Peer Review File

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Reviewer A

The authors present a potentially important risk prediction model for primary resistance to EGFR TKIs in NSCLC patients with activating mutations in EGFR. Overall, the presented results are interesting and warrants further validation in additional, future studies, including multicenter studies with a higher number of patients. However, one major point needs to be addressed before further consideration of publication.

- The retrospective study included 154 patients between 2020 and 2022. It is not mentioned which TKI (or TKIs) these patients received. Given the text in the introduction, discussing resistance mechanisms to EGFR TKIs, I assume these patients received 1st-generation EGFR TKIs, i.e. erlotinib or gefitinib. This needs to be fully disclosed since the usage of 1st-generation EGFR TKIs is limited to specific parts of the world today. Since the approval of the 3rd-generation EGFR TKI osimertinib, the relevance of 1st-generation EGFR TKIs is dramatically reduced in the western part of the world. Moreover, it needs to be mentioned if all 27 patients displaying primary resistance were treated with the same 1st-generation EGFR TKI or different EGFR TKIs.

This information is crucial to judge the relevance of the study. Markers for primary resistance is likely different between 1st-generation EGFR TKIs and later generation EGFR TKIs, given the largely different landscape of resistance mechanisms. If only 1st-generation EGFR TKIs were used in this study, the relevance of the study will be limited to specific parts of the world.

Reply: We sincerely appreciate the valuable comments. Yes, you are right. All these patients received treatment with first-generation EGFR-TKIs, such as gefitinib, erlotinib, and Icotinib. Although the use of third-generation EGFR-TKIs is widespread now, there is still a considerable number of patients in China who are using first-generation TKI drugs. And all 27 patients displaying primary resistance were treated with the 1st-generation EGFR TKI. Thank you once again for your valuable comments.

Changes in the text: Page2, line32-33.

Reviewer B

Title: “a risk prediction model”.

It looks like that you are creating “a predictive model”, not “a prediction model”. Both are used in data science and machine learning. However, there is a difference between them.

The objectives for predictive models are historical data and statistical algorithms to identify relationship between variables. Prediction models, on the other hand, are to identify patterns in data and make predictions about future events based on past data.

Reply: We agree with your assessment. We greatly appreciate your careful identification of this error. I sincerely apologize for the failure to distinguish between “a predictive model” and “a prediction model”. we have modified our text as advised.

Changes in the text: Page1, line3,11; Page2, line29,36; Page3, line54,59; Page 8, line159-163; Page14, line 252,255,261; Page15, line 266,277,278,281; Page16, line292,294; Page17, line306; Page1, line3,11; Page19, line354;

Line 22: “EGFR-positive”. Please use the precise description of which molecular alteration defines this group of patients. EGFR-positive is a term which may include EGFR-mutated, EGFR-amplified, and EGFR-fusion subgroups. Therefore, for this context it will be most relevant to use “EGFR-mutated”.

Reply: We sincerely appreciate the valuable comments. We have modified our text as advised. We have modified “EGFR-positive” to “EGFR-mutated”.

Changes in the text: Page2, line 26.

Line 30: what “serological examinations” mean?

Reply: We sincerely appreciate the valuable comments. We apologize for not being able to express ourselves correctly. “Laboratory test” would be more understandable than “serological examinations”. We have modified “serological examinations” to “Laboratory test”.

Changes in the text: Page2, line 34.

Line 35: Please develop the abbreviation for serum NSE, serum ProGRP – it may be confusing for readers both what these factors are and why have you chosen them?

Reply: We sincerely appreciate the valuable comments. We have modified our text as advised. “Neuron-Specific Enolase”, “Pro-Gastrin-Releasing Peptide”. They are commonly used lung cancer markers in clinical practice. We have defined these abbreviations in both the Abstract and the Main Text.

Changes in the text: Page3, line 52-53; Page7, line 127-129.

Highlight box: “…providing a scientific basis for early identification of primary resistance patients.” What kind of resistance: on-target? off-target? If you identify such patients, what are the clinical/therapeutic consequences?

Reply: We sincerely appreciate the valuable comments. They are on-target primary resistance to EGFR-TKIs. If identify such patients who are high-risk EGFR-TKIs primary resistance, in clinical practice, chemotherapy can be added on the basis of TKIs treatment, and combined with immunotherapy and anti-vascular therapy. Furthermore, through NGS sequencing, if resistance-related MET amplification is detected in patients, a combination therapy using EGFR and MET-TKIs can be employed for treatment.

