The handling of toxicity in newly approved melanoma therapies: Targeted therapy toxicities

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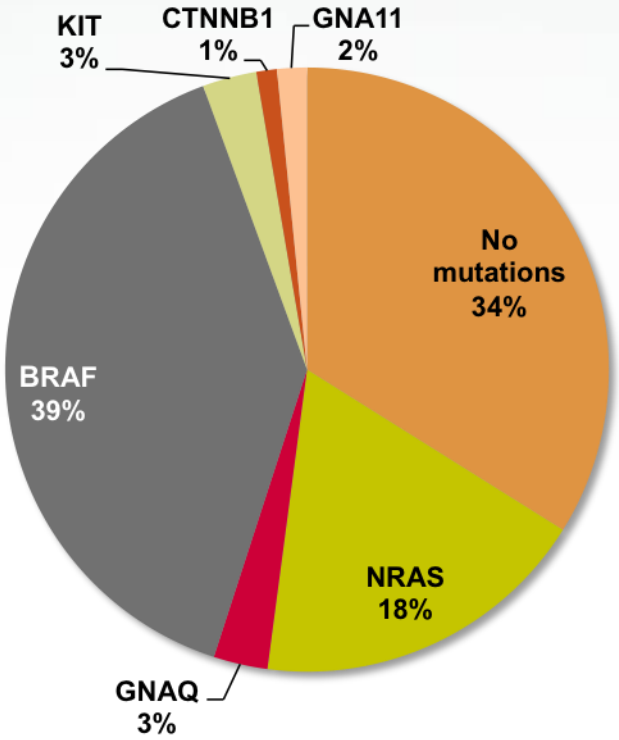
Disclosure slide

- OM is an occasional consultant for BMS and Roche
- OM has received honoraria from BMS and Roche for participation in advisory boards and to speak at sponsored meetings
- OM declares no conflicts of interest

Melanoma molecular profiling



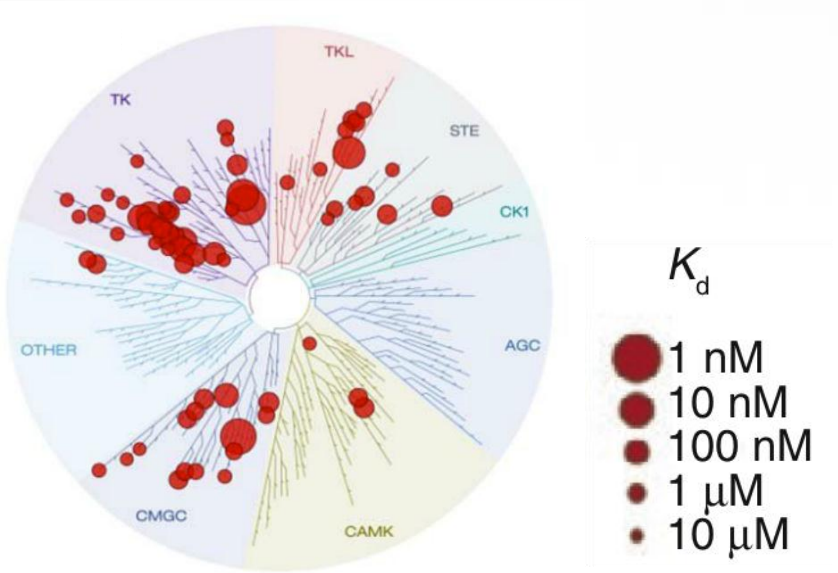
MAPK pathway activated in ≈ 60% of melanoma!

Melanoma molecular profiling results
(616 samples from a systematic profiling at VICC
Sosman J., ASCO 2012)

BRAF type II inhibitor: Sorafenib

- Sorafenib is the first BRAF (and CRAF, VEGFR, cKIT, PDGFR) inhibitor tested in melanoma (type II inhibitor)
- Disappointing activity:
  - *Hauschild & al, JCO 2009*

Target Kinase	IC50 (nM)
BRAF V600E	38
BRAF WT	22
VEGFR2	90



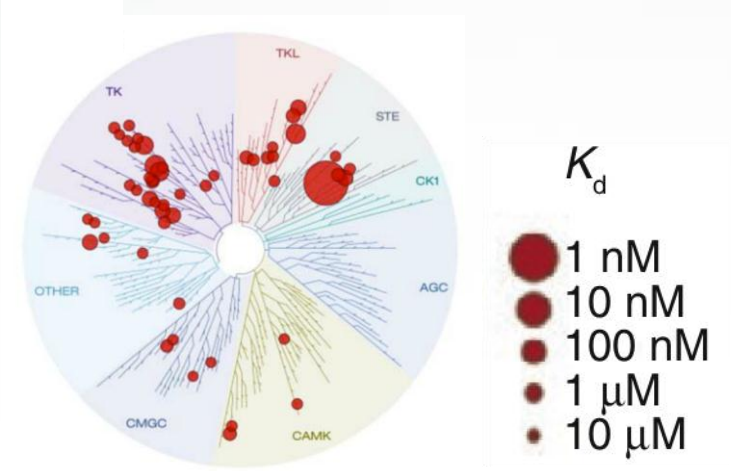
Davis & al. *Nat. Biotech.* 2011

Skin toxicity:
Arnault & al. *Clin Cancer Res* 2012

- Rash, folliculitis
- Hand & foot syndrome
- Keratoacanthoma (KA)
- SCC

BRAF V600E type I inhibitors: Vemurafenib

- Vemurafenib is a first in class inhibitor targeting activated BRAF V600E kinase (type I inhibitor)



Davis & al. *Nat. Biotech.* 2011

Target Kinase	IC50 (nM)
BRAF V600E	31
BRAF WT	100
CRAF	48

Bollag & al. *Nature* 2010

- First TKI to provide OS benefit in BRAF V600E stage IV patients (Chapman & al, *NEJM*, 2011), FDA and EMA approved in 2011-12

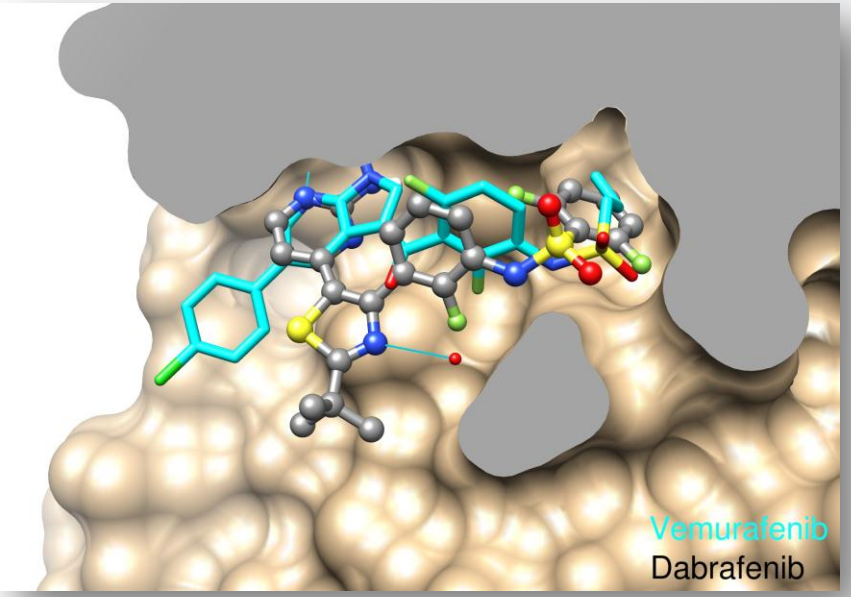
BRAF V600E type I inhibitor: Dabrafenib

- Dabrafenib is another type I inhibitor of BRAF V600E with the same mode of action (active conformation ATP pocket competitor) and a very specific inhibition profile (GSK, internal data)

