Author's response to reviews

Title: The clinical response to vemurafenib in a patient with a rare BRAF V600D/K601del mutation-positive melanoma.

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Version: 3
Date: 12 August 2014

Author's response to reviews: see over
Author's response to reviews

MS: 1229210720127879

Title: The clinical response to vemurafenib in a patient with a rare $BRAF^{V600DK601del}$ mutation-positive melanoma.

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Version: 2    Date: 29 April 2014

Author's response to reviews: see over
Reviewer's report

Title: The clinical response to vemurafenib in a patient with a rare BRAFV600DK601del mutation-positive melanoma.

Version: 2   Date: 29 June 2014

Reviewer: Jochen Gaedcke

Reviewer's report:

The report by Trudel et al. is well and clearly written, and comes to the important information that patients with the retrieved, specific mutation are well treated by vemurafenib.

In this context the authors describe the difficulties in detecting rare mutations/deletions and the potential misleading (not in this case). Therefore, the authors should comment whether the retrieved data in the past from V600E mutations have the potential of being misdiagnosed.

The reviewer is correct and we have added this sentence (and reference 32) to the Discussion:

However, in a retrospective study of 47 metastatic melanoma from our centre, we have compared the V600 mutation detection by molecular techniques with the BRAF^{V600E} mutant protein expression by immunohistochemical analysis using highly specific anti-BRAF^{V600E} monoclonal antibodies and no other cases of misidentified p.V600E mutation was found [32].

Second, the authors state that rare mutations are not known to be targeted by vemurafenib. They should comment if their analyzes are a potential approach to answer the question before treatment is started. Or, alternately, which approach they would suggest.

The reviewer is correct and we have added these sentences (and reference 31) to the Discussion:

In a more general way, performing predictive in silico structural analysis before the treatment is started could be helpful to evaluate the activating character of a mutation when the clinical efficacy is not well established. Moreover, this approach is currently being used in the French clinical trial AcSé crizotinib [31].

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests
Reviewer's report

Title: The clinical response to vemurafenib in a patient with a rare BRAFV600DK601del mutation-positive melanoma.

Version: 2 Date: 13 July 2014

Reviewer: Leisl Packer

Reviewer's report:

The paper by Trudel et al. describes a rare BRAF mutation (V500DK601del) in a melanoma patient treated with vemurafenib. A short-lived partial response was observed in this patient, but after 2 months, the patient relapsed. This mutation has been previously documented, again with a short-lived response. However, this is the first paper to show that this complex mutation occurred on the same allele. They went on to perform predictive structural analysis in attempt to explain how this mutant protein interacts with vemurafenib. This study provides insight into complex BRAF mutations and suggests that more comprehensive mutational analysis should be performed when screening melanoma patients for vemurafenib treatment. The paper is well-written and will be of interest to the melanoma field, as BRAF remains the major target of therapy in this disease.

My only comment is that reference number 25 is not complete. Please include the volume, pages etc of this reference.

The reference has been completed.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.