

Managing Skin toxicity from targeted agents

Caroline Robert

IGR

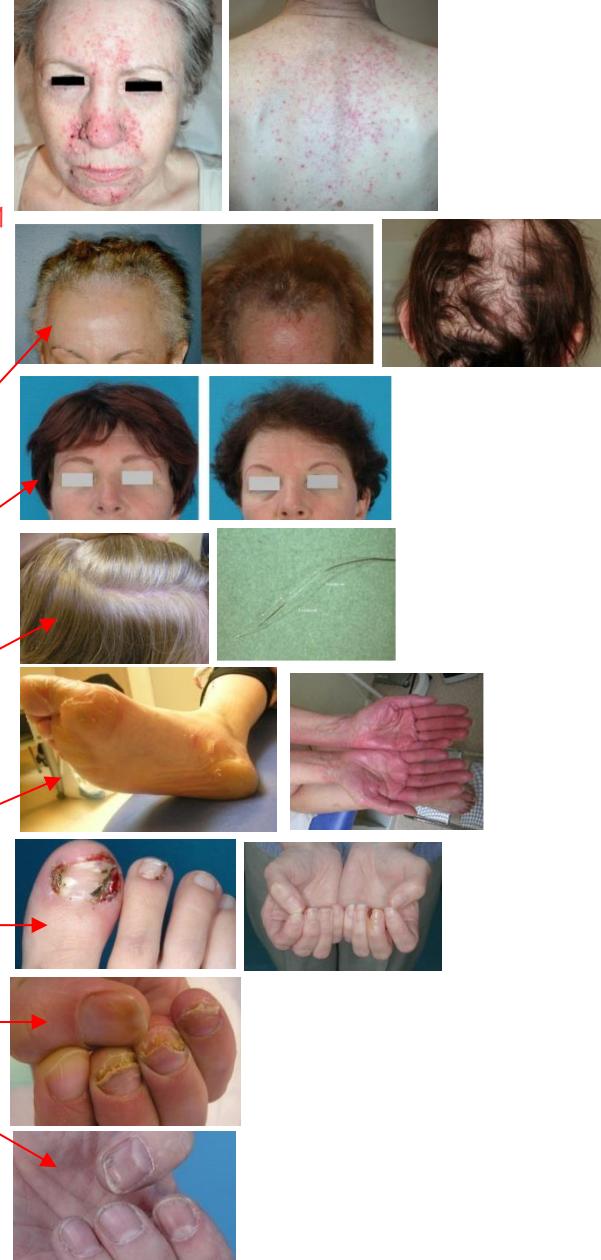
Villejuif/paris-Sud

Disclosure slide

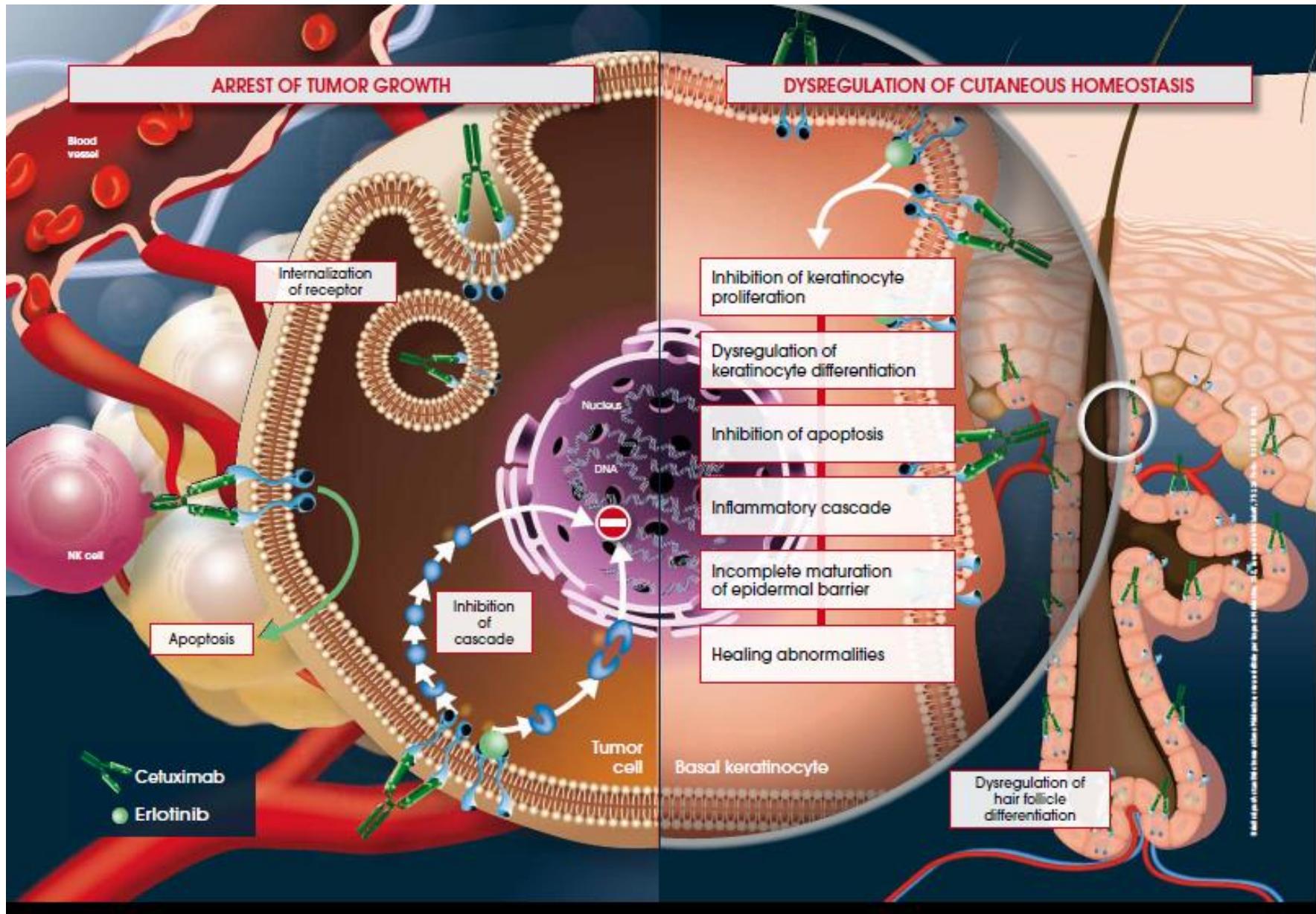
- Consultant for MSD, BMS, Amgen, Novartis, Amgen

Study of targeted agent-induced skin side effects

	Frequency	Symptoms	Frequency
Skin	78%	Folliculitis	71%
		Xerosis	25%
		Maculo-papular eruption	28%
Hair	31%	Alopecia	20%
		Hair texture alteration	12%
		Color modification	5%
Mucosae			18%
Hand-Foot Skin reaction			26%
Nail	30%	Paronychia	13%
		Onycholysis	9%
		Sub-ungueal hemorrhage	4%

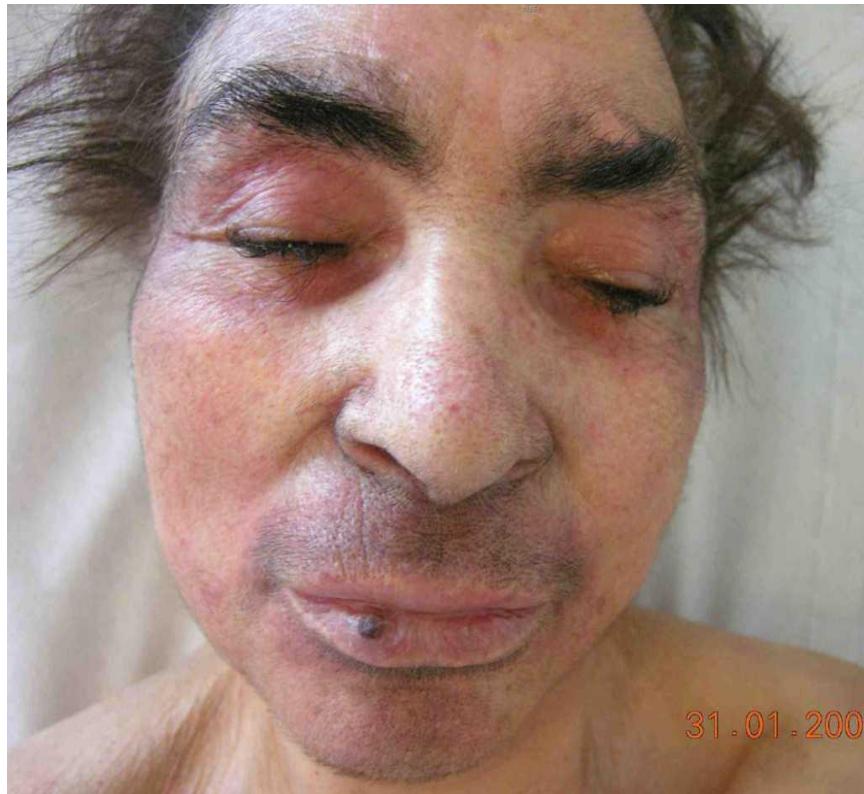


EGFR inhibitors



EGFRi skin toxicity

Symptoms	Incidence % (grades III-IV)	Delay (weeks)	Site	
Folliculitis	60-100 (5-20)	1-3	Face, trunc	
xerosis	15-35	2-4	fingers diffuse	
paronychia	10-20	4-8	>1 st toenail	
Hair modification	100	4-8	Scalp (fuzzy hair, frontal alopecia), Facial hair and eyelashes growth	

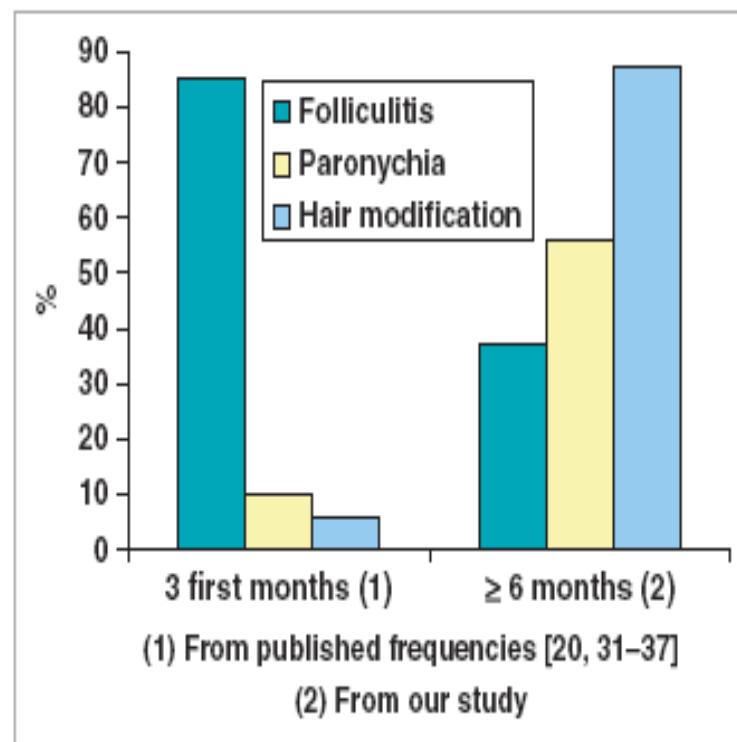


C Robert et al, Lancet Oncology 2005

(a)



3 months



(b)



12 months

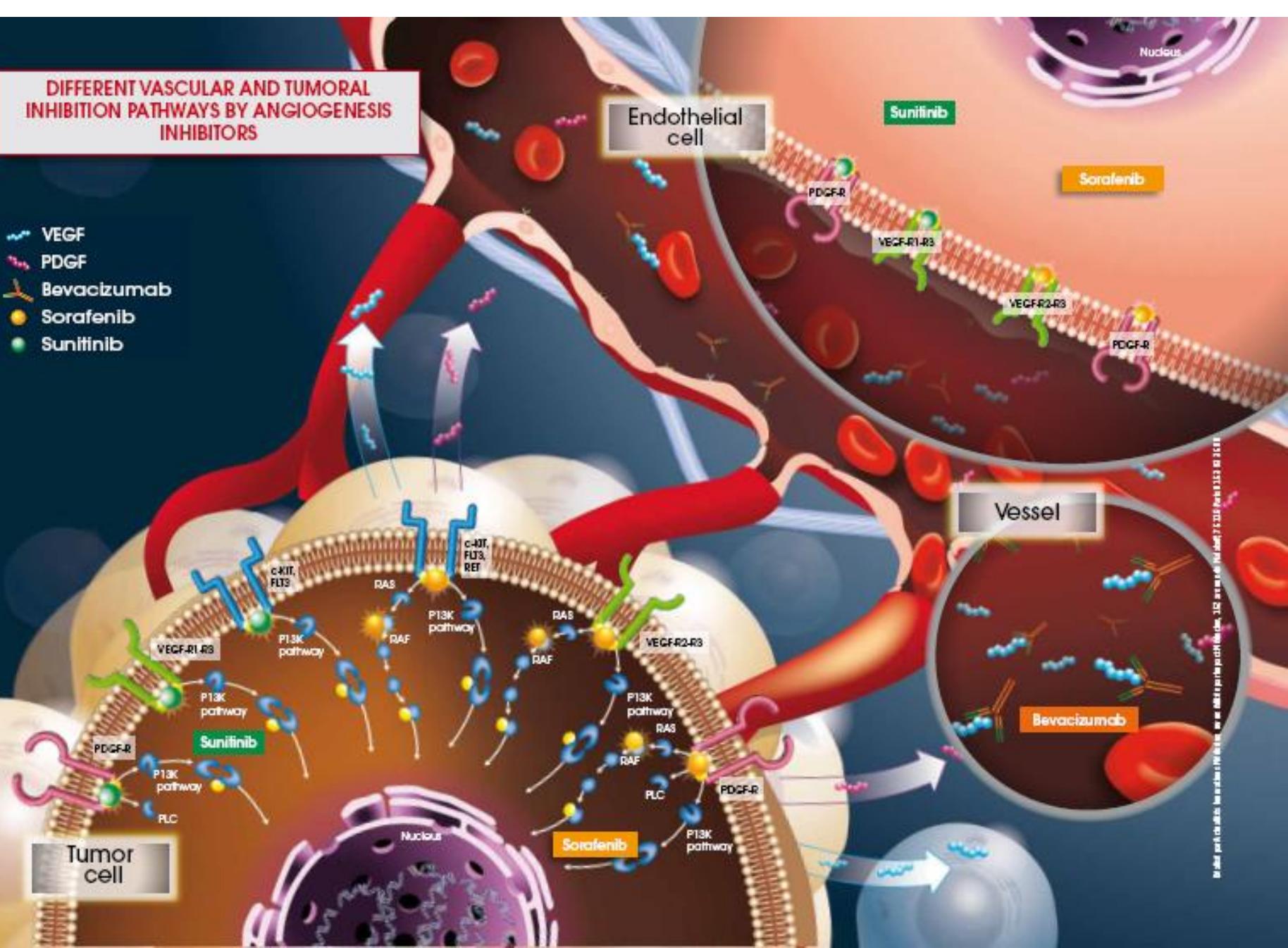


Osio et al, British J Dermatol



DIFFERENT VASCULAR AND TUMORAL INHIBITION PATHWAYS BY ANGIOGENESIS INHIBITORS

- VEGF
- PDGF
- Bevacizumab
- Sorafenib
- Sunitinib



Sorafenib associated skin manifestations

Symptoms	Incidence	Time to occurrence (weeks)	Comments	
Facial rash	> 60%?	1-2	+ paresthesia	 
Subungual hemorrhages	60	4-8	Reversible	 
HFSR	30	2-3	+ paresthesia	
Hair modification	100?	6-12	Reversible alopecia curly regrowth	 

