Review of: "Progression-free survival as a primary end-point: Counting the cost"

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The author presents a sort of editorial discussing on issues about possible shortcomings related to the use of PFS as primary endpoint in the analysis of clinical trials on effectiveness of drugs. He concludes that patient's QoL should play a pivotal role when analyzing PFS vs OS data. In my opinion, the manuscript is interesting but I would also include in the consideration the different types of cancers addressed by the clinical trials, as well the (length of) life expectancy of patients enrolled in the trial.

The manuscript refers to several studies providing detailed data on most of them. While this is commendable showing the author's knowledge of the literature, in my opinion the too many data make the reading a bit difficult. Shortening the text (see some proposal later on) and the too many details might help the reader to get the key message of the author. A more appropriate use of paragraphs would also help the reading.

Acronyms are extensively used but I suggest to be consistent with them across the manuscript (e.g. second line R-CHP should be "Polivy + R-CHP" as used cross the manuscript (the original authors indeed used the "pola+R-CHP" acronym). Another example is SOC for "standard of care": I would not use it (used only twice)which can easily and more clearly be substituted by R-CHOP On the other hand, E2100 is mentioned without any further detail. DLBCL is also not spelled out at its first mention (2nd line of the introduction). VRD should always be VRD and not RVD.

Specific comments:

Introduction, first paragraph

Please see below my proposal for a shortening of the text:

"On April 19, 2023, the American Food and Drug Administration (FDA) approved polatuzumab vedotin (Polivy) with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola + R-CHP) as the first line treatment for diffuse large B cell lymphoma (DLBCL) in newly diagnosed patients who have an International Prognostic Index (IPI) score of 2 or greater. That approval was based on a significantly improved PFS in the pola + R-CHP arm vs former standard of care (SOC) based on the association of rituximab, cyclophosphamide, doxorubicin, oncovin, and prednisone (R-CHOP). [1]. However, that study did not show any improvement in the OS of the pola + R-CHP patients. Polivy was already approved in 2021 for previously treated DLBCL patients."

The next sentence starting with “Unlike” might be moved to new paragraph. But it should also better be explained for which cancers ibrutinib and zanubrutinib were used.

Introduction, last paragraph

From “Pasalic et al onward: I think that the discussion should also address the different values/significance based on cancer types, their “curability” and overall length of life expectancy in which QoL should have the paramount role.

PFS in perspective … “

Third line: not clear what the “new surrogate” refers to. Is the PFS or the alternative drug?

The sentence which start with “These arguments” might be shortened see below my suggestion:

These arguments may not be entirely true; the recent initiation of the withdrawal of belantamab mafodotin- (Blenrep®) from the US market for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) is a case point[10]. The withdrawal was based on the outcome of the DREAMM-3 phase III confirmatory trial of Blenrep monotherapy vs. pomalidomide in combination with low-dose dexamethasone (PomDex) in RRMM patients in which Blenrep did not meet its primary endpoint, PFS, despite showing a better response rate compared to PomDex (25% vs. 8%). Moreover, the median duration of response (DOR) was not reached for belantamab mafodotin (95% CI: 17.9, -) vs. 8.5 months (95% CI: 7.6, -) for PomDex. The median OS was 21.2 and 21.1 months for belantamab mafodotin and PomDex, respectively, with an HR of 1.14 (95% CI: 0.77, 1.68). Bevacizumab (Avastin), which got FDA-accelerated approval in 2008 for metastatic breast cancer based on PFS improvement (E2100; NCT00028990), had the approval withdrawn in 2011 when data from confirmatory studies showed that the PFS was significantly smaller than expected with no improvement in OS or QoL.

In the text above I think is should also better describe how the median DOR has been calculated. I do not understand how/why a median can’t be reached (value NR) and then provide 95% CI which I understand go to infinite?).

The paragraph starting with “in a different scenario” still reports about multiple myeloma which is the same as two paragraphs before. Why not to move this paragraph before the one on breast cancer?

The paragraph staring with “in another setting” it is not clear how a trial can be run against the “physician’s choice” (TPC - make sense using this acronym?) which is indeed better specified few lines below.

In the same paragraph the occurrence of adverse events in the two trials are reported without informing the reader if the differences were statistically significant.

The E2100 trial is not described.

Here below a proposed alternative text for the paargraph

In conclusion: the “innovative” drugs in DREAM3 and E2100 were not approved by FDA since did not ….., while those in

DETERMINATION were approved because improved PFS despite lack of OS benefit and in some cases increased risk of adverse events.

Paragraph starting with “so if PFS ...”

AS in previous comments, here the author refers to non-small cell lung cancer. Indeed I think thatt in he approach on PFS, the background type of cancer (survival) should be taken into consideration.

depends The third line before the last states “the only study ...” I believe indeed thatthera are several studies, some of theme are referenced here: https://pubmed.ncbi.nlm.nih.gov/32246379/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4744081/; https://pubmed.ncbi.nlm.nih.gov/28399678/

Last paragraph before the Table: the author refers to assessment time bias in the estimation. I think this can be solved by rigorous trials (as all should be). ...

Counting the cost

The sentence “the in-group PFS was also seen as an advantage” is not clear to me.

When referring to “other malignancies” I think that it depends on what type of malignancies is being referred to.

The last sentence in the paragraph referring to Kovic et al is not clear. No information on what type of drugs they are referring. More explanation is needed. Otherwise delete the sentence.

The crossroads:

“most cancers” What type of cancers?

Also in this paragraph 95% CI are reported without upper limit. Is this because a very small sample size or for what reason? If significant results were found this should be stated.

The comment “thus proving a significant benefit in OS ...” might be revised. Indeed, it is certain that reaching OS could be difficult. But primary and other endpoints are selected due to studies’ objectives. And surrogating is under the considerations by drug approval authorities; for instance if a mortality-related primary endpoint is determined as an outcome, only a mortality-related outcome may be investigated due to “surrogating” as QoL-related outcomes don’t be used instead of mortality-related outcomes. But, known as clinical trials can be designed to object both mortality-, morbidity-, and QoL-related outcomes.

Here below I’m proposing an alternative text for shortening part of the paragraph:

“With a >2-fold increased risk of death (HR 2.03 (95% CI ...) in the venetoclax arm as compared to placebo .... “

Last paragraph: marginal zone lymphoma is now brought up. This change in disease focus might confuse the reader.

Please consider revising the paragraph.

Last lines: The sentence starting with “The most recent ...” needs further details to be well understood.

Finally, There are recommendations by authorities should be mentioned in related sections in the paper:

1. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-6_en.pdf (Please consider to interpret also its Appendix 1)
2. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics
3. https://www.iqwig.de/methoden/general-methods_version-6-1.pdf