8th canadian melanoma conference research frontiers

February 20-23, 2014

The Rimrock Resort Hotel, Banff, Alberta, Canada

Melanocytic Lesion Volatility in Patients on BRAF-inhibitors

Feb 22, 2014
8:30-9:00 AM

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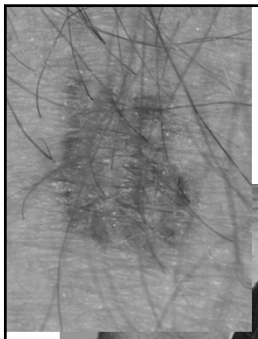
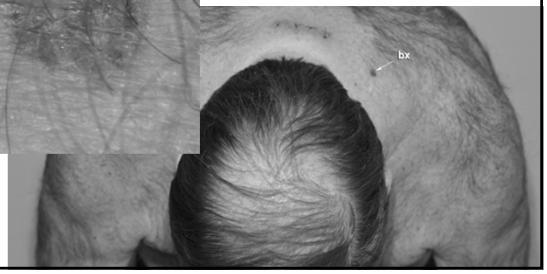
Associate Professor
Memorial Sloan-Kettering Cancer Center

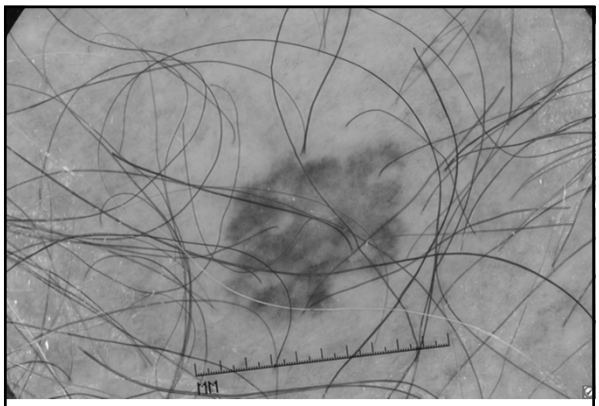
Objectives

- Define the changes that occur in melanocytic lesions in patients on BRAF- inhibitors.
- Acknowledge the increased risk for developing melanoma in patients on BRAF-inhibitors.
- Provide the most likely explanation for why patients on BRAF-inhibitors develop changes in their melanocytic lesions.

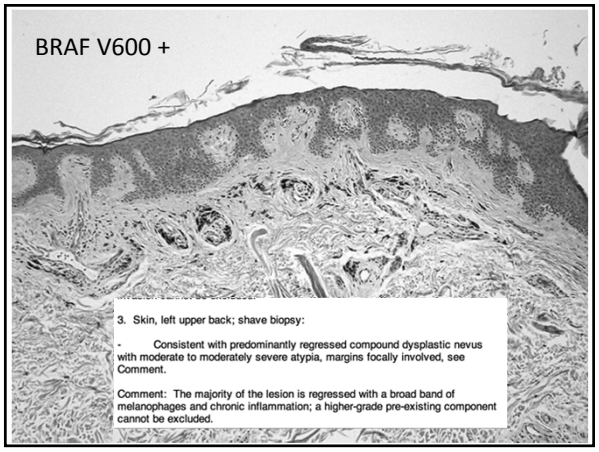


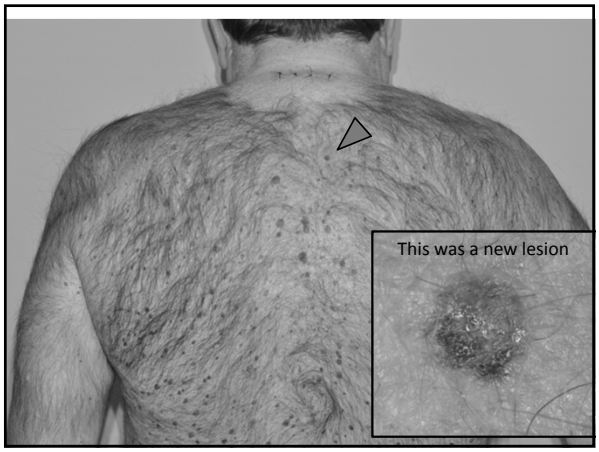
- 62 yo male with hx of metastatic MM & is on BRAF inhibitor therapy
- Within 8-10 weeks of therapy it was noted that he was developing new & changing pigmented lesions
- This lesion appeared to be fading

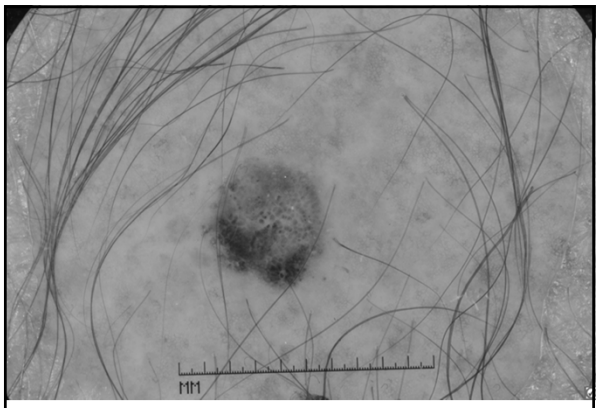


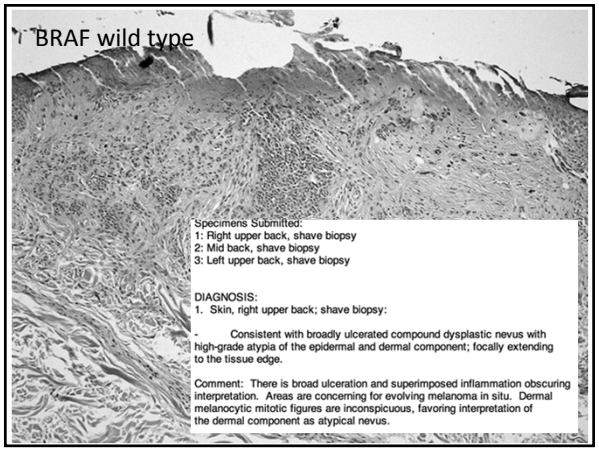


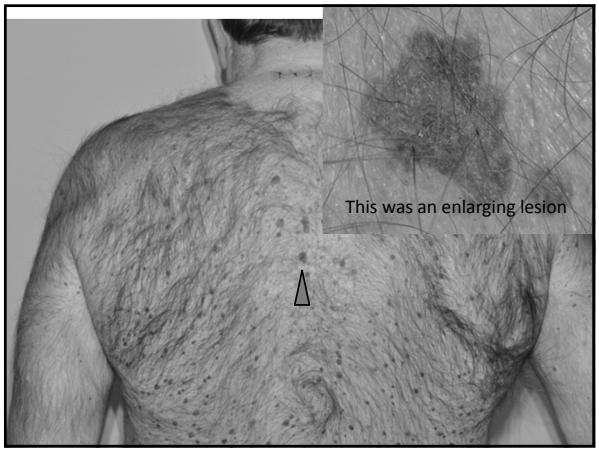
BRAF V600 +

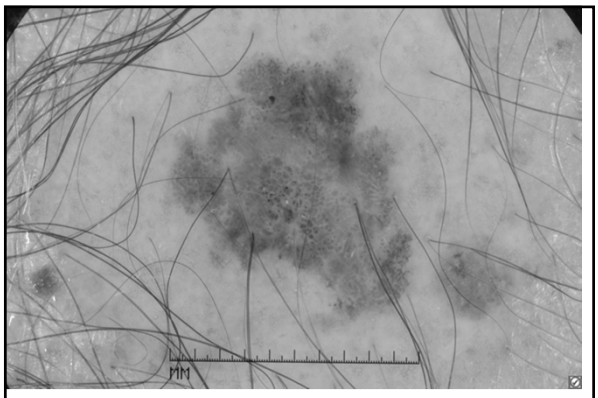

3. Skin, left upper back; shave biopsy:
- Consistent with predominantly regressed compound dysplastic nevus with moderate to moderately severe atypia, margins focally involved, see Comment.
Comment: The majority of the lesion is regressed with a broad band of melanophages and chronic inflammation; a higher-grade pre-existing component cannot be excluded.


