Erdheim-Chester disease and Skin issues

For ECD global Alliance meeting
Milano 2019

STÉPHANE BARETE, MD, PHD

UNIT OF DERMATOLOGY

PITIÉ -SALPÊTRIÈRE HOSPITAL

PARIS

stephane.barete@aphp.fr

Introduction

- Erdheim-Chester (ECD) is an orphan disease included in the spectrum of systemic non-langerhans cell histiocytosis with frequent recurrent $BRAF^{V600E}$ mutation
- Skin manifestations of ECD are already described and recent classification has updated ECD in « L » category of the new classification of histiocytoses
- As many molecular targeted therapies (MTT) are currently used for patients with BRAF mutation, one might expect MTT toxicities including skin side effects

Skin issues

- ECD skin manifestations
- ECD and MTT skin toxicities

ECD and skin manifestations

- Recently described ≃ 7 years

  Arnaud L et al Blood 2011, Haroche J et al Blood 2012, Haroche J et al Rheum Dis Clin North Am. 2013.

- Prevalence: 19-28 % of ECD patients

- Various clinical manifestations

- First Series n=40 pts

  Chasset F, Barete S, Charlotte F et al JAAD. 2016;74:513-20

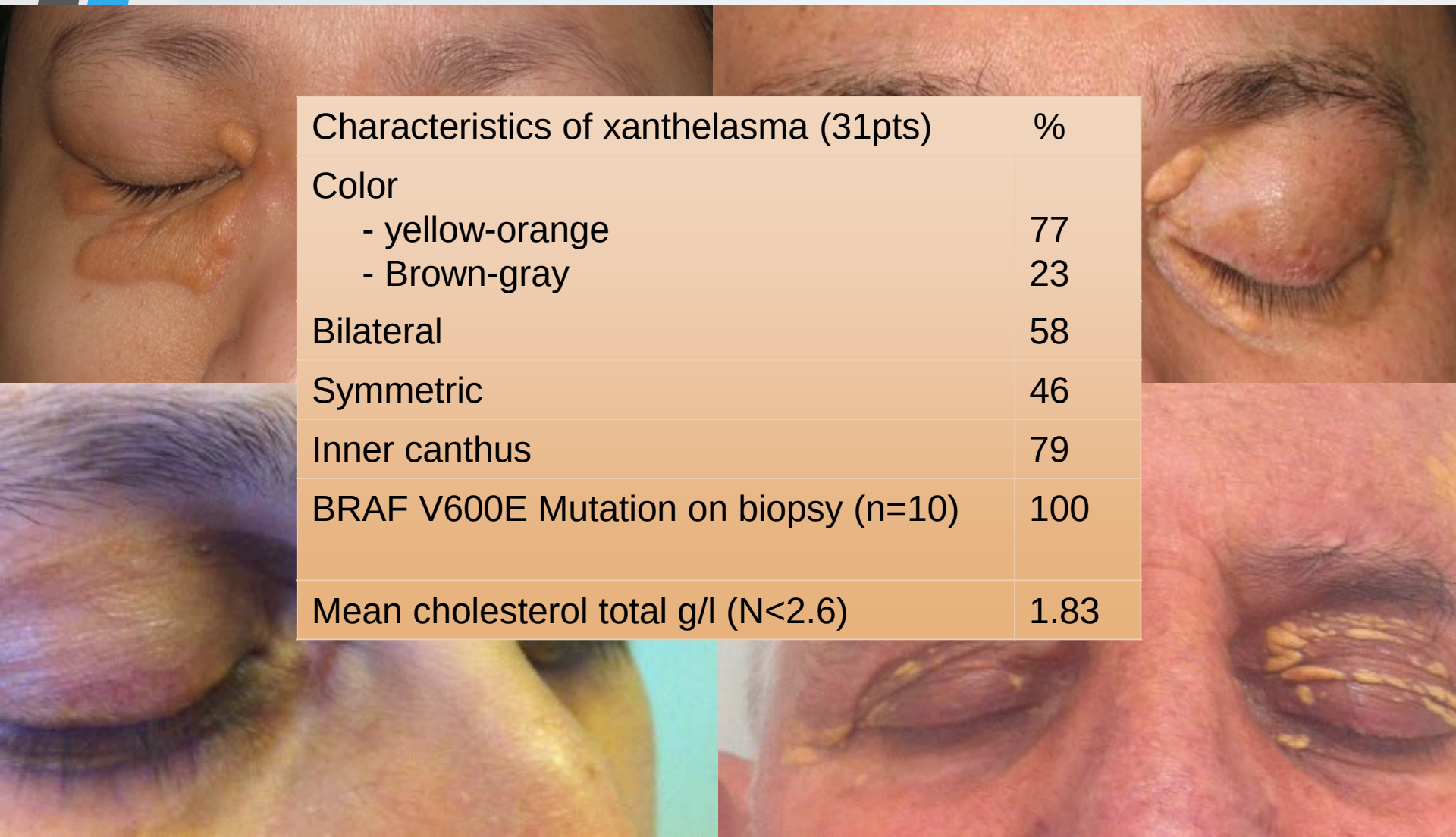
Patients and methods

- Retrospective study, 40 patients with ECD
- Aims:
  - Describe skin manifestations associated with ECD
  - Search for xanthelasma-like lesions considered as specific
  - Search for others « histiocytic cells » lesions
  - Pathology analysis of skin biopsies
  - Case-control study on *xanthelasma-like* ECD compared with *classic xanthelasma* as controls with morphology and immunohistochemical parameters analysis .
    - 7 cases compared each to 2 controls without ECD
  - BRAF-status on skin biopsies

Results: ECD characteristics

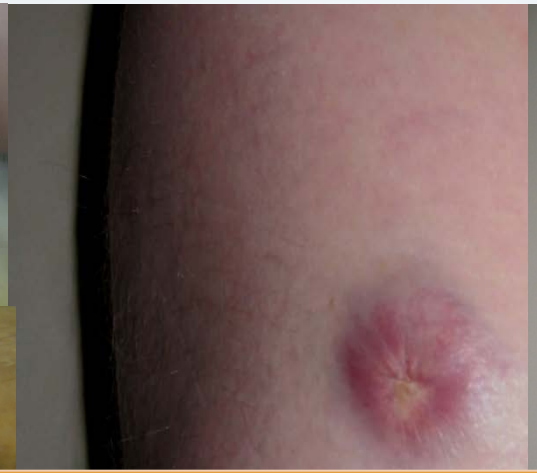
Variables	n (%)
ECD	31 (25)
ECD + Langerhans cells histiocytosis	9 (7)
Male sex	27 (67)
Median age at first symptom, y (range)	51 (23-80)
Median age at diagnosis, y (range)	54.5 (26-81)
Diagnostic delay, y (range)	3 (0-17)
Alive at last follow-up	33 (83)
First symptom	
Cutaneous	12 (30)
Xanthelasma-like lesions	10 (83)
Other lesions	2 (17)
Neurologic symptoms*	7 (18)
Bone pain	5 (12)
Diabetes insipidus	6 (15)
Respiratory symptoms†	4 (10)
Others‡	6 (15)
Site of the first biopsy	
Skin	15 (38)
Perirenal fat	14 (35)
Cerebral	3 (7)
Bone	2 (5)
Other§	6 (15)
Appearance of specific skin lesion before diagnosis	26 (79)
ECD diagnosed based on the skin lesion	14 (36)
BRAF^{V600E} status	
Positive	25 (76)
Negative	8 (24)
Noninformative sample or NA	7 (18)

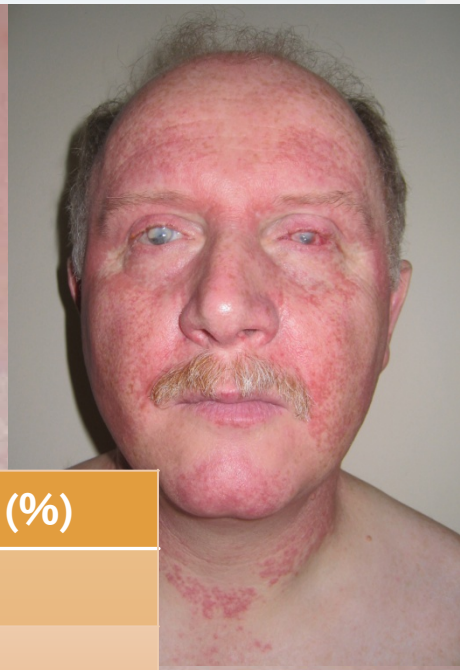
Xanthelasma-like lesions



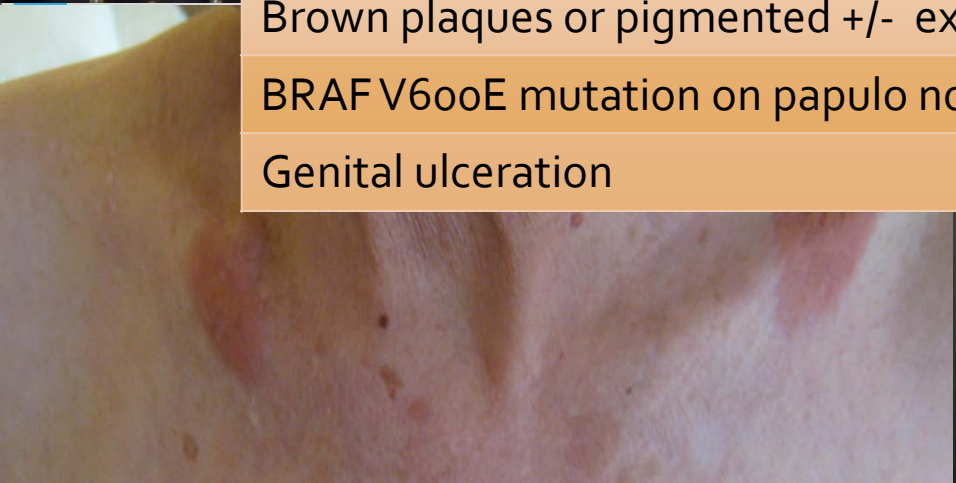
Characteristics of xanthelasma (31pts)	%
Color - yellow-orange - Brown-gray	 77 23
Bilateral	58
Symmetric	46
Inner canthus	79
BRAF V600E Mutation on biopsy (n=10)	100
Mean cholesterol total g/l (N<2.6)	1.83

