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Letter to the Editor

Letter to the Editor re Yu and Holmgren

Yu and Holmgren [1] argue that the traditional endpoint of progression-free survival (PFS) may not be appropriate for evaluating cytostatic agents combined with chemotherapy in cancer clinical trials. They claim that time to regrowth (measured with respect to baseline) is a more suitable measure than PFS (measured with respect to nadir tumor size) for tumors with Gompertzian growth kinetics.

However, Yu and Holmgren [1] do not appear to consider the multifactorial nature of PFS. A patient can have documented disease progression if there is a new lesion, recurrence of a lesion or death without a 20% increase in the sum of the longest diameters relative to the nadir [2]. For example, osseous metastases are often nonmeasurable. It is not clear if the definition of time to regrowth considers a new lesion or death prior to return to baseline size as an event or if the calculations in Section 5 considered these criteria. Yet, occurrence of new lesions indicative of distant metastases is the prime cause of poor prognosis in breast cancer [3,4]. Therefore, incidence of new lesions, etc. prior to return to baseline size should be classified as events because of their clinical importance.

A frequency table of the events in a PFS analysis by basis of progression ($\geq$20% increase over nadir size vs. events without such an increase (new lesions, recurrence of lesions, death)) and treatment in the referenced metastatic breast cancer study [5] may be helpful to assess the potential merits of the time to event endpoint.

It is not clear how time to regrowth is calculated for patients without any tumor shrinkage or for patients with a maximum shrinkage of 10%. Traditional PFS would require an increase to 120% of baseline and 108% of baseline.

Finally, documented disease progression is a paradigm for patient management as well as an endpoint. There often is a change in therapy after documented progression rendering a subsequent time to regrowth endpoint is difficult to interpret. Perhaps the correlation with overall survival is the most appropriate assessment of time to regrowth vs. PFS, assuming that patients remain on treatment until the later event occurs.

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William Mietlowski
Jinping Wang
Biostatistics and Statistical Reporting, Oncology Business Unit, Novartis Pharmaceuticals, East Hanover, New Jersey 07936, United States
E-mail address: William.Mietlowski@novartis.com.

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