VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# 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: A Report From the PROMID Study Group

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Submitted March 20, 2009; accepted June 24, 2009; published online ahead of print at www.jco.org on August 24, 2009.

Written on behalf of the PROMID Study Group and endorsed by the European Neuroendocrine Tumor Society.

Supported by grants from Novartis, Nürnberg, Germany.

Novartis participated in the development of the study design and provided the verum medication and funding, but did not participate in the collection, analysis, and interpretation of the data.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).



0732-183X/09/2728-4656/$20.00

DOI: 10.1200/JCO.2009.22.8510

## ABSTRACT

### Purpose
Somatostatin analogs are indicated for symptom control in patients with gastroenteropancreatic neuroendocrine tumors (NETs). The ability of somatostatin analogs to control the growth of well-differentiated metastatic NETs is a matter of debate. We performed a placebo-controlled, double-blind, phase IIIB study in patients with well-differentiated metastatic midgut NETs. The hypothesis was that octreotide LAR prolongs time to tumor progression and survival.

### Patients and Methods
Treatment-naive patients were randomly assigned to either placebo or octreotide LAR 30 mg intramuscularly in monthly intervals until tumor progression or death. The primary efficacy end point was time to tumor progression. Secondary end points were survival time and tumor response. This report is based on 67 tumor progressions and 16 observed deaths in 85 patients at the time of the planned interim analysis.

### Results
Median time to tumor progression in the octreotide LAR and placebo groups was 14.3 and 6 months, respectively (hazard ratio [HR] = 0.34; 95% CI, 0.20 to 0.59; $P = .000072$). After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group and 37.2% of patients in the placebo group. Functionally active and inactive tumors responded similarly. The most favorable effect was observed in patients with low hepatic tumor load and resected primary tumor. Seven and nine deaths were observed in the octreotide LAR and placebo groups, respectively. The HR for overall survival was 0.81 (95% CI, 0.30 to 2.18).

### Conclusion
Octreotide LAR significantly lengthens time to tumor progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs. Because of the low number of observed deaths, survival analysis was not confirmatory.

*J Clin Oncol 27:4656-4663. © 2009 by American Society of Clinical Oncology*

## INTRODUCTION

Antiproliferative treatment options for patients with metastatic well-differentiated neuroendocrine tumors (NETs) are intended to reduce tumor burden, delay tumor progression, and prolong life. They encompass tumor debulking,[1-5] chemoembolization,[6-9] receptor-targeted radiotherapy,[10-12] cytotoxic drugs, inhibitors of angiogenesis or vascular endothelial growth factors,[13-16] ablative methods,[17] and liver transplantation.[18] Adverse effects associated with most of these treatments are frequent and can compromise quality of life. Because of minimal adverse effects, somatostatin analogs, which exhibit antiproliferative activity in vitro,[19,20] have been offered to patients with metastatic disease when surgical cure was impossible. Somatostatin analogs, such as octreotide LAR, are currently indicated for the relief of symptoms in patients with functionally active NETs.[21]

Whether or not somatostatin analogs control the growth of well-differentiated metastatic NETs is still under debate. Uncontrolled studies showed tumor shrinkage and tumor disappearance in

response to short-acting somatostatin analogs[22-25] and their combination with interferon alfa.[26] Complete regression could not be confirmed in subsequent trials, but tumor stabilization occurred in up to 50% of patients.[27-34] These studies were not placebo controlled. The observed effects on tumor growth may reflect spontaneous phases of tumor growth or stabilization. We performed a randomized, placebo-controlled study in patients with metastatic midgut NETs to demonstrate that octreotide LAR prolongs time to tumor progression and long-term survival. To avoid a heterogeneous patient population, only patients with well-differentiated metastatic midgut tumors were included. This report presents results from a planned interim analysis based on 67 tumor progressions and 16 observed deaths in 85 randomly assigned patients.

## PATIENTS AND METHODS

### Patients

Main inclusion criteria were as follows: locally inoperable or metastatic NET; midgut primary tumor or tumor of unknown origin believed to be of midgut origin if a primary within the pancreas, chest, or elsewhere was excluded by multiphasic computed tomography (CT) or magnetic resonance imaging (MRI); proof of a well-differentiated histology by pathology; measurable disease by CT or MRI; a Karnofsky performance status more than 60%; and no curative therapeutic options. Patients with symptoms of carcinoid syndrome and increased urinary 5-hydroxyindole acetic acid were classified as having a functional tumor.

