

# BRAF INHIBITORS THERAPY AND RADIOTHERAPY FOR MELANOMA BRAIN METASTASES (MBM): TOXICITY AND CLINICAL OUTCOME

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Franzese C.\*, De Rose F.\*, Comito T.\*, Iftode C.\*, Tozzi A.\*, Reggiori G.\*, Lobefalo  
F.\*, Tomatis S.\*, Scorsetti M.\*<sup>^</sup>

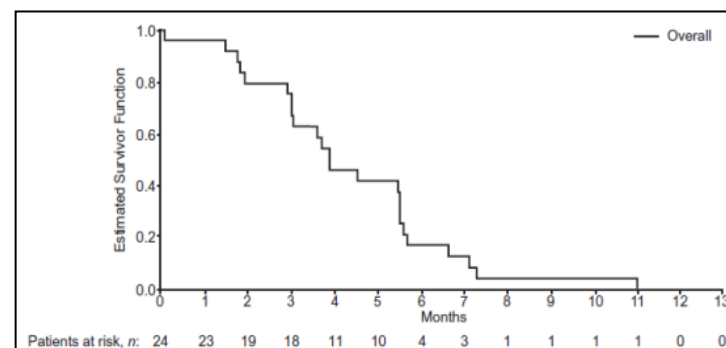
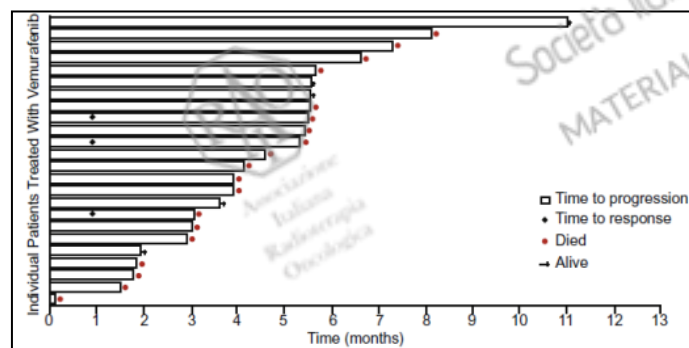
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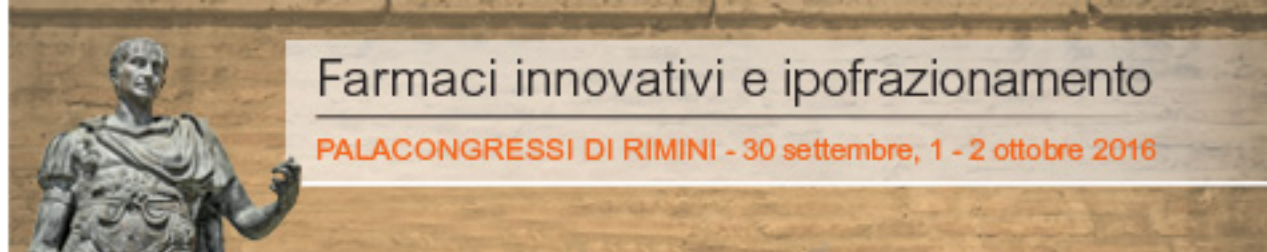
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## Vemurafenib in patients with $BRAF^{V600}$ mutation-positive melanoma with symptomatic brain metastases: Final results of an open-label pilot study

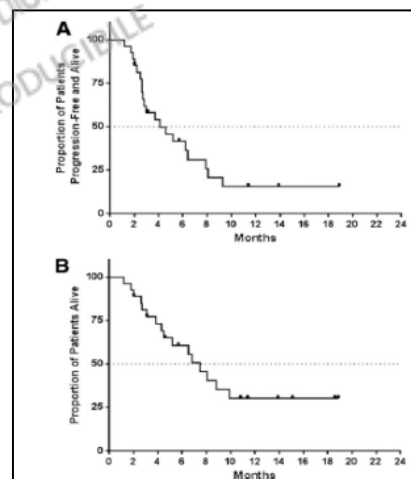
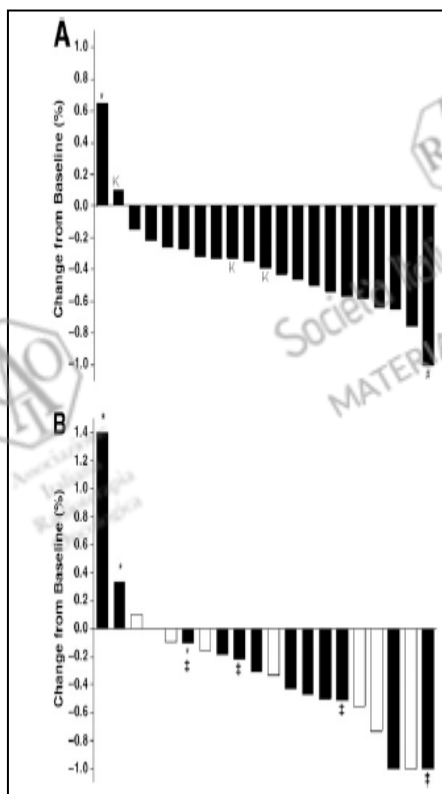
Reinhard Dummer<sup>a,\*</sup>, Simone M. Goldinger<sup>a,1</sup>, Christian P. Turtzchi<sup>a</sup>,  
Nina B. Eggmann<sup>a</sup>, Olivier Michielin<sup>b</sup>, Lada Mitchell<sup>c</sup>, Luisa Veronese<sup>c</sup>,  
Paul René Hilfiker<sup>d</sup>, Lea Felderer<sup>a</sup>, Jeannine D. Rinderknecht<sup>a</sup>