Target Kinase	IC50 (nM)
BRAF V600E	0.6
BRAF WT	3
CRAF WT	5

Selectivity against 270 kinase panel

- 10 of 270: IC50 10-100nM
- 260 of 270: IC50 from 100nM to >10,000nM



- Clinical efficacy: Hazard ratio for PFS of 0.30 (95% CI 0.18-0.51), Hauschild & al. *Lancet* 2012

MEK inhibitors: Trametinib

- Trametinib is a potent MEK1 and MEK2 allosteric inhibitor (not an ATP pocket competitor) that has been recently tested as a single agent or in combination with Dabrafenib in V600E BRAF melanoma
  - Single agent data: Flaherty & al. *NEJM* 2012
    - First line comparison to DTIC in a Phase III (METRIC)
      - Hazard ratio for death: 0.54 (95% CI, 0.32 – 0.92, p=0.01)
  - Combination with Dabrafenib: Weber & al. ASCO 2012
    - Very encouraging response rate (PR and CR)
    - Encouraging early PFS data
    - Good toxicity profile

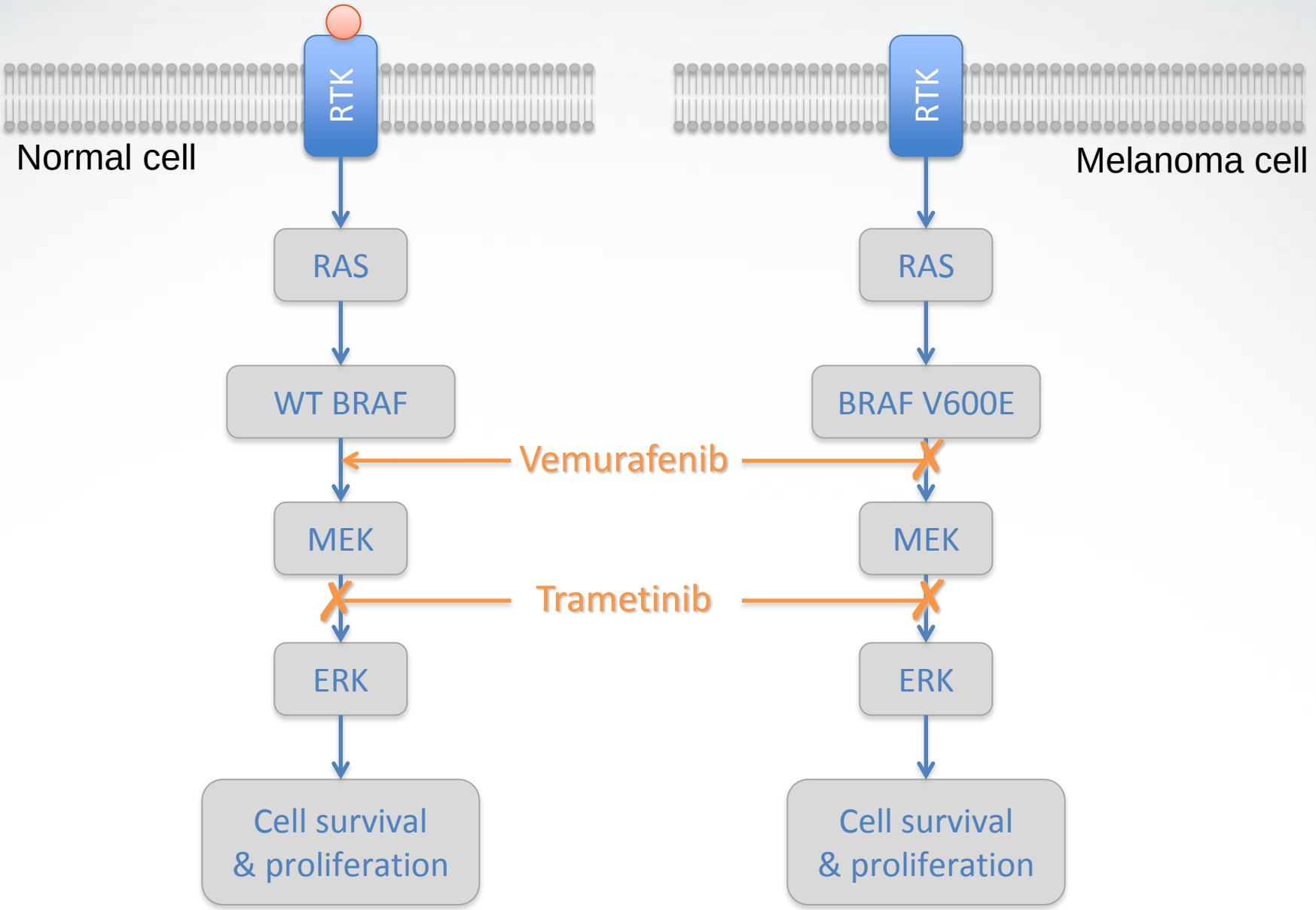
Skin toxicity observed with TKIs

Drug	Sorafenib	Sunitinib	Erlotinib gefitinib cetuximab
Targets	VEGFR2–3, RAF, PDGFR, FLT3	VEGFR1–3, KIT, PDGFR-α,β, FLT3	EGFR
Keratoacanthoma SCC	+	–	–
Hand foot skin reaction	++	+	–
Folliculitis	+/–	+/–	++
Hair	Alopecia, curly	Depigmented	Alopecia, brittle
Paronychia	–	–	++
Oedema	–	+	–
Subungual hemorrhages	+	+	–

