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PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 69115

Title: Dramatic response to immunotherapy in an EGFR-mutant non-small cell lung cancer：A case report

Reviewer's code: 00503561

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2021-07-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-07-04 23:53

Reviewer performed review: 2021-07-16 02:36

Review time: 11 Days and 2 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

1. Why the authors did not use 2nd generation TKIs? Absence of T790M mutation exclude the chance? 2. Biomarkers for this effectiveness should be searched for more robustly such as PDL1 FISH and/or CD8 infiltration in the tumors.

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PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 69115

Title: Dramatic response to immunotherapy in an EGFR-mutant non-small cell lung cancer：A case report

Reviewer's code: 05524138

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Chief Doctor, Consultant Physician-Scientist

Reviewer's Country/Territory: Kazakhstan

Author's Country/Territory: China

Manuscript submission date: 2021-07-04

Reviewer chosen by: Ze-Mao Gong

Reviewer accepted review: 2021-07-24 10:48

Reviewer performed review: 2021-07-24 10:52

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

This study is interesting in its results and will be interesting for oncologists and chemotherapists.

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PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 69115

Title: Dramatic response to immunotherapy in an EGFR-mutant non-small cell lung cancer： A case report

Reviewer's code: 05326255

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Czech Republic

Author's Country/Territory: China

Manuscript submission date: 2021-07-04

Reviewer chosen by: Ze-Mao Gong

Reviewer accepted review: 2021-07-22 06:51

Reviewer performed review: 2021-07-28 10:44

Review time: 6 Days and 3 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Mr Li and his coauthors describe a case report illustrative of potential treatment benefit from immonotherapy in EGFR-positive patients with NSCLC harboring specific mutations despite the general opinion that these patients are immunotherapy-resistant. The manuscript is nicely written, well organized and meets all the criteria for high quality standards. The language is professional, the texflow fluent and the authors´opinions and conclusions are presented in an adequate fashion. I recommend acceptance of the manuscript for publication in W J of Clin Cases journal - after minor correction. The authors should choose only one corresponding author, thank you. 1 Title. Does the title reflect the main subject/hypothesis of the manuscript? YES 2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? YES 3 Key words. Do the key words reflect the focus of the manuscript? YES 4 Background. Does the manuscript adequately describe the background, present status and significance of the study? YES 5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? N/A 6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? N/A 7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? YES 8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? N/A 9 Biostatistics. Does the manuscript meet the requirements of biostatistics? N/A

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10 Units. Does the manuscript meet the requirements of use of SI units? YES 11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? YES Does the author self-cite, omit, incorrectly cite and/or over-cite references? NO 12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? YES 13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? YES 14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? YES

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PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 69115

Title: Dramatic response to immunotherapy in an EGFR-mutant non-small cell lung cancer：A case report

Reviewer's code: 05658248
Position: Peer Reviewer
Academic degree: FRACP, MBBS
Professional title: Academic Research, Assistant Lecturer, Consultant Physician-Scientist, Doctor
Reviewer's Country/Territory: Australia
Author's Country/Territory: China

Manuscript submission date: 2021-07-04
Reviewer chosen by: Ze-Mao Gong
Reviewer accepted review: 2021-07-25 09:17
Reviewer performed review: 2021-08-03 05:46
Review time: 8 Days and 20 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [Y] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [Y] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

While this case is interesting, it is not new and cannot be submitted as a case report. Moreover, the PFS in the timeline figure is only 5 months although in the text it mention 10 months!. This The usage of immunotherapy is not recommended for EGFR-mutatnt NSCLC patients unless there is depletion of the EGFR targeted therapy. There is some evidence for efficacy in patients with PDK1>25% (see below) when used in further lines of treatment. Please see: Yu S, Liu D, Shen B, Shi M, Feng J. Immunotherapy strategy of EGFR mutant lung cancer. Am J Cancer Res. 2018;8(10):2106-2115. Published 2018 Oct 1.

and Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Garassino MC, Cho BC, Kim JH, Mazières J, Vansteenkiste J, Lena H, Corral Jaime J, Gray JE, Powderly J, Chouaid C, Bidoli P, Wheatley-Price P, Park K, Soo RA, Huang Y, Wadsworth C, Dennis PA, Rizvi NA, ATLANTIC Investigators. Lancet Oncol. 2018 Apr; 19(4):521-536.