## A Retrospective Evaluation of Vemurafenib as Treatment for BRAF-Mutant Melanoma Brain Metastases

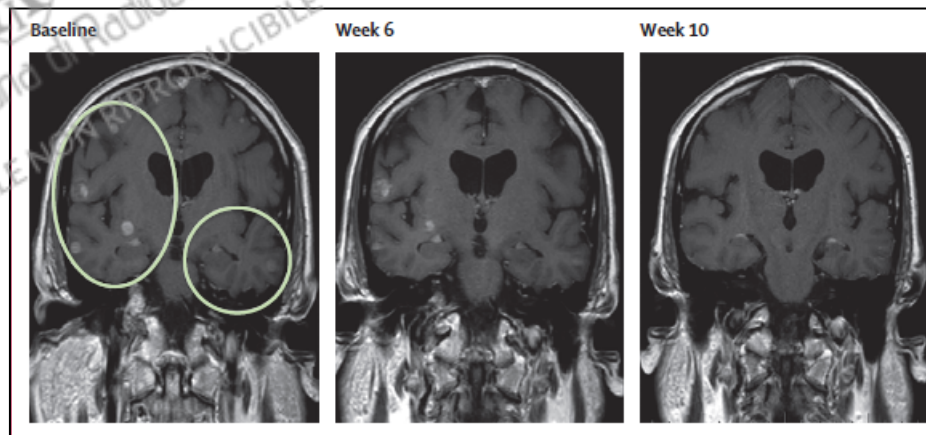
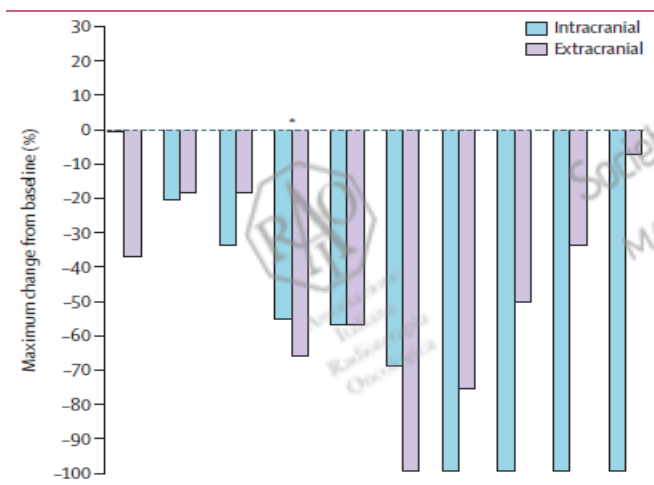
JAMES J. HARDING,<sup>a,c</sup> FEDERICA CATALANOTTI,<sup>d</sup> RODRIGO R. MUNHOZ,<sup>a</sup> DONAVAN T. CHENG,<sup>d</sup> AMIN YAQUBIE,<sup>a</sup> NICOLE KELLY,<sup>a</sup> GREGORY C. McDERMOTT,<sup>c</sup> ROMONA KERSELLIUS,<sup>c</sup> TAHA MERGHOUB,<sup>e</sup> MARIO E. LACOUTURE,<sup>a</sup> RICHARD D. CARVAJAL,<sup>a</sup> KATHERINE S. PANAGEAS,<sup>b</sup> MICHAEL F. BERGER,<sup>d</sup> NEAL ROSEN,<sup>a,c,f</sup> DAVID B. SOLIT,<sup>a,c,d</sup> PAUL B. CHAPMAN<sup>a,c</sup>





