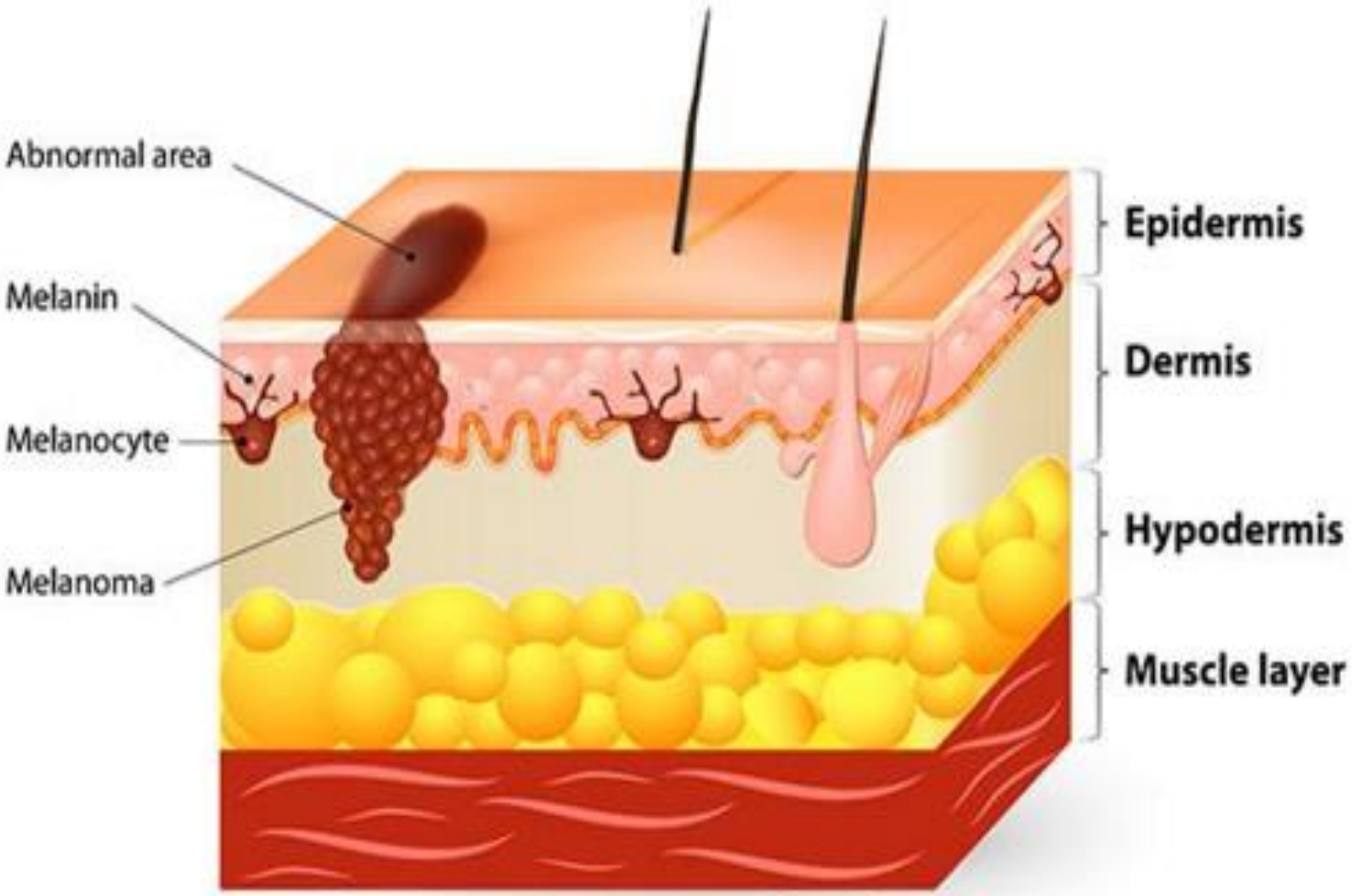
INIBITORE di BRAF nel MELANOMA

Paola Agnese Cassandrini

Negrar,29 novembre 2016

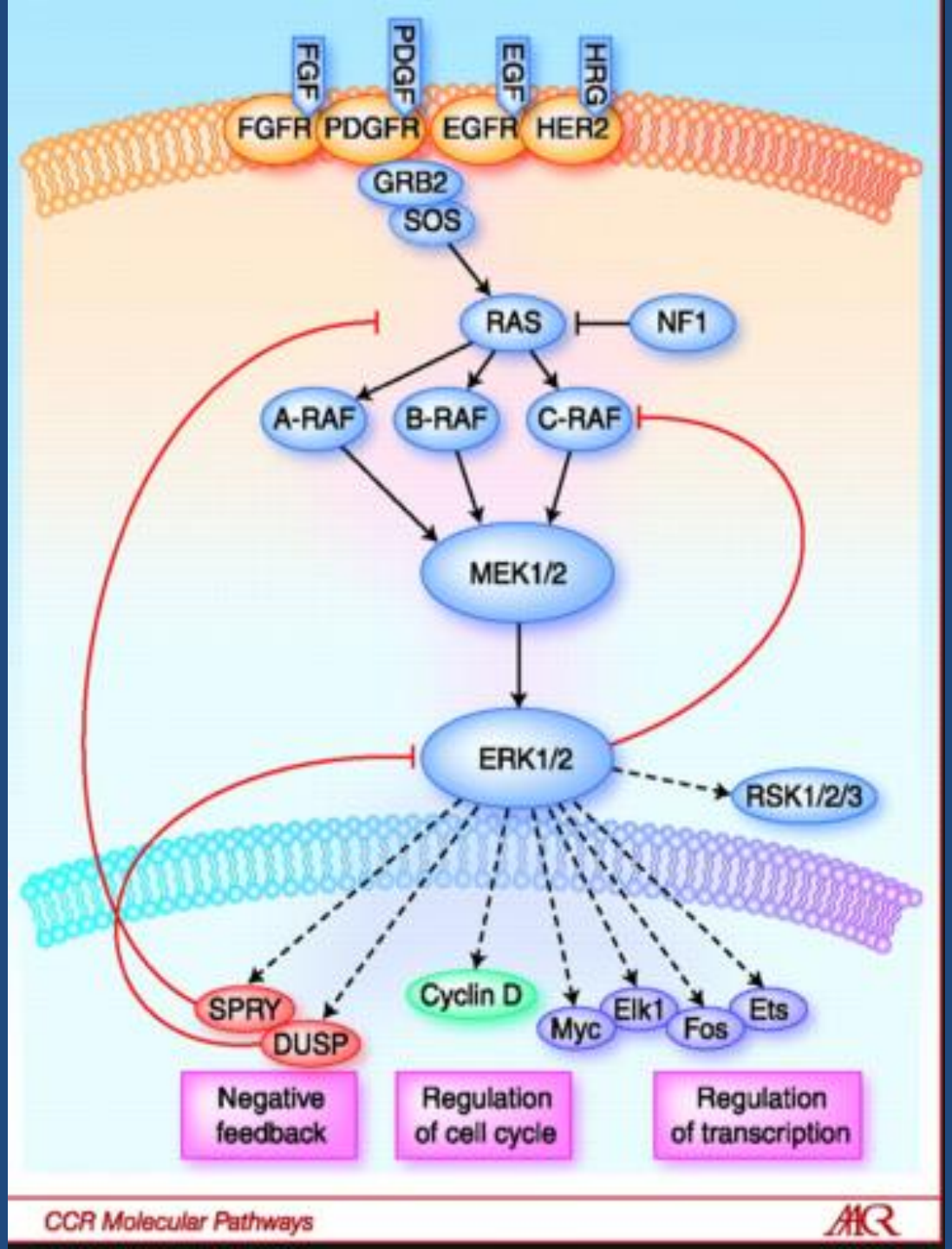
MELANOMA


Abnormal area
Melanin
Melanocyte
