

February 27, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8896 edited.doc).

Title: Apoptosis block as a barrier to effective therapy in non small cell lung cancer

Author: Ian Paul, J Mark Jones

Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 8896

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated as suggested by the Editor

2 Revision has been made according to the suggestions of the reviewers:

- (1) It was suggested:
"Strategies to overcome mitochondrial apoptosis block" was not sufficient because there was too small suggestion. This section seems to be main section of this manuscript, so please show the further suggestion.

This was not the main section of our manuscript and was included only as examples of potential future study for development of novel targeted agents. We are reluctant to expand this section in more detail as it is not the central message of the review. We are focusing on how apoptosis can be a barrier to therapy.

- (2) The section "FLIP inhibits extrinsic apoptosis pathway" was unclear for 2 separate reviewers so we have removed this from the manuscript as it is not an essential component of the review.
- (3) The abbreviation for non small cell lung cancer (NSCLC) has been standardized throughout the text.
- (4) It was suggested that our manuscript 'only describes pro-apoptotic therapeutic strategies centered on the intrinsic apoptotic pathway. The authors should discuss current clinical data on extrinsic apoptosis targeting strategies in NSCLC'

The pro-apoptotic strategies described in our manuscript are for cancer cells harbouring mitochondrial apoptosis block in particular class B block as defined in the section 'Apoptosis block in cancer'. We feel expanding to cover extrinsic apoptosis targeting is outside the scope of our manuscript and will also be ineffective in cancer cells with class B block as the mitochondrial pathway is also required in extrinsic apoptosis.

- (5) The authors should provide: a) further molecular details on how current approved targeted treatments for NSCLC enhance apoptosis and b) future perspectives regarding potential combination targeted strategies on apoptosis of lung cancer.

It is not known what role apoptosis plays in the effective response to molecular targeted

therapies in NSCLC. These therapies are only briefly mentioned to complete the review of all current therapies in NSCLC. Apoptosis block is of interest as a mechanism of drug resistance to standard chemotherapeutic agents but its significance is not known in the newer targeted therapies.

- (6) The paragraph on five year survival following surgical resection of NSCLC has been expanded for clarification.

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3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Clinical Oncology*.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Mark Jones', followed by a long horizontal flourish.

Mr J Mark Jones MD, FRCSEd(CTh)

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