Peer Review File

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Reviewer A

#	Comment	Reply	Changes in Text
1	From sentence 24-30: the arguments supporting the "Why Osimertinib is a treatment with a broad spectrum of action" could be a little more detailed in the operation.	Given that Osimertinib (3rd generation) irreversibly binds to EGFR-mutant receptors only "i.e., mutant-selective" with higher response rates than 1st generation and lower toxicity than 1st & 2nd generations, therefore Osimertinib is the only agent in its class that is currently approved in the adjuvant setting in early-stage NSCLC, in addition to 1st line in mNSCLC, and even as a 2nd line after progression on 1st line early-generation EGFR TKI (in T790M+), rendering it a treatment with a broad spectrum of indications (rather than mechanisms of action).	None
2	From sentence 24-25: On which source do you base your claim that Osimertinib targets T790M?	We added the reference.	5. Nagano T, Tachihara M, Nishimura Y. Mechanism of Resistance to Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors and a Potential Treatment Strategy. *Cells*. 2018;7(11):212. doi:10.3390/cells7110212
3	Sentence 40: Was Osimertinib indeed combined with a MET inhibitor or not? If so, see comments 38 to 41.	Osimertinib was combined with savolitinib (MET TKI) in a number of phase I & II trials as described later in the text and summarized in table 1.	None
4	Sentence 38 to 41: The arguments follow on from one another quickly and could be presented more	We have added a sentence "Single agent capmatinib has shown activity in patients with MET-amplified NSCLC. Therefore" to allow for a	Added reference 12. Wolf J, Seto T, Han J-Y, et al. Capmatinib in MET Exon 14–Mutated or MET -Amplified

	pedagogically to highlight the phenomena of mutation-related resistance.	better flow of the text.	Non–Small-Cell Lung Cancer. *N Engl J Med*. 2020;383(10):944-957. doi:10.1056/NEJMoa2002787
5	In paragraph 42 - 59: What do we really conclude from the clinical phases paragraph, and can it be shortened to keep only the essentials?	This paragraph describes the main outcomes of the first early-phase trials that investigated the combination of Osimertinib with Savolitinib (MET TKI), upon which subsequent ongoing phase III trials are built on.	We shortened the paragraph to keep only the essentials. The data are summarized in a new table (table 2).
6	From sentence 81 - 89: This is where the argument for combining Osimertinib and Savolitinib comes in. Would it be possible to support the argument with additional sources? or further explanation of the mechanisms?	We have rewritten this section with more detailed explanation of the mechanisms.	Page 4, paragraph 2.

Reviewer B

#	**Comment**	**Reply**	**Changes in Text**
1	I suggest considering an addendum regarding adverse events related to the SAVANNAH trial, ORCHARD trial, and INSIGHT2 trial. Providing a summary comment such as "The results of adverse events were similar to those observed in the TATTON trial" would enhance the readers' understanding of the results.	We summarized the published results of these trials in a new table. However, not all of them published the adverse events yet.	We added table (2).

Reviewer C

#	Comment	Reply	Changes in Text
1	The GEOMETRY-E trial has meanwhile been terminated based on a business consideration of Novartis (https://clinicaltrials.gov/study/NCT04816214)	Thank you for this comment. Probably, the trial was terminated during or after writing the manuscript. This comment is taken into consideration and made clear in the text.	We changed the text to: "The GEOMETRY-E was another phase III trial that was investigating the role of osimertinib plus capmatinib against platinum doublet chemotherapy, but unfortunately was terminated based on business_consideration of the funding company."