

## To Refree 1

The article deals with the treatment of patients affected by NSCLC in stage IIIB or IV using chemotherapy and epidermal growth factor receptor tyrosine kinase inhibitors. In detail, it focuses on long-term survivors of more than 5 years. In the article they take into account several patients characteristics (i.e. PS, sex, histology and TKI treatment and so on) in order to identify possible prognostic factors. It is an important field of research since there are very little clinical factors at the time of diagnosis that help to distinguish future long-term survivors from short-term survivors. The following items should be improved: 1) Before a possible publication the English should be improved in the paper and in the abstract. 2) Please, add data on available TKI inhibitors in NSCLC such as erlotinib and afatinib. 3) Indicate the timing for follow up in your study. 4) It could be of interest to specify: comorbidities, number and type of therapeutic lines, use of TKI, use of palliative radiotherapy, response to first chemotherapy defined by RECIST criteria, duration of treatment-free interval between first- and second-line therapy. 5) Please, improve the text: page 6, write the acronym of MRI = Magnetic resonance imaging. 6) The following papers/studies should also be considered in the article: - IPASS study (Mok NEJM 2009); SIGNAL study (Han JCO 2012), NEJ002 (Inoue Annal of Onc 2013), WTOG0203 (Takeda JCO2010); OPTIMAL study (Zhou 2011), EURTAC Rosell 2012, Sequist JCO2013. 7) Please, apply the RECIST criteria 1.1. to evaluate the response rate Conclusion. This article may be of note since it suggests and

underlines possible prognostic role of some patients' characteristics and outcomes. In addition, the article reports the results of several recent phase III studies focusing on chemotherapy and EGFR-TKI treatment and their impact on response rate. Finally, the article underlines the lack of a clear definition of "long-term survivors". The study confirm the existence of long-term survivors in patients with advanced NSCLC. The study however has many limitation (i.e. sample size, patients' characteristics are not detailed). There needs to be major revision if this paper is to be considered for publication and I would not recommend its acceptance in its present form.

Response) Thank you for your generous comments for our paper.

- 1) Our paper was carefully edited by a native English speaker for a possible publication.
- 2) In our retrospective study, gefitinib or erlotinib was administered as EGFR-TKI by the chief doctor's direction. Afatinib was not administered in this population. This information was added in our paper.
- 3) The median follow-up period was 323 days (range, 13 to 2069 days). This sentence was added in Methods.
- 4) The efficacy in first-line treatment achieved a 29% (19/65) of partial response. The median duration of treatment-free interval between first- and second-line therapy was 518 days (range, 26 to 1901 days). The median total therapeutic lines was 4 (range, 1 to 13 lines). These sentences were added in Results section.

- 5) Magnetic resonance imaging (MRI) was added in Methods.
- 6) Recent clinical trials described by reviewer were discussed in our paper.
- 7) The description of “the RECIST criteria 1.1.” was added in Methods.

As described by reviewer, there are many limitations in our study. According to your suggestions, we revised our paper. We believe that our retrospective is informative for respiratory clinicians.

## To Refree 2

In this retrospective study Dr.Kaira and coworkers sought to analyze the prognosticators of long-term survival (i.e.>3-years) in advanced non-small cell lung cancer (NSCLC) The study is interesting and focus on a challenging patients' cohort. My main comments and concerns are the following: 1) The statement that epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) play an important role in determining long-term survival should be deleted since a) this factor was not included in the univariate/multivariate analysis; b) most of the evaluated patients received it and c) there is no information regarding who had mutated EGFR. 2)In the overall cohort multivariate analysis should be performed including only factors that resulted significantly associated with long-term survival at the univariate analysis (i.i.log rang test). 3) Multivariate analysis in 65 long-term survival cannot be performed since there were no significant factors in the univariate analysis 4)I cannot understand the meaning of Table 5 since resemble results of table 4 except for the number of patients 60 instead of 65 5) The overall Kaplan Meier survival curve should be implemented with survival curves constructed according to factors that correlated significantly with survival in the univariate analysis. 6) English should be revised by a native language The authors are to be commended for a study conducted on a difficult cohort and for their satisfactory results.

Response) Thank you for your generous comments for our paper.

1) According to reviewer's comment, this sentence was deleted.

- 2) In multivariate analysis, significant factors were adjusted by the clinical variables such as sex, age and stage.
- 3) According to reviewer's comment, multivariate analysis was deleted in Table 4. Therefore, Table 4 was revised.
- 4) Table 4 shows survival analysis comparing between PS of 0-1 and PS of 2-3, whereas Table 5 divided PS between 0 and 1. This is apparently different between Table 4 and Table 5.
- 5) According to reviewer's comment, the overall Kaplan Meier survival curve according to PS was added as Figure 2.
- 6) Our paper was carefully edited by a native English speaker for a possible publication.

To Refree 3

The article "Long-Term Survivors of More Than 3-years in Patients with Advanced Non-Small Cell Lung Cancer Treated by Chemotherapy" is interesting but does not bring anything new. The sample size is small and we do not know how prevalent are the EGFR mutations in this group of patients. So the conclusions are nothing new.

Response) Thank you for your generous comments for our paper. According to several reviewer's comments, we revised our paper.

#### To Refree 4

Dear Editor, I thank you very much for giving the opportunity to review this manuscript. This is a retrospective study in a small number of advanced NSCLC patients receiving chemotherapy in single institute. The result does not surprise me and does not add any knowledge to previous studies. I have some comments in this study. In addition, the authors should consider professional and/or native English speaker advice for writing the text. I would like to review again after the authors reanalyze and rewrite this manuscript. Concerns in the study ? Table 2, 4, 5 overall survival What is the meaning of the overall survival? Which time did the authors decide as alive or dead? At the time of manuscript written? Please understand that all of the patients did not be enrolled at the same time. Therefore, I think the authors should decide which time they would like to study (for example, 3 years as table 3). I think table 2, 4, 5 and everything about prognostic factors in overall survival should be removed. Only 3 years period is enough. ? Page 7 “As the first line treatment of patients without ....”. It would be better if these sentences were shown by table 3. ? Table 3 demonstrates only univariate analysis. Please further analyse by multivariate analysis. ? Page 8 Survival analysis in long-term survivors of more than 3 years This analysis should be removed as mentioned above. ? Discussion was too long. Only PS, the authors mentioned for 2 pages. Please shorten it. ? Figure 1 I suggest using years instead of days in X-axis. In conclusion, I would like the authors to further analyse multivariate analysis in significant factors in Table 3 (sex, PS,

smoking, histology and EGFR-TKI therapy) and then rewrite the manuscript after they find the results. Analysis in overall survival, as they have done, made the result confusing. Therefore, the authors should remove them from the manuscript. I would like to review again after the authors reanalyze and rewrite this manuscript.

Response) Thank you for your generous comments for our paper. Our paper was carefully edited by a native English speaker for a possible publication. We decided as alive or dead at the time more than 3 years since final registration, then, we wrote this paper on July 2010. According to reviewer's suggestions, this was added in Methods. Discussion was revised according to reviewer's comments.



To Refree 5

The study describes a large series of stage IV non-small cell lung cancer for a single institution and the prognostic markers influencing outcome. The distinction of long term survivals at 3 and 5 years are very important, as are the prognostic factors that can influence in each subset of patients. The study is well written and clear and although there is nothing new it could be useful for clinical investigators and others interested in lung cancer. The main limitation of the study is described in the discussion: the lack of complete information on EGFR mutation status of the patients.

Response) Thank you for your generous comments for our paper. We deeply appreciate that you decided to accept our paper for publication. However, we revised our paper according to several reviewer's comments.