Is Progression Free Survival the Right Endpoint for Judging the Clinical Benefit of Maintenance Rituxan following First Therapy for Indolent Lymphoma?

Here we cite our concerns with the use of Progression Free Survival (PFS) as the primary endpoint in the assessment of observation versus maintenance Rituxan following initial primary therapy with Rituxan-based chemotherapy. This commentary was motivated by the sponsor's remarks (ASCO 2010) stating *"The PRIMA study provides evidence for a new standard of care for FL patients in need of treatment."*

This commentary does not apply to other settings, such as this use of Rituxan following first or second relapse, or following Rituxan monotherapy.

Background:

The natural history of indolent b-cell lymphoma is highly variable. Survival can range from a less than a year in a small subset of patients to decades, [1] with some few reports of patients never requiring treatment – remaining asymptomatic throughout their lives.

Median survival is reported to be 8 to 14 years, depending on the center, with young age being a favorable prognostic factor. For example, Rosenberg notes a median survival of 18 years for patients treated at Stanford, but the median age was 49 years,[2] well below that of patients diagnosed with indolent lymphoma overall (SEER), about 64 years.

Clinical trials tend to recruit younger patients. For example, in the PRIMA study, the median age was "56 years (range 22-87)" [3] - therefore the interpretation and use of endpoints must be based on expectations in this age group.

Disease and patient heterogeneity makes the assessment of study protocols challenging, which is partially mitigated by the use of prognostic indicators, such as the FLIPI. In the PRIMA study the participants were reported as:

> *"21% FLIPI 0-1: 36% FLIPI 2; 43% FLIPI 3-5"*
> *(Higher FLIPI (3-5) is associated with higher prognostic risk.)*

But FLIPI is far from adequate for predicting individual outcomes, and a population with a mixed FLIPI scores further complicates the utility of FLIPI.

"Currently available clinical prognostic scores, such as the follicular lymphoma

---

[1] Dave SS, Wright G, Tan B *N Engl J Med* Prediction of Survival in Follicular Lymphoma Based on Molecular Features of Tumor-Infiltrating Immune Cells
vol. 351, 2159 - 2169, 2004

[2] Follicular lymphoma revisited. J Clin Oncol. 2008;26(4):515–516.

[3] Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy. ASCO 2010 http://bit.ly/b39mX5

international prognostic index, are not able to optimally predict transformation or poor outcome." [4]

Limits of the Survival Endpoint in Evaluating Therapies for Indolent Lymphomas

Showing a survival benefit for one therapy versus another is widely recognized as the ideal or the most reliable measure of clinical benefit, because it accounts for known and unknown treatment effects – positive and negative. However, it is not a practical endpoint for assessing therapies for indolent lymphoma, because of the long median survival of these patients. Further, on relapse the study participants will have opportunities to benefit from other therapies, which confound assessment.

Is PFS the Right endpoint for this Indication?

Progression free survival (PFS) measures time to progression, relapse, and to death from any cause; measured from the initiation of therapy or randomization. The PFS endpoint is a commonly used surrogate predicting clinical benefit in cancers; however, its significance depends on the duration of the remission period with consideration of potentially offsetting toxicities. Similar to a marathon race, an improvement in PFS does not necessarily predict improved survival (clinical benefit) … who will finish first is not necessarily the runners who leads at the first or second lap.

However, the PFS endpoint has been accepted as a valid endpoint in many cancers in order to address significant unmet clinical needs. So, as always, the context matters; this includes consideration of the natural history of the disease, and what is available to effectively treat the condition.

Here we provide reservations about PFS as the primary endpoint in this patient population: previously untreated follicular lymphoma:

(1) Achieving durable remissions, without requiring additional treatment to sustain it, is the urgent need in this population, not delaying it with regularly scheduled treatments.

Also speaking to the lack of urgency for rapid assessment about this use of Rituxan is that oncologists can use their judgment and prescribe it based on the clinical circumstances (such as poor response to induction therapy, or strong patient preference). Anecdotally, this use of Rituxan already appears to be quite common.

Further, patients have access to many effective protocols for this indication at relapse, including Rituxan used as needed, which could be as good or a better use of the study drug in the long term – which seems to be the primary clinical question about which there remains genuine uncertainty.

Consider that for this indication, treatment is not always required at first or

[4] LeBrun D, Baetz T, Foster C, et al. Predicting outcome in follicular lymphoma by using interactive gene pairs. Clin Cancer Res. 2008;14(2):478–487.

subsequent relapse, as there can be sustained periods of observation where patients will have few or no symptoms. That is, the time to relapse is not the same as time-to-being-sick, or time-to-requiring-more-treatment. (Noting that for second or third relapse, the significance of PFS could increase as the interval between therapies generally decreases with each relapse.)

(2) Concerns remain about the potential for therapy-related side effects, such as immune compromise from regularly scheduled b-cell depleting therapy, which may require more follow up time to characterize.

For example, Hypogammaglobulinemia and the need for IVIG therapy have been reported to be common in patients receiving maintenance Rituxan by an independent group. [5] Other reported risks are associated with Rituxan therapy, such as reactivation of hepatitis, the development of progressive multifocal leukoencephalopathy, and late onset neutropenia.[6]

(3) Concern remains about the potential negative impact of this use of Rituxan on response to subsequent treatment protocols, which are many times based on Rituxan. That is, will patients on a 2-year schedule of maintenance Rituxan respond as well to Rituxan-based chemo (a mainstay of therapy) when treatment is again needed, compared to those who were observed?

