Peer Review File

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Reviewer A

Comment:	Reply:	Changes in the text:
Overall, there are only 15 references included in the manuscript. To give the reader more information and data on the topic it would be very helpful to provide more references supporting claims made by the authors.	We have included more references in this edit	
There could be two tables that support and illustrate the main information of this review: 1) a table comparing different approaches to the development and pricing of cancer drugs across Asia. 2) advantages and disadvantages of pharmaceutical policy options for governments in Asia to address the challenges outlined by the authors.	This article is written as a brief summary of the issues related to cancer drug costing in East Asia. We have tried to summarize the main issues involved. It would be difficult to go into the specifics of each country.	
The authors could outline the disadvantages of the NRDL's price cut, e.g. lower prices may discourage pharmaceutical development efforts.	We have included that in the discussion regarding NRDL and its disadvantages	Line 161-163 “Furthermore, a lower drug price negotiated due to the NRDL may discourage pharmaceutical development efforts as well.”
The authors may want to mention differences in the design and conduct of clinical trials between the US / EU and China. This is particularly important given that the FDA has recently rejected NDA/BLA submissions by pharmaceutical companies based on clinical trials that were mainly conducted in Asia.	We have included a paragraph regarding this point	Line 205-209: “Despite these possible cost savings, United States Food and Drug Administration (FDA) has rejected cancer drug submissions by pharmaceutical companies based on clinical trials that were mainly conducted in Asia, on the basis that they were concerned that these trials did not enrol a population diverse enough for the results to be applicable to patients in the United States. “
There is an ongoing debate regarding the development and approval of new cancer drugs in the EU and Asia. Anti-cancer drugs were shown to provide a marginal clinical benefit of merely 2.8 months in OS (doi: 10.1200/JCO.22.00535), whilst cancer drug prices beyond $10,000 per month are generally not associated with this	We have discussed this in our article. We have put in the example of China some of the studies that were done there reflecting on the debate between clinical benefit and overall cost.	Line 56 – 64 “As cancer is often seen as a significant threat to life and well-being, the motivation to provide the perceived best care, which tends to involve using the latest cancer medications, driving strong demand and contributing to

marginal benefit nor R&D costs (doi: 10.2139/ssrn.4422454 and doi: 10.1001/jamanetworkopen.2022.18623). The authors may want to reflect on this with a particular focus on Asia (specifically China, Japan, and Singapore) (doi: 10.1001/jamanetworkopen.2022.25973).		cancer costs, is one of the limiting factors for access to these treatments. However, a recent study in China showed that anti-cancer drugs provided a only a marginal clinical benefit of 4.1 months in overall survival(8). China ranked the second-poorest affordability in a recent survey of six countries with a median monthly treatment price of $3173 in 2016 for patented anticancer drugs(9). The cost of cancer care has outstripped other diseases and the high cost may not be associated with the clinical benefit nor the cost from research and development.”
The authors well outline recent developments in modern oncology: personalized medicine, particularly targeted therapies, immuno-oncology, and gene & cell therapies, have transformed cancer care around the globe. These new treatment strategies allowed physicians to personalize and individualize treatment for each patient subject to the cancer's genetic profile. Thereby, pharmaceutical companies began to target subsets of common diseases, resulting in more and more indications for "narrower", sometimes even ultra-rare diseases, patient populations to be approved (10.1371/journal.pmed.1002190 and 10.1038/d41573-020-00059-3). This ultimately challenges traditional rare (orphan) disease policies that were signed into law in the 20th century and poses a significant burden for patients and health insurers (10.2139/ssrn.4421181). The authors may want to reflect on this problem in their article and outline how these issues can be addressed in Asia.	We have included this discussion in the paragraph regarding health care expenditure in Asia.	Line 85 – line 94 “With the development of modern oncology, this has allowed the growth of precision medicine particularly in the field of targeted therapies, immune-oncology and gene and cell therapies. In turn, many pharmaceutical companies are working to develop “orphan” drugs in oncology and rare cancers which ultimately challenges traditional disease policies(15) and posing a significant burden for patients and health insurers(16). Pharmaceutical expenditure has exceeded the steady increase in per-capita health care spending by 0.5%, with a 6% per annum increase growth rate in Asia. Countries like China, Thailand, Laos, Vietnam and the Philippines have increased expenditure on medications by 9% annually. Within Asia Pacific, pharmaceutical spending is about an average 31% of public sector expenditure on health care and it is clear that cancer medications form a large cut on this increasing cost (17).”