This was a new lesion

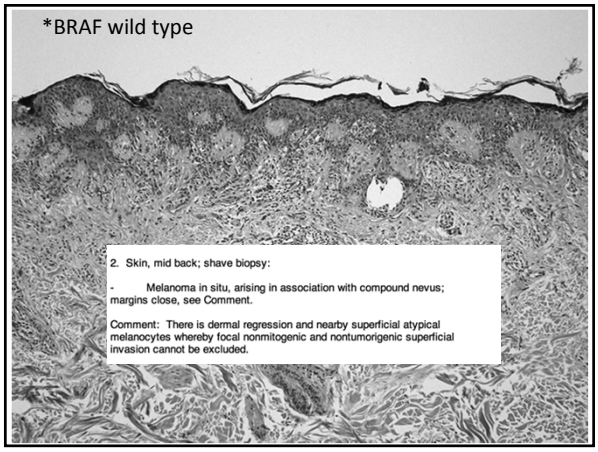

MM


BRAF wild type
Specimens Submitted:
1: Right upper back, shave biopsy
2: Mid back, shave biopsy
3: Left upper back, shave biopsy
DIAGNOSIS:
1. Skin, right upper back; shave biopsy:
- Consistent with broadly ulcerated compound dysplastic nevus with high-grade atypia of the epidermal and dermal component; focally extending to the tissue edge.
Comment: There is broad ulceration and superimposed inflammation obscuring interpretation. Areas are concerning for evolving melanoma in situ. Dermal melanocytic mitotic figures are inconspicuous, favoring interpretation of the dermal component as atypical nevus.


This was an enlarging lesion



*BRAF wild type



Case series & reports…

Atypical Melanocytic Proliferations and New Primary Melanomas in Patients With Advanced Melanoma Undergoing Selective *BRAF* Inhibition

Lisa Zimmer, Uwe Hillen, Elisabeth Livingstone, Mario E. Lacouture, Klaus Busam, Richard D. Carvajal, Friederike Egberts, Axel Hauschild, Mohammed Kashani-Sabet, Simone M. Goldinger, Reinhard Dummer, Georgina V. Long, Grant McArthur, André Scherag, Antje Sucker, and Dirk Schadendorf

A B S T R A C T

Purpose
Selective inhibition of mutant *BRAF* by using class I RAF inhibitors in patients with metastatic melanoma has resulted in impressive clinical activity. However, there is also evidence that RAF inhibitors might induce carcinogenesis or promote tumor progression via stimulation of MAPK signaling in RAF wild-type cells. We analyzed melanocytic lesions arising under class I RAF inhibitor treatment for dignity, specific genetic mutations, or expression of signal transduction molecules.

Patients and Methods
In all, 22 cutaneous melanocytic lesions that had either developed or considerably changed in morphology in 19 patients undergoing treatment with selective *BRAF* inhibitors for *BRAF*-mutant metastatic melanoma at seven international melanoma centers within clinical trials in 2010 and 2011 were analyzed for mutations in *BRAF* and *NRAS* genes and immunohistologically assessed for expression of various signal transduction molecules in comparison with 22 common nevi of 21 patients with no history of *BRAF* inhibitor treatment.

Results
Twelve newly detected primary melanomas were confirmed in 11 patients within 27 weeks of selective *BRAF* blockade. In addition, 10 nevi developed of which nine were dysplastic. All melanocytic lesions were *BRAF* wild type. Explorations revealed that expression of cyclin D1 and pAKT was increased in newly developed primary melanomas compared with nevi ($P = .01$ and $P = .03$, respectively). There was no *NRAS* mutation in common nevi, but *BRAF* mutations were frequent.

Conclusion
Malignant melanocytic tumors might develop with increased frequency in patients treated with selective *BRAF* inhibitors supporting a mechanism of *BRAF* therapy–induced growth and tumorigenesis. Careful surveillance of melanocytic lesions in patients receiving class I RAF inhibitors seems warranted.

OBSERVATION

ONLINE FIRST

Dynamic Changes in Nevi of a Patient With Melanoma Treated With Vemurafenib

Importance of Sequential Dermoscopy

Holger A. Haenssle, MD; Sophie L. Kraus, MD; Franziska Brehmer, MD; Lutz Kretschmer, MD; Bernward Volker, MD; Hiba Asper, MD; Alexander Kapp, MD; Ralf Gutzmer, MD

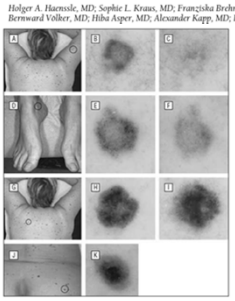


Figure 1. Clinical and dermoscopic analysis of representative melanocytic lesions at baseline and after 3 months of vemurafenib treatment. A-F, Centrally papillomatous nevi with a mixed globular and homogeneous dermoscopic pattern show a uniformly decrease in pigmentation and thickness. G-I, Flat reticular lesion with increasing size and pigmentation. Newly developed irregular dark-brown-purple pigmentation in the center of the lesion led to the decision to excise (I). J and K, Newly developed lesion. The lesion was excised (K) owing to a central irregular dark brownish-purple pigmentation.

Eruptive Melanocytic Nevi in a Patient Undergoing Treatment With Sunitinib

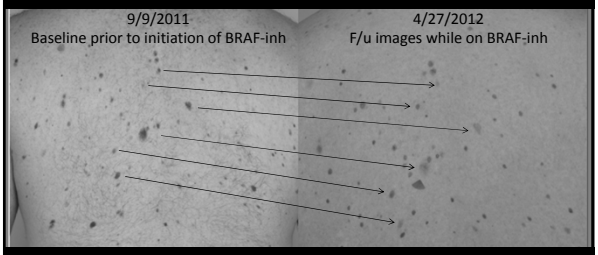
We believe that the development of EMN in our patient was probably owing to an exceptional inhibition of the $BRAF^{V600E}$/MAP/ERK pathway by sunitinib, and this triggered the proliferation of melanocytes owing to the loss of senescence induced by $BRAF^{V600E}$. Our hypothesis is supported by the fact that the MN appeared primarily on the back, an area intermittently exposed to sunlight, and histologic evaluation showed compound MN, and both conditions are associated with an increase in the frequency of $BRAF^{V600E}$.

How dynamic are melanocytic lesions?

Pilot study

- 22 stage IV melanoma patients (9 females /13 males); mean age 53
- Average length on BRAF-inh therapy = 332 days

- Average length of photography f/U = 319 days



- All new, changing, & involuting melanocytic lesions on torso recorded/counted/documented (clinical & dermoscopic images)

Table 1. Melanocytic lesion counts from overview photographs.

