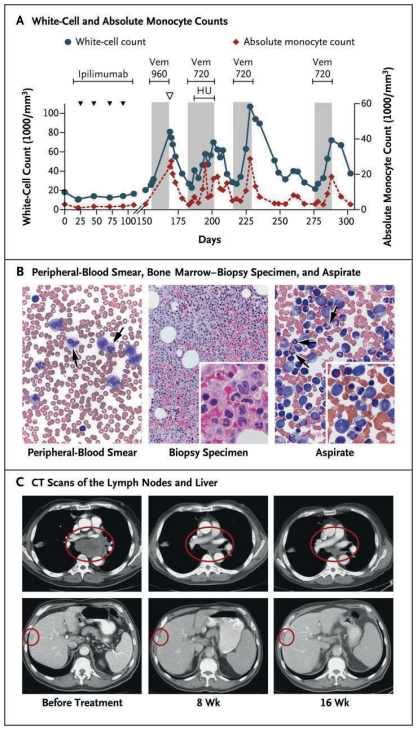
## Frequenti mutazioni di RAS nei tumori cutanei secondari (Su et al., NEJM 2012)




## Vemurafenib stimola i tumori con mutazioni di RAS

Decorso di un paziente con un melanoma *BRAF*-V600K mutato e una Leucemia mielomonocitica cronica con mutazione *NRAS*-G12R durante il trattamento con Vemurafenib

NEJM, 2022



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

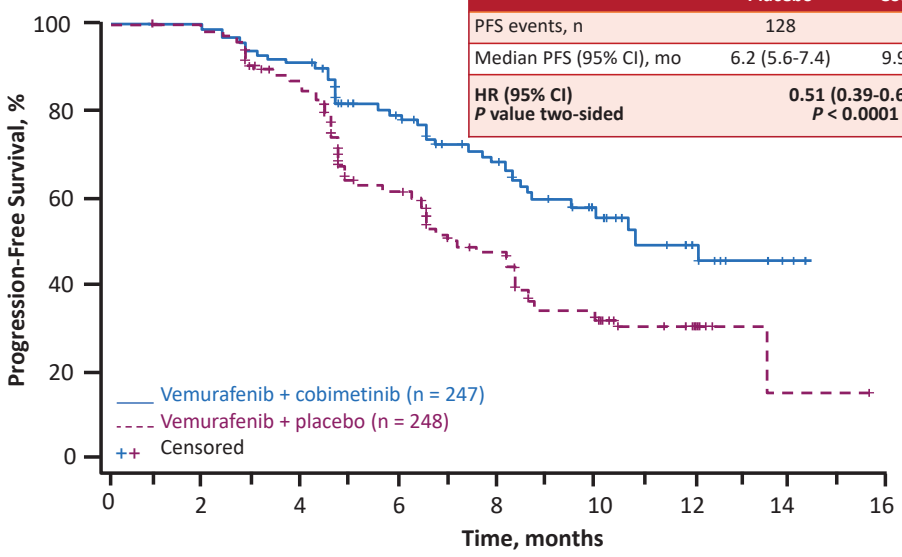
# Combined Vemurafenib and Cobimetinib in *BRAF*-Mutated Melanoma

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.

Larkin J et al. N Engl J Med. **2014** Nov 13;371(20):1867-76

## Investigator-Assessed PFS

| | Vemurafenib+ Placebo | Vemurafenib + Cobimetinib |
|---|---|---|
| PFS events, n | 128 | 79 |
| Median PFS (95% CI), mo | 6.2 (5.6-7.4) | 9.9 (9.0-NE) |
| **HR (95% CI)**<br>***P* value two-sided** | **0.51 (0.39-0.68)**<br>***P* < 0.0001** | |



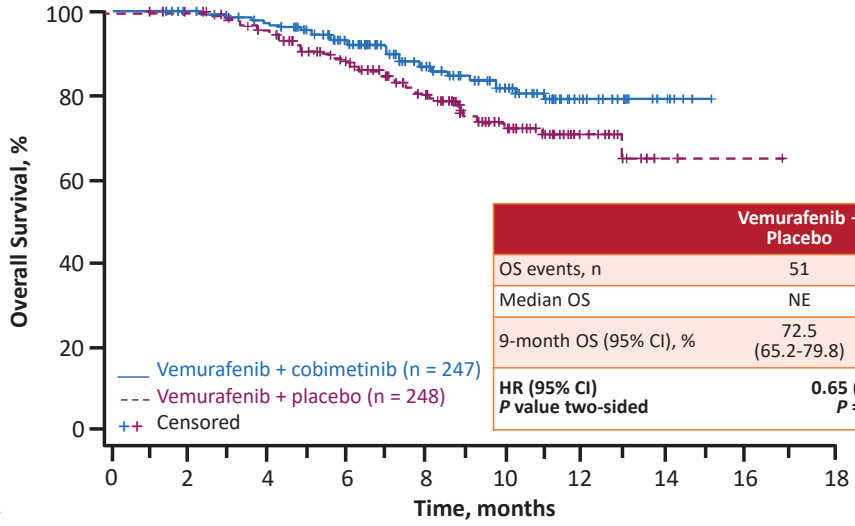

| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Vemurafenib + cobimetinib | 238 | 215 | 152 | 96 | 46 | 14 | 3 |
| Vemurafenib + placebo | 240 | 200 | 118 | 68 | 34 | 12 | 1 |

CI, confidence interval; NE, not estimable.

Data Cutoff: May 9, 2014

Larkin J et al. N Engl J Med. **2014** Nov 13;371(20):1867-76

## Overall Survival




| | Vemurafenib + Placebo | Vemurafenib + Cobimetinib |
|---|---|---|
| OS events, n | 51 | 34 |
| Median OS | NE | NE |
| 9-month OS (95% CI), % | 72.5 (65.2-79.8) | 81.1 (74.7-87.5) |
| **HR (95% CI)** ***P* value two-sided** | **0.65 (0.42-1.00)** ***P* = 0.046*** | |

Data Cutoff: May 9, 2014

| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Vemurafenib + cobimetinib | 243 | 229 | 182 | 112 | 62 | 20 | 6 | 0 |
| Vemurafenib + placebo | 245 | 227 | 166 | 101 | 53 | 21 | 2 | 1 |

CI, confidence interval; NE, not estimable.
* Descriptive p-value. Did not cross the pre-specified stopping boundary for the interim analysis (boundary p <0.0000037)

Larkin J et al. N Engl J Med. **2014** Nov 13;371(20):1867-76

# Studi di combinazione, fase III

- Studio di fase III di dabrafenib + trametinib vs dabrafenib + placebo (COMBI-D)
- Studio di fase III di vemurafenib + cobimetinib vs vemurafenib + placebo
- Studio di fase III di dabrafenib + trametinib vs vemurafenib (COMBI-V)

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

The NEW ENGLAND JOURNAL of MEDICINE

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## Combined Vemurafenib and Cobimetinib in *BRAF*-Mutated Melanoma

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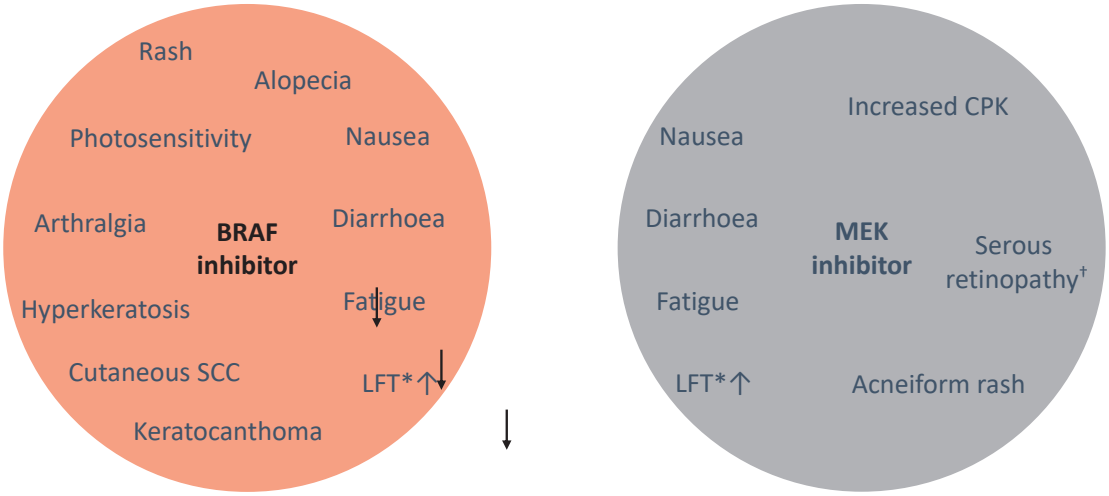
ORIGINAL ARTICLE

