External validity of somatostatin analogues trials in advanced neuroendocrine neoplasms: the GETNE-TRASGU study

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Research article

Manuscript title: External validity of somatostatin analogues trials in advanced neuroendocrine neoplasms: the GETNE-TRASGU study

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ABSTRACT

Introduction: Somatostatin analogues (SSA) prolong progression-free survival (PFS) in patients with well-differentiated gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs). However, the eligibility criteria in randomized clinical trials (RCTs) have been restricted, which contrasts with the vast heterogeneity found in NENs.

Methods: We identified patients with well-differentiated (Ki67% $\leq 20\%$), metastatic GEP-NENs treated in first-line with SSA monotherapy from the Spanish R-GETNE registry. The therapeutic effect was evaluated using a Bayesian Cox model. The objective was to compare survival-based outcomes from real world clinical practice versus RCTs.

Results: The dataset contained 535 patients with a median age of 62 years (range: 26-89). The median Ki67% was 4 (range: 0-20). The most common primary tumor sites were: midgut, 46%; pancreas, 34%; unknown primary, 10%; and colorectal, 10%. Half of the patients received octreotide LAR (n=266) and half, lanreotide autogel (n=269). The median PFS was 28.0 months (95% CI, 22.1-32.0) for octreotide vs 30.1 months (95% CI, 23.1-38.0) for lanreotide. The overall hazard ratio for lanreotide vs octreotide was 0.90 (95% credible interval, 0.71-1.12). The probability of effect sizes $>30\%$ with lanreotide vs octreotide was 2% and 6% for midgut and foregut NENs, respectively.

Conclusion: Our study evaluated the external validity of RCTs examining SSAs in the real world, as well as the main effect-modifying factors (progression status, symptoms, tumor site, specific metastases, and analytical data). Our results indicate that both octreotide LAR and lanreotide autogel had a similar effect on PFS. Consequently, both represent valid alternatives in patients with well-differentiated, metastatic GEP-NENs.

Introduction

Somatostatin is a hormonal peptide that naturally inhibits endocrine and exocrine secretion. In neuroendocrine neoplasms (NENs), somatostatin slows tumor growth and has antiproliferative, antiangiogenic, and proapoptotic effects [1]. Somatostatin acts through a family of G-protein-coupled receptors, five subtypes of which are known (SSTR1-SSTR5); their activation brings about a complex intracellular cascade [2]. Given that, most gastroenteropancreatic NENs (GEP-NENs) express several SST receptors (SSTR) isoforms, synthetic somatostatin analogues (SSAs) have been developed with antisecretory and antiproliferative effects.

Octreotide LAR and lanreotide autogel are the only SSAs currently available that have proven their efficacy in randomized-controlled trials (RCTs) with progression-free survival (PFS) as their primary end-point [3,4]. However, evidence continues to be relatively scant, given that these RCTs, in addition to having small sample sizes, have applied restricted eligibility criteria, in stark contrast with the tremendous clinical and molecular heterogeneity exhibited by NENs. In the PROMID study, 85 German patients with advanced NENs of midgut origin and Ki-67 values of up to 2% (95%) were randomized to receive octreotide LAR 30 mg or placebo every 4 weeks [3]. While the octreotide LAR-treated participants had a longer PFS (14.3 vs 6 months, $P < 0.001$), this population is by no means representative. Thus, barely 16% of the Spanish National Cancer Registry (R-GETNE) sample would have met these selection criteria [5]. More recently, the CLARINET trial randomized 204 patients with advanced, Ki-67 $< 10\%$, non-functioning, SSTR-positive NENs to lanreotide autogel 120 mg or placebo every 4 weeks [4]. This sample was greater, insofar as the trial enrolled subjects with NENs of pancreatic, midgut, hindgut, or unknown origin. Treatment with lanreotide autogel significantly prolonged PFS (median not reached vs 18 months, respectively, $p = 0.0002$). Nevertheless, it is crucial that we bear in mind that 96% had documented stable disease, which happens in $< 10\%$ of the individuals when deciding on treatment [6]. Moreover, 68% of the NENs were Ki-67 $\leq 2\%$, while in the real world, this group comprises approximately one quarter of the tumors [7]. Despite the fact that CLARINET is a larger RCT, given the variability of tumor sites, each of the strata comprises very few patients (e.g., the inference regarding hindgut tumors is based on 14 individuals). Therefore,

the statistical evidence was limited for pancreatic (hazard ratio [HR]=0.58; 95% confidence interval [CI], 0.32-1.04) or hindgut NENs (HR=1.47; 95% CI, 0.16-13.24), which could be due to the small size of these subgroups.

