



New Frontiers in
ONCOLOGY

**Paradigm Shift in the Treatment of
Well-differentiated Neuroendocrine Tumours**

A report from the
**6th Annual ENETS Conference for the Diagnosis and
Treatment of Neuroendocrine Tumor Disease**
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Granada - The treatment of choice for primary neuroendocrine tumours (NETs) is surgery, but once metastatic disease occurs, options are limited. Management has generally focused on controlling symptoms using somatostatin analogues. Importantly, results from a phase III trial first presented at ASCO GI in January 2009 demonstrate solid evidence that underlying disease progression can now be slowed using the somatostatin analogue octreotide LAR, as confirmed here during the scientific sessions. In addition, a better understanding of the biology of NETs has helped identify new targets. For example, everolimus, an mTOR inhibitor, has shown promising results in a phase II study. Taken together, these developments suggest that new options are becoming available.

Neuroendocrine tumours (NETs) have generally been considered rare; however, as Prof. Kjell Öberg, Department of Endocrine Oncology, University Hospital Uppsala, Sweden, pointed out, "If we look at the data, the number of patients with all types of well-differentiated NETs has increased over the last 30 years." To give an idea of the numbers involved in the European population, estimated at 850 million people, there are about 80,000 new cases per year with about 250,000 patients having such tumours at any one time. "This is a substantial tumour burden on physicians and therefore enormously important in terms of diagnosis and therapy," explained Prof. Irvin Modlin, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

Symptoms Associated with NETs

In normal physiologic conditions, serotonin released by enterochromaffin cells modulates the secretion of water and electrolytes, gut motility and fibroblast proliferation. In functioning NETs, excessive release of serotonin and other substances is thought to be responsible for many of the symptoms such as diarrhea and flushing, and serious conditions like carcinoid heart disease.

Serotonin release can be blocked by somatostatin, an effect that may also be achieved with the use of somatostatin analogues such as octreotide. "This control of symptoms had a large impact on patients' quality of life," stated Prof. Modlin. At present, new somatostatin

analogues such as pasireotide are in development. This compound has high functional activity at sst1, 2, 3 and 5 receptors.

Beyond Symptom Control

Ever since octreotide started to be used to control symptoms, evidence from preclinical cancer models had been mounting that the compound might have antitumour activity (Weckbecker et al. *Digestion* 1996;57(Suppl 1):22-8). In a clinical setting, survival in patients with metastatic NETs increased after the introduction of this agent from 19 months (1973 to 1987) to 39 months (1988 to 2004) (Yao et al. *J Clin Oncol* 2008; 26(18):3063-72), which for Prof. Modlin was “evidence that for the first time outcomes were being altered.”

Advances in basic cell biology of NETs suggested a feasible mechanism by which somatostatin analogues might help restrict tumour growth through blockade of the pathways that induce cell growth and proliferation. However, solid evidence for such effects has been lacking.

PROMID:

