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Côme Lepage, J-M. Phelip, Astrid Lièvre, Karine Le Malicot, L Dahan, et al.. Lanreotide as maintenance therapy after first-line treatment in patients with non-resectable duodeno-pancreatic neuroendocrine tumours: An international double-blind, placebo-controlled randomised phase II trial – Prodiges 31 REMINET: An FFCD study. *European Journal of Cancer*, 2022, 175, pp.31-40. 10.1016/j.ejca.2022.07.033 . hal-03810530

HAL Id: hal-03810530

<https://hal.science/hal-03810530>

Submitted on 20 Jan 2023

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Original Research

Lanreotide as maintenance therapy after first-line treatment in patients with non-resectable duodeno-pancreatic neuroendocrine tumours: An international double-blind, placebo-controlled randomised phase II trial – Prodiges 31 REMINET: An FFCD study



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Received 24 March 2022; received in revised form 18 July 2022; accepted 29 July 2022

Available online 7 September 2022

Abbreviations: LAN, lanreotide autogel 120 mg; PBO, placebo; L1, first-line treatment.

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<https://doi.org/10.1016/j.ejca.2022.07.033>

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KEYWORDS

Clinical trial;
 Non-resectable;
 Duodeno-pancreatic;
 Neuroendocrine
 tumours;
 Maintenance

Abstract Background: Following European guidelines, patients with aggressive metastatic or locally advanced, non-resectable, duodeno-pancreatic (DP) neuroendocrine tumours (NETs) should receive systemic combination chemotherapy until progression. Aggressive disease is defined as progressive and/or symptomatic metastases with or without significant hepatic invasion (>30–50%), and/or bone metastases.

Methods: This academic randomised, double-blind, placebo-controlled phase II study aims to evaluate lanreotide autogel 120 mg (LAN) as maintenance treatment after at least 2 months of first-line treatment (L1) in aggressive G1-G2 DP-NET. Patients were randomly assigned in a 1:1 ratio to receive LAN or placebo (PBO), every 28 days, until progression or toxicity. The primary end-point was progression-free survival (PFS) at 6 months.

Results: Among the 118 planned patients, 53 were included. Of these, 81.1% had a G2 tumour, and 90.6% had metastatic disease. L1 therapy consisted of chemotherapy (96.8%). Median duration of L1 was 4.6 months (range: 2.0–7.7). At the time of randomisation, 81.1% of patients had stable disease. Median follow-up was 27.0 months (95% CI: 19.5; 31.2). PFS at 6 months was 73.1% (90% CI: 55.3; 86.6) in LAN versus 54.2% (90% CI: 35.8; 71.8) in PBO. Median PFS was 19.4 months (95% CI: 7.6; 32.6) and 7.6 months (95% CI: 3.0; 9.0), respectively. Median overall survival was 41.9 months in PBO and was not reached in LAN. The toxicity profile was mainly grade 1–2 expected toxicities.

Conclusions: The encouraging results of lanreotide autogel 120 mg as a maintenance treatment after L1 in aggressive G1/2 DP-NET should be confirmed.

Trial registration: NCT02288377 (clinicaltrials.gov).

1. Introduction

The incidence of neuroendocrine tumours (NETs) is increasing, and their prevalence is high [1]. Duodeno-pancreatic (DP) NETs are the second most frequent digestive NET, and 5-year survival for these tumours is about 30% in metastatic patients [1,2]. More than half of these tumours are diagnosed at a locally advanced or metastatic stage, and 75% of patients have liver metastases [3]. Patients with metastatic or locally advanced non-resectable DP-NET, especially those with the following poor prognostic features: progressive disease or tumour-related symptoms or a significant tumour burden (liver invasion >30–50%) or bone metastases [4], are treated in accordance with the European Neuroendocrine Tumour Society and the French Intergroup clinical practice recommendations [5,6] that is to say with systemic chemotherapy or targeted therapy (everolimus or sunitinib) in patients with a contraindication to cytotoxic chemotherapy. Chemotherapy [7–9] generally induces a response rate from 30% to 70% and a median progression free-survival (PFS) of 12–23 months. Targeted therapies [10,11] have response rates ranging from 2% to 9% and a median PFS of 11 months. However, because of chemotherapy toxicity and the long-life expectancy of these patients, some physicians prefer to stop chemotherapy (i) once disease control has been obtained (stable disease, objective response) and (ii) before complications or progression under treatment arise. Unlike many other tumours, NET often show long periods of non-progression after the first induction anti-tumour treatment. Resuming treatment is

recommended only in the event of progression and can be done either with the induction treatment or a second-line therapy. In most cases, the induction treatment is reinitiated [5,6].

