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Commentary

Sotorasib Treatment Could Worsen the Prognosis of Advanced KRASG12C-Mutated Non-Small Cell Lung Cancer

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Sotorasib, the first RAS inhibitor FDA-approved drug for advanced, KRASG12C-mutated non-small cell lung cancer (NSCLC), was approved in May 2021 under the FDA-Accelerated Approval program. This commentary critically reviews the results on progression-free survival (PFS) and overall survival (OS) of the CodeBreaK 200 trial, a randomized, open-label, phase 3 trial published in The Lancet in 2023. The study reported increased PFS with sotorasib based on a reduced hazard ratio (HR). Despite the FDA's rejection of regular approval for sotorasib in October 2023, the accelerated approval status is maintained pending further confirmatory trials. We stress the crucial role of journal editors in ensuring the comprehensive reporting of statistical analyses in RCTs, particularly for publications in highly-ranked journals like The Lancet, which can heavily influence the clinical practice of oncology. Their role in upholding the highest scientific integrity and transparency standards is essential for informing oncologists, patients, and decision-makers of public health systems.

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Introduction

As of December 26, 2023, sotorasib has been administered to over 15,000 patients worldwide through its clinical development program, early access, and commercial use[1]. Sotorasib, a small-molecule drug, is the first $KRAS^{G12C}$ inhibitor to receive approval from the US FDA, under accelerated approval in May 2021[2]. The approval was based on the results of the CodeBreaK 100 trial, a multicenter, single-arm, open-label study that involved patients with locally advanced or metastatic NSCLC with $KRAS^{G12C}$ mutations.

The results of the CodeBreaK 200 study, "Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with $KRAS^{G12C}$ mutation: a randomized, open-label, phase 3 trial", were published in *The Lancet* in March 2023[3].

The study was a randomized, open-label phase 3 trial at 148 centers in 22 countries of patients aged 18 years and older with $KRAS^{G12C}$-mutated advanced NSCLC who progressed after previous platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor. The results from the publication's abstract are as follows[3].

"Between June 4, 2020, and April 26, 2021, 345 patients were randomly assigned to receive sotorasib (171) or docetaxel (174). The primary endpoint was PFS, assessed by a central independent review of the intention-to-treat population. After a median follow-up

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of 17.7 months, the study met its primary endpoint of a statistically significant increase in PFS for sotorasib, compared with docetaxel (median PFS 5.6 months (95% CI 4.3-7.8) vs. 4.5 months (95% CI 3.0-5.7); HR 0.66 (95% CI 0.51-0.86); p=0.0017). Median OS was 10.6 months (95% CI 8.9–14.0) in the sotorasib group and 11.3 months (95% CI 9.0-14.9) in the docetaxel group, HR 1.01 (95% CI 0.77 1.33); p=0.53.

The study conclusions were that sotorasib significantly increased PFS and demonstrated a more favorable safety profile than docetaxel in patients with advanced NSCLC with the $KRAS^{G12C}$ mutation who had previously been treated with other anticancer drugs. These findings underscore the potential of sotorasib as a promising treatment option for this patient population.

There are 3 key issues from this study:

1. The absolute risk for PFS

According to the data from the Supplementary Appendix, Table S5, Primary Analysis of Progression-free Survival as Assessed by the Blinded Independent Central Review Committee[3], these are the number of PFS events in each arm.

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Patients	Sotorasib	Docetaxel
	N = 171	N= 174
PFS events (%)	122 (71.3)	101 (58.0)

With these data, the Absolute Risk of PFS is as follows:

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Treatment	Number with no PFS events	Number with PFS events	Absolute Risk of PFS events	Number-Needed-to-Harm (NNH)
Sotorasib	49	122	**Increase 13.30%**** 95% CI [3.31 - 23.28]	**7*** 95% CI [4.3 - 30.2]
Docetaxel	73	101		

**The Absolute Risk increase and number needed-to-harm (NNH) for PFS are statistically significant*

These results mean that for every 7 patients treated with sotorasib, 1 PFS event will occur beyond those that would have happened under docetaxel.

