TRIAL SUMMARY: Interferon alpha-2b vs bevacizumab in combination with octreotide

While treatment options for advanced carcinoid tumours (NETs) remain limited, somatostatin analogues (SSA) have been shown to prolong time to progression in treatment naive patients (pts) and improve progression-free survival (PFS) in patients with established disease progression. When added to SSA, interferon (IFN) and bevacizumab (BEV) have, in separate early trials, been associated with antitumour activity. In this phase III study, 402 eligible pts with metastatic or unresectable, well-differentiated, grade 1/2 NETs with progressive disease or other poor prognostic features were randomly assigned to receive the SSA octreotide (OCT) for injectable suspension 20 mg q 21 days with either bevacizumab (BEV) 15 mg/kg every 21 days or interferon α-2b (IFN) 5 million units 3 times per week. PFS by central review was the primary endpoint.

Results: Patients were enrolled between December 2007 and September 2012. Median PFS by central review was 16.6 months (95% CI 12.9–19.6) in the BEV arm and 15.4 months (95% CI 9.6–18.6) in the IFN arm (HR 0.93; 95% CI 0.73–1.18; p=0.55). By investigator review, median PFS was 15.4 months (95% CI 12.6–17.2) in BEV arm and 10.6 months (95% CI 8.5–14.4) in the IFN arm (HR 0.90; 95% CI: 0.72 - 1.12; p=0.33). Time to treatment failure (TTF) was significantly longer with BEV compared to IFN (HR 0.72; 95% CI 0.58–0.89; p=0.003). Median TTF was 9.9 months (95% CI 7.3–11.1) in the BEV arm and 5.6 months (95% CI 4.3–6.4) in the IFN arm. Confirmed radiologic response rates were 12% (95% CI 8%–18%) in the BEV arm and 4% (95% CI 2%–8%) in the IFN arm. Common adverse events with BEV+OCT included hypertension (32%), proteinuria (9%) and fatigue (7%); and with IFN+OCT included fatigue (27%), neutropenia (12%) and nausea (6%). BEV+OCT was associated with longer TTF compared to IFN+OCT; radiologic responses also appeared to be more frequent among pts treated with BEV+OCT. However, no significant differences in PFS were observed, suggesting that BEV and IFN have similar antitumour activity in these pts.

COMMENTARY: Gastrointestinal carcinoids, which are well- and moderately well-differentiated gastrointestinal neuroendocrine tumours (GI-NET), remain rare despite a rising incidence over the last 3 decades.1 Although prognosis is better than with other GI malignancies, few treatment options have been shown to improve survival outcomes for GI-NETs. In the setting of unresectable advanced or metastatic GI-NET, first-line treatment options are currently limited to SSA, such as OCT, which demonstrated improved TTP in the PROMID trial,2 and lanreotide, which improved PFS in nonfunctional GI-NET in the CLARINET trial.3

Interferon alpha (IFNα) has also demonstrated an ability to stabilize disease, and is recommended for control of carcinoid-syndrome-associated symptoms upon resistance to SSA.4 The antiproliferative benefit of combining IFNα and SSA has previously been investigated, with equivocal results.5,6,7 Although 1 randomized study noted a reduction in risk of progression with the combination, 2 other prospective studies showed no benefit in combining SSA with IFNα.

As carcinoids are vascular tumours with increased angiogenesis, treatment with agents inhibiting vascular endothelial growth factor (VEGF), such as BEV, have also been investigated. These studies have mostly evaluated the effect of BEV in combination with other agents such as 2-methoxyestradiol,8 temozolomide9 and capcitabine.10 BEV was also compared to pegylated IFNα (PEG-IFNα2b) in a random assignment phase II trial where both agents...
were combined with SSA, and BEV was noted to produce a higher objective response rate and longer PFS.\textsuperscript{11}

In the SWOG S0518 study, Dr. Yao and his colleagues compared the use of SSA with either BEV or pegylated IFNα2b (PEG-IFNα2b) in patients with progressive disease or poor prognostic features, in a phase III trial where the primary endpoint was PFS by central review. The authors noted a longer TTF and higher radiologic response rate (RR) in the BEV arm, though no significant PFS benefit was found. The use of PEG-IFNα2b as the comparator in this study was a debatable choice given the equivocal evidence of antiproliferative benefit with PEG-IFNα2b use in earlier trials. As the PEG-IFNα2b + SSA combination is not the current standard of care, it makes the lack of PFS benefit difficult to interpret since a PFS benefit may have been more likely had the comparator arm been SSA alone, which is more often used as first-line treatment. Furthermore, patients treated with PEG-IFNα2b experienced significant rates of grade 3 fatigue, making this a less desirable treatment option for a malignancy that is often characterized by an indolent course.

Also at issue is the difficulty of interpreting these results given the heterogeneity of GI-NETs as a group with regards to prognosis, and the context of previous studies where TTP and PFS varied considerably. In the PROMID study, the SSA-treated arm demonstrated a TTP of 14.3 months, while in the CLARINET study the SSA-treated arm had an estimated PFS of 65% at 24 months. Since the SWOG S0518 PFS results ranged from 15.4 to 16.6 months in both SSA+BEV and PEG-IFNα2b arms, it is debatable whether there is a PFS benefit due to the adjunctive treatment activity in patients with poor prognostic features, or whether we are witnessing a lack of response in a group of patients with more indolent tumours.

Ultimately, further investigation is warranted with regards to angiogenesis inhibitor use in the treatment of unresectable GI-NET. Currently underway is a phase II study investigating pazopanib, a multitargeted VEGF/platelet-derived growth factor (PDGF)/c-KIT/fibroblast growth factor (FGF) receptor tyrosine kinase inhibitor, for the treatment of progressive unresectable NET.\textsuperscript{12} At present, the role of angiogenesis inhibitors in the treatment of advanced GI-NET remains undefined, while the use of PEG-IFNα2b in combination with SSA is unlikely to become standard of care.

### References