Melanoma
Epidermis
Dermis
Hypodermis
Muscle layer

BRAF is a serine/threonine protein kinasi

encoded on chromosome 7q34

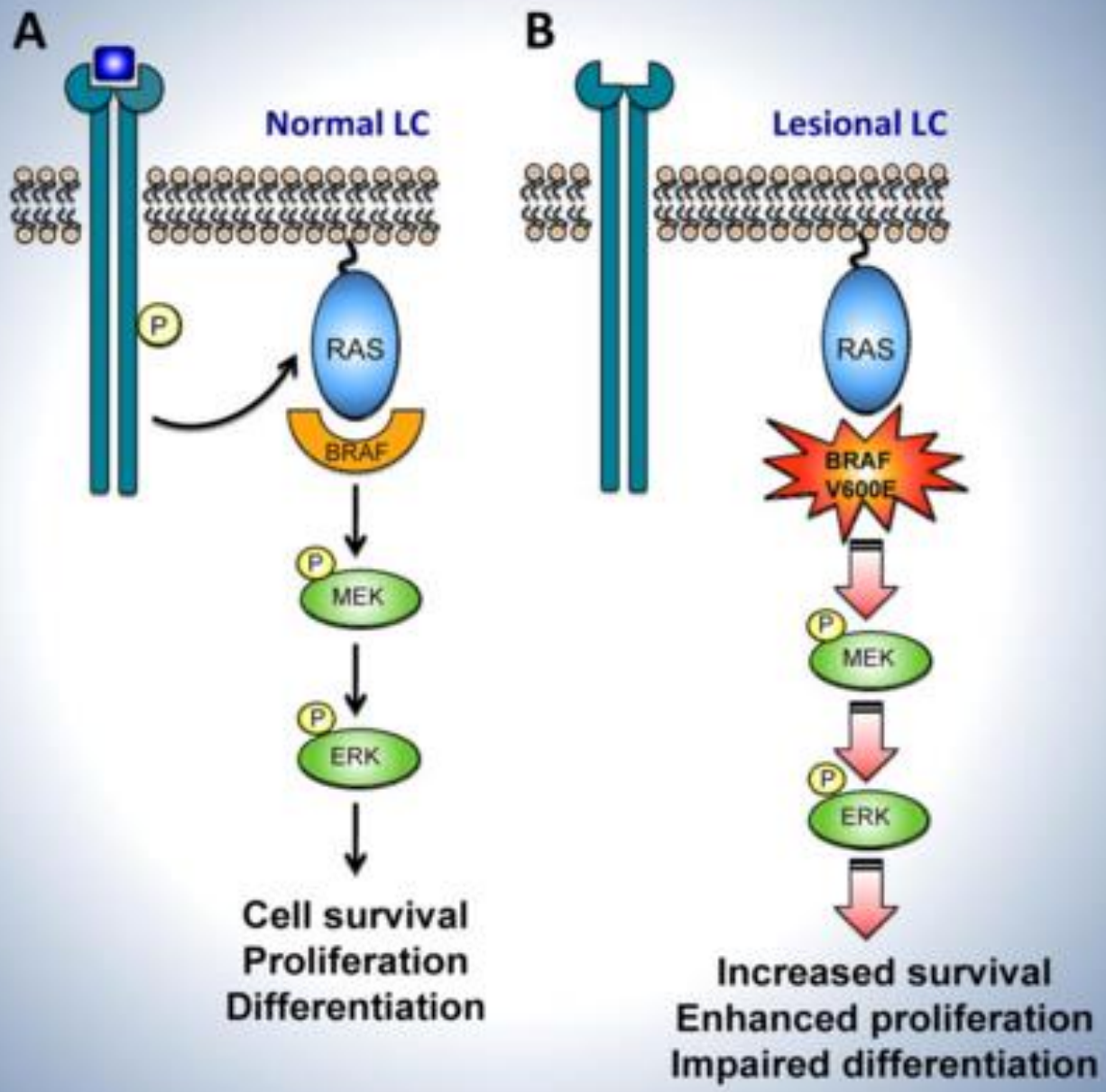
that activates the MAP kinase/ERK-segnaling pathway

