

Surrogate end points for overall survival. *Festina lente* (more haste, less speed)

Maeda and Kurokawa's pledge for accepting surrogate end points in the Japanese regulatory to approve oncology drugs quickly in Japan could have been more balanced [1].

First, despite disease-free survival is a surrogate end point for overall survival in studies ($n = 2$) of adjuvant chemotherapy involving patients with non-small-cell lung cancers (at individual level $\rho^2 = 0.83$) and progression-free survival in those ($n = 4$) of chemotherapy and radiotherapy for patients with locally advanced lung cancers ($\rho^2 = 0.87 = 4$), the time gain is limited: 0.9–1.8 years and 3.8–6.4 months, respectively [2]. Improving delays for trial approval and for patients recruitment may be more important issues. Surrogate end point are not a panacea, they require more effort to control quality (regularity of follow-up and reliability of assessments which require independent assessment).

Second, the risk of error or of not clinically relevant benefit despite statistically significant surrogate end point cannot be ignored. This is a major concern as revocation of marketing approval is a too long time process. Bevacizumab was approved for metastatic breast cancer in February 2008 under the Food and Drug Administration's (FDA) accelerated program. Revocation waited until November 2011 as the drug was not shown to be safe and effective. Such long delay are unnecessarily costly to health care system and harmful too patient. Quicker revocation process must be a mandatory pre-requisite before considering quicker approval. We must not put the cattle before the horse.

Third, since too long drug development is on a slippery slope. From 11 December 1992, to 1 July 2010, the FDA granted accelerated approval to 35 oncology products for 47 new indications. Clinical benefit was confirmed in postapproval trials for only 26 of the 47 new indications and confirmatory trials were not carried out as requested by the Agency for 14 new indications [3]. Surrogate end points are a strategy of for-profit organizations [4]. The unsustainable rise of drug prices make this a major concern as too many new drugs have only marginal benefits, not necessarily clinically relevant over existing ones [5].

Last, surrogate end points have not been validated for trials of targeted therapy, yet.

Patients deserve relevant outcomes: overall survival and quality of life. The bar must be raised. However, surrogate end points may be relevant for independent data-monitoring committees to discontinue trials [6].

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disclosure

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Reply to the letter to the editor 'Surrogate end points for overall survival. *Festina lente* (more haste, less speed)' by Braillon

In the letter to the editor, Dr Braillon has made critical comments on using surrogate end points in clinical trials in oncology for drug approval from several viewpoints [1]. First of all, we would like to express our respect to him for giving thoughtful comments on our paper. There are some parts we agree with and some parts we don't.

First, taking lung cancer which has a poor prognosis, he pointed out that the time gain was limited by using progression-free survival (PFS) instead of survival as the end point. The time gain with PFS generally depends on estimated median survival post-progression time of each cancer type. Although it is difficult to validate PFS as the surrogate end point, the time gain