	Average # Lesions NEW	Average # Lesions GROWING/DARKENING	Average # Lesions (New + Growing/Darkening)	Average # Lesions INVOLUTING
Upper Posterior Trunk* (n=9)	4.3	8.8	13.1	8.0
			Upper back	
Lower Posterior Trunk* (n=5)	6.8	9.6	16.4	4
			Lower back	
Upper Anterior Trunk* (n=8)	4.3	5.3	9.5	4.3
			Chest	
Lower Anterior Trunk* (n=7)	3.3	2.9	6.1	3.4
			Abdomen	

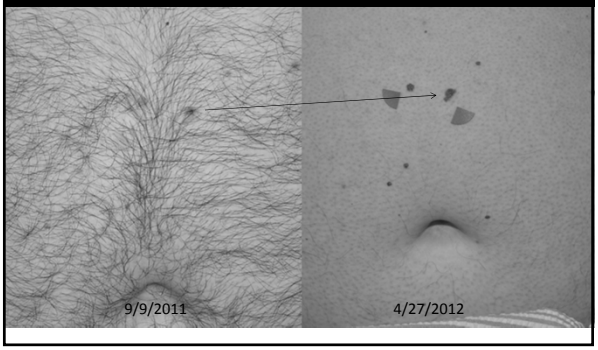
Note: Any anatomic area that had not been photographed at baseline or at follow-up visits was excluded.
Incidence rates of new and growing/darkening nevi are 53 and 77 per 1000 person years of BRAF inhibitor therapy respectively

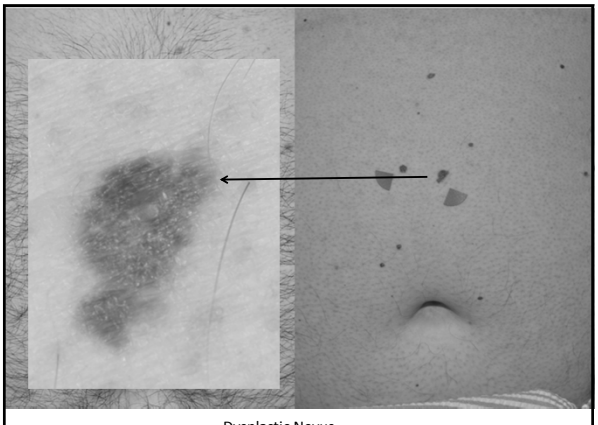
How dynamic are melanocytic lesions?

	Average # Lesions Per person NEW	Average # Lesions CHANGING	Average # Lesions INVOLUTING
Total (Anterior and Posterior Trunk) (n=22)	19	27	20

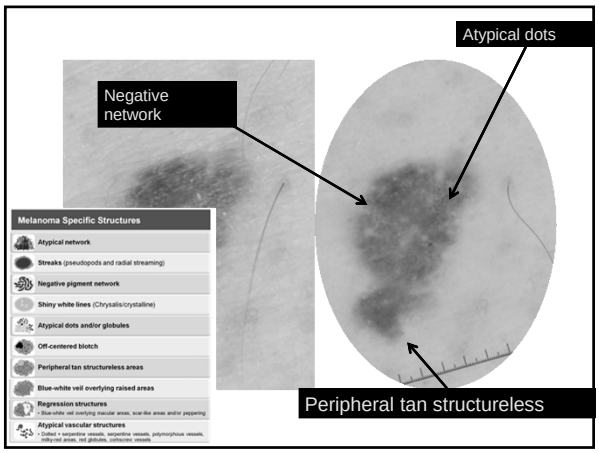
- Rate of new nevi is approximately **83** times higher than previously reported [Banky 2005; Archives]
- Rate of changing nevi is **91** times higher than has been reported [Banky 2005; Archives]
- Rate of involuting nevi is *X* times higher than reported……No comparison group in literature

Darkening & Growing melanocytic lesions

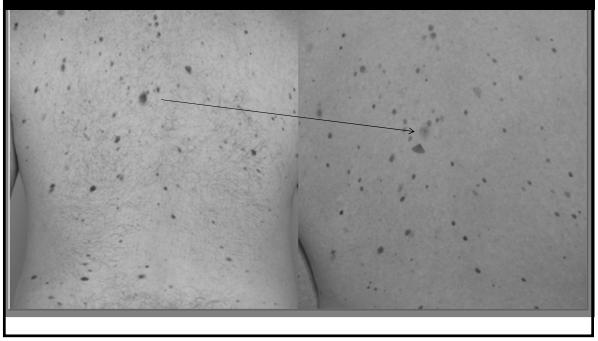




Dysplastic Nevus

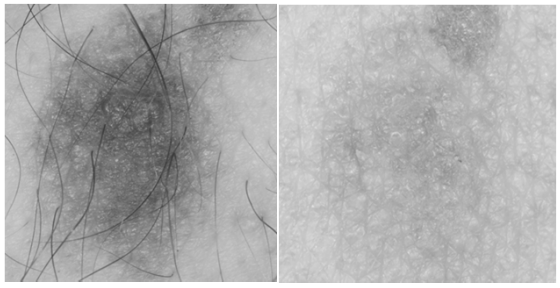


Involuting melanocytic lesions



Involuting CMN: *clinical images*

9/9/2011 4/27/2012

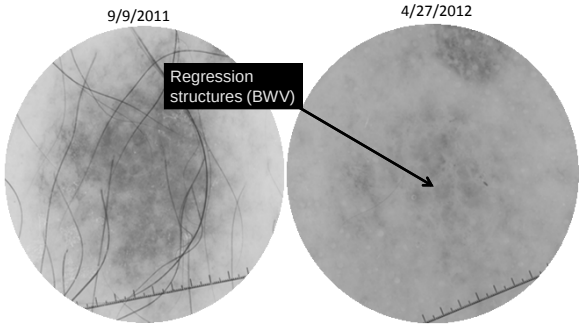


Congenital Nevus

Dermoscopy Images

9/9/2011

4/27/2012



Congenital Nevus

Table 2. Summary of dermoscopic features of new and changing suspicious lesions

	DERMOSCOPIC FEATURE	# Benign (#B/35)	# Melanoma (#M/7)	Benign vs. melanoma
	NEGATIVE NETWORK	3 (9%)	4 (57%)	0.0016*
	ATYPICAL NETWORK	14 (40%)	4 (57%)	0.4028
	ATYPICAL DOTS/GLOBULES	8 (23%)	3 (43%)	0.2719
	OFF CENTER BLOTCHES	9 (26%)	2 (29%)	0.8753
	BLUE WHITE OVER RAISED	5 (14%)	2 (29%)	0.3545
	BLUE WHITE OVER FLAT	3 (9%)	1 (14%)	0.6382
X	STREAKS/PSEUDOPODS	0 (0%)	0 (0%)	-
	POLYMORPHOUS VESSELS/VASCULAR BLUSH	5 (14%)	3 (43%)	0.0789
	PERIPHERAL STRUCTURELESS	4 (11%)	2 (29%)	0.2367
X	CHRYSTALINE STRUCTURES	0 (0%)	1 (14%)	0.0236*

*p<0.05, using a proportion test

Similar high rate of change noted in….

