Peer Review File

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Reviewer A

A systematic review discusses the usefulness of dacomitinib for uncommon mutations and brain metastases in NSCLC.

Dacomitinib has limited use in clinical practice, and this review will assist in practice.

This study is very interesting but requires the following revisions.

#1. Please discuss the side effects of dacomitinib compared to the common mutation in this review.

Reply 1: Thanks for your suggestions. We have modified our text as advised (see Page 13, line 425)

Changes in the text: Concerning the side effects of dacomitinib, the common side effects of dacomitinib in NSCLC patients with common EGFR mutations include diarrhea, paronychia, dermatitis acneiform, stomatitis, decreased appetite, and so on in the clinical trial[6]. Nevertheless, data on the side effect of dacomitinib for NSCLC patients harboring uncommon mutations is limited. A phase II trial demonstrated the common side of dacomitinib for NSCLC patients harboring uncommon mutations may include rash, diarrhea, oral mucositis, oral mucositis, paronychia, dry skin, and so on[3]. Data suggest that patients with uncommon mutations have similar common side effects of gastrointestinal and skin disorders when treated with dacomitinib compared to common mutations. However, those have yet to be proven due to limited data.

#2. Please discuss any findings in this review regarding racial group response rates.

Reply 2: Thanks for your suggestions. In populations with uncommon EGFR mutations, understanding the responsiveness of different ethnicities to dacomitinib is critical and has important implications for clinical treatment decision-making. However, due to the scarcity of study populations, we still need more evidence to determine whether there is a racial difference in efficacy. We want to seek your understanding in this matter. We have modified our text (see Page 13, line 425)

Changes in the text: Whether the efficacy of dacomitinib is affected by ethnic differences in NSCLC populations with uncommon EGFR mutations is a worthwhile consideration for clinical drug selection. Due to the scarcity of the study population, evidence of response rates on dacomitinib for diverse ethnicities is still limited. Further efforts should focus more on the efficacy differences in diverse populations.

#3. Please discuss the circumstances under which dacomitinib was used in this study in patients with CNS metastases.

Reply 3: Thanks for your suggestions. We have modified our text as advised (see Page 12, line 373).

Changes in the text: It needs to note that some case reports have reported the clinical benefits of dacomitinib in patients with brain metastases who have non-common EGFR mutations; the usage of dacomitinib has been focused on posterior-line therapy[1, 5]. One study also suggests a clinical benefit after first-line dacomitinib intervention in patients with brain metastatic lung cancer who have non-common mutations[4]. Due to the scarcity of patients with uncommon EGFR mutations, further studies are needed to determine whether dacomitinib can provide clinical benefit to patients with uncommon EGFR mutations in the settings of first-line therapy.

#4. What is the benefit of a second generation TKI compared to in line 342? Also, please provide evidence.

Reply 4: Thanks for your suggestions. We apologize for the inconvenience caused by the error in the description, and we have corrected the manuscript. (see Page 11, line 342). Without head-to-head comparative data, it is impossible to determine whether there is a difference in the efficacy of second or third-generation TKI in patients with uncommon EGFR mutations. In fact, P-loop and C-helix compressing (PACC) mutations, including G719X, S786I, and exon 18 deletions, could interfere with third-generation TKI binding, and in vitro assays also illustrated that second-generation TKIs were indeed more effective in PACC mutations[2]. Therefore, patients with PACC mutations benefited more from afatinib than osimertinib[2].

Changes in the text: Apart from osimertinib, evidence suggested that 2G TKI was also favorable for this subset of patients. A combined post-hoc analysis by Yang et al. demonstrated that for G719X (n = 18), L861Q (n = 16), and S768I (n = 9), the ORRs of afatinib were 77.8%, 56.3%, and 100%, and the mPFS were 13.8 months, 8.2 months, and 14.7 months, respectively[8]. A previous study conducted by Yang et al. also showed that the median time-to-treatment failure was 14.7, 10.0, and 15.6 months in patients treated with first-line afatinib who had G719X, L861Q, and S768I mutations, respectively[7].

Reviewer B

1. Please confirm the article type of your manuscript is **Review Article**.

Answer: confirmed.

2. Abstract
   - The abstract should be structured with Background, Methods, Results, and Conclusions. Please modify your abstract to it.

- All abbreviations should be defined when they are first used in the Abstract and in the text. Please provide the full name of "**ASCO**" and "**ESMO**" in the Abstract.

Answer: modified.

3. Please note that keywords should be no more than 5.

Answer: modified.

4. Please rearrange the highlights as a Highlight Box in the following format. Please note that the box should be concise with no more than 150 words.

   Here is the template:

Answer: modified.

Key findings

- The efficacy of dacomitinib against different uncommon *EGFR* and *HER-2* mutation subtypes is highly heterogeneous, and the highly selective clinical application of dacomitinib is necessary for this setting.
- Dacomitinib has demonstrated good intracranial tumor control and should be considered clinically.

What is known and what is new?