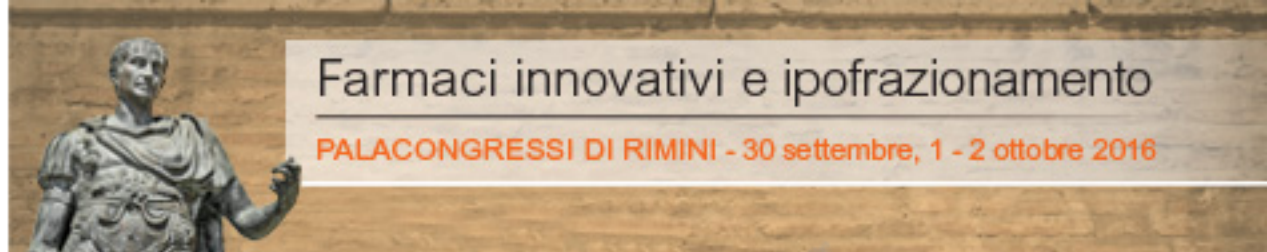
## Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial

Gerald S Falchook\*, Georgina V Long\*, Razelle Kurzrock, Kevin B Kim, Tobias H Arkenau, Michael P Brown, Omid Hamid, Jeffrey R Infante, Michael Millward, Anna C Pavlick, Steven J O'Day, Samuel C Blackman, C Martin Curtis, Peter Lebowitz, Bo Ma, Daniele Ouellet, Richard F Kefford



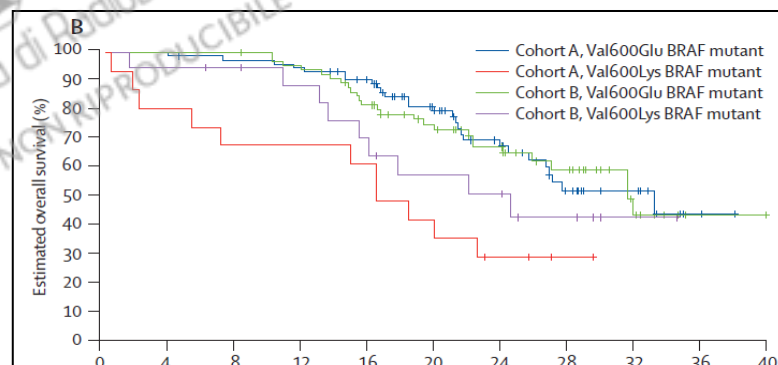
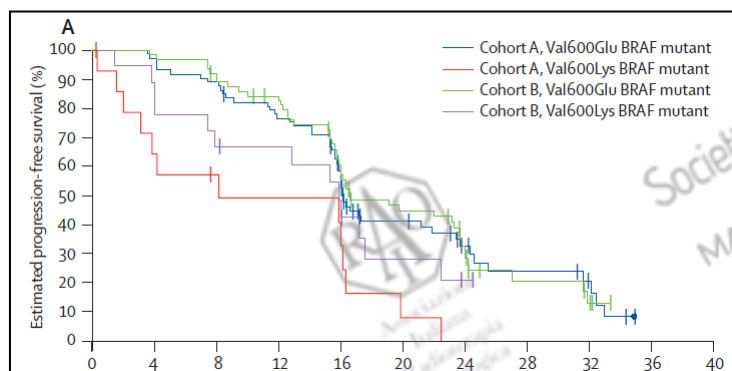
*In conclusion, dabrafenib is the first drug of its class to show activity in treatment of melanoma brain metastases.*





## Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial

Georgina V Long, Uwe Trefzer, Michael A Davies, Richard F Kefford, Paolo A Ascierto, Paul B Chapman, Igor Puzanov, Axel Hauschild, Caroline Robert, Alain Algazi, Laurent Mortier, Hussein Tawbi, Tabea Wilhelm, Lisa Zimmer, Julie Switzky, Suzanne Swann, Anne-Marie Martin, Mary Guckert, Vicki Goodman, Michael Streit, John M Kirkwood\*, Dirk Schadendorf\*



*Dabrafenib has activity and an acceptable safety profile in patients with Val600Glu BRAF-mutant melanoma and brain metastases irrespective of whether they are untreated or have been previously treated but have progressed.*