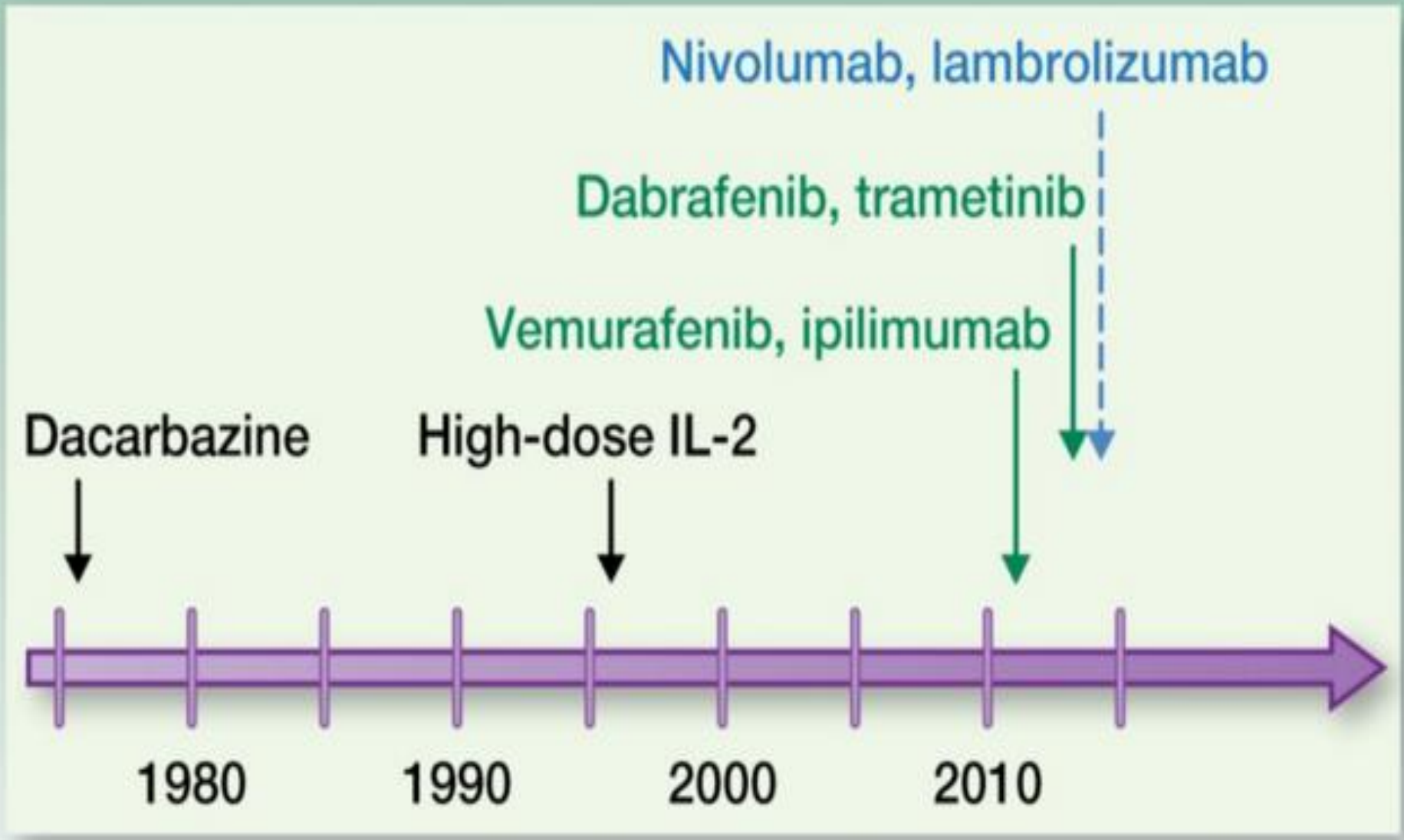

FGF
PDGF
EGF
HRG
FGFR
PDGFR
EGFR
HER2
GRB2
SOS
RAS
NF1
A-RAF
B-RAF
C-RAF
MEK1/2
ERK1/2
RSK1/2/3
SPRY
DUSP
Cyclin D
Myc
Elk1
Fos
Ets
Negative feedback
Regulation of cell cycle
Regulation of transcription