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PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 69115

Title: Dramatic response to immunotherapy in an EGFR-mutant non-small cell lung cancer： A case report

Reviewer's code: 05347388

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: China

Manuscript submission date: 2021-07-04

Reviewer chosen by: Ze-Mao Gong

Reviewer accepted review: 2021-07-27 02:25

Reviewer performed review: 2021-08-05 21:19

Review time: 9 Days and 18 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Well presented case report - patient with stage IV EGFR L858R mutant lung cancer progressed on targeted therapy with gefitinib, followed by treatment with carboplatin and pemetrexed along with pemetrexed maintenance, on further progression was treated with a checkpoint inhibitor pembrolizumab and responded to the treatment for 10 months. Comments: 1. I see that in conclusion patients with PDL1 expression greater than 25%, L858R mutation, smoking history or pemetrexed treatment may benefit from immunotherapy. I see that he does not have any history of smoking [is it both active and passive - please clarify], second I did not see PDL1 expression mentioned in the manuscript in this patient - can you please mention the PDL1 expression. 2. Although first-generation TKI such as erlotinib or gefitinib used to be the standard front-line treatment for advanced EGFR mutant non-small cell lung cancer, new data improved survival outcomes with front-line of osimertinib compared with the first-generation tyrosine kinase inhibitors. In the phase 3 FLAURA clinical trial, comprising of approximately 550 patients with advanced EGFR mutated non-small cell lung cancer, osimertinib improved progression free survival, duration of response as well as overall survival [18.9 months versus 10.2 months for progression free survival, 17.2 months versus 8.5 months for duration of response, 38.6 months versus 31.8 months for overall survival]. Also grade 3 toxicities were lower in patients with osimertinib. What was the reason for choosing gefitinib in this patient. 2. It was mentioned that patient did not have T790M mutation - which are responsible for approximately 50% of the patients with acquired resistance to early generation tyrosine kinase inhibitors. Other mechanisms include MET gene amplification, sometimes they can be histological transformation of the lung cancer as well which can contribute to resistance. Is anything else identified in this patient apart from not having T790M mutation. 3.

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Also it is worth mentioning IMpower 150 clinical trial, where addition of Atezolizumab to combination chemotherapy with carboplatin and paclitaxel along with wedge of targeted therapy with bevacizumab - this clinical trial has approximately 110 patients with EGFR mutations or ALK translocation who progresses on prior targeted therapy with an improvement in progression free survival. There was also some evidence in phase 3 trials with bevacizumab and ramicuramab combinations with erlotinib improved progression free survival but not overall survival. 4. Thank you for discussing Atlantic clinical trial. Although there was some benefit in patients with PDL 1 expression greater than 25% [97 patient were EGFR positive, 77 patients with greater than 25% of tumor cells expressing PDL1] - 8 patients completed 12 months of treatment, 93 patients discontinued treatment [almost 86 patients due to disease progression] - progression free survival was similar in patients with PDL 1 expression less than or greater than 25% but overall survival was better in patients with PDL 1 greater than 25% with approximately around 13 months versus 10 months with PDL 1 levels less than 25%. I agree that we need more prospective trials in this group of patients to see if there is any benefit from single agent immunotherapy. 5. Also regarding second line of treatment with chemotherapy followed by immunotherapy as third line of treatment, it is reasonable to consider this approach, is there any contraindication for considering a combination of carboplatin pemetrexed and pembrolizumab was not considered as a second line of treatment which can be followed by pemetrexed and pembrolizumab maintenance. 6. Is there any data on pembrolizumab monotherapy in patients with EGFR mutant advanced lung cancer, that progressed on targeted therapy third line setting and beyond. Is it based on Atlantic trial - this patient was treated with pembrolizumab [they allowed to prior lines of therapy including targeted therapy with tyrosine kinase inhibitors and platinum based therapy before being treated with durvalumab]