Main exclusion criteria were as follows: pretreatment with somatostatin analogs for $\geq$ 4 weeks or previous treatment with interferon alfa, chemotherapy, or chemoembolization. Only patients tolerating flushing without intervention or responding to treatment with loperamide or cholestyramine in case of diarrhea were included. All patients were discussed in the institutional tumor boards of the study hospitals, and surgery for regional or distant tumor spread was declined.

### Study Design

This study was a randomized, double-blind, placebo-controlled trial conducted at 18 German academic centers. The trial conformed to the Helsinki Declaration, Good Clinical Practice Guidelines, and German Drug Law and was approved by the ethical committees of participating centers. All patients provided written informed consent.

### Interventions

Either placebo (sodium chloride) or octreotide LAR 30 mg (Sandostatin-LAR; Novartis, Nürnberg, Germany) was administered intramuscularly every 28 days by study nurses or physicians not involved in further patient care. Patients were blinded, and all clinical assessments were performed without knowledge of the assigned treatment. Treatment was continued until CT- or MRI-documented tumor progression. Additional antiproliferative therapy was not allowed. Poststudy treatment in patients with tumor progression was at the discretion of the investigator.

### Random Assignment

The allocation scheme used stratification with respect to factors to be balanced, biased coin techniques in case of major imbalances, and a prespecified list of computer-generated random numbers. The 1:1 random assignment was dynamically balanced for study center and the possible prognostic factors of tumor functionality, presence of distant metastases (liver or elsewhere), Ki-67 index, and age. All screened patients were registered centrally. After central assessment of Ki-67, the central office informed the participating study center of the patient's assigned treatment group.

### Outcomes

The primary efficacy end point was time to tumor progression calculated from the date of random assignment until the date of first progressive disease or tumor-related death. The blinded central reader judged tumor response according to WHO criteria[27,30] and quantified hepatic tumor load from four to six slices of a CT/MRI scan with the most amount of disease by a semiquantitative three-dimensional approach.[35] Hepatic tumor burden was categorized as 0%, more than 0% but $\leq$ 10%, more than 10% but $\leq$ 25%, more than 25% but $\leq$ 50%, or more than 50%. Secondary end points were survival time, quality of life, and clinical and biochemical response. Survival time was calculated from the date of random assignment until the date of tumor-related death. Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 at random assignment and at 3-month intervals until tumor progression.[36] Global quality of life was expressed on a scale of 0 (extremely bad) to 100 (excellent).

In patients with carcinoid syndrome, a clinical response was judged to be a reduction of symptoms to less than one flush per week, fewer than four stool movements per day, and disappearance of abdominal pain. Biochemical response was defined as a decrease in tumor markers to the normal SD. Determination of plasma chromogranin A (CgA) and urine 5-hydroxyindole acetic acid was performed in the individual study center. Because CgA assays varied between centers, the respective data from each center were transformed and given as deviations in percentage of the upper limit of normal in the respective study center.

Tumor response, clinical and biochemical responses, and change in quality of life are presented 6 months after study entry. All adverse events occurring during the study were documented according to either WHO criteria or National Cancer Institute Common Toxicity Criteria (version 2.0).

### Statistical Analysis

Confirmatory analysis encompassed the two efficacy end points of time to tumor progression and survival time. Survival curve estimation was performed using the Kaplan-Meier method. Mantel-Cox log-rank tests compared the resulting curves, and 95% CIs for the hazard ratios (HRs) were calculated. Testing differences at a type I error level of 5%, two-sided stratified tests were applied adjusting for functional activity (active *v* inactive) according to the protocol. The primary confirmatory analysis was a conservative analysis based on the intent-to-treat (ITT) principle.

The primary end point was time to tumor progression or tumor-related death. According to ITT, the primary end point could be assessed in all patients regardless of deviations from protocol. However, in patients in whom assessments of tumor progression deviated importantly from protocol, censoring time to progression at random assignment was considered. The results of the ITT analysis and the most conservative result within all possible combinations of decisions for or against censoring for such patients (cITT) are presented.

On the basis of previous results,[27] a median time to tumor progression of 9 months was assumed for the placebo group. An HR of 0.6 was postulated as a clinically meaningful difference to be detected with a power of 80%. An optimized group sequential design, with one interim analysis after observation of 64 progressions and the final analysis after observation of 124 progressions, with a local type I error level of 0.0122 at interim, was fixed in the protocol. A use function in the sense of DeMets and Lan[37] was set up by reoptimization, resulting in the type I error level of 0.0125 after observation of 67 progressions. According to Schoenfeld and Richter[38] and compensating for a lost to follow-up rate of 10%, recruitment of 162 patients was planned.