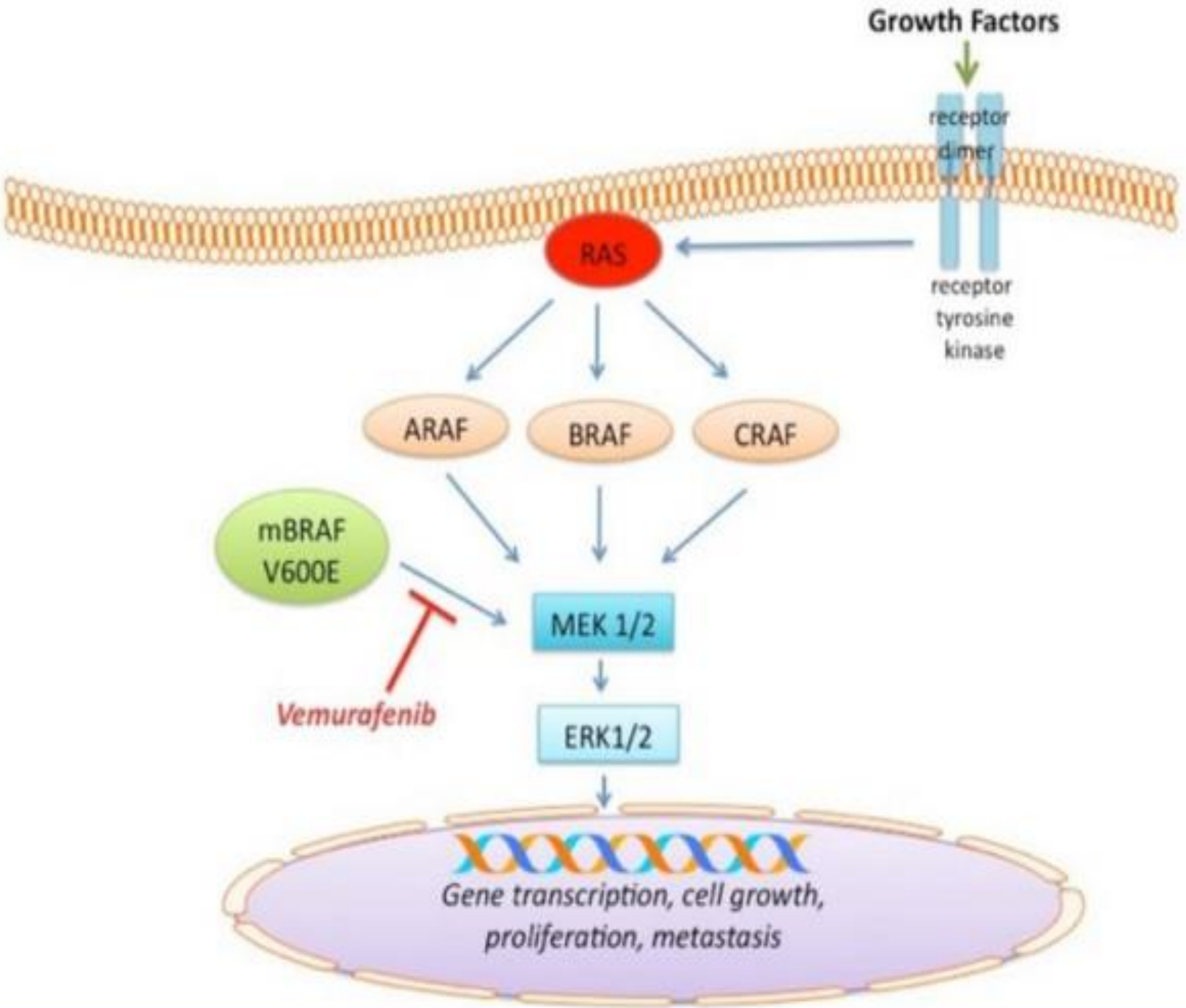
Circa il 50% dei melanomi hanno mutazioni di BRAF

Tra le mutazioni di BRAF osservate nel melanoma circa il 90% sono nel codone 600 e tra queste circa il 90% sono mutazioni di un singolo nucleotide che si esplicita con la sostituzione di una valina con un acido glutammico (BRAFV600E)

La seconda mutazione più comune è la sostituzione di una valina con una lisina (BRAFV600K)


A
Normal LC
P
RAS
BRAF
P
MEK
P
ERK
Cell survival
Proliferation
Differentiation
B
Lesional LC
RAS
BRAF
V600E
P
MEK
P
ERK
Increased survival
Enhanced proliferation
Impaired differentiation




Growth Factors
receptor dimer
RAS
receptor tyrosine kinase
ARAF
BRAF
CRAF
mBRAF V600E
MEK 1/2
Vemurafenib
ERK1/2
Gene transcription, cell growth, proliferation, metastasis

Phase III randomized, open-label, multicenter trial (BRIM3) comparing BRAF inhibitor vemurafenib with dacarbazine (DTIC) in patients with ^{V600E}BRAF-mutated melanoma.

2011 ASCO Annual Meeting

Safety and efficacy of vemurafenib in *BRAF*^{V600E} and *BRAF*^{V600K}mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study

The LANCET Oncology Volume 15, No. 3, p323–332, March 2014

675 patients were enrolled from 104 centres in 12 countries between Jan – Dec 2010.

337 pz vemurafenib
338 pz dacarbazine.

Median overall survival: vemurafenib 13,6 months
dacarbazine 9·7 months

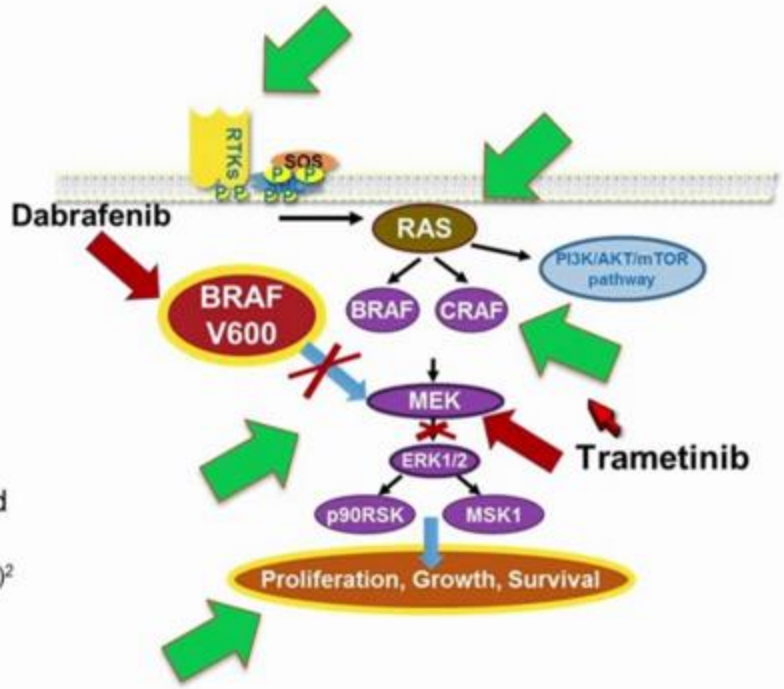
median progression-free survival : vemurafenib 6·9 months
dacarbazine 1·6 months

For the 598 (91%) patients with *BRAF*^{V600E} disease,
median overall survival : vemurafenib 13·3 months
I dacarbazine 10,0 months
median progression-free survival :
vemurafenib 6·9 months
dacarbazine 1·6 months

For the 57 (9%) patients with*BRAF*^{V600K} disease,
median overall survival :
vemurafenib 14·5 months
dacarbazine group 7,6 months

BRAF and Dabrafenib

- BRAF
  - Protein kinase
  - Active in regulating RAS/RAF/MEK/ERK signaling pathway, which regulates cell growth
- *BRAF* mutations commonly cause cancer[1]
- Dabrafenib
  - Orally available, selective ATP-competitive inhibitor of BRAFV600-mutated kinase
  - Approved in multiple countries in adults with unresectable or metastatic BRAFV600-mutated melanomas
    - Approval based on pivotal phase 3 clinical trial (BREAK-3)[2]
    - Adult dose of 150 mg capsule twice a day based on pharmacokinetics, pharmacodynamic endpoints[3], and favorable benefit risk[2]



1. Davies H, *et al.*, *Nature* 2002417:949–954; 2. Hauschild A, et al., *Lancet* 2012;380:358-365; 3. Falchook GS, *et al.*, *Lancet* 2012;379:1893-1901.