When all the SSA RCTs are pooled, the scant representativity of certain tumor subtypes is conspicuous, such as grade 2 NENs, extraintestinal tumors, or those in progression, pointing to the need to ascertain the external validity of these RCTs with real world evidence (RWE). External validity is a broad construct that refers to the ability to generalize the inference of the RCTs, extrapolating trial outcomes from one population to another [8,9]. The concept is not purely statistical; instead, it covers a whole series of determinants that include eligibility criteria, pathological traits, access to new therapies, geographic disparity, etc. Given the changing conditions of clinical practice and the target population, it is fitting that a revision of the inferential generalizability of past RCTs be undertaken from time to time [9–12]. This notion is particularly germane in this case, given the paucity of data regarding effect-modifying factors [6,13].

In addition to these gaps in knowledge, there is the fact that no RCT has directly compared the anti-tumor effect of both SSAs and it is unlikely that such a study will materialize in the immediate future. Although both SSAs target SSTR2, exhibiting lower affinity for SSTR5, relevant differences between both drugs may potentially influence their antiproliferative activity, including different affinities for the receptor, their ability to stabilize their active conformations, drug formulation, administration route, pharmacokinetics, bioavailability, and the different antiproliferative doses. As for endocrine secretion control, a small crossover trial found that lanreotide autogel and octreotide LAR appeared equally effective in alleviating carcinoid syndrome, inducing similar reductions of urinary 5-hydroxyindole acetic acid (5-HIAA) and plasma serotonin [14]. However, as for their antiproliferative effects, caution must be exercised when assuming bioequivalence by virtue of molecular similarities, and the relative sensitivity of individual GEP-NET subtypes to a particular SSA has yet to be elucidated [15].

Our study sought to shed light on these vital issues. Accordingly, we endeavored to explore the trend observed in RCTs in a national registry of GEP-NENs (R-GETNE) with the aim of

contrasting RCTs with a broader and contextually rich series, as well as to evaluate the differential effect of octreotide LAR vs lanreotide autogel on PFS.

Materials and Methods

Patients

Participants were from the hospital-based National Cancer Registry (R-GETNE) (data cut-off date for analyses: December 2018) with the participation of 74 Spanish centers and The Christie NHS Foundation Trust, ENETS Centre of Excellence, Manchester, United Kingdom. Patients initiated therapy between 2002 and 2017. The design, characteristics, and quality criteria of this registry have been previously reported [5,6,16–18]. Data from a total of 4,068 available cases were screened for eligibility and additional quality controls were implemented for this analysis (double-checking of data, monitoring of discrepancies, and unjustified missing data).

Eligibility criteria for this sub-study included: (1) presence of advanced disease measurable by RECIST v1.1 that had been monitored by computed tomography (CT) at least every 3-6 months until documentation of disease progression [19], (2) histologically-confirmed GEP-NEN, (3) well-differentiated tumor as per the WHO 2010 classification with Ki-67 $\leq 20\%$ [20], and (4) use of SSA (lanreotide autogel or octreotide LAR) in monotherapy, as first-line antiproliferative treatment, with the intention of disease control until radiological progression. Patients were excluded if they received other concurrent systemic therapies, underwent surgery for metastases, or had inadequate documentation (preventing effective analysis of clinical information). All consecutive cases meeting these eligibility criteria, without any subsequent sample matching, were selected. The flow-chart reflecting the selection process can be found in Annex Fig. 1.

Objectives & variables of interest

The primary endpoint of this study was PFS, defined as the period of time between initiation of SSA treatment and tumor progression or death due to any cause, censoring individuals with no event at last follow-up. The main objective was to compare survival-based outcomes from real world clinical practice versus RCTs. Other objectives were to explore the potential

appropriateness of PFS as a surrogate endpoint for overall survival (OS), and to compare the treatment effect of lanreotide autogel vs octreotide LAR on PFS, which was designed as an exploratory objective, interpretable as a hypothesis generator.