Sorafenib skin adverse reactions

Symptoms	Incidence	Time to occurrence	Comments	
Eruptive nevi	?	3-24 months		
KA, KA-SCC	6-7%	3-9 months	multiple	
Genital rash	?	3-4 weeks	Both males and females	
hypersensitivity rash	?	Days-weeks		

Hand Foot Skin Reaction to Regorafenib





7.58



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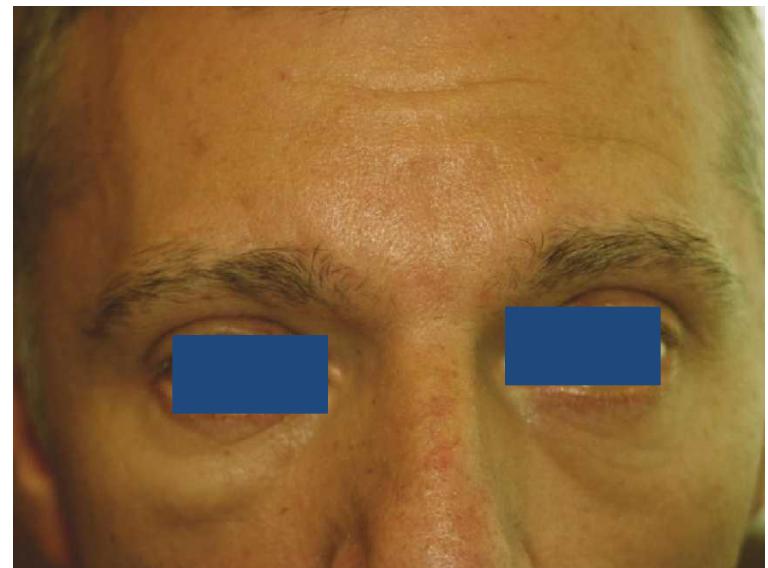
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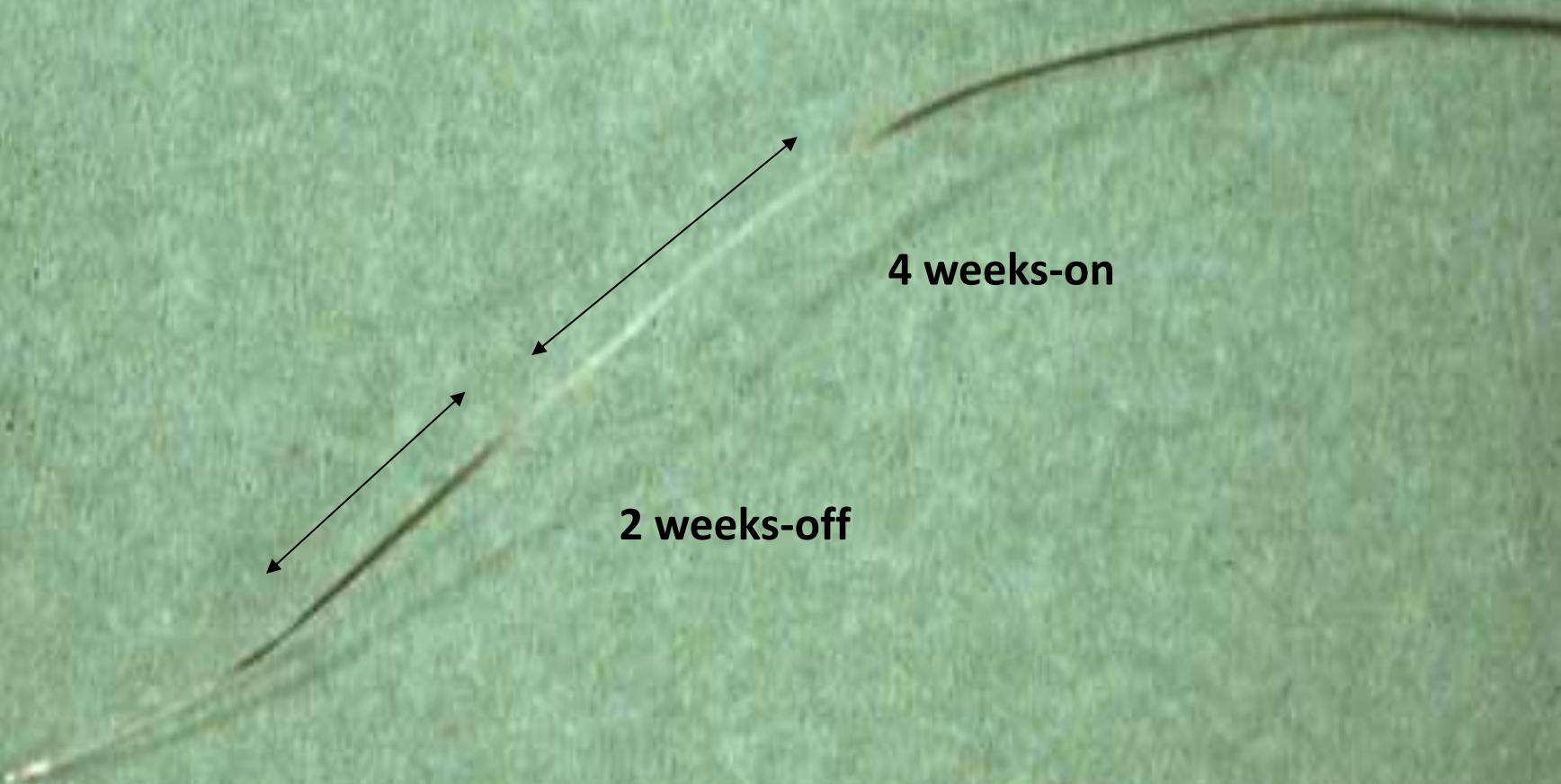


Sunitinib; Yellow-skin



Sunitinib; Reversible hair depigmentation





Robert et al, Lancet, 2003

facial erythema

Cysts, KA, SCC

Eruptive nevi

HFSR

**Subungual
hemorrhages**

Genital rash

Yellow skin

**Hair
depigmentation**

Sorafenib

Sunitinib

Correlation between targeted molecules and skin manifestation

Drug	sorafenib	sunitinib	imatinib	Vandetanib	trametinib
targets	VEGFR 1-3 RAF PDGFR, FLT3	VEGFR1-3, KIT, PDGFR FLT3	KIT, PDGFR	Met VEGFR EGFR	MEK
KA, SCC	+	--	-	-	-
Nevi	+	-	-	-	-
HFSR	++	+	-	+	?
Folliculitis	+/-	+/-	-	++	++
Hair	Alopecia, curly	depigmentation		+	+
paronychia	-	-	-	+	+
skin colour	Red (face)	yellow	+ or -	Blue dots	NI
oedema	-	+	+	-	+
SUH	+	+	-	+	-

Correlation between targeted molecules and skin manifestation

Drug	sorafenib	sunitinib	imatinib	Vandetanib	trametinib
targets	VEGFR 1-3 RAF PDGFR, FLT3	VEGFR1-3, KIT, PDGFR FLT3	KIT, PDGFR	Met VEGFR EGFR	MEK
KA, SCC	+	--	-	-	-
Nevi	+	-	-	-	-
HFSR	++	+	-	+	?
Folliculitis	+/-	+/-	-	++	++
Hair	Alopecia, curly	depigmentation		+	+
paronychia	-	-	-	+	+
skin colour	Red (face)	yellow	+ or -	Blue dots	NI
oedema	-	+	+	-	+
SUH	+	+	-	+	-

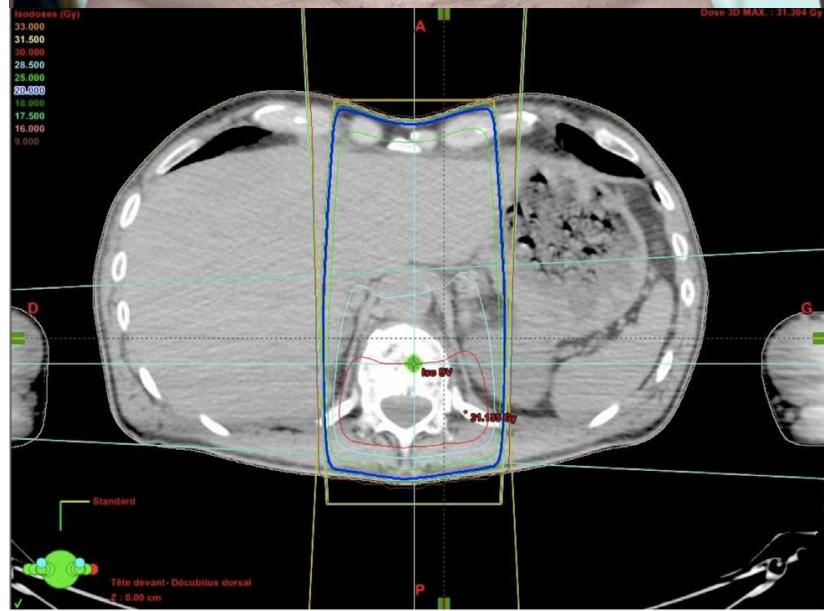
BRAF-I-associated skin manifestations (1)

Symptoms	Incidence vemu %	Incidence dabra%	Comments	
Rash	37-52 Grade 3: 6-8	22	Maculopapular Keratosis pilaris	
Photosensitivity	33-49	3	UVA-induced	
HFSR hyperkeratosis	10-50	50	Rubbing, pressure areas	
Hair modification Alopecia	100 8	100	Can be reversible	

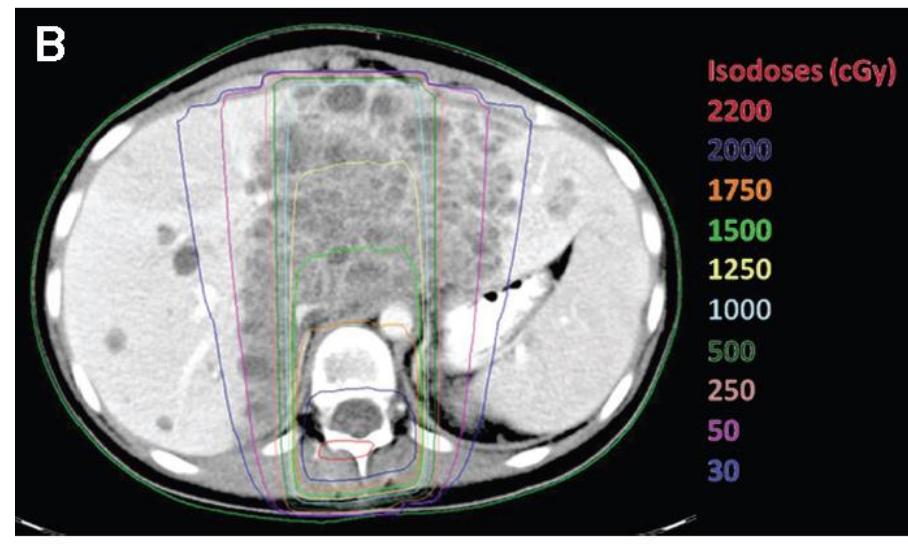
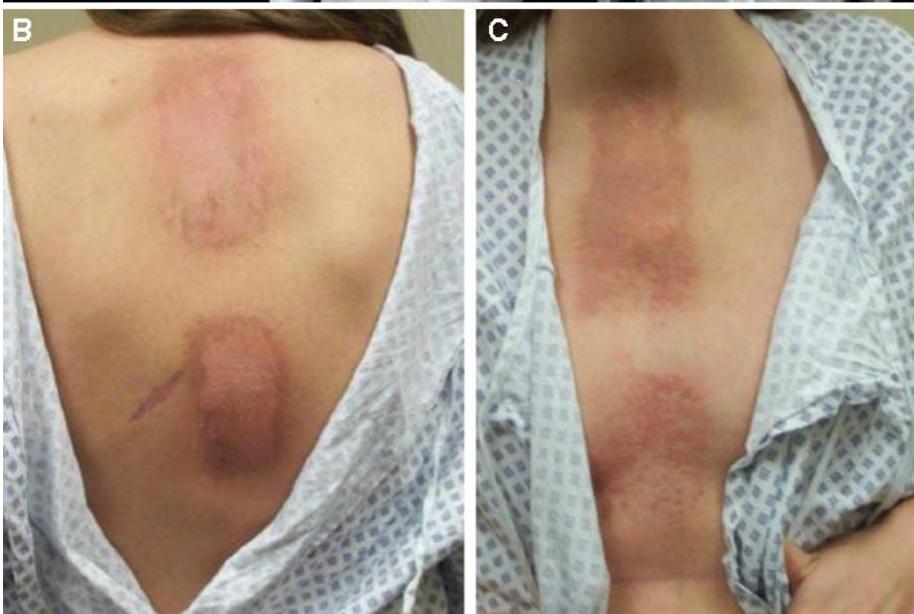
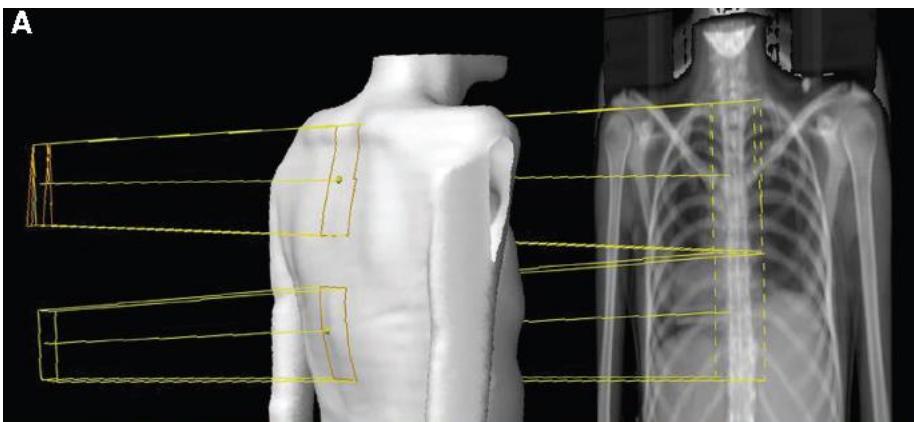
BRAF-I-associated skin manifestations (2)

