Author's response to reviews

Title: Neoplastic leptomeningitis and treatment with BRAF inhibitors in melanoma: a case report.

Authors:

Ester Simeone (ester.simeone@gmail.com)
Eleonora De Maio (eleonora.demaio1981@gmail.com)
Fabio Sandomenico (f.sandomenico@virgilio.it)
Franco Fulciniti (franco.fulciniti@gmail.com)
Pasquale Aprea (pasqualeaprea@alice.it)
Stefania Staibano (staibano@unina.it)
Vincenzo Montesarchio (enzo.montesarchio@inwind.it)
Giuseppe Palmieri (g palmieri@yahoo.com)
Nicola Mozzillo (nimozzi@tin.it)
Paolo A Ascierto (paolo.ascierto@gmail.com)

Version: 2 Date: 22 February 2012

Author's response to reviews: see over
Napoli, 16th February 2012

Author’s covering letter for revised manuscript version submission
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Authors:
Ester Simeone (ES) ester.simeone@gmail.com
Eleonora De Maio (EDM) eleonora.demaio1981@gmail.com
Fabio Sandomenico (FS) f.sandomenico@virgilio.it
Franco Fulciniti (FF) franco.fulciniti@gmail.com
Sebedo Lastoria (SL) selastor@tin.it
Pasquale Aprea (PA) pasqualeaprea@alice.it
Stefania Staibano (SS) staibano@unina.it
Vincenzo Montesarchio (VM) enzo.montesarchio@inwind.it
Giuseppe Palmieri (GP) gpalmieri@yahoo.com
Nicola Mozzillo (NM) nimozzi@tin.it
Paolo A. Ascierto (PAA) paolo.ascierto@gmail.com

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Professor Michael Kidd AM,
Editor-In-Chief,
Journal of Medical Case Reports

Dear Professor Kidd,

Please find enclosed the revised version of the manuscript by Simeone et al., entitled “Neoplastic leptomeningitis and treatment with BRAF inhibitors in melanoma: a case report” to be considered for publication in Journal of Medical Case Reports as Case Report.

Revision of the manuscript was based on the Reviewer and Editorial Team remarks. Changes have been highlighted in yellow into the paper and here listed point-by-point.

Reviewer comments:
Confidential comments to editors I thought that this article was reasonable to publish, although anecdotal and a case where the issues will ultimately require prospective trials to address, not case reports. Minor grammar and syntax issues are evident in the article.
We corrected the minor grammar mistakes evidenced by the Reviewer.

**Editorial Team remarks:**
In addition, would like to request for formatting changes required for your manuscript, as it does not conform to the journal's style. Kindly address the following:

*Please include the study design in your title, i.e. Case report. For example: A presenting with B in C: a case report.*

We corrected the title in the current form: “Neoplastic leptomeningitis and treatment with BRAF inhibitors in melanoma: a case report.”

*Please restructure the Abstract into the following three sections: Introduction, Case presentation, and Conclusion. The abstract should be no longer than 350 words.*

We restructured the abstract as suggested by the Editorial Team:

**Introduction:** Leptomeningeal metastases (LM) are occurring at higher frequency in cancer patients. The prognosis of LM is poor and standard treatment, which includes radiotherapy and chemotherapy, is mostly ineffective. Among others, melanoma represents one of the tumours with the highest incidence of LM. For such a disease, the BRAF inhibitors (BRAFi) have been recently demonstrated to be effective on melanoma brain metastases harbouring the V600EBRAF mutation.

**Case presentation:** We report a case of advanced melanoma with brain, lung and peritoneum metastases in a 39-year-old Italian woman, harboring the V600EBRAF mutation. On August 2010 she was enrolled into the BRIM3 trial and after the randomization process she received dacarbazine. After 2 cycles, she met a disease progression, on peritoneal and lung. For this reason, she was enrolled into another clinical trial with the GSK2118436 BRAF inhibitor (dabrafenib) as second line of therapy. She met a partial response that was maintained until 13 weeks of treatment. On January 2011 she developed symptoms typical for brain metastase and reveived a diagnosis of leptomeningeal involvement of melanoma cells after the cerebral spinal fluid (CSF) exam - with MRI negative for meningitis or brain metastases. Analysis of CSF sample confirmed that melanoma cells still carried V600EBRAF mutation. After few days, the patient went into coma and died.

**Conclusion:** Starting from a clinical case, here we discuss about the pathogenesis of LM and whether leptomeninges may represent a “sanctuary” where melanoma cells may generate resistance and/or BRAFi can not reach the adequate concentration for their activity. This in order to assess whether the treatment with BRAFi in melanoma patients should be interrupted as soon as disease progression appears or continued beyond progression, through administration of additional compounds.

**Abstract words count:** 281

*Please include the ethnicity of the patient in the abstract and case presentation section of the manuscript.*

We included the ethnicity of the patient both in the abstract and case presentation section of the manuscript: “a 39-year-old Italian woman”
Please replace the header ?Background? to ?Introduction.? 
We corrected the header as suggested.

Please remove writings found in figures 1c and 1d. 
We removed the writings in figures 1c and 1d.

Moreover, please we added Dr Secondo Lastoria as Author. Because he provided the PET scan analysis.

We look forward to hearing from you in due course.

Yours sincerely,

Paolo A. Ascierto, MD 
Unit of Medical Oncology and Innovative Therapy 
Istituto Nazionale Tumori Fondazione "G. Pascale" 
Via Mariano Semmola 
80131 Napoli - Italy 
Tel/Fax +39 081 5903841 
Mobile +39 338 740 2333 
email: paolo.ascierto@gmail.com