In this non-randomized study, confounding factors were chosen after reviewing the literature and consulting the Spanish Taskforce Group of Neuroendocrine Tumors (GETNE) experts, in such a way that all variables potentially involved in prognosis and treatment selection were taken into account. Thus, in order to adjust for the differential effect of the SSAs, patient (age, gender, Eastern Cooperative Oncology Group Performance Status [ECOG-PS]), tumor (primary tumor site, Ki-67%, histological differentiation, hepatic tumor burden, peritoneal metastases, bone metastases, documented progression status prior to initiating SSA [tumor progression vs stable disease not documented or <3 months, vs stable disease ≥ 3 months], symptoms), laboratory (alkaline phosphatase, neutrophil-lymphocyte ratio [NLR], hemoglobin, platelets), and treatment-related variables (year initiated, dosage) were taken into consideration.

Given the small number of patients in each specific location, tumors were grouped into three subgroups for analysis: foregut (stomach, pancreas), midgut (duodenum, jejunum, ileum, appendix, ascending colon), and hindgut (descending and sigmoid colon, and rectum) [4].

Statistical analysis

Therapeutic effects were evaluated by means of Bayesian Cox models. A detailed justification of the advantages of Bayesian models, as well as their interpretation, have been extensively described by several authors [21–25]. In particular, instead of null hypothesis significance testing, the intention was to estimate the actual probability of benefit in favor of one of the drugs [22]. Acknowledging the absence of previously published information, a weakly informative prior was applied for the therapeutic effect, and covariates: $\sim N(0, 10)$. Considering the rationale of this research (see above), subgroup effects were explored with moderate skeptic priors on all interactions $\sim N(0, 0.5)$.

To measure convergence, we used trace plots for Markov Chain Monte Carlo (MCMC) sample and Gelman-Rubin convergence measurement (Rhat) for all variables, denoting adequate

convergence ($R_{\text{hat}} < 1.1$ for all parameters, see Annex Figure 2). Covariates with $>20\%$ missing values were discarded. Multiple imputation by chained equations was used in the remainder variables. In no case were data-driven methods used to select covariates (see above). Continuous variables were evaluated using restricted cubic splines. Correlation between PFS and OS was computed by means of Kendall's τ associated with Clayton's copula models for bivariate survival data. Analyses were performed with the R software package v3.1.6, with mice, splines, bayestestR, rms, brms, and rstanarm packages [26–28]. To visualize certain effects, interactive graphics have been generated with the Plotly R graphing library [29].

RESULTS

Patients

A total of 535 consecutive, eligible patients were included. **Table 1** displays the baseline characteristics of these patients. One-half received lanreotide autogel ($n=269$) and the other half, octreotide LAR ($n=266$). A median of 21 doses were administered (range 1-168). Treatment was started at the usual recommended dose in 80% (octreotide LAR, 30 mg) and 86% (lanreotide autogel, 120 mg every 4 weeks) of patients. Dosage was increased in 14% during follow-up and reduced in 0%; only 3.6% interrupted therapy for more than 1 month during treatment. The clinico-pathological characteristics were similar for both SSAs. The use of lanreotide autogel has increased over time (72% of SSAs used from 2016 onward). At the time of analysis, 350 progression events and 228 of death were reported, with a median PFS of 27.6 months (95% CI, 23.5-30.7) and median OS of 85.9 months (95% CI, 71.5-96.6) (**Fig. 1**). Death without radiological confirmation of progression occurred in 19 patients (14 with lanreotide autogel, 5 with Sandostatin LAR).

PFS correlated modestly with OS (Kendall's $\tau = 0.553$, standard error [SE] = 0.027). Both SSAs, lanreotide vs octreotide, were well tolerated with diarrhea being the most frequent toxicity (20.2% vs 20.0%, respectively); serious adverse events were infrequent with cholelithiasis being the most common (7.2 vs 10.2%, respectively) (**Table 2**).

Comparison of octreotide LAR and lanreotide autogel

At the time of analysis, 159 progression and 103 death events had been detected in the lanreotide autogel group, compared to 191 progression and 125 death events with octreotide LAR. The median PFS and OS for lanreotide autogel vs octreotide LAR were 28.6 months (95% CI, 23.2-31.1) vs 27.3 (95% CI, 20.9-31.1), and 85.0 months (95% CI, 65.5-103.4) vs 85.9 (95% CI, 70.1-96.6), respectively (see global PFS data in [interactive graph](#)).

