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Shicheng Guo <shg047@eng.ucsd.edu>

Thank you for the review of JTO-D-15-01079

1 message

Journal of Thoracic Oncology <em@editorialmanager.com> Mon, Nov 9, 2015 at 8:31 AM
Reply-To: Journal of Thoracic Oncology <mary.todd@iaslc.org>
To: Shicheng Guo <shg047@eng.ucsd.edu>

RE: JTO-D-15-01079, entitled Intermittent exposure to EGFR tyrosine kinase inhibitors selects less EGFR T790M mutant clones than continuous exposure in lung cancer cell lines, by Dr Youngjoo Lee

Dear Dr Guo,

The editors have made a decision on the above-referenced manuscript that you previously reviewed for JTO. The decision letter is included below. If you have any questions or comments please feel free to contact the journal office via email to Mary.Todd@iaslc.org.

Thank you for your time and efforts,

Mary Sharkey Todd, MFA
Managing Editor
Journal of Thoracic Oncology

To: ********
cc: ********
From: "Journal of Thoracic Oncology" mary.todd@iaslc.org
Subject: JTO Decision
CC: ********

Nov 09, 2015

RE: JTO-D-15-01079, entitled "Intermittent exposure to EGFR tyrosine kinase inhibitors selects less EGFR T790M mutant clones than continuous exposure in lung cancer cell lines"

Dear ******** ********,

I have received the comments of the reviewers on your manuscript. Unfortunately, according to the guidelines set for the journal, your submission did not receive a high enough priority rating to warrant its publication.

We receive many submissions and due to space limitations are only able to accept a small portion of them. The specific comments of the reviewers are included below. You may want to take their recommendations into

account should you decide to prepare the manuscript for submission to another journal.

Thank you for submitting your manuscript to the Journal of Thoracic Oncology. We would be happy to review your future work.

http://jto.edmgr.com/

Your username is: ********
Your password is: ********

With Kind Regards,

Dr D. Ross Camidge
Associate Editor
Journal of Thoracic Oncology

Reviewer Comments:

Reviewer #1: Comments to the Authors,

This manuscript reported a comprehensive description to the dynamic process of the initiation of drug-resistant cell lines with the treatment of Gefitinib to lung cancer cell line PC-9. Meanwhile, the re-sistance recovery were also investigated with the 8 weeks of drug-free culture. The study was per-formed rigorously and the findings sound very interesting. What's more, it would be an exciting exam-ple to explore the mechanism of the drug-resistant cell lines. However, I have several major concerns.

Major Compulsory Revisions

1, T790M is one of most important molecular mechanism of resistance. However, I do not think it is the unique mechanism.
2, How to understand the Y-axis of Figure 1B. What's the initial cell number is according to this figure? Can the author provide the cell number for the whole process?
3, What's the time point for Figure 1C?
4, For the Figure 2A and 2B, the sensitivity of the PC-9/GRc cells to gefitinib after the drug-free culture can be detected after 8 weeks, However, How the cell viability were estimated for the contrast "before"?
5, In the Figure 3, there is a huge increasing of the allele frequency of T790M between 0.02 and 0.04. The fold-change come up to 24.75. What happened for this change?
6, What's the accuracy for the allele estimate with the method in Figure 5 and 6. Is there any calibration curve to make the inference?
7, How many generations would be generated during 72h cell culture? Do you think the epi-genetic which is corresponding to the drug treatment would be passed down as the cell pro-liferation?

Reviewer #2: This is a well-written, straight forward preclinical study that potentially has clinical implication. However, the conclusion seems to be wrong. The shorter drug exposure time in the intermittent exposure arm has likely contributed to the low frequency of T790M compared to the continuous exposure arm. "With continuous exposure to gefitinib (PC-9/GRc cells), drug resistance was observed after 42 weeks, whereas with intermittent exposure (PC-9/GRi cells), drug resistance was observed after 18 weeks." Thus, preclinical intermittent dosing of gefitinib leads to early treatment resistance comparing to continuous dosing, supporting current clinical practice against drug holiday in patients receiving an EGFR TKI.