PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The frequency of EGFR and KRAS mutations in non-small-cell-lung cancer (NSCLC) – Routine screening data for Central Europe
AUTHORS	Bauer, Torsten; Boch, Christian; Kollmeier, Jens; Roth, Andreas; Stephan-Falkenau, Susann; Misch, Daniel; Grüning, Wolfram; Mairinger, Thomas

VERSION 1 - REVIEW

REVIEWER	van Zandwijk, N The Netherlands Cancer Institute
REVIEW RETURNED	05-Feb-2013

GENERAL COMMENTS	This study provides data on the EGFR and KRAS mutation status of a large unselected cohort of NSCLC patients in Germany and reveals that the incidence of EGFR mutations is about half of what is predicted from other series. Lifestyle is assumed to play a major role in inducing the mutations observed and it is interesting to speculate about smoking and what other lifestyles associated with the current outcome and how genetics might have interfered. The authors mention reference 4 and suggest a positive effect of EGFR TKI's on patients with wild type EGFR. Please note that such 'positive' conclusions could not be drawn from trials comparing EGFR TKIs with standard chemotherapy. It is important to address this point in either introduction or discussion and to underline that the current data are applicable to a unselected cohort of NSCLC patients in Germany. Please check names of reference 5 .

REVIEWER	Dr David F Heigener Thoracic Oncology Lung Clinic Grosshansdorf Germany
REVIEW RETURNED	06-Feb-2013

THE STUDY	A very important information is missing: Stage distribution of participating patients. This might be a bias, because one could assume that the Stage 4 patients -who are mostly diagnosed with a small biopsy only- contribute to the fairly high dropout rate out of proportion compared to surgical cases, where abundant material is available.
GENERAL COMMENTS	This paper provides an important information, because histologic selection bias (like in the Rosell-Study; NEJM 2009) is eliminated by the study design. However, I am afraid that this might be replaced by a "stage-bias", mentioned above.

	However, with information about disease stages, the manuscript is definitely worth being published.

VERSION 1 – AUTHOR RESPONSE

Reviewer1: N van Zandwijk
This study provides data on the EGFR and KRAS mutation status of a large unselected cohort of NSCLC patients in Germany and reveals that the incidence of EGFR mutations is about half of what is predicted from other series. Lifestyle is assumed to play a major role in inducing the mutations observed and it is interesting to speculate about smoking and what other lifestyles associated with the current outcome and how genetics might have interfered.
No changes required

The authors mention reference 4 and suggest a positive effect of EGFR TKI's on patients with wild type EGFR. Please note that such 'positive' conclusions could not be drawn from trials comparing EGFR TKIs with standard chemotherapy. It is important to address this point in either introduction or discussion……
Agreed and changed and the paragraph reads now: …was able to achieve not only a better tolerability of the therapy and an improvement in progression-free survival (PFS) in observational studies (2-4), but also compared to platinum-based chemotherapy (5). However, the effect on overall survival (OS) is still controversial one study could not detect a benefit (6), whereas Zhou and coworkers reported a significant increase in OS (7).

…and to underline that the current data are applicable to a unselected cohort of NSCLC patients in Germany.
Agreed and information added to the manuscript: We have added the word “German”to the possible limitations.

Please check names of reference 5 (became No. 2 in the current version)
Agreed and changed: van Zandwijk N, Mathy A, Boerrigter L, Ruijter H, Tielen I, de JD, et al. EGFR and KRAS mutations as criteria for treatment with tyrosine kinase inhibitors: retro- and prospective observations in non-small-cell lung cancer. Ann Oncol 2007 Jan;18(1):99-103.

Reviewer2: Dr David F Heigener

A very important information is missing: Stage distribution of participating patients. This might be a bias, because one could assume that the Stage 4 patients -who are mostly diagnosed with a small biopsy only- contribute to the fairly high dropout rate out of proportion compared to surgical cases, where abundant material is available.

Agreed and information added to the manuscript: When we analysed the distribution according to clinical stage, we found a bias with regard to higher clinical stages in the non tested group (Table 5). However, when stages IIIB and IV were compared to the potentially operable stages (IA – IIIA) we found this difference not to be statistically significant (not tested: 102/180; 56.7% versus tested: 277/552; 50.2%, p = 0.077).

This paper provides an important information, because histologic selection bias (like in the Rosell-Study; NEJM 2009) is eliminated by the study design. However, I am afraid that this might be

replaced by a "stage-bias", mentioned above.
Not agreed and no changes made to the manuscript. We found a trend towards higher stages in the cohort of patients excluded from analyses, which was not significant when a comparison was made between operable and non operable patients. Moreover, we did not see any stage bias in the very low and thus operable stages. We therefore do not include any comments on this issue. However, all information is now given in Table 5

However, with information about disease stages, the manuscript is definitely worth being published.
No changes required