## 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.

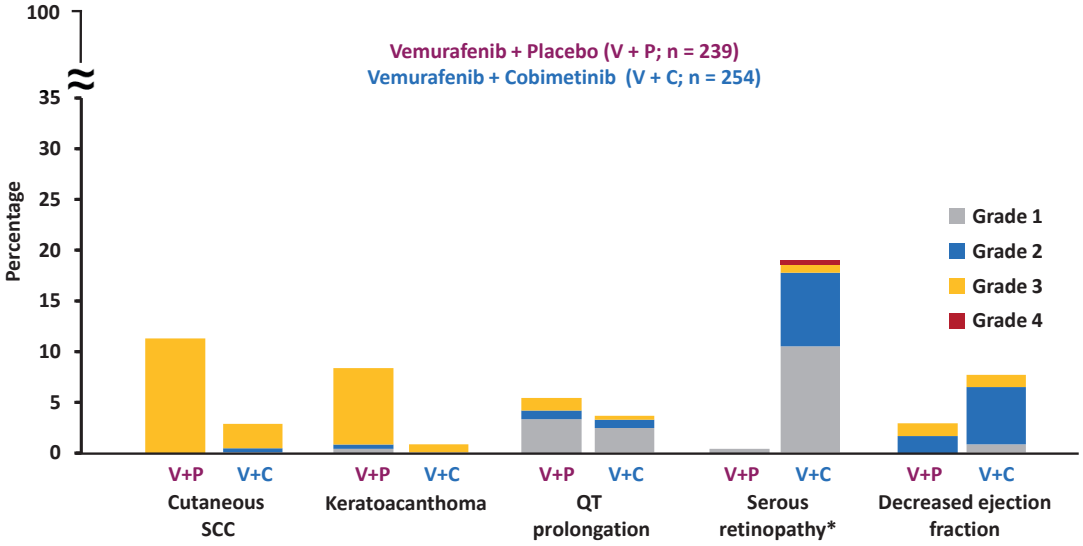
# La terapia combinata ha un profilo di effetti collaterali più esteso, ma minor rischio di tumori secondari




* Liver function tests, incluse ASAT e ALAT; † Include la corioretinite e il distacco retinico

1. Gibney GT, et al. Nat Rev Clin Oncol 2013; 2. Grimaldi AM, et al. Curr Opin Oncol 2014

# Riassunto di eventi avversi selezionati



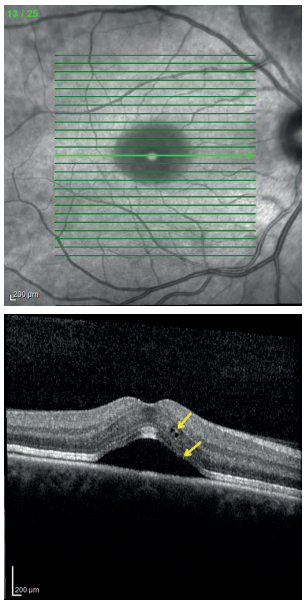

SCC, squamous cell carcinoma.

**No cases of retinal vein occlusion were reported.**
***Includes specific terms chorioretinopathy and retinal detachment.**

Data Cutoff: May 9, 2014

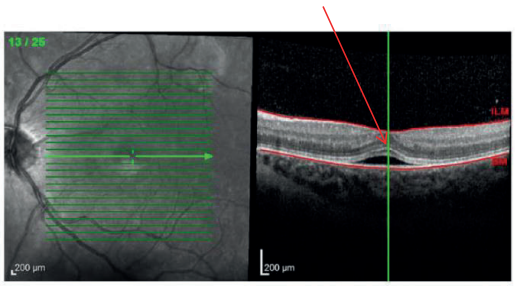
Larkin J et al. N Engl J Med. **2014** Nov 13;371(20):1867-76

# L'inibizione di MEK è associata ad una tossicità retinica, generalmente transitoria



- Retinal conditions resembling serous retinopathy are observed with MEK inhibitors[1]
- Ocular toxicities are relatively common with both targeted and cytotoxic agents[2-4]

Transient subretinal oedema



*Partially resolved 1 hour later*

1. Urner-Bloch U, et al. Ann Oncol 2014; 2. Renouf DJ, et al. J Clin Oncol 2012;
3. Huillard O, et al. Eur. J. Cancer 2014; 4. van der Noll R, et al. Cancer Treat Rev 2013

# Tre opzioni attuali di BRAFi/MEKi

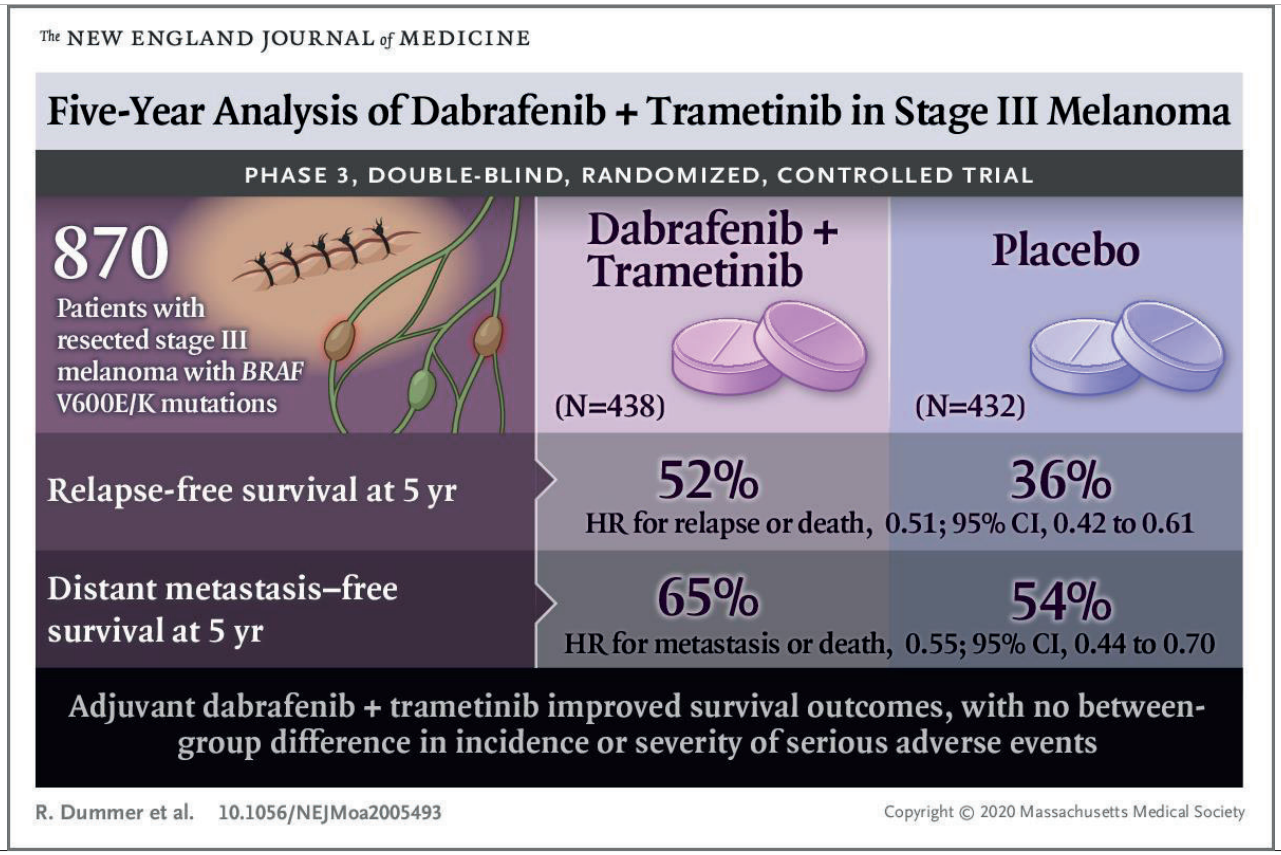
Vemurafenib 960mg 2x (2x 4 cpr) + Cobimetinib 60 mg 1x (3 cpr) 21/28
(Zelboraf/Cotellic, Zelboraf a stomaco vuoto, CAVE: fotosensibilità)