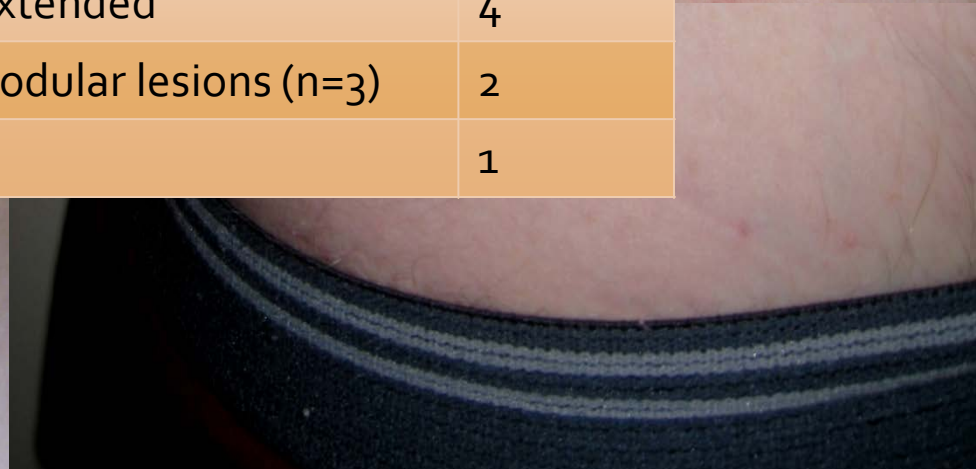
Others specific lesions of ECD



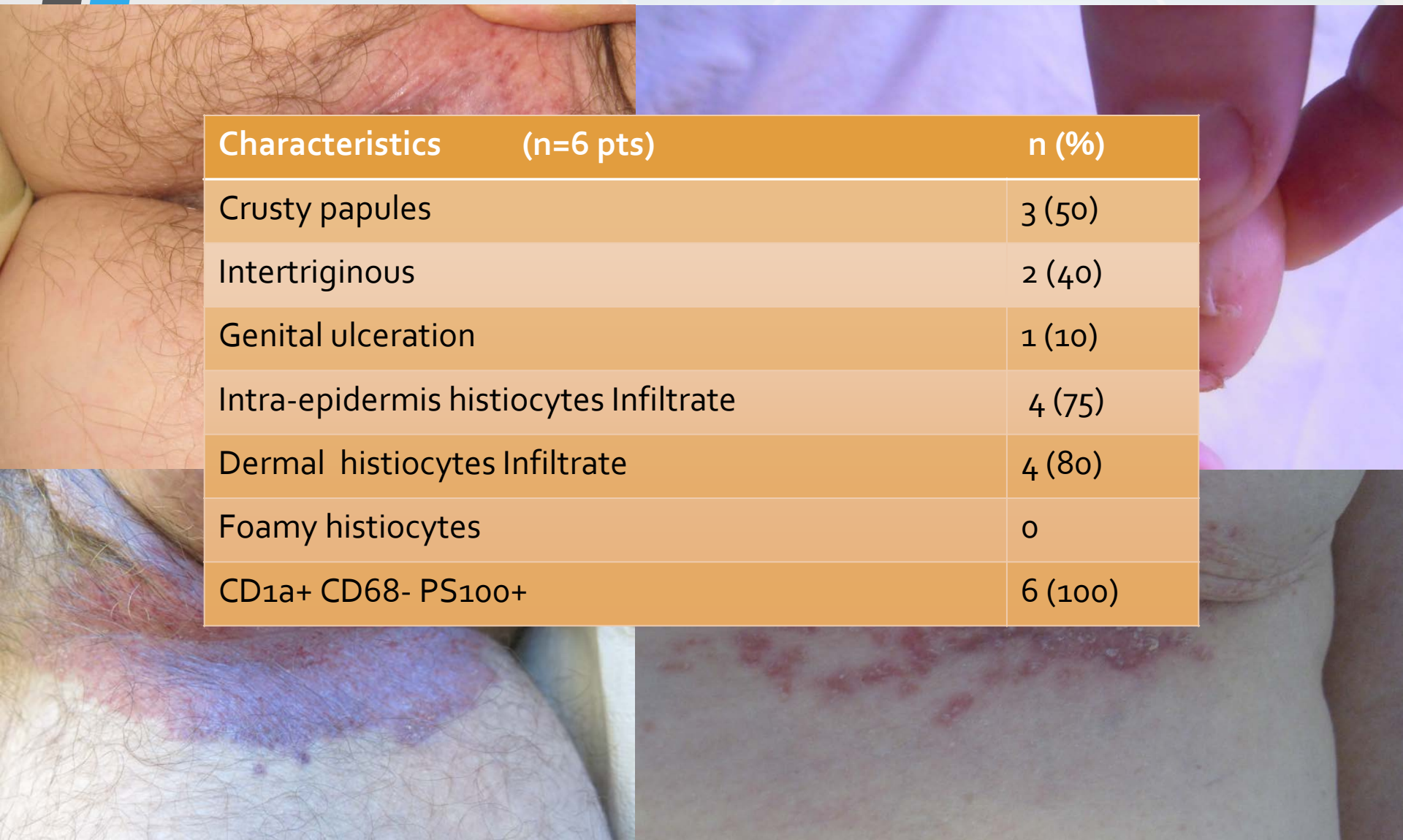


Characteristics of others lesions (n=9 pts)	n (%)
Papulo nodular lesions	4
Brown plaques or pigmented +/- extended	4
BRAF V600E mutation on papulo nodular lesions (n=3)	2
Genital ulceration	1





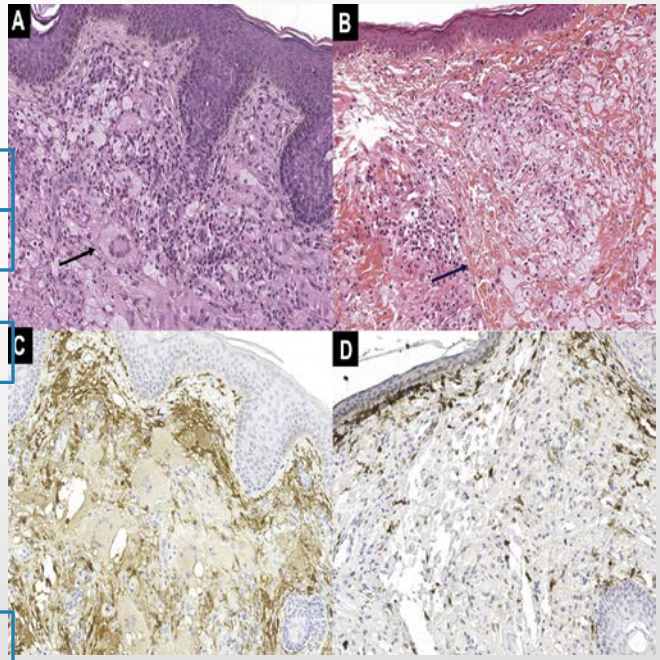
Associated langerhans cells histiocytes (mixed form)



Characteristics (n=6 pts)	n (%)
Crusty papules	3 (50)
Intertriginous	2 (40)
Genital ulceration	1 (10)
Intra-epidermis histiocytes Infiltrate	4 (75)
Dermal histiocytes Infiltrate	4 (80)
Foamy histiocytes	0
CD1a+ CD68- PS100+	6 (100)

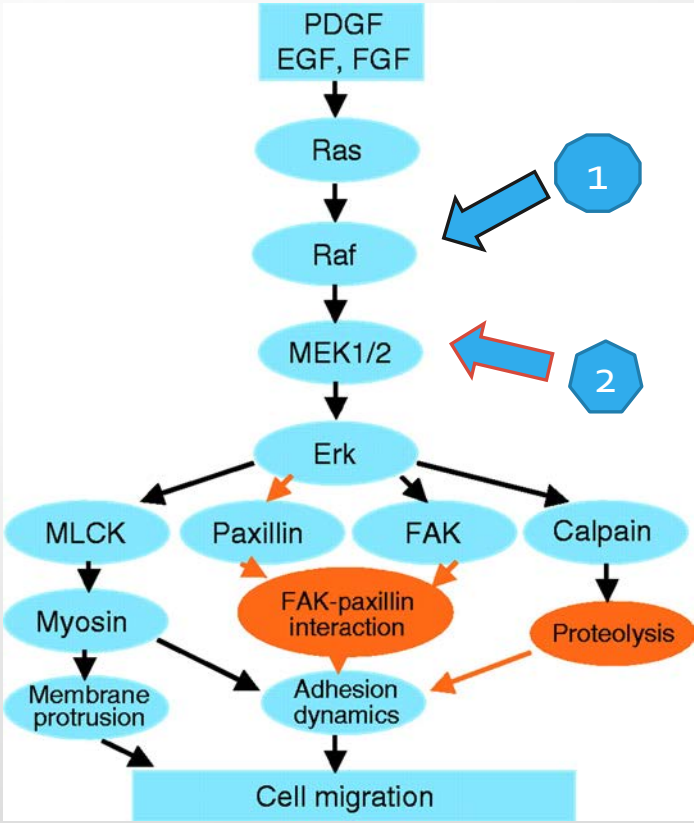
Pathological comparison between ECD xanthelasma like lesions and classic xanthelasma

Features	ECD XLL	Classic xanthelasma	*P* value
Histiocyte infiltrate reaching more reticular dermis	3/7	0/14	.02
High density of multinucleated cells (score = 2)	3/7	0/14	.02
High density of Touton cells (score = 2)	5/7	1/14	.005*
High density of foamy cells (score = 2)	7/7	14/14	NS
Fibrosis	3/7	14/14	.005*
Immunostaining with $CD68^+$ >50% of the histiocytes	7/7	14/14	NS
Immunostaining with $CD163^+$ >50% of the histiocytes	7/7	14/14	NS
Immunostaining with S100 $protein^+$	1/7	2/14	NS
Immunostaining with $CD1a^+$	0/7	0/14	NS
Immunostaining with $FXIII^+$ >30% of the foamy cells	7/7	3/14	.001*



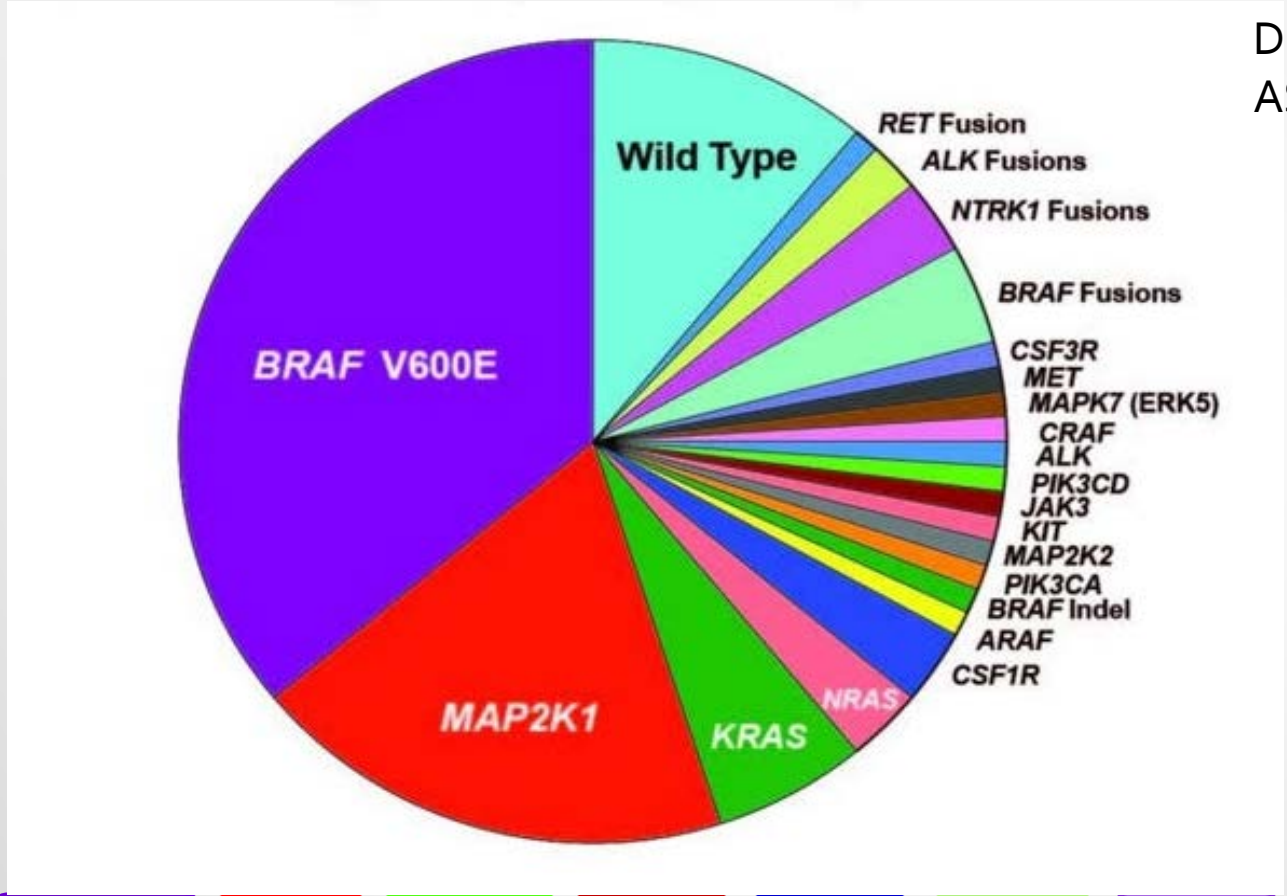
ECD therapy and skin toxicities

- Large developpement of MTT in metastatic melanoma with BRAF mutation has improved global knowledge about skin MTT toxicities
- MTT are required for ECD patients with BRAF mutation (>55%)
- Targets are kinases on MAPK pathway using:
  - BRAF inhibitor
    - (vemurafenib/dabrafenib)
  - MEK inhibitor
    - (cobimetinib/trabetinib)
  - Combinations of KI (combotherapy)



