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Reviewer Invitation for Intermittent exposure to EGFR tyrosine kinase inhibitors selects less EGFR T790M mutant clones than continuous exposure in lung cancer cell lines

1 message

Journal of Thoracic Oncology <em@editorialmanager.com> Tue, Oct 13, 2015 at 12:41 PM
Reply-To: Journal of Thoracic Oncology <mary.todd@iaslc.org>
To: Shicheng Guo <shg047@eng.ucsd.edu>

Journal of Thoracic Oncology
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Oct 13, 2015

Dear Dr Guo,

I am writing in hopes that you may be able to review manuscript 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.

Please find the manuscript abstract listed below.

If you should choose to accept this assignment, you will be given 14 days to complete the assignment.

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Thank you for your time and efforts,

D. Ross Camidge, M.D., PhD
Associate Editor
Journal of Thoracic Oncology

Background: Drug-resistant cell lines are essential tools for investigating the mechanisms of resistance to molecular-targeted anti-cancer drugs. However, little is known about how to establish clinically relevant drug-resistant cell lines. Our study examined the impact of a drug-free period on the establishment of a cell line with

clinically relevant resistance to molecular-targeted drugs.
Methods: We used PC-9 cells, a lung cancer cell line carrying EGFR mutation, because this is a validated target for EGFR tyrosine kinase inhibitors (TKI). PC-9 cells were intermittently or continuously exposed to increasing concentrations of gefitinib (0.01 μM to 1.0 μM) and the emergence of the most common acquired resistance mutation in EGFR, T790M, was determined.
Results: T790M was detected at a 25-fold lower drug concentration in cells continuously exposed to gefitinib (PC-9/GRc) than in cells intermittently exposed to gefitinib (PC-9/GRi) (0.04 μM vs 1.0 μM, respectively). The mutation frequencies at those drug concentrations were 19.8% and 8.0% in PC-9/GRc and PC-9/GRi cells, respectively. After drug-free culture for 8 weeks, resistance to gefitinib decreased in the PC-9/GRi cells but not in the PC-9/GRc cells. In the PC-9/GRc cells, the frequency of the T790M mutation was consistently about 20% from 0.04 μM to 1.0 μM of gefitinib. In the PC-9/GRc cells, the T790M mutation was detected in all single-cell clones, at frequencies ranging from 7.0% to 37.0%, with a median of 19.5% (95% confidence interval, 17.3%-20.9%).
Conclusion: Intermittent exposure to EGFR-TKIs reduces the emergence of the EGFR T790M mutation in a lung cancer cell line.