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]

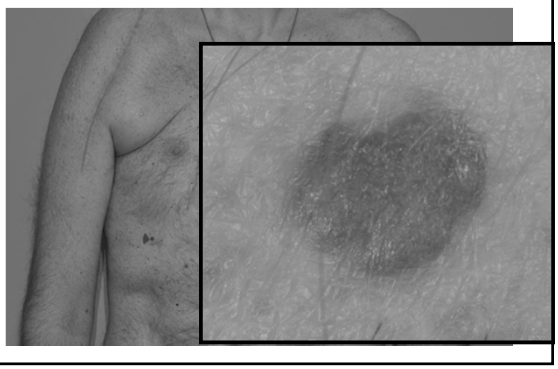
Second primary melanomas (SPMs) induced by vemurafenib have been recently described. The aim of this study was to define the dermoscopical signs of melanoma in this context. Patients underwent a total body examination before receiving vemurafenib. Each single melanocytic lesion was registered before therapy by digital dermoscopy (DD), and then repeated monthly until therapy disruption. Forty-two patients were included, the mean duration of follow-up was 6.7 months, and a mean number of 51 lesions per patients were captured and followed. A total number of 2,155 lesions were recorded, of which 56.1% presented at least one change during the study. More common changes concerned the color of the lesions (up to 15%) and appearance or disappearance of globules (14.6%). Thirty-six of the melanocytic lesions were surgically excised, 21 were classified as a nevus, 1 was a lentigo, and 14 as a second new primary melanoma (occurring in 21% of our patients). DD allowed us to excise only 36/2,155 (1.6%) of the lesions and permitted us to detect 14 SPM in the 42 patients with a highly efficient malignant/benign ratio of 63.6%. Although vemurafenib is now tested in an adjuvant setting DD should be systematically used in order to accurately detect SPM and reduce the number of unnecessary excisions.

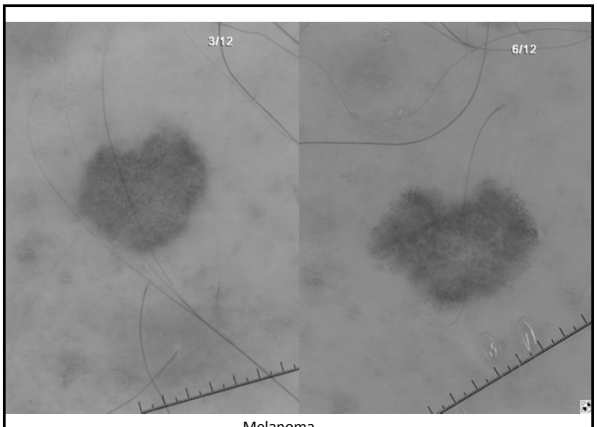
Journal of Investigative Dermatology advance online publication, 5 December 2013; doi:10.1038/jid.2013.462

Objectives

- Define the changes that occur in melanocytic lesions in patients on BRAF- inhibitors.
- Acknowledge the increased risk for developing melanoma in patients on BRAF-inhibitors.
- Provide the most likely explanation for why patients on BRAF-inhibitors develop changes in their melanocytic lesions.

Second Primary Melanomas

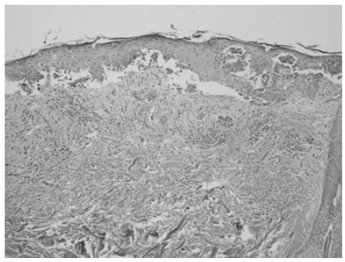




Melanoma

Histopathology

- Melanoma 0.45mm
- BRAF wild type



Rate of new melanomas

- ❑ 7 of 42 (17%) of biopsied new or changing lesions were diagnosed as unequivocal new primary melanomas
- ❑ The incidence rate of new melanomas was 435 per 1000 person-years
- ❑ Rate of second primary melanomas was calculated to be 17 times times higher as compared to an atypical nevus syndrome population with MM *[Marghoob 1996; BJD]*

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]

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7 new Melanomas

1. At least 0.6mm
2. Melanoma in epidermis with evidence of micro-invasion and with melanoma cells present in one dermal lymphatic channel
3. 0.45mm superficial spreading melanoma
4. 0.3mm melanoma
5. Melanoma in situ (MMIS) in association with an inflammed compound melanocytic nevus
6. MMIS
7. MMIS arising in a compound melanocytic nevus

- ❑ There was no difference in amount of BRAF-inh exposure (duration) between patients who developed melanomas and those who did not (p=0.4246)
- ❑ There was no correlation between the number of melanomas developing and the length of exposure to the B-RAF inhibitor (p=0.1061)

- *Ongoing <u>experience</u> not captured in current study:*
  - ✓ *The volatility of nevi & rate of new MMs eventually becomes quiescent (between 4 months-12 months). Thus, the longer you follow them the less new changes you will see!*
  - ✓ *This stabilized or equilibrated state is similar to what occurs with new SCCs/KAs/verruca*

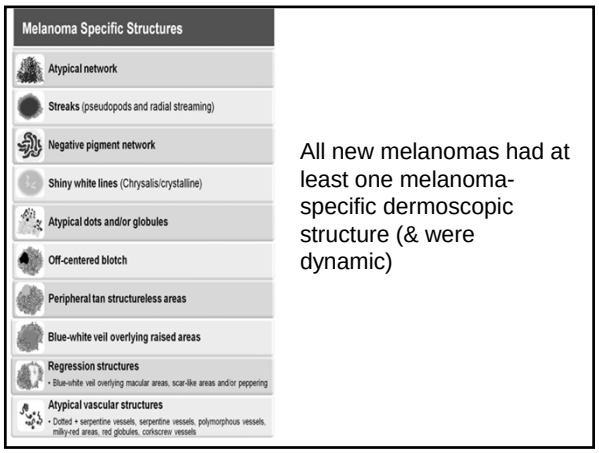
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 26, 2010 VOL. 363 NO. 9

Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

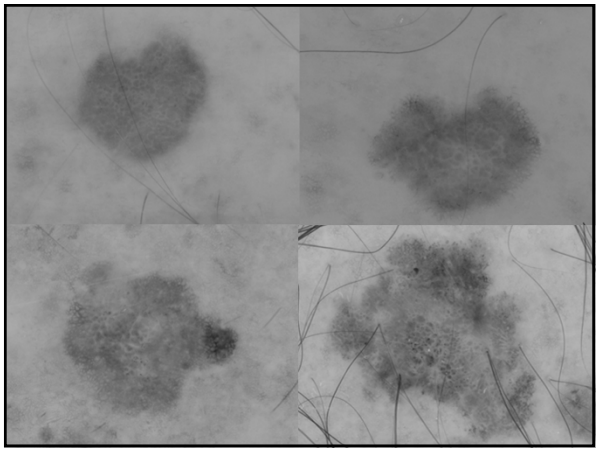
Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D.,

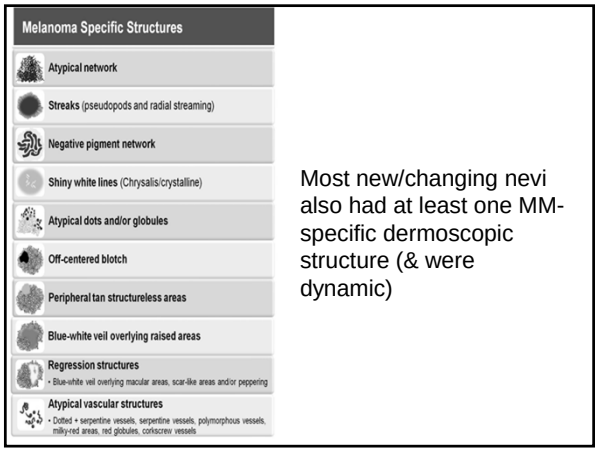
acanthoma. The median time to the appearance of a cutaneous squamous-cell carcinoma was 8 weeks; the majority of the carcinomas were

- ❑ Similarly, new & changing nevi/MM also appear early after initiation of BRAF-inh therapy. After this "induction" period the rate of change diminishes.
- ❑ Verrucous lesions induced by BRAF-I often involute after stopping therapy (observation). Remains to be elucidated whether this also happens to new nevi/MM that develop while on BRAF-inh therapy.

