nature portfolio

Peer Review File

NALIRIFOX versus Gemcitabine plus Nab-Paclitaxel in Chinese Patients with Advanced Pancreatic Adenocarcinoma: A Randomized, Open-Label Phase II Trial

Corresponding Author: Professor Jihui Hao

This manuscript has been previously reviewed at another journal. This document only contains information relating to versions considered at Nature Communications.

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 1:

Reviewer comments:

Reviewer #2

(Remarks to the Author)
The authors have adaquately addressed th reviewers' comments.

Reviewer #3

(Remarks to the Author)
This phase II trial confirms the findings of the NAPOLI-3 study (Wainberg et al. Lancet October 07, 2023) in a Chinese population, demonstrating a PFS benefit with NALIRIFOX over gemcitabine plus nab-paclitaxel, reaching its primary endpoint. However, unlike NAPOLI-3, the present trial was not powered to demonstrate an OS advantage and only a non-significant trend for OS has been found. The study achieves its primary endpoint and limitations of the current trial (lack of stratification, small subgroup sizes,...) have been adequately discussed in the manuscript. However, it would be recommended to acknowledge the lack of patient-reported outcomes.

Reviewer #4

(Remarks to the Author)
Authors have addressed adequately to the reviewers' comments.

Reviewer #5

(Remarks to the Author)
There are two major concerns with the trial:

1) In the NAPOLI 3 trial (Wainberg ZA et al, Lancet 2023), progression-free survival (PFS) was clearly defined. PFS was defined as the time from randomization to first documented disease progression using RECIST version 1.1 by investigator review or death due to any cause, whichever occurred first.

Neither in the protocol (HE072-CSP-004) nor in the revised manuscript is progression-free survival clearly defined in terms of how deaths were handled.

In any case, the definition of PFS used in the HE072-CSP-004 trial can’t be the same as the definition of PFS used in the NAPOLI 3 trial. In the revised manuscript, the authors write:

“53 patients (67.9%) in the NALIRIFOX group and 30 (76.9%) in the gemcitabine plus nab-paclitaxel group had experienced disease progression or death.”

and

“At the time of analysis, 60 patients (76.9%) in the NALIRIFOX group and 32 (82.9%) in the gemcitabine plus nab-paclitaxel group had died.”

If the progression-free survival endpoint included death as an event (as in the NAPOLI 3 trial), there would have to be at least as many PFS events as the number of overall survival (OS) events. But the number of PFS events are lower than the number of OS events in the respective arms.

What does that mean given that the data cut off used for both PFS and OS was on the same date (June 30, 2024)? It means that PFS was likely defined as the time from randomization until disease progression. Patients who did not have documented disease progression were censored on the last disease evaluation and patients who died were censored in the PFS analysis.

The PFS endpoint would, therefore, be different from the NAPOLI 3 trial. More worrisome is that the primary endpoint, PFS, was not explicitly defined in the protocol using the standard definition wording (e.g., progression or death due to any cause, whichever occurred first).

Furthermore, in the design of the trial, the authors assumed a median PFS of approximately 5 months on the gemcitabine plus nab-paclitaxel arm to design / power the phase II study; in the studies that informed the trial design, the definition of PFS would have included deaths (e.g. E2297, JCO 2002).

2) The HE072-CSP-004 trial is reporting the primary results based on an unplanned analysis and is inconsistent with the design of the trial, which included a single final analysis after 125 PFS events were observed. There were no interim analyses planned per the protocol Section 9.4.9. At the time of the unplanned analysis, there were 83 PFS events (53 NALIRIFOX; 30 gemcitabine plus nab-paclitaxel). That is not appropriate, and the rationale provided for analyzing the data prior to the prespecified targeted number of events was unsatisfactory. If an unplanned analysis was performed, the protocol should have been amended with a revised statistical design section. It was also unusual that there was not a data and safety monitoring board overseeing the conduct of the trial.

Version 2:

Reviewer comments:

Reviewer #5

(Remarks to the Author)
The response by the authors clarified the observed discrepancy between the number of PFS and OS events – i.e., the number of PFS events were lower than the number of OS events in the respective arms (NALIRIFOX: 60-53=7 fewer; Gemcitabine + Nab-paclitaxel: 32-30=2 fewer). To facilitate the interpretation and reproducibility of the trial results, the authors should include in the primary endpoint definition how censoring was handled. For example, the authors could write something like the text below (***), but they need to ensure that it reflects exactly how censoring was handled in their definition of PFS.