Mutational Landscape of HCL And Targets

N= 218 patients
Durham BH et al.
ASH 2018



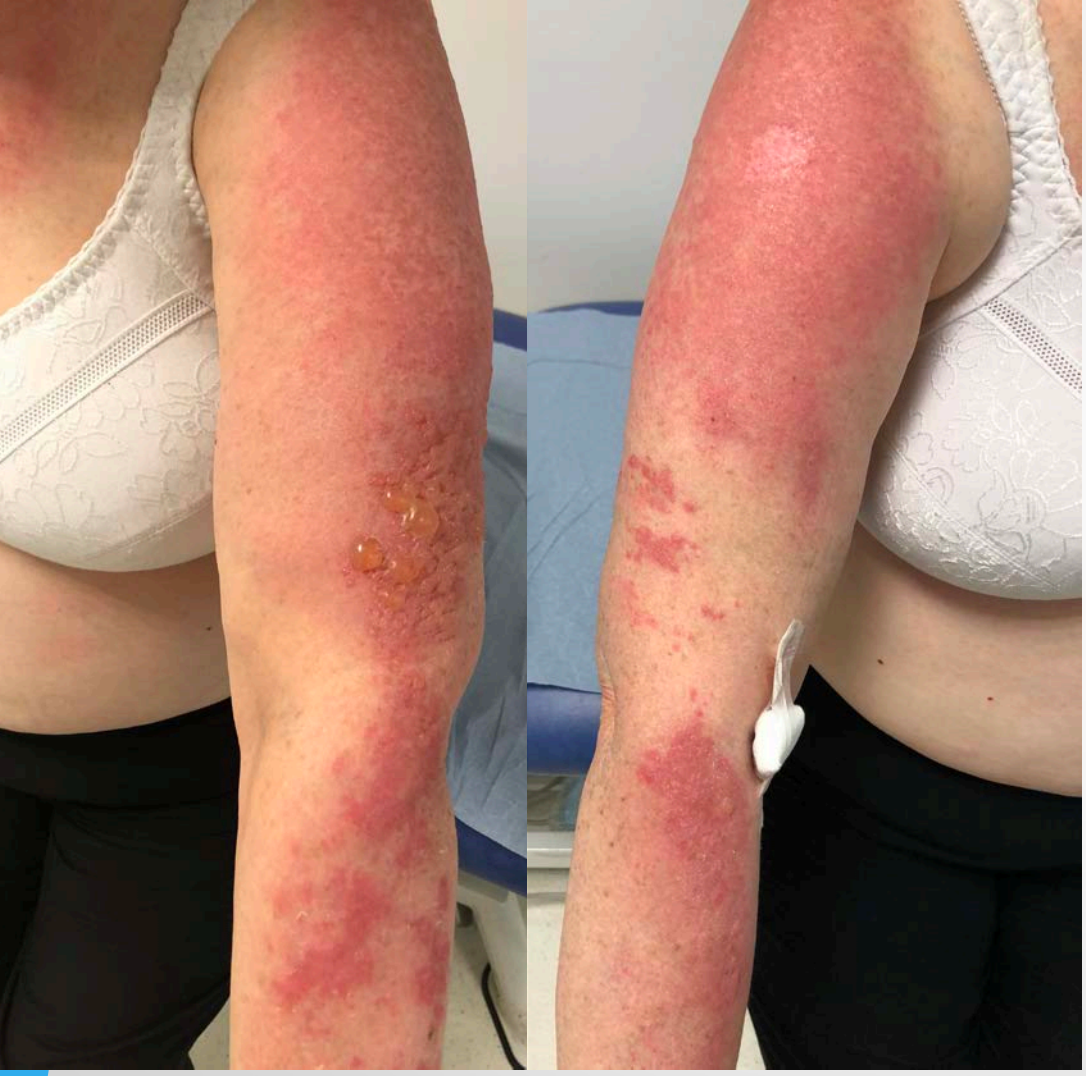
BRAF V600E	MAP2K1 /K2	Other RAF/MAPK KRAS/NRAS mutations	BRAF fusion	CSF1R	ALK Fusions	NRTK fusion
BRAF inhibitors Vemurafenib+++ dabrafenib	MEK inhibitors Cobimetinib+++ trametinib			CSF1R inhibitor	ALK inhibitor	NRTK Fusion Inhibitor

Currently available

Eli L Diamond et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms
Nature 2019, 521-525

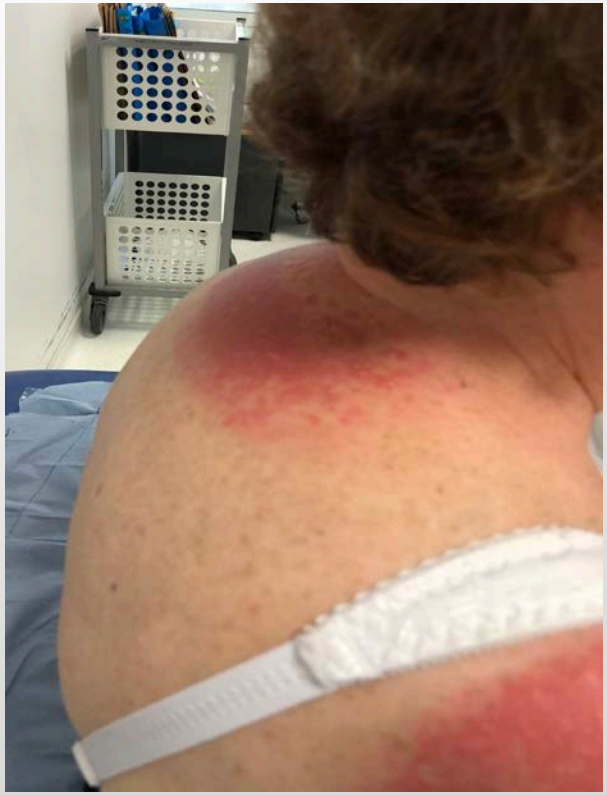
MTT skin toxicities (BRAFi)

- Toxicities with BRAF inhibitors alone
  - Vemurafenib
  - Dabrafenib
- Firstly observed (2012)
- Updating management
- Dermatological support

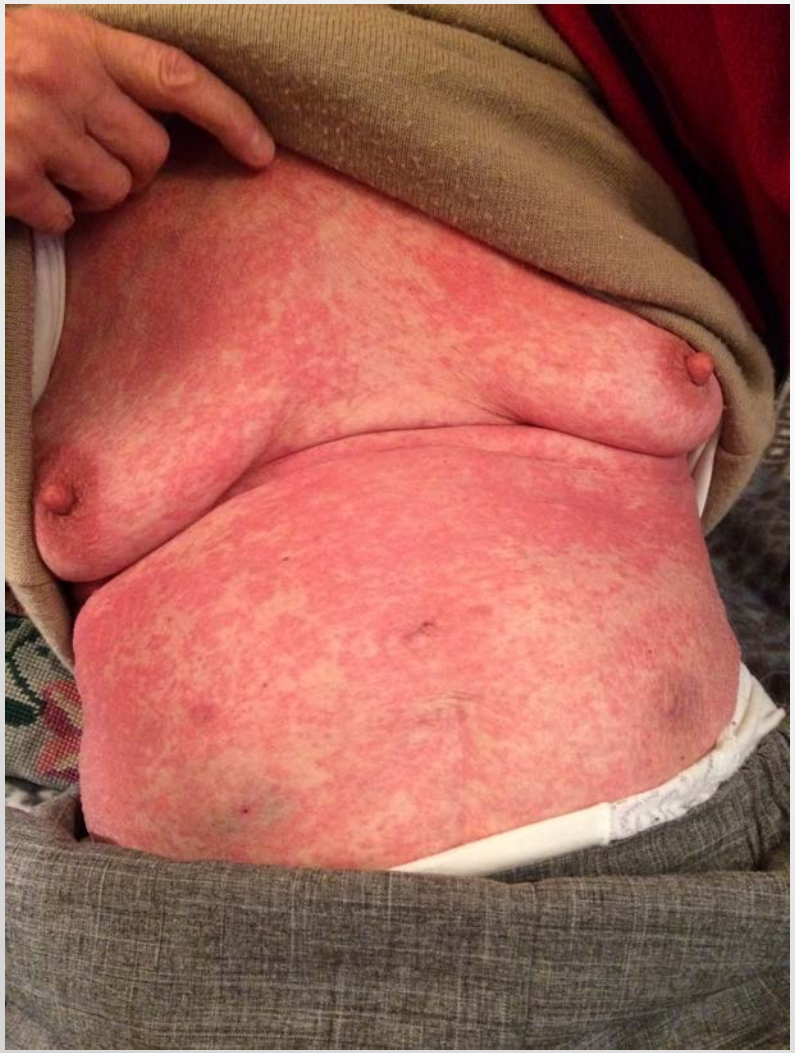


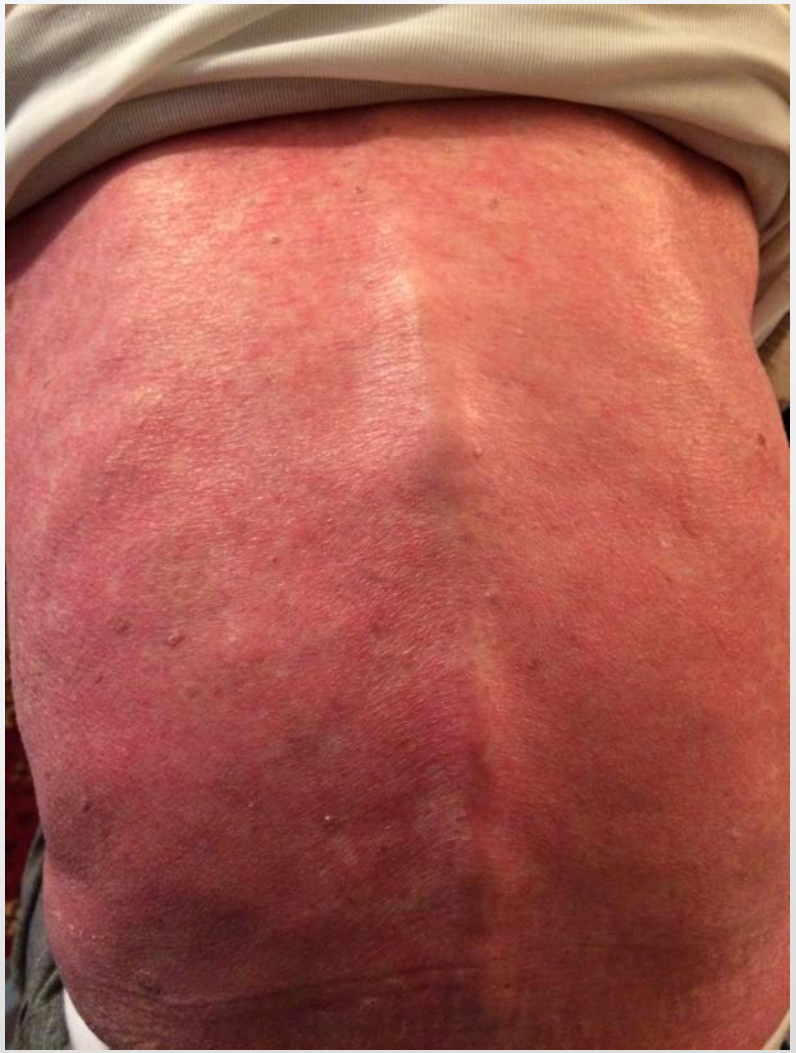
Photosensitivity with vemurafenib and sunburn with blisters of the harms and back.

- Explanation for sun-behavior
- Prevention
- Education
- Sun protection

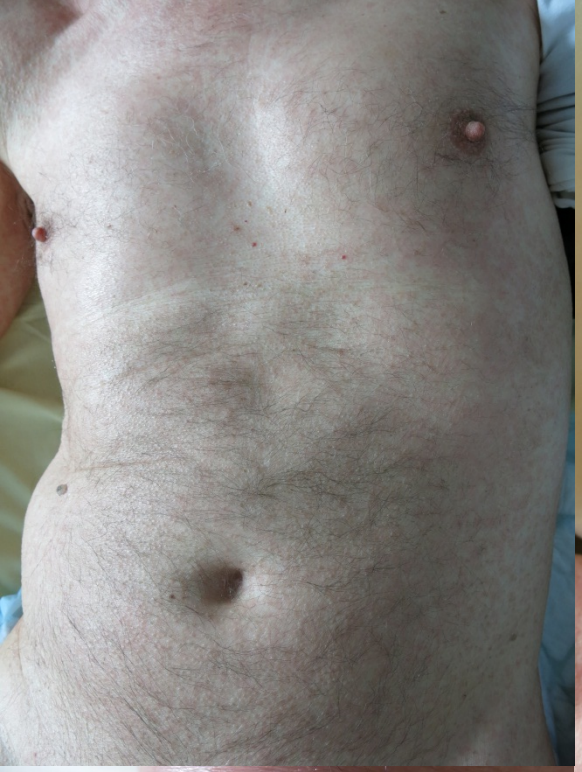


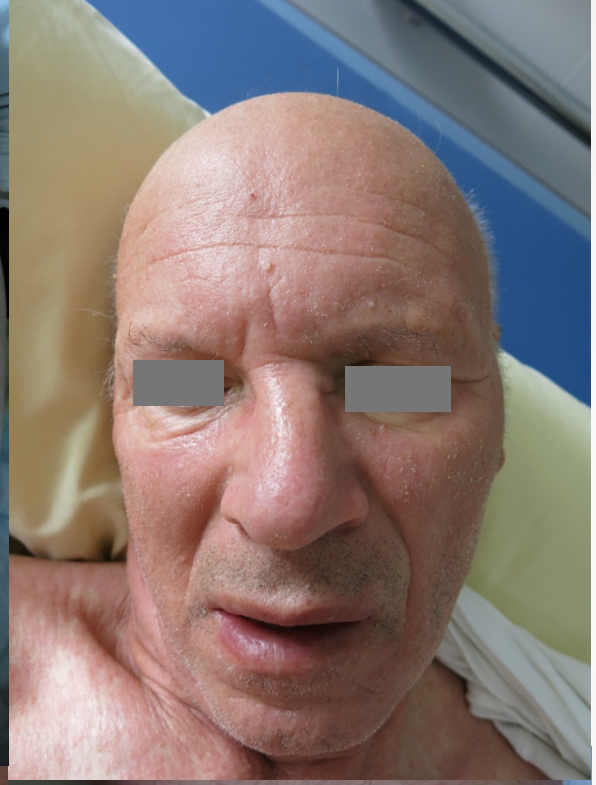
Maculo-papular erythema of the trunk with vemurafenib at D21

