PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Anticancer drug prices and clinical outcomes: a cross-sectional study in Italy
AUTHORS	Trotta, Francesco; Mayer, Flavia; Barone-Adesi, Francesco; Esposito, Immacolata; Punreddy, Ranadhir; Da Cas, Roberto; Traversa, Giuseppe; Perrone, Francesco; Martini, Nello; Gyawali, Bishal; Addis, Antonio

VERSION 1 – REVIEW

REVIEWER	Peter Baade Cancer Council Queensland Australia
REVIEW RETURNED	19-Sep-2019

GENERAL COMMENTS	The premise for the study is based on the statement that “cancer drug prices far exceed the cost of their development”(Page 4, line 20). It would be useful to include references to support this statement. Even with this, the methods and interpretation of the prices seem to ignore any differences in the cost of drug development, and that the clinical benefits, I assume, are only known after the price has been set. Also, I assume volume of drug use would be important, so it would be expected that treatments for a common cancer type would be able to be negotiated to a lower price more easily than treatments for a very rare cancer. Clarification of these points would determine the validity of the statistical approaches and interpretation used in this manuscript. Using the median alone from each study gives no indication of the variability within studies - nor the number of people who that median represents. Was the regression weighted by the number of cancer patients for each drug? Taking absolute differences in clinical outcomes does have merits, however, given (I assume) that the treatments included in the studies are for a range of different cancer types, each with different survival outcomes, a differences of 5 weeks might be important if the median survival was 10 weeks, however less important if the median survival was 200 weeks. I realise this is partially addressed with the %difference measures in the supplementary figures, however some further clarification of this would be helpful for the interpretation. Data for the OS were only available for 17 (49%) of the 35 indications, and 29 (82%) of the other two measures. How representative were the 17 OS indications included? The number of indications included in the figures is sometimes lower (eg Figure 21 have 16, 28 amd 28 respectively).

	Table and Figures – include footnotes for abbreviations How were outliers handled in these analyses, and influential observations? For example Supp figures 1b and 1c have clear outliers.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Peter Baade
Institution and Country: Cancer Council Queensland, Australia
Please state any competing interests or state 'None declared': None declared

The premise for the study is based on the statement that "cancer drug prices far exceed the cost of their development"(Page 4, line 20). It would be useful to include references to support this statement. Even with this, the methods and interpretation of the prices seem to ignore any differences in the cost of drug development, and that the clinical benefits, I assume, are only known after the price has been set. Also, I assume volume of drug use would be important, so it would be expected that treatments for a common cancer type would be able to be negotiated to a lower price more easily than treatments for a very rare cancer. Clarification of these points would determine the validity of the statistical approaches and interpretation used in this manuscript.

Authors' reply:
We thank the reviewer for this comment that offers the opportunity to fully reference the point.
A reference to the recent article by Tay-Teo K and colleagues published in JAMA Netw Open has been added. Among the key points, the Authors "Cancer drugs, through high prices, have generated incomes for the companies far in excess of research and development costs".
Furthermore, we confirm that the current regulatory approval process does not include any evaluation on drug development costs; however, the clinical benefit (although partial/not consolidated) at the time of approval is known and should be one of the driving forces for the price setting. For this reason we decided to evaluate how clinical outcomes (OS; PFS; ORR) correlates with the negotiated price. We also agree that volume of drug use would be important; however, this information is not known at the time of approval. The incidence/prevalence of cancer types (or the number of patients exposed) could be used to further evaluate whether there is any relationship with the price. However, these further correlations were beyond the scope of our article and might be considered in future research projects. Our analyses that also took into account tumour type gave consistent results with the primary analysis; this mitigated the different prevalence/incidence of cancer types across the study. This issue has been further specified in the discussion section.

Using the median alone from each study gives no indication of the variability within studies nor the number of people who that median represents. Was the regression weighted by the number of cancer patients for each drug?

Authors' reply:
We are aware of this issue, which represents a source of heterogeneity across different trials and is already reported in the discussion as a study limitation. We did not collect the information on patients' numbers since we were interested in the relationship between outcomes and price, thus we trusted the measures of outcomes reported in the EPAR [?] and the regression was not adjusted by the

number of patients. This means that we assumed that any trial had the appropriate sample size calculation to confirm the hypothesis tested. Moreover, adjusting by cancer type could be considered as a general proxy of an adjustment by incidence/prevalence of cancer types which ultimately means an adjustment by number of patients.

Taking absolute differences in clinical outcomes does have merits, however, given (I assume) that the treatments included in the studies are for a range of different cancer types, each with different survival outcomes, a differences of 5 weeks might be important if the median survival was 10 weeks, however less important if the median survival was 200 weeks. I realise this is partially addressed with the %difference measures in the supplementary figures, however some further clarification of this would be helpful for the interpretation.