The primary endpoint was PFS, which was defined as the time from the start of the study drug to the first documentation of disease progression or death, whichever occurred first. If a patient died without documentation of a disease progression and missed their last 2 scheduled tumor assessments, the patient was censored at their last disease evaluation. If a patient initiated another anticancer treatment before disease progression, they were censored at the date of initiation of this anticancer treatment. Otherwise, patients were censored at their last disease evaluation.

In regard to the second major concern, the context that the authors provided and the additions made to the discussion section were satisfactory.

Reviewer #5 (Remarks to the Author)

There are two major concerns with the trial:
1) In the NAPOLI 3 trial (Wainberg ZA et al, Lancet 2023), progression-free survival (PFS) was clearly defined. PFS was defined as the time from randomization to first documented disease progression using RECIST version 1.1 by investigator review or death due to any cause, whichever occurred first.
Neither in the protocol (HE072-CSP-004) nor in the revised manuscript is progression-free survival clearly defined in terms of how deaths were handled.
In any case, the definition of PFS used in the HE072-CSP-004 trial can't be the same as the definition of PFS used in the NAPOLI 3 trial. In the revised manuscript, the authors write:
"53 patients (67.9%) in the NALIRIFOX group and 30 (76.9%) in the gemcitabine plus nab-paclitaxel group had experienced disease progression or death."
And
"At the time of analysis, 60 patients (76.9%) in the NALIRIFOX group and 32 (82.9%) in the gemcitabine plus nab-paclitaxel group had died."
If the progression-free survival endpoint included death as an event (as in the NAPOLI 3 trial), there would have to be at least as many PFS events as the number of overall survival (OS) events. But the number of PFS events are lower than the number of OS events in the respective arms.
What does that mean given that the data cut off used for both PFS and OS was on the same date (June 30, 2024)? It means that PFS was likely defined as the time from randomization until disease progression. Patients who did not have documented disease progression were censored on the last disease evaluation and patients who died were censored in the PFS analysis.
The PFS endpoint would, therefore, be different from the NAPOLI 3 trial. More worrisome is that the primary endpoint, PFS, was not explicitly defined in the protocol using the standard definition wording (e.g., progression or death due to any cause, whichever occurred first).
Furthermore, in the design of the trial, the authors assumed a median PFS of approximately 5 months on the gemcitabine plus nab-paclitaxel arm to design / power the phase II study; in the studies that informed the trial design, the definition of PFS would have included deaths (e.g. E2297, JCO 2002).
Response: We appreciate the reviewer's observation regarding the definition of progression-free survival (PFS) and the discrepancy between the number of PFS events and overall survival (OS) events.
First, the definition of PFS in this study (HE072-CSP-004) was consistent with that in the NAPOLI 3 trial. This definition was explicitly detailed in the original study protocol (which was defined as the time from the start of the study drug to the first documentation of disease progression or death, whichever occurred first. Section 8.2, page 65) but may not have been sufficiently highlighted in the revised manuscript. We include this key definition in the manuscript to prevent any potential misunderstanding.
Second, PFS is a composite endpoint. A PFS event is defined as either "disease

progression" or "death from any cause," whichever occurs first. If a patient dies without a previously recorded disease progression, the death itself constitutes the PFS event. Conversely, if disease progression is documented first and is followed later by death, the PFS event is considered to have occurred at the time of progression; the subsequent death then contributes to the OS analysis and does not alter the PFS data. Furthermore, patients who initiated new anticancer therapy or had missed tumor assessments for more than two scheduled assessment cycles were censored in the PFS analysis. Consequently, some patients may be censored for PFS due to these criteria but subsequently experience an OS event. In contrast, OS is a single endpoint where an event is defined solely as death from any cause. This fundamental distinction in definitions directly accounts for the observed phenomenon of discrepant event counts between PFS and OS.
Given that the PFS definition follows established standards and the event count discrepancy is methodologically expected, the use of this endpoint and its associated statistical assumptions remains appropriate in the context of this trial's design.

