Author's response to reviews

Title: Long-term outcome and effect of maintenance therapy in patients with advanced sarcoma treated with trabectedine. An analysis of 181 patients of the French ATU compassionate use program

Authors:

Jean-Yves Blay (jean-yves.blay@lyon.unicancer.fr)
Antoine Italiano (a.italiano@bordeaux.unicancer.fr)
Isabelle Ray-Coquard (isabelle-ray-coquard@lyon.unicancer.fr)
Axel Le Cesne (axel.lecesne@igr.fr)
Florence Duffaud (Florence.DUFFAUD@ap-hm.fr)
Maria Rios (m.rios@nancy.unicancer.fr)
Olivier Collard (Olivier.COLLARD@clioire.fr)
Francois Bertucci (BERTUCCIF@ipc.unicancer.fr)
Emmanuelle Bompas (Emmanuelle.Bompas@ico.unicancer.fr)
Nicolas Isambert (NIsambert@cgfl.fr)
Loic Chaigneau (chaigneau.loic@orange.fr)
Philippe Cassier (philippe.cassier@lyon.unicancer.fr)
Gauthier Decanter (g-decanter@o-lambret.fr)
Olfa Derbel (olfa.derbel@lyon.unicancer.fr)
Caroline Even (carline.even@igr.fr)
Binh Bui (b.bui@bordeaux.unicancer.fr)
Jean-Michel Coindre (j.coindre@bordeaux.unicancer.fr)
Patrick Zintl (pzintl@pharmamar.com)
Nadia Badri (nbadri@pharmamar.com)
Nicolas Penel (n.penel@o-lambret.fr)

Version: 2 Date: 31 December 2012

Author's response to reviews: see over
Dear Editor,

Thank you very much for your recent correspondence, and please accept our apologies for the delayed response for a revised version. I actually had missed the first e-mail informing us of the revisions needed for our article entitled “Long-term outcome and Impact of maintenance therapy in patients with advanced sarcoma treated with trabectedine. An analysis of 181 patients of the French ATU compassionate use program”, by JY Blay et al.

We would like first to thank the reviewers for their helpful comments and critics. These helped us to improve the quality of our manuscript in the revised version which you will find enclosed.

Hereunder are the answers to the different points raised by the two reviewers:

**Reviewer 1:**

**Minor essential revisions**

1. We agree with this comment. This point was added in the Material and method section of the revised version.

2. The different typographical errors were corrected. “Cycles “ is now used consistently.

3. The acronyms (EORTC, STBQSG, FSG,...) were described

**Discretionary revisions:**
1. We agree in general with this comment of the reviewer. The term “compassionate” is however the translation of the term “compassionale” which is the official term. We therefore chose to keep it.

2. We have modified the title sentence accordingly in the revised version.

3. The Succeed paper is still submitted for publication.

4. We agree with this proposition and have added the following sentence in the discussion: “Among the 11 centres participating to the study, 5 had participated to the phase II EORTC trial, reflecting the experience of the centres with this agent. This is therefore a selected subgroup of the ATU series, but this selection makes comparison with phase II data maybe more relevant.”

Reviewer 2:

Major compulsory revision 1. We agree with this interpretation. We have modified the section accordingly in the revised version.

Major compulsory revision 2. “Complementary” was indeed inaccurate. We have removed this from the revised version, and actually, the sentence should have been “A total of 56 (31.1%) patients were in SD or PR after 6 courses. In 16, the treatment was stopped, whereas in 40 patients it was continued beyond 6 courses for a median of 9 complementary cycles (range 7-19)”.
**Major Compulsory revision 3:** We agree that this is a very important point. Actually, it is difficult to compare directly the historical database of STBSG initially published in 1999, since this included mainly first line patients, while the present series gathers patients in all lines (from first line metastatic in patients pretreated in the adjuvant setting to fourth line patients”. Possibly the best comparison can be obtained with the subsequent paper by Judson et al, reporting separately 2nd line + patients. In this case, the median progression free rate is 2.3 months for the whole series of patients. Comparisons between histological subtypes are however challenging, since histological classifications and inclusion criteria varied considerably between the 2 series. For instance, GIST were mixed amongst leiomyosarcoma in the former series. The exhaustive histological review of the previous series has not been performed with the classifications of 2002 or 2013.

The following section has been added in the discussion section of the revised version: “It is challenging to compare the present series with the EORTC database of the pre trabectedin era (2,3) published since 1999 for several reasons: 1) the former series included mainly first line patients, while the present series gathers patients in all lines (from first line metastatic in patients pretreated in the adjuvant setting to fourth line patients. 2) histological classifications and inclusion criteria varied considerably between the 2 series; for instance, GIST were mixed amongst leiomyosarcoma in the former series. The exhaustive histological review of the previous series has not been performed with the classifications of 2002 or 2013.

Possibly the best comparison can be obtained with the subsequent paper by Van Glabbeke et al, reporting separately second line + patients. In this case, the median progression free rate is 2.3 months, and a 1 year PFR rate of 7% in the whole series, and 12% for the series of patients treated with “active agents” (5). The results observed with the present ATU series, median PFS of 3.6 months, and 12 months PFS close to 30% compare therefore favorably with these historical controls, despite all these limitations.”
Minor revisions:

The different modifications proposed by the reviewer were inserted in the revised version.

In the present revised version, we have attempted to address all different points raised by both reviewers. We remain at your disposition for further information.

Thank you in advance for the attention you will pay to this work.

With kind regards

JY Blay, M.D., Ph.D