SPINET: a randomized, double-blind, placebo-controlled phase 3 study of lanreotide autogel/depot in patients with advanced lung neuroendocrine tumors

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Background

- Metastatic lung neuroendocrine tumors (NETs) are rare and no prospective trials specific to lung NETs have been reported.[1,2]
- Surgical resection remains the mainstay for lung NETs; other approved treatment options for advanced lung NETs are limited, with no standard therapeutic regimen.[3]
- For advanced lung NETs:
  - Currently, recommendations for most treatment options rely on data available for well-differentiated digestive NETs or a few retrospective studies in lung NETs, while emphasizing that the disease parameters differ.[3,4]
  - The mTOR inhibitor everolimus was recently approved as a treatment option for lung NET in the US and EU based on one placebo controlled phase 3 trial (RADIANT 4) in a mixed population of patients with advanced progressive gastrointestinal and lung NETs.[5]
- Somatostatin analogs (SSAs) are among targeted treatments that have recently demonstrated increased progression-free survival (PFS) among patients with NETs, particularly those with gastroenteropancreatic NETs.[5–7]
- The large multinational phase 3 CLARINET study demonstrated antitumor efficacy with the SSA lanreotide depot (also known as autogel) vs. placebo for metastatic gastroenteropancreatic NETs.[8,9]
- Patients with lung NETs were not included in CLARINET, and prospective randomized studies of SSA therapies for these particular NET subtypes are currently lacking.
- High levels of expression of the somatostatin receptors SSTR2A and SSTR3 in these malignancies[10] provide a rationale for a management approach involving SSAs.

Objective

- The large multinational phase 3 investigational study SPINET aims to evaluate the antitumor efficacy and safety of lanreotide depot 120 mg vs. placebo, both in addition to best supportive care (BSC), in patients with metastatic and/or unresectable, typical or atypical (well-differentiated) lung NETs.

Methods

Patients

- 216 patients with lung NET will be enrolled from around 80 sites across the USA, Canada, and Europe.
- Key inclusion and exclusion criteria are shown in Table 1.

Study design

- SPINET is a phase 3 prospective randomized investigational study comprising a double-blind period and an optional open-label extension period (NCT02683941; EudraCT: 2015-004992-62) (Figure 1).
- Patients are randomly allocated (2:1) to either lanreotide depot 120 mg or placebo every 28 days, both arms also receiving BSC. Randomization is stratified for typical vs. atypical NETs and prior vs. no prior chemotherapy.

Table 1. Key inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Adult patients (≥18 years) with metastatic and/or unresectable, pathologically confirmed well-differentiated, typical or atypical lung NETs	Previous SSA treatment (>15 days of short-acting SSA or ≥2 doses of long-acting SSA within 6 weeks of randomization)
Mitotic index <2 mitoses/2mm² for typical tumor; or <10 mitoses/2mm² and/or foci of necrosis for atypical tumor	More than 1 course of CTx (cytotoxic CTx, MTT, or IFNα) for lung NET at any time prior to randomization
Positive somatostatin-receptor imaging (grade 2 or higher on Krenning scale)	CTx treatment (cytotoxic CTx, MTT, or IFNα) for lung NET within 4 weeks of randomization
≥1 lesion of the disease is measurable with RECIST v1.1 on CT or MRI	PRRT at any time prior to randomization
ECOG performance status score of 0–1	Surgical treatment within 6 weeks prior to randomization
Negative pregnancy test, non-lactating and using acceptable method of birth control (as applicable)	Functional disease requiring SSA treatment for symptom management

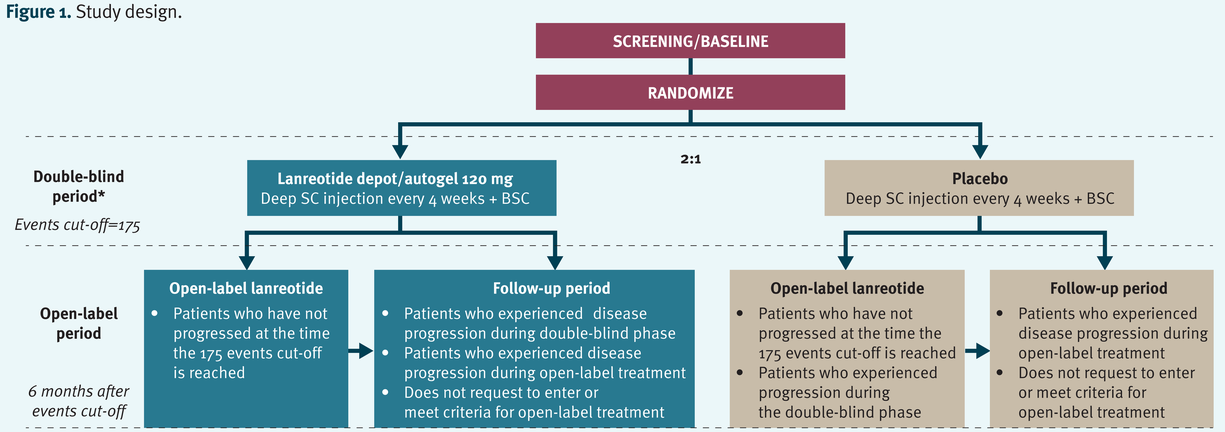
CT, computed tomography; CTx, chemotherapy; ECOG, Eastern Cooperative Oncology Group; IFNα, interferon α; MRI, magnetic resonance imaging; MTT, molecular targeted therapy; NET, neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; RECIST, response evaluation criteria in solid tumors; SSA, somatostatin analog.