2. Informative censoring

The stark contrast in the results, with PFS reduction measured by HR and the increase in absolute risk, suggests that this discrepancy likely resulted from informative censoring. This factor can significantly impact the study outcome. In a time-to-event analysis, participants are censored when information on the outcome of interest (PFS event for PFS or death event for OS) is unavailable because the participants are no longer seen in follow-up. The Kaplan-Meier Survival analysis method, while widely used, assumes the existence of non-informative censoring, meaning there is no difference between the patients censored in the control and experimental arm. This assumption can introduce bias, as censored patients are no more or less likely to experience the event than those who followed.

On the contrary, informative censoring occurs when the reasons for censoring are related to the study intervention, which can introduce post-randomization bias. There is a pressing need for consensus on how significant the percentage difference in censoring events between the experimental and the control arm must be to be considered informative censoring. However, a difference higher than 10% between arms would suggest its existence. In addition, the pattern of censoring (early or left, late or right) helps interpret the study results. Left censoring, a particularly concerning form of informative censoring, is evident in the study. Early drug discontinuation, withdrawal of consent, or loss to follow-up, or initiating a new anticancer therapy before documenting the event of interest are the leading causes of informative censoring, typically occurring early during the study. Early censored patients, in general, are those less fit and more prone to withdraw from the study because of poor tolerance to treatment[4][5].

Figure 1 (Figure 2A[3]) shows that this study provides essential clues on the existence of informative censoring. Firstly, for the total study duration, 13.35% more patients were censored in the docetaxel arm than in the sotorasib arm: 49 (28.6%) vs. 73 (41.3%). Secondly, left censoring is evident. At both point times, 6 and 12 months of follow-up, the number and percentages of censored patients in the docetaxel group were more than double, suggesting that the docetaxel arm may have experienced more adverse events or early discontinuations, leading to informative censoring.

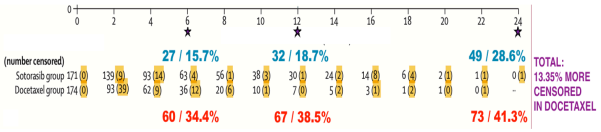

Figure 1. Distribution of censored patients as shown in Figure 2A[3].

In the results section, the authors state in the trial profile (Figure 1[3]) that while only 2 patients assigned to sotorasib did not receive the allocated intervention, 23 were for docetaxel. Moreover, the authors highlight the implications for treatment efficacy and patient selection in the text. They note that among these 23 patients, in comparison with the 151 patients treated with docetaxel, they were more likely to have a history of central nervous system (CNS) involvement, to be refractory to previous therapy, to have an Eastern Cooperative Oncology Group (ECOG) performance status of 1, and to have liver metastases at baseline. Based on the above, we recalculated the Absolute Risk for PFS under three scenarios.

Scenario 1. All censored patients in the sotorasib arm are counted as if they had the event (number in red). This is the result:

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Treatment	Number with no PFS events	Number with PFS events	Absolute Risk of PSF events	Number-Neded-to-Harm (NNH)
Sotorasib	22	**149**	**Increase 29.09%*** 95% CI [20.20 - 37.97]	**4*** 95% CI [2.6, 4.9]
Docetaxel	73	101		

The absolute risk for having the event further increased from 13.30% to 29.09%, and NNH decreased from 7 to 4.

Scenario 2. All censored patients in the docetaxel arm are counted as if they had the event (number in red). This is the result:

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Treatment	Number with no PFS events	Number with PFS events	Absolute Risk of PFS events	Number-Neded-to-Treat (NTT)
Sotorasib	49	122	**Reduction 21.18%*** 95% CI [3.31-23.28]	**7*** 95% CI [4.3 - 30.2]
Docetaxel	13	**161**		

In this scenario, the absolute risk of having an event decreases, a 21.18% reduction, while the number needed-to-treat (NNT) is now 7.

