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

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.

Results
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 greater in the infirm with more advanced disease, an outcome that favors a toxic therapy by censoring before progression those likely to do poorly. Emphasis in published reports on G3/4 toxicities is misleading since it ignores the burden of continuous G1/2 toxicities in daily therapy that often lead to drug discontinuation and was likely responsible for informative censoring in these trials. 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. In addition to the noted informative censoring, there was also a concerning increase in censoring in the control arm upon central review compared to investigator assessment. This

occurred early in the trial and suggests investigators scored control arm patients as having disease progression at a rate higher than actual. And, finally, an inexplicable high rate of censoring in the overall survival analysis unrelated to data lockdown in R4, a very rare occurrence, is unexplained. In the more recent Lutathera® trial, design flaws are also of concern. 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. This has led to loss of the survival advantage on longer follow-up, an evolution also likely impacted by the poor chemotherapy tolerance often seen following PRRT, limiting the utility of post-Lutathera® options.

Conclusion

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.

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.

Lay Abstract

I believe poor interpretation of clinical trial results and poor trial design have hindered progress in the therapy of neuroendocrine cancers (NECs). To date no randomized trial of everolimus has achieved statistically meaningful prolongation of survival - not only in NECs, but also in renal cell carcinoma and breast cancer, where everolimus is now rarely used. Regulatory approvals in these three cancers were granted for a controversial regulatory endpoint that looks at how rapidly disease progresses – but were never rescinded even though a survival advantage was never achieved. So, you might ask how can a therapy delay the progression of the cancer but not impact the patient's survival from their cancers? The answer lies in the way we analyze data, especially the way we analyze data on how rapidly a cancer progresses on a therapy. We do this using Kaplan–Meier (KM) plots that provide a solution to one of the most common problems in medical studies, that of incomplete follow-up. KM analyses allow you to analyze incomplete data but only if you comply with very restrictive assumptions that unfortunately everolimus trials have consistently violated. Regulatory agencies – FDA, EMA, others – are generally very good but with rare cancers can be downright flawed and missed this. 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 may ameliorate but never eliminate toxicity at doses whose efficacy is unproven/likely non-existent. And as regards PRRT with Lutathera®, its pivotal trial benefited from a control arm many would have predicted would be ineffective and could lead to imbalance. This therapy is effective in a fraction of patients but the timing of its administration in the course of disease is unsettled, and its survival benefit undefined. I have spent my career analyzing clinical trial data, published on this extensively in excellent peer-reviewed journals and feel I am qualified to provide a viewpoint supported by analysis of the published data. I also know that my viewpoint 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.

References

1. Inappropriate censoring in Kaplan-Meier analyses. Fojo T, Simon RM.Lancet Oncol. 2021; 22:1358-1360. PMID: 34592177
2. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Statist Assoc. 1958; 53:457–481
3. Simon R and Wittes RE. Methodologic Guidelines for Reports of Clinical Trials Cancer Treatment Reports. 1985; 69:1-3. PMID: 3967252
4. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, Klimovsky J, Lebwohl D, Jehl V, Wolin EM, Öberg K, Van Cutsem E, Yao JC; RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011; 378:2005-2012. PMID: 22119496.
5. Pavel ME, Baudin E, Öberg KE, Hainsworth JD, Voi M, Rouyrre N, Peeters M, Gross DJ, Yao JC. Efficacy of everolimus plus octreotide LAR in patients with advanced neuroendocrine tumor and carcinoid syndrome: final overall survival from the randomized, placebo-controlled phase 3 RADIANT-2 study. Ann Oncol. 2017; 28:1569-1575. PMID: 28444114
6. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG, Tomassetti P, Pavel ME, Hoosen S, Haas T, Lincy J, Lebwohl D, Öberg K; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011; 364:514-23. PMID: 21306238
7. Yao JC, Pavel M, Lombard-Bohas C, Van Cutsem E, Voi M, Brandt U, He W, Chen D, Capdevila J, de Vries EGE, Tomassetti P, Hobday T, Pommier R, Öberg K. Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Overall Survival and Circulating Biomarkers From the Randomized, Phase III RADIANT-3 Study. J Clin Oncol. 2016; 34:3906-3913. PMID: 27621394
8. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, Tomasek J, Raderer M, Lahner H, Voi M, Pacaud LB, Rouyrre N, Sachs C, Valle JW, Fave GD, Van Cutsem E, Tesselaar M, Shimada Y, Oh DY, Strosberg J, Kulke MH, Pavel ME; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016; 387:968-977. PMID: 26703889.
9. Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi GN. Everolimus in Postmenopausal Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2012; 366:520-9. PMID: 22149876
10. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D, Ravaud A; RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008; 372:449-56. PMID: 18653228