- Dacomitinib has been approved for first-line treatment for *EGFR*-mutated non-small cell lung cancer (NSCLC); however, evidence of dacomitinib for uncommon *EGFR*/ *HER-2* mutations and brain metastases in NSCLC is currently limited.
- This study aimed to give a comprehensive review of its potential applications by compiling available publications.

What is the implication, and what should change now?

- Dacomitinib exhibited promising efficacy in patients with major uncommon *EGFR* mutations (including G719X, S768I, and L861Q).
- Dacomitinib showed an encouraging intracranial tumor control ability, regardless of uncommon mutations.

5. Figures and tables

   - If possible, please provide Figures 2 and 3 with a higher resolution.

   Answer: Provided.

   - All abbreviations in figures/tables and legends should be explained. ASCO in Figure 1 for example. Please check all abbreviations and revise.
   - Checked and revised.

- For references cited in **Tables 1-3**, please number them according to the first identification of the table. In your manuscript, Table 1-3 is behind ***Ref 14***, thus, all references first appear in Table 1-3 should be numbered from ***15***. Please check all your citations (including those in tables) and rearrange the reference list.
- Checked and revised. "In your manuscript, Table 1-3 is behind ***Ref 14***, thus, all references first appear in Table 1-3 should be numbered from ***15***." In fact, the references in the table have already started to be cited in the text and therefore will appear in the table with a number less than 14. We have carried out a check and there are no problems.
- The publication year mentioned in your tables is inconsistent with the corresponding references. Please check all your tables and revise.
- Checked and revised.

Reckamp (19)	P	2013
Peng (14)	R	2020
Mizusaki (51)	R	2020

- *19. Reckamp KL, Giaccone G, Camidge DR, et al. A phase 2 trial of dacomitinib (PF-00299804), an oral, irreversible pan-HER (human epidermal growth factor receptor) inhibitor, in patients with advanced non-small cell lung cancer after failure of prior chemotherapy and erlotinib. Cancer 2014;120:1145-54.*
- *14. Peng W, Pu X, Jiang M, et al. Dacomitinib induces objective responses in metastatic brain lesions of patients with EGFR-mutant non-small-cell lung cancer: A brief report. Lung Cancer 2021;152:66-70.*
- *51. Mizusaki S, Otsubo K, Ninomiya T, et al. Remarkable response to dacomitinib in a patient with leptomeningeal carcinomatosis due to EGFR-mutant non-small cell lung cancer. Thorac Cancer 2021;12:114-6.*

6. Tables 1-3

Answer: revised.

1) Please add units for Age, PFS and OS in Tables 1-3.

Table 1 A summary of published clinical data on uncommon *EGFR* mutations

er	Age	Histology	LOT	Mutation subtype	Method	Dosage	Best response	ORR	DCR	PFS	OS	
e	62	AC	1	G719A	NGS	30mg	PR	NA	NA	6.6	NA	
e	64	AC	1	L861Q	NGS	30mg	non-CR/non-	NA	NA	10+	NA	

2) In Table 3, please indicate how data is presented in below cell, for example, median (range).

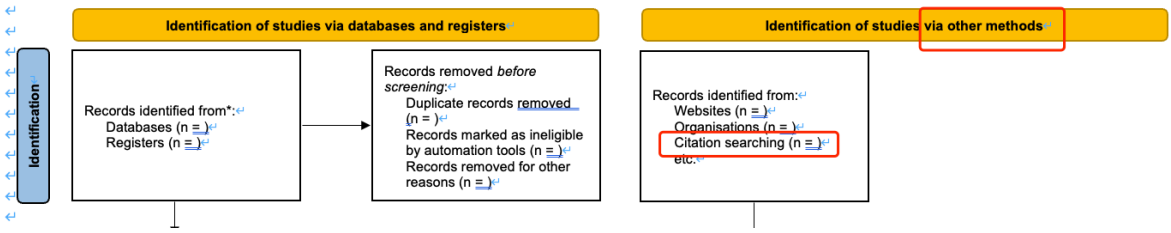
Li (4)	R	2022	China	23 (20 were evaluable)	14 were female	Median: 57.5	AC	2~5	5 19del, 14 L858R, 4 G719X	NGS	Mostly (12) received 30 mg	NA	NA #	NA #	15%	85%	6.5 (2.6-10.4)	NA
Biswas (22)	CA	2021	India	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	80%	NA	NA	NA

7. Figure 1:

Answer: modified.

1) Please provide an editable version of Figure 1 as a stand-alone WORD file, so that the editor can slightly and properly adjust the lines and structures, and text during the editing.

2) The format of your Figure 1 cannot meet our requirement. Because you searched references, it should be reported via other methods. Please redraw your Figure 1 based on the attached template.



8. In the text, the citations of references should be in regular round brackets with a **space before**. Please check through and revise.

Answer: modified.