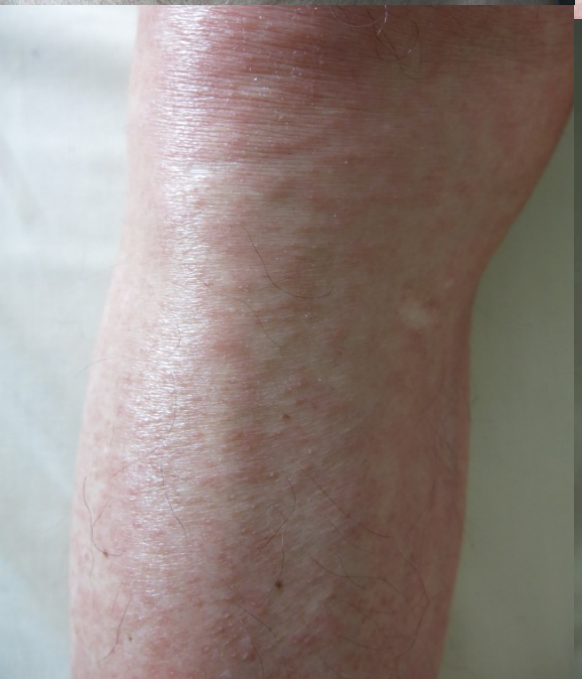


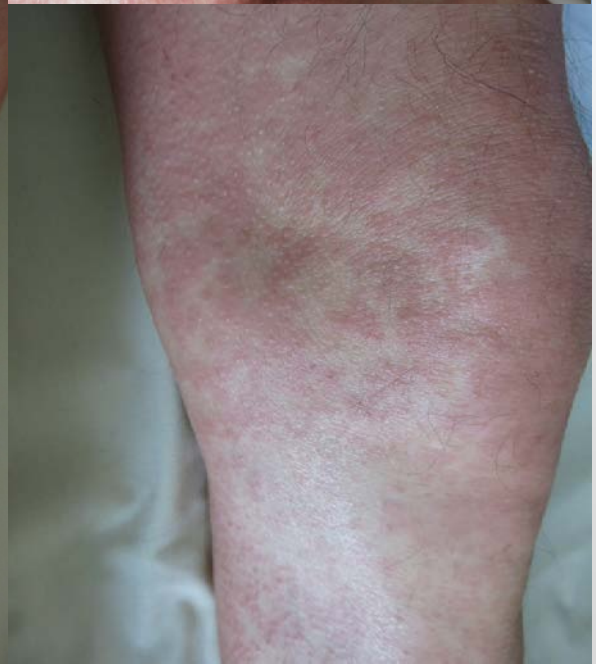


Munch M, Peuvrel L, Brocard A, Saint Jean M, Khammari A, Dreno B, Quereux G. Early-Onset Vemurafenib-Induced DRESS Syndrome. Dermatology. 2015 Sep 30.







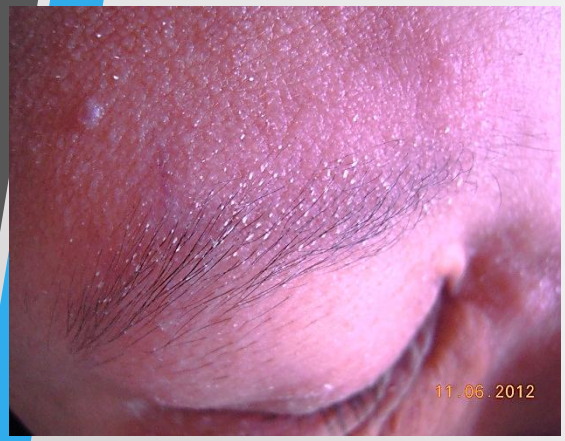


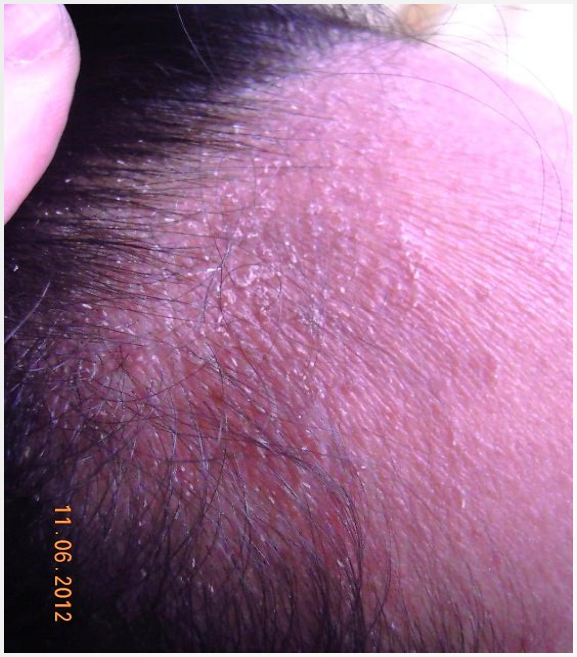
DRESS with vemurafenib

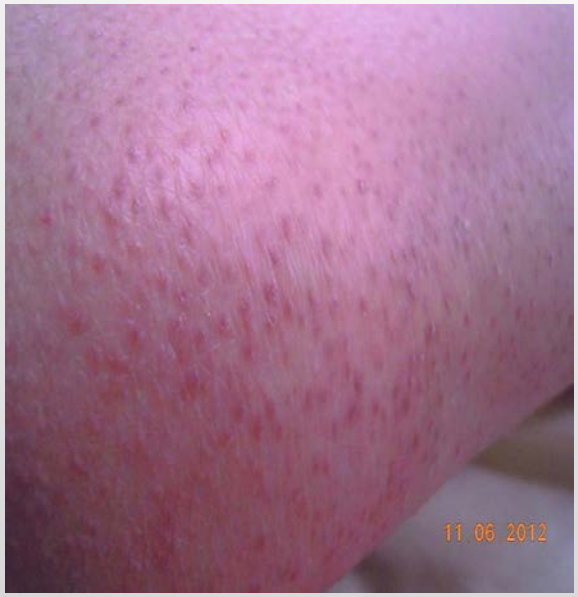
- Potential life threatening
- Need to stop drug
- Declare for PV
- Crossreact with dabrafenib++

1: Wenk KS, Pichard DC, Nasabzadeh T, Jang S, Venna SS. Vemurafenib-induced DRESS. JAMA Dermatol. 2013 Oct;149(10):1242-3.

2: Gey A, Milpied B, Dutriaux C, Mateus C, Robert C, Perro G, et al.Severe cutaneous adverse reaction associated with vemurafenib: DRESS, AGEP or overlap reaction? J Eur Acad Dermatol Venereol. 2014 Aug 29.



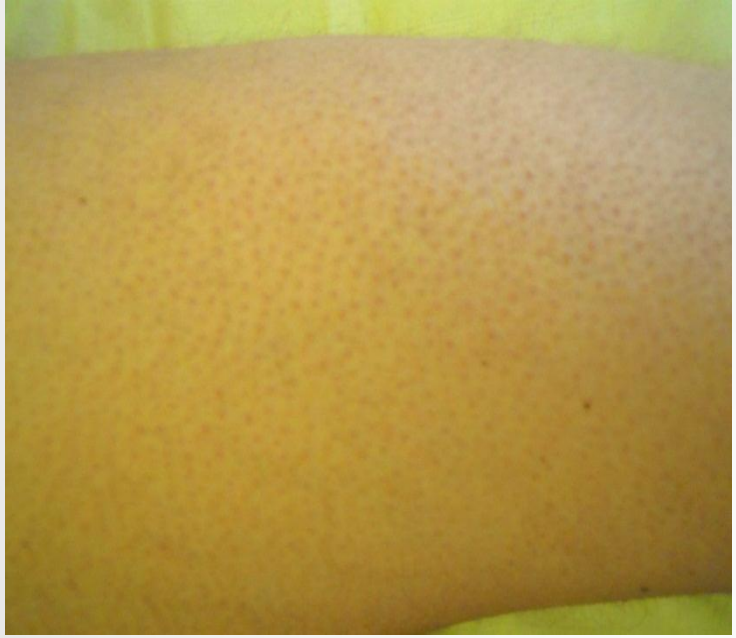


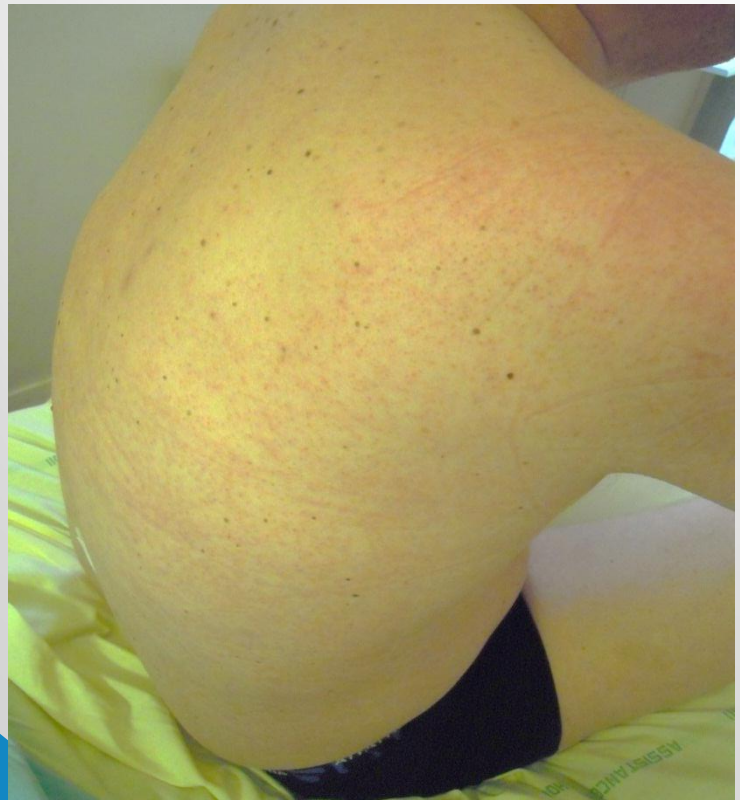


Follicular/pilaris Hyperkeratosis

- Most frequent AE (60%)
- Start D7 or later
- Face , Limbs
- Emollient usefull
- Exfoliative cream
- Disappear with stop of the drug