Symptoms	Incidence Vemu%	Incidence dabra%	Comments	
Cystic lesions	30%	?	Multiple, face	 
Papillomas Warts	20-50	?	Multiple	 
Keratoacanthomas SCC	20-30	7	Multiple	 
Eruptive navi Melanomas	?	?	Median time to occurrence 6-8 wks	 

Radiosensitization & radiation recall



Radiosensitization: liver toxicity



Correlation : targeted molecules and skin manifestation

Drug	sorafenib	imatinib	trametinib	Vemurafenib
targets	VEGFR1-3 RAF, PDGFR	KIT, PDGFR	MEK	RAF
KA, SCC	+	-	-	++
Nevi	+	-	-	+
HFSR	++	-	-	+
Folliculitis	+/-	-	++	+/-
Hair	Alopecia, curly		+	+
paronychia	-	-	+	-
skin colour	Red (face)	Pigment +/-	NI	Red (face)
Photosensitivity	-	-	-	+

Vemurafenib

Photosensitivity

facial erythema
Hair modif
Cysts, KA, SCC
Eruptive nevi

HFSR

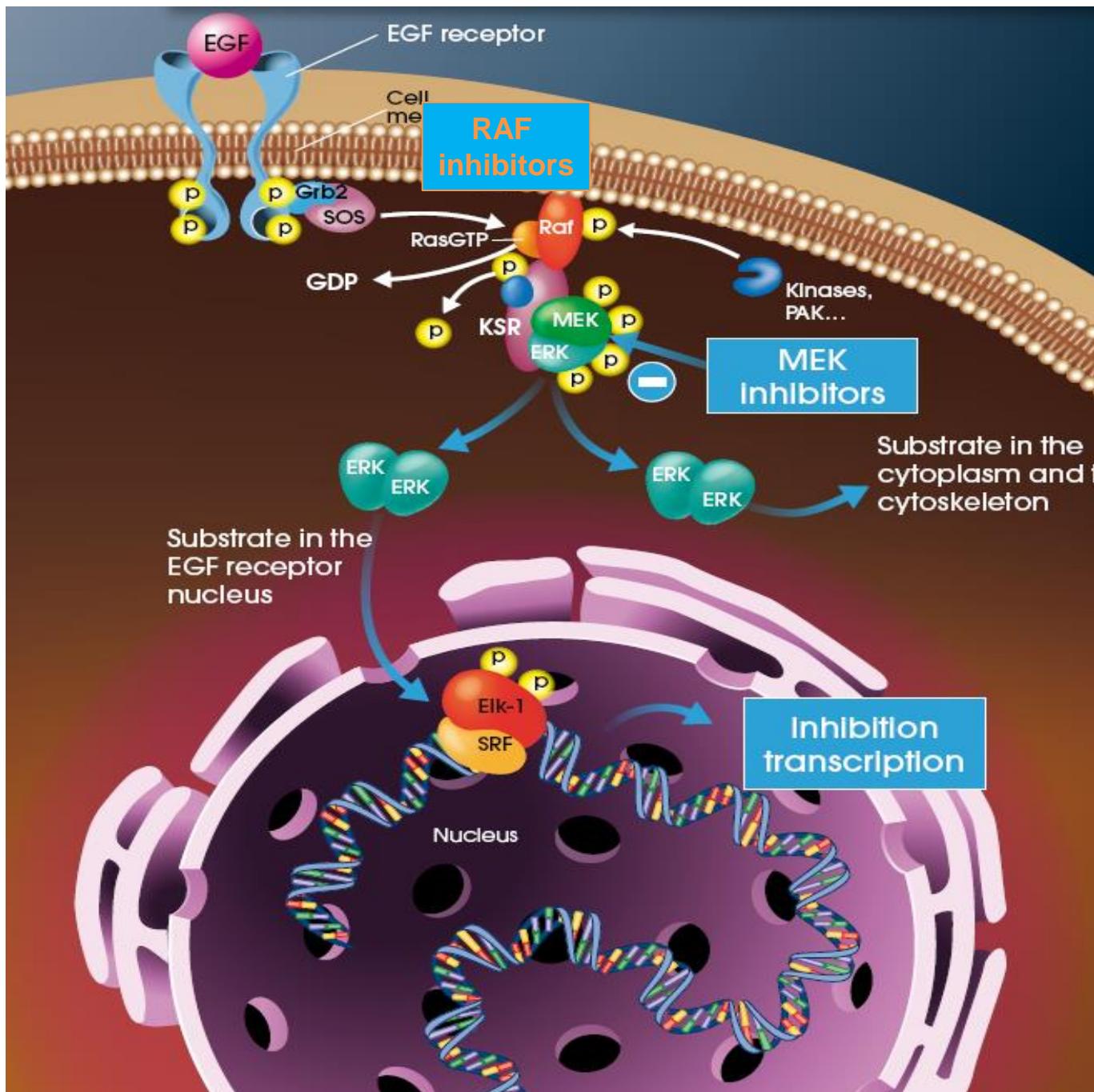
Genital rash
SUH

Yellow skin

Hair
depigmentation

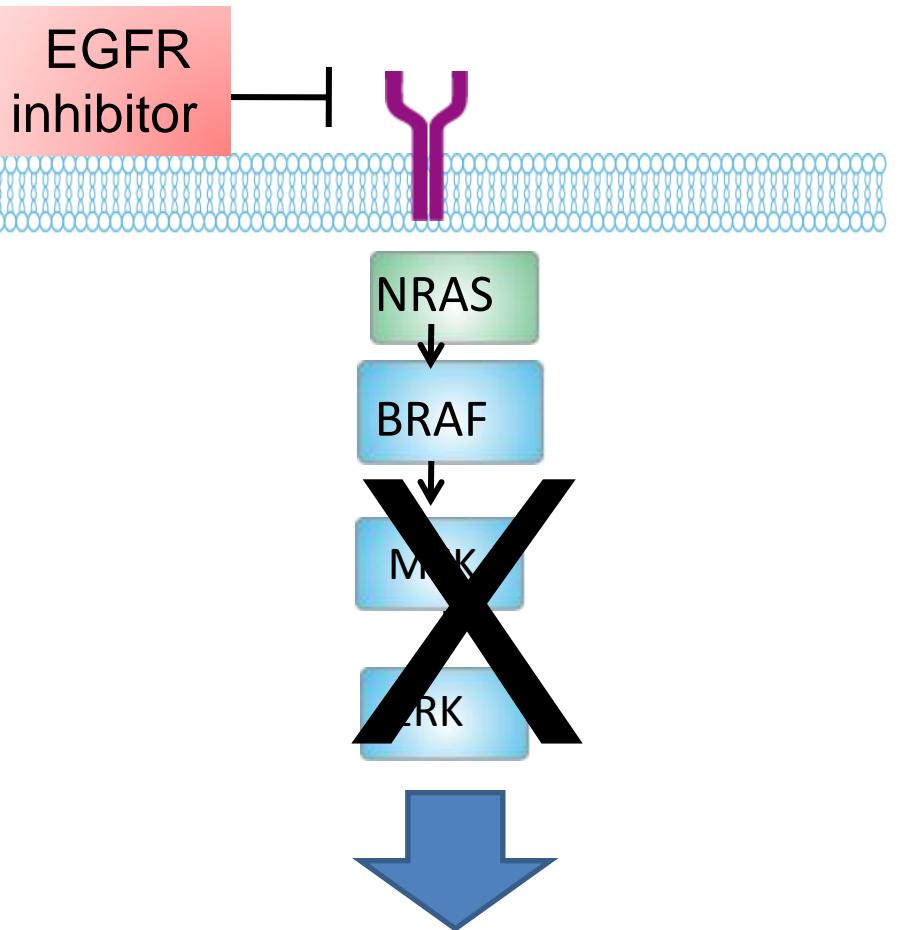
Sorafenib

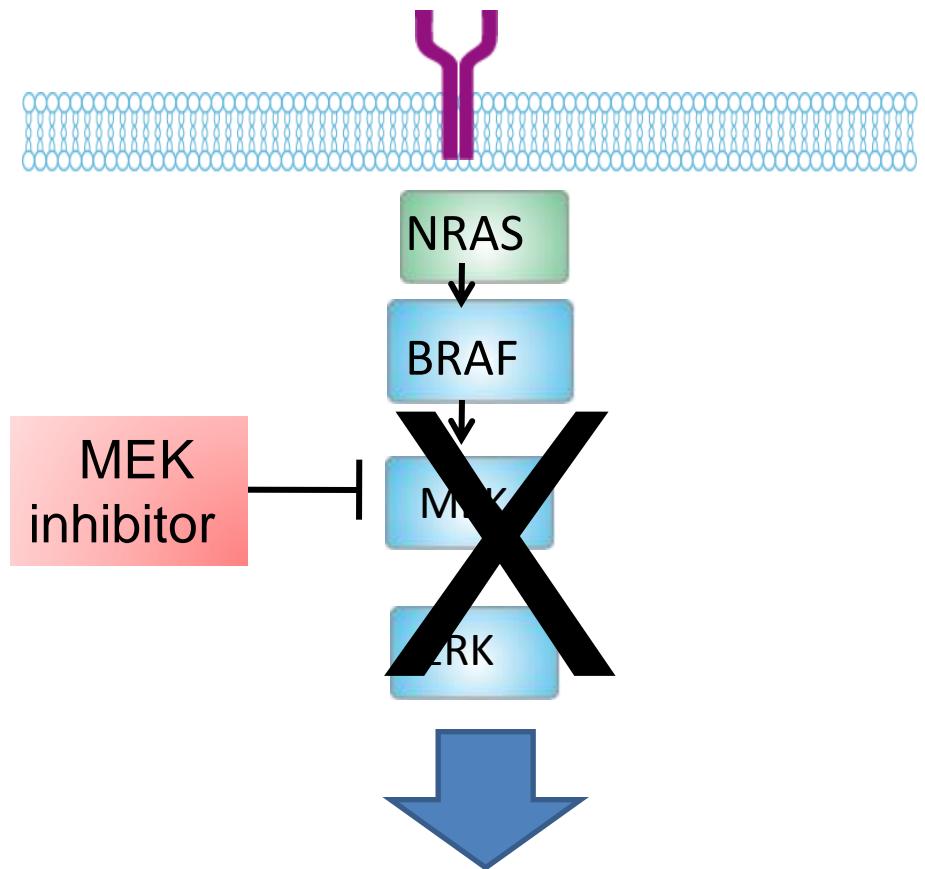
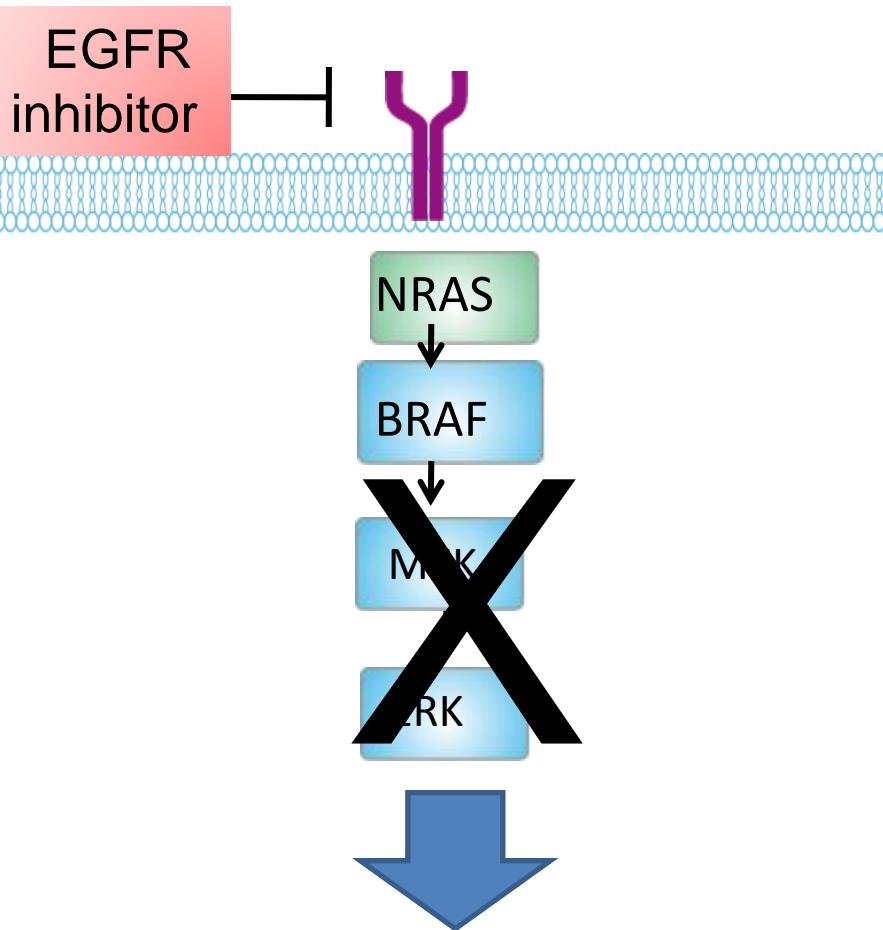
Sunitinib





Anti-MEK skin adverse events





Mechanism of tumor initiation with BRAF inhibitors?