## Radiobiology

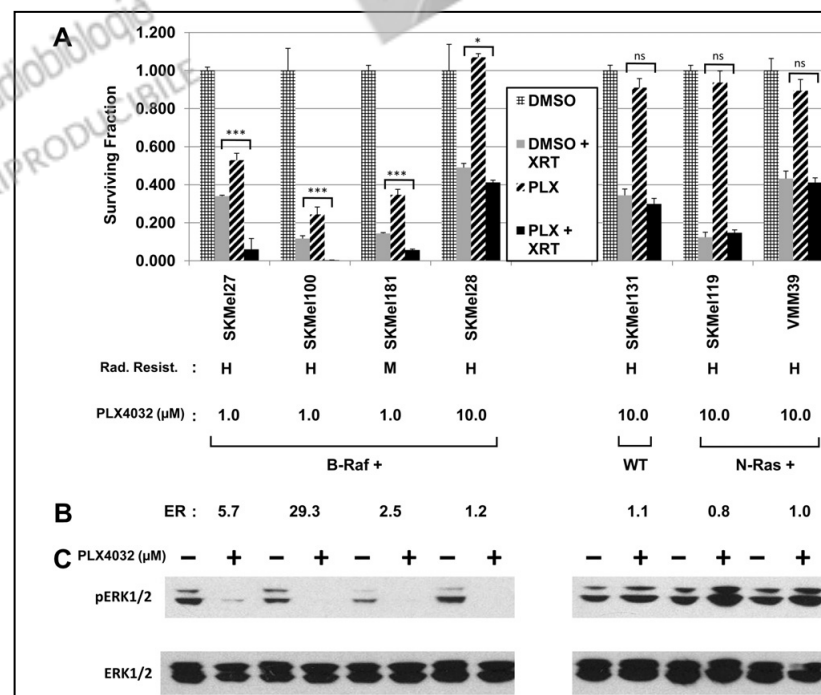
Melanoma cells show a heterogeneous range of sensitivity to ionizing radiation and are radiosensitized by inhibition of B-RAF with PLX-4032

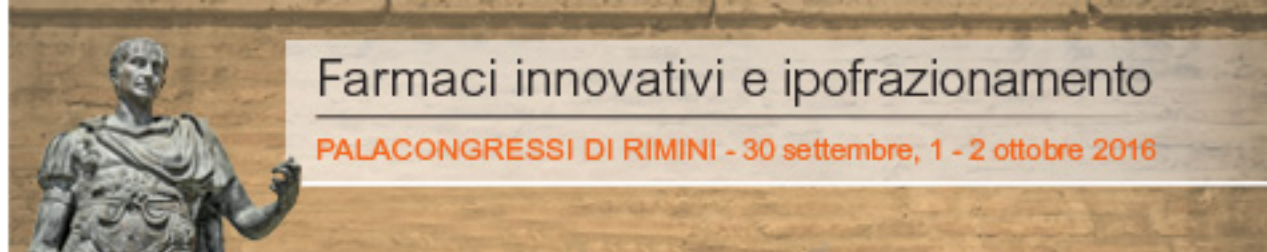
Maria J. Sambade<sup>c,e</sup>, Eldon C. Peters<sup>b,e</sup>, Nancy E. Thomas<sup>b,e</sup>, William K. Kaufmann<sup>c,d,e</sup>, Randall J. Kimple<sup>a,e</sup>, Daniel M. Shields<sup>a,b,e,\*</sup>

*Treatment of B-Raf+ cells with the B-RAF inhibitor PLX-4032 in combination with radiation provided enhanced inhibition of both colony formation and invasion, and radiosensitized cells through an increase in G1 arrest.*

*Conclusions: Our data suggest that melanomas are not uniformly radioresistant with a significant subset displaying inherent radiosensitivity.*

*Pharmacologic inhibition of B-RAF with PLX-4032 effectively radiosensitized B-Raf+ melanoma cells suggesting that this combination approach could provide improved radiotherapeutic response in B-Raf+ melanoma patients.*



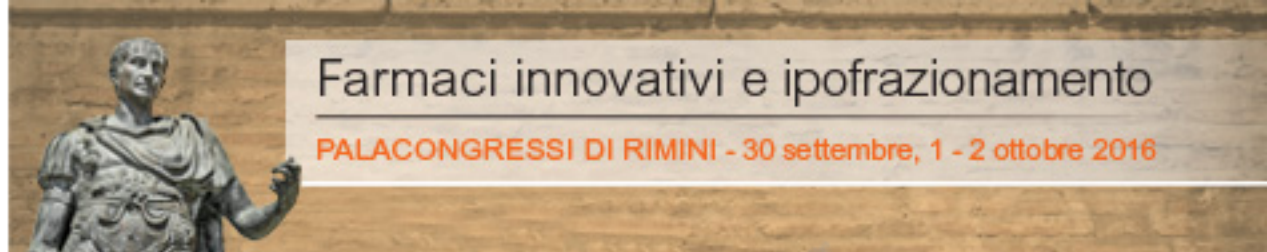


# Vemurafenib and Radiosensitization

Lise Boussemart, MD; Catherine Boivin, MD; Joël Claveau, MD; Yun Gan Tao, MD; Gorana Tomasic, MD; Emilie Routier, MD; Christine Mateus, MD; Eric Deutsch, MD, PhD; Caroline Robert, MD, PhD