By contrast, in patients with no symptoms, a low tumour burden, a non-progressive tumour and a Ki67 $\leq 10\%$, current recommendations are simply to monitor the tumour until progression (watch-and-wait strategy) or to treat with somatostatin analogues (SSA) [5,6]. Indeed, the Clarinet study [11] demonstrated the anti-tumour effect of SSA in first-line therapy in selected patients with these good prognostic factors. Therefore, we designed a clinical phase II study to determine whether lanreotide 120 mg administered every 4 weeks can maintain the objective response/stabilisation induced by the first-line treatment in patients with non-resectable DP-NETs. Indeed, SSA seem to be the best candidates for this indication as they are well tolerated and effective for patients with less severe disease [12]. The full rationale and study design details have already been published [13].

2. Methods

2.1. Study design and participants

This study was a European, prospective, multicentre, double-blind Phase II/III randomised study to evaluate lanreotide autogel (LAN, 120 mg every 28 days until disease progression) versus placebo (PBO) in patients with metastatic/locally advanced, non-resectable,

duodeno-pancreatic NETs. Before inclusion, all patients had to have been treated with at least 3 months of chemotherapy or 6 months of targeted therapy according to guidelines [5,6]. All the inclusion/exclusion criteria were reported in the design paper [13]. This clinical research was approved by an independent ethics committee (CPP Est I, 20th February 2014). All patients gave their informed consent for participation in this trial.

2.2. Randomisation and masking

In order to guarantee blinding of the investigator and all the staff, all injections were administered by a specifically trained and qualified person (for example, a nurse) otherwise not involved in the study procedures in the centre. Patients were given a randomisation/treatment arm number according to their order of entry into the study by an Interactive Web Response System (IWRS). Randomisation was done according to the minimisation technique using a 1:1 ratio and was stratified according to the following criteria: centre, grade 1 versus grade 2, first-line treatment: chemotherapy versus targeted therapy.

2.3. Procedures

Before randomisation, standard examinations (biological, clinical, ECG) and quality of life evaluations (QLQ-C30 + GINET 21) as well as the EQ-5D questionnaire including the Spitzer scale were done. In terms of imaging, chest, abdomen and pelvis CT scan with early arterial timing, or abdominal and pelvic MRI with contrast + chest CT-scan with contrast were done. In the event of a contraindication to the use of a contrast medium, abdominal and pelvic MRI + chest CT scan without contrast could be done.

The study treatment consisted of either placebo injection (1 mL of a 0.9% saline solution provided by the sponsor prepared out of the patient's view) or lanreotide autogel 120 mg. In order to maintain the blind, the placebo/lanreotide syringe was prepared out of the patient's view. The treatment had to be initiated within 6 weeks following the confirmation of stable disease or an objective response. The treatment was administered every 28 days subcutaneously.

During the study treatment, a clinical examination was done before every injection, and every 3 months, a clinical examination and CT scan were done.

2.4. Outcomes and statistical analysis

The primary end-point for this phase II study was the proportion of patients alive and progression free at 6 months after randomisation and evaluated according to the results of the imaging assessment done by the investigator in line with RECIST 1.1 criteria. LAN was considered effective in the arm if more than 45% of the

patients were alive and without progression at 6 months (63% was expected). With a one-sided alpha risk of 5%, a power of 85% (using a binomial-exact method), and with 5% of patients not evaluable or lost to follow-up, 59 patients per arm were to be randomised.

Secondary end-points included progression-free survival (PFS; at 12 months and median), overall survival (OS), toxicities (using the NCI-CTC AE version 4.0), the response rate (complete or partial response to the treatment) according to RECIST 1.1 criteria at 6 months, time to progression and quality of life (QLQ-C30, including module NET 21, the Spitzer visual analogue scale).

PFS was defined as the time between randomisation and the date of the first event (radiological or clinical progression or death). Patients who were alive and progression free were censored at the time of the last news. The duration of disease control (DDC) was defined as the sum of PFS on the treatment protocol.

Overall survival considered all deaths, and time was calculated from randomisation to death. Time to progression was calculated from the date of randomisation to the date of the first progression (clinical or radiological) according to the investigator.

The baseline description was done on the Intent-to-treat population, i.e., all randomised patients. Efficacy and safety analyses were done according to the modified intent-to-treat population, i.e., all patients randomised and treated. They were analysed according to the treatment assigned at randomisation. The population at baseline was described using descriptive statistics: percentages for categorical and ordinal variables, and means (with standard deviations), and medians (with inter-quartiles intervals and min–max) for continuous variables. The results are presented by treatment arm and for the overall population. For the efficacy analysis, time-to-event end-points were calculated from the date of randomisation and were estimated using the Kaplan–Meier method. All toxicities were described by treatment group according to the 'Common Terminology Criteria for Adverse Events v 4.0 scale' (NCI-CTCAE, Version 4.0, May 2009).