The overall HR for lanreotide was 0.90 (95% credible interval [CrI], 0.71-1.12). The probability that this parameter was in the region of practical equivalence (ROPE, corresponding to HR=1, +/- 0.1) was 48% (see density plots in **Fig. 2**). The posterior probability that the therapeutic effect of lanreotide exceeded that of octreotide by more than 15% and 30% (HR <0.85 and <0.7) was 31% and 2%, respectively. In the frequentist Cox model, the effect size was comparable (HR=1.03, 95% CI, 0.81-1.32, p=0.792) (**Fig. 3**).

Therapeutic effect was estimated in the subgroup with a positive octreotide scan in a sensitivity analysis; no substantial variations were revealed (HR for progression of 0.98, 95% CI, 0.77-1.24). Median PFS was 29.2 months (95% CI, 24.9-31.8) if the octreotide scan was positive, versus 19.4 months (95% CI, 15.7-29.8) if an octreotide scan had not been performed (log-rank, p-value=0.06).

Conditional effects

Figures 4 and 5 illustrate the PFS/OS Kaplan-Meier curves for the different tumor locations. For lanreotide autogel, PFS medians were 20.3, 42.4, and 47.9 months for foregut, midgut, and hindgut tumors, respectively. Similarly, PFS medians were 22.2, 41.9, and 18.4 months in the case of octreotide LAR, in the same strata. Depending on the primary tumor site, the Bayesian probability of a HR <0.70 in favor of lanreotide was 6%, 2%, 37% and 47% for foregut, midgut, hindgut and tumors of unknown origin, respectively.

The remaining conditional effects are summarized in **Table 3**. Among these, the probability of effect size >30% in favor of lanreotide (HR <0.70) was 76% for those patients with prior stable disease for more than three months at time of SSA initiation.

The interaction between the therapeutic effect and Ki67 was also explored using a Cox frequentist model (see [interactive graph](#)); nevertheless, the statistical support in favor of the interactions was modest. The effectiveness of both SSAs was stable over the years (**Fig. 6**).

DISCUSSION

With this study, we have updated the external validity of the international bibliography as regards first-line SSA treatment for advanced GEP-NENs [3,4]. Overall, our data reveal substantial similarities and differences with respect to previous RCTs. Thus, the median PFS we detected in the lanreotide autogel-treated group (28.6 months) is consistent with long-term follow-up reports of the CLARINET RCT (30.8 months in a *post hoc* analysis) [30,31]. When broken down by tumor type, discreet differences are found in the median PFS in the CLARINET trial (29.7 and 61.5 months for foregut and midgut tumors) *versus* our series (20.3 and 42.4 months) [32]. Conversely, the median OS here is approximately seven years, and it was not reached after 9.2 years of follow-up in the CLARINET study [31]. As for the PROMID trial, our OS data are comparable (median of 84.7 vs 85.9 months). The most sizable difference is the shorter median PFS in the PROMID trial (14.3 months) relative to our data (41.9 months in midgut tumors), which is congruent with data reported by other authors [33,34]. All this indicates that PFS varies depending on the tumor type, which must be considered when comparing studies. Thus, the favorable PFS and OS in the CLARINET study is linked to the good baseline prognosis of the sample, i.e., enriched with stable, grade 1 NENs.

Contrary to the longer time-to-event reported in the CLARINET study, our data point toward a scant probability that either SSA can be associated with a substantial increase in PFS in patients with foregut and midgut NENs. This conclusion would support the pharmacokinetic similarities of both drugs, their comparable affinity profile for SSTR2 and SSTR5 [15,35], apparent equivalence on symptomatic control, similar reduction of biochemical markers in patients with both carcinoid syndrome and acromegaly [14,36–40], and similar antiproliferative effect [41]. Therefore, the different results between the two studies are probably due to the composition of the samples.

Assessing therapeutic equivalence could be more complex, given that SSTR2 and SSTR5 distribution and density vary and are often low for effective biological interaction. Thus, pharmacodynamic aspects could be crucial. While octreotide has more *in vitro* affinity for SSTR2 and SSTR5 than lanreotide autogel [15,35], this does not translate directly to SSA activity, given the different formulations of both drugs. In fact, the most effective antiproliferative doses have scantily been studied and have instead, been merely extrapolated from their antisecretory effects [42]. Additionally, several studies have shown that SSTR2 and SSTR5 are expressed heterogeneously in different tumor sites and depending on the degree of differentiation [43–45], with potential clinical and prognostic impact [43,44].