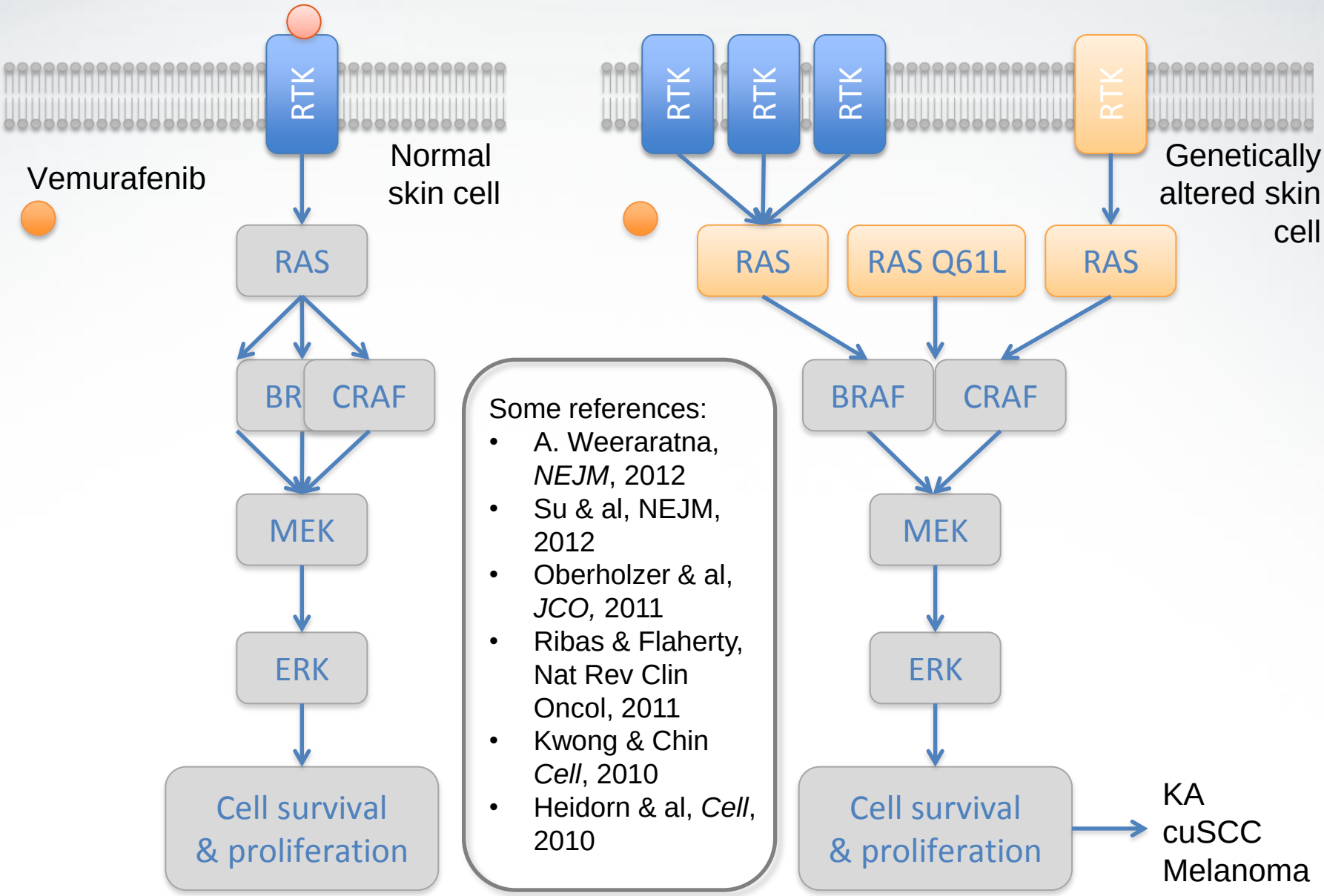
Drug	Everolimus temsirolimus	Imatinib	PLX4032
Targets	mTOR	KIT, PDGFR-β	RAF
Keratoacanthoma SCC	–	–	++
Hand foot skin reaction	–	–	+/–
Folliculitis	+	–	–
Hair	–	+/–	–
Paronychia	+	–	–
Oedema	+	+	–
Subungual hemorrhages	–	–	–

C. Robert & al.
Current Opinion in Oncology, 2011

WT and V600E BRAF signaling:



Paradoxical MAPK activation in BRAF WT cells



Some references:

- A. Weeraratna, *NEJM*, 2012
- Su & al, NEJM, 2012
- Oberholzer & al, *JCO,* 2011
- Ribas & Flaherty, Nat Rev Clin Oncol, 2011
- Kwong & Chin *Cell*, 2010
- Heidorn & al, *Cell*, 2010

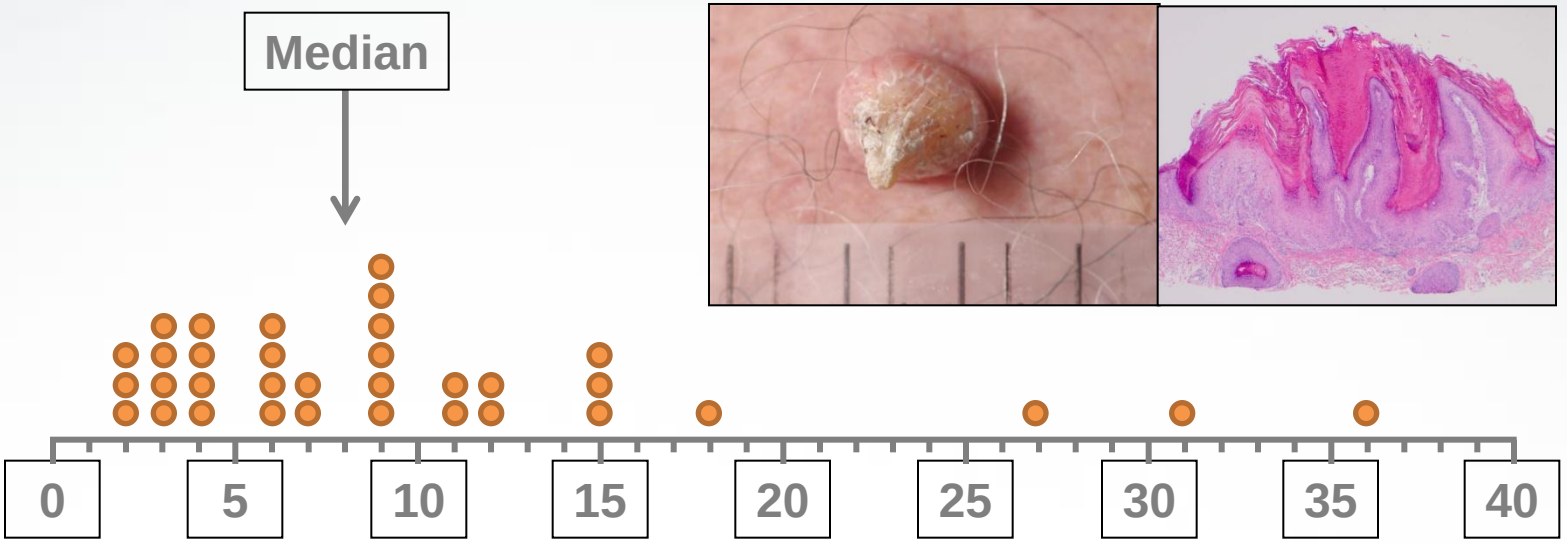
Toxicities of type I BRAFi and MEKi

	Vemurafenib[1]	Dabrafenib[2]	Trametinib[3]	Dabra+Tram[4]
Main skin toxicities				
Rash	10 (G2), 8 (G3)	Rare	19 (G2), 8 (G3)	13
Photosensitivity	12 (G2 + G3)	Rare	Rare	Rare
Hyperkeratosis	5 (G2), 1 (G3)	12 (G2), 1 (G3)	0	4 (G2), 0 (G3)
SCC/KA	2 (G2), 18 (G3)	2 (G2), 4 (G3)	0	0 (G2), 3 (G3)
Acneiform dermat.	Rare	Rare	9 (G2), 1 (G3)	
Other main toxicities				
Diarrhea	5 (G2), 1 G(3)	Rare	6 (G2), 0 G(3)	
Pyrexia	0	11	0	8
N & V	12	2	5	1(G3)
Arthralgia	18 (G2), 3 (G3)	5 (G2), 1 (G3)	rare	
Fatigue	11 (G2), 2 (G3)	5 (G2), 1 (G3)	5 (G2), 4 (G3)	1 (G3)

Note: all number in %, G: Grade of toxicity, SCC: Squamous Cell Carcinoma, KA: Keratoacanthoma

(1) Chapman & al, *NEJM* 2012
(2) Hauschild & al, *Lancet* 2012
(3) Flaherty & al, *NEJM* 2012
(4) Weber & al, ASCO 2012