For survival time, a fixed-sample test based on 121 observed deaths was defined in the protocol. Controlling the family-wise error rate at the level of 5%, this test was planned as a confirmatory test in the event of a significant result for the primary end point, with the option of a redesign according to Müller and Schäfer.[39,40]

A sensitivity analysis was performed on a per-protocol basis. Other secondary end points and safety variables were analyzed descriptively. Explorative analyses were performed to investigate potential prognostic factors for time to tumor progression and survival time. During the study, hepatic tumor involvement was recognized as a further possibly important factor.[35]

Statistical analyses were performed using log-rank tests, univariate and multivariate Cox regression models, Fisher's exact test, and Wilcoxon-Mann-Whitney test, with or without stratification. They were performed with SAS Version 9.1 (SAS Institute, Cary, NC) and StatXact of Cytel Studio Version 6.2.0 (Cytel, Cambridge, MA). *P* values quantified results of confirmatory or explorative tests or imbalances between treatment groups with respect to

baseline characteristics occurring despite random assignment. For the primary efficacy analysis, exact *P* values were provided.

## RESULTS

### *Study Population*

Ninety patients were registered between March 2001 and January 2008; five patients could not be randomly assigned, 42 patients were randomly assigned to receive octreotide LAR, and 43 patients were randomly assigned to receive placebo. For this interim analysis, patients were observed until June 2008. Patient flow is presented in Figure 1, and patient demographics and clinical characteristics are listed in Table 1. Overall, the median time between diagnosis and random assignment was 4.3 months.

The primary tumor was removed in 66% of patients. In 21 patients, the site of the primary was unknown. Five of these patients had a carcinoid syndrome. Patient S106 (assigned to octreotide LAR), with an unknown primary and progressive disease during follow-up, developed a NET in the head of the pancreas that was resected. This patient was censored at random assignment for the per-protocol analysis.

Seventy-three patients had liver metastases. Hepatic tumor load was ≤ 10% in most patients. Of 12 patients without liver involvement, six had regional lymph node involvement unresectable by surgery, one had a nonresectable primary tumor, and one had residual tumor after surgery. Of the remaining four patients, octreotide LAR recipient S119 had a lesion identified as a hemangioma by radiologic review. Liver metastases of two patients in the octreotide LAR group (S1003 and S1307) and lymph node involvement of placebo recipient S1502, described by local radiology, could not be confirmed by central radiologic review. However, octreotide LAR recipient S1307 and placebo recipient S1502 developed progressive disease early after random assignment, whereas octreotide LAR recipient S1003 remained tumor free. These four remaining patients were considered for censoring in the cITT analysis for time to tumor progression or tumor-related death. The two patients in the octreotide LAR group without tumor disease (S119 and S1003) were censored at random assignment, as was patient S1502 with progressive disease in the placebo group. The