Dabrafenib 150 mg 2x (2x2cpr) + Trametinib 2 mg 1x (1cpr)
(Tafinlar/ Mekinist, entrambe a stomaco vuoto, CAVE: iperpiressia)

Encorafenib 450 mg 1x (9 cpr) + Binimetinib 45 mg (3cpr) 2x/dì
(BRAFTOVI/MEKTOVI, entrambe indipendenti dai pasti)

# Terapia adiuvante del melanoma *BRAF*-V600mut con Dabrafenib e Trametinib (12 mesi)

- Risultati a lungo termine: positivi per melanomi di stadio IIIB-D in termini di riduzione delle recidive (Riduzione del 45%)
- Svantaggio
  - Teoricamente le terapie a bersaglio molecolare hanno un minor effetto a lungo termine rispetto all'immunoterapia (recidive tardive?)
- Vantaggio:
  - Minor rischio di eventi avversi irreversibili (endocrini) rispetto all'immunoterapia



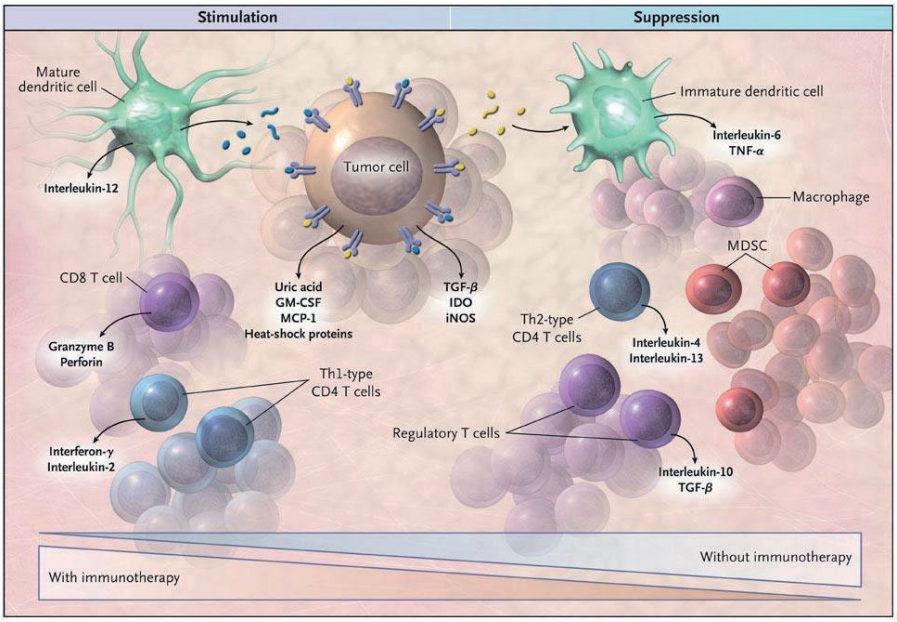

# Immunoterapia e melanoma

Melanoma come modello per l'immunoterapia

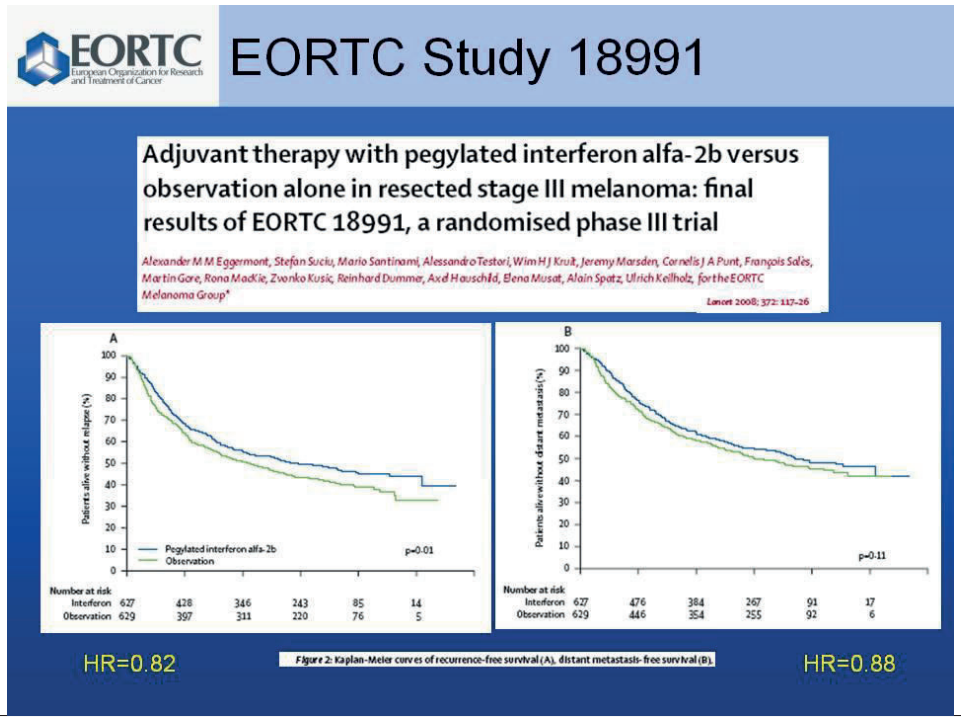
# Immunoterapia e melanoma, sommario

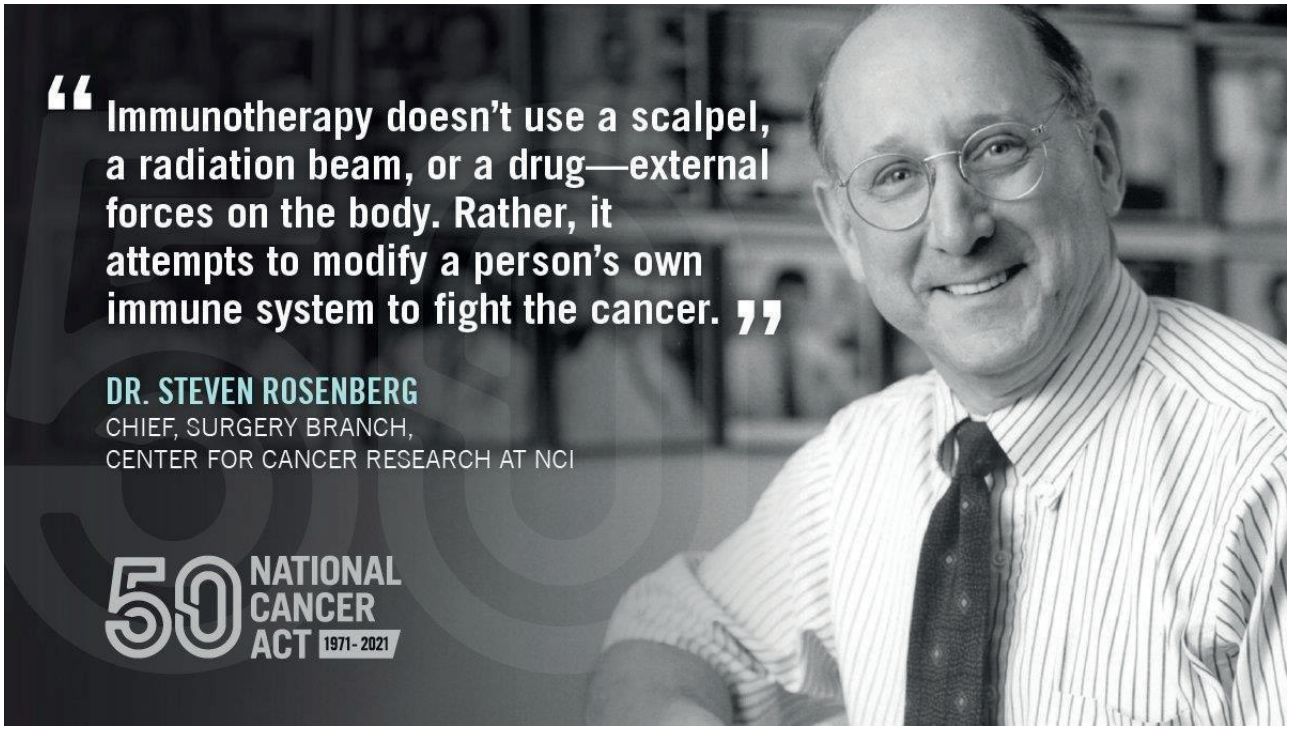
- Melanoma = neoplasia più sensibile all'immunoterapia
- Efficacia, seppur limitata, dell'interferone (come terapia adiuvante)
- Esperienza con i «tumour-infiltrating lymphocytes» (TILs) e con interleuchina-2 sin dagli anni '80
- Scoperta di CTLA-A e PD1 negli anni '90 e primi studi clinici con Ipilimumab (anti-CTLA-4) nel melanoma (2010-2012)
- In seguito introduzione degli anti-PD1 (Pembrolizumab e Nivolumab) in monoterapia e in combinazione con Ipilimumab (studio Checkmate-67 2013-2016)