Kinetics of appearance of cuSCC/KAs



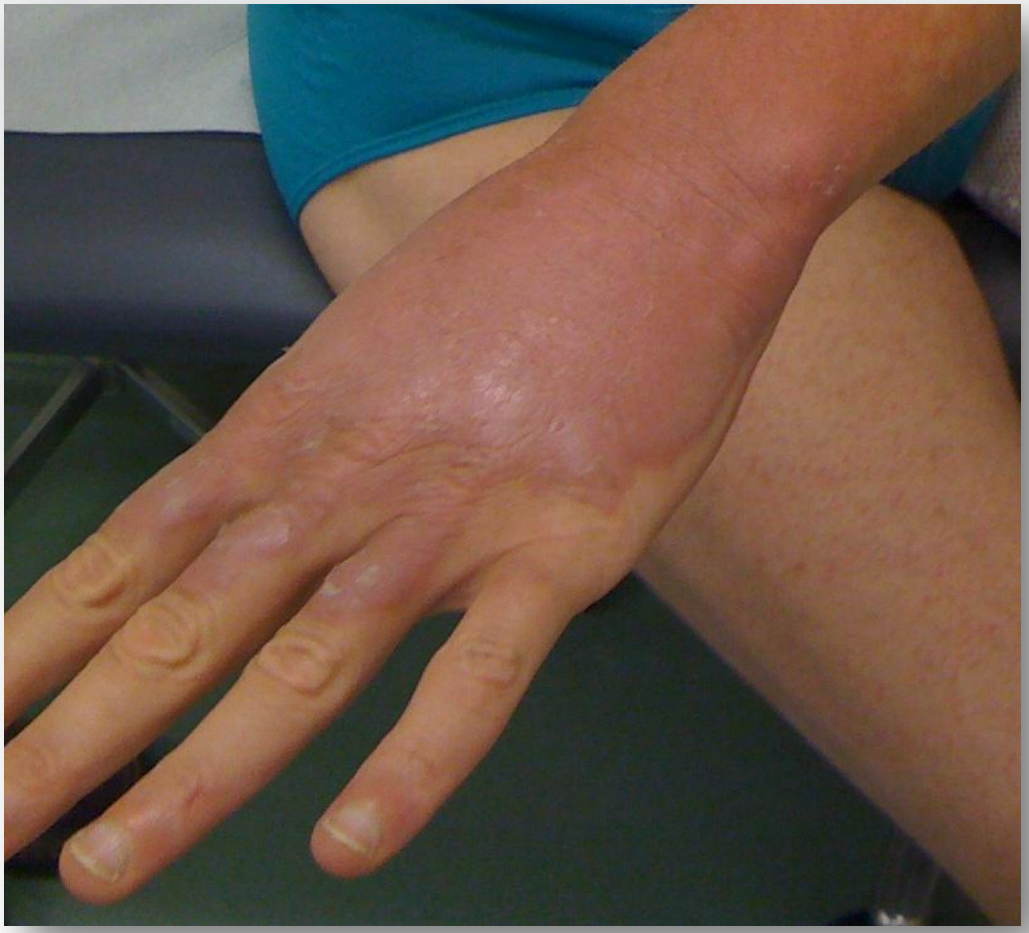
- Median time 8-10 weeks (2–36)
- Median number of cuSCC/KAs per patient 1 (range 1 to 7)
- Each dot represents occurrence of first cuSCC/KA lesion

VIENNA 2012 ESMO congress

ASCO 2011, update in Su & al. *NEJM* 2012

Examples of skin toxicities observed in our clinic under Vemurafenib from 5.2010 until now

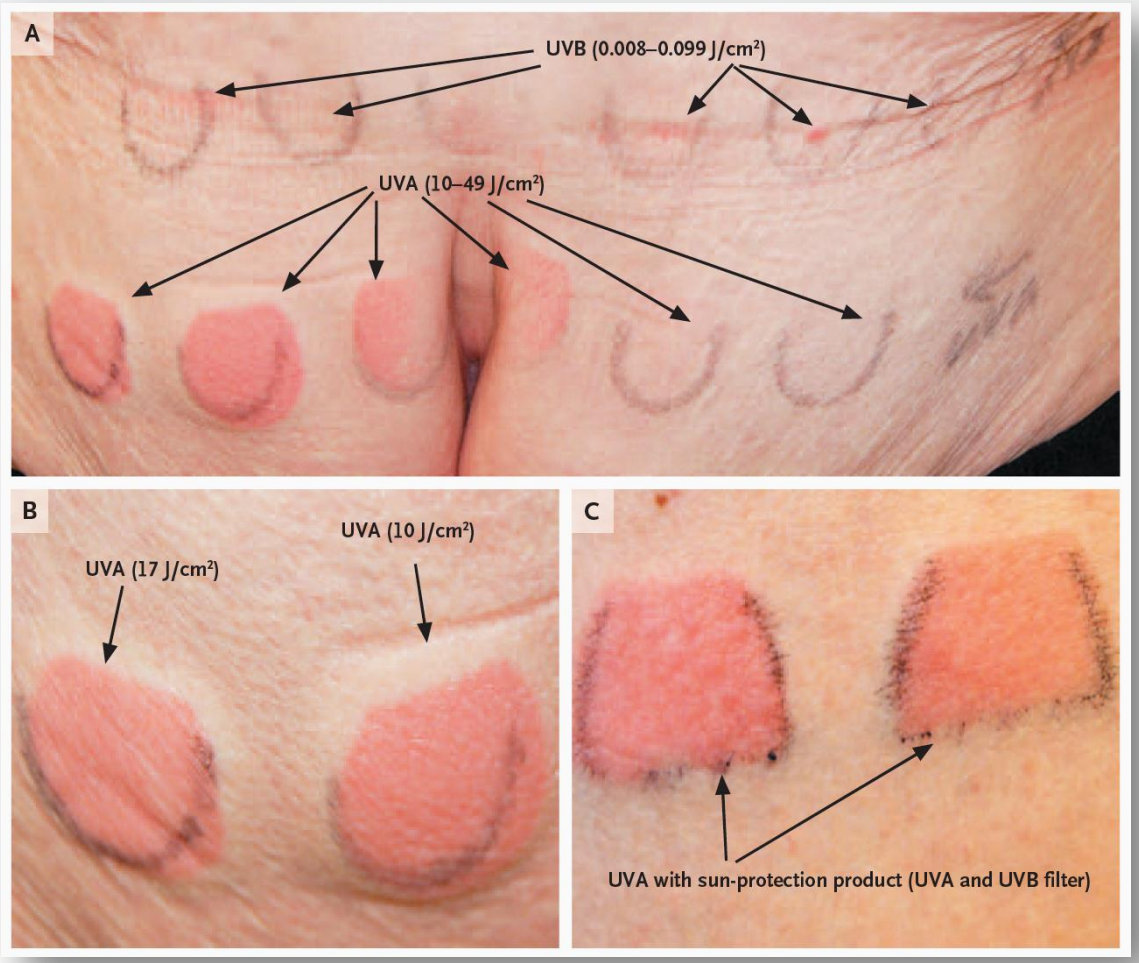
Photosensitivity



- 40 years old male patient
- 3 weeks on Vemurafenib
- Inadvertent exposition of 30 minutes on a cloudy day

- Lesions responded well to topical steroids (betametasonum valeras)
- Intensification of sun protection and no further event

Photosensitivity



Minimal erythema dose

- Normal for UVB
- Much reduced for UVA

UVA properties:

- Penetrate glass
- Constant intensity regardless of daylight & season

Recommendations:

