Reviewer’s report

Title: Heterogeneous components of lung adenocarcinomas confer distinct EGFR mutation and PD-L1 expression

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Reviewer: Craig Stiles

Reviewer's report:

Abstract - echos - mentions 'readings were blinded to type therapy used' does this mean blinded to DA therapy full stop, or blinded to choice between CBG or BC?

Median cumulative CBG exposure is small (115mg) compared to other studies, exposure time is short at median 2.8-3.2 years

Page 7 line 38 - 13 studies actually

Page 7 line 47 - 3 studies were meta analysed for moderate/severe tricuspid regurg for treatment &gt;12months. More studies were meta analysed for mild tricuspid regurg (non clinically significant) and for other valves

Page 8 - line 9-18 what evidence is there to support the statement about the membership of this particular health insurance scheme being highly representative of the local population? I know nothing of the scheme, but one might imagine that a system that involves payments would favour less representation from amongst lower socio economic groups.

Page 11 line 35 - you claim that 'cabergoline only' exposed patients were more likely to have grade 2+ aortic regurg and yet the p value is &gt;0.05!

Page 11 line 38 - another claim for something being more likely, but the p value is &gt;0.05!

Page 7 line 40 - interesting data, pulmonary valve data is not widely reported elsewhere. I think that this is quite a tricky valve to echo (?) and so how certain can you be about the results here? Were a lot of the mild/moderate calls close? Looking at table 2, it appears that there was some doubt about calling valvular thickening in the pulmonary valve (23 in the inconclusive column - no 'inconclusive' calls in the other valves), which makes me wonder about the accuracy of calling regurgitation in this valve. The tricuspid valve data is consistent with the wider literature. If anything, taking this data at face value reinforces claims for an effect on the right heart from DA drugs - which is logical considering drug absorption from the portal hepatic circulation and therefore probably a greater effect on the right heart as this is where it will be present in greatest concentrations.

Practically all the results talk about regurgitation scores of 2+ - why not separate into mild (2) and mod (3)/severe (4) - as the latter two are clinically significant. Looking at table 2, the answer probably is because there was only one occurrence of moderate valvular regurgitation - and this was in a mitral valve. 'Mild' regurgitation in one or more heart valve is not necessarily pathologic and is relatively common. This is not to say that the analysis methodology is incorrect, rather it goes towards defining whether cabergoline is causing clinically relevant valulopathy or not. Nevertheless, the finding mild
regurgitation may yet be an interesting finding - all valve lesions that one day become moderate/severe were presumably mild at some point in their evolution.

Page 12 - strictly speaking the statistics quoted here are true. But seeing as there was only one moderate valve lesion in the whole study it feels a little disingenuous to quote 'mild to moderate' persistently.

Page 12 lines 31-61 these patients were on vastly higher doses, 3mg/day compared to 1mg/week. The association between the former dose and valvulopathy is already well proven.

Page 13 lines 24-29 yes, but the regurgitation found in your study is non clinically significant.

Page 13 a table showing the breakdown of the specific valve lesions by drug might still be useful to the reader even without statistical analysis.

Tables - there is no breakdown of the occurrence of valvular regurgitation and its gradation by drug type.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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No

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