Reynolds et al, Am J Med Genet 1986;
Jeffries et al, Pediatr Dermatol 2009
Hernandez-Martin et al Actas Dermosifillogr 2011
Siegel et al Br J Dermatol 2012

Cardiofaciocutaneous Syndrome

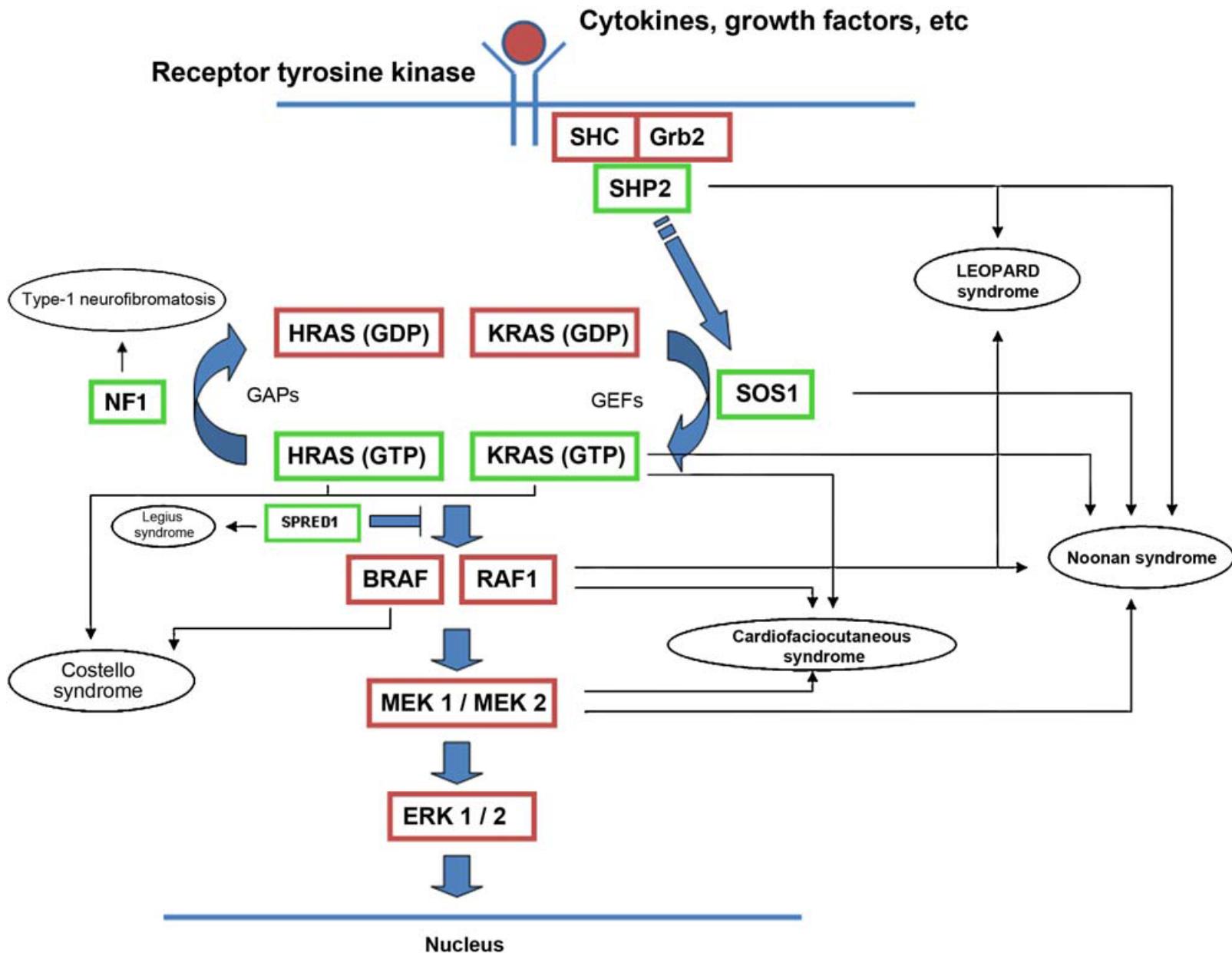


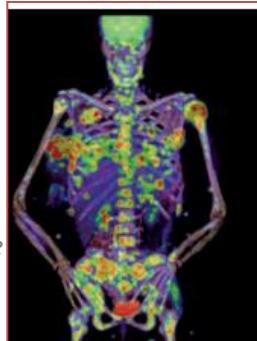
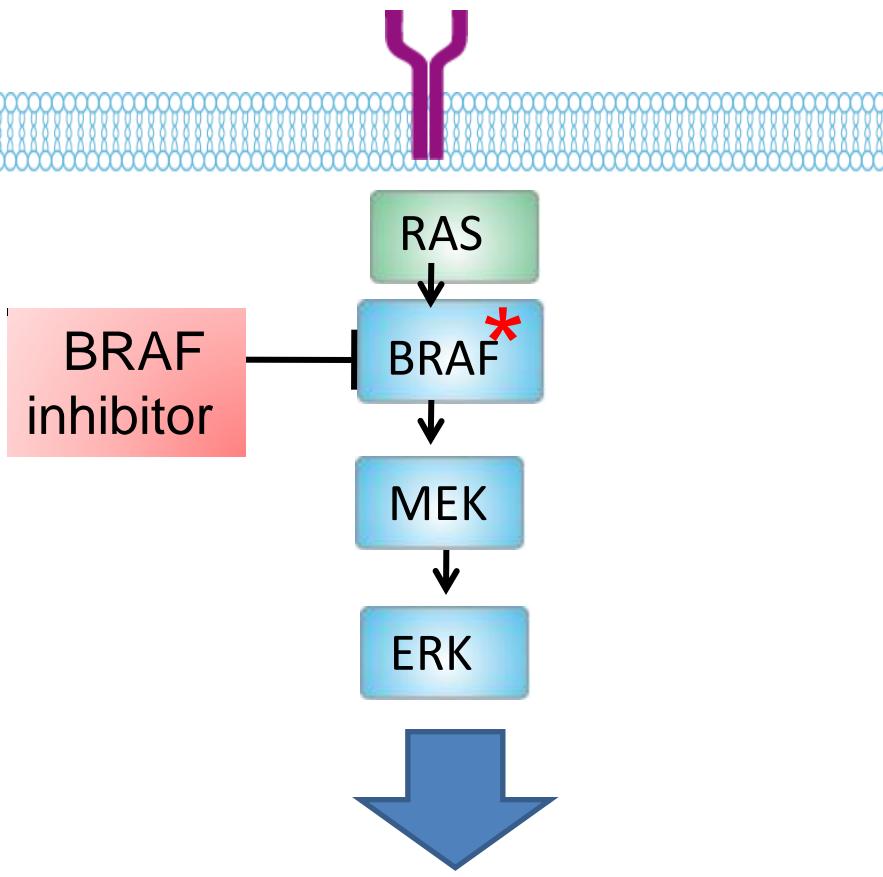
Reynolds et al, *Am J Med Genet* 1986;

Jeffries et al, *Pediatr Dermatol* 2009

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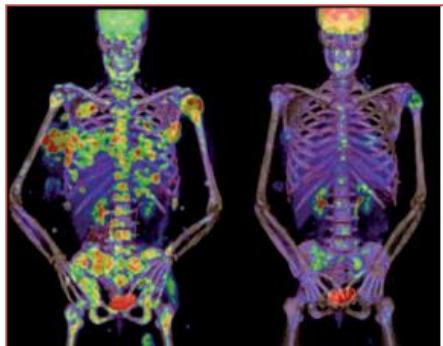
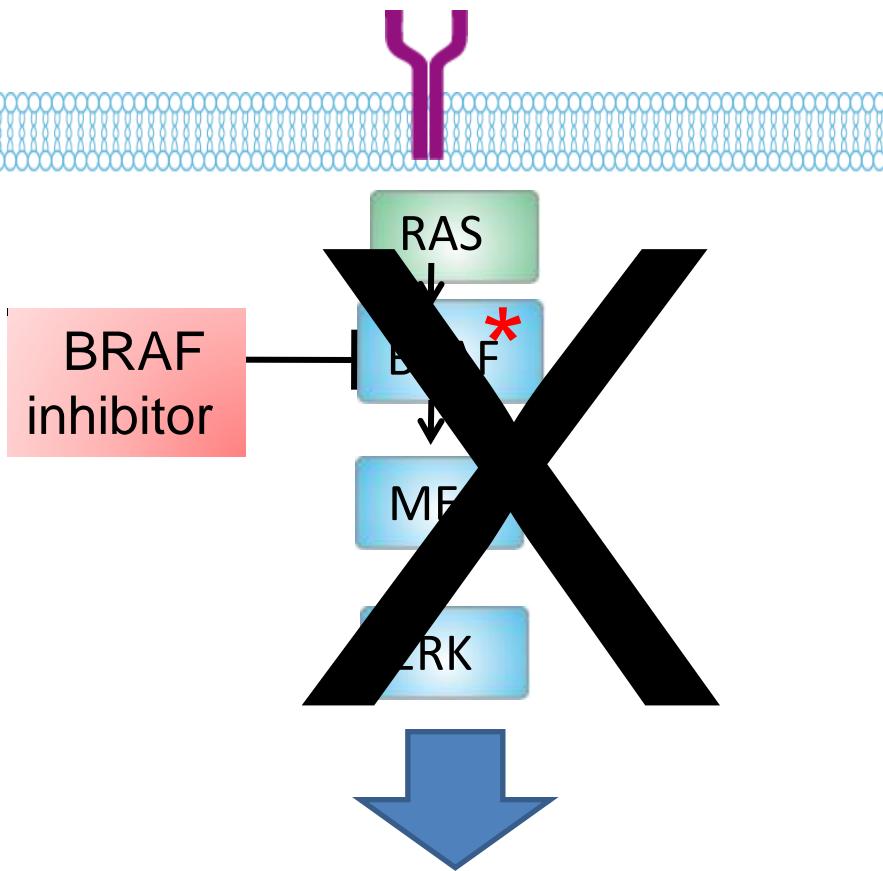
Siegel et al *Br J Dermatol* 2012





