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viewpoint

Neuroendocrine Tumours: Revised Strategies from New Trial Data

Viewpoint based on presentations from the
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Introduction

NET is a term for a genetically diverse group of solid tumours arising from secretory cells of the neuroendocrine cell system. The incidence and prevalence have been growing over the past several decades, possibly due to improved surveillance. In Canada, the incidence has climbed to about 6 per 100,000 individuals (Hallet J *et al. Cancer* 2015;121:589-97). NETs most commonly occur in the GI tract but can occur in other tissue, such as the pancreas and the lung. In the GI tract, the NET incidence is greater than the combined incidence of tumours in the stomach and oesophagus (Yao JC *et al. J Clin Oncol* 2008;3063-72). Treatment options for NETs are expanding with new clinical trials.

Three recently completed and reported phase III randomized and controlled trials evaluating treatments for neuroendocrine tumours (NETs) provide a context for re-evaluating optimal management of these malignancies. The three trials were presented at the most recent European Cancer Congress (ECC) held in Vienna, Austria (September 25-29, 2015). In the first trial, RADIANT-4, everolimus was demonstrated to prolong progression-free survival (PFS) in non-functional NETs occurring in the lung and the gastrointestinal (GI) tract. In the NETTER-1 trial, a radiolabeled somatostatin analogue (SSA) demonstrated efficacy in mid-gut NETs when compared to dose escalation of SSA in patients progressing on standard dose SSA. In the third trial, TELESTAR, a novel therapy was found effective in relieving diarrhoea induced by NET-associated carcinoid syndrome, providing a basis for a likely new drug approval.

First Phase 3 Trial to Include Lung NETs

Everolimus, an oral mTOR inhibitor, is currently one of the approved treatments for pancreatic NETs. The RADIANT-4 (Yao JC *et al.* Abstract LBA5), study compared everolimus to placebo in patients with progressive, metastatic NET originating in the lung or GI tract. Relative to placebo, everolimus was associated with a significant improvement in the primary endpoint of PFS. This was accompanied by an encouraging but not yet statistically significant improvement in overall survival (OS). RADIANT-4 suggests indications for everolimus should be expanded beyond pancreatic NET to include those in both the lung and the GI tract. Importantly this study was the first study to establish an effective treatment for Lung NETs.

In the second study, called NETTER-1 (Ruszniewski P *et al.* Abstract LBA6), which, like RADIANT-4 was a highlight at the ECC, the study agent was a SSA radiolabelled with ^{177}lutetium. This agent, known as ^{177}Lu-DOTATATE (Lutathera), is a member of a treatment class known as peptide receptor radionuclide therapy (PRRT). To date there have been no randomized trials of PRRT and all evidence has been retrospective case series. Patients with metastatic midgut NETs that progressed on standard dose SSA were randomized to receive ^{177}Lu-DOTATATE concurrent with octreotide LAR 30 mg every 28 days or to a dose escalation of octreotide LAR of up to 60 mg every 28 days. The combination of PRRT with standard octreotide displayed a superior PFS although the dose escalation arm had a PFS of 8.6 months. Again, like everolimus in RADIANT-4, ^{177}Lu-DOTATATE was associated with a promising but not yet statistically significant improvement in OS.

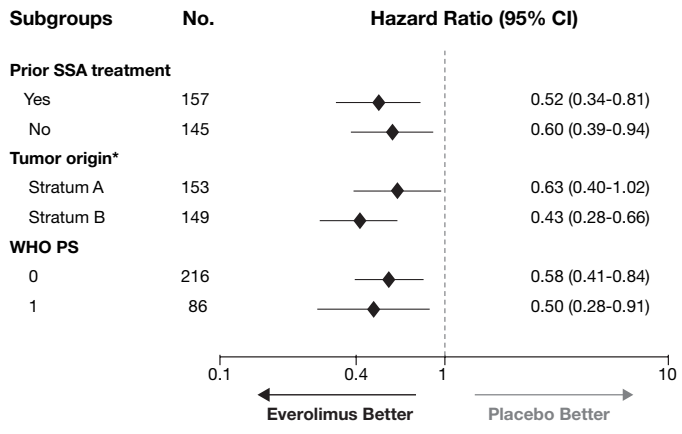
Both studies provide data valuable for guiding therapeutic choices in NET and may best be considered

to be complementary in expanding an evidence-based approach to treatment. In patients with a midgut NET, a subset of those treated in RADIANT-4, both everolimus and ^{177}Lu-DOTATATE may eventually be needed to prolong disease control. However, it is important to recognize differences in how these therapies are administered and where they have demonstrated benefit.