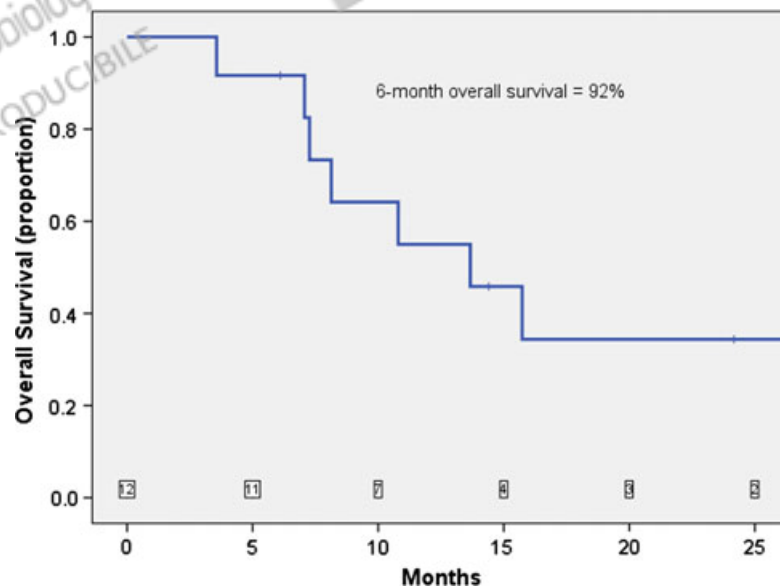
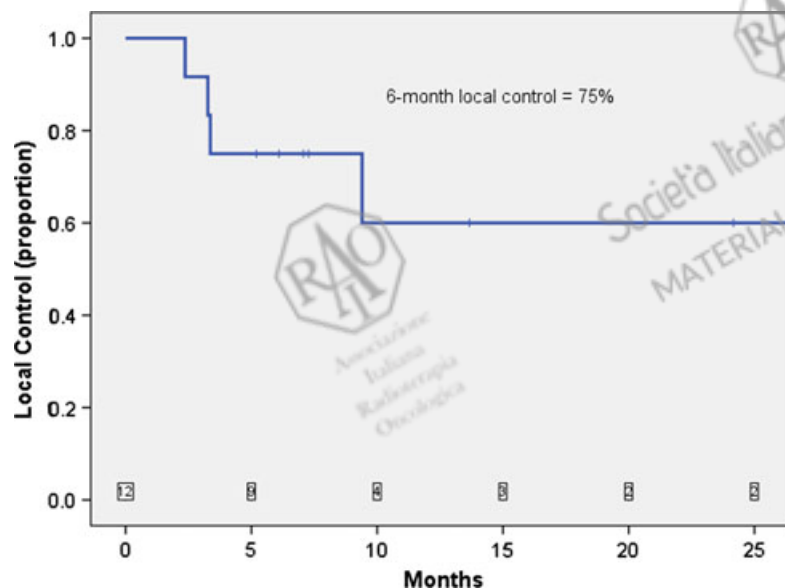




