unwanted toxicities and economic and other costs associated with anti-PD1 adjuvant therapy. Existing and future candidate prognostic biomarkers must be integrated into the design of future randomised controlled trials.[10] Candidate biomarkers should not be used to select patients for adjuvant therapy without validation in prospective randomised controlled trials or at least well designed and controlled analyses using biospecimens from completed randomised controlled trials. More effort should be invested towards predictive biomarkers, which would allow clinicians to treat only those predicted to benefit from adjuvant therapy where promising candidates exist.[10]

Finally, for surgically resected melanoma, there is a need to limit adjuvant therapy to patients who have a higher risk of relapse and death and a higher likelihood of deriving benefit. This must be the focus of future adjuvant trials rather than casting the net even broader to treat more patients, which has been the trend.

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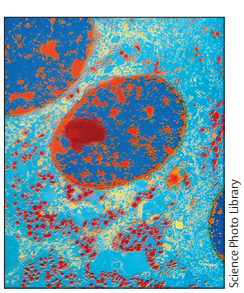
Angiogenesis inhibitors in neuroendocrine tumours: finally coming of age

Neuroendocrine tumours (NETs) are considered rare in the world of epithelial neoplasms yet, in the past 30 years, have shown increasing trends in incidence and prevalence.[1] The seminal epidemiological studies that led to these observations have been crucial in raising awareness about NETs and promoting the feasibility and value of rigorous scientific study.

Over the past decade, multiple randomised trials have led to US Food and Drug Administration (FDA)-approved treatments for advanced, well differentiated NETs, including everolimus, sunitinib, lanreotide, and ^{177}Lu-Dotatate. Angiogenesis inhibitors have strong scientific rationale in NETs because of their high vascularity and expression of VEGF.[2] Sunitinib, an inhibitor of multiple receptor tyrosine kinases including VEGFR, platelet-derived growth factor receptor (PDGFR), RET, and c-KIT, was approved on the basis of a phase 3 study of sunitinib versus placebo in 171 patients with advanced pancreatic NETs.[3] Median progression-free survival was 11·4 months for sunitinib versus 5·5 months with placebo (hazard ratio [HR] 0·42; 95% CI 0·26–0·66; p<0·001) and the objective response rate was 9·3% for sunitinib and zero for placebo. These data led to the US FDA approval of sunitinib for advanced pancreatic NETs in 2011.

To date, other angiogenesis inhibitors have had limited success in NETs, but not for lack of trying. Bevacizumab, a monoclonal antibody that inhibits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VEGF-A, has been studied in two randomised trials in NETs. SWOG 0518[4] was a randomised phase 3 trial of octreotide plus interferon alfa-2b versus octreotide plus bevacizumab in 427 patients with advanced gastrointestinal NETs, although it did not meet its predefined primary endpoint. CALGB 80701[5] examined bevacizumab in a randomised phase 2 trial of everolimus and octreotide with or without bevacizumab in 150 patients with advanced pancreatic NETs. The addition of bevacizumab to everolimus led to a small, but statistically significant, increase in median progression-free survival of 16·7 months versus 14 months (HR 0·80; 95% CI 0·55–1·17; p=0·12). Response rates were higher in the bevacizumab group (31% *vs* 12%; p=0·005). However, these small efficacy gains were at the expense of increased grade 3 adverse events, and bevacizumab was not pursued further in NETs.

Although the development of bevacizumab for NETs was halted, hope remained for tyrosine kinase inhibitors given the earlier success with sunitinib. Pazopanib, an inhibitor of VEGFR, PDGFR, c-KIT, and fibroblast growth factor, was studied in ALLIANCE 021202,[6] a randomised phase 2 trial of pazopanib versus placebo in 171 patients with advanced carcinoid tumours. Median progression-free survival was 11·6 months for pazopanib and 8·5 months for placebo (HR 0·53; 1-sided 90% upper confidence limit 0·69; p=0·0005); response rates were low in both groups at 2% and 0, respectively. Although a phase 3 trial with pazopanib was not done, these results confirmed that the VEGF signalling pathway remained a valid target for advanced carcinoid tumours.

In *The Lancet Oncology,* two randomised phase 3 trials show the efficacy of surufatinib in extrapancreatic and pancreatic NETs, almost a decade after the sunitinib US FDA approval. Surufatinib, an inhibitor of receptor tyrosine kinases, specifically targets VEGFR-1, VEGFR-2, VEGFR-3, fibroblast growth factor receptor (FGFR1), and immune evasion via macrophage colony-stimulating factor 1 receptor (CSF1R). In the SANET-ep study by Jianming Xu and colleagues,[7] 289 patients with advanced, well differentiated, extrapancreatic NETs were randomly assigned (2:1) to receive surufatinib or placebo. Surufatinib showed longer progression-free survival compared with placebo (9·2 months [95% CI 7·4–11·1] *vs* 3·8 months [3·7–5·7]; HR 0·33, 95% CI 0·22–0·50; p<0·0001) and a higher response rate (10% *vs* 0; p=0·0051). In the parallel SANET-p study by Xu and colleagues,[8] 172 patients with advanced, well differentiated, pancreatic NETs were randomly assigned (2:1) to receive surufatinib or placebo. In this study, surufatinib similarly showed a longer progression-free survival (10·9 months [95% CI 7·5–13·8] *vs* 3·7 months [2·8–5·6]; HR 0·49, 95% CI 0·32–0·76; p=0·0011) and higher response rate (19% *vs* 2%; p=0·0021) than the placebo. Both studies met their prespecified primary endpoints and China's National Medical Products Administration granted priority review status to the new drug application (NDA) for surufatinib.