# Nel microambiente tumorale (TME) prevalgono fattori di immunosoppressione

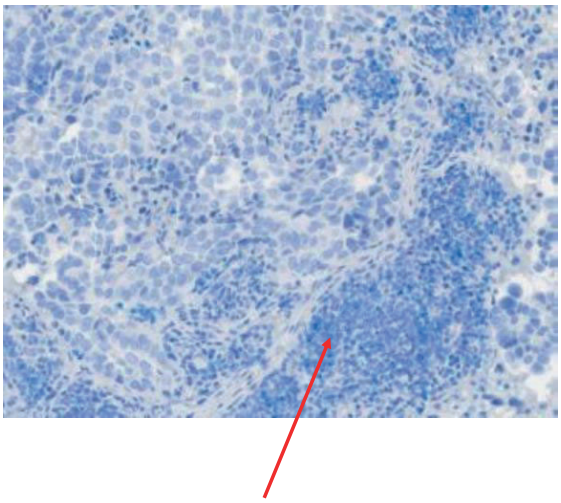


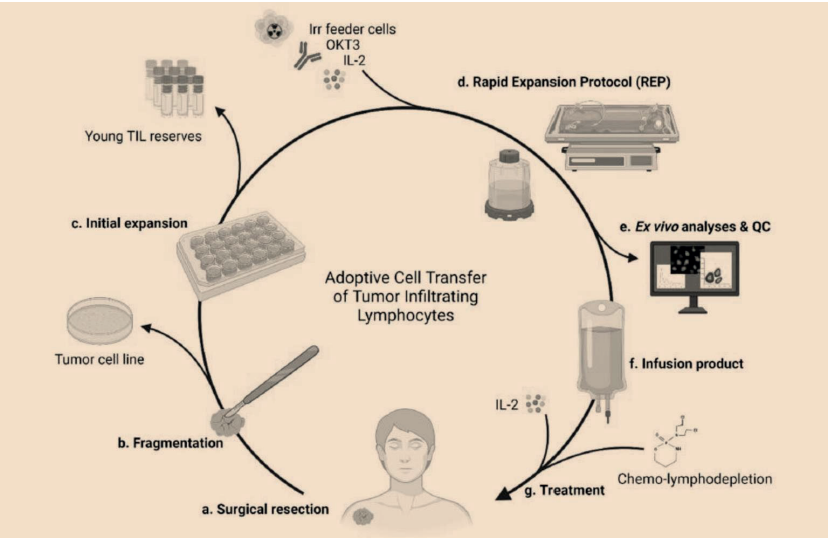
# Efficacia, seppur limitata, dell'interferone