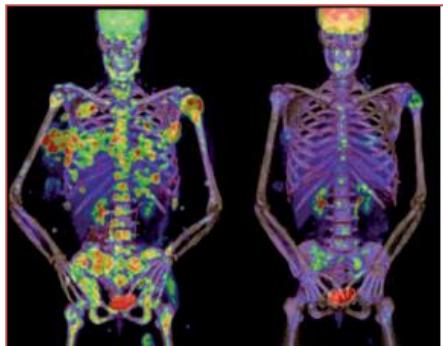
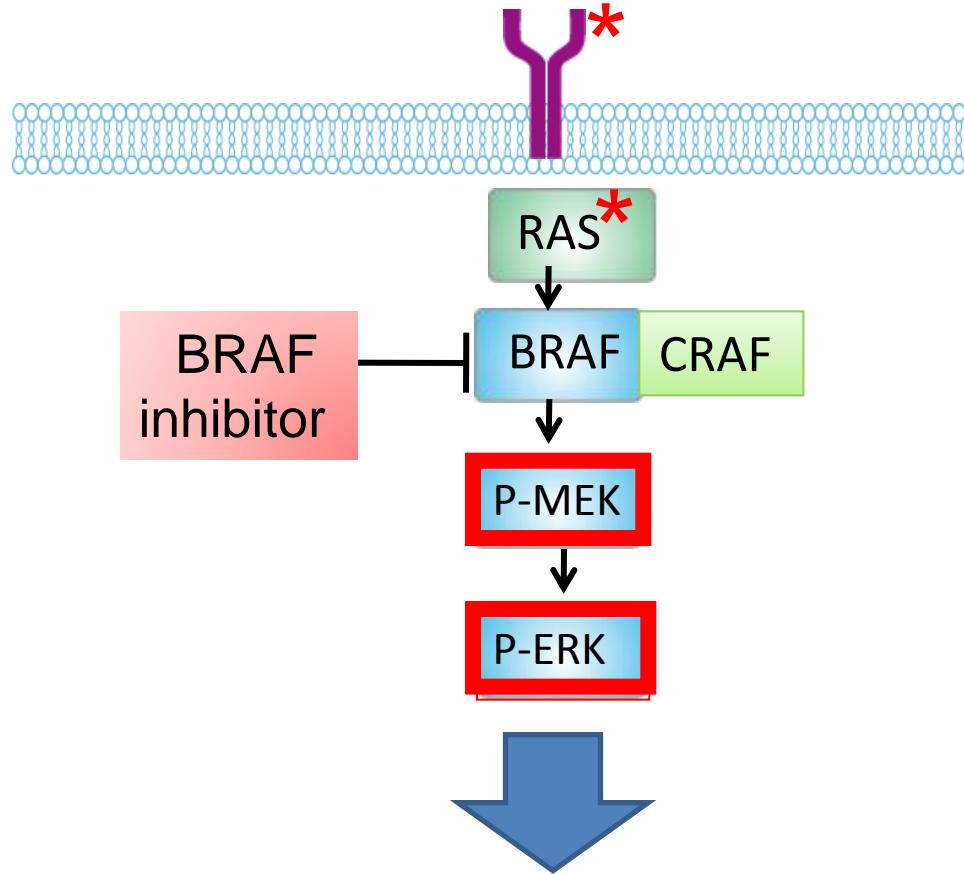
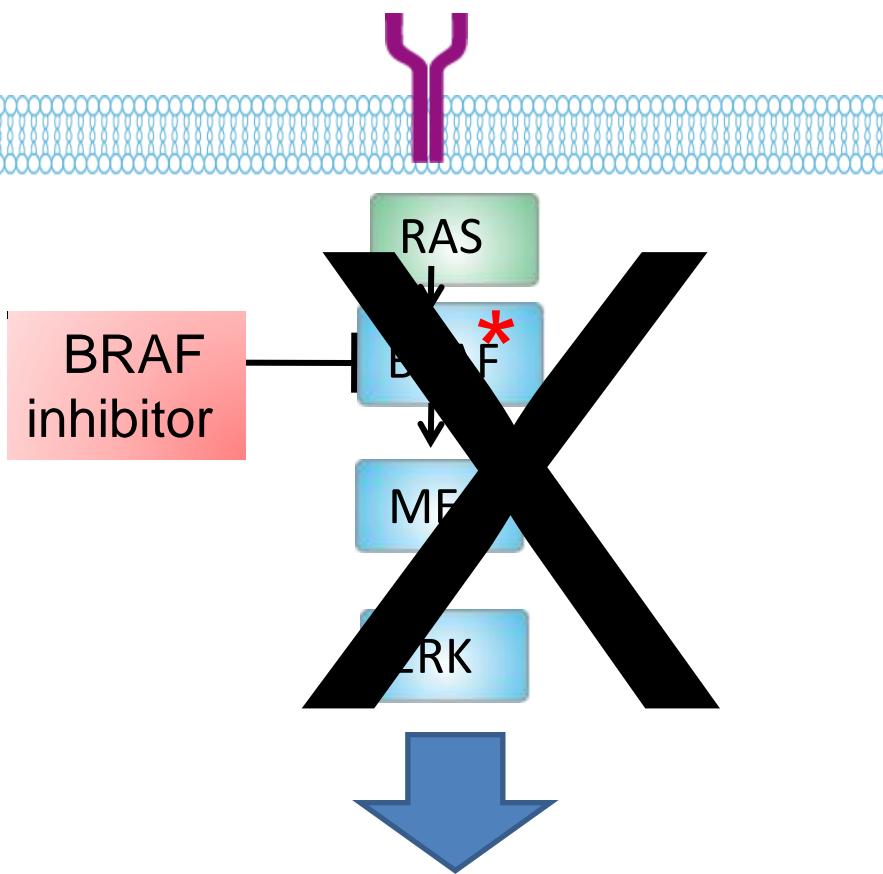
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Bollag et al. *Nature Rev. Drug Discovery* 2012



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Bollag et al. *Nature Rev. Drug Discovery* 2012

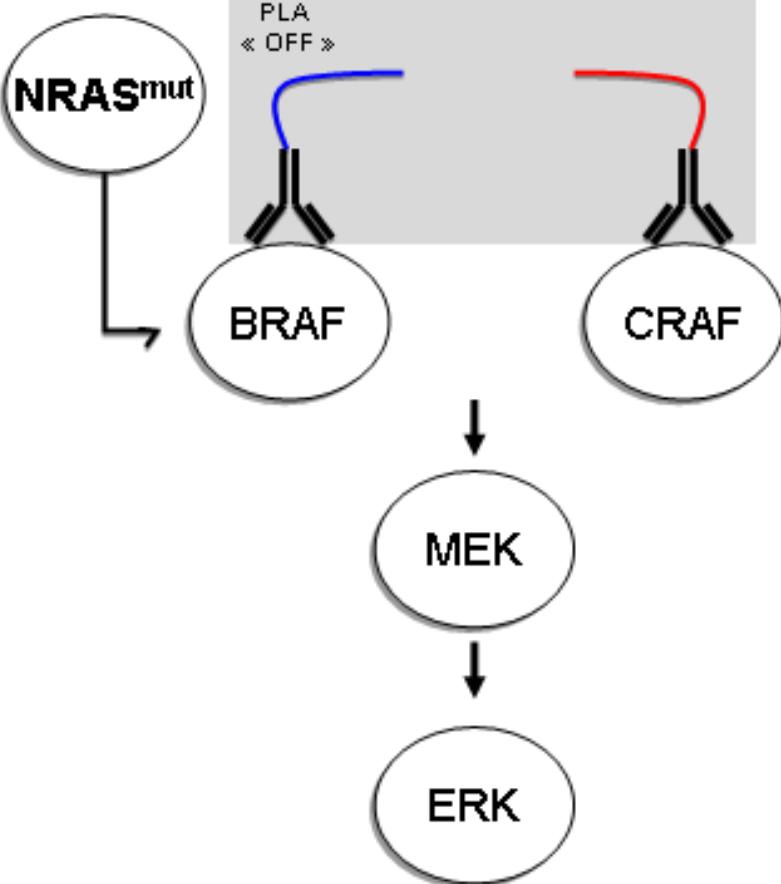


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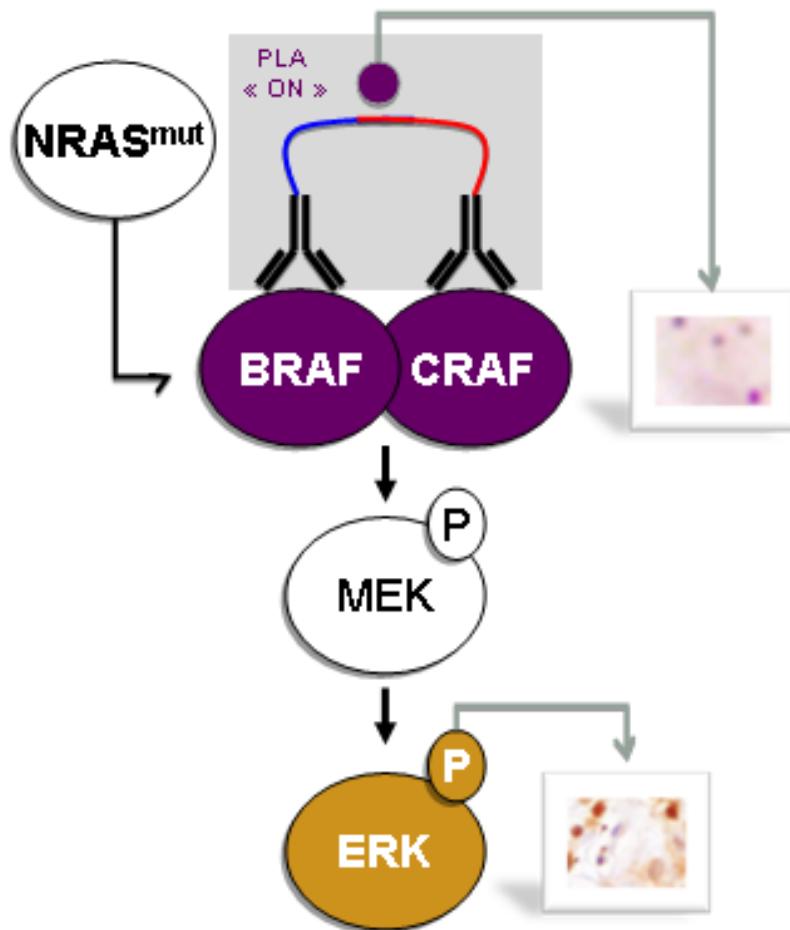
Bollag et al. *Nature Rev. Drug Discovery* 2012

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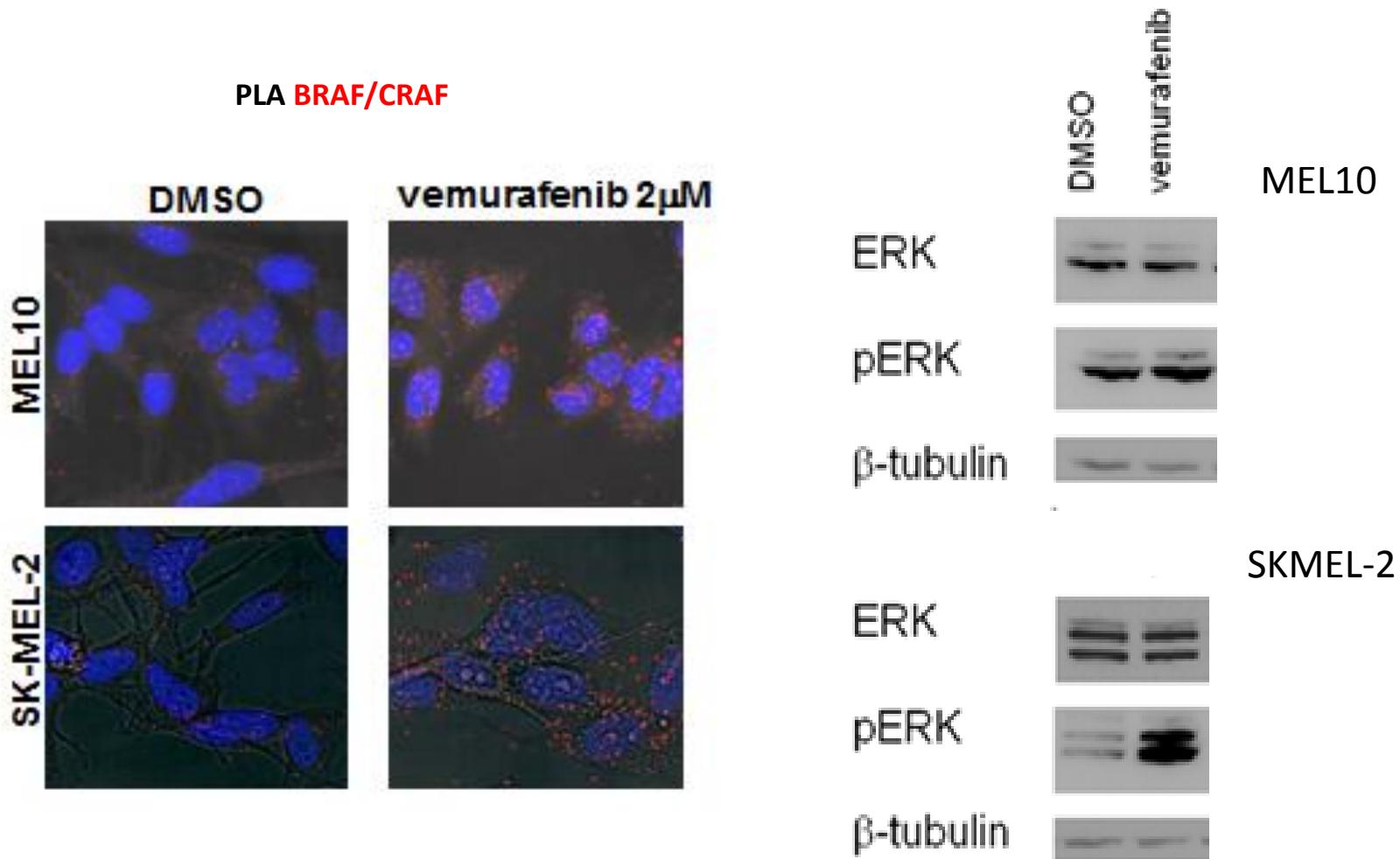
untreated



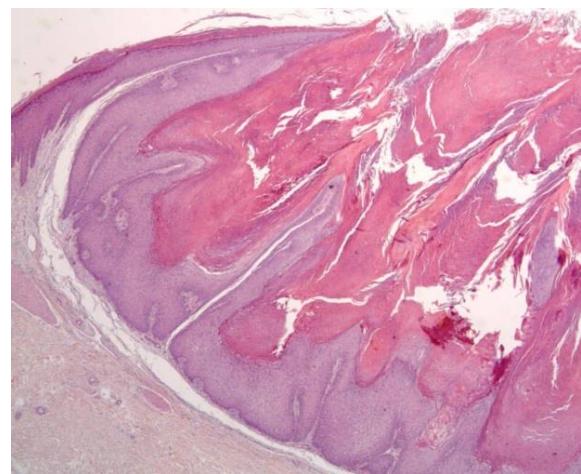
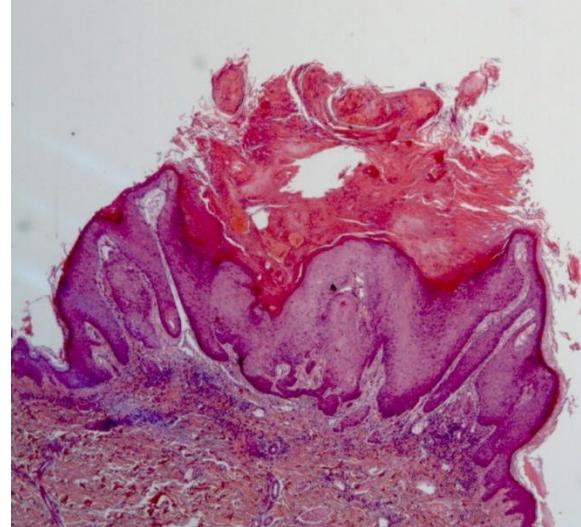
vemurafenib-treated