Lancet. 2012 Jul 28;380(9839):358-65.

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

250 patients

187 pz dabrafenib (150 mg x 2/die)

63 pz dacarbazine (1000 mg/mq 21g)

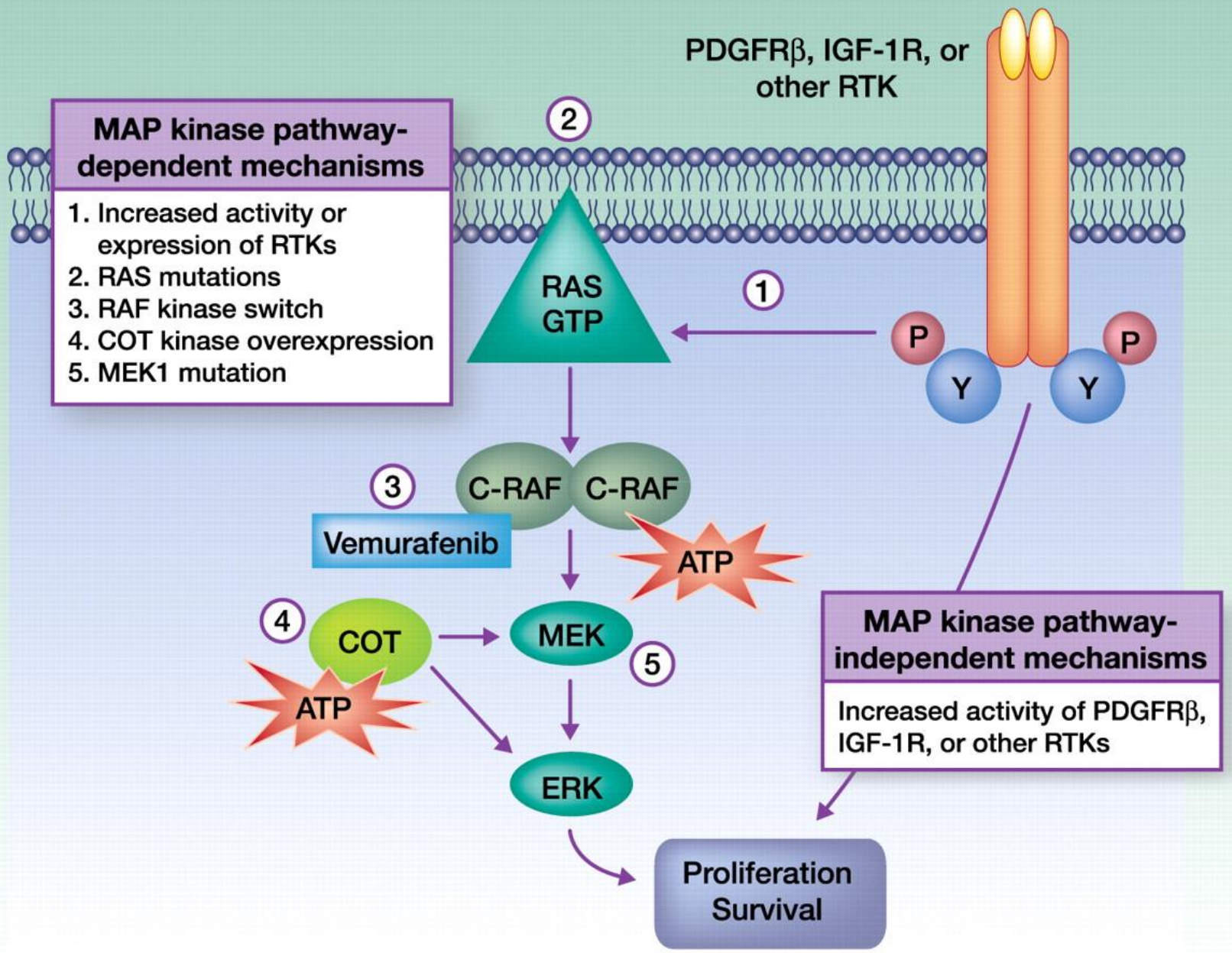
Median progression-free survival :

dabrafenib 5,1 months

dacarbazine 2,7 months

INTERPRETATION:

Dabrafenib significantly improved progression-free survival compared with dacarbazine.