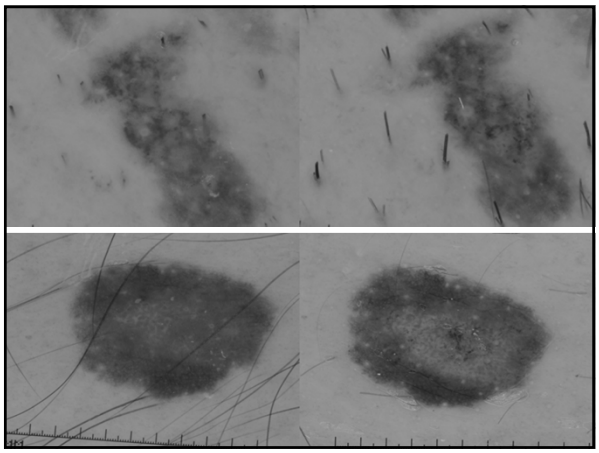


All new melanomas had at least one melanoma-specific dermoscopic structure (& were dynamic)





Most new/changing nevi also had at least one MM-specific dermoscopic structure (& were dynamic)



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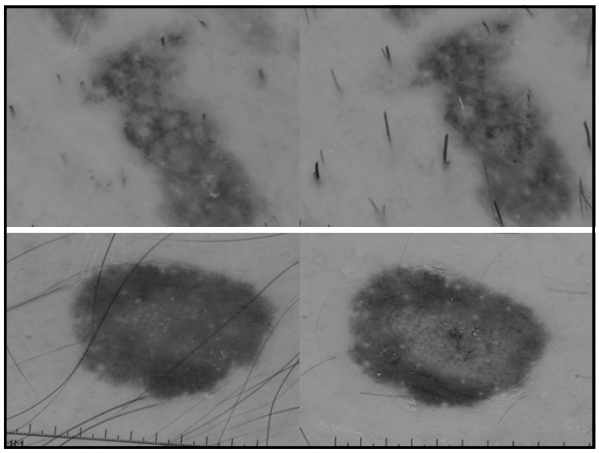
*p<0.05, using a proportion test

Questions arising

- Could the “melanomas” arising in these patients simply reflect a new type of "eruptive" dysplastic nevus?
  - Our pathologist are noticing that many of these clinically atypical changing lesions in BRAF-inh treated patients are quite unusual (severe DN vs MM).
  - They are starting to mention this in their reports ….



DIAGNOSIS:
1. Skin, right upper back; excision:

- Atypical intraepidermal melanocytic proliferation arising in association with compound nevus; side margin involved, see Comment.

Comment: Similar morphologic findings can be seen in changing melanocytic lesions associated with BRAF targeted therapy; however, clinical correlation is needed and the biologic potential of such lesions is currently unclear. There is dermal lichenoid inflammation, regression and a focal osteoma. In the absence of BRAF inhibition, the findings would mandate re-excision with concern for evolving melanoma in situ.

2. Skin, right lower back; excision:

- Atypical intraepidermal melanocytic proliferation arising in association with compound nevus; margins negative, see Comment.

Comment: Similar morphologic findings can be seen in changing melanocytic lesions associated with BRAF targeted therapy; however, clinical correlation is needed and the biologic potential of such lesions is currently unclear. There is dermal lichenoid inflammation and regression. In the absence of BRAF inhibition, the morphologic features are concerning for evolving melanoma in situ.

In other words,
Morphology and Biology may not be linked!

The true biologic potential of these “melanomas” & “DN” remains to be determined

Questions arising

- Could the “melanomas” arising in these patients simply reflect a new type of "eruptive" dysplastic nevus?
  - Our pathologist are noticing that many of these clinically atypical changing lesions in BRAF-inh treated patients are quite unusual (severe DN vs MM).
  - They are starting to mention this in their reports ….
  - With this in mind, all 7 MMs in our study were re-reviewed & our pathologist felt that these lesions had enough features that they had to be classified as MMs.
- Since BRAF-inh primarily give rise to KA-like SCCs, is it possible that BRAF-inh might give rise to a certain type of melanoma?
  - *unifying histopathologic theme: these MMs tended to exhibit hypermelanosis and pagetoid spread*

Objectives

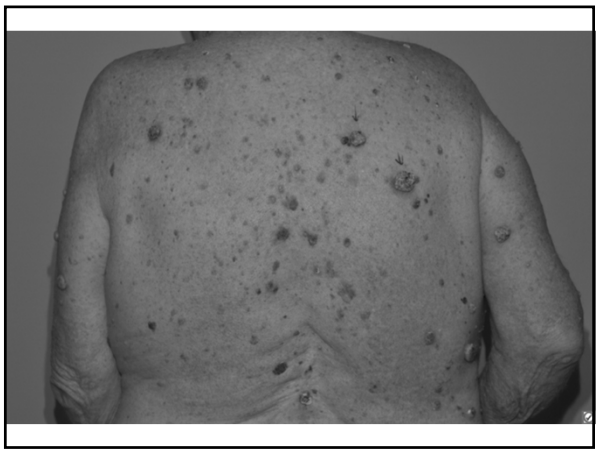
- ❑ Define the changes that occur in melanocytic lesions in patients on BRAF- inhibitors.
- ❑ Acknowledge the increased risk for developing melanoma in patients on BRAF-inhibitors.
- ❑ Provide the most likely explanation for why patients on BRAF-inhibitors develop changes in their melanocytic lesions.

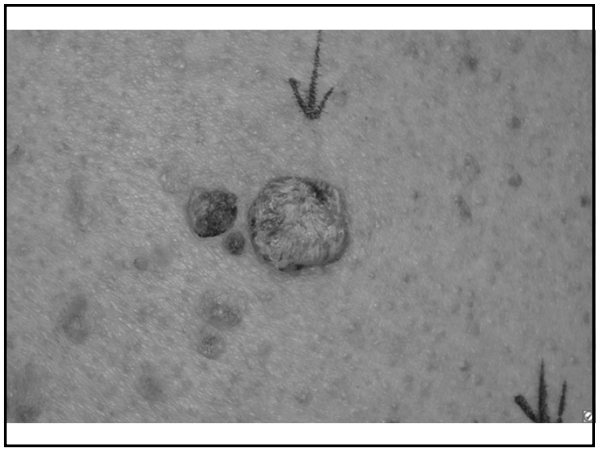
Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