Hyperkeratotic papules

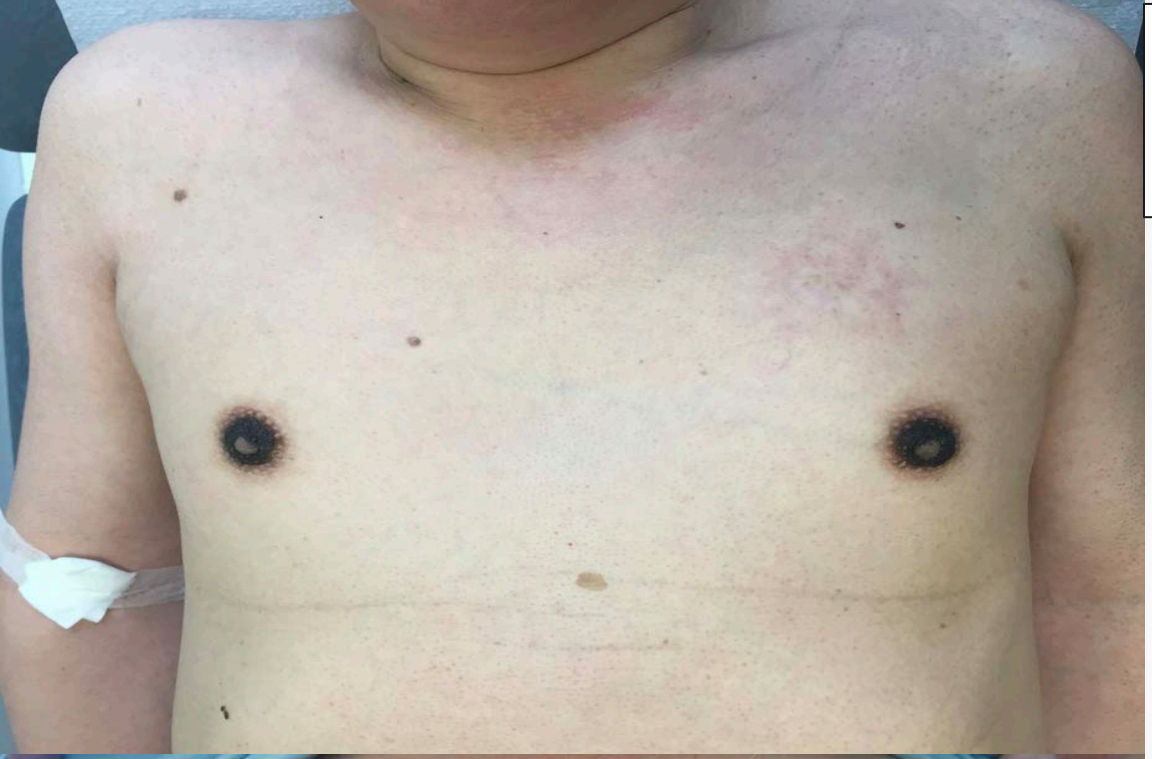


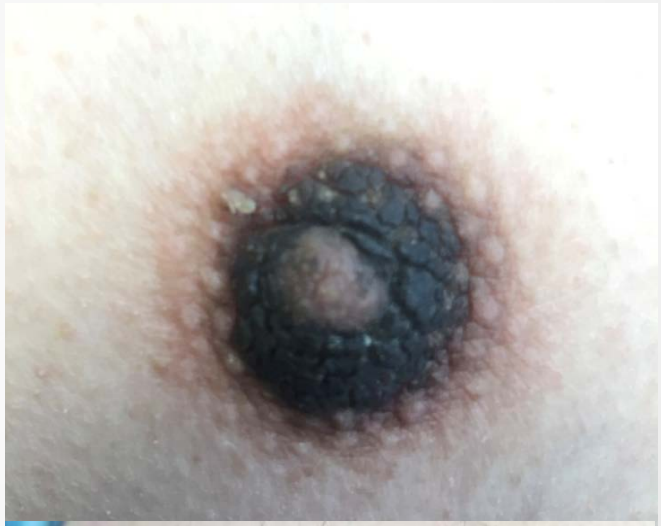


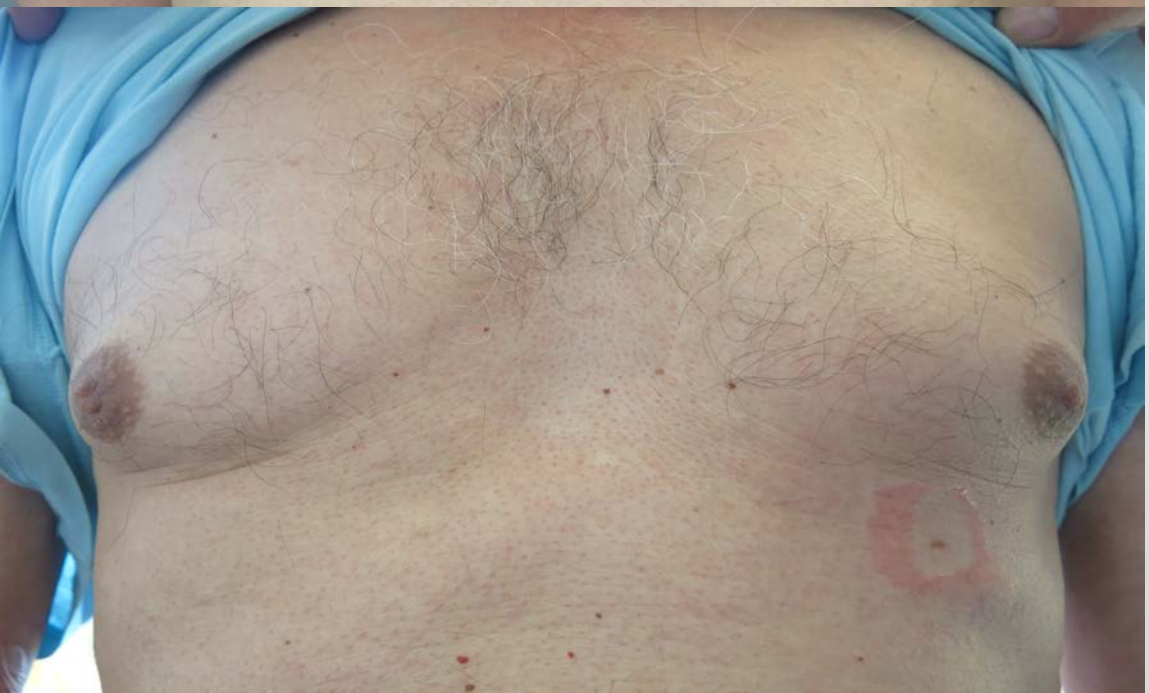
Follicular hyperkeratosis of the limbs and back

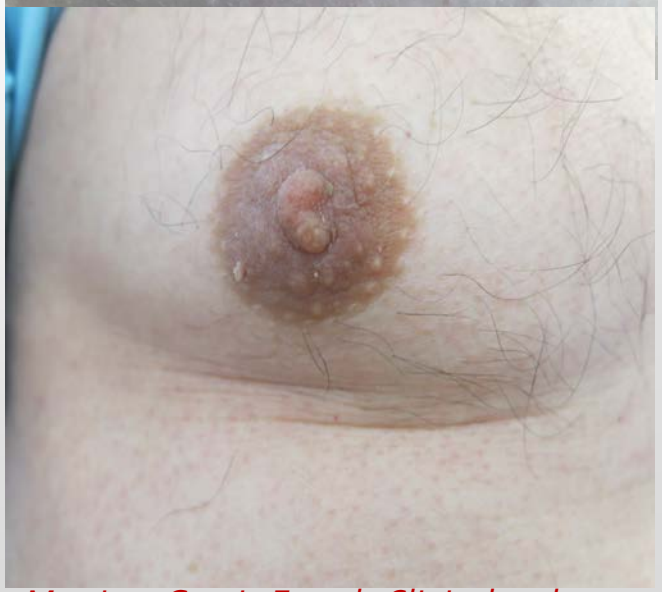
- Itching
- Aesthetical impairment
- Moisturizing cream
- Exfoliating cream
- Educational program: Inform the patient for the frequent observation of this side effect

Kyperkeratosis of the nipples and areola after 3 months of vemurafenib









Martinez Garcia E et al . Clinical and experimental dermatology 2016; 41 : 148-151

RASopathic alopecia:
Hair changes associated with vemurafenib therapy

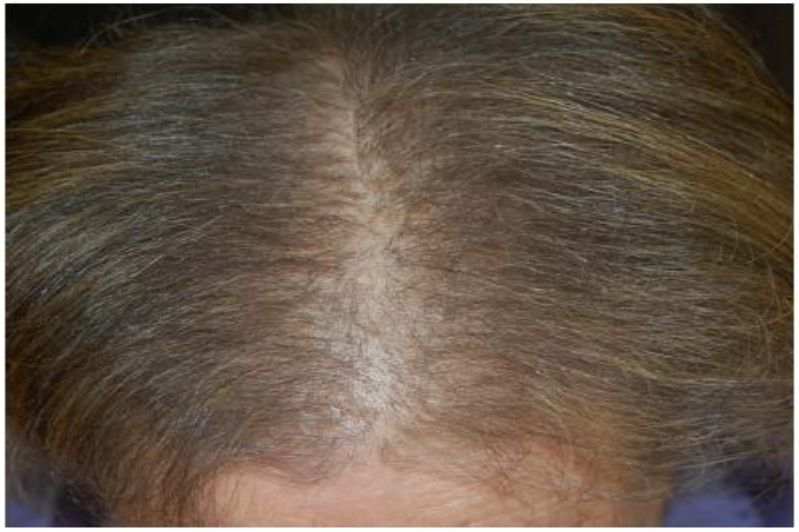


Fig 1. Clinical presentation of hair effects induced by vemurafenib. Diffuse hair loss and dystrophic aspect of the hair on global photography.

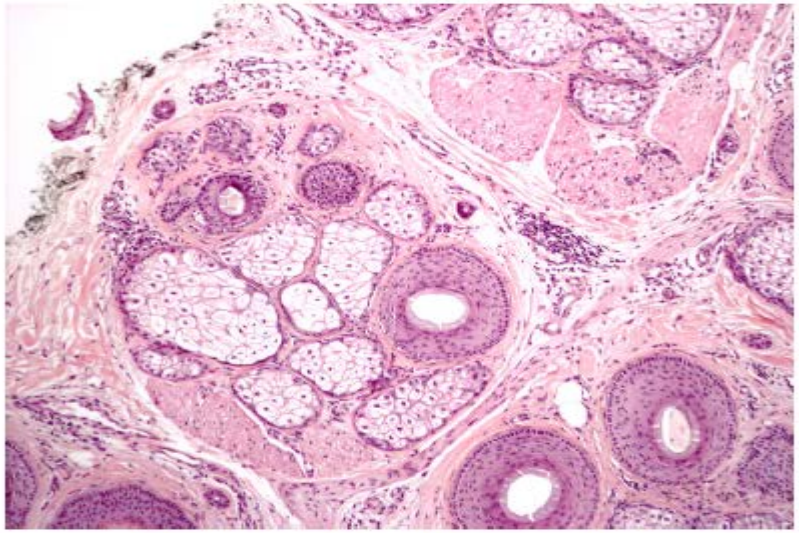
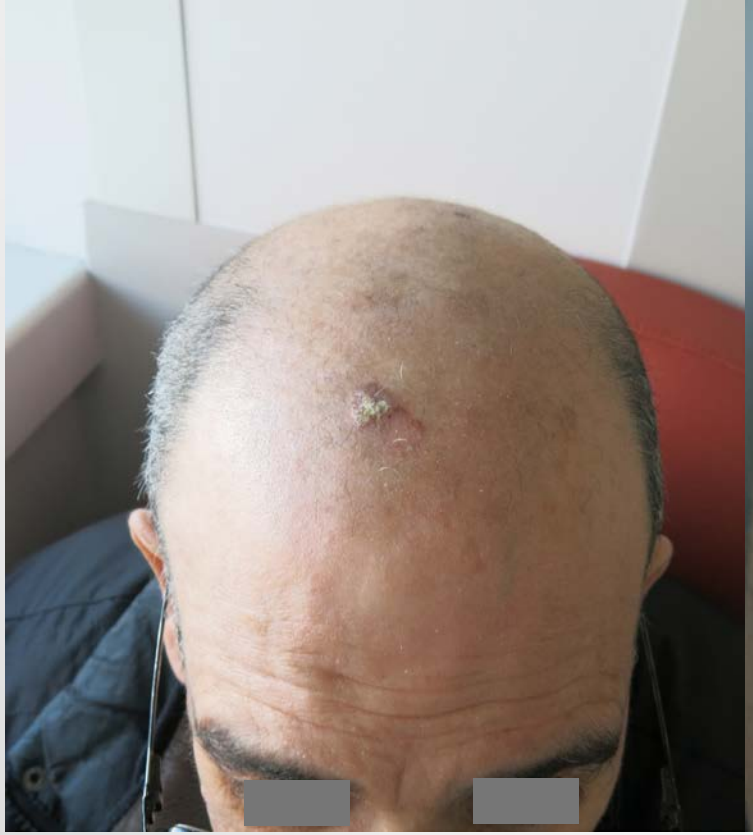
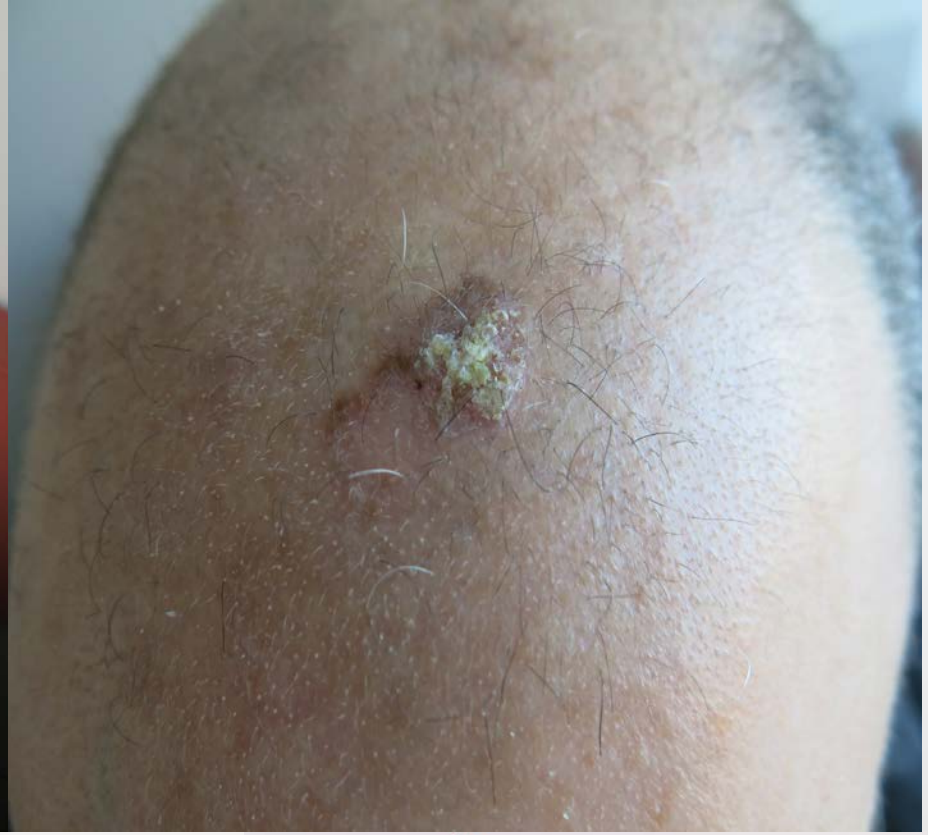


Fig 2. A detailed view of a horizontal section showing telogen germinal units. (Hematoxylin-eosin stain; original magnification: ×20.)