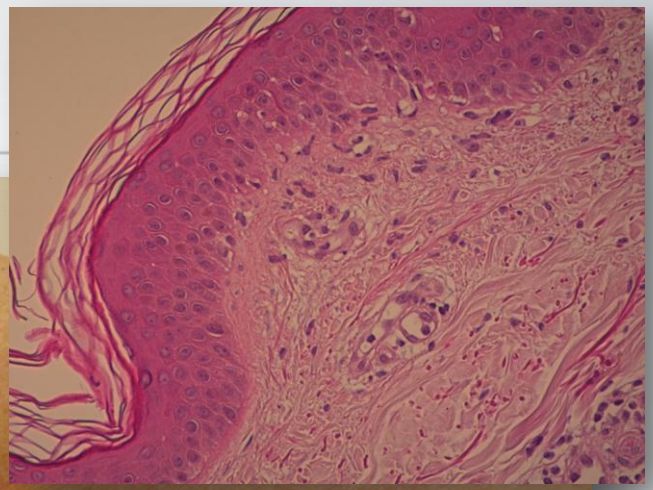
- Broad-spectrum UVA+UVB sun screen protection

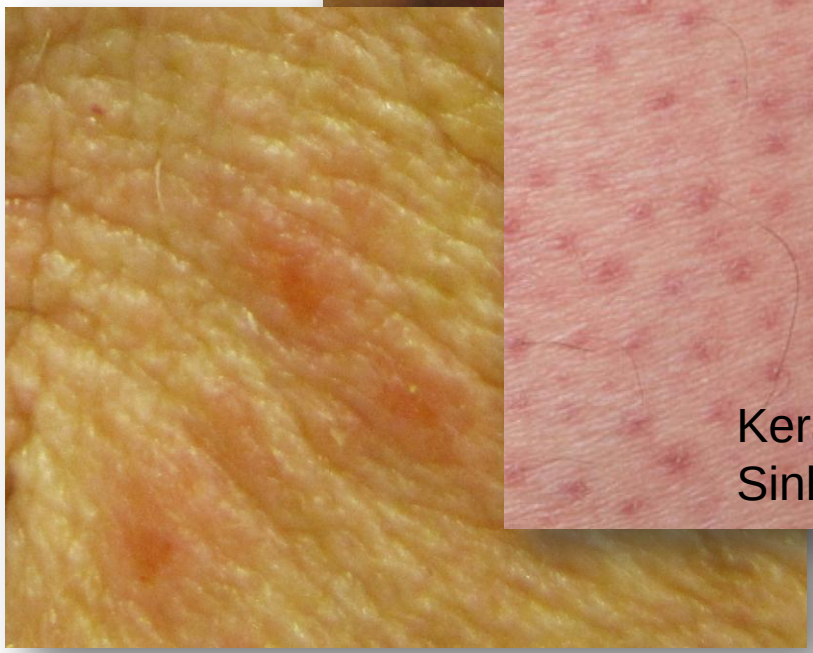
Dummer & al. NEJM 2012

Various forms of rash

- 63 years old woman
- 2 weeks of Vemurafenib:
- Folliculocentric, maculopapular rash, and keratosis pilaris

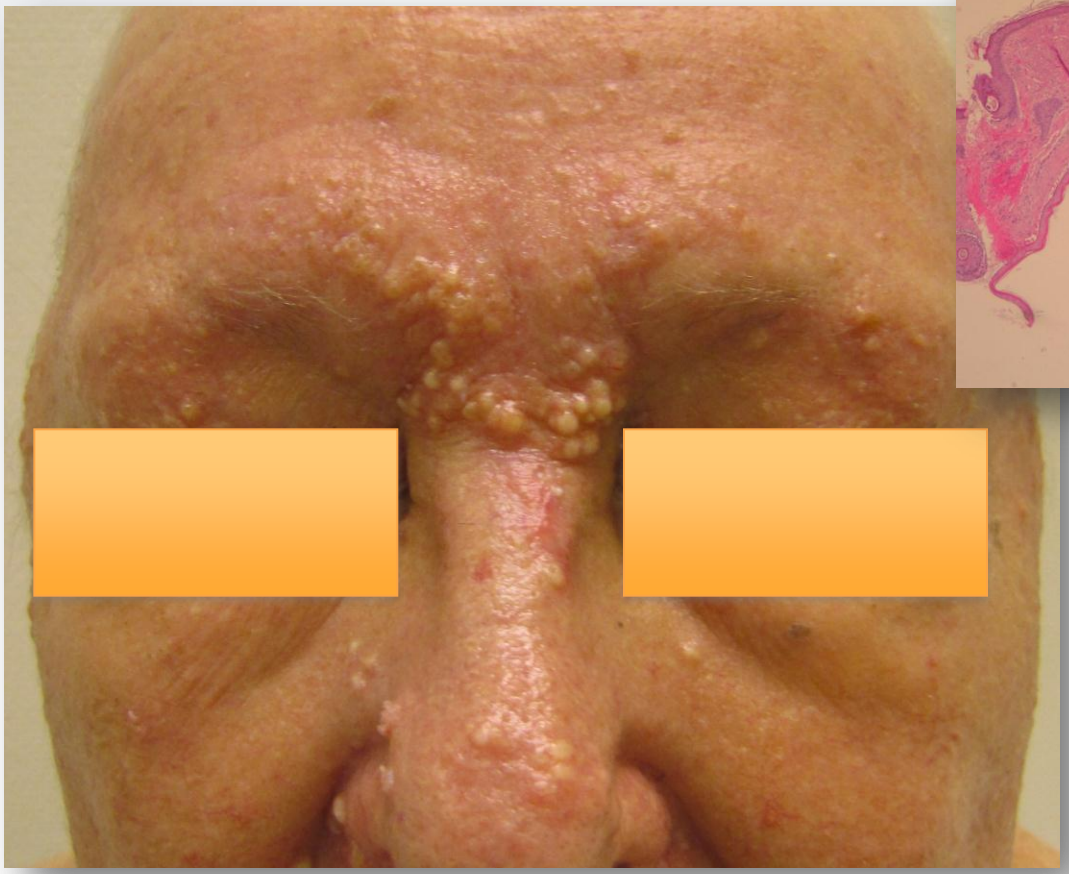
- Interruption of treatment and re-challenge at 75% of the dose
- Good tolerance

