MultipleMyelomaHub

General MM

Are surrogate endpoints a suitable alternative to survival in clinical trials?

Emily Smith | Aug 09, 2019

In July 2019, Professor Shaji Kumar and Dr Vincent Rajkumar published a cautionary comment in *The Lancet* about the use of surrogate endpoints in oncology clinical trials and highlighted the recent results from the BELLINI trial.[1]

Background on BELLINI[1,2]

The results of the BELLINI trial were recently presented by Prof. Kumar at the European Hematology Association (EHA) meeting, 2019, held in Amsterdam, NL. BELLINI was a double-blind, randomized, placebo-controlled, phase III trial in patients with relapsed/refractory multiple myeloma (RRMM). The study compared venetoclax (Ven) + bortezomib (B) + dexamethasone (d, Ven-Bd) to Bd alone. The primary endpoint was progression-free survival (PFS) and key selected efficacy data are shown in **Table 1.**

There was two-fold increase in progression-free survival (PFS) in the Ven-Bd arm, as well as significant improvements in overall response rate (ORR), very good partial response or better (≥ VGPR), and undetectable minimal residual disease (uMRD) compared with the Bd arm. However, there were also twice as many deaths in the Ven-Bd arm *versus* the Bd arm, with a hazard ratio (HR) for death of 2.03 (95% CI, 1.04–3.94).

Following an analysis of the BELLINI data, the United States (US) Food & Drug Administration (FDA) placed a partial hold on trials involving venetoclax in MM.[3]

Table 1. BELLINI key data

	Ven-Bd	**Bd**
N	194	97
Deaths	41 (21.1%)	11 (11.3%)
ORR	159 (82%)	66 (68%)
≥ VGPR	59%	36%

≥ CR	26%	5
PFS	22.4 months	11.5 months
MRD negative rate	26 (13.4%)	1 (1%)

Other recent examples in MM, the KEYNOTE-183 and KEYNOTE-185 studies showed that treatment with pembrolizumab increased the risk of death compared to the control arm. However, unlike BELLINI, there was no associated improvement in efficacy.[4,5]

What is the ideal endpoint for a trial?

- Improvement in overall survival (OS) or improvement in a validated patient-reported outcome (PRO) in a randomized controlled trial (RCT) is the gold-standard
- These endpoints encompass both efficacy and safety data
- The limitation of using OS as an endpoint is that it takes significant time to obtain the data
- It is also important to note that since OS encompasses both efficacy and safety

Surrogate endpoints – what are they and why use them?

- PFS, response rates and MRD-negativity rates are often used as surrogate endpoints
- They are used because:
- The results are obtained within a quicker timeframe compared with OS
- Advantages to the pharmaceutical company with regards to extending patent life
- Regulatory authorities can approve drugs within a faster timeframe, dependent upon the unmet medical need

Limitations of surrogate endpoints

- Improvements in PFS and response rate do not often correlate with OS
- The lack of correlation is typically attributed to: different salvage therapy approaches, a small sample size or a lack of follow-up
- A PFS event may not be noticeable to the patient (in MM, a PFS event can be an asymptomatic increase in monoclonal protein concentrations by 25%). This, therefore, can give mixed messages to the patient that a new treatment will extend their life. **Patients should be given a full explanation of surrogate endpoints during the informed consent process to avoid confusion of any anticipated benefit**
- Without a control arm, surrogate endpoints may be interpreted favorably. Control arms should be the current standard-of-care (at the time of design) to indicate a clear clinical benefit

Implications of using surrogate endpoints

The implications of the BELLINI trial are far-reaching, since surrogate endpoints are used across different therapy areas, not just hemato-oncology. Specifically, Prof. Kumar and Dr Rajkumar note the interpretation of surrogate endpoint data has an impact on:

- Clinical trial design
- Research priorities
- Regulatory decisions
- Clinical practice

Conclusion

Prof. Kumar and Dr Rajkumar believe:

- For regulatory bodies considering the expansion of a drug indication, there should be an observed, or trend for improvement in, OS
- This is particularly important if the original license was granted based on surrogate endpoint data
- For regulatory bodies considering licensing a new drug, combination, or sequence of therapies, there should be in observed improvement in OS
- Depending on the unmet clinical need and how rare the disease is, surrogate endpoints may be accepted in certain scenarios

Prof. Kumar and Dr Rajkumar conclude that healthcare professionals and researchers need to be dedicated to monitoring and reporting survival data, to avoid any inaccurate conclusions being drawn.

Twitter

Dr Rajkumar shared the original article from *The Lancet* on Twitter, which has stimulated great conversation. Some of the responses have been summarized below, as direct quotes from the Twitter accounts indicated.

Dr Rajkumar (@VincentRK) questioned how a drug that significantly improves response and PFS can cause worse OS. He explained two ways this might happen:

- "Double edge sword: This happens when a drug does have efficacy, but also has serious toxicity and leads to many more deaths than the number of people helped. (In Venetoclax trial, serious toxicity & infections were identical in two arms)"
- "Wolf in sheep's clothing: This happens when the drug deceives by reducing a biomarker or by shrinking a tumor but behind the scenes it is altering underlying the disease biology in such a way that when patients do relapse, the relapse is explosive and rapidly fatal."

Rafael Fonesca, MD (@Rfonsi1): "Great editorial and thread by @VincentRK on the implications of the stop of Bellini (must read). The article highlights some of the nuances, and reminds us all that surrogate endpoints are not infallible to determine effects on OS (by a couple of mechanisms)." "The reality is sobering, but also quite nuanced. In this case we

urgently need to see the data from this trial (being cleaned & hopefully reported soon). We need to know why, how, when and where. All relevant. The answers are more complex once you consider t(11;14)"

Razelle Kurzock, MD (@DR_R_Kurzrock): "Wrong debate. It's not if surrogate endpoints can ever be wrong; of course they can. RCT can be wrong too. But are they wrong often enough to delay approval for years, with lives lost awaiting RCT. Reviews of approved drugs without RCT show vast majority fare well with time."

David Baer (@davidmbaer): "Thank you for emphasizing this important point. I am old enough to remember when PFS was introduced as a surrogate for OS in the setting of adjuvant chemotherapy for colon cancer. Extensive data supported the validity of PFS in this setting. We have since become too uncritical."

References

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3. Pharmiweb.comPharmiweb.com. AbbVie Provides Update on VENCLEXTA®/VENCLYXTO® (venetoclax) Multiple Myeloma Program. https://www.pharmiweb.com/press-release/2019-03-19/abbvie-provides-update-on-venclexta-venclyxto-venetoclax-multiple-myeloma-program [Accessed 2019 March 19]
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5. Usmani S.Z. *et al*., Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185): a randomised, open-label, phase 3 trial. Lancet Hem. 2019 Jul 18. DOI: 10.1016/S2352-3026(19)30109-7