Therefore, pancreatic NENs express more SSTR2 than gastrointestinal NENs [44]. Similarly, studies with ¹¹¹Indium-DOTA-[Tyr3]-octreotide (¹¹¹In-DOTA-TOC) suggest lower receptor density in hindgut NENs [46]. Tumors with lower SSTR2 and SSTR5 density may require adapted doses. Likewise, in patients with acromegaly, it has been speculated that titrated doses of SSAs are more effective than fixed doses [47,48]. Although data are limited, high doses or switching between SSAs is sometimes effective in clinical practice after progression to antiproliferative doses [13,49] which would appear to endorse this hypothesis.

Lanreotide autogel and Sandostatin LAR have different approved indications. Both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved lanreotide autogel as an antiproliferative treatment for grade 1-2 GEP-NENs, while Sandostatin LAR was approved by EMA for midgut or unknown primary tumors, or as a symptomatic therapy. Still, both are prescribed off-label interchangeably, as demonstrated by the similarity of use in this registry. With this in mind, our study has sought to explore the anti-proliferative effects as a function of the primary tumor site.

Our results replicate the trends observed in RCTs and suggest that octreotide LAR and lanreotide autogel are equally effective in foregut (pancreas and stomach) and midgut NENs (small bowel, appendix and right colon). Colonic NENs deserve additional attention; in our series, right colon NENs had a prognosis comparable to all other midgut NENs, while tumors originating in the left colon and rectum (hindgut) were the most aggressive [6]. The few existing data in the literature

indicate that hindgut NENs have a somewhat different molecular biology and SSTR expression pattern [50,51]; hence, they might respond differently to therapy. In fact, the EMA excluded all colorectal NENs from the indication for lanreotide autogel, due to lack of evidence in the CLARINET study (HR=1.47, 95% CI 0.16-13.24) [52]. In contrast, our data support SSA treatment for right colorectal tumors, taking into consideration the factors that predict benefit [6]. In interpreting the results, it is also important to note that the endpoint currently considered clinically relevant (i.e., PFS), depends on radiological progression according to morphological criteria (RECIST). This entails certain limitations in NENs, as functional differences are not factored in [18]. For its part, PFS is deemed an acceptable surrogate endpoint for OS in RCTs of NENs [53]. Nonetheless, there is little information specific for SSA-treated patients, and Imaoka *et al's* analysis points to a substantially lower correlation in this context, probably because tumors treated in first-line with SSAs are indolent and have multiple possibilities of subsequent therapies [53]. Our data coincide with Imaoka's in that the correlation of PFS and OS is modest, with no relevant variations in OS estimates.

Moreover, to the extent that PFS differences between the two SSAs are small and the molecules are similar, the local pharmacoeconomic context should be considered as another relevant aspect in the treatment decision [54,55]. However, variability in cost between different countries and the imminent introduction of biosimilars makes such analysis challenging.

Certain limitations to this study are worth highlighting. One is the retrospective nature of the database, although all information in R-GETNE was double-checked and inconsistencies were monitored in both cohorts. While the series comprises patients treated from 2000 onwards, our analysis denotes that the propensity to declare progression has not changed, nor have differential effects been substantially diluted over the years. However, this must be taken into account in the interpretation of the analysis. Second, subgroup analyses have obvious limitations, such as low statistical power and uncertainty when the subject falls into subgroups that reveal opposite effects, leading to possibly spurious inferences [56]. Third, this is a non-randomized study and although multivariable models have contemplated the most important covariates in NENs, the presence of residual confounding bias in favor of lanreotide autogel cannot be ruled out,

particularly in the case of stable or hindgut NENs. Fourth, although no intervention was made on the timing of the CT-scans, an evaluation by RECIST v1.1 was required at least every 6 months, in the absence of any suspicion of a different time pattern for each therapy. Therefore, as for interpretation, these results should be considered as hypothesis-generators, and aspire to stimulate the development of rigorous RCTs and expand the information available on minority subgroups, particularly hindgut NENs. Finally, the reader should understand that all subjects in this series received first-line treatment with SSA in monotherapy. Inasmuch as the results uphold the absence of substantial differences between drugs, the design does not enable inferences to be made about different strategies, such as combinations or watch and wait.