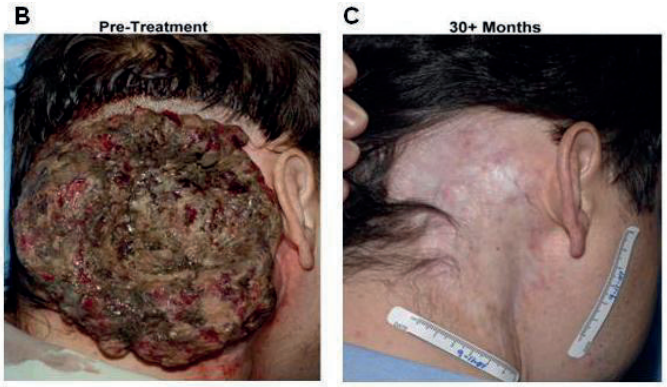



# TILs: tumour infiltrating lymphocytes





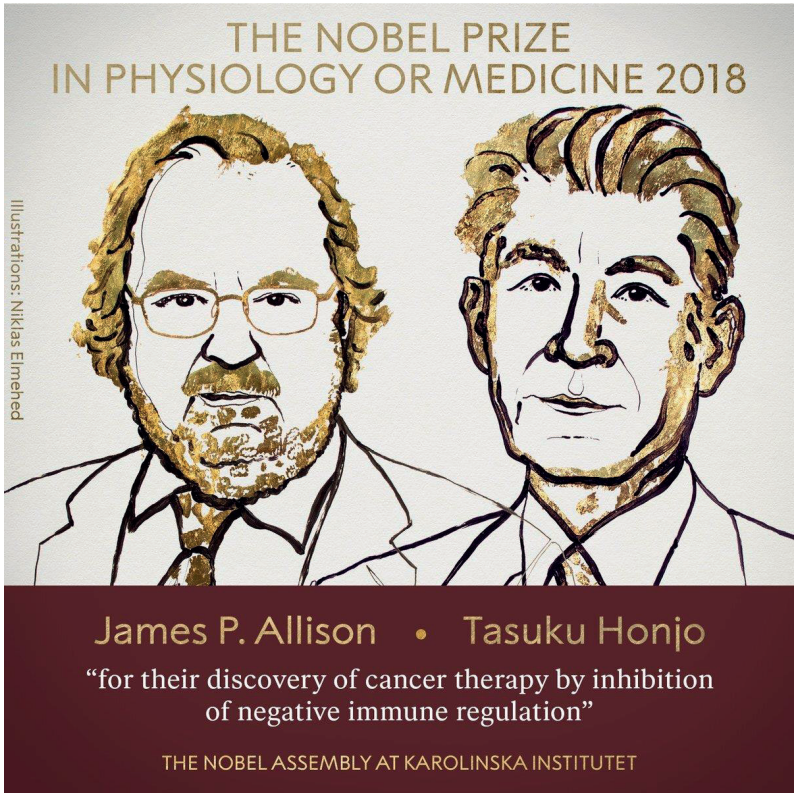

# Esperienza con i «tumour-infiltrating lymphocytes» (TILs) e con interleuchina-2 sin dagli anni ‘80



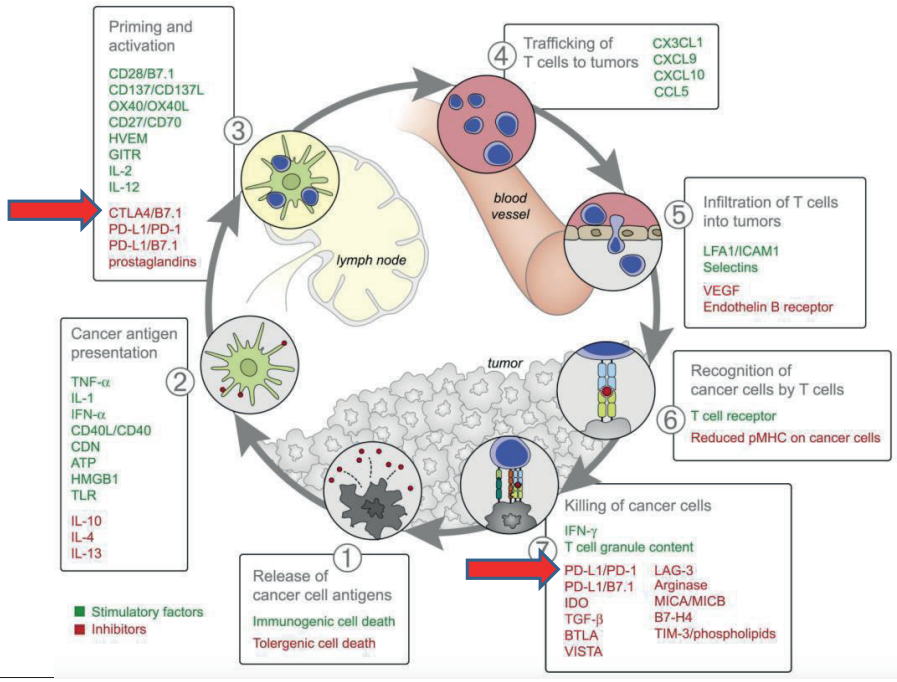

B) Inoperable scalp lesion of patient 2427 prior to ACT treatment. C) Scalp area of patient 2427 after two courses of ACT treatment consisting of non-myeloablative chemotherapy, TIL 2427 F7 and high dose IL-2 therapy.

# La rivoluzione delle immunoterapie basate sui checkpoint inhibitors

Dal melanoma a tutti (o quasi) i tumori solidi



# La risposta immunologica al tumore dipende da una regolazione a più livelli, con fattori positivi e negativi




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

## Study MDX010-20


**Steven O'Day**[1], F. Stephen Hodi[2], David McDermott[3], Robert Weber[4], Jeffrey Sosman[5], John Haanen[6], Xiaoping Zhu[7], Michael Yellin[7], Axel Hoos[8], Walter J. Urba[9]

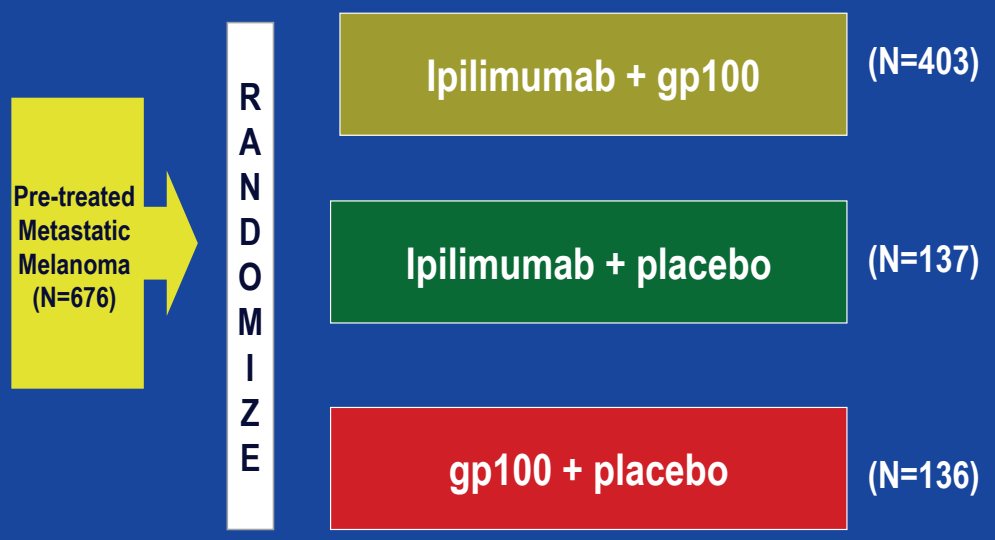
[1]The Angeles Clinic and Research Institute, Santa Monica, CA; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Beth Israel Deaconess Medical Center, Boston, MA, [4]Saint Mary's Medical Center, San Francisco, CA; [5]Vanderbilt-Ingram Cancer Center, Nashville, TN; [6]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [7]Medarex Inc., Bloomsbury, NJ; [8]Bristol-Myers Squibb Co., Wallingford, CT; [9]Earle A. Chiles Research Institute, Portland, OR

# MDX010-20: Study Design Details

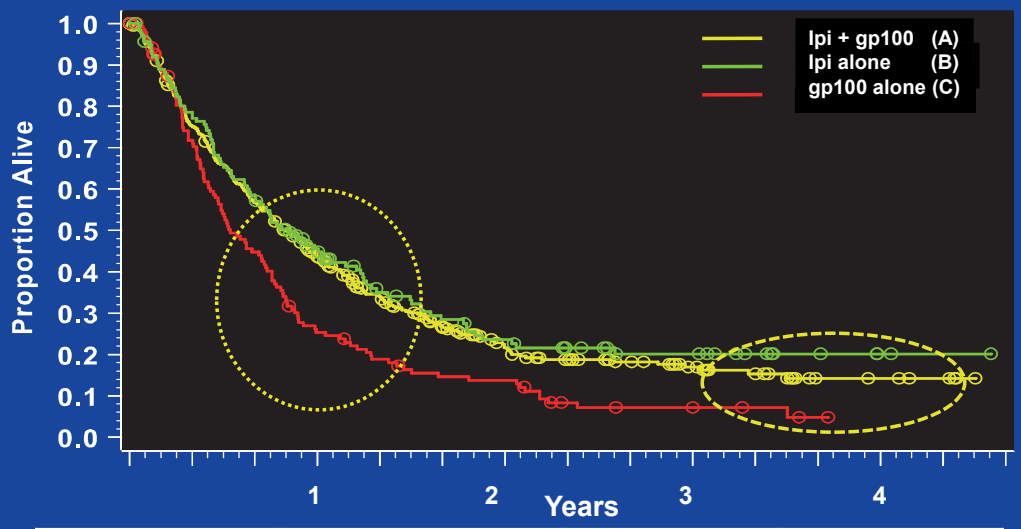
- Accrual: September 2004 – July, 2008
  - 125 Centers in 13 Countries
- Randomized (3:1:1), Double-Blind
- Stratified for M-Stage and prior IL-2
- Induction
  - Ipilimumab: 3 mg/kg q 3 weeks X 4 doses
  - gp100: 1mg q 3 weeks X 4 doses
- Re-induction (same regimen) in eligible patients



# MDX010-20: Study Design



# Kaplan-Meier Analysis of Survival

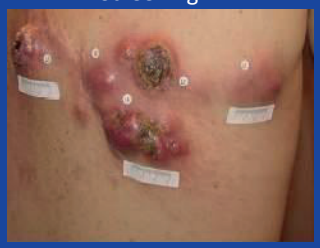



| Survival Rate | Ipi + gp100 N=403 | Ipi + pbo N=137 | gp100 + pbo N=136 |
|---|---|---|---|
| 1 year | 44% | 46% | 25% |
| 2 year | 22% | 24% | 14% |

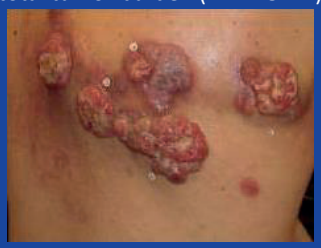


# Risposta dopo iniziale aumento del carico tumorale

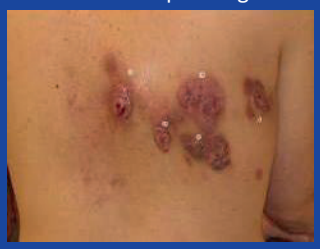
Screening



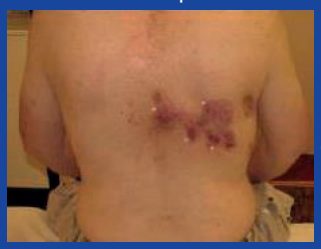
Week 12: initial increase in total tumor burden (mWHO PD)