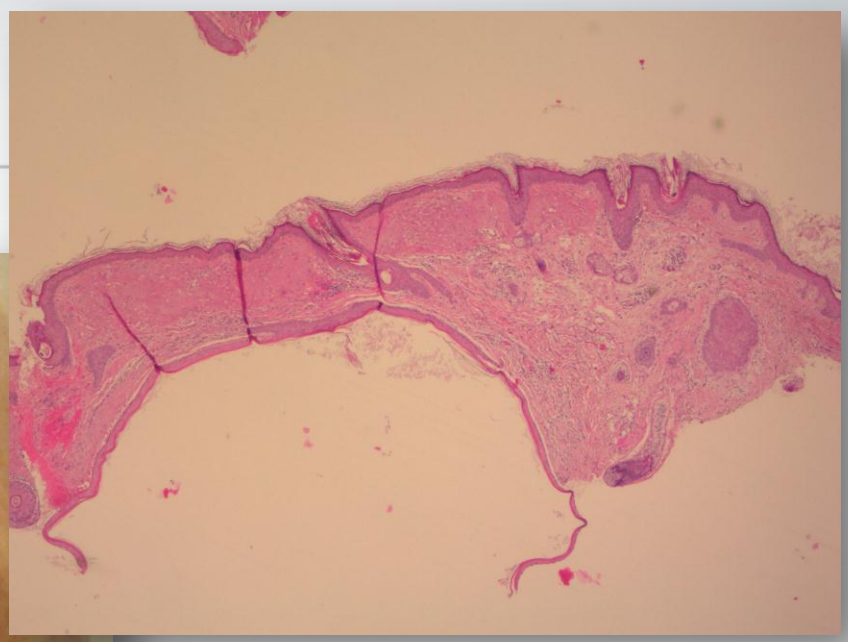




Keratosis pilaris
Sinha & al, *BJD*, 2012

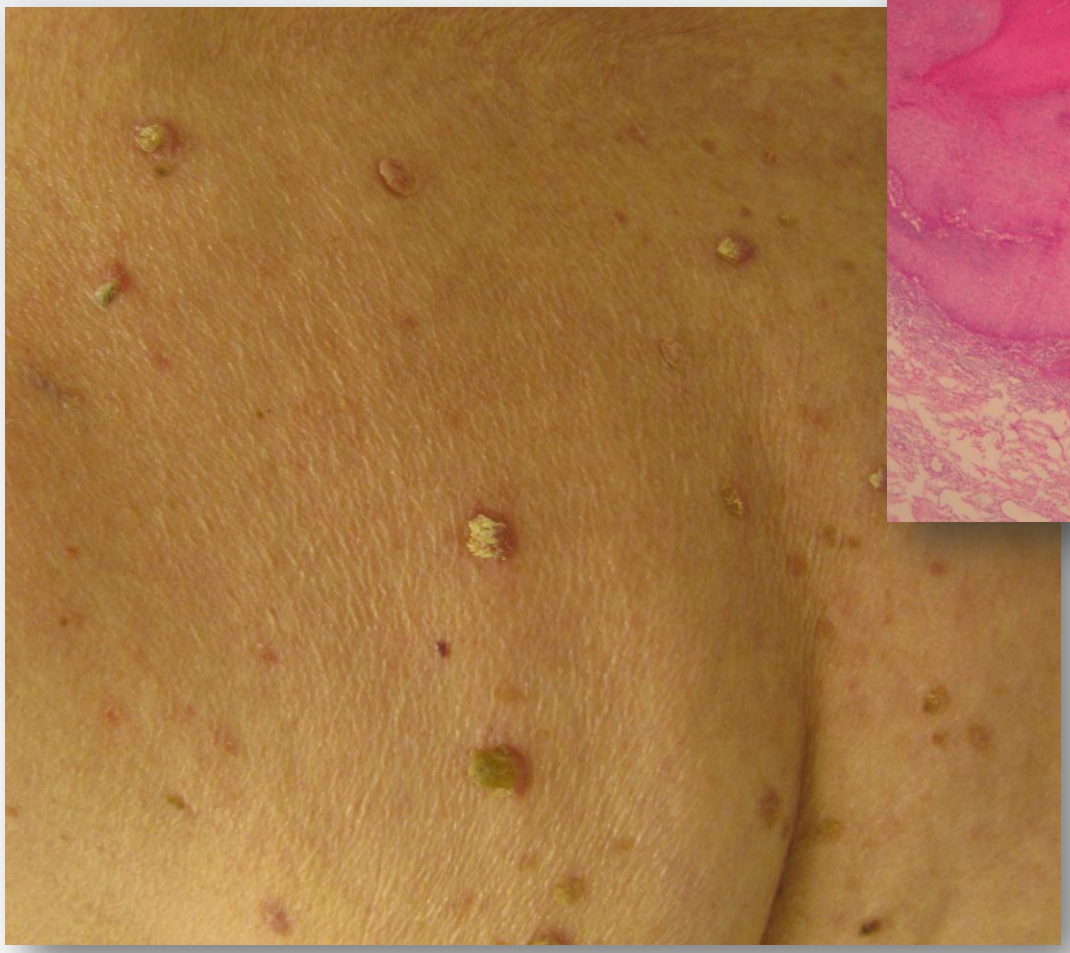
Follicular cysts

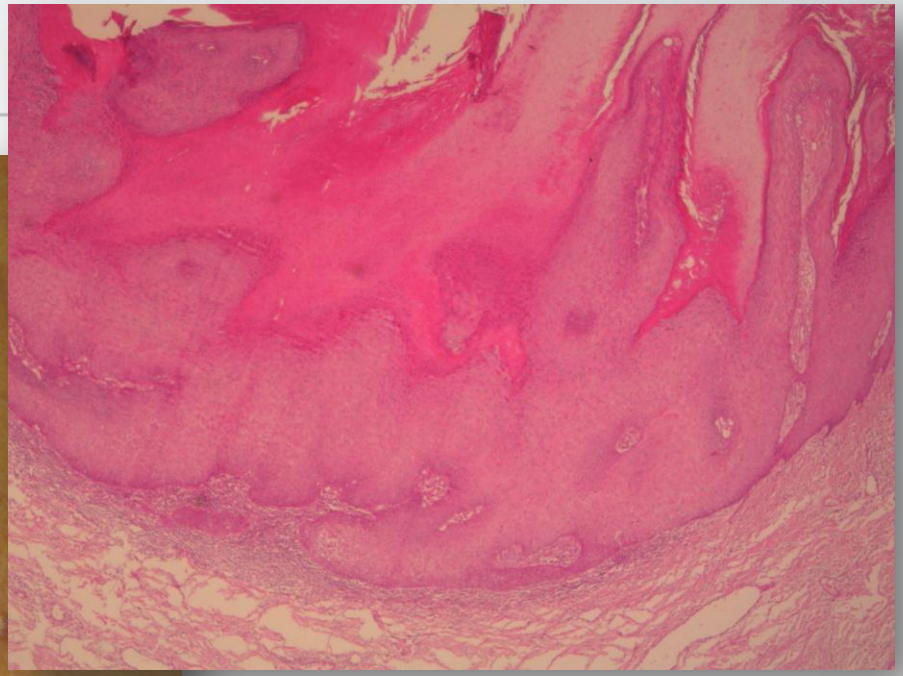




- Vemurafenib has been reduced to 75% of the dose (for an extended rash), with improvement of the lesions and a controlled disease