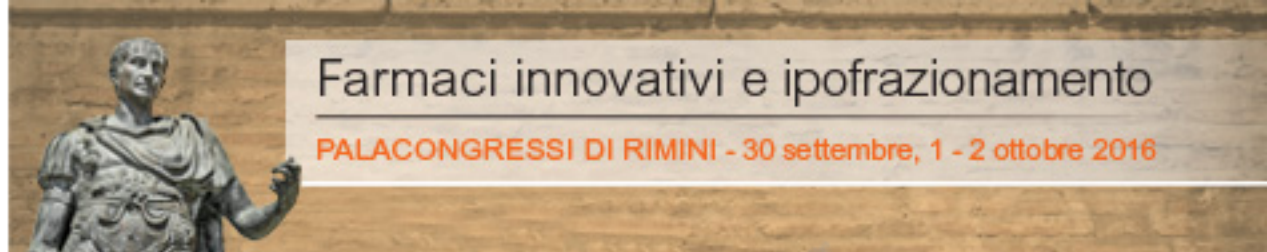


## Vemurafenib and radiation therapy in melanoma brain metastases

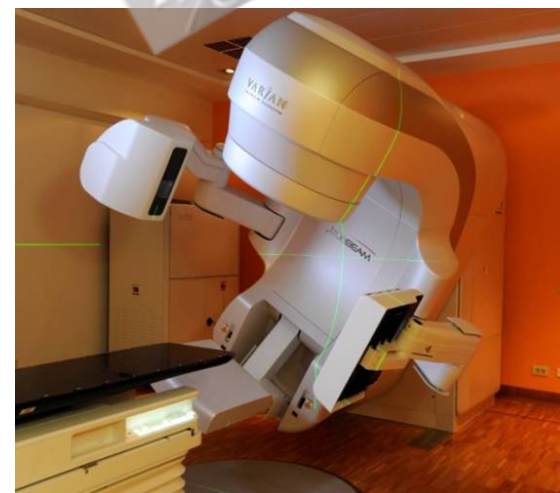
Ashwatha Narayana · Maya Mathew · Moses Tam · Rajni Kannan ·  
Kathleen M. Madden · John G. Golfinos · Erik C. Parker · Patrick A. Ott ·  
Anna C. Pavlick







# Humanitas experience



# Patient's demographics and treatment characteristics

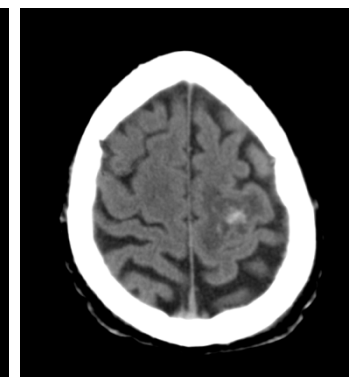
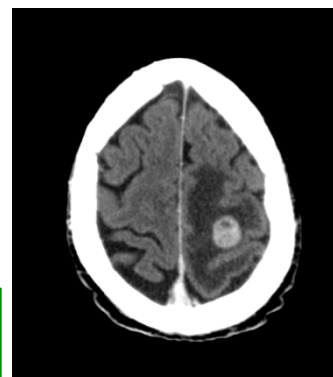
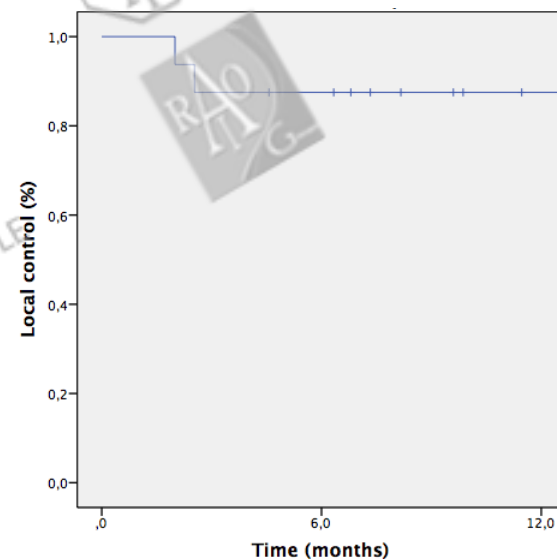
| Parameter                  | Number of cases (frequency)                                  |
|----------------------------|--|
| Number of patients         | 16   |
| Number of lesions          | Single: 6 (37.5%)<br>Two: 5 (31.25%)<br>Multiple: 5 (31.25%) |
| Median age (range) [years] | 53 [29-81]   |
| Sex Male/Female            | 9 (56%) / 7 (44%)  |
| Performance status         | 0 12 (75%)<br>1 2 (12.5%)<br>2 2 (12.5%)                     |
| Extracranial disease       | Yes 8 (50%)<br>No 8 (50%)                                    |
| Systemic therapy           | Vemurafenib 7 (43%)<br>Dabrafenib + Trametinib 9 (57%)       |
| RT type                    | RS 10 (62.5%)<br>WBRT 6 (37.5%)                              |