Week 14: responding



Week 20: response

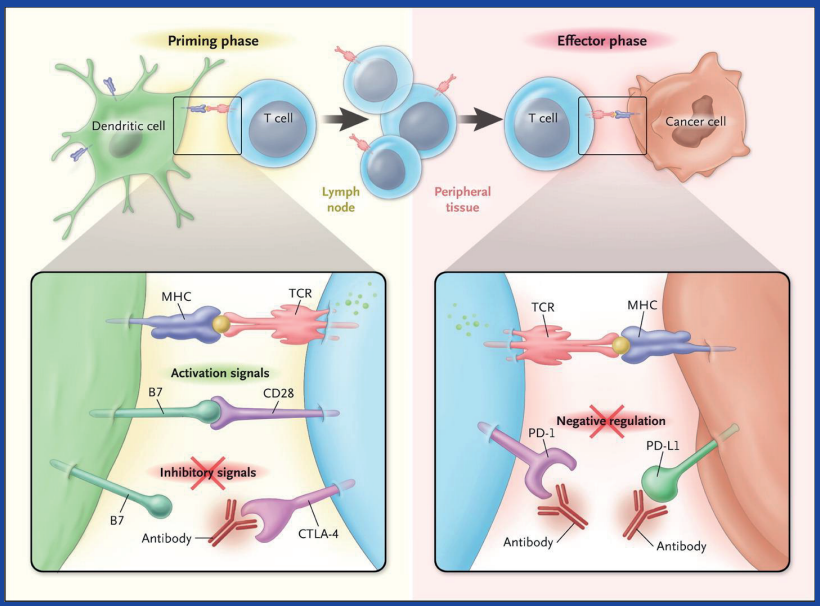


Follow-up ongoing

Patient treated with 10 mg/kg ipilimumab monotherapy in study CA184-008

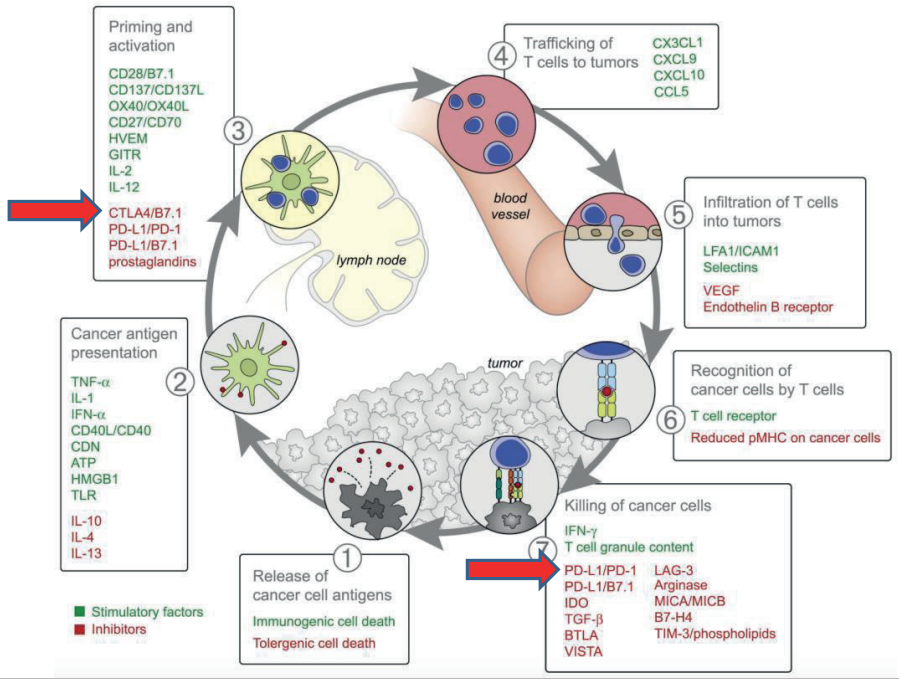
*Courtesy of Hubert Pehamberger, Department of Dermatology, University of Vienna, Vienna, Austria*

## L'effetto di "blocco" di CTLA-4 e PD-1 avviene in due fasi distinte

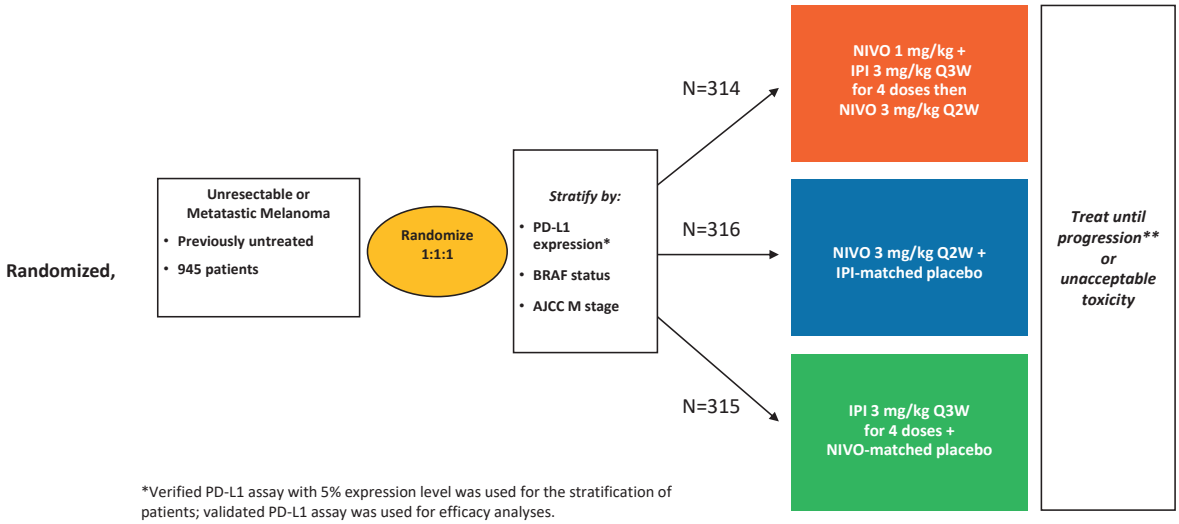



Ribas A. N Engl J Med 2012;366:2517-2519.

## La risposta immunologica al tumore dipende da una regolazione a più livelli, con fattori positivi e negativi



# CA209-067: Study Design



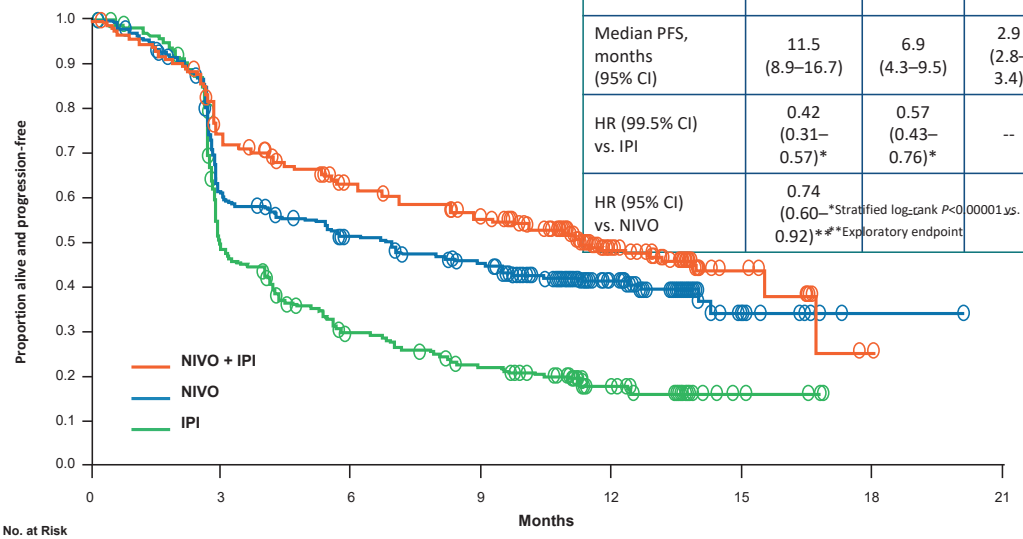

*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

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

# PFS (Intent-to-Treat)

| | 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)* | 0.57 (0.43–0.76)* | -- |
| HR (95% CI) vs. NIVO | 0.74 (0.60–0.92)** | | |