Line 52-55: They are well-known facts – how they contribute to your work. Introduction should provide the reason why you have made this model.

Reply: We sincerely appreciate the valuable comments. Yes, they are well-known facts that lung cancer poses a serious threat to people's health, with adenocarcinoma accounting for the vast majority. Patients with EGFR- mutations in lung adenocarcinoma are treated with EGFR-TKIs drugs, and some patients develop primary resistance. This leads to the research goal of establishing a risk predictive model that can predict the occurrence of primary resistance to EGFR-TKIs in patients

Line 56-57: why do you refer to only these three biomarkers? According to NCCN and ESMO guidelines there are 10 biomarkers representing genomic-defined subgroups of NSCLC.

Reply: We sincerely appreciate the valuable comments. EGFR, ALK, ROS1 are the most common gene mutations in clinical lung adenocarcinoma patients and there are corresponding targeted drugs, so only these three biomarkers are mentioned in this article.

Line 58: "EGFR-mutations are the most frequent…" Advantageously, you may rather provide a precise number of incidences, especially in Asians as the article describes this ethnical group.

Reply: We agree with your assessment. we have modified our text as advised.

Changes in the text: Page5, line 70.

Line 65: "after 9-12 months". Do you mean first generation of EGFR-TKIs? Data fra FLAURA study shows 18 months mPFS (Cheng, Y., He, Y., Li, W. et al. Osimertinib Versus Comparator EGFR TKI as First-Line Treatment for EGFR-Mutated Advanced NSCLC: FLAURA China, A Randomized Study. Targ Oncol 16, 165–176 (2021). https://doi.org/10.1007/s11523-021-00794-6, and

Ramalingam, S. S., Yang, J. C., Lee, C. K., Kurata, T., Kim, D. W., John, T., Nogami, N., Ohe, Y., Mann, H., Rukazenkov, Y., Ghiorghiu, S., Stetson, D., Markovets, A., Barrett, J. C., Thress, K. S., & Jänne, P. A. (2018). Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 36(9), 841–849. https://doi.org/10.1200/JCO.2017.74.7576)

Reply: We sincerely appreciate the valuable comments. Yes, the first generation of EGFR-TKIs will show progression after 9-12 months. We have clearly stated in the article that it refers to the first-generation TKIs. Meanwhile, thank you very much for providing the references, which have given me a deeper understanding of third-generation EGFR-TKIs. The references show a median progression-free survival of 18 months with the third-generation TKIs.

Changes in the text: Page5, line 79

Line 65: "EGFR re-mutations, with T790M mutation being the most common, accounting for approximately 55%" – please specify that it represent the group of patients treated with the first generation of EGFR-TKI.

Reply: We agree with your assessment. we have modified our text as advised.

Changes in the text: Page5, line 80.

Line 67: "histological changes" – please rephrase to "phenotypical changes"

Reply: We sincerely appreciate the valuable comments. We have modified our text as advised.

Changes in the text: Page5, line 82.

Line 69-71: "These patients represent a subtype of lung adenocarcinoma commonly referred to as primary resistance by the international academic community (9-11)". The definition of the primary/intrinsic resistance versus acquired resistance is described in Santoni-Rugiu, E. et al. Intrinsic resistance to EGFR-Tyrosine Kinase Inhibitors in EGFR-Mutant Non-Small Cell Lung Cancer: Differences and Similarities with Acquired Resistance. Cancers, 2019,11(7), 923.

https://doi.org/10.3390/cancers11070923, and you can advantageously add this citation. The primary resistance is considered to occur up to six months after initiation of EGFR-TKI.

Reply: We sincerely appreciate the valuable comments. Thank you very much for providing this citation, which has given me a deeper understanding of primary resistance and acquired resistance. I have already added this citation to the list of references in this text.

There is currently no specific time frame defined for determining whether primary resistance occurs within 3 months or 6 months after initiation of EGFR-TKIs. Some studies suggest that it occurs within 3 months, while others argue for a timeframe of 6 months.