(4) Comparing an active drug against observation does not seem a fair test, using PFS as the primary endpoint.

Since Rituxan is reported to have a 50% response rate in relapsed follicular lymphoma, it should be expected that it will extend remissions if continued after induction therapy, compared to observation. The primary study question should address what isn't known or expected by common sense.

(5) PFS is a composite endpoint, lumping together death and progression from any cause, which begs the question: How many deaths, versus how many progressions where delayed by maintenance in this study? Further, as above, what is the clinical significance of delaying progression by maintenance in this population?

(6) Another interpretation of the PFS data in the PRIMA study is that two-thirds (66%) of the participants achieved the same results without extra treatment.

"2-year PFS 82%; 95% CI [78-86%] vs. 66% [61-70%] for observation)."

Hopefully the study data can identify biomarkers that predict responses, such

---

[5] Hypogammaglobulinemia in pts receiving rituximab immunotherapy and the impact of rituximab maintenance, ASCO 2010 http://bit.ly/9h1Tc3

[6] Rituxan Full Prescribing Document
http://www.gene.com/gene/products/information/pdf/rituxan-prescribing.pdf

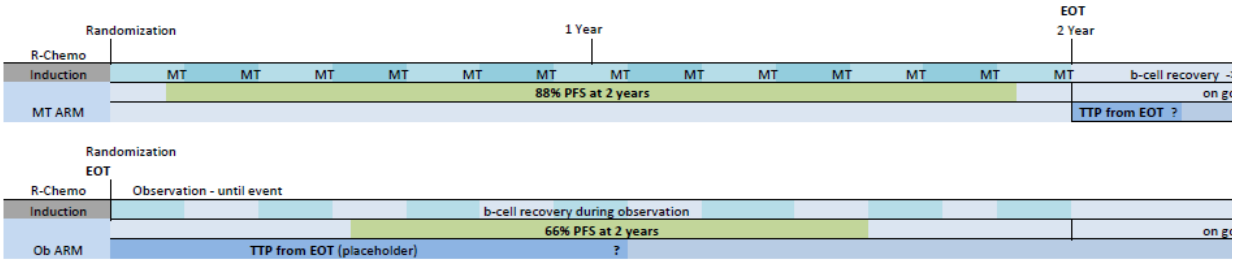
as a durable remission without maintenance. Will the sponsors ever do this kind of analysis if not required to when seeking to expand the label for approved drugs, or proposing it as the new standard of care?

Proposing Interim Endpoints to Supplement PFS

As noted, the survival and PFS endpoints each have limitations, specific to this population. Here we propose additional interim endpoints (surrogates for survival) that may allow regulators and clinical experts to accelerate the assessment of the study data with greater confidence:

A) Compare Time to Progression, measured from the cessation of therapy in both arms of the study (TTP-EOT).

Example: An advantage in TTP-EOT in the study arm, measured from end of maintenance, compared to beginning of observation in the control group, would strongly suggest that maintenance improves the quality of the remission – that it does not just mask a relapse.



Note: The Blue bar representing TTP from EOT is a placeholder in the graph above. This information was not provided in the ASCO 2010 abstract.

B) Compare Conversions of Partial Responses (PR) to Complete Responses (CR).

Example: A significantly higher percentage of conversions from PR to CRs in the maintenance arm would support the notion that that this approach provides clinical benefit, because CRs are generally associated with longer remissions and better overall survival, compared to partial responses.

C) Compare also the number of persistent Complete Responses.

Patients want to know that an aggressive initial therapy followed by maintenance therapy increases also the odds for cure, or of realizing a sustained disease free status lasting many years. An increase in the number of persistent CRs in the maintenance arm, for example, would be evidence in support of this potential.

It should be noted that some single arm studies using competing therapies (Radioimmunotherapy) show median PFS was not reached at 8 years, and a significant rate of Complete Responses continued past 12 years. (Kaminski, Kaminski, Leonard).

In Conclusion

The survival and PFS endpoints each has limitations, specific to previously untreated follicular lymphoma.

A 16% improvement in PFS for the maintenance group at two years seems insufficient to judge if it provides meaningful clinical benefit compared to observation; noting that 66% of the participants who were observed did as well at 2 years, exposed to no added toxicity, risk, or expense. That is, the data does not tell us who this protocol is for, which speaks to the need to identify biomarkers that predict response and toxicity.

In order to provide more confidence in any decisions made about the place of maintenance Rituxan in the short term, we propose the use of interim endpoints, such as Time to Progression measured from end of treatment, conversions of Partial Responses to Complete Responses, and comparisons of ongoing Complete Responses.

As always, longer follow up is needed to compare other potential long-term effects of extended b-cell depleting therapy, such as immune-related complications, incidence of transformation, and responses to subsequent Rituxan-based therapy.

We appreciate the efforts of the sponsor, and hope they will continue to follow these participants to capture, evaluate and report on survival differences and to more fully characterize the longer-term risks and benefits of maintenance Rituxan in this unique population.

Achieving durable remissions, without requiring additional treatment to sustain it, seems the more urgent need in this population, not delaying it with regularly scheduled treatments – unless the follow up data shows that the remissions are sustained to a significant degree when maintenance is discontinued.

Karl Schwartz
Patients Against Lymphoma