Neuroendocrine Tumours (NETs) are a heterogeneous group of neoplasms whose incidence has increased significantly in recent years, and whose optimal management remains controversial. We report the latest innovations in their management, in particular the results of three trials concerning the use of the mammalian target of rapamycin (mTOR) inhibitor, everolimus, in non-functional NETs of lung/gastrointestinal (GI) origin, the first randomised trial of radiolabelled 177Lu-DOTATATE in patients with mid-gut NETs, and the use of the 5-HT synthesis inhibitor, telotristat etiprate, in patients with the carcinoid syndrome.

Abstract
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Keywords
Neuroendocrine tumours, treatment, everolimus, 177Lu-DOTATATE, 5-HT synthesis inhibitor, telotristat etiprate

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Neuroendocrine tumours (NETs) represent a heterogeneous group of neoplasms that originate from different types of neuroendocrine cells throughout the body.1 While previously considered to be relatively uncommon, their overall incidence has been reported as increasing for reasons which are unclear.2–4 Surgery is the only truly curative therapy, but there are now a variety of other treatment options although their specific use and sequencing remains controversial.5 However, somatostatin analogues (SSAs), particularly the long-acting formulations of octreotide and lanreotide, are highly effective for symptomatic patients with secretory syndromes, and recent studies have also shown their ability to retard tumour progression in the PROMID, CLARINET and RADIANT-2 trials.5,6 The multi-ligand SSA pasireotide was also shown to control the symptoms of carcinoid syndrome in patients with advanced NETs refractory/resistant to octreotide long-acting release (LAR) therapy.7 Recently, at the European Cancer Congress (ECC) of the European Society for Medical Oncology (ESMO) in Vienna, in September 2015, three trials were presented which provide novel data on therapeutic options.

Previous studies have demonstrated the efficacy of everolimus, an inhibitor of mammalian target of rapamycin (mTOR) (a serine–threonine kinase that stimulates cell growth, proliferation and angiogenesis)8–10 to slow tumour progression of pancreatic NETs (RADIANT-3)11 and symptomatic mid-gut tumours (RADIANT-2).12 RADIANT-4 was a placebo-controlled, double-blind, phase III study carried out in 13 European centres on the efficacy and safety of everolimus in patients with advanced, progressive, non-functional NETs of the lung and gut.13 Non-functional NETs are often diagnosed later when the cancer has become advanced, and at present there are limited treatment options available. This is particularly important for patients with lung carcinoids, as there is currently no approved treatment for such patients. The trial included 302 patients in which the patients were randomised (2:1) to everolimus (10 mg/d) or placebo and were stratified by tumour origin, World Health Organization performance status and prior SSA treatment. There was a statistically significant 52% reduction in the relative risk of progression or death in favour of everolimus, with a clinically relevant 7.1-month prolongation of progression-free survival (PFS) compared with those who had taken placebo. In addition, everolimus was well tolerated and its established safety profile confirmed.

Over many years, peptide receptor radionuclide therapy (PRRT) using radiolabelled octreotide has been extensively used for the treatment of progressive NETs, and while individual results have been encouraging, there has been no formal assessment of such therapy. For most NETs, molecular-targeted radiation therapy involves the systemic administration of a radiolabelled peptide designed to target somatostatin receptors on tumour cells with high affinity and specificity.14 Over the past 15 years, PRRT with the radiolabelled somatostatin receptor agonist, such as 90Y-DOTATOC, 177Lu-DOTATATE and 177Lu-DOTATOC, have been successfully used to target metastatic and inoperable NETs.15–17 Now, Strosberg and colleagues have presented data from the NETTER-1 trial,18 a phase III multicentre, stratified, open, randomised, controlled trial evaluating the efficacy of 177Lu-DOTATOC (90Y-DOTATATE or lutathera) against placebo in patients with metastatic and progressive mid-gut, non-functional NETs progressing on SSA therapy. The trial recruited 230 patients from 35 sites in eight European countries and 15 centres in the US, with grade 1–2 mid-gut NETs. Patients were randomised to receive either
at the ECC meeting, Kulke and colleagues presented the results of TELESTAR,21 a pivotal phase III global clinical trial evaluating the efficacy of TE in treating patients with CS inadequately controlled by SSA therapy. This trial included 135 patients with metastatic NETs and inadequately controlled CS (≥4 daily BMs on SSA therapy) who were randomly assigned to receive TE (250 or 500 mg) or placebo while continuing SSA over a 12-week double-blind period. The primary objective was met, with at least a 30% reduction in BM frequency for ≥50% of the time on study in 20%, 44% and 42% on placebo, TE 250 mg three times daily (tid) and TE 500 mg tid, respectively (p=0.040 for both TE doses versus placebo). Secondary objectives including changes in urinary 5-HIAA, cutaneous flushing episodes and abdominal pain were met for both dosage regimes, but reductions in flushing and abdominal pain were not statistically significant. Thus, TE appears to be a new approach to the treatment of the CS, which is generally safe and well tolerated, and represents a promising new class of therapy for patients who have metastatic NETs with CS not controlled by SSAs.

How do these new studies alter our approach to patients with NETs? It would seem that everolimus can retard the progression of all NETs regardless of their origin or functional status, although the tumours are generally stabilised rather than shrunken, and it is unclear as to when this therapy should be initiated and how robust is its long-term efficacy. For PRRT, we have long considered this may be of value: it is now reassuring to see this confirmed in a formal study, and it is hoped that Lutathera will soon become commercially available. However, the sequencing of such treatments, and the costs of their administration, remain problematic matters. Finally, it will be very useful to have TE added to our armamentarium of agents for CS-associated symptoms; while its therapeutic efficacy is perhaps not as major as one might have anticipated, the possible effects on avoiding or minimising mesenteric fibrosis and cardiac valvular dysfunction remains an exciting possible innovation.22

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