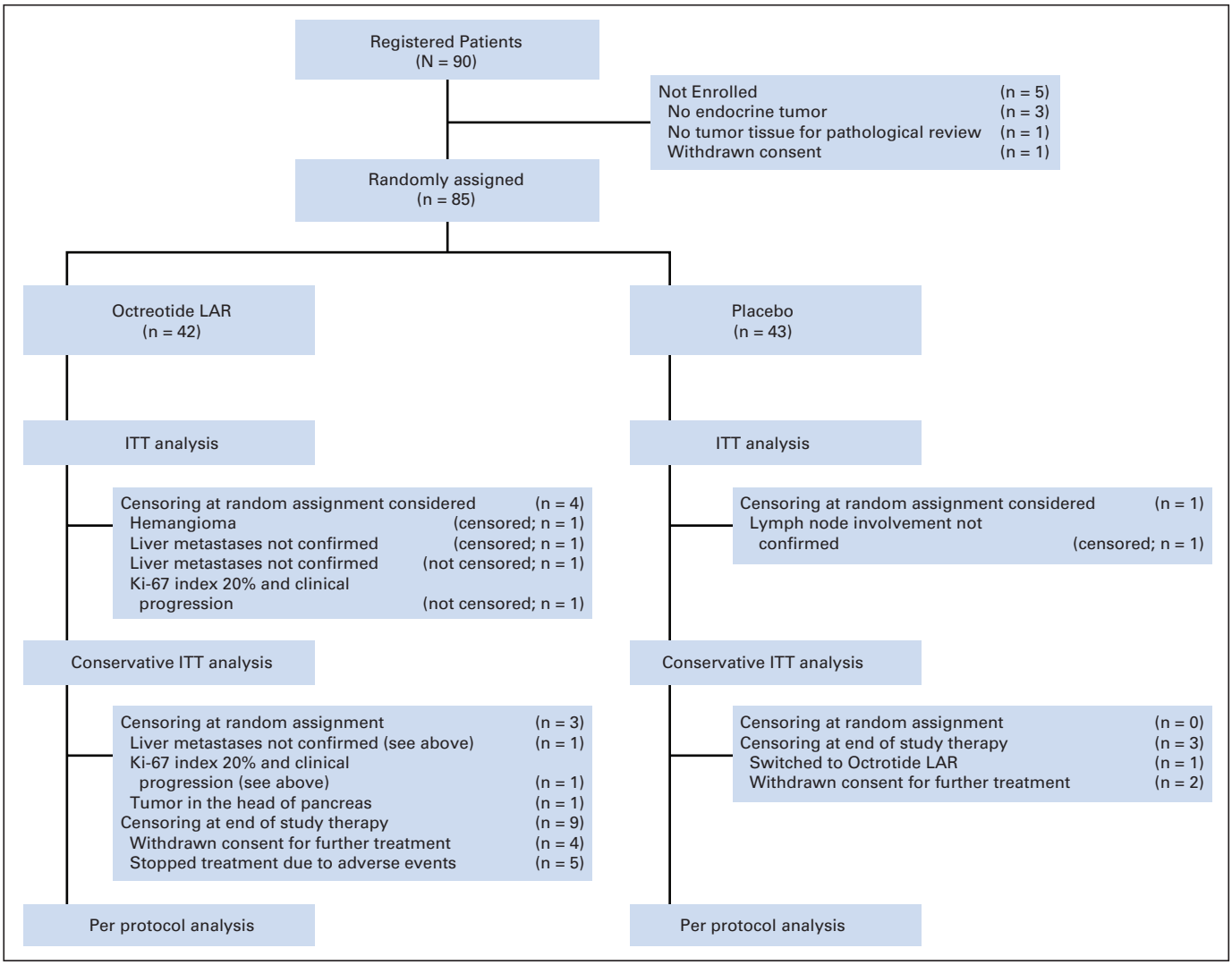


**Fig 1.** Study flow chart for time to progression or tumor-related death. ITT, intent to treat.

  

**Table 1.** Baseline Patient Demographics and Clinical Characteristics

| Demographic or Clinical Characteristic | Octreotide LAR (n = 42) | | Placebo (n = 43) | | Total (N = 85) | | *P* |
|---|---|---|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % | No. of Patients | % | |
| Age, years | | | | | | | .5355 |
| Median | 63.5 | | 61 | | 62 | | |
| Minimum | 38 | | 39 | | 38 | | |
| First quartile | 54 | | 52 | | 54 | | |
| Third quartile | 70 | | 67 | | 68 | | |
| Maximum | 79 | | 82 | | 82 | | |
| Male | 20 | 47.6 | 23 | 53.5 | 43 | 50.6 | .6665 |
| Time since diagnosis, months | | | | | | | .0096 |
| Median | 7.5 | | 3.3 | | 4.3 | | |
| Minimum | 0.8 | | 0.8 | | 0.8 | | |
| First quartile | 3.5 | | 1.8 | | 2.5 | | |
| Third quartile | 19.8 | | 8.9 | | 14.3 | | |
| Maximum | 271.7 | | 109.4 | | 271.7 | | |
| Karnofsky performance status > 80% | 35 | 83.3 | 38 | 88.4 | 73 | 85.9 | .5486 |
| Carcinoid syndrome | 17 | 40.5 | 16 | 37.2 | 33 | 38.8 | .8256 |
| Resection of primary tumor | 29 | 69.1 | 27 | 62.8 | 56 | 65.9 | .6487 |
| Ki-67 up to 2% | 41 | 97.6 | 40 | 93.0 | 81 | 95.3 | .6160 |
| Octreoscan | | | | | | | .8806 |
| Positive | 32 | 76.2 | 31 | 72.1 | 63 | 74.1 | |
| Negative | 4 | 9.5 | 6 | 14.0 | 10 | 11.8 | |
| Liver involvement | | | | | | | .7700 |
| 0% | 7 | 16.7 | 5 | 11.6 | 12 | 14.1 | |
| 0%-10% | 25 | 59.5 | 27 | 62.8 | 52 | 61.2 | |
| 10%-25% | 3 | 7.1 | 2 | 4.7 | 5 | 5.9 | |
| 25%-50% | 5 | 11.9 | 4 | 9.3 | 9 | 10.6 | |
| > 50% | 2 | 4.8 | 5 | 11.6 | 7 | 8.2 | |
| Chromogranin A | | | | | | | .7409 |
| Elevated | 26 | 61.9 | 30 | 69.8 | 56 | 65.9 | |
| Not elevated | 15 | 35.7 | 12 | 27.9 | 27 | 31.8 | |

octreotide LAR recipient S1307 with early progression was censored at random assignment for the per-protocol analysis.

