Meaningful progress in the therapy of neuroendocrine cancers, needs rigorous interpretation of data and balanced trial designs

Tito Fojo, MD, PhD - Columbia University and James J. Peters VAMC

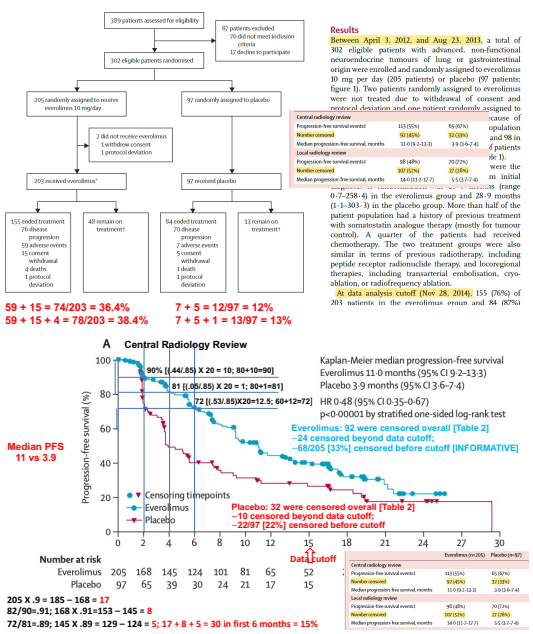
Background/Significance

While Kaplan–Meier (KM) plots provide a solution to one of the most common problems in medical studies, that of incomplete follow-up, they are based on a key and very restrictive assumption. The assumption is that censoring is only determined by a random entry time and a fixed follow-up schedule, not by patient prognosis. Stated differently, censoring is assumed to be, and indeed must be, non-informative, meaning that an individual censored at a time has a prognosis that is identical to those of all other patients who are alive at that time but not censored. In everolimus trials this assumption has been consistently violated.

Material and Methods

Published studies reporting results for everolimus in neuroendocrine cancers in RADIANT 2 (R2), RADIANT 3 (R3), and RADIANT 4 (R4), were evaluated. CONSORT diagrams in the primary or a subsequent publication were examined to inform rates of treatment discontinuation for adverse event and consent withdrawal. Kaplan Meier graphs were analyzed using a validated methodology to estimate the rates of censoring throughout the trial, important information that unfortunately was not provided for R2, R3 or R4 but could be estimated. Toxicity tables were examined and compared across all three trials. OS results for R2 and R3 were available as full publications, but for R4 had not achieved statistical significance at the second interim analysis published as an abstract five years ago, have never been updated, cannot be found in ClinTrial.gov and presumably did not show statistical superiority for everolimus. Trial enrollment and data lockdown dates were provided for only R4 but could be inferred for the others. The efficacy of peptide receptor radionuclide therapy (PRRT) with Lutathera® was assessed in published reports and recently updated information presented in abstract form at the ASCO 2021 meeting.

Impact Statement I provide a viewpoint supported by analysis of the published data that is shared by many but not often discussed. In my opinion, the hesitancy to discuss these issues openly has impacted the progress of therapy for NECs. The effort with everolimus has been disproportionate to any marginal benefit it has provided but sadly reflects the reality that pharmaceutical support is needed to conduct clinical trials. That we lack data for the several chemotherapy options that are used, all of which are far more effective than everolimus, underscores this unfortunate reality. With Lutathera we now see a rush to its earlier and earlier deployment despite our lack of robust data. There is no doubt this is an effective therapy at some level, but it likewise suffers from decades of experience in Europe with less-than-optimal data collection and critical analysis. My opinion expressed here informs my discussions with my patients.



Figures – [Above] Analysis of data from R2/R3/R4 show that reported PFS gains have been largely not real gains, but rather apparent gains driven by informative censoring. Rates of **informative censoring** with everolimus, amongst the highest in randomized trials, approach nearly 40%, occur early and contrast with rates in control arms of ~12%. The higher rates of informative censoring with everolimus are driven by toxicity, with burden likely greater in the infirm with more advanced disease, an outcome that favors a toxic therapy by censoring before progression those likely to do poorly. Because RADIANT 4 provides essential information of enrollment period and data analysis cutoff date, one can with good accuracy estimate the number censored using both the data presented and the number censored at each time, leveraging the KM plot and the number at risk. 36% of patients randomized to everolimus discontinued study participation for AEs or "consent withdrawal" compared with only 12% of those randomized to placebo, numbers very similar in all studies. 33% were censored before data cutoff and censoring can thus not be ascribed to data cutoff. Half of these were censored in the first six months of the study.

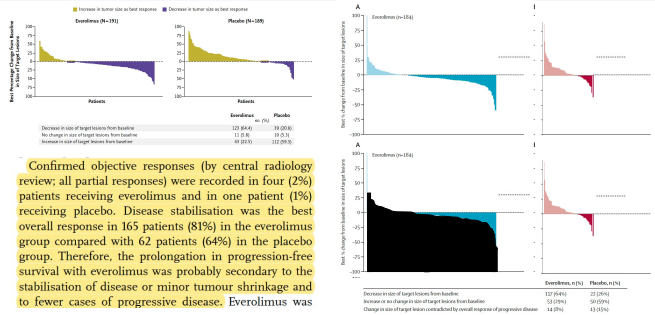


Figure – ORRs on all everolimus arms have been <2%, and waterfall plots fail to convince clinicians who know transient decreases of a few percent in tumor burden is not meaningful to patients. The latter is underscored by the comparison on the left. Black shows not how much tumor has disappeared but how much remains after treatment – remembering as in all waterfall plots this is the "best result". The prognosis depends not on what was eliminated but on what remains [a lot] and how fast it grows.

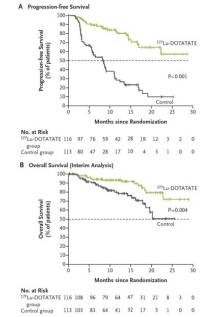


Figure – Left - For example, the failure of Lutathera® to score on OS in an updated analysis despite an impressive "initial survival advantage" can be ascribed to lack of a balanced trial design. Randomizing a patient whose disease was progressing on octreotide LAR to merely a higher and likely ineffective dose of the same – an approach few would endorse and has no support in guidelines – meant a meaningful fraction of the control arm was assigned a therapy without realistic expectation of benefit at a time disease was progressing and other therapies such as CAPTEM would have been indicated. This imbalance led to rapid progression and more early deaths in the control arm, exaggerating the PFS advantage and impacting the OS analyses.

CONCLUSIONS:

Gains in the therapy of NECs have been wanting because of poor trial result interpretation and design. Very few patients achieve meaningful benefit from everolimus but nearly all encounter quality-of-life altering toxicity. The latter is often managed with dose reductions that sometimes ameliorate but never eliminate toxicity at doses whose efficacy is unproven and likely non-existent. PRRT with Lutathera® in its pivotal trial benefited from a control arm many would have predicted would be ineffective and could lead to imbalance in the rates of PFS and OS. An ORR of 18% means responses can be expected but durability remains to be defined. Additionally, the timing of its administration in the course of disease is unsettled but certainly not as early as sometimes used. Meaningful progress in the therapy of neuroendocrine cancers, will need rigorous interpretation of data and balanced trial designs. It will also require strategies that limit informative censoring in outcomes assessment.

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