- The double-blind period will continue until progressive disease (PD) centrally assessed/death (or withdrawal from the study treatment for unacceptable toxicity or any other reason) or until the date of data cut-off/primary study analysis (when 175 PD according to central review or death events are reached).
  - Patients with centrally assessed PD on placebo may opt to enter the open-label extension period.
  - Patients without centrally assessed PD on lanreotide depot 120 mg at the data cut-off date of double-blind period may opt to enter the open-label extension period.
- The open-label period will last until 6 months after the data cut-off date.
- All patients who experience PD will be followed to document survival, quality of life (QoL), and subsequent anti-cancer treatments; eligible patients who do not choose to receive open-label lanreotide will also be followed.

Study assessments and endpoints

- Efficacy and safety endpoints are shown in Table 2.
- Study visits in the double-blind phase occur at screening, baseline, weeks 8 and 12, and every 12 weeks thereafter, with a post-treatment/early withdrawal visit within 30 days of last study drug injection. The latter can serve as the baseline visit for the open-label extension phase.
- Scans of the thorax and abdomen are performed at baseline, every 12 weeks (or earlier if clinically indicated) and at the post-treatment/early withdrawal visit (computed tomography [CT] scan of thorax and abdomen or magnetic resonance imaging of the abdomen with CT scan of thorax).

Figure 1. Study design.



*Double-blind period will end when 175 events (centrally assessed progressive disease or death) have occurred (data cut-off for primary endpoint analysis); at this point, all remaining patients without progressive disease who are still receiving blinded study treatment will enter the open-label extension period (treatment or follow-up periods).
BSC, best supportive care; SC, subcutaneous.

Table 2. Study endpoints.

Primary endpoint: PFS
Time from randomization to PD or death from any cause
Centrally assessed every 12 weeks (RECIST v1.1)

Main secondary efficacy endpoints
- PFS according to local review
- Time to treatment failure
- Disease control rate*
- Objective response rate†
- Overall survival
- Changes in plasma CgA levels
- Changes in urinary 5-HIAA levels‡
- Lanreotide pharmacokinetics
- QoL (EORTC QLQ-C30)
- Patient satisfaction (TSQM-9 scale)

Secondary safety endpoints
- Adverse events#
- Clinical evaluations
- Gallbladder echography, if warranted

Exploratory endpoints
Baseline factors associated with PFS, including:
- Mitotic count
- SRI (Krenning scale)
- CgA level
- Number of metastatic organs
- Hepatic and intrathoracic tumor load

PFS will be estimated in the intention-to-treat population (all randomized patients) using the Kaplan-Meier method within each treatment arm; median PFS and its associated 95% CI will be estimated, and the treatment effect will be compared using a stratified log-rank test. *Disease control rate is the proportion of patients with a best overall response of PR, CR or SD. †Objective response rate is proportion of patients with a best overall response of PR or CR. #Adverse events will be assessed for all patients (safety population) throughout the study and up to 30 days after the last study drug administration, coded by medical dictionary for regulatory activities (MedDRA) preferred term, and graded by National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) v4.03. ‡5-HIAA will only be assessed post-baseline if clinically indicated or elevated at baseline.
5-HIAA, 5-hydroxyindoleacetic acid; CgA, chromogranin A; CR, complete response; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; PD, progressive disease; PFS, progression-free survival; PR, partial response; QoL, quality of life; RECIST, response evaluation criteria in solid tumors; SD, stable disease; SRI, somatostatin receptor imaging; TSQM, Treatment Satisfaction Questionnaire for Medication.

Discussion

- Treatment of advanced lung NETs continues to be an area of unmet need; the role of SSAs and other molecular targeted therapies on these diverse and clinically challenging tumors requires further research.
- Results from ongoing phase 3 clinical trials such as this study will provide the data needed to help evaluate the efficacy and safety of potential new treatment options for advanced lung NETs.
- SPINET is the first prospective, placebo-controlled, randomized study designed to assess the effect of lanreotide depot/autogel 120 mg on typical and atypical carcinoid lung NETs.

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