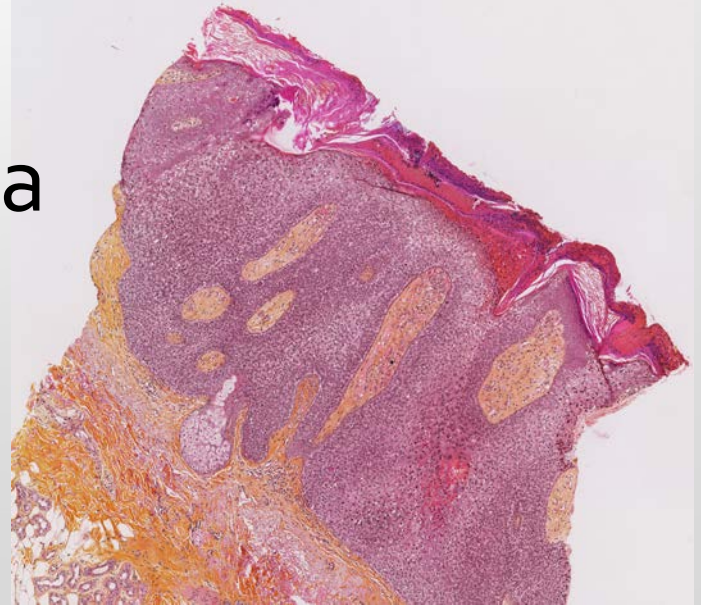
https://doi.org/10.1016/j.jaad.2015.01.011



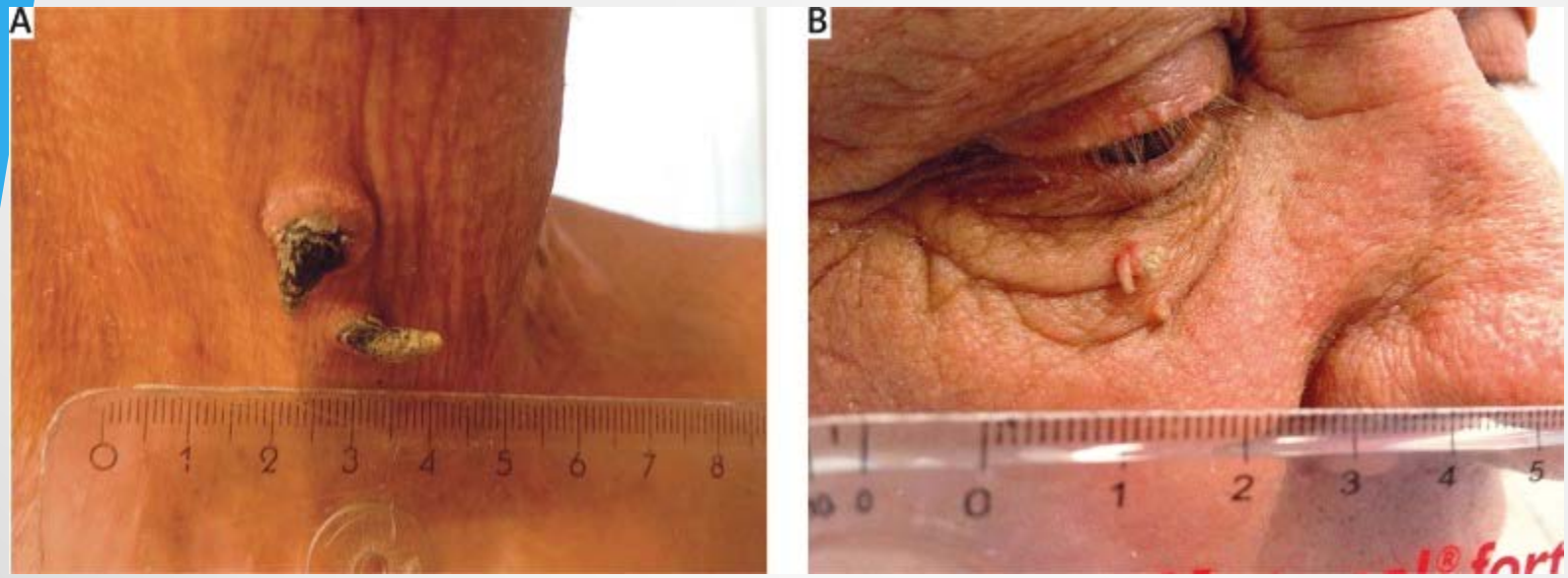


Bowen disease/ squamous cell carcinoma

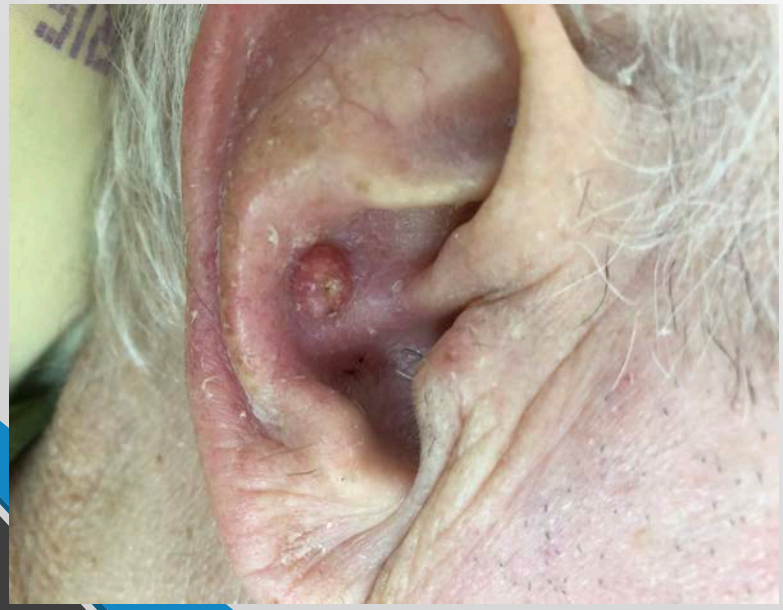
- Onset < 3 months
- Or later
- UVA/B protection ++
- Education

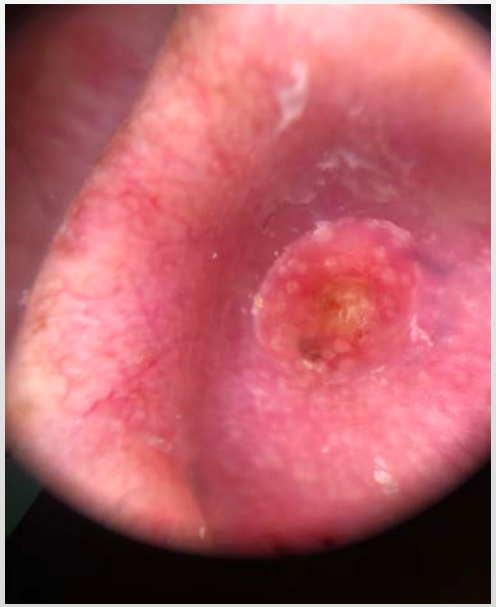


Keratoacanthomas/ Epidermoid carcinoma on the face and ear



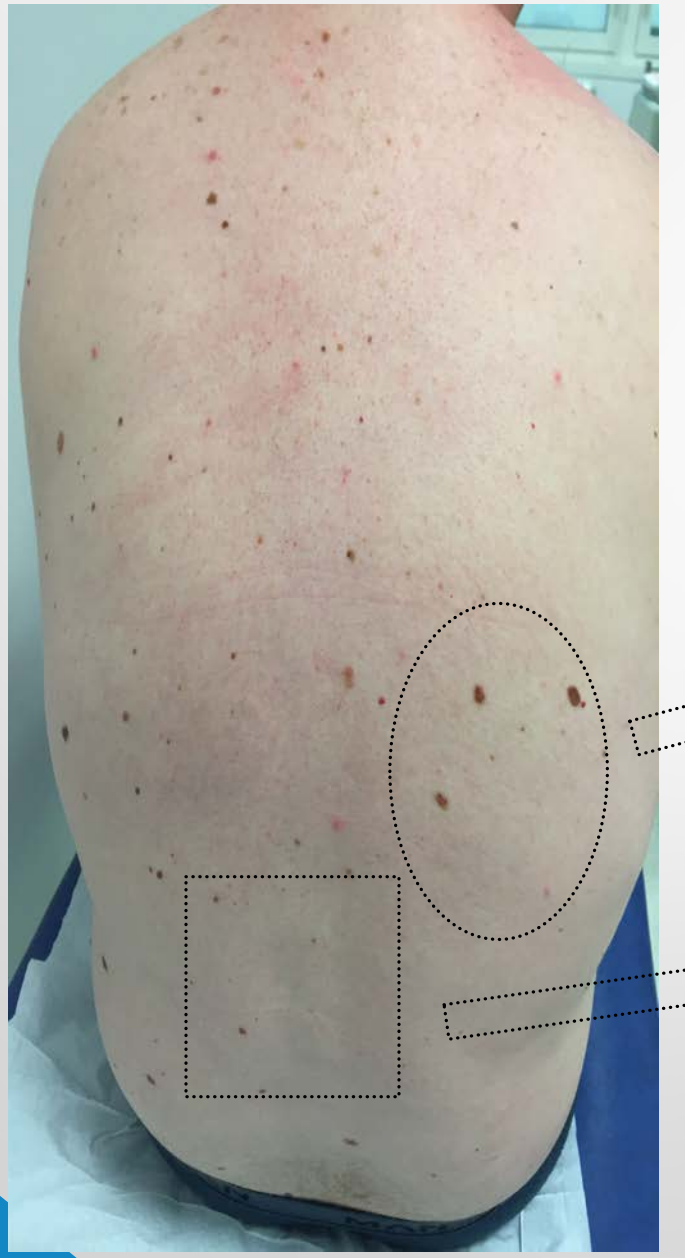
Nowara E, Huszno J, Slomian G, Nieckula J. Skin toxicity in BRAF(V600) mutated metastatic cutaneous melanoma patients treated with vemurafenib. Postepy Dermatol Alergol. 2016 Feb;33(1):52-6.