Change in the Manuscript
The primary endpoint was PFS, which was defined as the time from the start of the study drug to the first documentation of disease progression or death, whichever occurred first. Secondary efficacy endpoints included OS (defined as the time from the start of the study drug to death from any cause), ORR (defined as the proportion of subjects with a best overall response of complete response or partial response), disease control rate (DCR, defined as the proportion of subjects with a best overall response of complete response, partial response, and stable disease), and DoR (defined as the time from the start of the first tumor assessment of complete response or partial response to the first assessment of disease progression or death from any cause). (Line 346-354, Page 14)

2) The HE072-CSP-004 trial is reporting the primary results based on an unplanned analysis and is inconsistent with the design of the trial, which included a single final analysis after 125 PFS events were observed. There were no interim analyses planned per the protocol Section 9.4.9. At the time of the unplanned analysis, there were 83 PFS events (53 NALIRIFOX; 30 gemcitabine plus nab-paclitaxel). That is not appropriate, and the rationale provided for analyzing the data prior to the prespecified targeted number of events was unsatisfactory. If an unplanned analysis was performed, the protocol should have been amended with a revised statistical design section. It was also unusual that there was not a data and safety monitoring board overseeing the conduct of the trial.
Response: We appreciate the reviewer's request for clarification regarding this unplanned analysis. This study was discontinued due to COVID-19-related disruptions that affected patient recruitment and adherence to scheduled visits. The last subject was enrolled in November 2022, which was prior to the announcement of the NAPOLI 3 results. When the NAPOLI 3 study announced its positive results in September 2023, we learned that the median OS in the experimental group was 11.1 months, which was significantly longer than the 9.2 months in the control group. In this study, with median follow-up times of 18.7 months and 12.1 months in the two groups, respectively, it was confirmed that the current PFS and OS data had reached sufficient maturity, therefore the analysis was performed.

The investigational drug HE072 is a generic irinotecan liposome. Other clinical trials have demonstrated that its efficacy and safety profiles are comparable to the original product Onivyde. Onivyde was approved in 2015, and its combination regimen with 5-fluorouracil and leucovorin has been used in pancreatic cancer patients for nearly a decade, resulting in a well-established safety profile with no unknown risks. Although an independent Data and Safety Monitoring Board has not been established, the study team, together with the investigators, continuously monitor patient safety and periodically submit reports such as the DSUR to regulatory authorities.

Change in the Manuscript

The main limitation of this study is its premature termination, which prevented us from reaching the predetermined sample size. This was predominantly attributable to disruptions caused by the COVID-19 pandemic, which adversely affected both patient recruitment and protocol adherence. Consequently, the statistical power of our analyses was reduced, and the results should therefore be interpreted with appropriate caution. ~~The primary limitation of our study was the inability to achieve the prespecified enrollment target, largely due to COVID-19-related disruptions that affected patient recruitment and adherence to scheduled visit.~~ (Line 279-285, Page 11)

Reviewer #5 (Remarks to the Author):

The response by the authors clarified the observed discrepancy between the number of PFS and OS events – i.e., the number of PFS events were lower than the number of OS events in the respective arms (NALIRIFOX: 60-53=7 fewer; Gemcitabine + Nab-paclitaxel: 32-30=2 fewer). To facilitate the interpretation and reproducibility of the trial results, the authors should include in the primary endpoint definition how censoring was handled. For example, the authors could write something like the text below (***), but they need to ensure that it reflects exactly how censoring was handled in their definition of PFS.

The primary endpoint was PFS, which was defined as the time from the start of the study drug to the first documentation of disease progression or death, whichever occurred first. If a patient died without documentation of a disease progression and missed their last 2 scheduled tumor assessments, the patient was censored at their last disease evaluation. If a patient initiated another anticancer treatment before disease progression, they were censored at the date of initiation of this anticancer treatment. Otherwise, patients were censored at their last disease evaluation.

Response: We appreciate your valuable suggestions, and add the statement in the revised manuscript as followed.

Change in Manuscript:

The primary endpoint was PFS, which was defined as the time ~~from the start of the study drug to the first documentation of disease progression or death, whichever occurred first.~~ randomization to the earliest occurrence of either radiologically documented tumor progressio n (per RECIST 1.1) or death from any cause. If a patient had neither disease progression nor death by the data cutoff date or before initiating any subsequent anti-tumor therapy, PFS would be censored at the date of the last tumor assessment prior to the data-cutoff date or prior to the start of the subsequent anti-tumor therapy, whichever occurred first. If a patient experienced progression or death after missing two or more consecutive tumor as sessments, PFS would be censored at the date of the last valid radiological tumor assessmen t prior to the missed assessments. (Line 376-385, Page 15)