Given that both trials were done in China only, a phase 1/2 study of surufatinib was done in the USA to evaluate safety and antitumour activity in a US patient population.[9] This study evaluated 32 patients with NETs and a preliminary analysis confirmed antitumour activity with a response rate of 18% in pancreatic NET and 0 in extrapancreatic NET with a disease control rate of 100% in both cohorts. Median progression-free survival was not reported and no new safety signals were observed. In June, 2020, the US FDA announced in that they would allow NDA submission on the basis of the phase 3 trials done in China along with data from the phase 1/2 trial in the USA.[10]

Angiogenesis inhibitors have finally come of age in the field of NETs. Although earlier randomised studies with bevacizumab and pazopanib did not lead to US FDA approvals, they laid crucial groundwork for subsequent studies of angiogenesis inhibitors. Surufatinib yields a meaningful progression-free survival benefit and response rate in heavily pretreated patients with NETs. Notably, this is the first positive phase 3 study of tyrosine kinase inhibitors in extrapancreatic NETs. I commend Xu and colleagues on well done and clinically meaningful trials. Ongoing clinical trials of tyrosine kinase inhibitors include a phase 2/3 study of octreotide plus axitinib versus octreotide plus placebo in non-pancreatic NETs (NCT01744249), and a phase 3 study of cabozantanib versus placebo in gastroenteropancreatic NETs (A021602; NCT03375320).

Key questions remain about angiogenesis inhibitors in NETs. Why has surufatinib crossed the finish line when other angiogenesis inhibitors have not? Some have credited its novel angioimmune mechanism. The target, CSF1R, promotes tumour immune evasion through the activation of tumour-associated macrophages. More

than likely, the success of surufatinib is attributable to both its novel mechanism of action and favourable business decisions around its development. In addition, we do not yet know how surufatinib will fit into the complex treatment algorithm for NETs. Evidence regarding sequence of therapies is a crucial need in the field, although might be impractical to study in prospective clinical trials. We also need to study mechanisms of resistance to tyrosine kinase inhibitors, develop and validate predictive biomarkers, understand reasons for heterogeneity in objective response, and identify better quantitative radiological response criteria in the setting of angiogenesis inhibition. Last, but not least, we must also keep patients with NETs at the core of how we think about optimal treatment strategies. Given the chronicity of well differentiated NETs, these patients will experience an accumulation of toxicities over years that include non-trivial drug side-effects, particularly with tyrosine kinase inhibitors.

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A roadmap for the early detection and diagnosis of cancer

If we are to beat cancer, early detection and diagnosis are arguably the most effective means we have at our disposal. Progress during the past 40 years has transformed the prospects of people diagnosed with cancer in the UK, with survival doubling since the 1970s.[1] However, further improvements are still greatly needed, because cancer remains the leading cause of death in the UK,[2] with a stark projection of rising incidence to more than half a million cases per year by 2035.[3] Patients diagnosed with cancer at an early stage have the best chance of curative treatment and long-term survival; for example, 57% of people with lung cancer survive their disease for 5 years or more when diagnosed at stage I compared with only 3% of those diagnosed at stage IV.[4] Despite cancer screening programmes, improved awareness, and more streamlined diagnostic pathways, only 54% of patients with cancer in England had their cancer detected at stage I or II in 2018.[5] With lower survival rates in the UK than in similar countries, such as Australia, Canada, or Norway,[6,7] and notable inequalities in survival across the UK,[8,9] there is a pressing need to see a paradigm shift in our ability to accurately detect and diagnose cancer at an early stage.

Beyond the clear potential for health benefit, the UK has the capacity to be a world leader in developing a thriving early detection and diagnosis industry, capitalising on its excellent science base and vast National Health Service (NHS) and data infrastructure, and attracting global investment. This potential for health and wealth benefit is recognised by UK's national governments, with ambitious targets set in NHS England's Long Term Plan (ie, a commitment to detect 75% of cancers at stage I and II by 2028) and the Scottish Government's Beating Cancer strategy,[10] and investments to support progress in early detection and diagnosis (eg, the Accelerating Detection of Disease


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For more on **NHS England's Long Term Plan for cancer** see https://www.england.nhs.uk/cancer/strategy/