Testing treatment effect when hazards are non-proportional

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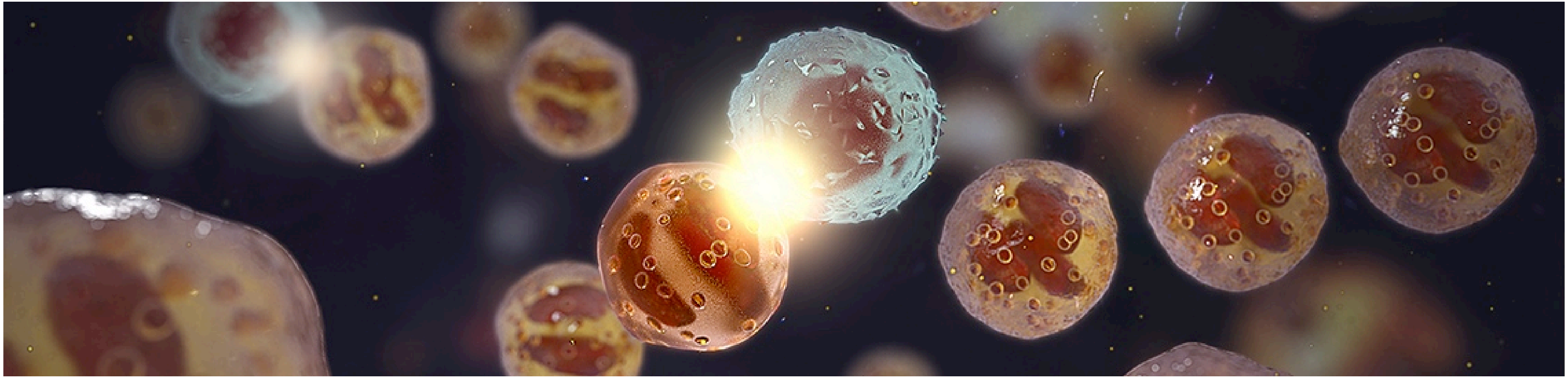
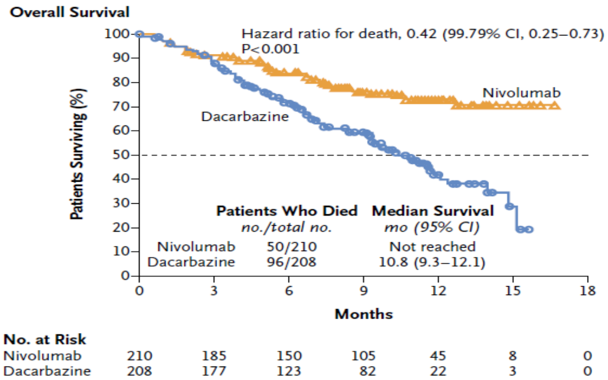
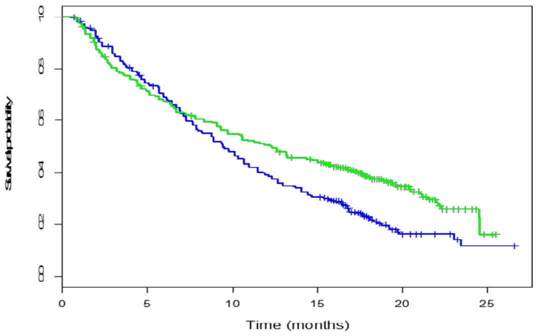


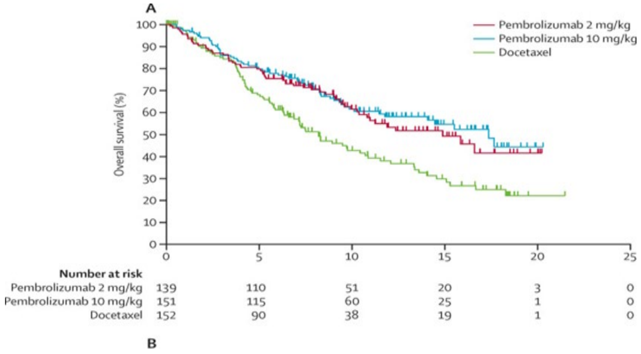
Recent IO trials have brought the concept of NPH in the forefront….