Reviewer B

Comment:	Reply:	Changes in the text:
Abstract. “[B]ulk purchasing“ is not mentioned in the main text.	Thank you reviewer for that feedback. We have removed that from our abstract	
Please state the goal of the article.	This is a narrative review on some of the cost concerns regarding cancer drugs and development in Asia.	We have changed our title to include the intent: “A Narrative Review on Paying for Advanced Cancer Therapeutics: Hard Truths and Realities in Asia”
Reference 8. Please cite the original study: Tay-Teo K, Ilbawi A, Hill SR. Comparison of Sales Income and Research and Development Costs for FDA-Approved Cancer Drugs Sold by Originator Drug Companies. JAMA Netw Open. 2019 Jan 4;2(1):e186875.	Thank you for the citation. This has been added to our paper	Reference 8 changed
Please discuss the following argument in favor of higher prices: “Volatility in the RoI is generally higher in the pharmaceutical industry than for the overall market, with an upward trend, providing evidence that the risk sustained by this industry has been increasing over the years [Citation32]. To retain shareholders and attract new ones, the pharmaceutical industry has to offset the increasing risk by offering a higher RoI. This can have undesirable implications for drug prices because the higher RoI can only be achieved by boosting profitability.” (Moreno SG, Epstein D. The price of innovation - the role of drug pricing in financing pharmaceutical innovation. A conceptual framework. J Mark Access Health Policy. 2019 Mar 20;7(1):1583536)	Thank you for the review. Due to word limitation, it would be difficult to discuss the volatility of drug pricing based on pharmaceutical innovation. This article is meant to be a brief summary of the issues related to cancer drug cost in East Asia.	
Lines 59-60. „cost differences of 60 drugs between countries in Europe and Oceania.” From my understanding, the real focus of the article is on East (!) Asia. If so, this needs to be explicated in the title and text. Furthermore, the article needs to discuss the heterogeneity of East	We have included more comparative arguments within countries in Asia	Line 77-83 “Given the wide differences in resources, economic development, patient demographics, governmental healthcare structure and financing of health care, inequity of cancer drugs

Asian countries in terms of ability to pay more clearly (e.g., by providing the range of GDP per capita, percentage of public health expenditures spent on cancer drugs, co-payments, etc.).		availability exist within Asia. Access to cancer medications are limited when there is a high out-of-pocket (OOP) cost burden. In HM and HI countries, most of these medicines are on formulary and available at a subsidised cost(14) however in LMICs and LICs, formulary deficiencies are greater and survey showed that in these countries, patients incur large amount of OOP, even for generic and inexpensive cancer drugs(14). “
Lines 148-9. “negotiate for lower drug prices.” How were cancer drugs purchased before the implementation of the Cancer Drug List?	They were negotiated separately between the hospital institution and the pharmaceutical companies.	We have explained the intent of the cancer drug list in this article which is to lower drug prices.
Line 156. “homegrown.” Were did R&D took place?	We have removed that sentence and have explained the need for domestic innovation based on actual examples of sintilimab.	Line 198-200 “Since making it into the China’s national reimbursement drug list, Sintilimab, as the first PD-1 inhibitor, was listed with a price reduction of 64% (31). A comparison of wholesale acquisition cost for the drugs showed significant discounts in China compared with U.S. cost. “
Line 162. “develop.“ Please specify the types of clinical trials.	We have removed that sentence	
Line 172. “due to the market forces.” Please explain. What about purchase discounts as a reason?	These sentences have been removed.	
Lines 173-4. “competitive pricing, price reduction, with reduced pricing of production and cost of goods.” Do the three descriptions refer to the same thing?		
Line 175. “rise of biosimilars.“ Biosimilars of sintilimab?		
Lines 177-8. “$16,000 every 4 weeks in the United States compared with about $7,000.” Are these “wholesale acquisition costs“ or pharmacy sales prices?	The article referenced does not specify and we are unable to find out that information	
Line 202. “Australia.“ Non-Asian	We have removed Australia.	
Line 213. “becoming increasingly important.“ In Asia?	We meant to discuss this on a general term.	

Line 226. “Patient access programs.“ Mentioned in the conclusion but not before.	We have removed this discussion in the conclusion and added it into a new paragraph entitled “Patient Access Programs, Vial Sharing and Biosimilars”	Line 253-269 “In order to address the rising cost in cancer medication, many governments have come up with unique collaborations and innovative pricing strategies to cope. Patient access programs have been used to increase access to cancer drugs prior to regulatory approval, particularly in countries with high OOP payments or economically challenged populations. In Asia, this includes the Novartis CancerPath to Care program with eligible patients having access to ribociclib, letrozole as well as imatinib for breast cancer and gastrointestinal stromal malignancies(36) as well as the trastuzumab programs in the Philippines(37). Vial sharing and dose rounding have also shown, at a prescription level, to make a difference in the expenditure on cancer drugs(38). Biosimilars are also another innovative method to decrease the cost of cancer medication expenditure within the countries of access as well, well studied in the example of Trastuzumab in HER2 positive breast cancer(39). Substituting branded cancer drugs to generics have also been shown to be an effective way to reduce cost. In the last decade, Asian countries have increasingly participated in global clinical drug development. This is seen especially in developed Asian countries, such as South Korea, Hong Kong, China, Malaysia, and Singapore, where patients are able to have access to these drugs through these trials.”
The Conclusion section is too general. It should mention the annual increase in cancer drug expenditures in percent and the role of cancer drug lists. The abstract provides a much better summary.		