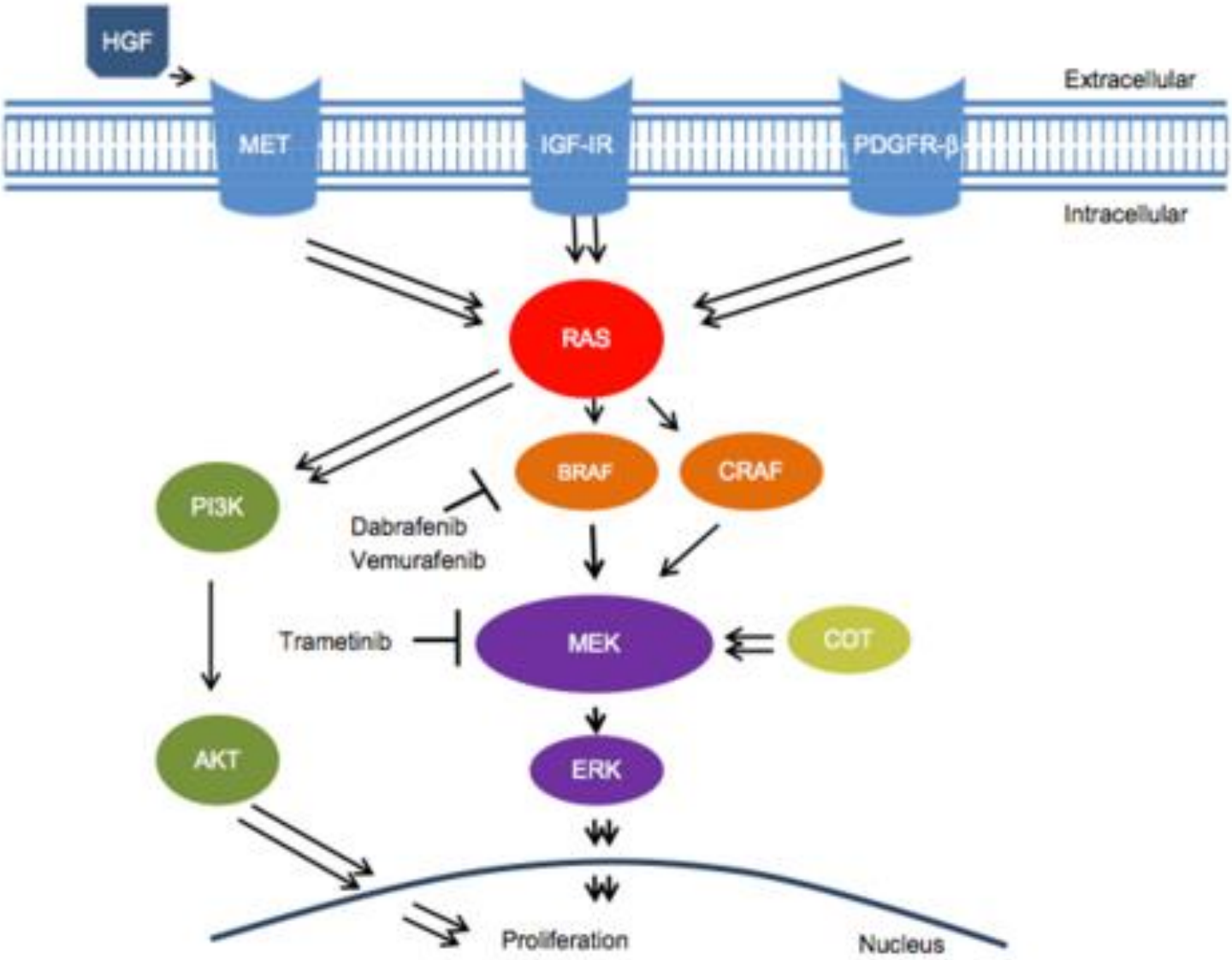


Figure 1 Redundancy of the MAPK signaling cascade and targeted inhibitors. Single arrows signify direct pathways. Double arrows reflect a culmination of multiple steps in the signaling cascade.

Note: Adapted from *Cancer Discov*, copyright 2013, 3(5), 487–490, Girotti MR, Marais R, Déjà vu: EGF receptors drive resistance to BRAF inhibitors, with permission from AACR.[19]

Abbreviations: HGF, human growth factor; IGF-IR, insulin-like growth factor 1 receptor; PDGFR-β, platelet-derived growth factor-β; PI3K, phosphoinositide 3-kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase.

Trametinib is a potent, highly specific inhibitor of MEK1/MEK2

N Engl J Med. 2012 Jul 12

Improved survival with MEK inhibition in BRAF-mutated melanoma.

Flaherty KT, Robert C, Hersey P, Nathan P, et al.METRIC Study Group.

phase 3 open-label trial

322 patients who had metastatic melanoma with a V600E or V600K BRAF mutation

- trametinib (2 mg orally) once daily
- or intravenous dacarbazine (1000 mg per square meter of body-surface area
- or paclitaxel (175 mg per square meter) every 3 weeks.

Patients in the chemotherapy group who had disease progression were permitted to cross over to receive trametinib. Progression-free survival was the primary end point, and overall survival was a secondary end point.

Median progression-free survival :

4.8 months in the trametinib group

1.5 months in the chemotherapy group

At 6 months, the rate of overall survival was 81% in the trametinib group and 67% in the chemotherapy group despite crossover

Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty, M.D., Jeffery R. Infante, M.D., Adil Daud, M.D., Rene Gonzalez, M.D., Richard F. Kefford, M.D., Ph.D., Jeffrey Sosman, M.D., Omid Hamid, M.D., Lynn Schuchter, M.D., Jonathan Cebon, M.D., Ph.D., Nageatte Ibrahim, M.D., Ragini Kudchadkar, M.D., Howard A. Burris, III, M.D., Gerald Falchook, M.D., Alain Algazi, M.D., Karl Lewis, M.D., Georgina V. Long, M.D., Ph.D., Igor Puzanov, M.D., M.S.C.I., Peter Lebowitz, M.D., Ph.D., Ajay Singh, M.D., Shonda Little, M.P.H., Peng Sun, Ph.D., Alicia Allred, Ph.D., Daniele Ouellet, Ph.D., Kevin B. Kim, M.D., Kiran Patel, M.D., M.B.A., and Jeffrey Weber, M.D., Ph.D.

N Engl J Med 2012; 367:1694-1703 | November 1, 2012 | DOI: 10.1056/NEJMoa1210093

In this open-label study involving 247 patients with metastatic melanoma and BRAF V600 mutations, we evaluated the pharmacokinetic activity and safety of oral dabrafenib (75 or 150 mg twice daily) and trametinib (1, 1.5, or 2 mg daily) in 85 patients and then randomly assigned 162 patients to receive combination therapy with dabrafenib (150 mg) plus trametinib (1 or 2 mg) or dabrafenib monotherapy. The primary end points were the incidence of cutaneous squamous-cell carcinoma, survival free of melanoma progression, and response. Secondary end points were overall survival and pharmacokinetic activity.