RADIANT-4: Design and Results

In RADIANT-4, 302 patients with advanced non-functional NET in the lung or GI tract were enrolled at centres in more than 20 countries including Canada, which provided 7 study centre sites and was a major recruiter for this trial. They were randomized in a 2:1 ratio to everolimus, which inhibits mTOR, a known molecular pathway of NET progression, or placebo. Everolimus was administered orally in a once-daily dose of 10 mg. The primary tumour site was the lung in 31%, ileum in 23%, and rectum in 12%. Other primary sites included the jejunum, stomach, duodenum, and colon. Slightly over half (53%) of patients had been previously treated with a SSA and slightly more than a quarter (26%) had previous treatment with chemotherapy.

Figure 1. Consistent PFS HR by Stratification Factors, Central Review

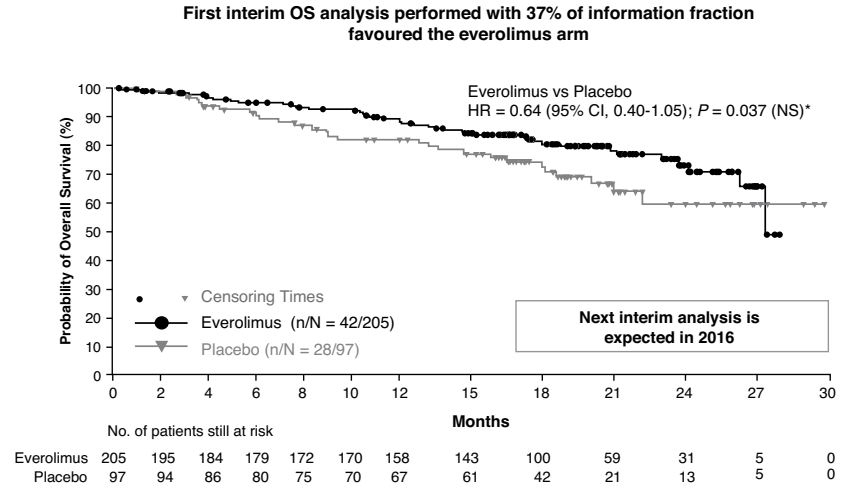


*Based on prognostic level, grouped as: **Stratum A** (better prognosis) - appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary site).
Stratum B (worse prognosis) - lung, stomach, rectum,and colon except caecum).

Hazard ratio obtained from unstratified Cox model.
NET, neuroendocrine tumours; SSA, somatostatin analogues;
WHO PS, World Health Organization performance status.

Adapted from Yao JC *et al.* ECC Abstract LBA 5.

Figure 2. Interim Overall Survival Analysis



**P*-value boundary for significance = 0.0002.
P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.
NS, not significant.

Adapted from Yao JC *et al.* ECC Abstract LBA 5.

The median PFS was 11.0 months for everolimus versus 3.9 months for placebo, producing a hazard ratio (HR) of 0.48 (P<0.00001) or a 52% reduction in the relative risk of progression or death. This large improvement in PFS was consistent whether or not patients received prior SSA therapy, had primary tumours in the lung or GI tract, or when comparing primary tumours for sites with a better or worse outcome (strata A and B, respectively) (See Figure 1).

The RADIANT-4 trial was designed with an endpoint of PFS. The interim OS analysis was encouraging with an HR of 0.64, but the P value for the advantage of everolimus over placebo (P=0.037) did not reach the prespecified level of statistical significance for this interim time point (See Figure 2). The next interim analysis for OS is planned in 2016. Tumour shrinkage of some degree was observed in 64% of everolimus patients versus 26% of patients randomized to placebo. Disease control was observed in 82.4% of those randomized to everolimus.

Adverse Events in RADIANT-4

Everolimus was generally well tolerated in RADIANT-4. Although grade 3 or higher adverse events were more common in those treated with the mTOR inhibitor relative to placebo, the only events occurring at this level of severity in 5% or more of patients were stomatitis (9% vs. 0%), diarrhoea (7% vs. 2%), and infections (7% vs. 0%). Other common side effects occurring at lower grades included

fatigue (31% vs. 24%), peripheral oedema (26% vs. 4%), and rash (27% vs. 8%).

The findings of RADIANT-4 are consistent with a substantial body of evidence that activation of the mTOR pathway is a factor in the pathogenesis of NET (Chan J and Kulke M. *Curr Treat Options Oncol* 2015;15:365-79). In the phase 3 double-blind RADIANT-2 trial, for example, everolimus was compared to placebo in patients with advanced NET associated with carcinoid syndrome when both groups were treated with octreotide (Pavel ME *et al. Lancet* 2011;378:2005-12). The addition of everolimus was associated with a 5-month increase in median PFS (16.4 vs. 11.3 months; *P*=0.026). In the RADIANT-3 trial, the pivotal study establishing the benefit of everolimus in pancreatic NET (Yao JC *et al. N Engl J Med* 2011;364:514-23), everolimus more than doubled PFS relative to placebo.