Scenario 3. In both groups, sotorasib and docetaxel, the censored patients are counted as if they had the event (numbers in red).

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Treatment	Number with no PFS events	Number with PFS events	Absolute Risk of PFS events	Number-Neded-to-Treat (NNT)
Sotorasib	22	**149**	Reduction 5.39% 95% CI [-0.97- 11.75]	**19** 95% CI [8.5 - Infinity]
Docetaxel	13	**161**		

Here, the absolute risk decreases but is not statistically significant, while the NNT is 19, which is also not statistically significant. These noticeable changes in absolute risks assigning different outcomes of censored patients underscore the importance of how censored patients may affect the study outcome. It would be critical that the authors had undertaken a sensitivity analysis to ensure the validity of their study conclusions.

Figure 2 shows the PFS curve of the sotorasib study[3] to illustrate further that HR reduction must not be communicated as risk reduction of progression, death, or any event. Indeed, absolute risk reduction is the difference in the total population's percentage of individuals experiencing an event. In contrast, the HR compares the instantaneous hazard rate of a treated patient versus that of a control subject at specific times and then averages. However, it does not provide the total number of events and patients in the arms compared. As such, HR does not inform on the relative or absolute risk of the study.

Shaded in blue are the times of the curve where the individual instantaneous HRs favored sotorasib, whereas the shaded in red favored docetaxel. It is clear that the HRs favored sotorasib more times throughout the time curve. Consequently, the final average HR is 0.66, which is statistically significant. However, the actual number of PFS events is higher in the sotorasib arm (122) than in the placebo arm (101). It means that in this study, patients randomized to sotorasib had a 13.30% higher risk of having a PFS event as compared to those being treated with docetaxel. As we stated above, this result most likely resulted from the informative censoring.

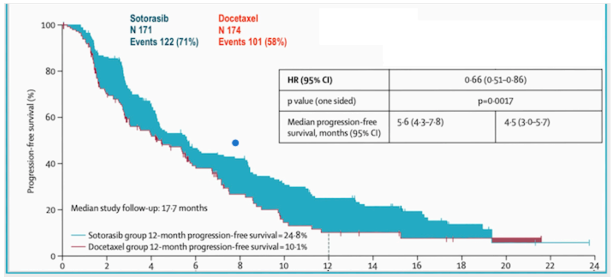

Figure 2. Graphic representation of how HR is distributed along the total time of the PFS curve. In this case, shaded blue indicates the times when the HR favored the sotorasib arm and shaded red the times when it favoured the docetaxel arm. The final HR was 0.66.

3. The Absolute Risk for Death

Regarding OS, the results as measured by HR, the median OS was 10.6 months (95% CI 8.9–14.0) in the sotorasib group and 11.3 months (95% CI 9.0-14.9) in the docetaxel group, HR 1.01 (95% CI 0.77 1.33); p=0.53. Though clearly non-statistically significant, there is a 0.7 months difference shorter for sotorasib, and both the HR number and 95% CI tend to convey a higher hazard for sotorasib patients.

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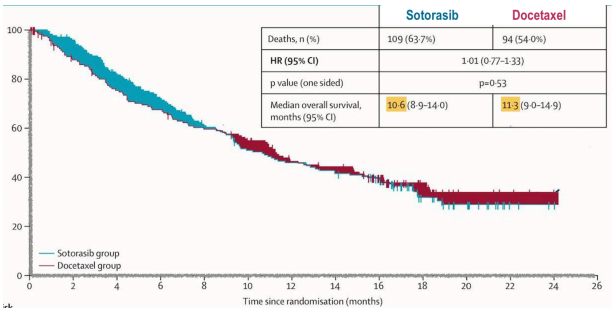

Figure 3. Graphic representation of how HR is distributed along the total time of the OS curve. In this case, shaded blue indicates the times when the HR favored the sotorasib arm and shaded red the times when it favoured the docetaxel arm. The final HR was 1.01.