In conclusion, our data confirm the applicability of the results of the RCTs of SSAs in GEP-NETs in a real-world registry. Nevertheless, the outcomes were slightly worse compared to the CLARINET study, albeit better in terms of PFS with respect to PROMID. To probe further into the reasons for these apparent discrepancies between trials and compared to a real-world series, we took the most significant effect-modifying factors into account. This is indispensable, given the biological diversity of this pathology. Our data suggest that both SSAs have approximately equivalent efficacy, at least in pancreatic and midgut NETs and are, therefore, acceptable alternatives in most situations. With these data in hand, there is a compelling need to design new RCTs in NETs that separate out the evaluation of effects based on clinical-pathological variables, with hindgut tumors being a clear priority area for future research.

Statements

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Statement of Ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human research (institutional and national) and with the Helsinki Declaration of 1964 and later versions. R-GETNE was approved by the Research Ethics Committee of reference (Principality of Asturias, nº 107/15, 30/07/2017), the Research Ethics Committee of each participating hospital, and by the Spanish Agency of Medicines and Medical Devices (AEMPS) (12/12/2014).

Informed consent (if applicable depending on the participating institution) was obtained from patients before they were included in the study.

Conflict of Interest Statement

PJF declares travel grants from Ipsen and consulting/advisory role for Roche, Celgene, Bristol, Mylan, Rovi, LEO Pharma, all outside of the scope of this work. ACB declares travel grants from Ipsen, Roche and Novartis and consulting/advisory role for Roche, Rovi, LEO Pharma, Pfizer, Esteve all outside of the scope of this work. AL has received travel and educational support from Ipsen, Pfizer, Bayer, Advanced Accelerator Applications (AAA), SirtEx, Novartis, Mylan and Delcath; speaker honoraria from Merck, Pfizer, Ipsen and Incyte; advisory honoraria from Eisai, Nutricia, Ipsen, QED and Roche; she is also a member of the Knowledge Network and NETConnect Initiatives funded by Ipsen. JB has received travel research and educational support from Ipsen, Pfizer, AAA, Novartis and Nanostring; speaker honoraria from Novartis, Pfizer and Ipsen; advisory honoraria from Nutricia. VA declares advisory role from Amgen, Roche, Merck, Servier, Sanofi, Bayer, Ipsen, Novartis; travel accommodations from Roche, Merck, Novartis, Ipsen, Sanofi; personal fees from Amgen, Roche, Merck, Servier, Sanofi, Bayer, Ipsen, Novartis, AAA and non-financial support from Roche, Merck, Novartis, Ipsen, Sanofi. TAG declares advisory role, travel grants and research funding from IPSEN, Novartis, Roche, BMS, Pfizer, Sanofi, Janssen, Astellas, Astrazeneca. MSC has received honoraria for advisory role from KyowaKirin, research funding from Leo Pharma, travel accommodations from Sanofi, MSD, Esteve, Amgen, Servier, Angelini, financial support for educational programs from Angelini, Sanofi, Rovi. JH declares speakers' bureau for Eisai, Ipsen, Roche, Angelini Pharma; travel, accommodations and expenses for Ipsen, Novartis, AAA, Roche, AstraZeneca and Eisai. CL has received honoraria from Roche, Merck, Sanofi, Pfizer, Eisai, Ipsen, Bayer; consulting or advisory role from Amgen, Roche, Sanofi, Merck, Servier, Pfizer, Ipsen, Bayer, Eisai; research funding from Amgen, Roche, Merck, Sanofi, Bayer, Ipsen, Eisai, Celgene and travel accommodations from Roche, Pfizer, Merck, Servier, Amgen and Ipsen. ALC has received grants for meetings from: Roche, Novartis, Amgen,

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Author contributions

A.C.B. and P.J.F developed the project, analyzed the data and drafted the manuscript. A.L. and J.B. contributed to generate the idea of the present manuscript. The other authors recruited patients and provided clinical information, comments, and improvements to the manuscript. All authors participated in the interpretation and discussion of data, and the critical review of the manuscript.

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Figure Legends

Table 1. Baseline patient characteristics.