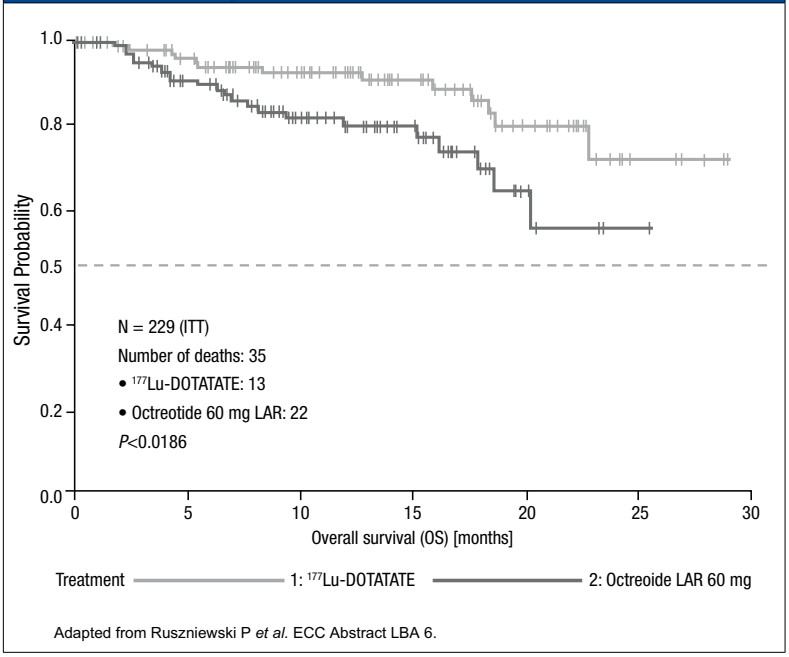
NETTER-1: Design and Results

In NETTER-1, 229 patients with metastatic inoperable well-differentiated functional or non-functional progressive midgut NETs progressing on standard dose SSA were randomized at centres in 11 countries primarily in Europe. The 116 patients in the experimental arm were planned to receive four injections of ^{177}Lu-DOTATATE every 8 weeks plus 30 mg of octreotide LAR. Patients in the "control arm" received a dose escalation of up to 60 mg of octreotide every 4 weeks. More than 80% of patients had metastases in the liver and more than 60% in the lymph nodes. Bone or lung metastases were each observed in about 10% of patients.

The median PFS has not yet been reached in the ^{177}Lu-DOTATATE group but was 8.4 months on high-dose octreotide. This translated into a HR of 0.209 (*P*<0.0001) or a nearly 80% reduction in the risk of progression or death. On the basis of initial calculations the median PFS on ^{177}Lu-DOTATATE may approach 3 years. The relative advantage was reflected in the objective tumour response rates, which reached 19%, including 1 complete response (CR) in the ^{177}Lu-DOTATATE group versus 3% (*P*<0.0004) for octreotide alone. Progressive disease was observed in 4% of those randomized to ^{177}Lu-DOTATATE versus 24% on high-dose octreotide.

The OS interim analysis in NETTER-1, like that of RADIANT-4, was encouraging. The curves separated within several months of treatment initiation (See Figure 3). However, as in RADIANT-4, the *P* value for the difference (*P*<0.0186) did not reach the prespecified definition of significance for this interim time point. It is notable that of the 35 deaths that have occurred so far in NETTER-1, 22 were in the high-dose octreotide group versus 13 in the group randomized to ^{177}Lu-DOTATATE. It should be noted that the NETTER-1 trial only included midgut patients as opposed to the broader range of GI and Lung NET patients in the RADIANT-4 trial.

Figure 3. **Overall Survival (interim analysis)**



Adapted from Ruszniewski P *et al.* ECC Abstract LBA 6.

Adverse Events in NETTER-1

The rate of adverse events related to treatment was higher in the ^{177}Lu-DOTATATE group (86% vs. 31%), as was the rate of serious treatment-related adverse events (9% vs. 1%) Discontinuations due to adverse events occurred in 5% of those randomized to ^{177}Lu-DOTATATE. Most of the serious adverse events were haematological, including 3 cases of lymphocytopenia and one case each of thrombocytopenia, neutropenia, and pancytopenia. There was one case of renal failure and two cases of acute kidney injury as well as one case of portal hypertension.