As above for PFS HR rates (Figure 2), Figure 3 shows that shaded in blue are the times of the curve where the individual instantaneous HRs favored sotorasib, whereas the shaded in red favored docetaxel. According to the overall HR, the HRs favored more times docetaxel than sotorasib throughout the time curve (the final average HR is 1.01). These results can also partly be explained because for OS, there were more censoring for sotorasib than for docetaxel (80 vs. 62).

Nonetheless, according to the data from Figure 3 of Overall Survival[3], these are the number of events.

Patients	Sotorasib	Docetaxel
	N = 171	N= 174
Death events (%)	109 (63.7%)	94 (54.0%)

With these data, the Absolute Risk of Death is as follows:

Treatment	Number alive	Number dead	Absolute Risk of death*	Number-Needed-to-Harm (NNH)
Sotorasib	62	109	Increase 9.72% 95% CI [-0.61- 20.05]	10 95% CI [5.0 - Infinity]
Docetaxel	80	94		

**The Absolute Risk of death increase and NNH are NOT statistically significant.*

Yet statistically non-significant, these results mean that for every 10 patients treated with sotorasib, 1 death would occur beyond those that would have happened under docetaxel treatment.

Comments

Recently, the FDA's decision to reject the supplemental new drug application (sNDA) for sotorasib for patients with previously treated locally advanced or metastatic $KRAS^{G12C}$-mutated NSCLC while maintaining the drug's accelerated approval status has significant implications for patient care. In October 2023, the FDA's Oncologic Drugs Advisory Committee (ODAC) found that the PFS data from the CodeBreaK 200 trial[3] could not be reliably interpreted[6].

If we strictly adhere to the Absolute Risk and NNH estimations for progression events from the trial, which are 13.30% and 7 respectively, it would suggest that out of the around 15,000 patients that had been treated with sotorasib[1], 1,995 patients were exposed to one event of PFS that could not happen if treated with docetaxel. A similar estimation can be suggested for Absolute Risk and NNH of death (remarking that these numbers were not statistically significant for OS). Among these 15,000 patients treated with sotorasib, 1,500 deaths could not have happened if treated with docetaxel.

The analysis presented here stresses the differences between what is measured by HR and what is with Absolute Risk. As it can be appreciated, they are very different, but the problem arises from how the results are presented. Firstly, HR reductions are presented as if HR were Risk reductions, which they are not. Secondly, actual Risks calculated from the total number of patients and events need to be presented, and even, in a few cases, the number of PFS or OS events goes unmentioned in RCT publications.

The most intriguing issue is how oncologists with no formal training in medical statistics could identify fundamental issues in the survival analysis that expert editors and peer reviewers were unaware of. This raises the immediate question of whether this was a genuine oversight or if market pressures played a role in the oversight.

This is a strong call to action for a more rigorous peer-review process. Such a process should include a comprehensive analysis of the statistical presentation of results, particularly in publications of high-ranked journals like *The Lancet*, which can heavily influence the clinical practice of oncology. By ensuring the highest standards of research, we can pave the way for more effective treatments and improved patient outcomes.

In conclusion, according to this analysis, Amgen, the FDA, and *The Lancet* may jeopardize lung cancer patients' prognosis. Not to mention the issues with doses and toxicity of sotorasib. It must be noted that this work is not intended for oncologists to encourage or discourage the prescription of sotorasib but to show how absolute risks of PFS and OS complement the information provided by HRs[3].

Statements and Declarations

Data and Software Availability

No data are associated with this article.

Competing Interests

The authors declare that they do not have conflicts of interest.

Grant Information

The authors declared that no grants were involved in supporting this work.

Author Contribution

The content and ideas expressed in this work are the sole responsibility of the authors.

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Declarations

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