The literature you mentioned also states that "Although most of the patients with advanced EGFRM+ NSCLC achieve objective response (OR) to TKIs, the extent and duration of responses are variable, and 20–30% of patients do not respond or respond for a very short time (typically <3 months) because of intrinsic resistance caused by de novo mechanisms believed to exist before treatment. Thus, in intrinsic/primary resistance the inefficacy of TKIs is immediately or very rapidly discernable, while in acquired/secondary resistance, disease progression occurs after an objective and sometimes prolonged clinical benefit from TKI-treatment. This benefit has been defined as either radiologically documented complete or partial response (CR, PR) or durable (≥6 months) stable disease (SD; defined by response evaluation criteria in solid tumors (RECIST) or World Health Organization (WHO) criteria) after TKI initiation and uninterrupted exposure without receiving additional systemic therapy after TKI discontinuation".

Therefore, progression within 3 months is defined as primary resistance, while resistance that occurs after 6 months of stable disease is classified as acquired resistance. However, there is no clear definition for disease progression between 3-6 months to determine whether it belongs to primary or acquired resistance. Therefore, in this study, in order to better represent patients with primary resistance, Progression-Free-Survival was defined as less than 3 months. In the future, we also plan to study defining PFS as less than 6 months for primary resistance, and then collecting clinical data separately for the resistant and sensitive groups for statistical analysis to obtain the risk factors of resistance. These risk factors will be compared with those obtained by defining PFS as less than 3 months in this text.

Line 74: add the space between "(113)" and "can". Please also precise, how NGS can identify the primary resistance and give some examples.

Reply: We sincerely appreciate the valuable comments. We have added the space between "(113)" and "can".

Studies have demonstrated that multiple gene co-mutations can lead to the occurrence of primary resistance in patients. "Lim SM, Kim HR, Cho EK, et al. Targeted sequencing identifies genetic alterations that confer 335 primary resistance to EGFR tyrosine kinase inhibitor (Korean Lung Cancer Consortium)". This references mentions that "All 132 patients with EGFR mutation were treated with gefitinib for their treatment of advanced NSCLC. Twenty patients showed primary resistance to EGFR TKI, and were classified as non-responders. A total of 543 somatic single-nucleotide variants (498 missense, 13 nonsense) and 32 frameshift insertions/deletions, with a median of 3 mutations per sample. TP53 was most commonly mutated (47%) and mutations in SMAD4 was also common (19%), as well as DDR2 (16%), PIK3CA (15%), STK11 (14%), and BRAF (7%)."

Therefore, in clinical practice, whole-genome sequencing can be performed on lung adenocarcinoma patients who are receiving EGFR-TKIs treatment for the first time. If the sequencing results indicate the presence of multiple concurrent gene mutations, the risk of developing primary resistance in these patients will be higher compared to those without concurrent gene mutations.

Changes in the text: Page5, line 89.

Line 75: "... high cost of sequencing limits its clinical application." The cost of sequencing is becoming significantly decreased: https://www.illumina.com/science/technology/next-generation-sequencing/beginners/ngs-cost.html, so maybe the relevant issue in your article is not cost but accessibility?

Furthermore, it may not be "Therefore", but rather "an alternative approach" for NGS to use some other data as e.g., from blood samples.

Reply: We sincerely appreciate the valuable comments. I apologize for not being aware of the significant reduction in sequencing costs at present. Indeed, with the decrease in sequencing costs, the availability of sequencing samples has become the main concern. And we have modified our text as advised.

Changes in the text: Page5-6, line 90-94.

Line 76-77: "…to guide individualized treatment strategies". It is quite debatable how you can individualize treatment strategies if you do not can identify mechanism of primary/intrinsic resistance by NGS. In such cases, e.g., if you identify a primary/intrinsic MET-amplification, you can combine EGFR and MET-TKI (Gainor J.F. et al. Dramatic response to combination erlotinib and crizotinib in a patient with advanced, EGFR-mutant lung cancer harboring De Novo MET-Amplification. J. Thorac. Oncol. 2016; 11:83–85. doi: 10.1016/j.jtho.2016.02.02.)

Otherwise, how can you specify what are these "treatment strategies"? Are these patients with primary resistance candidates to combining EGFR-TKI and chemotherapy up-front?

Reply: We sincerely appreciate the valuable comments. We can learn a lot of knowledge from your comments. Indeed, it is our oversight not to recognize that if the primary resistance mechanism cannot be identified through NGS, then discussing the development of individualized treatment strategies for patients becomes unreasonable. We have made the necessary revisions in the text. Indeed, if we identify a primary/intrinsic MET-amplification, we can combine EGFR and MET-TKI. Further extensive clinical trials are needed in the future to investigate whether it is appropriate to initially combine EGFR-TKIs with chemotherapy for patients at high risk of primary resistance. We also look forward to conducting separate studies on the prognosis of patients identified through NGS or resistance models as having a high risk of primary resistance, who receive treatment with EGFR-TKIs alone or in combination with chemotherapy. Once again, thank you for your thoughtful comments.

