Peer Review File
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Reviewer A

We really appreciate the reviewer's detailed and sincere comments. We could improve our manuscript, revising our manuscript according to the reviewer's guide. The reviewer commented that the paper is a well-written manuscript, addressing our work could be of great interest for clinical cancer practice readers. The reviewer requested revision of the manuscript, and we revised our manuscript carefully.

Comment 1 : Molecular testing of sensitizing EGFR mutations, BRAF V600E, as well as ALK, ROS1, and NTRK fusions, is now standard-of-care for patients with advanced NSCLC. Routine testing of RET fusions and MET exon 14 skipping mutations should also be considered standard-of-care based on the recent guidelines. Comprehensive biomarker testing is recommended for all patients diagnosed with non-sq NSCLC and should be initiated at the time of initial diagnosis. The authors should explain whether the patients received appropriate comprehensive genetic testing other than EGFR in their tissue-based analysis.

Reply1 : Thank you for the reviewer's comment. We added the discussion (page 16 line 337-348) regarding the issue that the reviewer suggested.

Changes in the text :
"Molecular testing of sensitizing EGFR mutations, BRAF V600E, as well as ALK, ROS1, and NTRK fusions, is now standard-of-care for patients with advanced NSCLC. Routine testing of RET fusions and MET exon 14 skipping mutations is also considered standard-of-care based on the recent guidelines. Thus, a comprehensive biomarker testing is recommended for all patients diagnosed with non-sq NSCLC. Currently, our technique using BALF is limited for EGFR mutation not including other targetable mutations, and further development for detecting other mutations will be required. A safe, sensitive and accurate detection of EGFR mutation in BALF is, nevertheless, beneficial for specific sub-population with high EGFR mutation frequency, such as Asian non-smoker whose frequency is 40-60%."

Comment 2 : This study confirms concordance with tissue diagnosis, but does not confirm genetic diagnosis using BALF in cases where tissue cannot be sampled by TBLB. Authors should describe that the diagnostic sensitivity for lesions that are difficult to diagnose histologically has not been validated.

Reply 2 : In the revised manuscript, we added an explanation about the two cases that histologically has not been validated in detail (page 9 line 215-220).

Changes in the text 2 :
Tissue samples were unobtainable in two patients out of total 120 patients due to the complication at the time of diagnosis. Both of two patients were confirmed to have EGFR

mutation later, one in pleural effusion and another in BALF cytology performed at progression time. The EGFR mutation results of these two patients obtained from BALF were consistent with the EGFR mutation results confirmed through other samples other than lung tissue.

Comment 3 : I think it is appropriate that response rate and progression-free survival should be analyzed for the 51 patients with EGFR mutations detected in BALF analysis, not for the 38 who were available for analysis about treatment with gefitinib.

Reply 3: We explained the reason in detail why 38 cases were analyzed, in the line 200 of 9 page of the revised manuscript.

Changes in the text 3 :
"Among 120 screened patients, 51 cases were detected to harbor EGFR mutations through EV-based BALF liquid biopsy. 11 patients among them were dropped because 4 were transferred, 2 had symptomatic brain metastasis, 2 had other organ cancers, 3 did not consent the trial and these 11 cases belong to exclusion criteria of this trial. Among 40 cases that were enrolled for immediate initiation of gefitinib treatment, two were dropped out early due to 1 transfer and 1 small cell lung cancer histology, and finally 38 patients were completed to be analyzed"

Comment 4 :
1) Gene symbols should be italicized.
2) Performance status should be described in table 1.

Reply 4 :
1) We made all gene symbols be italicized.
2) We added performance status in the table 1

Changes in the text 4 :
1) EGFR → *EGFR*
2) The performance status is inserted in the table 1.

Reviewer B

We really appreciate the reviewer's detailed and sincere comments. We could improve our manuscript, revising our manuscript according to the reviewer's guide. The reviewer commented that this study performed a clear and structured analysis to show that EGFR genotyping of BALF could be an adequate and useful tool for faster lung cancer diagnosis and treatment selection compared to tissue biopsies. The reviewer also commented that the novelty of this manuscript mainly covers the evaluation of treatment effectivity of Gefitinib after patient selection by BALF genotyping. The reviewer requested revision of the manuscript to emphasize the importance of this treatment evaluation after BALF genotyping and we revised our manuscript accordingly.