An ancillary study using samples from the bio-bank was planned to identify predictive factors other than conventional pathological staging systems to guide the identification of patients who are likely to relapse.

3. Results

3.1. Patients

Fifty-three patients were randomised in 15 centres between January 2015 and October 2018. Of these, 52 patients were treated: 25 patients in the PBO arm: and 27 patients in the LAN arm (Fig. 1). The study was terminated prematurely because of slow recruitment.

Among the 53 included patients, 81% had a G2 tumour and 90.6% had metastatic disease. Among the latter, 29.2% had extrahepatic metastases. The median time to the initial diagnosis of DPNET was 8.5 months. The proportion of patients previously treated using analogues was 14.8% (4/27) in the LAN arm and 19.2% (5/26) in the PBO arm with a median duration of 13 months [IQR: 1; 18] and 7 months [IQR: 4; 9], respectively. First-line treatment (L1) consisted of temozolomide-based (52.9%), dacarbazine-based (18.7%), streptozotocin-based (13.3%), or oxaliplatin-based (11.3%) chemotherapy or sunitinib (3.8%). The median duration of L1 was 4.6 months (range: 2–7.7). At the time of randomisation, a partial response had occurred in 18.9% and stable disease in 81.1% of patients. The baseline characteristics of patients are reported in Table 1. Table 2 lists the reintroduced treatment after progression in the LAN and PBO arms (restart of the first line or second line). For patients treated with first-line chemotherapy, a similar chemotherapy treatment was resumed at progression in 52% of cases, while a tyrosine kinase inhibitor or an mTOR inhibitor (everolimus or sunitinib) was introduced in 24% of cases.

3.2. Exposure to treatment

The median number of treatment cycles given in the LAN arm was 13 [IQR: 4; 28] versus eight [IQR: 3; 10] cycles in the PBO arm. Treatment was stopped prematurely mainly for disease progression in 21 (84.0%) and 16 (59.3%) patients in the PBO and LAN arms, respectively. Two patients in the LAN arm stopped the study for treatment-limiting toxicity: grade 3 digestive toxicity (abdominal pain, diarrhoea, and abdominal distension) in one patient and grade 2 hypoglycaemia in the other.

3.3. Efficacy

The median overall follow-up was 27 months (95% CI, 19.5–31.2). The main objective was reached: 6-month PFS was 73.1% (90% CI, 55.3–86.6) in the LAN arm versus 54.2% (90% CI, 35.8–71.8) in the PBO arm. Median PFS was 19.4 months (95% CI, 7.6–32.6) and 7.6 months (95% CI, 3.0–9.0) in the LAN and PBO arms, respectively (Fig. 2a) At 24 months, 95% ($\pm 5\%$) of the patients in the LAN arm were alive versus 26 ($\pm 14\%$) in the PBO arm. The objective response rate at 6