Abbreviations: ULN, upper limit of normal; LAR, long-acting release; ND, not documented; SSA, somatostatin analogue. * Defined as radiotracer uptake in the primary tumor or metastases. Proliferative doses are 120 mg for lanreotide and 30 mg each for octreotide; intermediate doses are 90 mg and 20 mg respectively; low doses are 60 mg and 10 mg, respectively.

Table 2. Most common adverse events.

Note: toxicity was evaluated according to NCI-CTC criteria v3.0.

Table 3. Evaluation of effect-modifying factors.

Abbreviations: CrI, credible interval; HR, hazard ratio; SD, stable disease; ULN, upper limit of normal. The estimates correspond to subgroup analyses (interactions). The full Bayesian Cox model (multivariable) has been used by adding one interaction at a time.

Fig. 1. Kaplan-Meier curves for PFS and OS. Abbreviations: PFS= progression-free survival, OS= overall survival.

Fig. 2. Posterior probability mass included in the Region of Practical Equivalence. Note: Continuous variables (Ki67%, year, NLR) were modelled through natural splines. A spline is a piecewise polynomial function that allows the evaluation of non-linear associations. Spline fits contain several coefficients labeled according to the number of knots; the overall effect is built by linear combinations of these estimates. Abbreviations: NLR = neutrophil-to-lymphocyte ratio, ULN = upper limit of normal.

Fig. 3. Cox proportional hazards model for PFS (frequentist approach). Note: interquartile range effects were used for continuous variables. Abbreviations: CI= confidence interval, NLR= neutrophil to lymphocyte ratio, SD = stable disease, UK = unknown, ALP= alkaline phosphatase, ULN=upper limit of normal.

Fig. 4. Kaplan-Meier curves for progression-free survival according to primary tumor site.

Fig. 5. Kaplan-Meier curves for overall survival according to primary tumor site.

Fig. 6. 6A Therapeutic effect of lanreotide autogel on PFS over time. 6B Effect of time on PFS

Table 1. Baseline patient characteristics.

Variables	All, n=535, n (%)	Lanreotide autogel (n=269) n (%)	Octreotide LAR (n=266) n (%)
Age, median (range)	63 (26-89)	64 (26-86)	64 (26-89)
Gender, female	253 (47.2)	147 (52.3)	134 (47.7)
Ki-67%, median (range)	4 (0-20)	4 (0-20)	4 (0-20)
0-2%	224 (41.8)	114 (42.3)	110 (41.3)
3-10%	251 (46.9)	129 (47.9)	122 (45.8)
11-20%	59 (11.0)	25 (9.2)	34 (12.7)
Missing values	1	1	0
Neutrophils, median (range, cells /mm ³)	290 (290-22000)	4000 (600-22000)	3700 (290-13800)
Missing values	45	19	26
Lymphocytes, median (range, cells /mm ³)	1500 (110-26400)	1700 (690-7850)	1600 (110-26400)
Missing values	56	23	33
Alkaline phosphatase			
Normal	339 (63.3)	174 (51.3)	165 (48.7)
1.1-2.5 ULN	113 (21.1)	55 (48.7)	58 (51.3)
>2.5 ULN	47 (8.7)	23 (48.9)	24 (51.1)
Missing values	36 (6.7)	17 (47.2)	19 (52.8)
Dose			
Antiproliferative dose	444 (82.9)	231 (85.8)	213 (80.0)
Intermediate	71 (13.2)	25 (9.2)	46 (17.2)
Low	13 (2.4)	11 (4.0)	2 (0.7)
Missing value	7 (1.3)	2 (0.7)	5 (1.8)
Primary tumor site			
Appendix	6 (1.1)	3 (1.1)	3 (1.1)
Right Colon	19 (3.5)	7 (2.6)	12 (4.5)
Unknown	55 (10.2)	30 (11.1)	25 (9.3)
Stomach	7 (1.3)	1 (0.3)	6 (2.2)
Small intestine	242 (45.2)	113 (42.0)	129 (48.4)
Pancreas	177 (33.0)	103 (38.2)	74 (27.8)
Hindgut	29 (5.4)	12 (4.4)	17 (6.3)
Months from metastases to SSA, median (range)	2.4 (0-84)	2.1 (0-84)	2.2 (0-80)
Documented progression status prior to SSA			
Tumor progression	190 (35.5)	93 (48.9)	97 (51.1)
Stable disease ND or <3 months	296 (50.2)	153 (51.7)	143 (48.3)
Stable disease for ≥3 months	49 (9.1)	23 (46.9)	26 (53.1)
Functioning tumor	159 (29.7)	77 (48.4)	82 (51.6)
Site of metastases			
Liver	454 (84.8)	226 (84.0)	228 (85.7)
Lymph nodes	229 (42.8)	113 (42.0)	116 (43.6)
Peritoneum	106 (19.8)	47 (17.4)	59 (22.1)
Bone	50 (9.3)	28 (10.4)	22 (8.2)
Lung	32 (5.9)	13 (4.8)	19 (7.1)
Other	30 (5.6)	16 (5.9)	14 (5.2)
Number of organs involved, mean (range)	1.7 (1-6)	1.7 (1-6)	1.7 (1-6)
Octreotide scan, performed	473 (88.4)	233 (49.2)	240 (50.8)
Positive*	431 (91.1)	213 (49.5)	218 (50.5)