Comment 1 : In the introduction (lines 72-82), a previous study performed by these authors

was described, where the performance and speed of EGFR genotyping of BALF was already compared to EGFR genotyping of tissue biopsy. Similar findings were presented in current research. What is the reason that similar analyses were performed again? Furthermore, it could be further elaborated what the importance of the therapy response analyses was, to better highlight the need of current research compared to previous research.

Reply 1: We appreciate the reviewer's detailed and valuable comments. We added remarks explaining the importance of this study in page 12 line 274-280.

The changes in the text 1:
"To the best of our knowledge, this work is the first prospective study reporting the efficacy of first line gefitinib by treating the patients with advanced EGFR-mutated NSCLC detected by EV-based BALF liquid biopsy even before conventional tissue-based genotyping. This study provides clinical evidence for the utility of EV- based EGFR mutation status check to ascertain eligibility for EGFR-TKI treatment not requiring tissue biopsy EGFR result. The earlier initiation of treatment with the help of EV- based EGFR mutation detection improves the treatment efficacy such as PFS and tumor response."

Comment 2: What is the reason that this study is called a phase II study? Was the study performed to show the performance of the drug Gefitinib (Iretinib) in NSCLC patients with EGFR mutations in general? Or to show the performance specifically in case where EGFR mutations were found in BALF? If the latter is the case, what would be expected differences compared to the efficacy in tissue-derived mutations, as it was also shown that the same patients would get treated with Gefitinib due to high concordance of BALF and tissue biopsy genotyping?

Reply 2: This study showed the performance specifically in case where EGFR mutations were found in BALF. Comparing the treatment by tissue based EGFR mutation detection, this study showed the improved treatment efficacy. We explained the strength of this study compared with tissue based EGFR mutation detection in page 12 line 273-280.

The changes in the text 2 : "To the best of our knowledge, this work is the first prospective study reporting the efficacy of first line gefitinib by treating the patients with advanced EGFR-mutated NSCLC detected by EV-based BALF liquid biopsy even before conventional tissue-based genotyping. This study provides clinical evidence for the utility of EV- based EGFR mutation status check to ascertain eligibility for EGFR-TKI treatment not requiring tissue biopsy EGFR result. The earlier initiation of treatment with the help of EV- based EGFR mutation detection improves the treatment efficacy such as PFS and tumor response."

Comment 3: In your previous work, a prospective study was performed and patients were included between June 2017 and August 2020. In this study, patients were included between January 2018 and August 2020. Are these two independent cohorts or were the same cohorts used in both studies? If so, how were the 120 patients selected from these 224 patients?

Reply 3 : This study used a part of the cohort used in the previous study. Among the patients, we selected patients highly expected to have EGFR mutation for this study**.** We explained the reason in method page 4 line 88-94.

The changes in the text 3:
"We preferentially screened patients of the cohort in the previous study using EV-based BALF liquid biopsy with favorable factors for EGFR mutation such as female, never smoker or minimally exposed smoker. Heavy smokers and the patients with central-type lung cancer were not included because likelihood of harboring EGFR mutations is significantly low. This study was planned to provide gefitinib to the selected patients before histologic confirmation to reduce the risk of misdiagnosis."

Comment 4: The study was powered to determine non-inferiority of response rate to Gefitinib using EGFR genotyping of BALF compared to genotyping of tissue biopsy. However, no clear conclusions were drawn with respect to this non-inferiority in the results section.