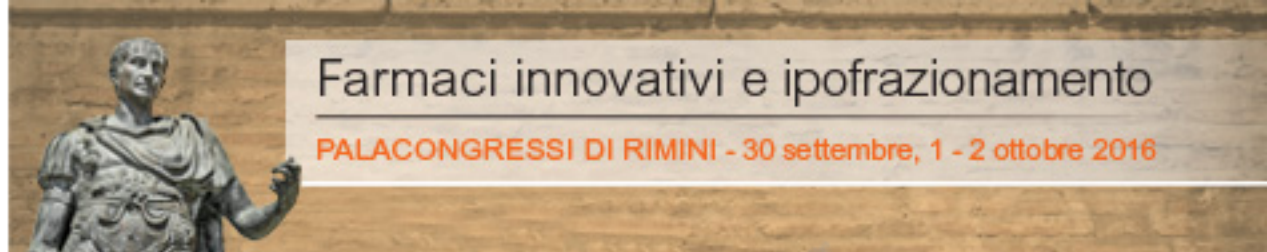


# Local control and distant failure

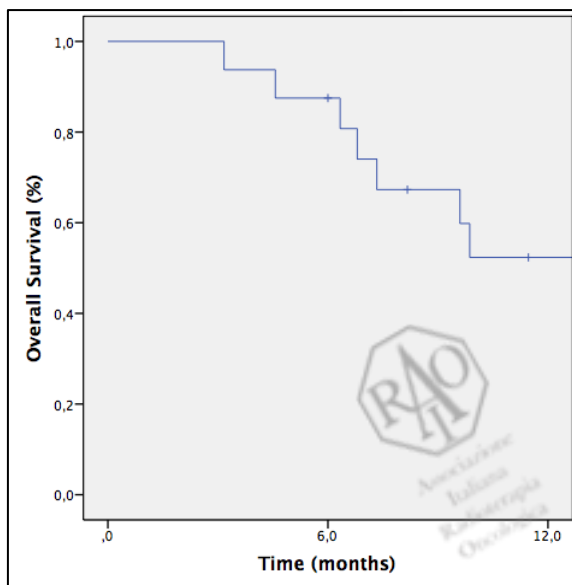
| Status  | Number of cases<br>(frequency) |
|---|--------------------------------|
| Complete response                                 | 1 (6.25%)                      |
| Partial Response                                  | 10 (62.5%)                     |
| Stable disease                                    | 3 (18.75%)                     |
| Progressive disease                               | 2 (12.5%)                      |
| Mean Time to progression [range] (months)         | 7,5 ( range 1.6-14.2)          |
| Intracranial progression                          | 11 (68.75%)                    |
| Time to intracranial progression [range] (months) | 7.6 (range 1.6-14.2)           |
| Extracranial progression                          | 3 (18.75%)                     |
| Time to extracranial progression [range] (months) | 5.4 (range 4.5-6.7)            |



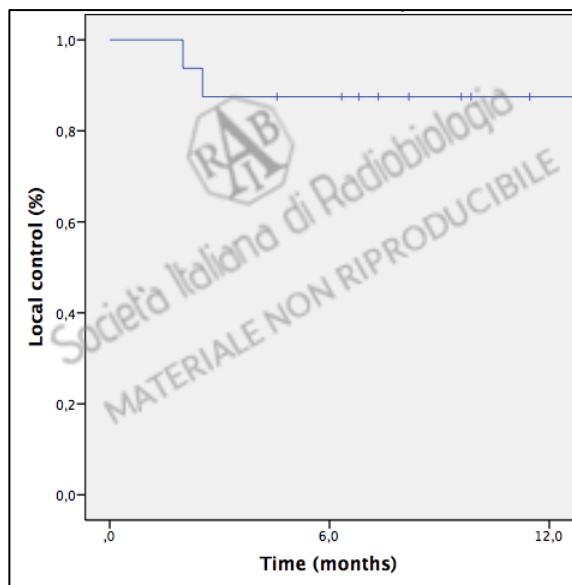




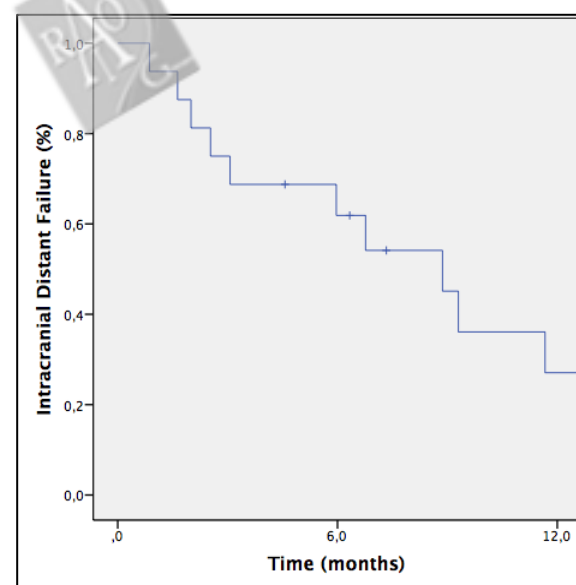
## Local control and distant failure



OS 6 87%  
12 52,4%



LC 6 87,5%  
12 87.5%.