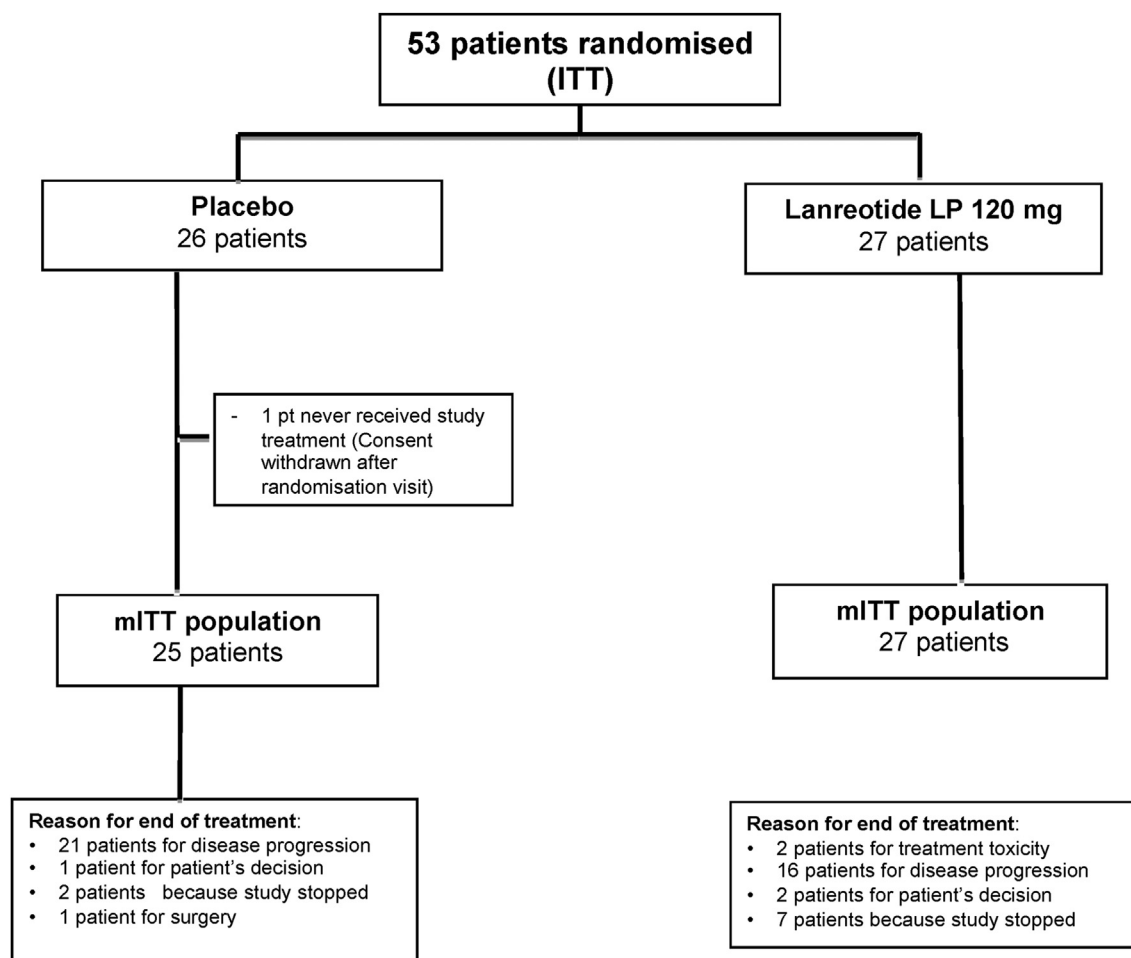


Fig. 1. CONSORT flow chart.

Table 1
Patients' baseline characteristics.

		Placebo (n = 26)	Lanreotide (n = 27)	Overall population (n = 53)
Sex	Male	13 (50.0%)	15 (55.6%)	28 (52.8%)
	Female	13 (50.0%)	12 (44.4%)	25 (47.2%)
Age	Median (IQR)	62.5 (51–71)	66.0 (57–72)	66 (56–72)
Time to initial diagnosis (months)	Median (IQR)	7.6 (6.3–11.7)	9.4 (6.7–50.0)	8.5 (6.5–41.4)
Cancer stage	Metastatic	24 (92.3%)	24 (88.9%)	48 (90.6%)
Number of metastatic sites	1	17 (70.8%)	19 (79.2%)	36 (75.0%)
	2	5 (20.8%)	4 (16.7%)	9 (18.8%)
	3	2 (8.3%)	1 (4.2%)	3 (6.3%)
Ki67 (%)	Median (IQR ^a)	5.1 (4.0–11.7)	5.0 (3.8–8.0)	5.1 (3.8–10.0)
	<3	5 (19.2%)	5 (18.5%)	10 (18.9%)
	[3–20]	20 (76.9%)	22 (81.5%)	42 (79.2%)
	≥20	1 (3.8%)	0 (0.0)	1 (1.9%)
SSA ^b pre-treatment		5 (19.2%)	4 (14.8%)	9 (17.0%)
First-line treatment (L1)	Chemotherapy	25 (96.2%)	26 (96.3%)	51 (96.2%)
	Sunitinib	1 (3.8%)	1 (3.7%)	2 (3.8%)
Details of chemotherapy	Temozolomide-based	14 (53.8%)	14 (53.8%)	28 (53.0%)
	5FU ^c + Dacarbazine	4 (15.4%)	6 (22.2%)	10 (18.9%)
	Streptozocin-based	4 (15.2%)	3 (11.4%)	7 (13.3%)
	Oxaliplatin-based	3 (11.4%)	3 (11.4%)	6 (11.4%)
Response to L1	Partial response	6 (23.1%)	4 (14.8%)	10 (18.9%)
	Stable disease	20 (76.9%)	23 (85.2%)	43 (81.1%)

Intent-to-treat.

^a IQR, Interquartile range.

^b SSA, somatostatin analogues.

^c 5-FU, 5-Fluorouracil.

months was 8.3% and 12.0%, respectively, and the median DDC (Fig. 2b) was longer in the LAN arm than in the PBO arm (46.85 months (95% CI 29.34; not reached) versus 28.15 months (95% CI 18.20; not reached)). Table 2 reports the reintroduced treatment after progression in the LAN and PBO arms.