Reply 4: We inserted comments about the non-inferiority of response rate and PFS compared with the previous tissue result in page 11 line 246-257**.**

The changes in the text 4:
76.3% ORR was better than 69.8-73.7% ORR of previous research. Median PFS 14.6 months was longer than other previous studies (9.7-10.8 months) (2, 18-21). The estimated one-sided confidence interval for gefitinib response rate, using BALF liquid biopsy was 0.635-1.0. The non-inferiority of the EGFR-TKI response rate of BALF liquid biopsy was proven, as the lower margin 0.635 of the calculated confidence interval was better than the pre-assumption lower margin 0.63 (=0.7-0.07) before the study. In the case of BALF, the ORR 76.3% was not less than 70%. (p=0.045)
The therapeutic outcomes of response and PFS were not inferior to the previous results. They are similar or better than the tissue-based results (2, 17-20). Our efficacy endpoints, ORR 76.3% and PFS 14.6 months were numerically better than previous Gefitinib efficacy based by tissue biopsy. The early initiation of gefitinib treatment by BALF EGFR mutation before disease progression can improve the clinical outcomes such as PFS and tumor response.

Comment 5 In this study, all patients with EGFR mutations were treated with Gefitinib, based on their BALF genotyping and therefore the TTI could be determined for BALF. How was the TTI for conventional tissue genotyping determined?

Reply 5: According to the reviewer's guidance, we clarified the definition of TTI for conventional tissue genotyping in page7 line 161-166;

The changes in the text :
" TTI was determined with time from the date of bronchoscopy or tissue biopsy to the date of starting treatment. All patients with EGFR mutations were treated with Gefitinib based on

their BALF genotyping, therefore, the TTI for BALF was determined. TTI for conventional-tissue biopsy was determined with the time from the date of tissue biopsy to the start date of chemotherapy after the confirmation of no EGFR mutation in tissue."

Comment 6 : Compared to the tissue biopsy results, one false positive result was obtained by BALF genotyping. It is described that this could be a result from heterogeneity of the tissue biopsy or low mutant allele frequency (lines 265-270). Was the MAF of the BALF genotyping known for this patient? Would you conclude that the BALF correctly identified an additional EGFR mutation compared to tissue biopsy or that this mutation would indeed be a false positive detection?

Reply6: Our test is a PCR based test. In this case, we cannot know the exact MAF compared with NGS test. We confirmed the case as a false positive case with both additional BALF and Tissue test. The detail is discussed in the revised manuscript.
We added the following to the manuscript in page 13 line 288-292:

The changes in the text 6:
"In one false positive case, we retested the EGFR genotyping in remained BALF and tissue and confirmed that the EGFR mutation was negative. The PANAmutyper EGFR PCR method have 0.1~1% error rate. After that case, we performed the EGFR mutation genotyping testing twice to reduce false positive cases."

Minor:
Comment 7
Lines 96-98: **treatment-naïve** and no previous TKI treatment describe the same thing
Reply 7 : We corrected the phrase by review's guide in page 4 line 85 and page 5line 101.

Comment 8
Line 97: In Table 1, S768I is described as well
Reply 8: We added S768I in line 100. We added the phrase "combination with rare EGFR mutation" on line 100.
The changes in the text "histopathologic confirmed and treatment-naive NSCLC patients with stage IIIB or IV advanced NSCLC; active EGFR mutation (E21L858R, E19DEL, E21L861Q, G719X or S768I) or combination with rare EGFR mutation in BALF".

Comment 9
Lines 145-146 and 158-159: Double information on the timing of CT-scans
Reply9: we deleted the line 158-159:

Comment 10
For the methods, what is the definition used for time to treatment initiation (TTI)?
Reply 10 : We clarified the meaning of TTI in page 7 line 161-166

The changes in the text10 ” TTI was determined with time from the date of bronchoscopy or tissue biopsy to the date of starting treatment. All patients with EGFR mutations were treated with Gefitinib based on their BALF genotyping, therefore, the TTI for BALF was determined. TTI for conventional-tissue biopsy was determined with the time from the date of tissue biopsy to the start date of chemotherapy after the confirmation of no EGFR mutation in tissue."

Comment 11

Sample size calculation: What study showed response of Gefitinib?

Reply11: We cited the reference of the Gefitinib response study in page 8 line 177.

Comment 12

Statistical analysis: How is the 95% CI computed?

Reply12: The Kaplan-Meier curve was performed to estimate the median and the 95% CIs for PFS by SPSS 23.