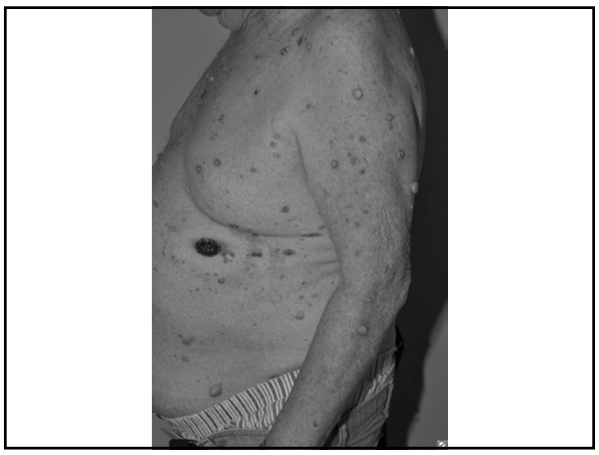
Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D., Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D., Joseph F. Grippo, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

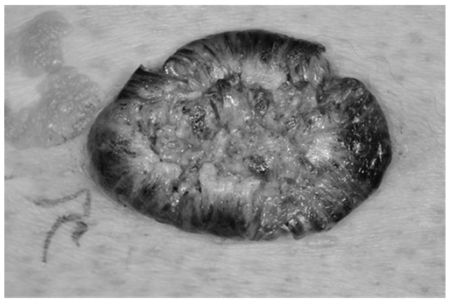
Before answering this let’s revisit the SCC story

acanthoma. The median time to the appearance of a cutaneous squamous-cell carcinoma was 8 weeks; the majority of the carcinomas were









The NEW ENGLAND JOURNAL of MEDICINE

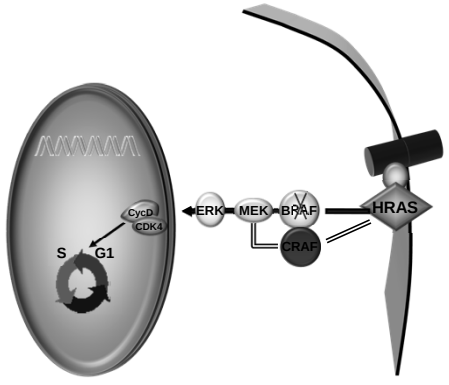
ESTABLISHED IN 1812 JANUARY 19, 2012 VOL. 366 NO. 3

RAS Mutations in Cutaneous Squamous-Cell Carcinomas in Patients Treated with BRAF Inhibitors

Fei Su, Ph.D., Amaya Viros, M.D., Carla Milagre, Ph.D., Kerstin Trunzer, Ph.D., Gideon Bollag, Ph.D., Olivia Spleiss, Ph.D., Jorge S. Reis-Filho, M.D., Ph.D., Xiangju Kong, M.S., Richard C. Koya, M.D., Ph.D., Keith T. Flaherty, M.D., Paul B. Chapman, M.D., Min Jung Kim, Ph.D., Robert Hayward, B.S., Matthew Martin, Ph.D., Hong Yang, M.S., Qiongqing Wang, Ph.D., Holly Hilton, Ph.D., Julie S. Hang, M.S., Johannes Noe, Ph.D., Maryou Lambros, Ph.D., Felipe Geyer, M.D., Nathalie Dhomen, Ph.D., Ion Niculescu-Duvaz, Ph.D., Alfonso Zambon, Ph.D., Dan Niculescu-Duvaz, Ph.D., Natasha Preece, B.A., Lídia Robert, M.D., Nicholas J. Otte, B.A., Stephen Mok, B.A., Damien Kee, M.B., B.S., Yan Ma, Ph.D., Chao Zhang, Ph.D., Gaston Habets, Ph.D., Elizabeth A. Burton, Ph.D., Bernice Wong, B.S., Hoa Nguyen, B.A., Mark Kockx, M.D., Ph.D., Luc Andries, Ph.D., Brian Lestini, M.D., Keith B. Nolop, M.D., Richard J. Lee, M.D., Andrew K. Joe, M.D., James L. Troy, M.D., Rene Gonzalez, M.D., Thomas E. Hutson, M.D., Igor Puzanov, M.D., Bartosz Chmielowski, M.D., Ph.D., Caroline J. Springer, Ph.D., Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Roger S. Lo, M.D., Ph.D., Antoni Ribas, M.D., Ph.D., and Richard Marais, Ph.D.

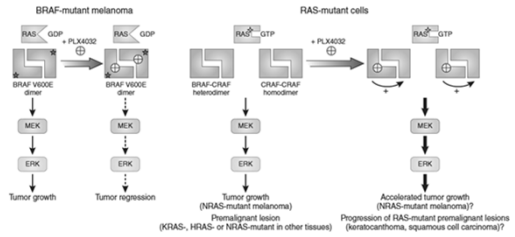
HRAS – in new SCC

THE RAS PARADOX



Targeting RAF: trials and tribulations

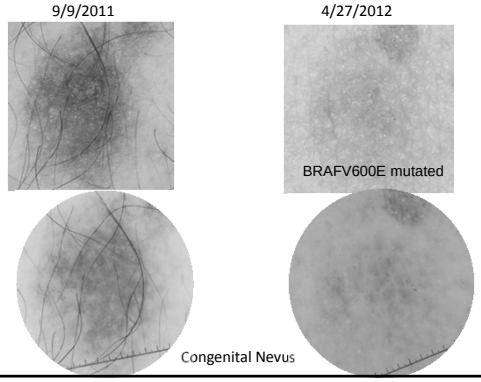
Julian Downward



2 theories as to why new nevi (& perhaps some melanomas) develop

1. BRAF can lead to senescence of nevi.
   - Blocking BRAF can lead to release of BRAF induced senescence & result in eruptive nevi
   - Eruptive nevi also manifest within weeks of therapy and then the process quiets down with continued therapy
   - No direct molecular data yet to support this theory
2. Different driver mutations (other than BRAF) lead to paradoxical activation of MAP-Kinase pathway
   - Incipient nevi (or MMs) with a non-BRAF V600E driver mutation will be stimulated to grow. This happens 8-12 weeks after starting therapy & then quiets down
   - Nevi (and MM) with a BRAF V600E mutation will involute
   - Much work to date is in support of this theory

Involuting Case



ORIGINAL ARTICLE

Distribution of BRAF T1799A(V600E) Mutations Across Various Types of Benign Nevi: Implications for Melanocytic Tumorigenesis

Julie Wu, MD,# Eli Rosenbaum, MD,†# Shanaz Begum, MD,*# and William H. Westra, MD*‡*

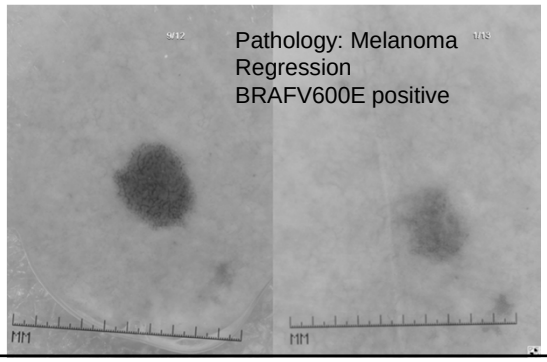
TABLE 1 . Prevalence of V600EBRAF Mutations by Nevus Type and Site