Changes in the text: Page5-6, line 90-94.

Table 1. Have you also taken in consideration other clinical symptoms like: weight loss, fatigue, pains, dyspnoea, etc.?

Reply: We sincerely appreciate the valuable comments. Yes, we considered clinical symptoms such as weight loss, fatigue, and pains during the study design phase. However, during the data collection phase, we found that the patient's weight information was not extensively recorded in the hospital medical record system, and subjective information such as fatigue and pains was not available. Perhaps due to the nature of lung cancer, clinical information regarding symptoms like coughing, sputum production, and hemoptysis were well-documented. As a result, this study only included coughing and hemoptysis as clinical symptoms, which is a major limitation. In the future, we will consider a more comprehensive and detailed assessment of clinical symptoms for further research.

Line 138: Can you explain why have you chosen these factors? Is there any evidence that the serological samples shown in the Table 2 may have any significance for primary resistance? Any references? Or it is the first time you explore importance of these serological factors? Please clarify and re-phrase the aim of this study together with your hypothesis. Additionally, as mentioned before, please develop all these abbreviations.

Reply: We sincerely appreciate the valuable comments. I apologize for not considering the rationality of clinical factors in our study. During the research design phase, we hypothesized that pulmonary inflammation and anemia may affect the efficacy of EGFR-TKIs, so we included WBC, HB, and PLT as factors. In addition, CEA, NSE, CYFRA21-1, and ProGRP are common tumor markers in clinical practice for lung cancer, so we also included these factors. We were unable to find any relevant studies on the correlation between patients' clinical characteristics, laboratory indicators, imaging findings, and primary resistance to EGFR-TKIs on PubMed. Therefore, our aim is to collect general clinical characteristics, laboratory indicators, and tumor imaging-related information of patients with lung adenocarcinoma, and through statistical analysis, identify risk factors for primary resistance to EGFR-TKIs and establish a risk prognosis model. Additionally, these abbreviations have to be defined in both the Abstract and the Main Text.

Changes in the text: Page3, line52-53; Page36-7, line115-129.

Line 151/152: "…The tumor diameter in patients with primary resistance [47 (34, 58) cm] was larger than that in the sensitive group [28 (22, 31) 152 cm]": Dou you mean 47 versus 28 cm? Or mm? Is this the diameter of the primary tumor or assembled measurement of all tumour lesions? What do you use if the primary tumor is not measurable, e.g., Tx or T0?

Reply 2: We greatly appreciate your careful identification of this error. We apologize for my carelessness. It means mm and we have revised it in the text. This is the diameter of the primary tumor. All patients included in our study had measurable diameter of the primary tumor.

Changes in the text: Page 10, line 197-198.

Line 154/155: "The Ki67 expression in the primary resistance group [15% (10%, 30%)] was significantly higher than in the sensitive group [15% (10%, 30%)], with a statistically significant difference ($P < 0.001$) (Table 3)." In the Table 3, Ki67 expression for R-group was 60% (50%, 70%). Please, correct.

Reply: We greatly appreciate your careful identification of this error. We apologize for my carelessness. We have modified our text.

Changes in the text: Page 10, line 200.

Table 4: "OR 值" Please explain or remove "值"

Reply: We greatly appreciate your careful identification of this error. We apologize for my carelessness. We have modified our text.

Changes in the text: Table 4.

Table 5: Please explain or remove the sign at Ki67.

Reply: We sincerely appreciate the valuable comments. Ki67 is a protein that is used as a biomarker to measure the growth rate of tumor cells. It is commonly used in cancer diagnosis and prognosis, as well as in research studies. Ki67 is expressed in the nucleus of actively dividing cells, and its presence can

indicate the level of proliferation or growth activity within a tumor. The higher the percentage of Ki67-expressing cells, the more aggressive and fast-growing the tumor is likely to be.

Line 227: “ProGRP” – first time you developed the abbreviation, which is too late for the readers.

Reply: We agree with your assessment. we have modified our text as advised. We have defined abbreviations in both the Abstract and the Main Text.

Changes in the text: Page3, line52-53; Page36-7, line115-129.

Line 231: “ProGRP(16)is”. Please add the relevant spaces between the three words.