We added the sentence in page 8 line 185-187

“The survival curves, median value of PFS and corresponding 95% confidence interval were calculated using the Kaplan–Meier method”

Comment 13

What method was used to identify the mutations in the tissue biopsies?

Reply 13: We added the detection method of the EGFR mutations in tissue in page 7 line 140-145.

“The tumor samples were prepared as formaline-fixed, paraffin-embedded (FFPE) tissues and tumor DNAs were purified using the TANBead OptiPure FFPE DNA Tube (Taiwan Advanced Nanotech, Taoyuan, Taiwan) according to the manufacturer’s protocol. Then, EGFR genotyping was done through PANAMutyper™ R EGFR kit (Panagene, Daejeon, Korea) according to the manufacturer’s protocol. To prevent the bias, two pathologists read tissue and BALF samples separately in a blinded manner."

Comment 14

Lines 184-185: ‘Most current smokers or the patients with central-type lung cancer were not included because likelihood of harboring EGFR mutations is significantly low’. Table 1 shows that still some current smokers were included in the study. Based on what criteria were these patients either included/excluded?

Reply14: We enrolled the current smokers, excluding current heavy smokers more than 30 pack-years with central tumor. We clarified the inclusion/exclusion criteria in page 4 line 90-91

The changes in the text 14:

We preferentially screened patients of the cohort in the previous study(11) using EV-based BALF liquid biopsy with favorable factors for EGFR mutation such as female, never smoker or minimally exposed smoker. Heavy smokers and the patients with central-type lung cancer were not included because likelihood of harboring EGFR mutations is significantly low (12).

Comment 15 Table 1:
o Age: Is the median or mean shown?
Reply 15: A mean value is used for the age. We clarified that in table1.

Comment 16 o Histology: could you further specify the NSCLC group? Are these patients without known further subtyping (Not otherwise specified)?
Reply16: No further subtyping of NSCLC group is possible. We added a note NOS(not otherwise specified) next to NSCLC in the table 1.

Comment 17 SCLC: 1 patient with SCLC in the BALF EGFR negative group, but also in the Gefitinib group
Reply17: We found a miscount in the table I regarding reviewer's inquiry, and it was corrected in the revised manuscript. Gefitinib was treated by EGFR mutation detection in BALF without histologic confirmation by study design, so one patient with SCLC classified to the Gefitinib group later the patient was dropped out by exclusion criteria.

Comment 18 EGFR type: 21 L858R occurs in 20 patients in total, but in 21 for BALF EGFR positive
Reply18: We clarified the reason in table1 footnote. "One case where 21L858R mutation was initially detected with BALF based test was later verified to have a wild type in the tissue-based test. The number of 21L858R cases is one more and the number of WT case is one less in BALF than in Tissue due to this false positive EGFR case."

Comment 19 Wild type EGFR: 1 patient missing in the BALF EGFR positive column
Reply19: The reason is explained in the same footnote in table I, "One case where 21L858R mutation was initially detected with BALF based test was later verified to have a wild type in the tissue-based test. The number of 21L858R cases is one more and the number of WT case is one less in BALF than in Tissue due to this false positive EGFR case."

Comment 20 Are the inclusion/exclusion criteria used to select the patients treated with Gefitinib or also to select the 120 advanced lung cancer patients?
Reply20: We used the inclusion/exclusion criteria to select the patients for treatment with Gefitinib. We added it in page4 line 97. "Inclusion criteria to select the patients treated with Gefitinib were"

Comment 21 Table 2: The TTI to Gefitinib for BALF genotyping and tissue genotyping are shown, but incorrectly indicated in the table2.
Reply21: The table 2 was modified not to cause a confusion.

Comment 22 Lines 206-207: 'The subtypes of EGFR mutations were exactly the same …'. Could you rephrase this sentence to make clearer what subtypes were indicated and based on what they were exactly the same?
Reply22 We rephrased it to make the meaning of sentence clearer. The rephrased sentence is

“The proportions of EGFR mutation subtypes were the same as reported in the previous research; the proportion of each sensitive mutation was 56.9% (29 cases) for E19del, 41.2% (21 cases) for E21L858R, and 2.0%(one case) for G719C/S769I compound mutation depending on BALF liquid biopsy” in page10 line 221-223.