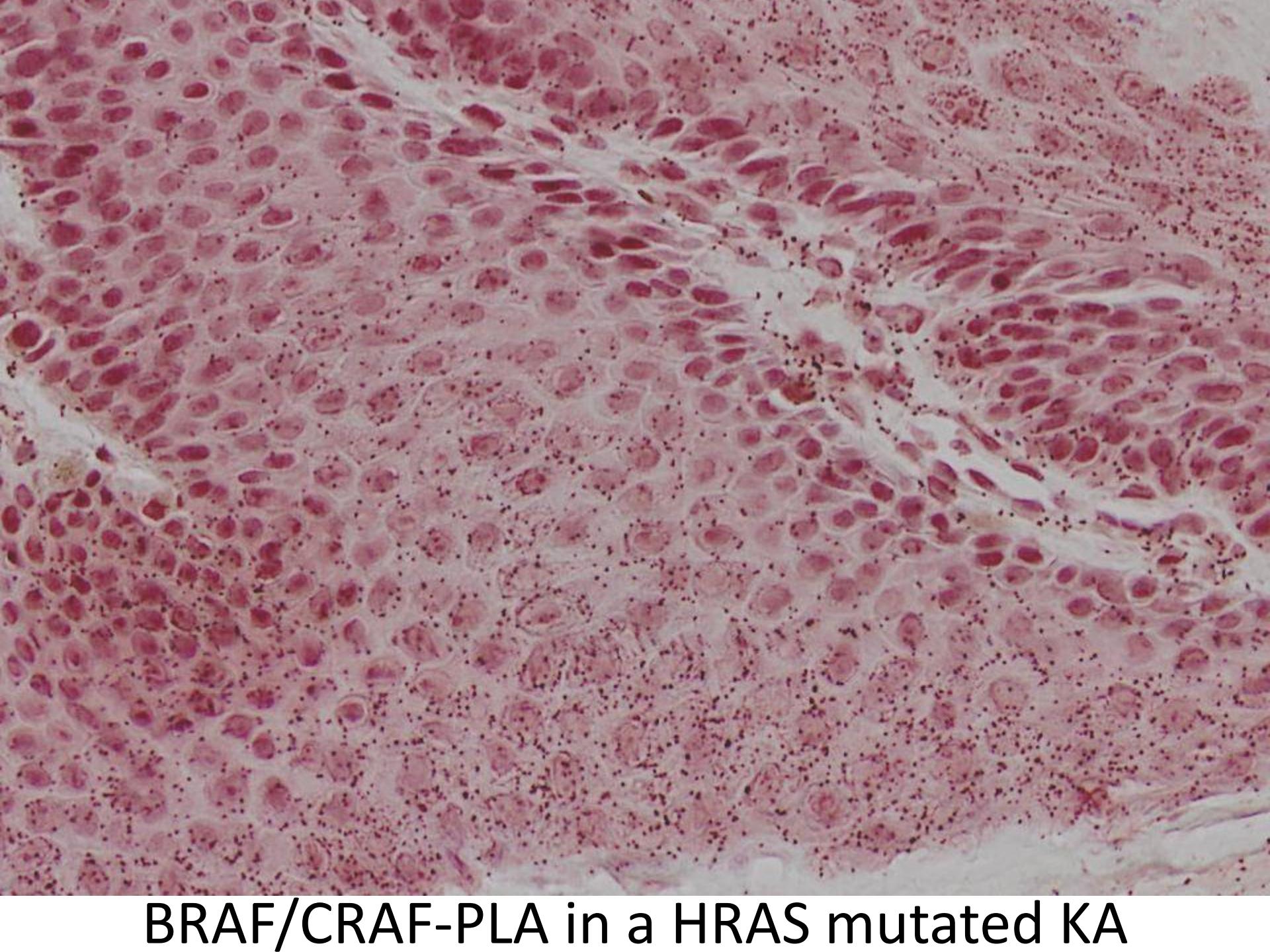


BRAF/CRAF link in NRAS mutated melanoma cell lines



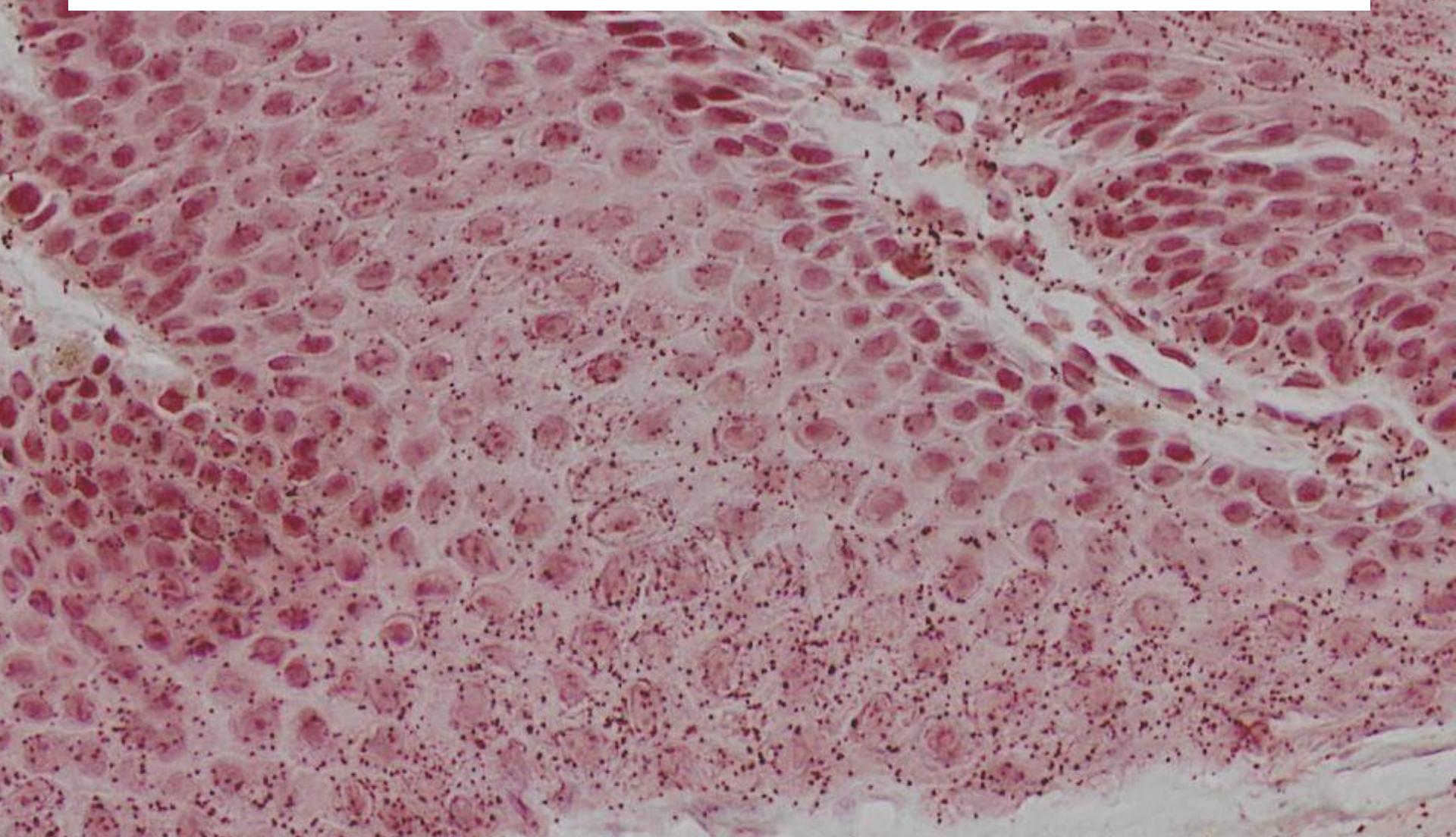
PLA in skin lesions from patients?





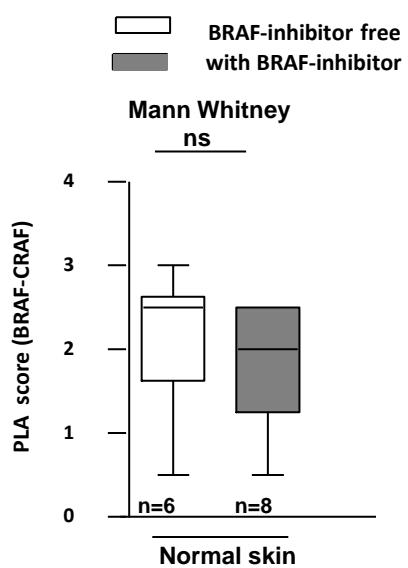
BRAF/CRAF-PLA in a HRAS mutated KA

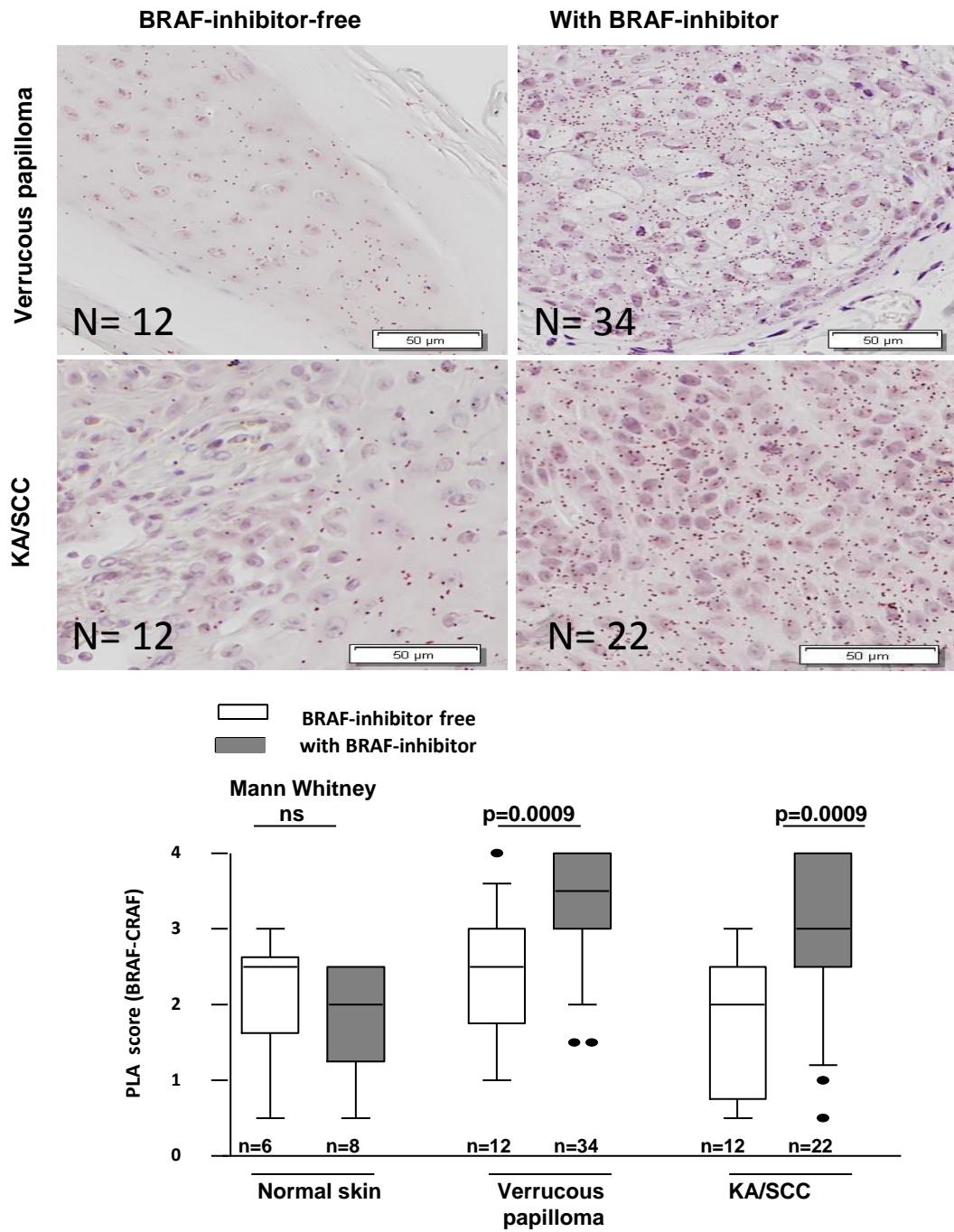
Are BRAF:CRAF heterodimers specific to tumors induced by BRAF inhibitors?