Table 2. Most common adverse events

Adverse event	Lanreotide autogel, %		Octreotide LAR, %	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Cholelithiasis	7.2	1.3	10.2	1.8
Hematology	6.3	0.9	4.1	0
Malabsorption	2.7	0	1.8	0
Cardiac	0.9	0.4	1.3	0.4
Liver	6.3	1.3	8.8	0
Diarrhea	20.2	0	20.0	0
Emesis	3.1	0	2.7	0
Asthenia	18.0	0.4	21.8	0.4
Other	7.2	1.3	6.5	0.9

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Table 3. Evaluation of effect-modifying factors.

Variables	Hazard ratio (95%, CrI)	Posterior probability HR <0.70
Tumor progression	1.07 (0.76-1.49)	1%
SD not documented or < 3 months	0.84 (0.62-1.13)	10%
SD ≥3 months	0.55 (0.29-1.05)	76%
Tumor or endocrine-related symptoms	1.00 (0.81-1.23)	0
No symptoms	0.65 (0.41-1.03)	60%
Peritoneal metastases: yes	1.37 (0.89-2.11)	1%
Peritoneal metastases: no	0.83 (0.67-1.02)	9%
Bone metastases: yes	1.00 (0.57-1.75)	15%
Bone metastases: no	0.89 (0.73-1.09)	2%
Unknown origin	0.71 (0.41-1.25)	47%
Midgut	1.01 (0.73-1.38)	2%
Foregut	0.91 (0.66-1.25)	6%
Hindgut	0.75 (0.48-1.18)	37%
Alkaline phosphatase >2.5 ULN	1.55 (0.91-2.66)	1%
Alkaline phosphatase 1.1–2.5 ULN	0.74 (0.52-1.07)	39%
Alkaline phosphatase normal	0.88 (0.69-1.13)	5%
No liver metastases	1.17 (0.72-1.91)	4%
Liver involvement >50%	0.73 (0.45-1.17)	42%
Liver involvement 25–50%	0.97 (0.68-1.38)	3%
Liver involvement 0–24%	0.85 (0.59-1.21)	14%

Survival probability

1.00
0.75
0.50
0.25
0.00

Progression-free survival (PFS)
Overall survival (OS)

0

50

100

150

200

Months

Number at risk

PFS:

535

101

26

8

2

OS:

535

210

58

14

2

Region of Practical Equivalence (ROPE)

Hazard Ratio (66,95,99% CI)

0.50 0.75 1.00 1.50 2.00 2.50 3.00 3.50

Lanreotide autogel

Ki67% – 8:2

Peritoneal metastases

Asymptomatic

Bone metastases

Year – 2015:2009

NLR – 3.3:1.6

Full dose

SD >3 months

Progressive disease

Hindgut vs midgut

Foregut vs midgut

UK vs midgut

Liver involvement, >50% vs 1–24%

Liver involvement, 25–50% vs 1–24%

Liver involvement, no vs 1–24%

AP 1.1-2.5 ULN

AP >2.5 ULN

Hindgut (n=29)

Foregut (n=184)

Midgut (n=267)

Unknown origin (n=55)

Months

A **B**

Annex Figure 1. Flow-chart

Accepted manuscript