3.4. Safety

Similar proportions of patients in the two groups had adverse events (96.3% in the LAN arm and 88.0% in the PBO arm) (Table 3). Most of these patients had moderate events. Grade 3/4 adverse events were seen in nine patients (33%) in the LAN arm versus six patients (22%) in the PBO arm. The most common grade 3/4 adverse events were abdominal pain (2 vs. 1), diarrhoea (2 vs. 0) hepatobiliary disorders (0 vs. 2), metabolic disorders (4 vs. 1) and sepsis (0 vs. 1). In the LAN arm, two patients stopped the study for treatment-limiting toxicity (cf.

above), and 18.5% of LAN patients had serious adverse events related to the study drug (vs. 12.0% in the PBO arm), most commonly gastrointestinal disorders (3 vs. 2 patients). Lanreotide-related adverse events included hyperglycaemia (in five patients who received lanreotide vs. no patients who received placebo; among these five patients, four had a history of diabetes) and cholangitis (in two patients who received lanreotide). A total of eight patients experienced 12 serious adverse events (nine in the LAN arm and three in the PBO arm). No clinically significant trends were observed in other safety assessments.

3.5. Quality of life

EORTC QLQ-C30 data were available for most of the patients at baseline and at cycles 4, 7 and 10. No overall difference was noted between study groups in global health related quality of life (Table 4); cognitive, emotional, physical and social functioning; or in other symptoms and scales either at baseline or at any other time point (data not shown). The overall difference for the Global Health Status (9 points for both cycle 7 and cycle 10) was not clinically meaningful, with the use of the minimally-important-difference approach, in which a change or between-group difference of less than 10 points is not considered clinically significant [14].

4. Discussion

This randomised trial [13] is the first to give results concerning the implementation of a maintenance

Table 2
Reintroduced treatment after progression in LAN^a and PBO^b groups (restart of the first line or second line).

	LAN ^a (n = 27)	PBO ^b (n = 25)
Treatment after progression		
Tyrosine kinase inhibitor	7.7%	25.0%
Chemotherapy	69.2%	50.0%
PRRT	—	12.5%
No further treatment	15.4%	12.5%
Other	7.7%	—

^a LAN Lanreotide autogel.

^b PBO Placebo.