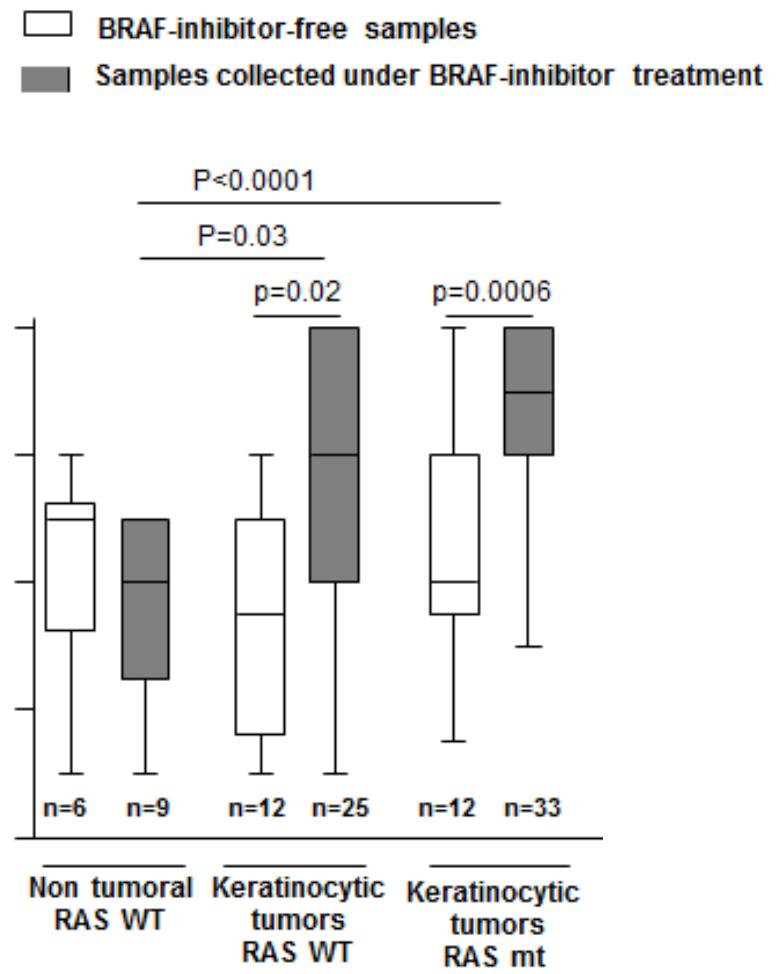
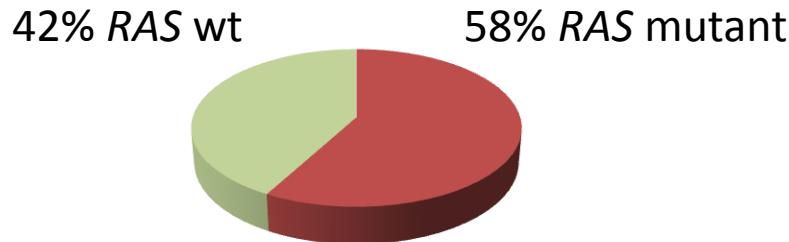
BRAF/CRAF-PLA in a HRAS mutated KA

Are BRAF:CRAF heterodimers specific to tumors induced by BRAF inhibitors?





Influence of RAS mutation: higher number of BRAF/CRAF heterodimers independently of the RAS mutational status



Induction of other tumor types?

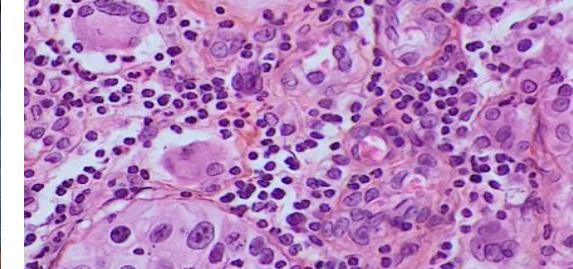
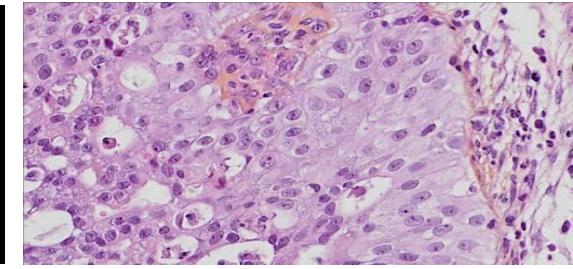
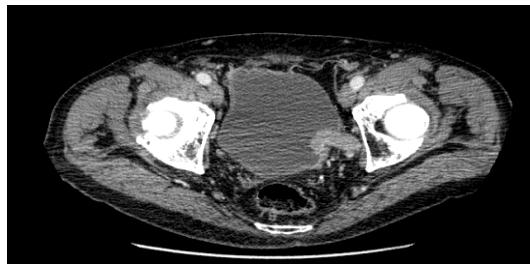
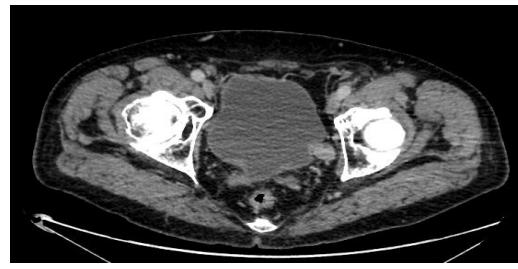
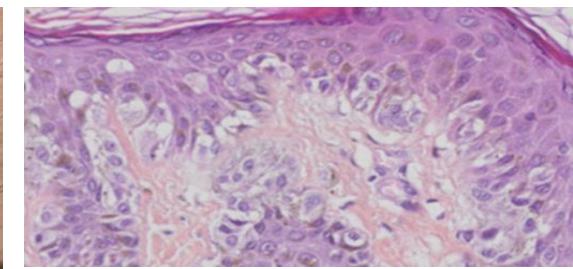
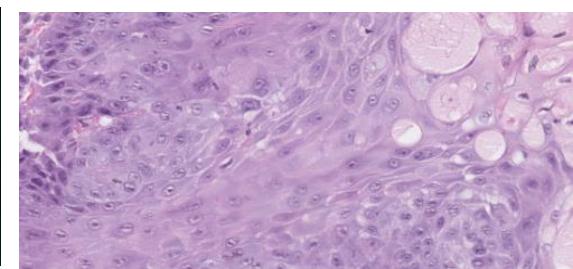
BRAF-inhibitor free



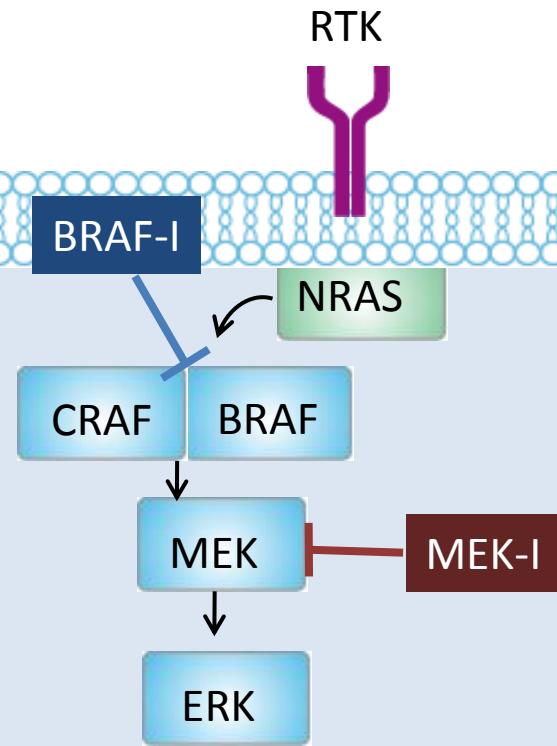
BRAF-inhibitor



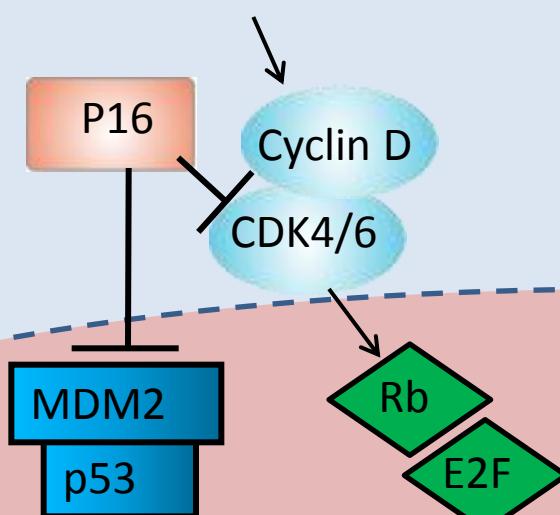
Pathology (H&E)



Anti-BRAF + anti-MEK

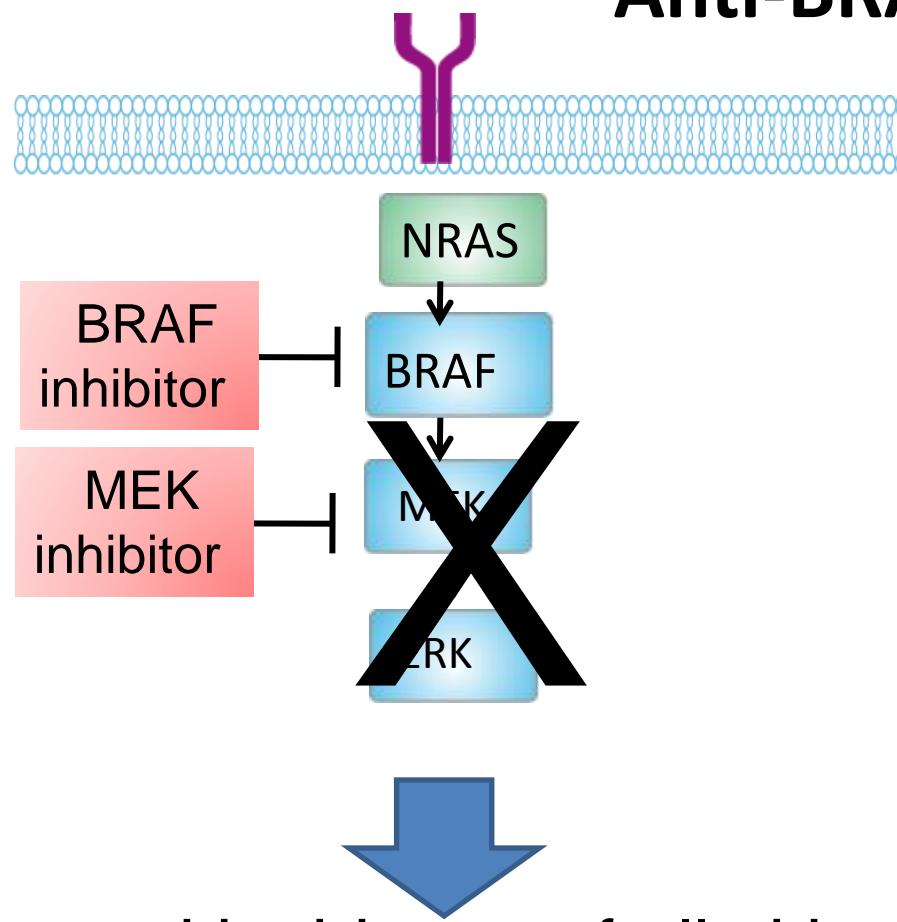


KA/SCC in 1 to 4%



Cell growth, prolif, survival

Anti-BRAF + anti-MEK



Decreased incidence of all skin adverse events:

- Rash: 27%
- Hyperkeratosis: 9%
- KA- SCC: 1- 4%
- Papilloma: 4%

Management

- Information of the patient before initiating the treatment +++++
 - Skin adverse effects *will* occur
- Collaboration with dermatologist can be needed

Management: in front of a rash

- Presence of severity indicators?
 - Systemic symptoms
 - Eosinophilia
 - Bullous lesions, epidermal detachment
 - Mucosal lesions
- Is it related to the drug?
 - Infection
 - Other drug
- Does it require treatment interruption?

First : look for severity markers

- DRESS: Drug Rash with Eosinophilia and Systemic Symptoms

- Diffuse rash
 - Eosinophils > 1500
 - Systemic signs:
 - Fever +Lymphadenopathy
 - Hepatitis, nephritis, neurologic signs...



- SJS; TEN
 - Bullous lesions
 - Mucosal lesions
 - Systemic signs



Skin Inflammation/Folliculitis/photosensibility



- Interruption of treatment : rapid improvement
- Topical treatment :
 - Clindamycin
 - Erythromycin
 - Metronidazole
 - Steroids
- Systemic treatment
 - Cyclines : doxycycline : 100 to 200 mg/ days –3-6 weeks

Camouflage make-up



C Robert et al Lancet Oncol 2005

Hand-foot skin reaction

*Before

- information (soft shoes)
- Sole examination (podologist if needed)

Grade 1	Moisturizing topics Urea 20%
Grade 2	Urea based ointment 20-50% Stop or reduce dosing if persists Podologist (soles if needed)
Grade 3	Stop treatment until back to grade 0 or 1 Topical Steroids in inflammation Pain treatment Podologist (soles if needed)

Paronychia

- Preventive measures
 - Avoid trauma (tight shoes, cutting nails too short..)
- Curative
 - Topical steroids (when non infected)
 - Antiseptic soaks
 - Silver nitrate, trichloracetic acid
 - Surgery and phenolisation