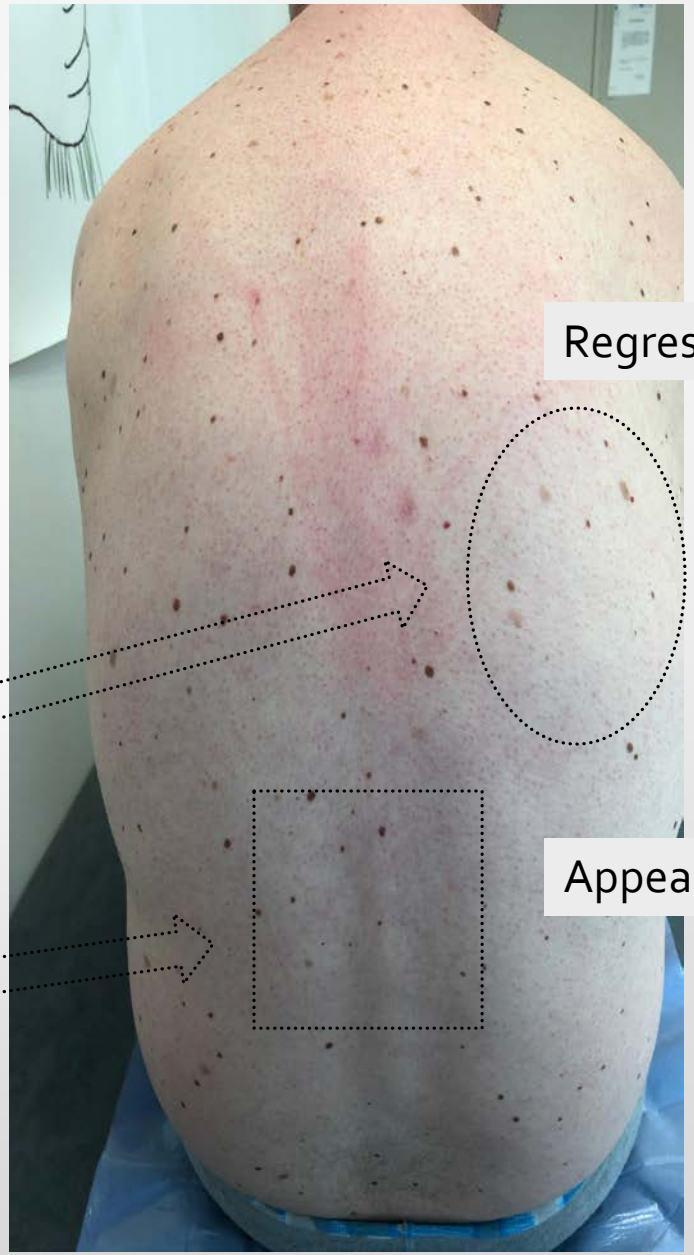




2016

2019





Regression

Appearance

Dalle. S et al. JAMA dermatol 2013; 149:488-490

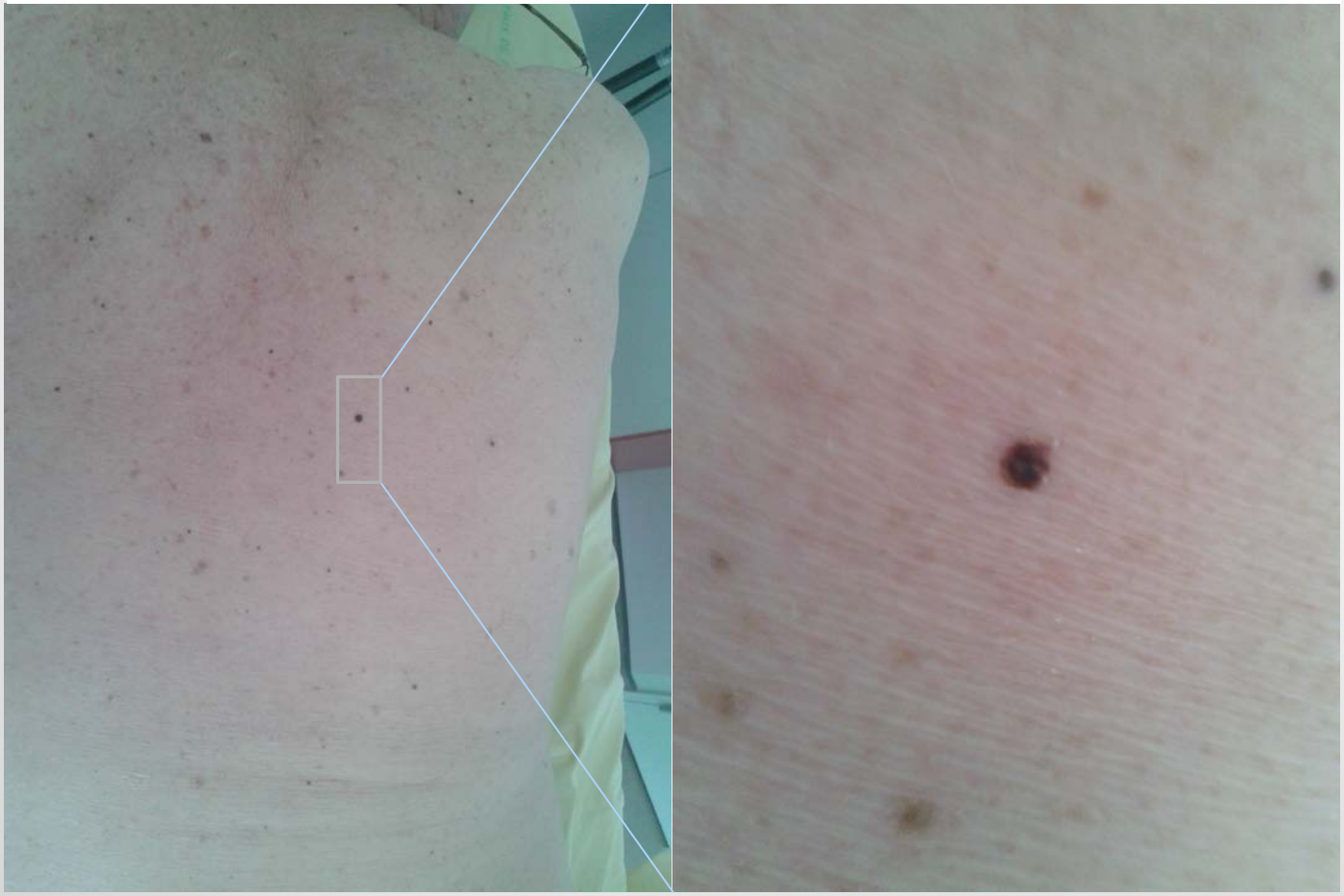
Melanoma in ECD and BRAF inhibitors

- Melanoma: 5 cases observed in our center in France.
- Always with monotherapy like vemurafenib or trabetinib
- Stage 1 of AJCC2019
- Surgery with stop of vemurafenib with good outcome
- ECD manageable with switch to MEK inhibitors
- Seems as observed in metastatic melanoma treated by combotherapy that this association prevents from skin melanoma and other skin non melanoma carcinoma.

Cohen Aubart F, Emile JF, Carrat F, Charlotte F, Benameur N, Donadieu J, Maksud P, Idbaih A, Barete S, Hoang-Xuan K, Amoura Z, Haroche J. Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study). Blood. 2017 Sep 14;130(11):1377-1380.

Melanoma Patients under Vemurafenib: Prospective Follow-Up of Melanocytic Lesions by Digital Dermoscopy

Marie Perier-Muzet[1,2], Luc Thomas[1,2], Nicolas Poulalhon[1], Sébastien Debarbieux[1], Pierre-Paul Bringuier[2,3,4], Gerard Duru[2], Lauriane Depaepe[4], Brigitte Balme[4] and Stephane Dalle[1,2,3] Journal of Investigative Dermatology (2014), Volume 134



- risk of 21% of a subsequent new primary melanoma,
- with mean time between start of treatment and diagnosis of 4.1 months.

S. Dalle, N. Poulalhon, L. Thomas. Vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med, 365 (2011), pp. 1448-1449

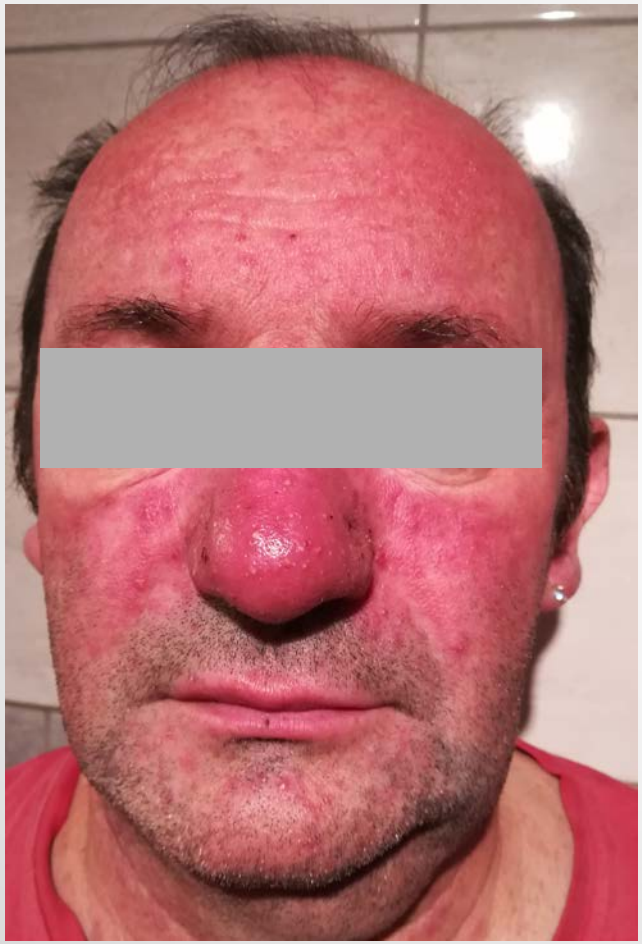
My Recommandations

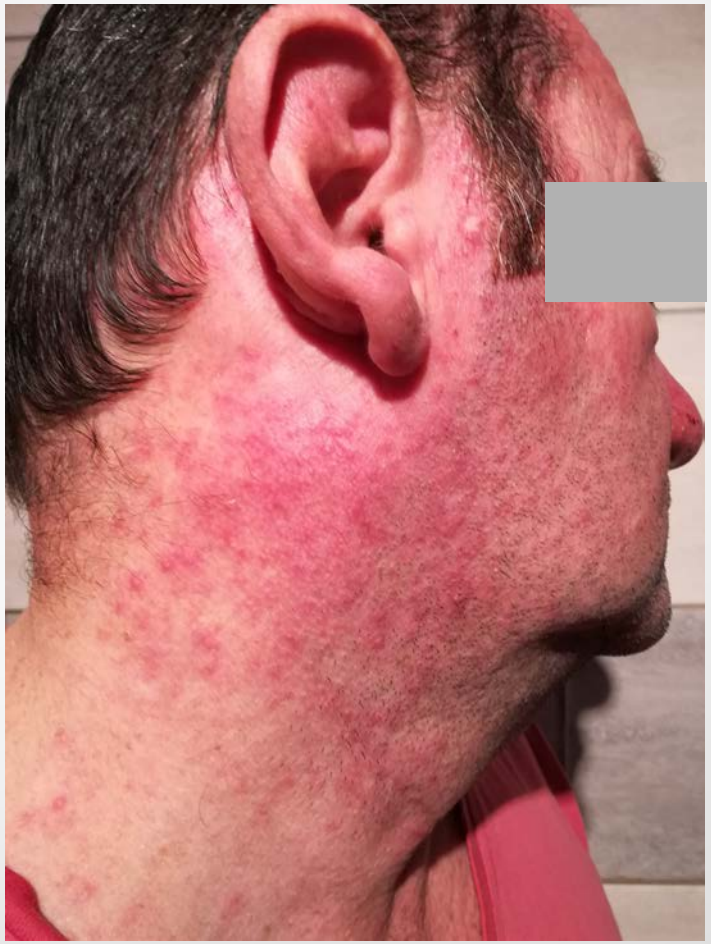
- Look initially for naevi and other non melanoma skin tumors before MTT
- Monthly examination by dermoscopy during at least the first 3 months followed by a check every 3 months.
- Surgical excision of one melanocytic lesion should be envisaged if observed modifications are
  - localized pigmentation change, appearance of structureless areas, and network or diameter changes during the first 3 months
- Avoid sun exposure++
- Protect skin with long garments / hats
- Apply sunscreen with high SPF≥50 on non-covered limbs, face and neck, reapply every two hours, even on cloudy days, and after swimming or sweating.
- follow-up for skin check

MTT skin toxicities (MEKi alone)

- Toxicities with MEK inhibitors alone:
  - cobimetinib
  - trabetinib
- Secondarilly observed in progressive BRAF inh treated patients or for intollerance to BRAF inh
- Updating management
- Dermatological support needed

Acnea induced by cobimetinib





1) Acnea with pustules and erythema
   - Frequent (>50%)
   - Within 1 to 2 months

2) Need dermatological supportive care

Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study)

Fleur Cohen Aubart,[1,2] Jean-François Emile,[3,4] Fabrice Carrat,[2,5,6] Frédéric Charlotte,[2,7] Neila Benameur,[8] Jean Donadieu,[9] Philippe Maksud,[10] Ahmed Idbaih,[11] Stéphane Barete,[12] Khê Hoang-Xuan,[11] Zahir Amoura,[1,2] and Julien Haroche[1,2]

Blood. 2017 Sep 14;130(11):1377-1380.