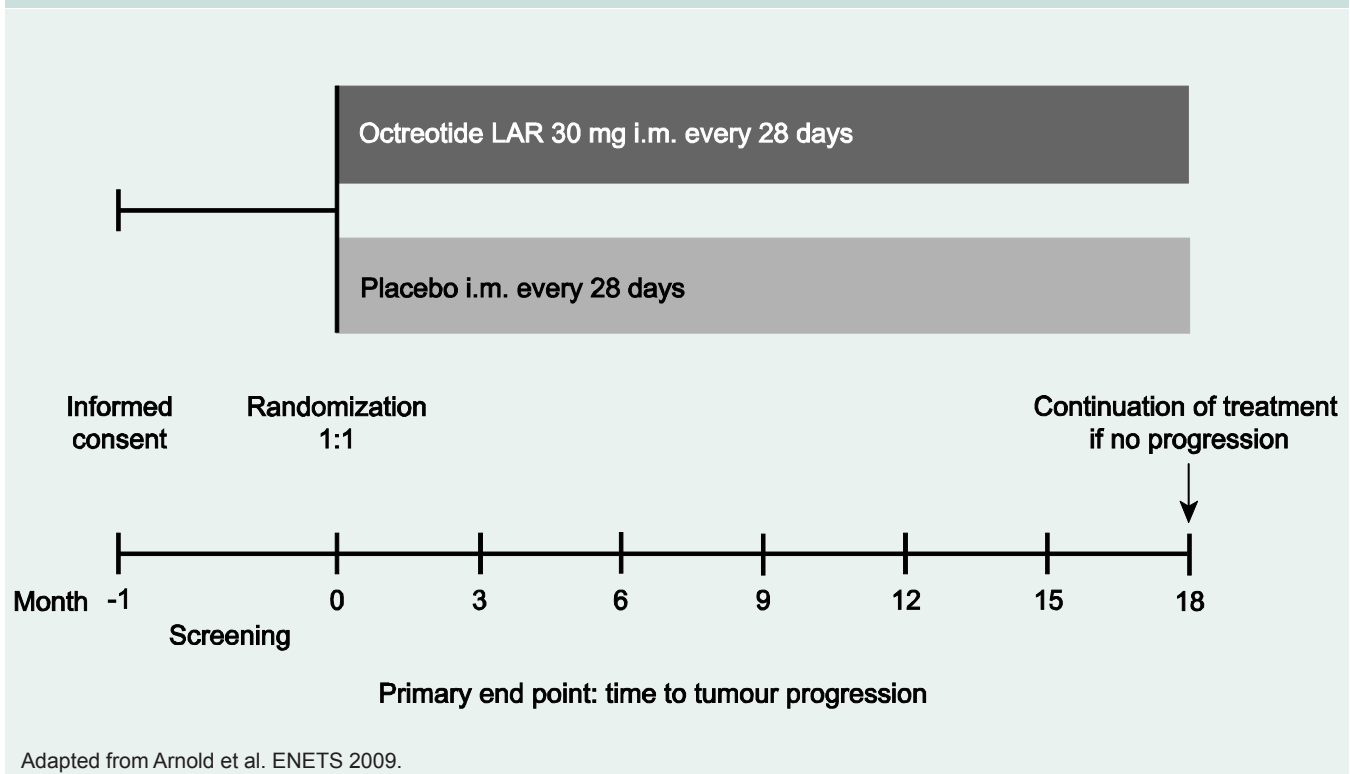
High-level Evidence for Antitumour Effects

The hypothesis that octreotide might have antiproliferative effects was tested in the randomized placebo-controlled PROMID (Placebo-controlled, Double-blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors). In total, 85 patients were treated between 2001 and 2008 (from a planned 162). Recruitment was stopped on the strength of the results, presented here, of the planned interim analysis.

The study population was well-defined—all patients had well-differentiated, non-functioning or functioning metastatic midgut NETs for which no other treatment was feasible, and all were treatment-naïve (Table 1). After screening, patients were randomized to receive either octreotide LAR 30 mg i.m. every 28 days or matching placebo for 18 months or until tumour progression (Figure 1).

The median time to tumour progression, the primary study end point, was 14.3 months (95% CI: 11.0-28.8) for octreotide LAR vs. 6.0 months (95% CI: 3.7-9.4) for

Figure 1. PROMID Study Design



Adapted from Arnold et al. ENETS 2009.

placebo (HR 0.34, 95% CI: 0.20-0.59, $P=0.000072$), which significantly favoured active treatment (Figure 2). Tumour stabilization was shown in patients with functioning and non-functioning NETs, and at six months was demonstrated in 28/42 (67%) patients in the octreotide LAR group vs. 16/43 (37%) in the placebo group.

Importantly, subgroup analysis showed that improved outcomes compared to placebo were obtained regardless of CgA status and in patients with both functioning and non-functioning tumours. This latter result is important, as it would support the use of octreotide in asymptomatic patients. The effect seen for patients with hepatic tumour load $\geq 10\%$ was not statistically significant, although the numbers of patients were small ($n=12$ and $n=11$, respectively).

Overall survival was a secondary end point of the study; group differences could not be determined. “Almost all patients on placebo who progressed received octreotide, so we could not investigate overall survival in an octreotide-free population,” explained Dr. Arnold.

Enhanced Antitumour Effects

The mTOR inhibitor everolimus also interferes with pathways that induce cell growth and proliferation and preclinical models had shown evidence of antitumour activity. Data

from a phase II trial presented here would seem to support that activity in a clinical setting. The study randomized patients with advanced pancreatic NETs refractory to chemotherapy to receive everolimus monotherapy or combined with octreotide LAR. Durable objective response and stable disease were seen in both arms. Comparison with historical controls showed higher progression-free survival at six months (28% vs. 65% for everolimus and vs. 71% for everolimus/octreotide). “Everolimus is active, both as monotherapy and in combination with octreotide in refractory pancreatic NETs,” summarized Prof. James Yao, M.D. Anderson Cancer Center, Houston, Texas.