Dose-limiting toxic effects were infrequently observed in patients receiving combination therapy with 150 mg of dabrafenib and 2 mg of trametinib (combination 150/2).

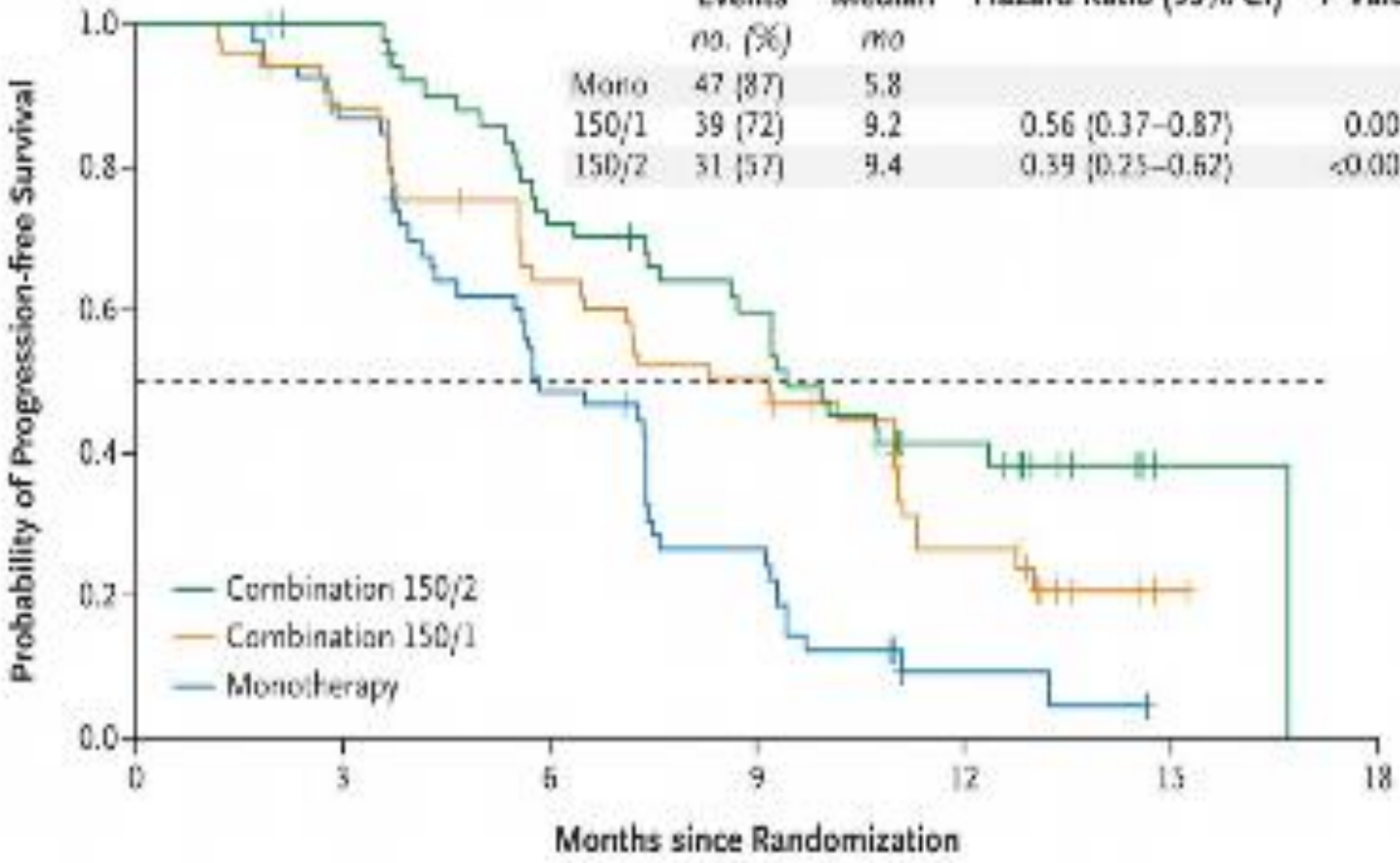
Cutaneous squamous-cell carcinoma was seen in 7% of patients receiving combination 150/2 and in 19% receiving monotherapy ,

whereas pyrexia was more common in the combination 150/2 group than in the monotherapy group (71% vs. 26%).

Median progression-free survival in the combination 150/2 group was 9.4 months, as compared with 5.8 months in the monotherapy group .

The rate of complete or partial response with combination 150/2 therapy was 76%, as compared with 54% with monotherapy .

A Progression-free Survival



	Events no. (%)	Median mo	Hazard Ratio (95% CI)	P Value
Mono	47 (87)	5.8		
150/1	39 (72)	9.2	0.56 (0.37–0.87)	0.006
150/2	31 (57)	9.4	0.39 (0.25–0.62)	<0.001

No. at Risk						
Monotherapy	54	46	25	13	2	0
Combination 150/1	54	47	33	26	11	1
Combination 150/2	54	52	36	29	15	1

Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous *BRAF*Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial

The Lancet Oncology volume 16 October2015

COMBI-v was an open-label, randomised phase 3 study
704 pz with metastatic melanoma with a *BRAF* Val600 mutation
352 pz combination of dabrafenib (150 mg twice-daily) and trametinib (2 mg once-daily)
352 vemurafenib monotherapy (960 mg twice-daily) orally as first-line therapy.
The primary endpoint was overall survival. I

treatment with the combination of a BRAF inhibitor plus a MEK inhibitor (dabrafenib plus trametinib) adds a clear benefit over monotherapy with the BRAF inhibitor vemurafenib


GRAZIE

Nivolumab is an anti-PD-1 drug, which is an antibody that promotes the tumor-killing effects of T-cells (white blood cells that help your body fight disease).

Ipilimumab is an anti-CTLA-4 drug, which is an antibody that helps strengthen the immune system by promoting the function and growth of T-cells.