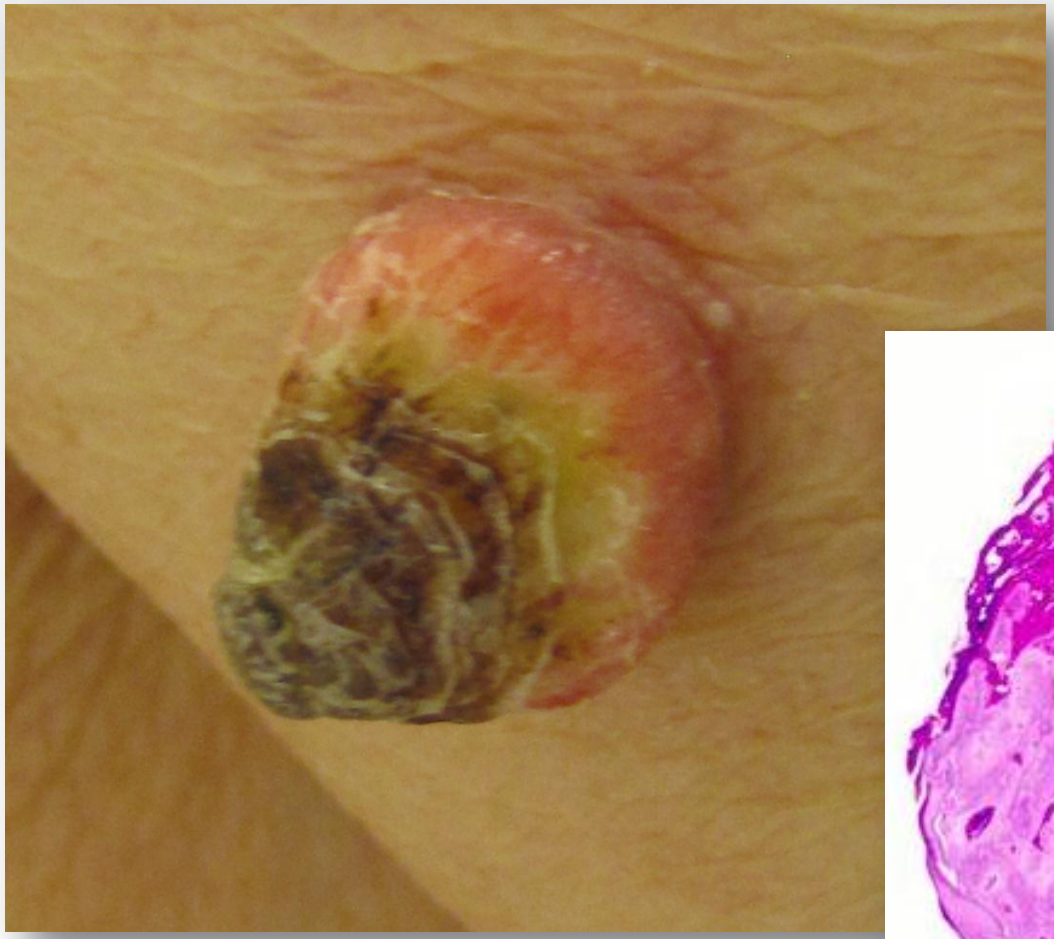
Acanthopapilloma



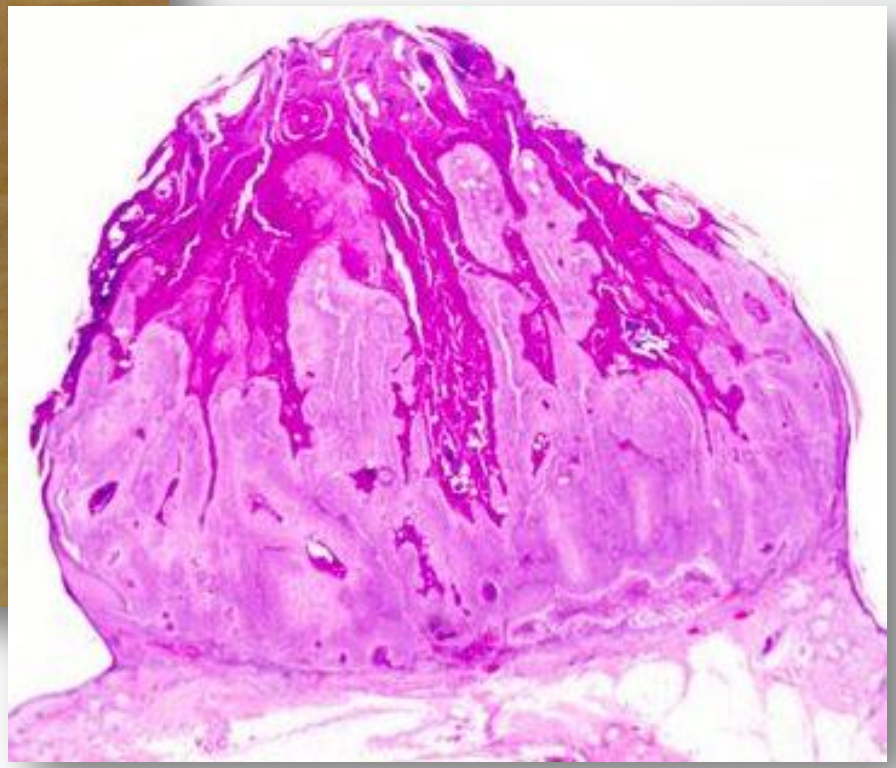


- Selected excisions of rapidly evolving or disgraceful lesions, and close follow up

Keratoacanthoma (KA) and SCC

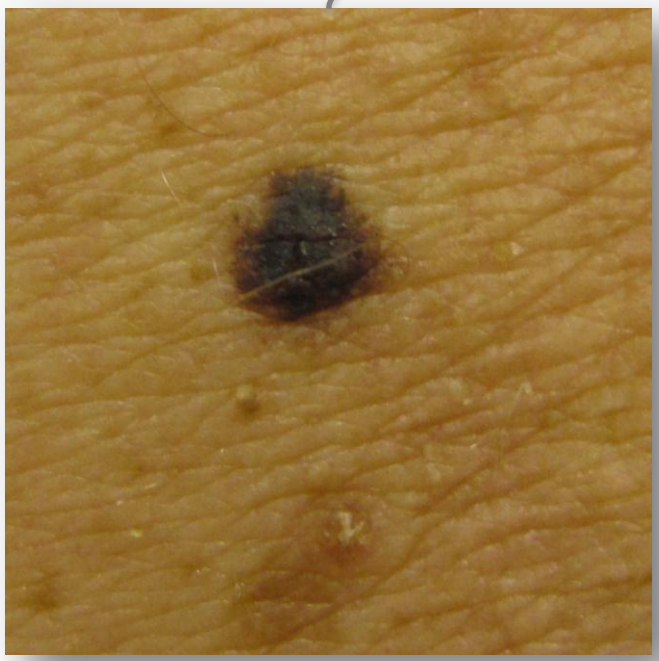


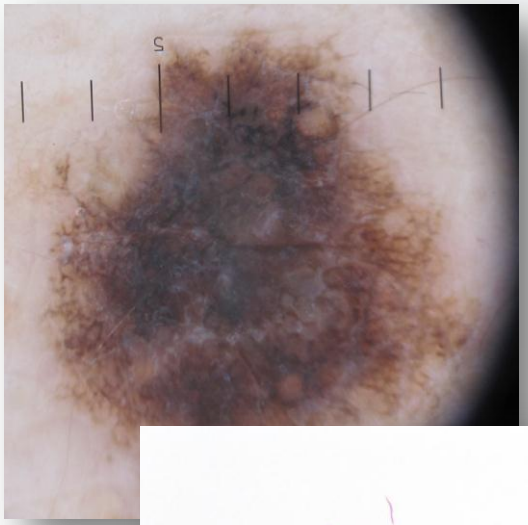
- 78 years old woman (same patient as follicular cysts)