Eighty-one patients had Ki-67 values up to 2%. Patient S1801 assigned to octreotide LAR had a Ki-67 index of 20% and was judged as having clinical progression by the investigator before start of study treatment. This patient was taken into account in the cITT analysis. He was not censored in cITT, whereas censoring at the time of random assignment was performed for the per-protocol analysis. The other three patients with Ki-67 levels greater than 2% were assigned to placebo. There were no relevant differences regarding the baseline characteristics between the two treatment groups.

Before progression, one patient switched from placebo to octreotide LAR, seven patients (five assigned to octreotide LAR and two assigned to placebo) withdrew consent for further treatment, and five patients (all in the octreotide LAR group) stopped study treatment because of adverse events. One of the patients in the octreotide LAR group who withdrew consent for therapy was lost to follow-up at the date of withdrawal. For the other patients, time to tumor progression was censored at the time of stopping study treatment for the per-protocol analysis.

### *Efficacy*

In the planned ITT analysis, 26 and 41 progressions were seen in the octreotide LAR and placebo groups, respectively (HR = 0.32; 95% CI, 0.19 to 0.55; $P = .000015$). For an American Society of Clinical Oncology presentation, the ITT analysis was updated (follow-up until May 2009) in an unplanned analysis with no confirmatory objectives. Compared with the planned confirmatory analysis, only marginal changes were seen for the primary end point with 27 and 41 progressions in the octreotide LAR and placebo groups, respectively (HR = 0.33; 95% CI, 0.19 to 0.55; $P = .000017$).

According to the cITT in the planned confirmatory interim analysis, 26 and 40 progressions or tumor-related deaths were observed in the octreotide LAR and placebo groups, respectively (HR = 0.34; 95% CI, 0.20 to 0.59; $P = .000072$; Fig 2A). Median time to tumor progression was 14.3 months (95% CI, 11.0 to 28.8 months) in the octreotide LAR group and 6.0 months (95% CI, 3.7 to 9.4 months) in the placebo group. Thus, antiproliferative efficacy was demonstrated.

In the per-protocol analysis, tumor progression or tumor-related death was observed in 19 and 38 octreotide LAR and placebo recipients, respectively (HR = 0.24; 95% CI, 0.13 to 0.45; $P = .0000036$). Treatment effect was similar in patients with functionally active (HR = 0.23; 95% CI, 0.09 to 0.57) and inactive tumors (HR = 0.25; 95% CI, 0.10 to 0.59; Table 2). Subgroup analyses suggested that the antiproliferative effect was influenced by hepatic tumor burden and resection of the primary tumor. Factors exploring heterogeneity of the effect size are listed in Table 2, and bivariate and multivariate analyses for possible prognostic factors are shown in Table 3. The extent of hepatic tumor burden seemed to be an important prognostic factor. Resection of the primary tumor and time since diagnosis may also