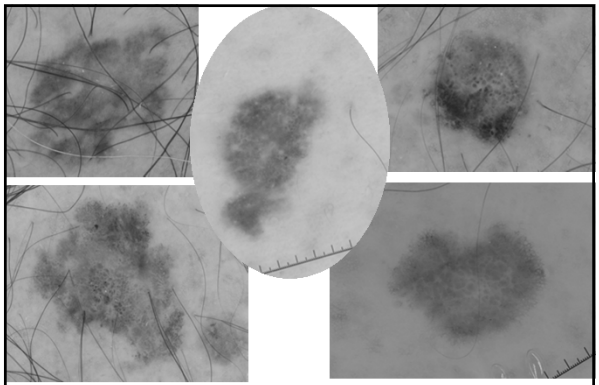
Type of Nevus	n	^{V600E}BRAF Mutations (%)
Acquired	101	83 (82)
Common cutaneous	76	64 (84)
Head and neck	15	15 (100)
Extremities	7	5 (71)
Trunk	54	45 (83)
Congenital type	34	26 (76)
Small	25	20 (80)
Large	9	6 (66)

11 dysplastic nevi

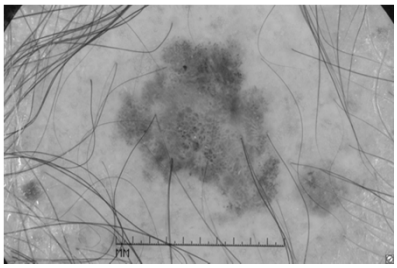
[Wu 2007; Am J Dermatopathol.]

Involuting BRAF-V600 mutated MM



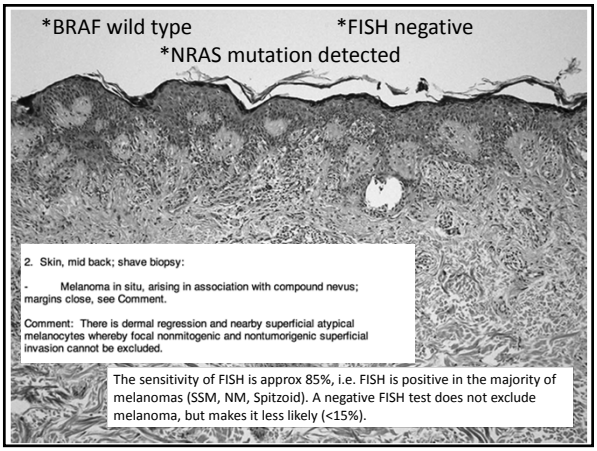


All new & changing (excluding involuting) lesions were BRAF-wild type



On further testing these BRAF-wild type MMs often had another mutation

*BRAF wild type *FISH negative
*NRAS mutation detected



2. Skin, mid back; shave biopsy:

- Melanoma in situ, arising in association with compound nevus; margins close, see Comment.

Comment: There is dermal regression and nearby superficial atypical melanocytes whereby focal nonmitogenic and nontumorigenic superficial invasion cannot be excluded.

The sensitivity of FISH is approx 85%, i.e. FISH is positive in the majority of melanomas (SSM, NM, Spitzoid). A negative FISH test does not exclude melanoma, but makes it less likely (<15%).

Atypical Melanocytic Proliferations and New Primary Melanomas in Patients With Advanced Melanoma Undergoing Selective *BRAF* Inhibition

Lisa Zimmer, Uwe Hillen, Elisabeth Livingstone, Mario E. Lacouture, Klaus Busam, Richard D. Carvajal, Friederike Egberts, Axel Hauschild, Mohammed Kashani-Sabet, Simone M. Goldinger, Reinhard Dummer, Georgina V. Long, Grant McArthur, André Scherag, Antje Sucker, and Dirk Schadendorf

A B S T R A C T

Purpose
Selective inhibition of mutant *BRAF* by using class I RAF inhibitors in patients with metastatic melanoma has resulted in impressive clinical activity. However, there is also evidence that RAF inhibitors might induce carcinogenesis or promote tumor progression via stimulation of MAPK signaling in RAF wild-type cells. We analyzed melanocytic lesions arising under class I RAF inhibitor treatment for dignity, specific genetic mutations, or expression of signal transduction molecules.

Patients and Methods
In all, 22 cutaneous melanocytic lesions that had either developed or considerably changed in morphology in 19 patients undergoing treatment with selective *BRAF* inhibitors for *BRAF*-mutant metastatic melanoma at seven international melanoma centers within clinical trials in 2010 and 2011 were analyzed for mutations in *BRAF* and *NRAS* genes and immunohistologically assessed for expression of various signal transduction molecules in comparison with 22 common nevi of 21 patients with no history of *BRAF* inhibitor treatment.

Results
Twelve newly detected primary melanomas were confirmed in 11 patients within 27 weeks of selective *BRAF* blockade. In addition, 10 nevi developed of which nine were dysplastic. All melanocytic lesions were *BRAF* wild type. Explorations revealed that expression of cyclin D1 and pAKT was increased in newly developed primary melanomas compared with nevi ($P = .01$ and $P = .03$, respectively). There was no *NRAS* mutation in common nevi, but *BRAF* mutations were frequent.

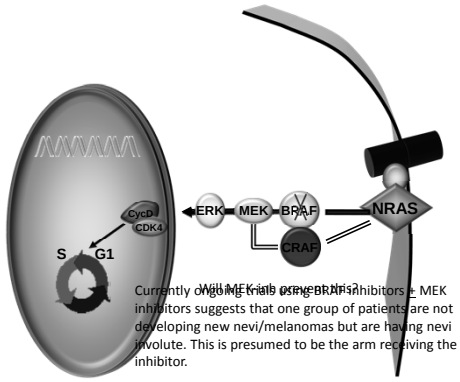
Conclusion
Malignant melanocytic tumors might develop with increased frequency in patients treated with selective *BRAF* inhibitors supporting a mechanism of *BRAF* therapy–induced growth and tumorigenesis. Careful surveillance of melanocytic lesions in patients receiving class I RAF inhibitors seems warranted.

Tracking of Second Primary Melanomas in Vemurafenib-Treated Patients

Results. Twenty-five SPMs were diagnosed in 120 patients. The delay of the SPM diagnosis after vemurafenib treatment initiation ranged from 4 to 42 weeks. The median delay was 14 weeks (**Table**).

Twenty-one melanoma samples were genotypically tested for *NRAS* and *BRAF* mutations. All the cases were wild-type mutations for *BRAF*; 1 case was *NRAS* Q61R mutated.

THE RAS PARADOX



Currently ongoing trials using BRAF inhibitors + MEK inhibitors suggests that one group of patients are not developing new nevi/melanomas but are having nevi involute. This is presumed to be the arm receiving the MEK inhibitor.

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 12, 2012 VOL. 367 NO. 2

Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma

Keith T. Flaherty, M.D., Caroline Robert, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Paul Nathan, M.D., Ph.D., Claus Garbe, M.D., Mohammed Milhem, M.B., Lev V. Demidov, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Peter Mohr, M.D., Reinhard Dummer, M.D., Uwe Trefzer, M.D., James M.G. Larkin, M.D., Jochen Utikal, M.D., Brigitte Dreno, M.D., Marta Nyakas, M.D., Mark R. Middleton, Ph.D., Jürgen C. Becker, M.D., Ph.D., Michelle Casey, Ph.D., Laurie J. Sherman, R.N., Frank S. Wu, M.D., Ph.D., Daniele Ouellet, Ph.D., Anne-Marie Martin, Ph.D., [illegible] and Dirk Schadendorf, M.D., for the METRIC Study Group

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty, M.D., Jeffrey 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.

