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Effect of dose reductions on clinical outcomes, or of outcomes on dose reductions?

Ismail et al. [1] conclude palbociclib dose-reductions didn't lead to poorer outcomes—time to next treatment or overall survival—of advanced breast cancer patients. The endpoints were defined from first palbociclib prescription date. One-third of patients had dose-reductions (median 69 days; interquartile range, 36—152).

Unfortunately this is a classic case of guarantee-time bias [2]. The Kaplan-Meiers (Fig. 3) have the tell-tale sign: "Yes dose-reduction" subgroup curves plateau at 100% for an extended period. Any analysis assuming dose-reduction subgroups were known at palbociclib prescription (time zero) is biased, here, the longer on treatment the greater chance to have dose-reduction.

Imagine patients' data revealed dynamically using swimmers plot; x-axis is time since palbociclib prescription. At time zero, there's no ordering of patients' swimmers bars. As cycles proceed, the bar of any patient experiencing dose-reduction dynamically jumps to the top of the plot forming the "dose-reduction subgroup." While remaining on treatment, a patient's bar has continued opportunity to join that subgroup. Once treatment stops for any reason—including severe AEs leading to treatment cessation and rapid disease progression—it's no longer possible to join that subgroup. A landmark analysis [3] is one alternative approach which could (should) have been conducted for an unbiased answer the authors research question.

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Declaration of competing interest

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