[e.g., Lung cancer remains one of the most common cancers with the second-highest morbidity and highest mortality worldwide (1),…]

9. Please note that there is no need to use "*et al.*" after Chan in the following sentence since the corresponding reference has only one author. Please recheck all your citations for it.

Answer: modified.

- *Chan et al.(35) and Shen et al.(36) respectively reported a case of an elderly woman, both of which were detected with L718Q mutation after osimertinib resistance.*
- *35. Chan D. P76.87 Efficacy of Dacomitinib in EGFR TKI Refractory Metastatic Non-Small Cell Lung Cancer (EGFR Mutant) with Leptomeningeal Metastases. Journal of Thoracic Oncology 2021;16(3 Supplement):S627.*

10. The authors you mentioned in the following sentences are inconsistent with the corresponding references. Please check and revise.

Answer: modified.

- *Besides, via instructing an L747P-mutant patient-derived xenograft mice model, Yang et al. showed that both dacomitinib and afatinib showed potent anti-tumor activities compared with osimertinib and poziotinib (4).*
- *4. Li HS, Zhang JY, Yan X, et al. A real-world study of dacomitinib in later-line settings for advanced non-small cell lung cancer patients harboring EGFR mutations. Cancer Med 2022;11:1026-36.*
- *In addition, a significant decrease in the HER2 amplification level clinically may suggest a better therapeutic efficacy of dacomitinib, according to the two responded patients (both cases got PR) reported by Reckamp et al. (39) and Kelly et al. (47).*
- *39. Li HS, Yang GJ, Wang Y. Case Report: Dacomitinib May Not Benefit Patients Who Develop Rare Compound Mutations After Later-Line Osimertinib Treatment. Front Oncol 2021;11:649843.*
- *In four brain-metastatic patients harboring G719X compound mutations, Li et al.'s study revealed an ORR of 25% and a DCR of 75% in the later-line settings (14).*
- *14. Peng W, Pu X, Jiang M, et al. Dacomitinib induces objective responses in metastatic brain lesions of patients with EGFR-mutant non-small-cell lung cancer: A brief report. Lung Cancer 2021;152:66-70.*
- *Peters et al. revealed that afatinib obtained an ORR of 19% and a median time-to-treatment failure (mTTF) of 2.9 months in treating HER2-mutant NSCLC, among which the A775_G776ins YVMA subtype achieved an ORR of 33% and an mTTF of 9.6 months (65).*
- *65. Liu Z, Wu L, Cao J, et al. Clinical characterization of ERBB2 exon 20 insertions and heterogeneity of outcomes responding to afatinib in Chinese lung cancer patients. Onco Targets Ther 2018;11:7323-31.*

11. Please check if any references should be added to the following sentence.

Answer: modified.

- *Consistent with Kris et al., we believe that efforts to build open, searchable databases to share precise molecular signatures of tumors to connect hospitals, institutes, and pharmaceutical companies could go a long way toward confronting these complexities.*

12. Please check if more references should be added to the following sentence.

Answer: no more references needed.

- *Pharmacokinetic studies* revealed that dacomitinib concentrations in rat whole brain homogenates were similar to those in plasma (brain: plasma ratio of 1.2: 1), and radiolabeling could be detected in most CNS tissues and cerebrospinal fluid of rats administered ^{14C}-dacomitinib for up to 48 hours(48).

Reference

1. Chan D (2021) P76.87 Efficacy of Dacomitinib in EGFR TKI Refractory Metastatic Non-Small Cell Lung Cancer (EGFR Mutant) with Leptomeningeal Metastases. Journal of Thoracic Oncology 16(3 Supplement):S627
2. Janning M, Süptitz J, Albers-Leischner C et al. (2022) Treatment outcome of atypical EGFR mutations in the German National Network Genomic Medicine Lung Cancer (nNGM). Ann Oncol 33:602-615
3. Li HS, Wang SZ, Xu HY et al. (2022) Afatinib and Dacomitinib Efficacy, Safety, Progression Patterns, and Resistance Mechanisms in Patients with Non-Small Cell Lung Cancer Carrying Uncommon EGFR Mutations: A Comparative Cohort Study in China (AFANDA Study). Cancers (Basel) 14
4. Peng W, Pu X, Jiang M et al. (2021) Dacomitinib induces objective responses in metastatic brain lesions of patients with EGFR-mutant non-small-cell lung cancer: A brief report. Lung Cancer 152:66-70
5. Shen Q, Qu J, Chen Z et al. (2021) Case Report: Dacomitinib Overcomes Osimertinib Resistance in NSCLC Patient Harboring L718Q Mutation: A Case Report. Front Oncol 11:760097
6. Wu YL, Cheng Y, Zhou X et al. (2017) Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 18:1454-1466
7. Yang JC, Schuler M, Popat S et al. (2020) Afatinib for the Treatment of NSCLC Harboring Uncommon EGFR Mutations: A Database of 693 Cases. J Thorac Oncol 15:803-815
8. Yang JC, Sequist LV, Geater SL et al. (2015) Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol 16:830-838