Less SCC – Yes

Less MM/DN – to be determined

Objectives

- ❑ Define the changes that occur in melanocytic lesions in patients on BRAF- inhibitors.
- ❑ Acknowledge the increased risk for developing melanoma in patients on BRAF-inhibitors.
- ❑ Provide the most likely explanation for why patients on BRAF-inhibitors develop changes in their melanocytic lesions.

Further Investigations necessary

- Rate and timing of flux in melanocytic lesions as relates to dose, length of therapy, type of therapy (intermittent, MEK-inh)
- Are the new MMs truly new or just incipient MMs that were already present prior to tx.
- Evolution of lesions after discontinuation of therapy
- Biologic potential of these MM/DN

Further Investigations necessary

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- Are the new MMs truly new or just incipient MMs that were already present prior to tx.
- Evolution of lesions after discontinuation of therapy
- Biologic potential of these MM/DN

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]

Second primary melanomas (SPMs) induced by vemurafenib have been recently described. The aim of this study was to define the dermoscopical signs of melanoma in this context. Patients underwent a total body examination before receiving vemurafenib. Each single melanocytic lesion was registered before therapy by digital dermoscopy (DD), and then repeated monthly until therapy disruption. Forty-two patients were included, the mean duration of follow-up was 6.7 months, and a mean number of 51 lesions per patients were captured and followed. A total number of 2,155 lesions were recorded, of which 56.1% presented at least one change during the study. More common changes concerned the color of the lesions (up to 15%) and appearance or disappearance of globules (14.6%). Thirty-six of the melanocytic lesions were surgically excised, 21 were classified as a nevus, 1 was a lentigo, and 14 as a second new primary melanoma (occurring in 21% of our patients). DD allowed us to excise only 36/2,155 (1.6%) of the lesions and permitted us to detect 14 SPM in the 42 patients with a highly efficient malignant/benign ratio of 63.6%. Although vemurafenib is now tested in an adjuvant setting DD should be systematically used in order to accurately detect SPM and reduce the number of unnecessary excisions.

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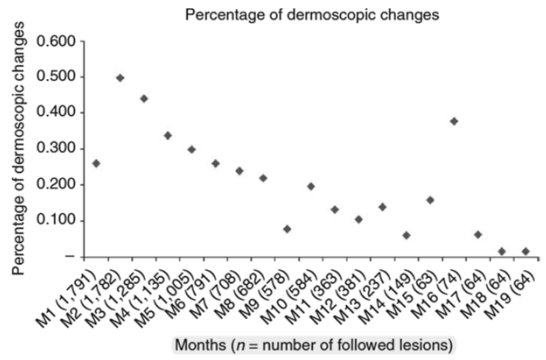


Figure 1. Percentage of dermoscopic changes observed during follow-up.

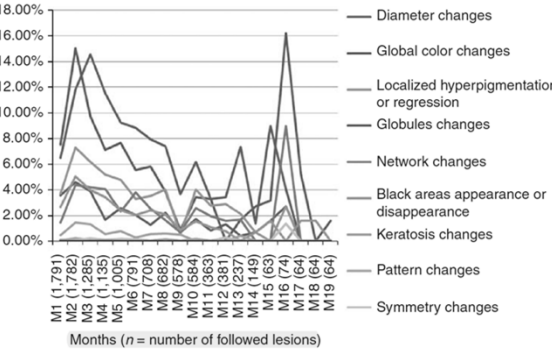
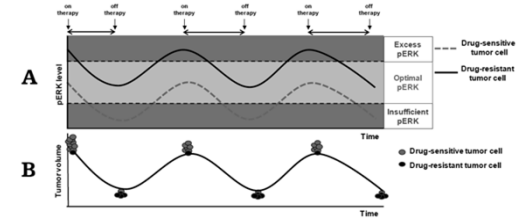


Figure 3. Evolution under vemurafenib of the 10 analyzed dermoscopic criteria (in percent) over the time.



o 2. Intermittent BRAF inhibitor therapy to forestall the onset of drug-resistant melanoma

Further Investigations necessary

- Rate and timing of flux in melanocytic lesions as relates to dose, length of therapy, type of therapy (intermittent, MEK-inh)
- Are the new MMs truly new or just incipient MMs that were already present prior to tx.
- Evolution of lesions after discontinuation of therapy
- Biologic potential of these MM/DN

CLINICAL AND LABORATORY INVESTIGATIONS British Journal of Dermatology

Second primary melanomas treated with BRAF blockers: study by reflectance confocal microscopy

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Conflicts of interest
None declared.

DOI 10.1111/bjd.12210

Summary

Background New primary melanomas arising in patients with stage IV melanoma and receiving BRAF inhibitors have recently been reported. This raises the question of the nature of the earliest cellular events identifiable within pre-existing moles.

Objectives To use reflectance confocal microscopy (RCM) to investigate changing moles in patients using vemurafenib.

Methods In the first part of the study 23 lesions were examined by RCM before excision (performed because of digital dermoscopy changes) and histopathological examination. In the second part, 10 randomly chosen lesions in two patients were examined before and after 3 months of vemurafenib treatment.

Results The first step permitted the highlighting of an unusual RCM pattern identified in five lesions characterized by areas of marked atypia in otherwise nondysplastic lesions. In the second step, four initially nondysplastic lesions developed focal or multifocal areas of marked atypia under treatment, which were not always correlated with digital dermoscopy changes, but did correlate with histopathology. All four lesions were finally diagnosed as melanomas.

Conclusions Although the clinical relevance of such findings remains questionable, RCM allowed us to observe, at the cellular level, the earliest events occurring within vemurafenib-induced changing moles. Moreover, repeated RCM examinations permitted to confirm that microscopic marked atypia that led to the histopathological diagnosis of melanoma appeared under treatment and were not pre-existing.

Further Investigations necessary

- Rate and timing of flux in melanocytic lesions as relates to dose, length of therapy, type of therapy (intermittent, MEK-inh)
- Are the new MMs truly new or just incipient MMs that were already present prior to tx.
- Evolution of lesions after discontinuation of therapy
- Biologic potential of these MM/DN

?

Further Investigations necessary

- Rate and timing of flux in melanocytic lesions as relates to dose, length of therapy, type of therapy (intermittent, MEK-inh)
- Are the new MMs truly new or just incipient MMs that were already present prior to tx.
- Evolution of lesions after discontinuation of therapy
- Biologic potential of these MM/DN

- *In the interim we recommend monitoring:*
  - *Digital whole body photography (overview level)*
  - *Digital dermoscopy (individual lesion level)*

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]

that DD should be performed in these patients at 1, 2, and 3 months of treatment; then, a trimonthly follow-up could be offered.

Special Thanks

Eileen Flores, MPH
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Steve Dusza, DrPH
Allan Halpern, MD
Hensin Tsao, MD
Sarah Yagerman

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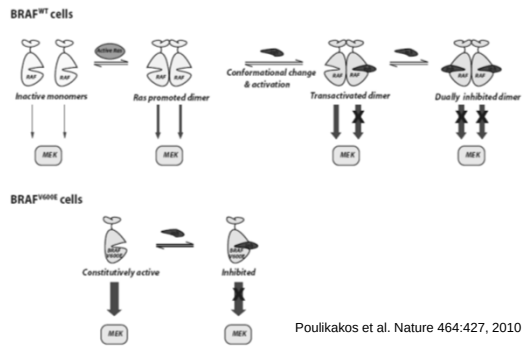
Model: Effects of RAF inhibitors in BRAF wild-type and BRAF-mutant cells



Poulikakos et al. Nature 464:427, 2010