Reviewer C

Comment:	Reply:	Changes in the text:
The article is not structured as we would expect a systematic literature review would be with an introduction, objective, methods, results, discussion and conclusion. Instead, a number of sub section are presented.		We have changed our title to include the intent: "A Narrative Review on Paying for Advanced Cancer Therapeutics: Hard Truths and Realities in Asia"
First a section on "The Burden of Cancer in Asia" is presented. This section does not adequate explain what the burden of cancer in Asia is. For example, how much does it cost? What kind of cancers are we seeing? Is there a difference between Asian countries?		We have expanded on the first section to discuss about the difference of socio-economic status in Asia. Regarding cost, we have included that in the discussion on the Cost Challenge (Line 64 onwards)
The next section is entitled "The Rise of Immuno-oncology". This section is lacking information on how immune-oncology rose and just states that some market research says that the cancer market will be "valued more than US$261.7 billion by 2031". The conclusion of this section is not supported by the evidence presented and should be taken out.	We have taken out the conclusion of this section and expanded it to discuss about the balance between the benefit and the cost of immune-oncology	Line 56 - 64 "As cancer is often seen as a significant threat to life and well-being, the motivation to provide the perceived best care, which tends to involve using the latest cancer medications, driving strong demand and contributing to cancer costs, is one of the limiting factors for access to these treatments. However, a recent study in China showed that anti-cancer drugs provided a only a marginal clinical benefit of 4.1 months in overall survival(8). China ranked the second-poorest affordability in a recent survey of six countries with a median monthly treatment price of $3173 in 2016 for patented anticancer drugs(9). The cost of cancer care has outstripped other diseases and the high cost may not be associated with the clinical benefit nor the cost from research and development."
Following this a section on "The Cost Challenge" is presented. This section is severely lacking in referencing and presenting of evidence. The authors seem to jump straight to conclusions such as: "Universal health coverage should be the aim of health care	We have majorly edited this session including more evidence and further discussions.	Line 66 – 83 "Universal Health coverage(10) should be the aim of health care systems across all countries, with the means of ensuring that essential cancer medications and high-value effective novel cancer treatments are available and

systems across all countries" and "access to cancer medications are limited when there is a high out-of-pocket cost burden".		accessible to all, without incurring undue financial hardship. However due to the consequence of diverse economic development, healthcare policies and investments, Asian countries have vastly different healthcare priorities with each country's expenditure per capita on health care varying greatly(11). The ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS)(12, 13) is a standardised validated approach to classify the magnitude of clinical benefit from anticancer therapies and is a critical step in addressing health equity across nations to deliver affordable and effective cancer care. Given the wide differences in resources, economic development, patient demographics, governmental healthcare structure and financing of health care, inequity of cancer drugs availability exist within Asia. Access to cancer medications are limited when there is a high out-of-pocket (OOP) cost burden. In HM and HI countries, most of these medicines are on formulary and available at a subsidised cost(14) however in LMICs and LICs, formulary deficiencies are greater and survey showed that in these countries, patients incur large amount of OOP, even for generic and inexpensive cancer drugs(14). "
The section on China's healthcare reform presents a very high-level description of the system but does a poor job of really informing the reader about the challenges. No reference is given to the zero mark-up policy and/or what the consequences are.		This article is written as a brief summary of the issues related to cancer drug costing in East Asia and would be difficult to discuss the all content in entirety. We have added a discussion on the consequence of the zero markup policy (Line 163 – 166)
The section on "Setting a Price Ceiling in Asia" suffers from the same issues as the previous sections. A lot of opinions with very little referencing and systematic analysis of the evidence. Moreover, it appears the authors do not fully understand how		We have added a discussion on the suggested content as well (Line 207 – 211)

cancer drugs are evaluated in Singapore. In Singapore ACE is heavily involved with setting the price for cancer drugs using HTA.	
Next a section entitled “Establishing Domestic Innovation: Homegrown Immunotherapy is presented. It starts with a statement saying that there are many “homegrown” immunotherapies in China, however no evidence is presented of this. Then a couple of specific drugs are mentioned but again no reference is given for the statement made in relation to these drugs. A simple comparison of wholesale costs is made to argue that there is pricing competition. However, the comparison is made of US prices vs Chinese price which is potentially a problem as prices are not comparable across jurisdictions.	We have removed the discussion on US prices and kept the discussion within Asia.
After this a section on China’s CAR-T cell therapy is presented. As with the other sections this section presents a lot of statements without references. I am not sure whether the authors understand what is actually involved with CAR-T therapies. These cannot be compared to PD1 inhibitors as there is a lot more involved as CAR-T therapies have to be customized for each individual patient.	We have edited and changed our manuscript. Thank you very much for your review.
Finally, the authors present a conclusion. The statements in the conclusion are not appropriate based on the data presented in the paper. For example, the authors say that “many governments have come up with unique collaborations and innovative pricing strategies to cope”. What are these unique and innovative things?? Asian payers are using HTA as a tool to manage the financial impact of expensive therapies. Just have a look at South Korea and Taiwan HTA is mandatory for new drugs.	