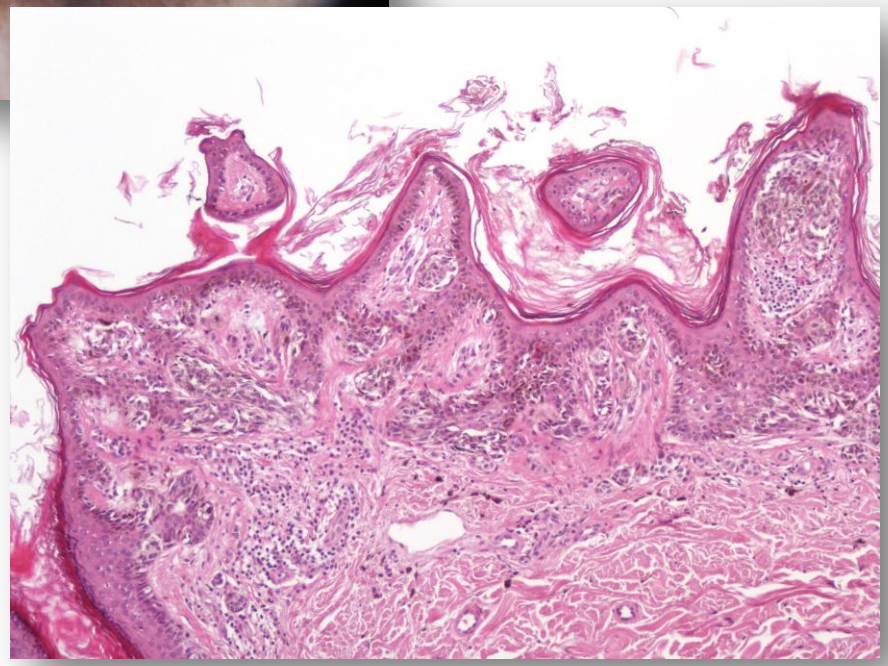


Melanocytic proliferations:

69 years old woman, 5 months on Vemurafenib, new pigmented lesion of the trunk







Diagnostic: BRAF WT dysplastic naevus

Results from phase I-III of class I inhibitors: Zimmer & al, *JCO* 2012

RAS & RAF profiling of 22 melanocytic lesions developed under Vemurafenib:

Characteristic	Primary Melanoma (newly developed)*†			Nevi Removed During *BRAF* Inhibition Therapy*†			Common Nevi*†		
	No.	Median	Range	No.	Median	Range	No.	Median	Range
Total No. of patients	11			8			21		
Female	4			1			12		
Age at diagnosis, years		51	22-77		48	44-66		45	20-76
No. of weeks receiving selective *BRAF* inhibition therapy		8	4-27		17.5	2-42		—	
No. of suspected chronic sunlight-exposed tumor localizations§		5			2			5	
BRAF V600E		0			0			8	
NRAS Q61K/Q61R		1			2			0	
pERK									
SI		2	1-3		2	1-2		2	1-3
NP		3	2-3		2	1-3		2.5	1-3
Score¶		5	4-6		4	3-5		4	3-6
pAKT									
SI		3	2-3		2	2-3		2	1-3
NP		3	3-3		3	2-3		3	2-3
Score¶		6	5-6		5	4-6		5	3-6

Clinical management of KA & SCC

- Surgical excision is the first option
- In case of large number of lesions
  - Surveillance and selected surgery
  - Dose reduction
  - Association of antiproliferative treatments
    - CAVE:
      - No randomized controlled trials
      - Mainly empirical results on small series

Non surgical management:

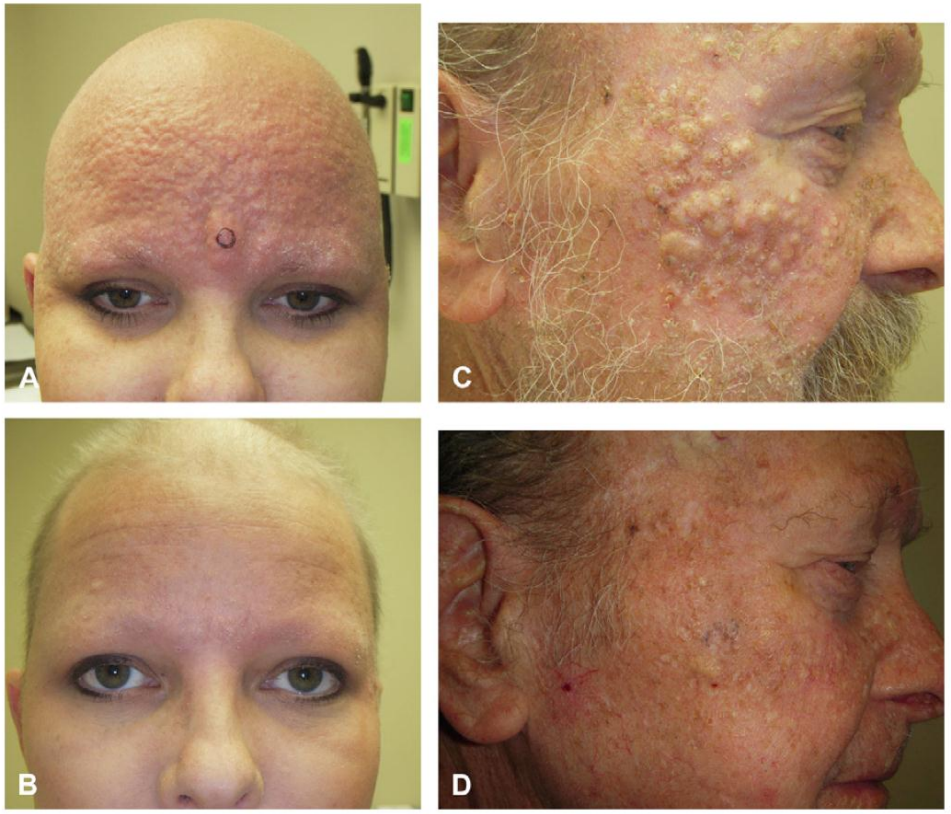
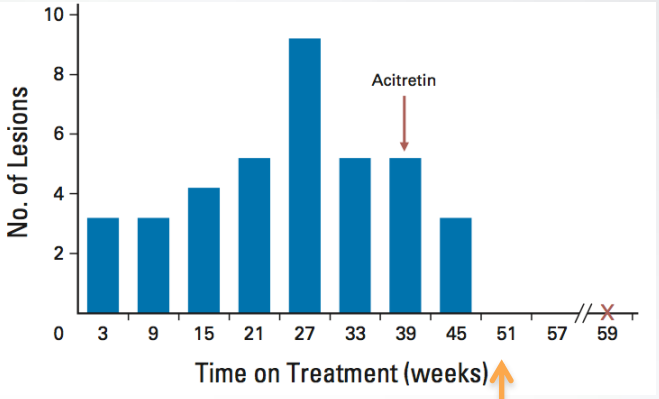


Fig 2. **A**, Well-demarcated erythema and cobblestone appearance of scalp. **B**, Improvement after 8 weeks of topical retinoid therapy. **C**, Prominent follicular plugging of the face. **D**, Improvement after 8 weeks of acitretin 10 mg daily.



Retinoids:

Anforth & al. *JCO,* 2012

Boyd & al. *JAAD,* 2012

5-FU:

Viros & al. *JID* 2012

Photodynamic therapy:

Alloo & al. *Arch. Dermatol.* 2012

Conclusion

- Type I BRAFi toxicities (Vemurafenib, Dabrafenib)
  - cannot be prevented (apart from photosensitivity)

  But
  - rarely necessitate permanent treatment discontinuation
  - generally manageable with
    - local complete surgical excision (KA, SCC)
    - antiproliferative treatment (retinoids, 5FU) association
    - supportive care (antihistaminic, NSAID, steroids)
    - dose reduction
    - and soon, adding a MEK inhibitor!

- CAVE: adjuvant setting and non cutaneous SCC!

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