Reply: We agree with your assessment. we have modified our text as advised.

Changes in the text: Page 17, line 312.

Line 232: “Studies have shown that ProGRP(16)is currently one of the best
auxiliary diagnostic serum markers for small cell lung cancer (SCLC)”. Why do you use it then for NSCLC?

Reply: We sincerely appreciate the valuable comments. Because ProGRP is a commonly used lung cancer marker in clinical practice, we included it in the data collection. Additionally, existing studies have shown that the transformation from adenocarcinoma to small cell lung cancer after EGFR-TKIs treatment is a major cause of resistance. We wanted to investigate whether there is a relationship between the levels of tumor markers for small cell lung cancer before initial EGFR-TKIs treatment and primary resistance. Therefore, we utilized ProGRP as a laboratory indicator.

Line 233: “(17)is”: Please add the relevant spaces between the two words.

Reply: We agree with your assessment. we have modified our text as advised.

Changes in the text: Page 17, line 314.

Line 236: “NSE(18)” and “cancer.One”: Please add the relevant spaces between the words.

Reply: We agree with your assessment. we have modified our text as advised.

Changes in the text: Page 17, line 317.

Line 239: “3%-10%(19)”: Please add the relevant spaces between the words.

Reply: We agree with your assessment. we have modified our text as advised.

Changes in the text: Page 17, line 320.

Line 238/239: “...the incidence of transformation from EGFR-positive lung adenocarcinoma to small cell lung cancer is 3%-10%”. It is actually higher and about 15% (Mambetsariev, I. et al. Small Cell Lung Cancer Transformation following Treatment in EGFR-Mutated Non-Small Cell Lung Cancer. J. Clin. Med. 2022, 11, 1429. https://doi.org/10.3390/jcm11051429) Furthermore, there are well-described molecular alterations present in SCLC transformed from NSCLC (e.g., Oser, M. G., Niederst, M. J., Sequist, L. V., & Engelman, J. A. (2015). Transformation from non-small-cell lung cancer to small-cell lung cancer: molecular drivers and cells of origin. The Lancet. Oncology, 16(4), e165–e172. https://doi.org/10.1016/S1470-2045(14)71180-5).

Reply: We sincerely appreciate the valuable comments. Thank you very much for providing the references. We have learned a lot from them. I apologize for not being able to grasp the latest literature and mistakenly believed that the incidence of EGFR-TKI-induced transformation from lung adenocarcinoma to small cell lung cancer was 3%-10%. We have updated our citation to reflect the latest literature and revised the incidence to 15%. Additionally, the reference you provided regarding molecular changes in non-small cell lung cancer transforming into small cell lung cancer is also cited in my manuscript. However, there was an error in my writing, which has now been corrected. Thank you again for your comments and the references provided.

Changes in the text: Page17, line320.

Line 241: "exist(20)": Please add the relevant spaces between the words.

Reply: We agree with your assessment. we have modified our text as advised.

Changes in the text: Page 18, line 325.

Line 245: "ProGRP and NSE… may have some predictive value…" I agree, but you do not provide any data of ProGRP and NSE that support this specific resistance mechanism – transformation from NSCLC to SCLC. ProGRP and NSE may also have some value in other potential resistance mechanisms.

Reply: We sincerely appreciate the valuable comments. Yes, I apologize for not providing research data that supports this specific resistance mechanism of ProGRP and NSE in transformation from NSCLC to SCLC. We have added relevant researches in our manuscript.

Changes in the text: Page18, line328-331.

Line 257: "(21)and prostate cancer(22)." : Please add the space between the words.

Reply: We agree with your assessment. we have modified our text as advised.

Changes in the text: Page 18, line 345.

Line 259: "patients(23).Research(24)has": Please add the space between the words.

Reply: We agree with your assessment. we have modified our text as advised.

Changes in the text: Page 19, line 347.

Line 269: "study(25)suggests": Please add the space between the words.

Reply: We agree with your assessment. we have modified our text as advised.

Changes in the text: Page 19, line 349.

Line 266: "nomogram(26)is": Please add the space between the words.

Reply: We agree with your assessment. we have modified our text as advised.

Changes in the text: Page 19, line 355.

Line 281: Regarding "external validation". Can you elaborate it a bit how external validation can be proceeded?