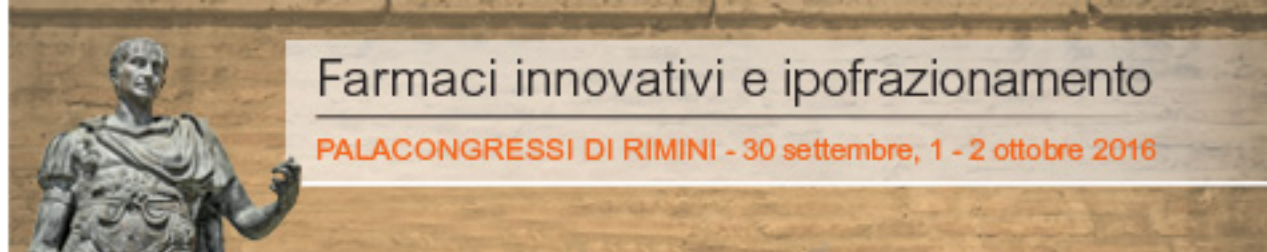


IDDC 6 61,9%  
12 21,7%



## Toxicity

- RADIATION NECROSIS → 2
- BLEEDING → 1
- SKIN TOXICITY → 0



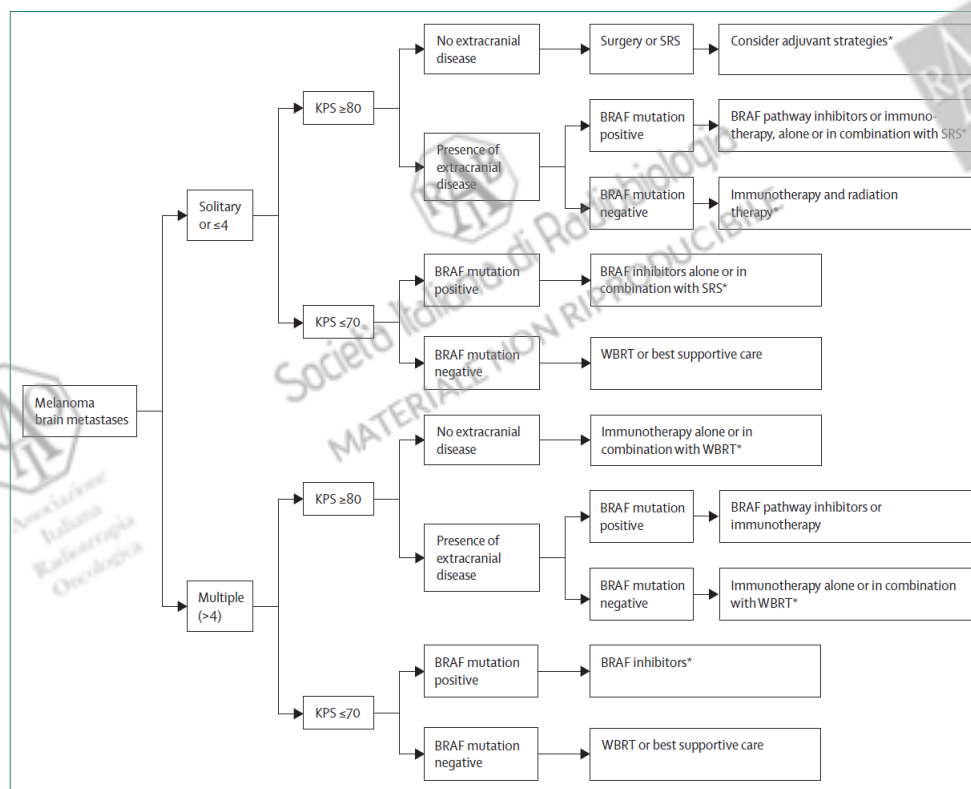
## THE LANCET

"Atrial Fibrillation is estimated to affect 33 million people worldwide... There are no excuses to ignore this common cardiac disorder."

2015

## Evolving treatment options for melanoma brain metastases

Thankamma Ajithkumar, Christine Parkinson, Kate Fife, Pippa Corrie, Sarah Jefferies







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PALACONGRESSI DI RIMINI - 30 settembre, 1 - 2 ottobre 2016

# Thanks for your attention!

## again

**HUMANITAS**  
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