Both medications:
Are a type of immunotherapy known as checkpoint inhibitors, a type of immunotherapy that energizes your body's own immune system to attack the cancer cells
Help slow or stop the growth and spread of melanoma cells

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

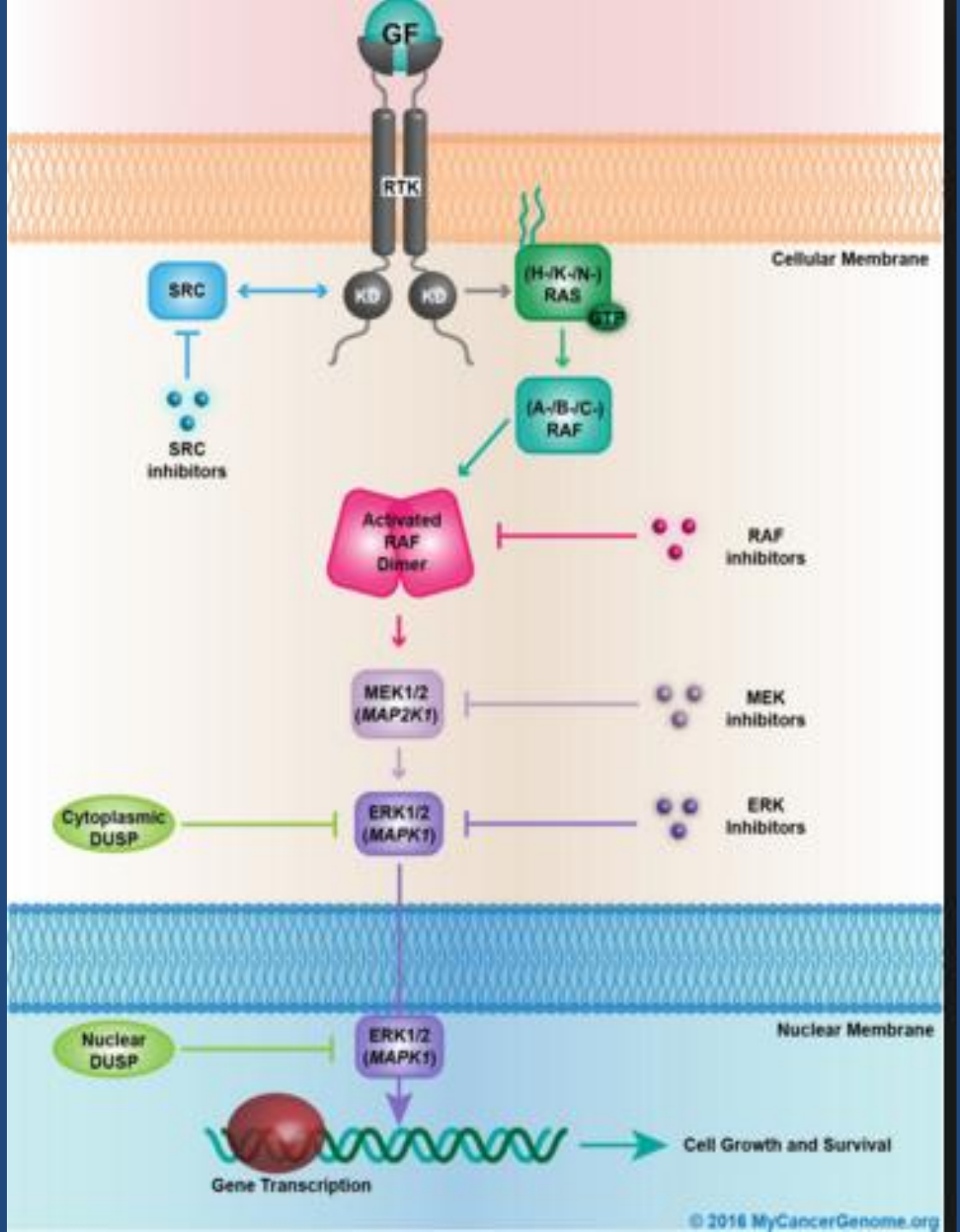
N Engl J Med 2015; 373:23-34July 2, 2015

in a 1:1:1 ratio, 945 previously untreated patients with unresectable stage III or IV melanoma
to nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone.

The median progression-free survival :

11.5 months nivolumab plus ipilimumab,
2.9 months with ipilimumab
6.9 months with nivolumab

In patients with tumors positive for the PD-1 ligand (PD-L1), the median progression-free survival was 14.0 months in the nivolumab-plus-ipilimumab group and in the nivolumab group, but in patients with PD-L1–negative tumors, progression-free survival was longer with the combination therapy than with nivolumab alone (11.2 months)


GF
RTK
Cellular Membrane
SRC
KD
KD
(H-/K-/N-) RAS
GTP
SRC inhibitors
(A-/B-/C-) RAF
Activated RAF Dimer
RAF inhibitors
MEK1/2 (MAP2K1)
MEK inhibitors
Cytoplasmic DUSP
ERK1/2 (MAPK1)
ERK inhibitors
Nuclear Membrane
Nuclear DUSP
ERK1/2 (MAPK1)
Gene Transcription
Cell Growth and Survival
© 2016 MyCancerGenome.org

ORIGINAL ARTICLE

Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

N Engl J Med 2016; 375:1845-1855 | November 10, 2016

Ipilimumab at a dose of 10 mg per kilogram (475 patients) or placebo (476) every 3 weeks for four doses, then every 3 months for up to 3 years or until disease recurrence or an unacceptable level of toxic effects occurre

At a median follow-up of 5.3 years, the 5-year rate of recurrence-free survival :

40.8% in the ipilimumab

30.3% in the placebo group

The rate of overall survival at 5 years:

65.4% in the ipilimumab group

54.4% in the placebo group

The rate of distant metastasis–free survival at 5 years :

48.3% in the ipilimumab group

38.9% in the placebo group

Adverse events of grade 3 or 4:

in 54.1% of the patients in the ipilimumab

26.2% of those in the placebo group.

Immune-related adverse events of grade 3 or 4

in 41.6% of the patients in the ipilimumab

in 2.7% of those in the placebo

In the ipilimumab group, 5 patients (1.1%) died owing to immune-related adverse events