Reply: We sincerely appreciate the valuable comments. Firstly, lung adenocarcinoma patients who have received EGFR-TKIs treatment at other hospitals and developed primary resistance can be

subjected to risk prediction using the model established in this study. The aim is to assess whether patients who experience primary resistance have higher risk scores. Additionally, in the future, the model can be applied to calculate the resistance risk of lung adenocarcinoma patients who are receiving EGFR-TKIs treatment for the first time in clinical practice. Follow-up observations can then be conducted to determine whether patients with higher resistance risk are more likely to develop resistance compared to those with lower resistance risk. By addressing these two points, further validation of the risk prediction model established in this study can be obtained.

Additionally, the discussion should be enriched with the evidence for these serological factors, why ProGRP and NSE were chosen in this group of patients. Furthermore, how would you implement your model in the clinic? The model is well-described and validated, but the comprehensive capital about implementation is needed to the manuscript. Is you model supposed to replace or work as a complementary approach to NSC testing? How can such model co-exist with standard up-front NGS testing, which is critical for detecting intrinsic resistance on diagnostic biopsy or rebiopsi in case of progression. Please provide your visions and thoughts, thank you.

Reply: We agree with your assessment. The discussion should be enriched with the evidence for these serological factors. I have made modifications in the discussion section. As for the implementation of the resistance risk predictive model in clinical practice, we believe that this model can complement Next-Generation Sequencing (NGS). The factors included in this model are routinely tested clinical data, eliminating the need for additional tests. By incorporating the required patient testing data into the risk model, the resistance risk can be determined, thereby reducing the financial burden on patients. For patients identified as having a high risk of resistance through the risk predictive model, further NGS testing can be conducted to explore the presence of other gene mutations that may contribute to the development of resistance.

Changes in the text: Page 18, line 328-331.

Reviewer C

①The image is blurry. Please make it clear and sharp.

Reply ①: We sincerely appreciate the valuable comments. We have modified our images as advised. And we have also separately uploaded a compressed folder containing images

Changes in the text: Fig.1, Fig.2, Fig.3, Fig.4, Fig.5.

②There are many typographical errors in the figure and the table. Please correct them, including instances where Chinese characters are left inappropriately.

Reply ②: We greatly appreciate your careful identification of these errors. We apologize for my carelessness. We have modified our text.

③Why was the cut-off value for distinguishing between the S group and R group set at PFS 3 months? Considering that the median PFS in the FLAURA trial is 18.9 months, for instance, a patient in the S group with a PFS of 4 months would be clinically perceived as a subgroup prone to early resistance.

Reply ③: We sincerely appreciate the valuable comments. There is currently no specific time frame defined for determining whether primary resistance occurs within 3 months or 6 months after initiation

of EGFR-TKIs. Some studies suggest that it occurs within 3 months, while others argue for a timeframe of 6 months.

The literature "Santoni-Rugiu, E. et al. Intrinsic resistance to EGFR-Tyrosine Kinase Inhibitors in EGFR-Mutant Non-Small Cell Lung Cancer: Differences and Similarities with Acquired Resistance. Cancers, 2019,11(7), 923. https://doi.org/10.3390/cancers11070923" states that "Although most of the patients with advanced EGFRM+ NSCLC achieve objective response (OR) to TKIs, the extent and duration of responses are variable, and 20–30% of patients do not respond or respond for a very short time (typically <3 months) because of intrinsic resistance caused by de novo mechanisms believed to exist before treatment. Thus, in intrinsic/primary resistance the inefficacy of TKIs is immediately or very rapidly discernable, while in acquired/secondary resistance, disease progression occurs after an objective and sometimes prolonged clinical benefit from TKI-treatment. This benefit has been defined as either radiologically documented complete or partial response (CR, PR) or durable (≥6 months) stable disease (SD; defined by response evaluation criteria in solid tumors (RECIST) or World Health Organization (WHO) criteria) after TKI initiation and uninterrupted exposure without receiving additional systemic therapy after TKI discontinuation".

Therefore, progression within 3 months is defined as primary resistance, while resistance that occurs after 6 months of stable disease is classified as acquired resistance. However, there is no clear definition for disease progression between 3-6 months to determine whether it belongs to primary or acquired resistance. Therefore, in this study, in order to better represent patients with primary resistance, Progression-Free-Survival was defined as less than 3 months. In the future, we also plan to study defining PFS as less than 6 months for primary resistance, and then collecting clinical data separately for the resistant and sensitive groups for statistical analysis to obtain the risk factors of resistance. These risk factors will be compared with those obtained by defining PFS as less than 3 months in this text.