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




No. at Risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| NIVO + IPI | 314 | 219 | 173 | 151 | 65 | 11 | 1 | 0 |
| NIVO | 316 | 177 | 147 | 124 | 50 | 9 | 1 | 0 |
| IPI | 315 | 137 | 77 | 54 | 24 | 4 | 0 | 0 |

# Differenze nel rischio di effetti collaterali

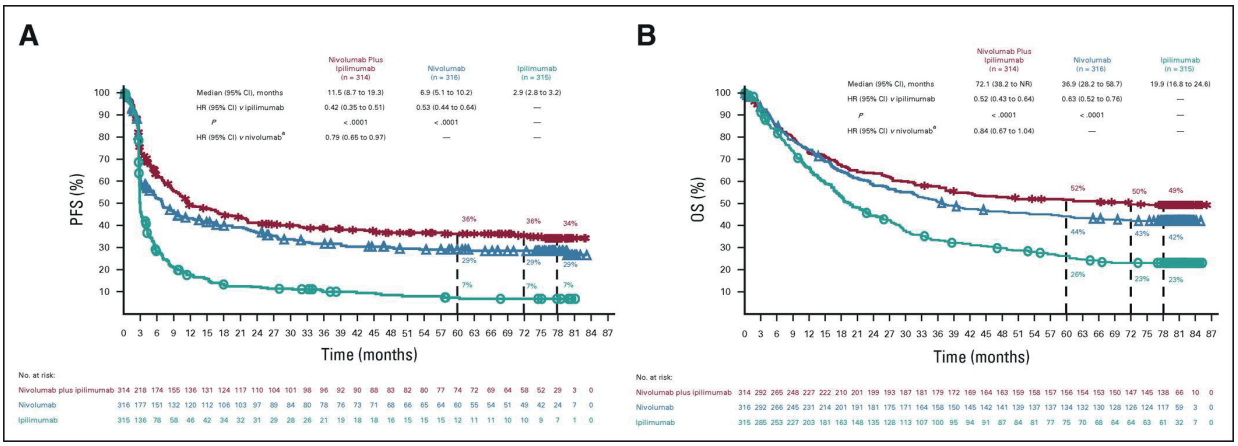
| Patients Reporting Event, % | NIVO + IPI (N=313) | | NIVO (N=313) | | IPI (N=311) | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3–4 | Any Grade | Grade 3–4 | Any Grade | Grade 3–4 |
| Treatment-related adverse event (AE) | 95.5 | 55.0 | 82.1 | 16.3 | 86.2 | 27.3 |
| Treatment-related AE leading to discontinuation | 36.4 | 29.4 | 7.7 | 5.1 | 14.8 | 13.2 |
| Treatment-related death* | 0 | | 0.3 | | 0.3 | |

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

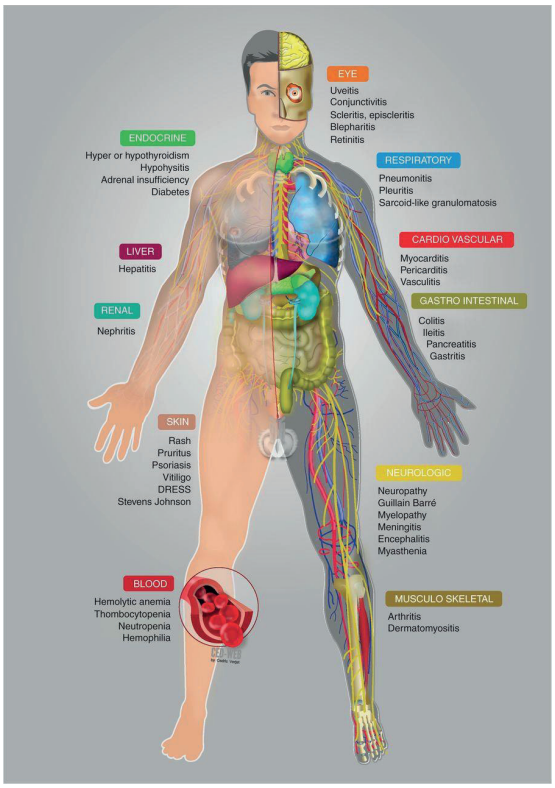


# Ipilimumab + Nivolumab: 52% sopravvivenza a 5 anni




Ultima analisi, follow-up minimo di 77 mesi

Wolchok, J Clin Oncol 2022




# Immunotossicità

-frequente: cute, intestino, fegato, ghiandole endocrine (tiroide)
-rara (ma potenzialmente fatale): polmone, cuore, rene, sistema nervoso
-potenzialmente su ogni organo

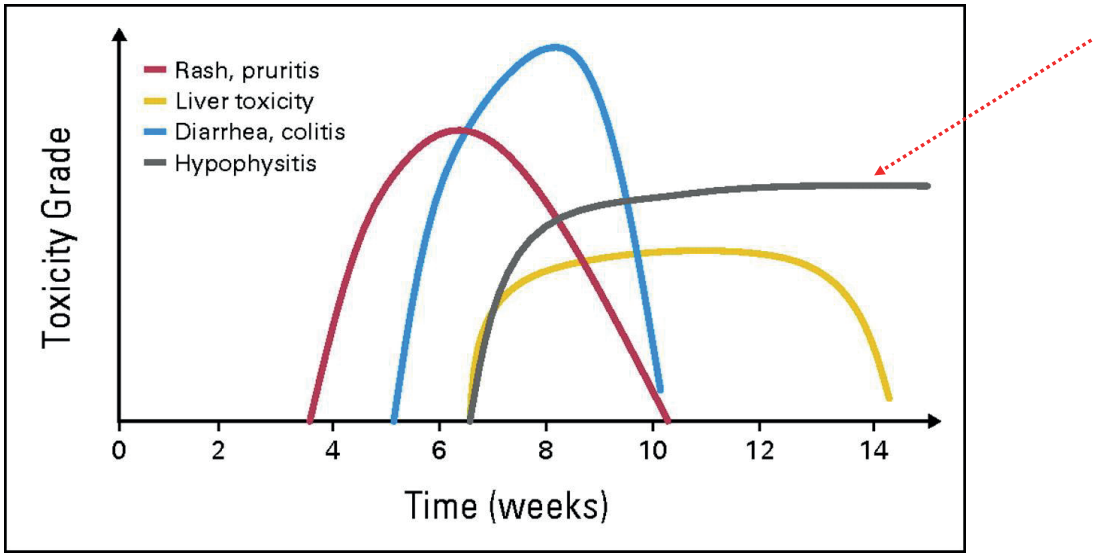
# Prevenzione:

-monitoraggio (visite, esami labor)
-attitudine pro-attiva dei curanti
-informazione del paziente

Annals of Oncology

S. Champiat et al. Ann Oncol 2016;27:559-574

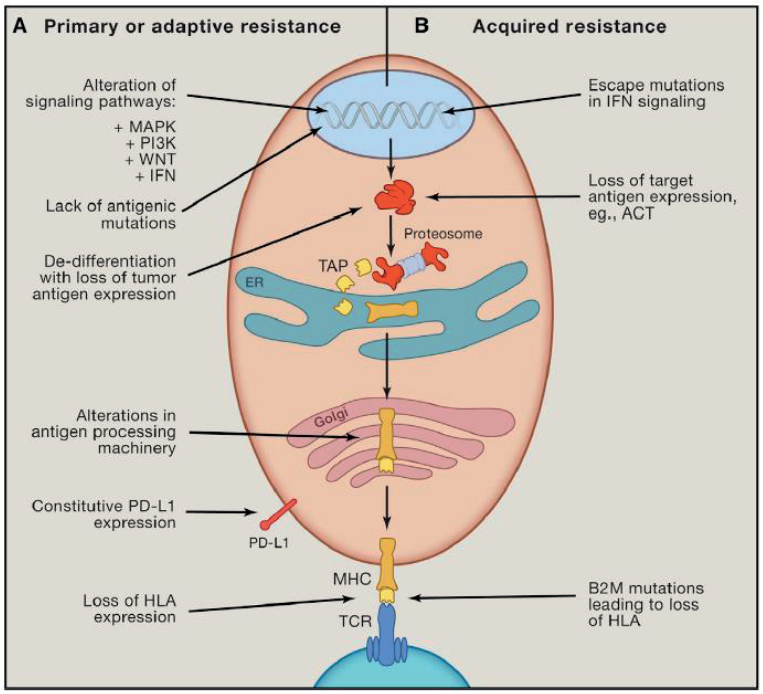
# Cinetica degli eventi avversi (ipilimumab)