Authors' reply:
We agree with the Referee; in the primary analysis we chose to consider the absolute differences in clinical outcomes to show the absolute magnitude of the improvement. We also included in the analysis the %difference measures to take into account this issue. We noted that results using the %difference measures were consistent with those applying the absolute outcome measures. However, we believe that it is fundamental to take into account differences due to the type of cancer. For this reason, we also decided to consider the percentage difference measures (supplementary figures 1a-1c) and to adjust all analyses by "cancer type" (supplementary table 1).

Data for the OS were only available for 17 (49%) of the 35 indications, and 29 (82%) of the other two measures. How representative were the 17 OS indications included? The number of indications included in the figures is sometimes lower (eg Figure 21 have 16, 28 amd 28 respectively).

Authors' reply:
In our analyses, as reported in the methods section, we used all the information relative to the new drugs approved by the EMA via a centralized procedure between January 2010 and June 2016 for the treatment of either solid or haematologic cancers, as reported in the European Public Assessment Reports - EPARs (summary table of the main study, Section 2.5.2) publicly available on the EMA website (www.ema.europa.eu). Prices were those officially negotiated in Italy by 31st December 2016. Unfortunately, information on OS, PFS and ORR was not available for all the 35 treatment indications. We did not exclude a priori any specific drugs to avoid any selection in the study sample. Thus, the drugs included in the study should be considered representative of the whole oncology trials that investigated the survival as a study outcome. To further increase representativeness of the sample we also analysed other surrogate outcomes such as PFS and ORR (also in such cases the correlation did not ameliorate). To provide the readers with all the available information we included all the outcome data by drug in table 1.
In the figures 2a-2c the information on discounted price of nivolumab for treatment of Renal Cell Carcinoma was not available at the time of the analysis, as reported in table 1, and therefore in these three figures one indication is lacking in comparison with the figures 1a-1c.

Table and Figures – include footnotes for abbreviations

Authors' reply:
Done. Please see footnotes for abbreviations in the figures uploaded. We reported the legend and footnotes for abbreviations also in the last page of the manuscript.

How were outliers handled in these analyses, and influential observations? For example Supp figures 1b and 1c have clear outliers.

Authors' reply:
We chose to include outliers in the analyses reported in the article to show all the available information. However, we conducted sensitivity analyses in which all the outliers were excluded and no differences in the correlation values emerged. Therefore, we have not reported these additional analyses in the article. This clarification has been added to the methods section.

VERSION 2 – REVIEW

REVIEWER	Peter Baade Cancer Council Queensland
REVIEW RETURNED	17-Oct-2019

GENERAL COMMENTS	I have read the revised version of the manuscript, and considered the authors' responses, however I note that the authors have made minimal changes to the manuscript in response to my comments. It would be helpful to at least include, within the manuscript itself, notes about the limitations raised in my comments. The authors have provided no data to support their assertion that "thus, the drugs included in the study should be considered representative of the whole oncology trials that investigated the survival as a study outcome." however, even if this is the case, this restricted representation is not reflected in the abstract, nor the conclusions of the paper.

VERSION 2 – AUTHOR RESPONSE

To the reviewer

Reviewer Name: Peter Baade

Institution and Country: Cancer Council Queensland

It would be helpful to at least include, within the manuscript itself, notes about the limitations raised in my comments.

The authors have provided no data to support their assertion that "thus, the drugs included in the study should be considered representative of the whole oncology trials that investigated the survival as a study outcome." however, even if this is the case, this restricted representation is not reflected in the abstract, nor the conclusions of the paper.

We uploaded a new version of the manuscript. We added two sentences in the discussion and in the conclusion sections reporting the potential limitation of our analysis. We also mentioned these limitations in the abstract section.

Regarding how these data may be considered representative of the whole oncology trials that investigated the survival as a study outcome we modified a paragraph of the discussion section as follows: “The main limitations of our study concern data completeness on clinical outcome and price. We used, as an estimate of benefit, data from pivotal trials retrieved from EPARs. Moreover, we are not aware if further (more robust) data became available at a later stage when the price was negotiated at the national level. Thus, we cannot exclude that the correlation between drug prices and therapeutic benefit might improve taking into account data acquired after the marketing of anticancer drugs.”

Furthermore, we try to clarify other paragraph of the discussion section in order to be more clear on these points.

VERSION 3 – REVIEW

REVIEWER	Peter Baade Cancer Council Queensland
REVIEW RETURNED	07-Nov-2019

GENERAL COMMENTS	Thanks for responding to my comments.