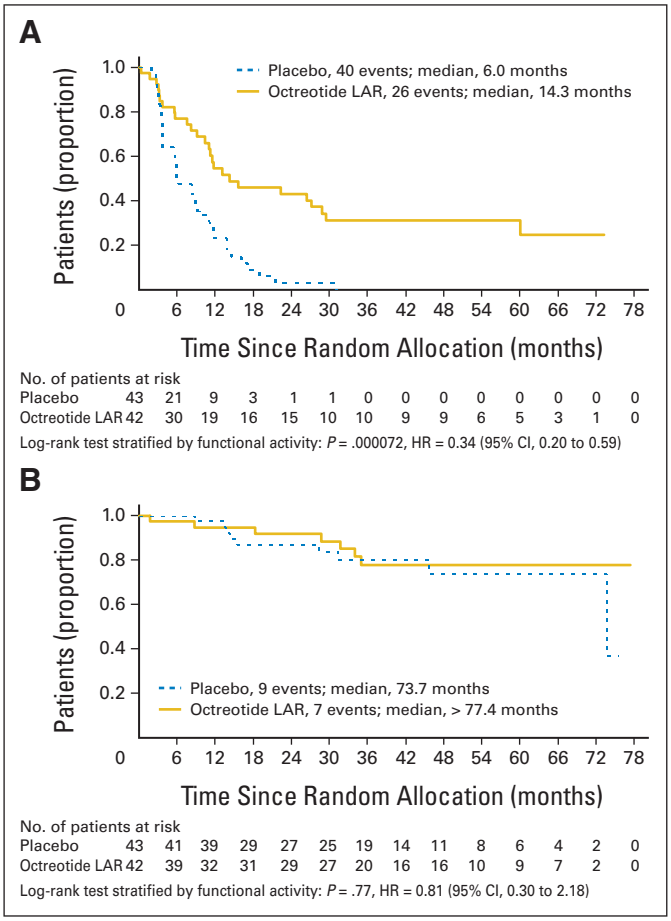


**Fig 2.** (A) Conservative intent-to-treat analysis of time to progression or tumor-related death. (B) Intent-to-treat analysis of overall survival. HR, hazard ratio.

**Table 2.** Per-Protocol Subgroup Analyses of Treatment Effects for Time to Progression or Tumor-Related Death

| Factor | No. of Patients | Per-Protocol Analysis: Median Time to Progression or Tumor-Related Death (months) Octreotide LAR | Placebo | HR | 95% CI |
|---|---|---|---|---|---|
| Carcinoid syndrome | 33 | 14.3 | 5.5 | 0.23 | 0.09 to 0.57 |
| Inactive tumor | 52 | 28.8 | 5.9 | 0.25 | 0.10 to 0.59 |
| Liver involvement | | | | | |
| 0% | 12 | 13.1 | 8.2 | 0.55 | 0.10 to 3.09 |
| 0%-10% | 52 | 29.4 | 6.1 | 0.17 | 0.08 to 0.40 |
| 10%-50% | 14 | 11.2 | 5.5 | 0.40 | 0.10 to 1.67 |
| > 50% | 7 | 4.6 | 2.8 | 0.71 | 0.11 to 4.45 |
| Chromogranin A* | | | | | |
| Elevated | 56 | 14.3 | 5.6 | 0.26 | 0.13 to 0.54 |
| Not elevated | 27 | 28.8 | 8.5 | 0.26 | 0.08 to 0.85 |
| Karnofsky performance status | | | | | |
| ≤ 80% | 12 | 11.5 | 6.1 | 0.32 | 0.05 to 1.98 |
| > 80% | 73 | 27.1 | 5.8 | 0.23 | 0.12 to 0.45 |
| Age, years | | | | | |
| < 63 | 43 | 28.8 | 8.3 | 0.23 | 0.08 to 0.63 |
| ≥ 63 | 42 | 14.3 | 5.7 | 0.23 | 0.10 to 0.53 |
| Primary tumor resection | | | | | |
| Yes | 56 | 29.4 | 5.9 | 0.16 | 0.07 to 0.36 |
| No | 29 | 10.3 | 5.6 | 0.84 | 0.35 to 2.06 |
| Time since diagnosis, months | | | | | |
| < 4.3 | 43 | 11.5 | 5.6 | 0.34 | 0.15 to 0.76 |
| ≥ 4.3 | 42 | 28.8 | 8.3 | 0.22 | 0.09 to 0.56 |

Abbreviation: HR, hazard ratio.
*Plasma chromogranin A levels were determined at the participating study centers. Because assay conditions varied between centers, the respective absolute values were transformed. Levels were considered elevated if greater than the upper limit of normal controls.

have an impact on time to tumor progression. The latter is suggested by a shorter time interval between diagnosis and start of treatment in patients with a poorer prognosis.

At the time of the planned interim analysis, nine patients continued to receive study medication. Seven and nine deaths were observed in the octreotide LAR and placebo groups, respectively. The cause of death was unrelated to the tumor disease in two octreotide LAR recipients (stroke) and one placebo recipient (myocardial infarction). In one placebo recipient, cause of death was unknown. Median overall survival time could not be estimated in the octreotide LAR group, and the estimation of 73.7 months in the placebo group is not robust because of the low number of deaths. The HR for overall survival was 0.81 (95% CI, 0.30 to 2.18; $P = .77$; Fig 2B).

### *WHO Response*

Tumor progression 6 months after random assignment occurred in 10 of 42 octreotide LAR recipients and 23 of 43 placebo recipients. Stable disease was observed in 28 of 42 and 16 of 43 octreotide LAR and placebo recipients, respectively. Only one partial remission was seen in either group. No complete response occurred. In six of 85 patients, tumor response was unknown. Comparison by the Wilcoxon-Mann-Whitney test showed a difference in favor of octreotide LAR ($P = .0079$).