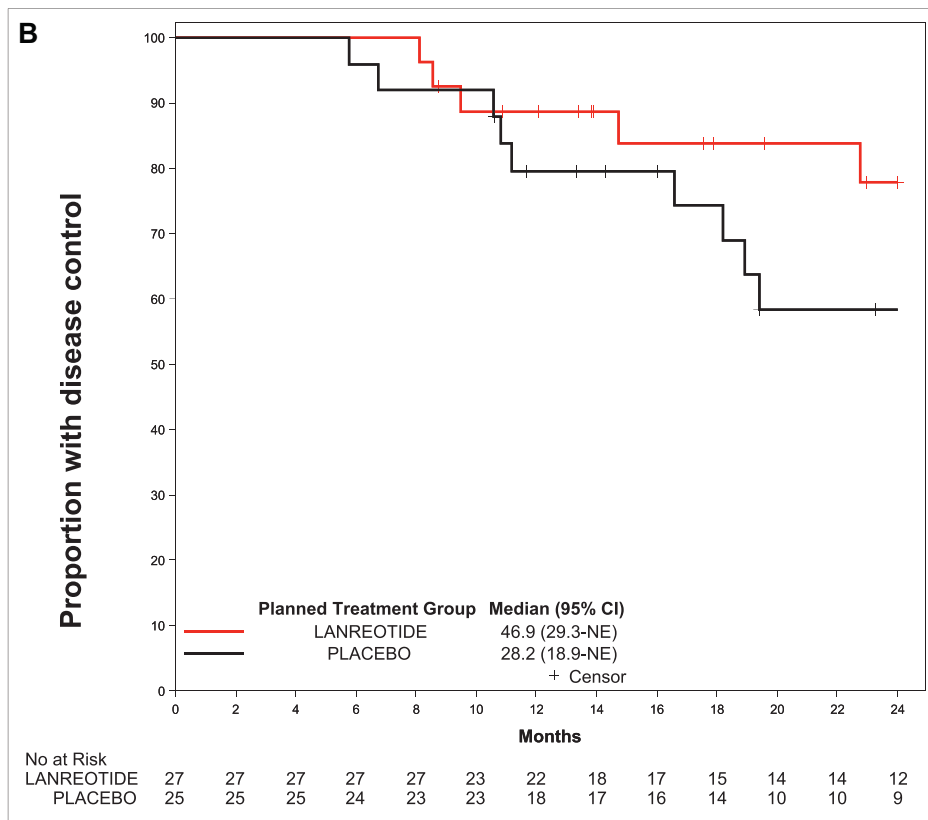
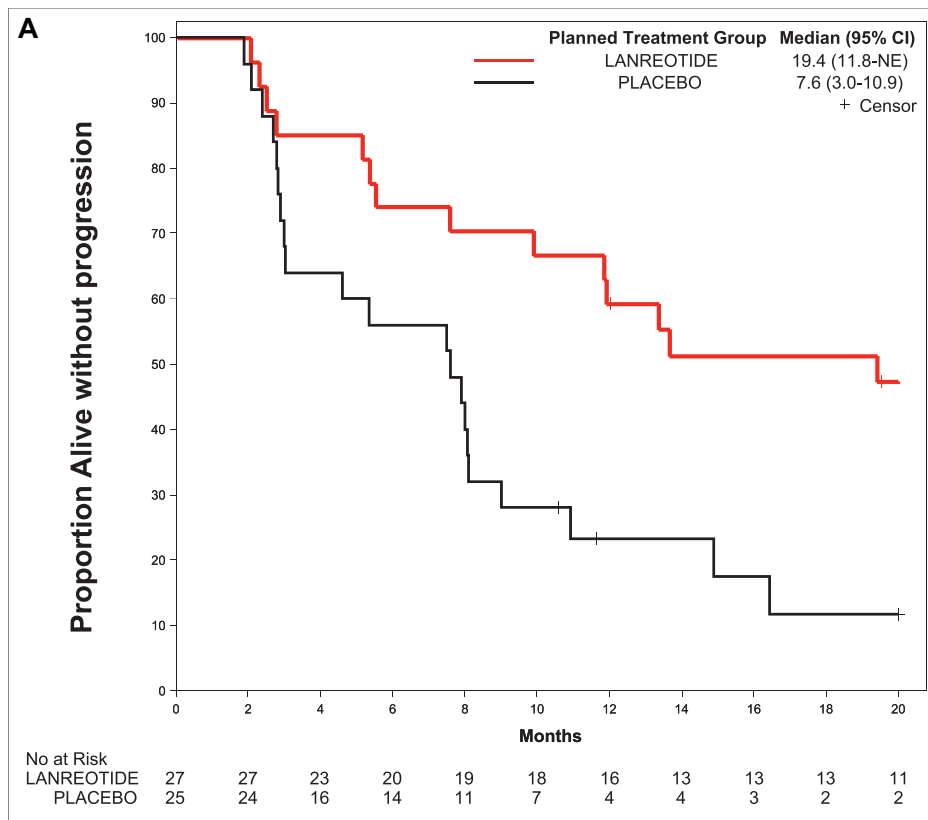


Fig. 2. a: Kaplan–Meier analysis of progression-free survival according to treatment. b: Kaplan–Meier analysis of duration of disease control according to treatment.

Table 3
Adverse events.

Event	Placebo (n = 25)	Lanreotide (n = 27)
Any adverse event	22 (88.0%)	26 (96.3%)
Any adverse event according to intensity [†]		
Severe (grade 3)	5 (20.0%)	9 (33.3%)
Moderate (grade 2)	15 (60%)	20 (74.1%)
Any serious adverse event	3 (12.0%)	5 (18.5%)
Diarrhoea	7 (28.0%)	20 (74.1%)
Abdominal pain	9 (36.0%)	13 (48.1%)
Flatulence	–	2 (7.4%)
Cholelithiasis	1 (3.7%)	–
Injection-site pain	1 (3.7%)	–
Nausea	4 (16.0%)	7 (25.9%)
Vomiting	1 (4.0%)	4 (14.8%)
Headache	4 (16.0%)	2 (7.4%)
Fatigue	7 (28.0%)	8 (29.6%)
Hyperglycaemia	4 (16.0%)	5 (18.5%)

[†] Side effects on LAN or PBO treatment.

Table 4
Baseline and follow-up values for global QoL in Table 4.

		Placebo (N = 24)	Lanreotide (N = 27)
QLQ-C30 – Global	n	24	27
Health Status – Baseline	Mean. (SD)	72.57 (19.27)	67.28 (21.17)
	Median	75.00	66.67
	Q1; Q3	54.17; 83.33	50.00; 83.33
	Min; Max	33.33; 100.00	33.33; 100.00
QLQ-C30 – Global	n	18	19
Health Status – Cycle 4	Mean. (SD)	67.59 (18.72)	72.81 (15.92)
	Median	66.67	75.00
	Q1; Q3	58.33; 83.33	66.67; 83.33
	Min; Max	33.33; 100.00	33.33; 100.00
QLQ-C30 – Global	n	14	18
Health Status – Cycle 7	Mean. (SD)	68.45 (25.77)	72.69 (17.10)
	Median	66.67	75.00
	Q1; Q3	50.00; 100.00	66.67; 83.33
	Min; Max	33.33; 100.00	33.33; 100.00
QLQ-C30 – Global	n	8	16
Health Status – Cycle 10	Mean. (SD)	67.71 (31.63)	71.88 (14.55)
	Median	75.00	75.00
	Q1; Q3	41.67; 95.83	66.67; 79.17
	Min; Max	16.67; 100.00	41.67; 100.00