Comment 23 Table 3: patient with CR not shown
Reply23 : We added the CR data in table 3.

Comment 24 Lines 43 and 236: The overall survival (OS) is not described in the results .
Reply24: OS was not our endpoint, so we changed OS to response rate in line 40 and 256.

Comment 25 Line 265: Concordance rate of 98.5% does not match the concordance rate mentioned in the results:
Reply25: 98.5% was obtained from the EGFR positive group(N=51) and 99.2% are from the whole patients (N=120). We explained the difference by specifying N numbers used for each calculation. (line 212-215, page 9)
Changes in the text 25 :
“. The concordance rate in EGFR mutation positive group detected by EV-based BALF liquid biopsy was 98.0% (=50/51). There was no false negative case in the wild-type EGFR patients by EV-based BALF liquid biopsy. Overall concordance rate in 120 screened patients was 99.2% (=119/120).”

Comment 26 In line 290 it is described that chemotherapy can be initiated early in wild-type cases of BALF genotyping. Would you start with chemotherapy in these patients without histological diagnosis of lung cancer? Are any other treatment types, such as immunotherapy, also possible for this wild-type group? What was the time to treatment initiation for these patients using BALF compared to tissue biopsies?
Reply 26: We start chemotherapy after histological diagnosis. We added it in line 309. In Korea, immunotherapy was not allowed for the first line therapy in patients with EGFR mutation. We clarified the TTI in page7 line 161-166.

Comment 27 Line 339: ‘Suspicious advanced lung adenocarcinoma’, this should be NSCLC or lung cancer
Reply27: We changed “Suspicious advanced lung adenocarcinoma” modified to suspicious advanced lung cancer in line 367.

Reviewer C

Study summary: Kim et al. report a prospective, interventional study on the clinical relevance of EGFR genotyping through EV-based BALF liquid biopsy in advanced NSCLC patients. Cell-free EV DNA was isolated in 120 patients, and EGFR genotyping was performed using a PNA-mediated PCR method alongside routine histologic work-up. Gefitinib treatment was initiated in patients with positive EGFR variant detected by BALF analysis. The performance of the liquid biopsy approach was compared with conventional tissue-based EGFR-testing by

evaluating clinical parameters such as ORR, PFS, TAT, TTI, and concordance rates between liquid and tissue analysis. While a false-positive case was identified using BALF analysis, there was 99.2% concordance rate between tissue- and liquid-based EGFR genotyping. Liquid-based analysis also resulted in shorter TAT and TTI in EGFRmut patients. Considering the duration of the study, OS and PFS were comparable with published tissue-based results.

Altogether, the findings reported in the manuscript are relevant in arguing the potential of BALF analysis as a non-inferior alternative and a less invasive approach for EGFR genotyping in advanced NSCLC compared to conventional tissue biopsies. I would support the publication of the manuscript. Nonetheless, there are issues and limitations to the study that the authors should address prior to acceptance and publication.

Major comments

Comment1: Were there DNA quality control checks that were done after nucleic acid isolation from BALF EVs? What was the size distribution profile of BALF EV-derived DNA? Was there any size selection done to the EV-derived DNA to minimize genomic DNA contamination?

Reply 1: DNA concentration and size were measured using Nanodrop and Tapestation (Fig. 1), respectively. Average concentration was 38.7ng/ul and average size ranged from 250 bp to 50 kbp, which puts them in similar size as genomic DNA, preventing selection by size. Therefore, genomic DNA contamination was minimized by removing cell and debris after centrifugation.

We made changes to the manuscript and added the following text in line 127-130.

“The concentration and purity of DNA samples were measured using the NanoDrop (Thermo Scientific, Waltham, MA, USA). The length of the purified DNA were analyzed using a 4200 Tapestion and Genomic DNA ScreenTape (Agilent Technologies, Santa Clara, CA, USA).