### *Symptomatic Response*

Ten and 12 patients had ≥ one flushing episodes per week at random assignment in the octreotide LAR and placebo groups, respectively. At 6 months, seven octreotide LAR recipients and three placebo recipients had less than one flushing episode per week. Of the six octreotide LAR and seven placebo recipients with diarrhea ≥ four times a day at random assignment, two patients and one patient, respectively, experienced a reduction in diarrhea frequency (Table 4).

### *Biochemical Response*

At random assignment, CgA was elevated in 26 of 41 octreotide LAR recipients and 30 of 42 placebo recipients; at 6 months, normalization of elevated CgA levels was observed in nine and four recipients, respectively (Table 4).

### *Quality of Life*

Both treatment groups had comparable levels of global quality of life at random assignment and after 6 months of follow-up (Table 4).

### *Adverse Events*

Treatment-related deaths did not occur. Serious adverse events were observed in 11 octreotide LAR–treated patients and 10 placebo

  

**Table 3.** Prognostic Factors for Time to Progression or Tumor-Related Death Adjusted for Treatment Based on the Per-Protocol Analysis

| Factor | Bivariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | *P* | HR | 95% CI | *P* | HR | 95% CI |
| Octreotide LAR *v* placebo* | | | | < .0001 | 0.27 | 0.14 to 0.49 |
| Functional active tumor *v* inactive tumor | .2420 | 1.38 | 0.81 to 2.37 | | | |
| Liver involvement > *v* ≤ 10% | .0009 | 2.81 | 1.53 to 5.18 | .0023 | 2.63 | 1.41 to 4.90 |
| Chromogranin A elevated *v* not elevated | .3098 | 1.36 | 0.75 to 2.48 | | | |
| Karnofsky performance status ≤ *v* > 80% | .6518 | 1.21 | 0.54 to 2.71 | | | |
| Age ≥ *v* < 63 years | .1709 | 1.47 | 0.85 to 2.56 | | | |
| Primary tumor not resected *v* resected | .1040 | 1.60 | 0.91 to 2.80 | .6784 | 1.45 | 0.60 to 2.20 |
| Time since diagnosis ≥ *v* < 4.3 months | .0806 | 0.62 | 0.36 to 1.06 | .2883 | 0.71 | 0.38 to 1.34 |

Abbreviation: HR, hazard ratio.
**P* value and effect size are only presented for multivariate analysis.

recipients. The most frequently observed severe adverse events affected the GI tract (octreotide LAR, n = 6; placebo, n = 8), the hematopoietic system (octreotide LAR, n = 5; placebo, n = 1), and general health status (fatigue and fever; octreotide LAR, n = 8; placebo, n = 2). Treatment discontinuation as a result of adverse events occurred in five octreotide LAR recipients and no placebo recipients.

WHO grade 2 to 4 adverse events, regardless of causal relationship to treatment, were observed more often in the octreotide LAR arm and included diarrhea and flatulence. Bile stones were recorded six times, with five of the instances occurring in octreotide LAR recipients.

### *Poststudy Treatment*

Poststudy treatment of patients in the octreotide LAR (n = 42) and placebo (n = 43) groups included octreotide LAR (25 *v* 33 patients, respectively), hepatic chemoembolization (four *v* nine patients, respectively), radioligand therapy (four *v* six patients, respectively), and chemotherapy (three *v* three patients, respectively).

## DISCUSSION

This study provides evidence that octreotide LAR inhibits tumor growth in patients with metastatic well-differentiated midgut NETs. The patients recruited represent the typical population of this tumor entity. The most favorable outcome was stabilization of tumor growth, resulting in a significantly prolonged time to tumor progression. Patients with functionally active and inactive tumors responded similarly, whereas the antiproliferative response was more pronounced in patients with a resected primary tumor and patients with low (≤ 10%) hepatic tumor load. Additional studies with higher patient numbers are necessary to identify further parameters that may influence the antiproliferative effect of octreotide LAR.