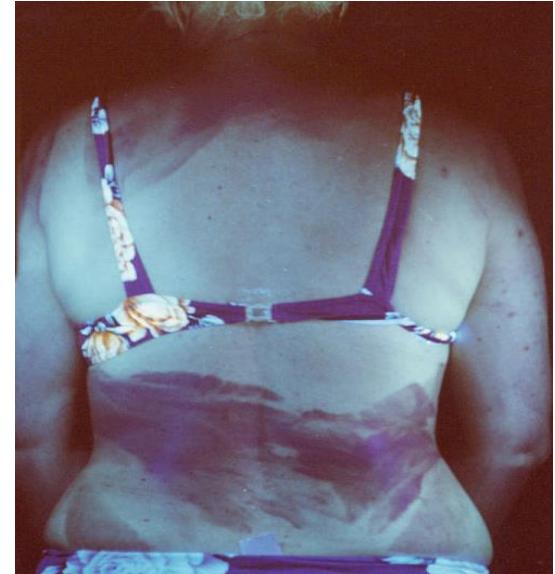
Additional measures

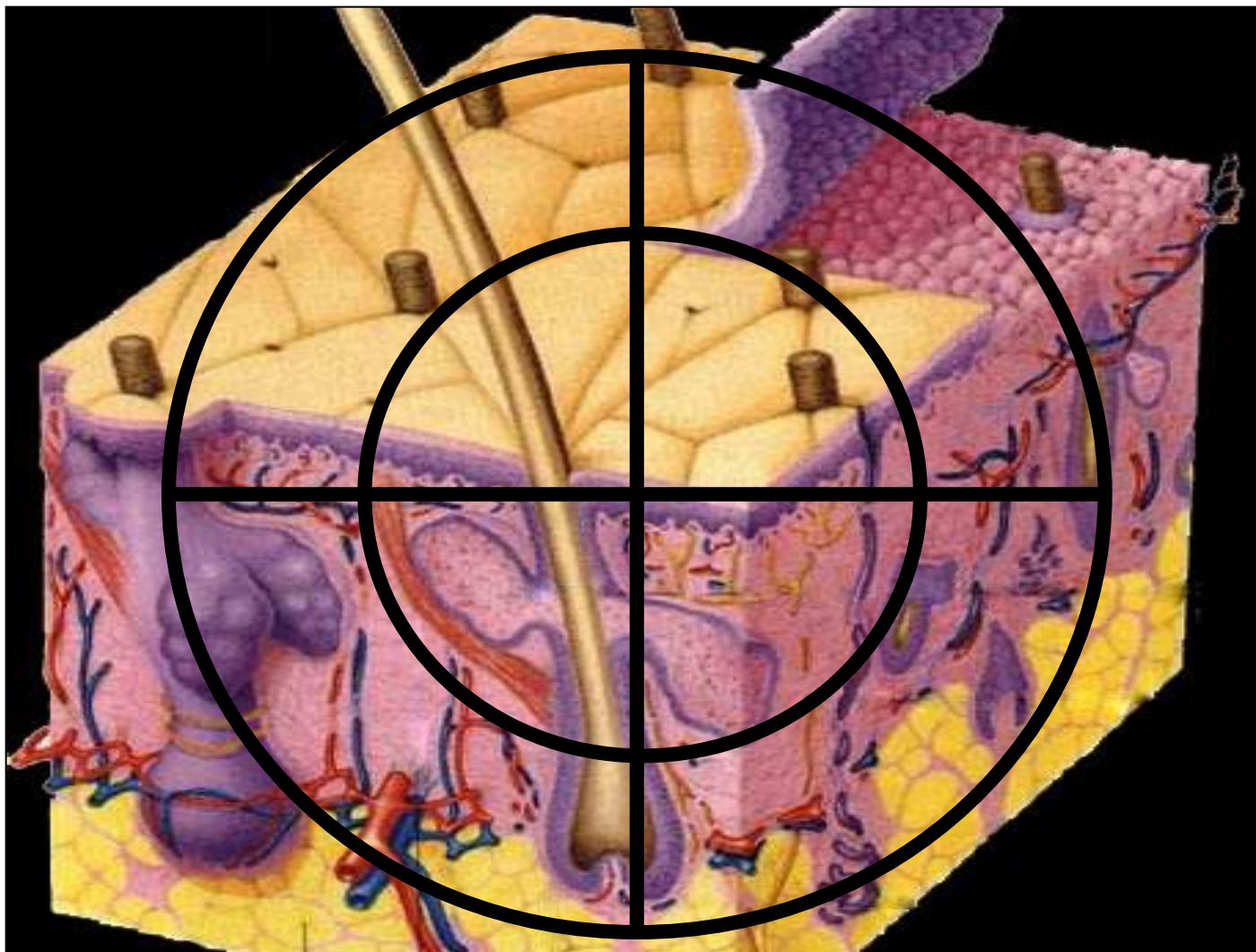
- Xerosis : emollients
- Hair
 - Facial unwanted: Wax depilation (facial hair)
 - Hair texture modification: conditionner..

Additional measures

- Strict photoprotective measures for photosensitive drugs
 - Sun avoidance, even through windows
 - Clothes
 - Sunscreen; high SPF: 30-50 (UVB and UVA)

How to apply sunscreen?





Gustave Roussy

Skin and Melanoma Team



Back up

Rash Classification CTCAE v 4

Skin and subcutaneous tissue disorders

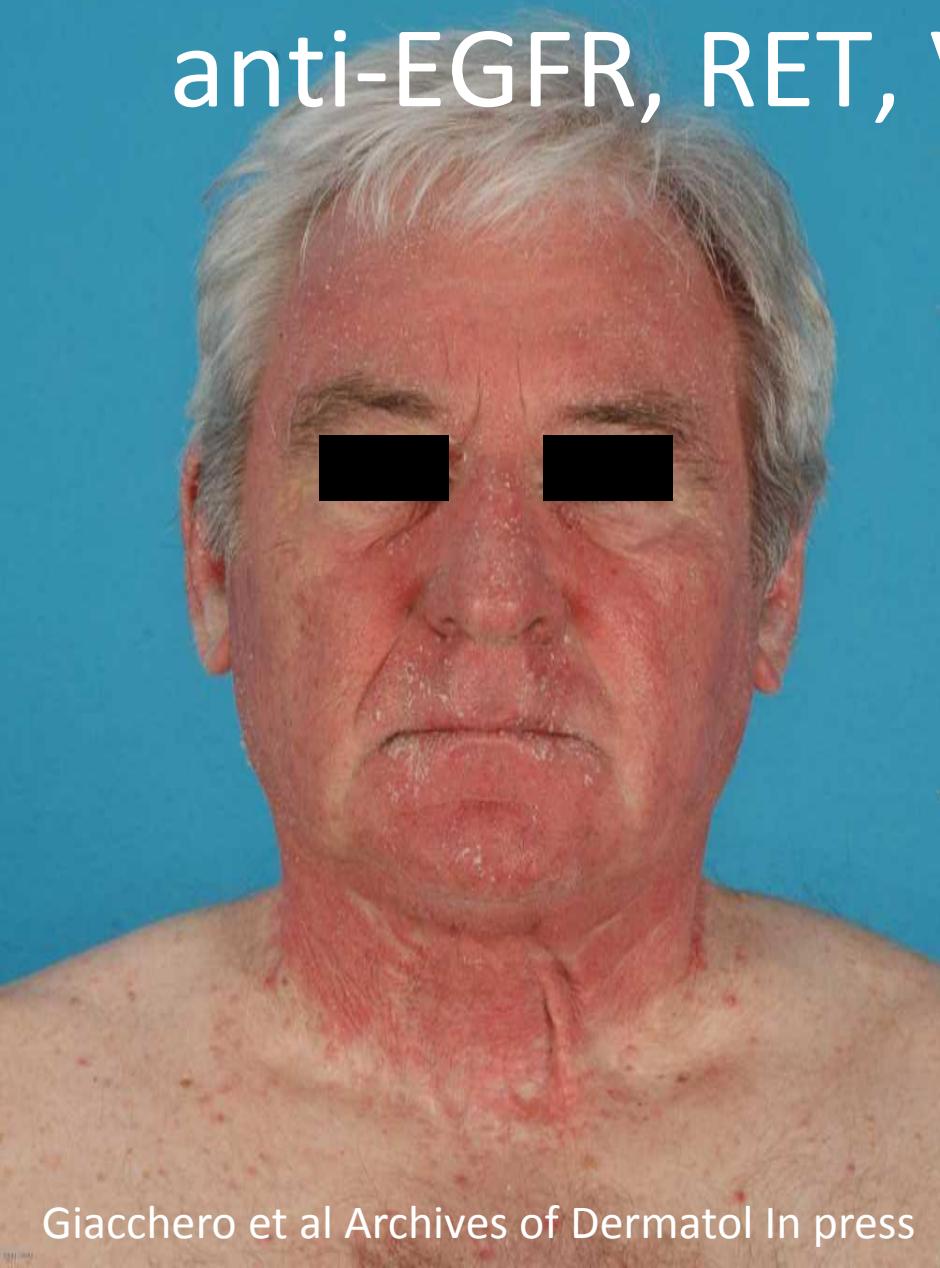
Adverse Event	Grade				
	1	2	3	4	5
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-

Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.

Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
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Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.

Vandetanib anti-EGFR, RET, VEGFR



Vandetanib-associated skin manifestations (observation of 63 patients with thyroid cancer included in 3 studies)

Skin side effects	n (%)	Time to occurrence	Grade (%)		
			1	2	3
Folliculitis	49 (77·8)	7d-5 w	73.5	24.5	2
Photosensitivity	23 (36·5)	7d-5 m	39	35	26
Dry skin	13 (20·6)	1-4 m	61.5	38.5	0
HFSR	5 (7·9)	ND	1	0	0
Genital rash	4 (6·3)	ND	25	75	0
Finger clefts	3 (4·8)	2 w-3 m	NA		
Subungual splinter hemorrhages	3 (4·8)	4 w-6 w	NA		
Scalp dysesthesia	3 (4·8)	ND	NA		
Hypertrichosis	3 (4·8)	ND	NA		
Cheilitis	2 (3·2)	ND	NA		
Periorbital edema	2 (3·2)	ND	NA		

« Late » cutaneous manifestations

Skin side effects	n (%)	Time to occurrence	Grade (%)
Blue-grey macules	12 (19)	2 m-21 m	NA
Paronychia	7 (11·1)	6 w-12 m	NA



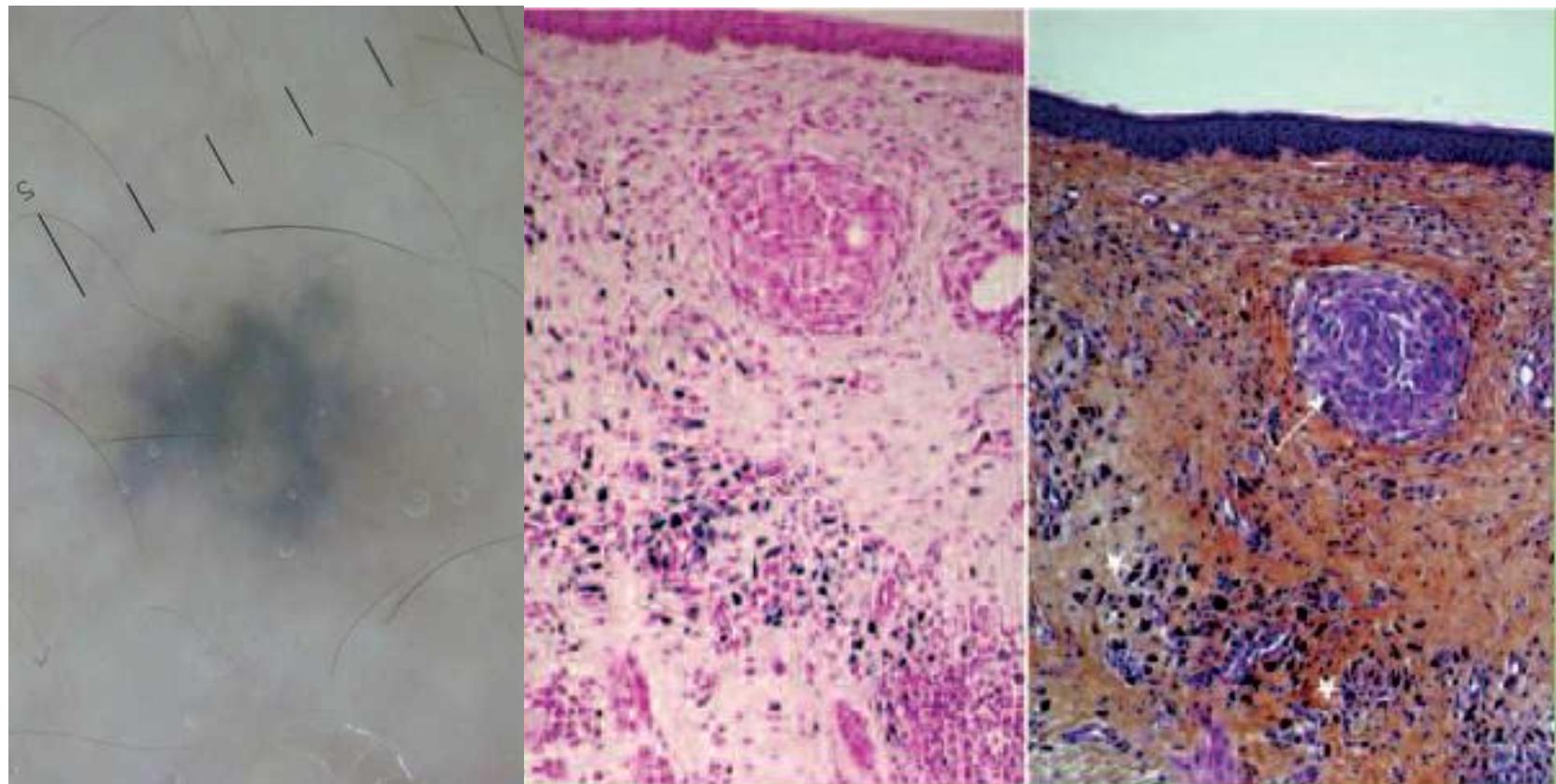








Intradermal pigment, Perls + melanin +





Photoinduced erythema multiforme with vandetanib

	Targeted molecules		
Skin manifestations	VEGFR	EGFR	VEGFR-EGFR-RET
Folliculitis	0	++	+
Hand-foot skin reaction	++	0	+
Genital rash	+	0	+
Perionyxitis	0	+	+
Subungual hemorrhages	+	0	+
Phototoxicity	0	0	+
Blue-grey macules	0	0	+

Correlation between targeted molecules and skin manifestation

Drug	sorafenib	sunitinib	imatinib	trametinib	Vandetanib
targets	VEGFR 1-3 RAF PDGFR, FLT3	VEGFR1-3, KIT, PDGFR FLT3	KIT, PDGFR	MEK	Ret VEGFR EGFR
KA, SCC	+	--	-	-	-
Nevi	+	-	-	-	-
HFSR	++	+	-	?	+
Folliculitis	+/-	+/-	-	++	++
Hair	Alopecia, curly	depigmentation		+	+
paronychia	-	-	-	+	+
skin colour	Red (face)	yellow	+ or -	NI	Blue dots
oedema	-	+	+	+	-
SUH	+	+	-	-	+