Table 2. Side effects of BRAF and MEK inhibitors

	Vemurafenib, n (%)	Cobimetinib, n (%)
Photosensibility, pilar keratosis	16 (32)	—
Acne rash	—	8 (53)
DRESS	2 (4)	—
DRESS-like*	1 (2)	—
Cutaneous allergy	1 (2)	1 (7)
Spinocellular carcinoma	4 (8)	—
Basocellular carcinoma	3 (6)	—
Melanoma	1 (5)	—
Actinic keratosis	2 (4)	—
Bowen disease	1 (2)	—
Multiple nevi	3 (6)	—
Eyelid keratoacanthoma	1 (2)	—
Nausea, vomiting	1 (2)	4 (27)
Arthralgia	7 (14)	—
Renal vasculitis	1 (2)	—
Tuberculosis	1 (2)	—
Deep vein thrombosis	1 (2)	—
Neutropenia	1 (2)	—
Scotoma and syncope	1 (2), combination therapy; ophthalmic examination was normal, and electrocardiogram and electrophysiological studies were also normal	
QT prolongation, torsade de pointes and cardiac arrest	1, treatment was resumed after ICD implantation (2)	—
Gastric cancer	1 (no RAF or RAS mutation) (2)	—
Cardiac failure	1 case, reversible when the dose was tapered (2)	—
Hypertriglyceridemia	1 (2)	—
Depressive episode	1 (2)	—
Rhabdomyolysis	—	4 (27)
Sarcoidosis-like disease	3 (6)	—

Strategy for modulation of treatment

	AE	Grade 1	Grade 2	Grade 3 [a]	Grade 4
Dermatological	Rash	- Skin moisturizers	- Topical glucocorticosteroids (maculopalpular r.) or topical antibiotics (papulopustular r.)	- Consult dermatologist	← - Severe forms (e.g. Steven-Johnson-syndrome, TEN): discontinue therapy
	Photo- / radiosensitivity reaction	- Preventive behavior [b], (educ.) - Topical glucocorticosteroids	←	- Consult dermatologist ←	← ←
	Palmoplantar hyperkeratosis	- Preventive behavior [c] (educ.) ← - 10% urea or salicylic acid creams; *only if inflammation*: ← - Topical glucocorticosteroids	← ←	- Consult dermatologist ← ←	(No CTC-AE grade 4)

[a] incl. Grade II toxicity, if considered as not tolerable; [b] strict avoidance of UVA; in case of concomitant radiotherapy, interruption of BRAFi therapy prior to irradiation might be considered; [c] strict avoidance of UVA, of pressure and friction

BRAFi-MEKi therapy: ***continue*** ***modify dose (i.e. delay/reduce)*** ***discontinue therapy***

Legend: ← Same recommendation, AE-grade adapted; ⇧ increase)

Heinzerling L, Eigentler TK, Fluck M, et al. Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management. ESMO Open. 2019 May 23;4(3):e000491. doi: 10.1136/esmoopen-2019-000491

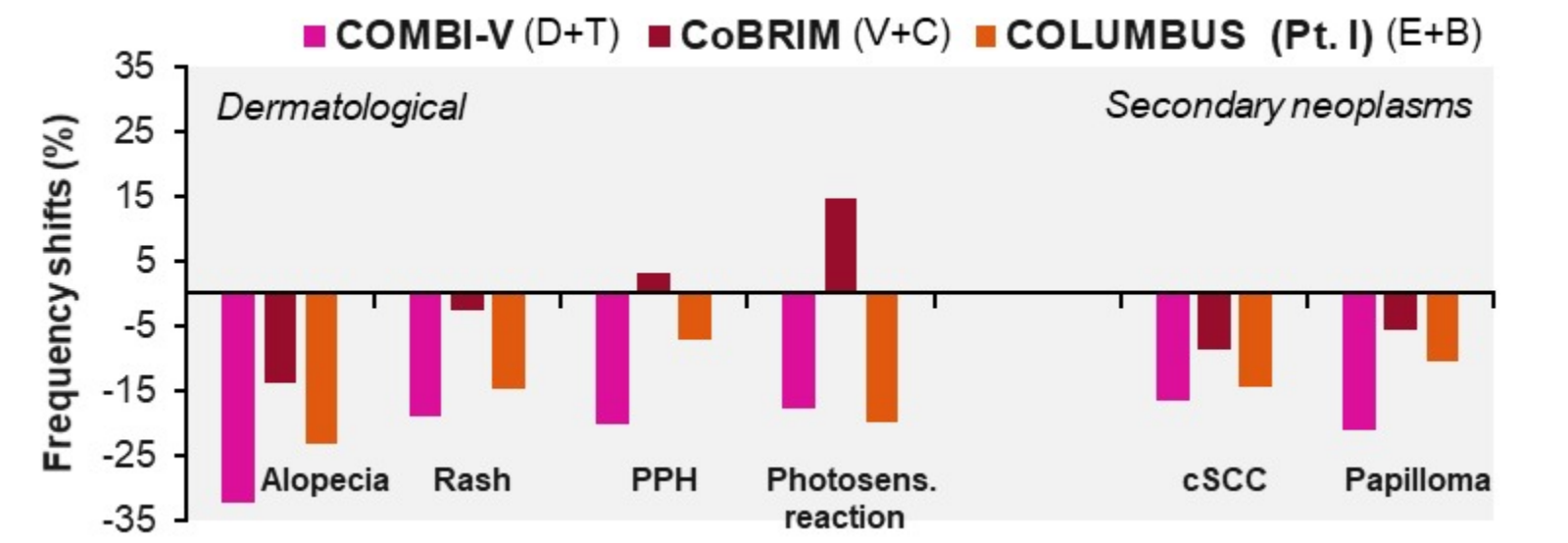
MTT skin toxicities (combo)

- Toxicities with combotherapies:
  - Cobimetinib/ vemurafenib
  - Trabetinib/ dabrafenib
- Reverse skin SE observed for BRAF inh or MEK inh taken individually
- Keep vigilant
- Dermatological support needed to check skin regularly

Dreno B, Ribas A, Larkin Jet al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. Ann Oncol 2017;28: 1137–1144.

Erfan G, Puig S, Carrera C. Development of cutaneous toxicities during selective anti-BRAF therapies: preventive role of combination with MEKinhibitors. Acta Derm Venereol 2017;97: 258–260.

Differences in adverse event frequencies: combination therapies versus vemurafenib monotherapy.



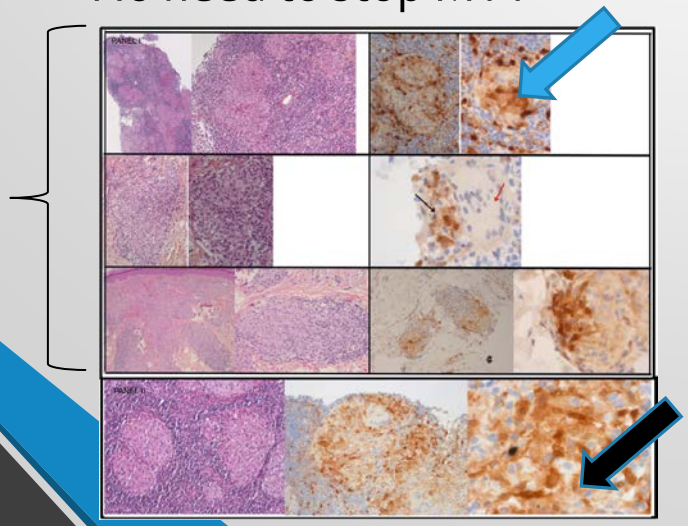
Many adverse events are :

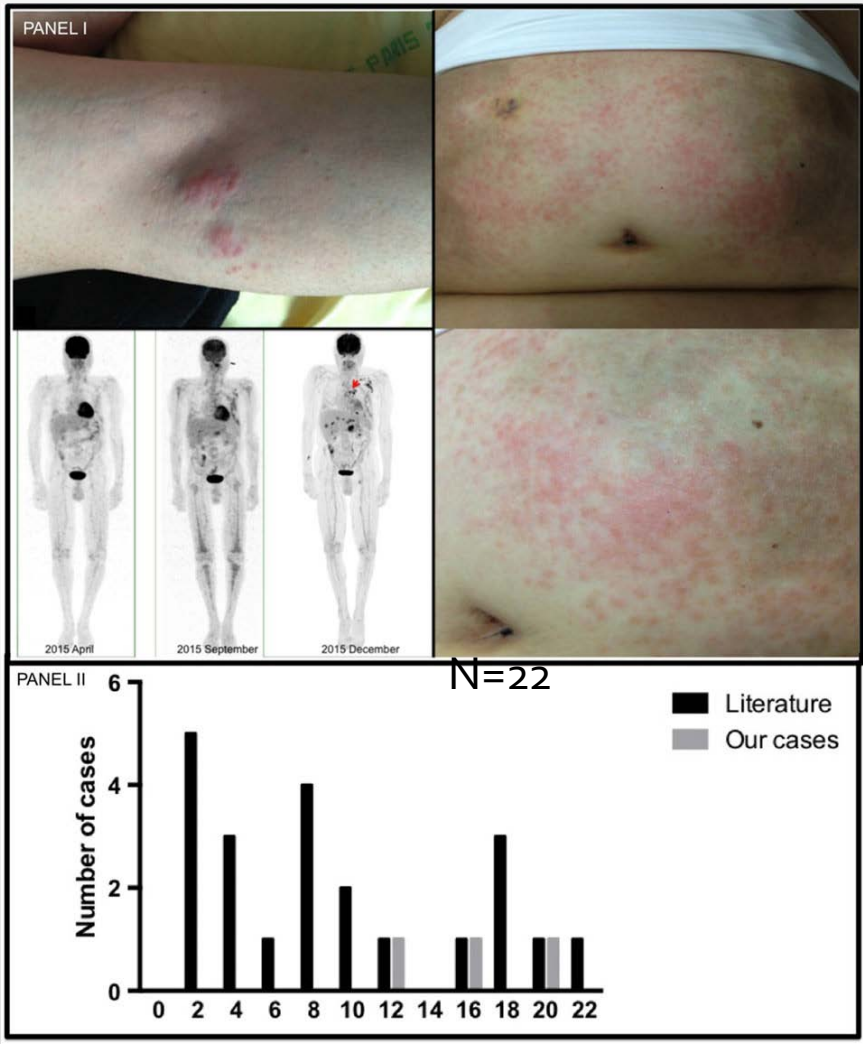
- class effects, such as cutaneous, gastrointestinal, ocular, cardiac and musculoskeletal events;
- some adverse events are substance associated.
  - photosensitivity (vemurafenib) are the most common and clinically prominent examples.

Heinzerling L, Eigentler TK, Fluck M, et al. Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management. ESMO Open. 2019 May 23;4(3):e000491. doi: 10.1136/esmoopen-2019-000491.

Sarcoidosis and ECD therapies

- Induction of sarcoidosis is possible with MTT in ECD
- 3 cases published recently by our team with sarcoidosis occuring after MTT (vemurafenib/dabrafenib)
- Mostly cutaneous, mechanism unknown but constant ERK-phosphorylation both in patients with sarcoidosis with or without MTT
- No need to stop MTT





A. Amoura, J. Haroche, J.-F. Emile, S. Barete, Z. Helias-Rodzewicz, F. Charlotte, T. Maisonobe, Z. Amoura, F. Cohen Aubart, JEADV 2019

My practice guidelines

- Avoid sun exposure with protective sunscreen with SPF 50 and protective dressing
- Educate patient to auto-screening of skin lesions to report to practitioner/dermatologist
- Talk with patients about frequency and severity of AEs
- Check skin with regular evaluation once a month for 3 months then each 3 months

Conclusion

- Skin issues in ECD
  - Diagnosis: XLL++
  - BRAF mutational status: easy, safe and usefull from skin biopsy
- Skin MTT toxicities
  - Increasing with emerging therapies (block signalling pathways)
  - Mostly manageable, sometime stop MTT
  - Need to be checked regularly and evaluated
  - Learn about physiopathology of the disease whatever mutational status of BRAF
  - Need for gathering experts for recommandation for management of skin AE with MTT
- Announcement for recruting protocol COBRAH (NCT04007848) in Pitié : cobimetinib versus placebo for WT LCH

Acknowledgements for working across medical specialities

- Clinical care team of Internal Medicine: J Haroche, F Cohen, Z Amoura
- Dermatological team: F Chasset, A Galezowski, H Bugaut
- French Referal center for histiocytosis
- MaRIH referal center for rare diseases

- Patients and families that contribute to our knowledge
- The ECD Global Alliance, Dr. Lorenzo Dagna, and the IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University