In Canada, only a few centres have the capacity to deliver PRRT. For patients not in proximity of these centres, the requirement for repeated courses may be a burden. While it is unclear which therapy should be considered first line in metastatic midgut NET, the very different mechanisms of everolimus and ^{177}Lu-DOTATATE introduce the possibility that one therapy could be employed after the other in the event of progression.

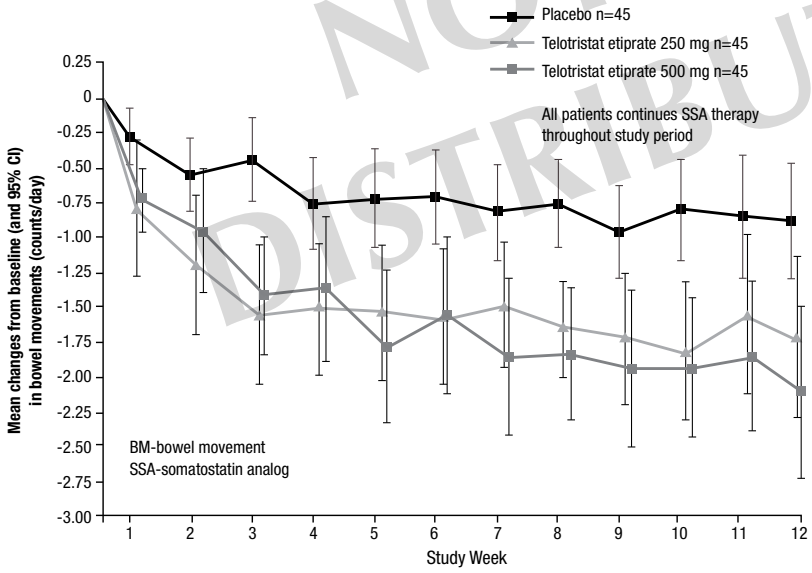
Trial in NET-Associated Carcinoid Syndrome

A third advance in the management of NET was provided by a phase 3 trial with telotristat etiprate (TE), a novel therapy that inhibits tryptophan hydroxylase (TPH). TPH is a rate-limiting enzyme that converts tryptophan to serotonin in the NET cell. Overproduction of serotonin is the major mechanism of NET-induced carcinoid syndrome. In the trial, called TELESTAR (Kulke M *et al.* Abstract LBA37), the primary objective was to reduce frequent bowel movements (BM), a complication along with diarrhoea, flushing, abdominal pain, and heart valve damage, that characterizes carcinoid syndrome.

In the study, 135 patients with metastatic NET and at least four BM per day despite a stable dose of SSA were randomized to 250 mg TE, 500 mg TE, or placebo; all were given three times daily while continuing SSA. The double-blind study was conducted over 12 weeks. Secondary objectives included change in cutaneous flushing episodes, abdominal pain, and urinary excretion of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA).

At week 12, the reduction in the mean number of BMs was 17% on placebo, 29% on 250 mg TE, and 35% on 500 mg TE. The reduction in BM frequency was durable over the course of the study (See Figure 4). The proportions achieving at least a 30% BM frequency reduction for at least 50% of the time on study were 20%, 44%, and 42%, respectively. The reductions in BM were supported by reductions in 5-HIAA, for which the median baseline level was 87.6 mg/24 hours and fell to approximately 30 mg/24 hours on both TE dosages ($P<0.001$). There was no significant reduction in flushing or abdominal pain, but <40% of patients had significant levels of either of these symptoms at study entry.

Figure 4. **Reduction in Daily Bowel Movement Frequency Averaged over Double-blind Treatment Phase**



Hodges-Lehmann estimator of treatment differences estimated a reduction versus placebo of
–0.81 BMs daily for telotristat etiprate 250 mg dose ($P<0.001$)
–0.69 for telotristat etiprate 500 mg dose ($P<0.001$)

Adapted from Kulke M et al. ECC Abstract LBA 37.

Adverse Events in TELOSTAR

Although there was a higher proportion of patients with treatment-related adverse events on the highest dose of TE (68.9%) versus the lower dose (33.3%) or placebo (26.7%), serious treatment-related adverse events were rare in all groups, and discontinuation due to adverse events was actually lower on either dose of TE than on placebo (6.7% for both vs. 13.3%).

These data support TE for the management of NET-induced carcinoid syndrome. Submission of these data for regulatory review for the approval of TE is expected.

Conclusion

The RADIANT-4 and NETTER-1 trials both introduce new exciting treatment options for NETs and immediately expand evidence-based data for the management of NET. As mentioned above, the RADIANT-4 trial is the first trial to show an effective treatment for Lung NETs. This certainly has been an exciting year for NETs. □

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