Canadian Perspective

The feeling at the conference was that the results of the PROMID study would influence the European guidelines on the treatment of NETs. According to delegate Dr. Simron Singh, Sunnybrook Health Sciences Centre, Toronto, Ontario, “We recently started reviewing the Canadian guidelines and we decided to include data from the PROMID study.” The PROMID study managed to obtain very clean data, in part because the study population was very well defined. Given that these studies are very hard to carry out, in Dr. Singh’s opinion, “I would be happy to extrapolate these results to other NETs.”

Table 1. Baseline characteristics of the patients included in the PROMID study

		Octreotide LAR (n=42)	Placebo (n=43)	Total (n=85)
Median age, years		63.5	61	62
Sex	Male (%)	47.6%	53.5%	50.6%
	Female (%)	52.4%	46.5%	49.4%
Time since diagnosis, months		7.5	3.3	4.3
Karnofsky score	≤ 80	16.7%	11.6%	14.1%
	> 80	83.3%	88.4%	85.9%
Carcinoid syndrome		40.5%	37.2%	38.8%
Resection of primary tumour		69.1%	62.8%	65.9%
Hepatic tumour load	0%	16.7%	11.6%	14.1%
	0-10%	59.5%	62.8%	61.2%
	10-25%	7.1%	4.7%	5.9%
	25-50%	11.9%	9.3%	10.6%
	$> 50\%$	4.8%	11.6%	8.2%
Octreoscan positive		76.2%	72.1%	74.1%
Ki-67 $\geq 2\%$		97.6%	93%	95.3%
CgA elevated		61.9%	69.8%	65.9%

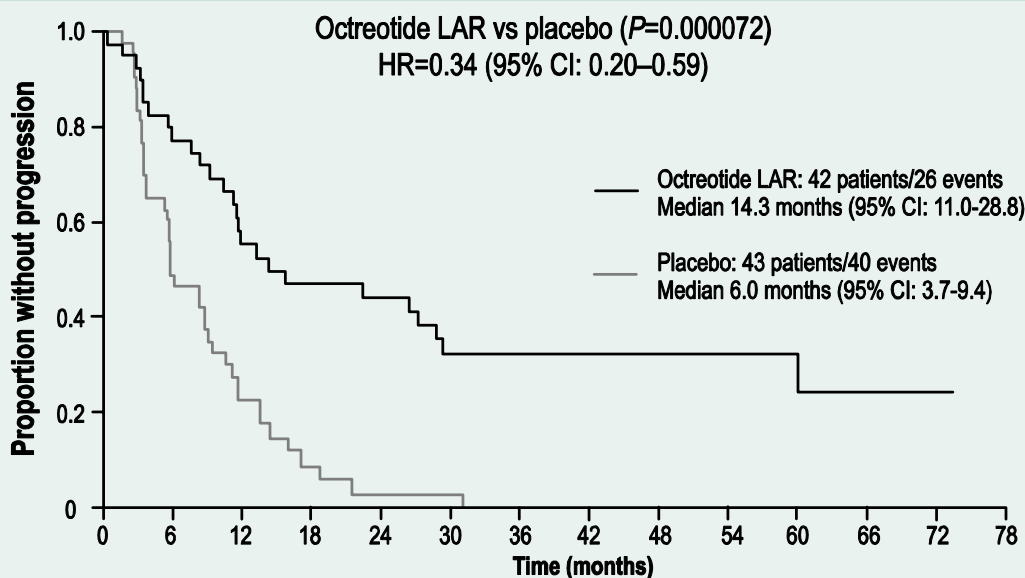
Adapted from Arnold et al. ENETS 2009.

Although it appeared that findings were not as promising for patients with a high hepatic load, Dr. Walter Kocha, London Health Sciences Centre, Ontario, pointed out, “The number of patients with high hepatic load was low, which would make it harder to obtain statistically significant results. In any case, these results are not concordant with my experience in clinical practice; I have seen patients with high hepatic load who have responded extremely well.” In terms of other questions about the effects on clinical practice, Dr. Kocha considered that the question of when to start treatment was important. “If we start treatment early, we may be able to prevent some of these deaths,” he noted.

Summary

There is renewed hope for patients with NETs. For the first time, there is solid evidence that medical treatment with octreotide LAR can extend time to tumour progression. These results will likely change the way physicians approach this patient population and open the way for the use of octreotide LAR in patients with non-functioning tumours. In addition, further understanding of cell biology is being applied to the development of new therapies which should further prolong survival and improve symptoms in these difficult-to-treat carcinomas. □

Figure 2. Kaplan-Meier Plots of Time to Tumour Progression



Adapted from Arnold et al. ENETS 2009.

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