strategy (using lanreotide autogel 120 mg, every 28 days) in the management of DP-NETs. The results showed that in patients pre-treated with L1 chemotherapy receiving a maintenance treatment until progression or toxicity, the proportion of patients alive without progression at 6 months was 73.1% (90% CI, 55.3–86.6) in the lanreotide arm versus 54.2% (90% CI, 35.8–71.8) in the placebo arm. The safety profile, as well as the quality of life, was good, as expected in patients treated with SSA.

During the past decade, the development of new therapies for NET has brought hope to patients and also led to a step-up treatment strategy, which is a traditional therapeutic approach in most diseases and is still being recommended in current guidelines. However, survival

in patients with metastatic NET is longer than that in other cancers. Chemotherapy treatments achieve the highest response rates but have limited tolerability and affect patients' quality of life. Their use is justified when the disease shows signs of aggressiveness.

The concept of maintenance therapy has been tested in the treatment of unresectable metastatic colorectal and breast cancer. In these patients, after a response or stabilisation following cytotoxic chemotherapy, the cessation of chemotherapy did not decrease PFS or overall survival as compared to PFS and OS in patients who underwent continued treatment until progression [15–17].

This approach allows rest periods for patients who will undergo several lines of treatment and thus improves tolerance and quality of life. In patients with metastatic colorectal cancer, the OPTIMO2 clinical trial [17] tested maintenance therapy or a therapeutic break after six courses of oxaliplatin-based induction treatment resulting in disease stabilisation at least. The induction therapy (oxaliplatin) was reintroduced in both arms in case of progression. The results highlighted the benefits of maintenance therapy as compared with a therapeutic break, as they showed shorter progression-free and overall survival in patients with a complete therapeutic break. Patients' quality of life was excellent in both arms due to well-tolerated treatment.

Moreover, among the mechanisms involved in secondary resistance, the selection of cell clones by chemotherapy seems to play a predominant role [18–20]. In practice, the combination of different drugs is intended to limit these mechanisms [21]. The temporary interruption of cytotoxic chemotherapy could also improve tumour chemo-sensitivity over time, by reducing these phenomena of acquired resistance [21,22]. This concept of maintenance has never been studied in NET, even though it makes a lot of sense in this disease, whose spontaneous prognosis is better than that in most cancers [2]. Maintenance therapy using SSA followed by a retreatment strategy if necessary is ideally suited to the management of DP-NET, as SSAs are both well tolerated and effective for patients with less severe diseases [23]. Finally, another benefit of this strategy is that it does not require hospitalisation since the injections are delivered by a nurse in an outpatient setting. We showed that between-group differences with respect to quality of life were not clinically significant. Our results are in line with the validation of this concept in DP-NET patients.

The major fear related to a maintenance strategy is that it could result in a loss of chance for patients in terms of efficacy as chemotherapy is more effective. This, however, was not the case in our study, which is reassuring. Of course, the response rates obtained with a shortened first line are not so good, but considering the strategy as a whole, including the response rates obtained using the maintenance treatment with LAN, our results are in keeping with the results obtained with

chemotherapy reported in the literature (30–35%) [7,8,24]. For more aggressive diseases (such as NETG3), one could consider extending the induction period until a satisfactory response is obtained before considering the maintenance phase. Moreover, if we consider the total PFS by adding the 4.6 months of L1 treatment, at the end of which the patients were included, to the 11 months of PFS obtained with LAN, we obtain a total PFS 1 of more than 15 months, which is more than that obtained in multichemotherapy studies and close to the results of the Better study (24 months) [25]. Above all, many of these patients will be stabilised again by reintroducing the same L1. This leads us to consider the DDC. Due to the small sample size, this study failed to demonstrate that chemotherapy discontinuation followed by maintenance therapy improves the DDC as compared with chemotherapy discontinuation without maintenance. However, the maintenance strategy was associated with a trend towards improved DDC, PFS and overall survival compared with the strategy involving complete treatment discontinuation. Finally, the number of patients included in the study was small and the types of treatment in the two arms were heterogeneous, making it difficult to draw any further conclusions, and the benefits of the maintenance strategy will have to be confirmed in future studies.