Only treatment-naive patients were included in this trial, and therefore, almost all patients had newly diagnosed tumor disease. Patients with high tumor load at diagnosis had a poorer prognosis than patients with few liver metastases. As such, we suggest that newly diagnosed patients with a low hepatic tumor burden and a resected

**Table 4.** Quality of Life and Symptomatic and Biochemical Response

| Quality of Life and Response | Study Entry | | | | | | Six Months | | | | | | Change From Study Entry to Six Months* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Octreotide LAR | | | Placebo | | | Octreotide LAR | | | Placebo | | | Octreotide LAR | | | Placebo | | | | | |
| | Total No. of Patients | No. of Patients with Events | % | Total No. of Patients | No. of Patients with Events | % | Total No. of Patients | No. of Patients with Events | % | Total No. of Patients | No. of Patients with Events | % | Total No. of Patients | No. of Patients with Events | % | Total No. of Patients | No. of Patients with Events | % | Δ (%)† | 95% CI (%)† | *P* |
| Quality of life: EORTC QLQ-C30 score | 38 | | | 42 | | | 29 | | | 24 | | | 25 | | | 24 | | | 2.1 | −7.8 to 12.0 | .6738 |
| Mean | | 64.0 | | | 65.7 | | | 68.1 | | | 64.2 | | | 0.0 | | | −2.1 | | | | |
| SD | | 22.3 | | | 24.7 | | | 23.2 | | | 19.6 | | | 18.5 | | | 15.8 | | | | |
| Symptomatic response | | | | | | | | | | | | | | | | | | | | | |
| Flushs | 42 | 10 | 23.8 | 43 | 12 | 27.9 | 32 | 4 | 12.5 | 25 | 3 | 12.0 | 10 | 7 | 70.0 | 12 | 3 | 25.0 | 45.0 | 7.5 to 82.5 | .0836 |
| Diarrhea | 42 | 6 | 14.3 | 43 | 7 | 16.3 | 32 | 7 | 21.9 | 25 | 7 | 28.0 | 6 | 2 | 33.3 | 7 | 1 | 14.3 | 19.0 | −26.7 to 64.8 | .5594 |
| Abdominal pain | 42 | 10 | 23.8 | 43 | 10 | 23.3 | 32 | 7 | 21.9 | 25 | 4 | 16.0 | 10 | 5 | 50.0 | 10 | 2 | 20.0 | 30.0 | −9.7 to 69.7 | .3498 |
| Biochemical response | | | | | | | | | | | | | | | | | | | | | |
| Chromogranin A elevated | 41 | 26 | 63.4 | 42 | 30 | 71.4 | 30 | 13 | 43.3 | 20 | 12 | 60.0 | 26 | 9 | 34.6 | 30 | 4 | 13.3 | 21.3 | −0.7 to 43.2 | .1106 |

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; SD, standard deviation.
*Quality of life: difference compared to study entry; symptomatic response: reduction of symptoms to < one flush per week and to < four stool movements per day and disappearance of abdominal pains compared with study entry; biochemical response: normalization of elevated plasma chromogranin A levels compared with study entry.
†Values are expressed as percentage of patients, except for quality of life values, which are expressed as EORTC QLQ-C30 scores.

primary tumor are candidates for treatment with octreotide LAR. Further studies are needed to determine whether patients with a high hepatic tumor burden that developed slowly respond to biotherapy more favorably.

Treatment of patients after tumor progression was at the discretion of the individual study center, and most patients from the placebo group received subsequent treatment with a somatostatin analog. In addition, many patients in the active treatment arm continued with-octreotide LAR. Thus, long-term observation of patients not receiving octreotide LAR is difficult. Although prolongation of time to tumor progression by antiproliferative treatment may influence overall survival, we cannot, from this study, make conclusions regarding overall survival.

According to the protocol, analysis of time to tumor-related death should be based on 121 events. Because of the observed positive effects of octreotide LAR on tumor growth and a slow recruitment rate, we decided to stop further enrollment without unblinding the nine patients still under treatment. Follow-up of this study population will continue on a yearly basis until death.

We conclude that octreotide LAR inhibits tumor growth in patients with metastatic midgut NETs. Further studies should investigate the role of hepatic tumor load in more depth because the number of patients with high tumor burden was low. The important secondary study aim of whether or not the favorable effect of octreotide LAR on time to tumor progression indicates prolonged overall survival could not be determined. We believe that biotherapy with octreotide LAR is the treatment of choice in patients with newly diagnosed, functionally active or inactive, well-differentiated metastatic midgut NETs and with a low hepatic tumor load. Additionally, octreotide LAR may be an attractive treatment option for patients after cytoreductive surgery with few remaining metastases. We propose that the impact of biotherapy on time to tumor progression and overall survival should be investigated further in clinical trials, in addition to studies including patients with NETs of other origins.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

**Employment or Leadership Position:** None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** Anja Rinke, Novartis; Michael Bläker, Novartis; Rudolf Arnold, Novartis **Research Funding:** Anja Rinke, Novartis; Klaus-Jochen Klose, Novartis; Peter Barth, Novartis; Rudolf Arnold, Novartis **Expert Testimony:** None **Other Remuneration:** None

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