

2. Methodology tip – shapes of Kaplan-Meier plots in the Maemondo study

Wittes (48) made an observation regarding Kaplan-Meier plots where two curves, for example representing study drug arm versus placebo arm, closely track each other during most of the course of the clinical trial, but where the two curves separate distinctly from each other towards the end of the clinical trial. This situation can be found, for example, in the Kaplan-Meier plot of survival, disclosed above, for the clinical trial by Maemondo et al. (49) (Fig. 12.2). In a general comment applicable to clinical trials for any disease or with any treatment, Wittes observed that the, “large white space between the two curves does not mean a dramatic benefit (or harm) of treatment if one waits long enough but, rather, likely reflects variability arising from the small sample sizes available for analysis at the end of the study.” For this reason, investigators noticing a remarkable separation between two study arms that materializes towards the end of a clinical trial should take care to observe the significance (P value) of the separation between the two curves.

3. Methodology tips – independent radiology assessments in the Gradishar study

In a study of breast cancer, Gradishar et al. (50) divided the subjects into four arms, as shown below. Paclitaxel and docetaxel are both classed as taxanes (51).

- Arm 1. Paclitaxel at 300 mg/m², every 3 weeks;
- Arm 2. Paclitaxel at 100 mg/m², weekly;
- Arm 3. Paclitaxel at 150 mg/m², weekly; or
- Arm 4. Docetaxel at 100 mg/m², every 3 weeks.

Objective response, that is, tumor size and number as measured by the RECIST criteria, was assessed by the investigator’s radiologist and also by an independent radiologist. Data on tumor size and number were used for calculating data on the endpoint of objective response, as well as for calculating data for the endpoint of PFS.

The Gradishar study is distinguished from almost all other oncology clinical trials in that the authors published separate Kaplan-Meier plots, one representing data collected by the investigator’s radiologist, and the other representing data from the independent radiologist. A related issue is as follows. The same radiologist may make duplicate measurements of tumor size and number, where the measurements are spaced about two weeks apart. The approach of using a first examination and a confirmatory examination was used by Bedikian et al. (52) and by Tarhini et al. (53) for example. The principal

⁴⁸ Wittes J. Times to event: why are they hard to visualize? *J Natl Cancer Inst.* 2008;100:80–81.

⁴⁹ Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *New Engl J Med.* 2010;362:2380–2388.

⁵⁰ Gradishar WJ, Krasnojon D, Cheporov S, et al. Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol.* 2009;27:3611–3619.

⁵¹ Woodward EJ, Twelves C. Scheduling of taxanes: a review. *Curr Clin Pharmacol.* 2010;5:226–231.

⁵² Bedikian AY, Millward M, Pehamberger H, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol.* 2006;24:4738–4745.

⁵³ Tarhini AA, Kirkwood JM, Gooding WE, Cai C, Agarwala SS. Durable complete responses with high-dose bolus interleukin-2 in patients with metastatic melanoma who have experienced progression after biochemotherapy. *J Clin Oncol.* 2007;25:3802–387.