Weber J S et al. JCO 2012;30:2691-2697

JOURNAL OF CLINICAL ONCOLOGY

# Resistenza all'immunoterapia: primaria e acquisita



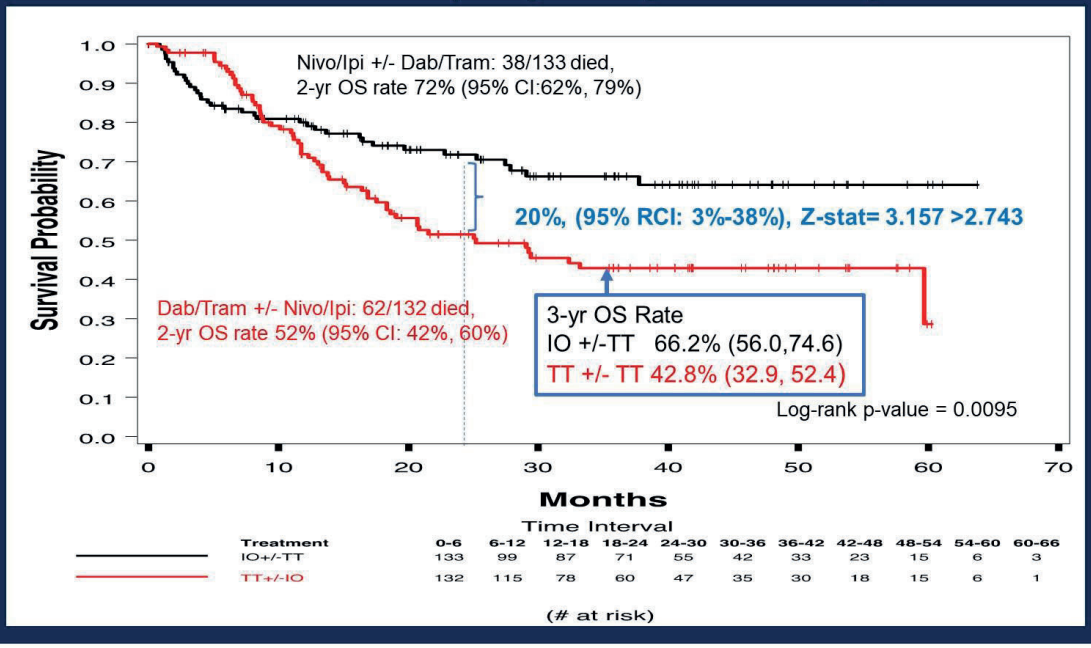

# Dati recenti di terapia sequenziale o combinata per il melanoma *BRAF*-V600 mutato

Dapprima terapia «targeted» e poi immunoterapia o l'inverso?

Utilità di una combinazione TT + IO (tripletta)?

# Overall Survival (OS): Step 1 +/- Step 2





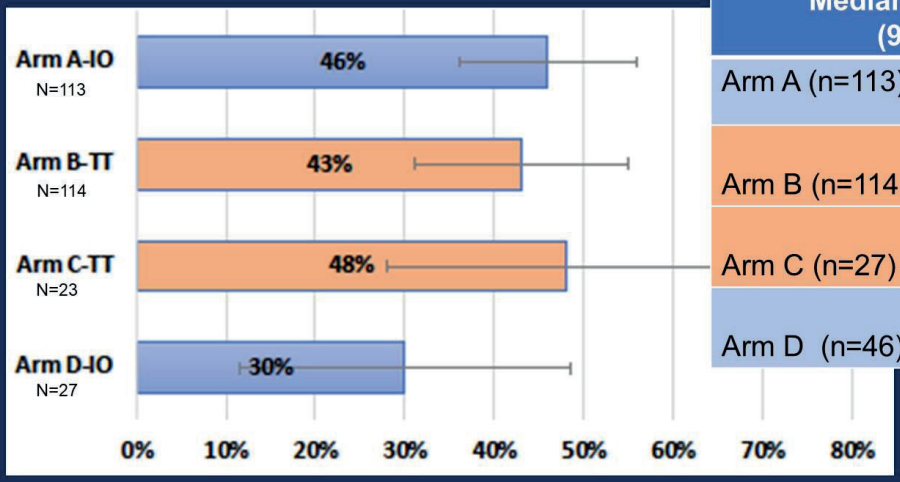




# ORR (%) By Treatment Arm*

Step 1

Step 2




| | Median PFS (Mos) (95% CI) |
|---|---|
| Arm A (n=113) | 11.8 (5.9,33.5) |
| Arm B (n=114) | 8.8 (6.5,11.3) |
| Arm C (n=27) | 9.9 (8.3. 20.6) |
| Arm D (n=46) | 2.9 (2.6, 8.9) |

*Bars represent 95% CI

Data missing on ~ 15% of pts

# E la combinazione di immunoterapia e terapia a bersaglio molecolare?

- Dabrafenib/Trametinib + Pembrolizumab or Placebo (Ascierto et al Nature Medicine, 2019)
  - Randomized phase 2, PFS primary endpoint
  - Longer median PFS (16.0 vs 10.3) and longer DOR but not statistically significant, with increase in toxicity (58% vs 27% G3-5)

- Dabrafenib + Trametinib + Spartalizumab or Placebo (Dummer et al, JCO, 2022) COMBI-I
  - Randomized phase 3, PFS primary endpoint
  - Longer median PFS (16.2 vs 12.0) but non significant, with increase in toxicity (55% vs 33% G3-5)

# Triple therapy for *BRAF*-V600 mutated melanoma

- Vemurafenib + Cobimetinib and Atezolimumab or Placebo (Gutzmer et al, Lancet Oncol 2020) IMSpire150
- Randomized (1:1), phase 3, double-blind, placebo controlled, n= 514
- Primary endpoint PFS
- No increase in ORR
- Longer PFS (15.1 vs 10.6), statistically significant (HR 0.78, CI 0.63-0.97) with increase in AE but overall tolerable (no change in treatment discontinuation)

## Attualmente «tripletta» non indicata

- Trials planned at the time when first line BRAFi/MEKi was standard (2013-2015)
- Nowadays a control group with anti-PD1 alone or in combination would be required
- Triple therapy can be a choice for patients for whom initial BRAFi/MEKi is considered (life-threatening disease)
- Longer follow-up needed to see how the tail of the curve compares with combination immunotherapy

## Conclusioni

- Due «rivoluzioni» nelle terapia medica del melanoma maligno negli ultimi 10 anni
- Le terapie con checkpoint inhibitors (in monoterapia e in combinazione) si usano in prima linea e sono adatte a tutti i pazienti (cave: tossicità, controindicazione: malattie auto-immuni «attive»)
- Le terapie a bersaglio molecolare si rivolgono ai pazienti con mutazione V600 di *BRAF* e si usano in genere in seconda linea
- La prognosi dei pazienti è notevolmente migliorata; tuttavia restano molti margini di ulteriore miglioramento (malattia con rapida crescita, metastasi cerebrali, pazienti recidivanti e refrattari)

*Grazie per l'attenzione!*

Dr. Med. Vito Spataro
Oncologia-Ematologia
Bellinzona