“

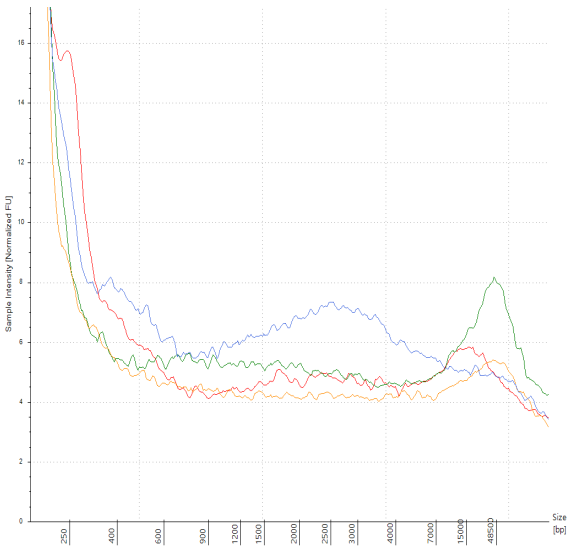

Fig. 1 Electropherogram of BALF EV-derived DNA on an Tapestation

Comment2. It is suggested that a brief description of the PNA-mediated PCR assay is included

in the methods section. The authors should specify which EGFR variants were included in the assay, how much input DNA was used, and how a positive variant result was called from the melt curve data. Was this done quantitatively, otherwise what was the threshold used? Was there a standard curve generated so that intrapolation of the number of mutant copies is possible, and this way estimate the tumor fraction in the EV-DNA? Responses to comments 1 and 2 must be clearly described in the method section.

Reply2 PNA-mediated PCR assay used in the experiment is from a company approved by the Korean Ministry of Food and Drug Safety (MFDS) and we used Real-time PCR Analyzer provided by that company. Table 1 shows the standards used for the analysis. 70 ng of DNA were used and tumor fraction in the EV-DNA were not analyzed as quantitative analysis weren't performed.

We added the following to the manuscript in page 6 line 133-136 .

All reactions had a total volume of 25 μL containing 70 ng of template DNA. Fluorescence was measured on all four channels (FAM, ROX, Cy5, and HEX). With the use of a mutant-type DNA specific PNA detection probe that had a fluorescent dye and quencher, EGFR mutations could be genotyped by melting peak analysis.

Table 1 The criteria of the mutation detection according to the fluorescent dye and melting temperature

Reagent	**Fluorescent Dye**	**Cut-off**	**Melting Temperature**	**Assessment**	
				Amino Acid Change	**Nucleotide Change**
G791X	FAM	100	56.5 ℃~61.0 ℃	p.G719A	c.2156G>C
			44.5 ℃~49.0 ℃	p.G719S	c.2156G>A
			49.5 ℃~55.0 ℃	p.G719C	c.2156G>T
/S768I	HEX	20	58.5 ℃~62.0 ℃	p.S768I	c.2303G>T
E19del /E20ins A /EIC	HEX	100	59.5 ℃~68.0 ℃	E19del	
	ROX	50	61.5 ℃~70.0 ℃	E20ins	
	Cy5	150	56.0 ℃~64.0 ℃	Valid	
E20ins B	ROX	50	61.5 ℃~70.0 ℃	E20ins	
T790M	HEX	40	58.0 ℃~63.0 ℃	p.T790M	c.2369C>T
L858R	ROX	20	55.0 ℃~58.0 ℃	p.L858R	c.2573T>G
			43.5 ℃~49.0 ℃	p.L858R	c.2573_2574 TG>GT
L861Q	ROX	100	48.0 ℃~54.50 ℃	p.L861Q	c.2582T>A

Comment3. How does the tumor cell content from tissue analysis and disease burden correlate with the mutation signal derived from BALF EV-DNA?

Reply3 : The correlations were not quantitatively analyzed.