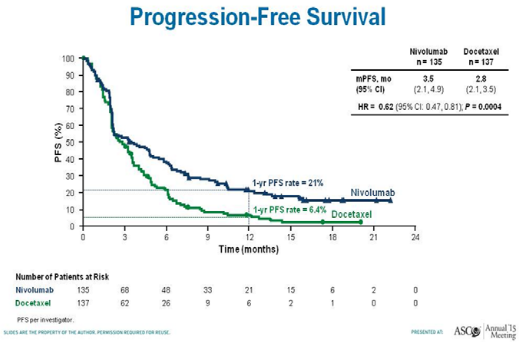
OS: Nivo in melanoma



OS: Nivo in NSCLC

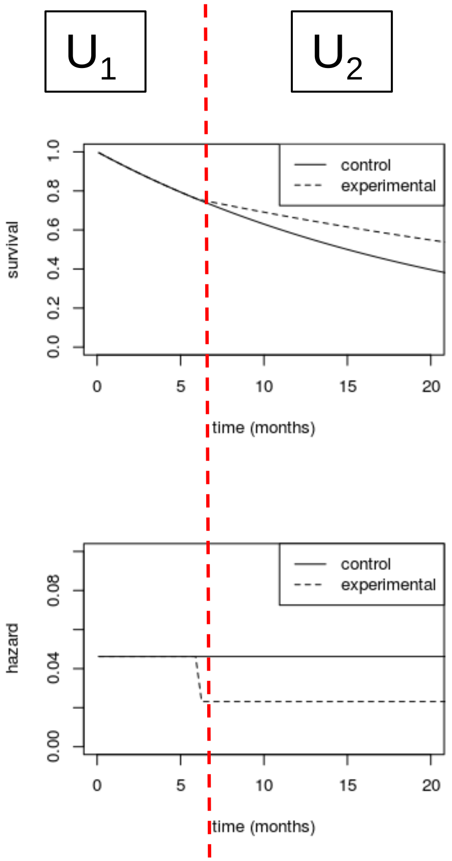


OS: Pembro in NSCLC



PFS: Nivo in NSCLC

Log rank test



$$U_1 = \sum_{t_i<6} O_{Ci} - EC_i$$

$$U_2 = \sum_{t_i>6} O_{Ci} - EC_i$$

The log-rank statistic, $U = U_1 + U_2$, may have very low power because $E(U_1) \approx 0$.

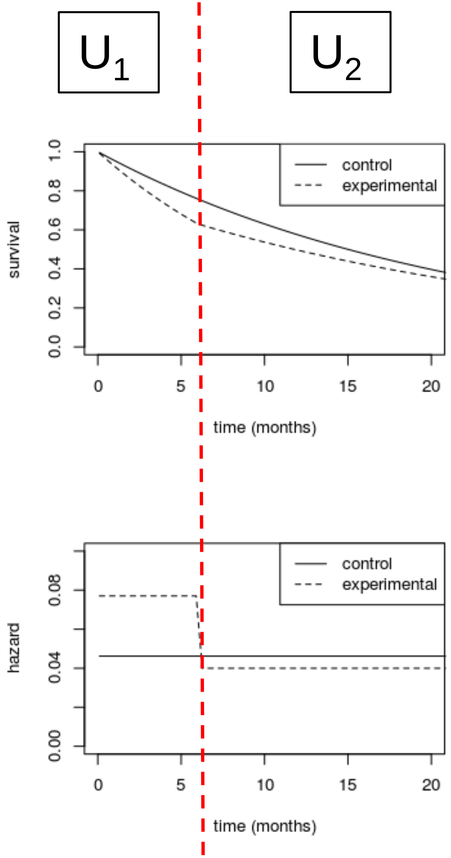
Since we expect $E(U_2) > 0$, there has been interest in using a weighted log-rank statistic, e.g.,

$$U_W = 0 \times U_1 + 1 \times U_2,$$

and claim a significant positive result when e.g.,

$$U_W / se(U_W) > 1.96.$$

Weighted log-rank test



The problem is that we can find situations where $E(U_2) > 0$, yet survival on the experimental arm is worse at all time points.

In this case pr($U_W / se(U_W) > 1.96$) may far exceed 2.5%.

We have proposed a "modestly weighted log-rank test" that avoids this problem but still manages to improve power over the standard log-rank test in delayed effect scenarios.

Magirr, D., & Burman, C. F. (2018). Modestly Weighted Logrank Tests. *arXiv:1807.11097*.

Discussion points

Which null hypothesis should we consider: $S_E(t) = S_C(t)$ or $S_E(t) \leq S_C(t)$?

Should hypothesis testing and estimation match up, or is it acceptable to use different approaches?