Comment4. For the one false positive case, was there any ambiguity in the calling of the mutation based on the melt curve profile? Did the duplicate reactions yield concordant results? Related to this, the authors mentioned the possibility of a low MAF in the matched tumor sample that led to the wild-type EGFR evaluation. Did the authors check the possibility that a metastatic lesion contributed to the positive call made from the BALF EV-DNA analysis, highlighting the limitation of tissue-based genotyping?
Reply 4: EGFR mutation testing using BALF EV-DNA was repeated four times and tissue was repeated twice. All retesting resulted in negative, therefore the first BALF EV-DNA result was deemed false positive.
We made the following changes to the manuscript in line 288-292.

Changes in the text 4 :
In one false positive case, we retested the EGFR genotyping in remained BALF and tissue and confirmed that the EGFR mutation was negative. The PANAmutyper EGFR PCR method have 0.1~1% error rate. After that case, we performed the EGFR mutation genotyping testing twice to reduce false positive cases.

Comment 5. Aside from PNA-mediated PCR, could the authors also discuss other alternative amplification methods (e.g., ddPCR, other FDA-approved companion diagnostics kits such as the therascreen EGFR RGQ PCR Kit and cobas EGFR Mutation Test) that could be applied for variant detection in this setting?
Reply 5: We made the following changes to the manuscript in 345-348.

We used PANAMutyper for EV-based BALF liquid biopsy approved by MFDS. But, other methods such as ddPCR and other FDA-approved companion diagnostics kits such as therascreen EGFR RGQ PCR Kit and cobas EGFR Mutation Test could be used for EV-based BALF liquid biopsy.

Comment 6. Contrary to the authors' statements that liquid biopsy using plasma DNA has low sensitivity to be used in real clinical routine practice, multiple publications have established the noninferiority of ctDNA analysis to standard of care tissue testing in NSCLC (PMIDs 30988079, 32365229, 32525942). The papers the authors cited for the low sensitivity of ctDNA analysis actually also argue that ctDNA testing could be an alternative to tissue biopsy for EGFR genotyping (manuscript ref. 3, 4). I suggest that the authors revise the manuscript and provide a more nuanced discussion on plasma DNA analysis.
We made the following changes to the manuscript in line 59-61.

The changes in the text 6:
Reply 6 Recently, plasma liquid biopsy using circulating tumor DNA has been introduced, but it has an intrinsic limitation of low sensitivity to be used in real clinical routine practice (3, 4). This low sensitivity issue could be overcome with the use of molecular barcoding and deep sequencing; however, they are still too pricy for routine practice.

Comment 7. Do the relative proportions of the EGFR mutants in this study reflect their frequency of occurrence in other cohorts?

Reply 7 According to our study, the proportion of the EGFR mutants was 42.5%, which is in range with other studies performed with Asians where the proportion was 30-50%.

Minor comments

Comment 8. The manuscript would benefit from additional proofreading to correct typographical/grammatical errors, formatting inconsistencies (e.g., font, spacing, table and figure labels), and in some cases clearer expression of point. The authors are also suggested to refrain non-academic phrases such as "super speed," "marvelous performance," and "marvelous concordance."

Reply 8: We checked manuscript carefully and corrected typographical/grammatical errors. We also deleted non-academic phrases such as "super" and "marvelous"

Comment 9. The first paragraph in the "Results: Patient characteristics" section would be better placed in the "Methods: Study design and patient population" section. The authors should also include that the newly diagnosed patients were treatment naïve.

Reply 9: We placed the "Result: Patient characteristics" to the "Methods: Study design and patient population" section **in line 90**.

Comment 10. Was the tissue work-up performed in a blind manner? The authors should specify this in the methods section.

Reply 10 : We explained more about tissue work up in blind manner in line 145**.**

Comment 11. In the safety analysis section, the adverse effects data should be shown as a supplement.

Reply11: We presented the adverse effects in supplemental table.

Comment 12. The EGFR gene should be italicized throughout the manuscript.

Reply12: We corrected them

Comment 13. In Figure 1, the footnote is incomplete.

Reply13: We completed the footnote in Figure1.

Comment 14. Lines 70-71 and 306-308 are unclear and should be rephrased.

Reply14: We rephrased them in line 71-73 and line 364-371.

8. Last sentence in line 159 is redundant.

Reply: We rephrased it in 185-187