5. Conclusion

In conclusion, we showed that maintenance treatment with SSA is feasible; it reduces treatment toxicity and is associated with a good QoL without compromising patients' outcomes. The encouraging results of lanreotide autogel 120 mg as a maintenance treatment after L1 in aggressive G1/2 DP-NET should be confirmed in future studies.

Data sharing

Prodige 31 REMINET data collection was made possible by the collaboration of 15 centres, all members of the FFCD network. The FFCD declares that the database is open to the scientific and medical community upon request to the cohort steering committee. The FFCD allows and encourages collaboration with other PIs in order to complement data already collected in other databases. All data will be made available (de-identified participant data, participant data with identifiers, data dictionary, or other specified data sets) depending on the collaboration in place. Study protocols, statistical analysis plans, informed consent forms and consortium status are available upon request. Data will be available from now onwards. Proposals should be addressed to Pr. Côme LEPAGE, PI of the study at: come.lepage@u-bourgogne.fr. Pr. LEPAGE will then prepare the dossiers for the steering committee, which

will evaluate the pertinence of the request before sending the database to any academic partners. After agreement of this Steering Committee, data requestors will have to sign a data access agreement to gain access to the database. The FFCD as the sponsor will be vigilant regarding requestors' compliance with the General Data Protection Regulation (GDPR). One aim of such collaborations will be to prepare national or international meta-analyses.

Author contributions

Côme Lepage: Conceptualisation, Investigation, Supervision, Writing- Original draft preparation, Writing - Review and Editing.

Thomas Walter: Conceptualisation, Investigation, Writing- Original draft preparation, Writing - Review and Editing.

Jean Marc Phelip: Investigation, Writing - Original draft preparation, Writing - Review and Editing.

Catherine Lombard-Bohas: Conceptualisation, Investigation, Writing - Review and Editing.

Jean-Yves Scoazec: Conceptualisation, Writing - Review and Editing.

Jean Louis Legoux: Conceptualisation, Investigation, Writing - Review and Editing.

Karine Le Malicot: Methodology, Data curation, Writing- Original draft preparation, Writing - Review and Editing.

Astrid Lievre, Laetitia Dahan, David Tougeron, Christos Toumpanakis, Frederic Di Fiore, Ivan Borbath, Romain Coriat, Thierry Lecomte, Rosine Guimbaud, Caroline Petorin, Pierre Michel, Denis Smith: Investigation, Writing - Review and Editing.

Funding

The Francophone Federation of Digestive Oncology (FFCD), sponsor of the study, is funded by the 'Ligue Nationale Contre le Cancer'.

This work was supported by a French Government grant managed by the French National Research Agency under the program "Investissements d'Avenir" with reference ANR-11-LABX-0021 for a biological ancillary study.

Ipsen supported the study by providing the lanreotide autogel, the placebo and financial support for study management.

Conflict of interest statement

Côme Lepage worked as a member of the advisory board for Novartis, personal fees from Novartis, IPSEN, grants from Merck, IPSEN. Thomas Walter worked as a member of advisory boards for AAA, IPSEN, Keocyt and Novartis. Astrid Lièvre reports

grants from Bayer Lilly, Merck and Novartis; personal fees from AAA, Amgen, Bayer, Bristol-Myers Squibb, Celgene, HaliDx, Incyte, Ipsen, Lilly, Merck, Novartis, Pierre Fabre, Roche, Sandoz, Sanofi and Servier; non-financial support from AAA, Amgen, Bayer, Incyte, Ipsen, Merck, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Servier and Integragen. David Tougeron reports grants from Bristol-Myers Squibb and Novartis; personal fees from Amgen, Bayer, Bristol-Myers Squibb, Ipsen, Novartis, Pierre Fabre, Roche, Sanofi and Servier. Catherine Lombard-Bohas worked as a member of advisory boards for AAA, IPSEN, Keocyt, Novartis. Jean-Louis Legoux worked as a member of an advisory board for Novartis, reports personal fees from Novartis, Pfizer (clinical research), Novartis, Keocyt, Servier (courses, training), Merck, Servier, Keocyt (invitations to national or international congresses). All remaining authors have no conflicts of interest to declare.

Acknowledgements

Thanks to P. Bastable for his kind review.

The study is sponsored by the Fédération Française de Cancérologie Digestive (FFCD), which was responsible for the study management. The authors thank all participating patients already enrolled and their families, and the study groups and investigators from the participating countries.

An ancillary bio-bank is supported by a French Government grant managed by the French National Research Agency under the program “Investissements d’Avenir” with reference ANR-11-LABX-0021, and IPSEN’.

References

- [1] Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 2017;3:1335. <https://doi.org/10.1001/jamaoncol.2017.0589>.
- [2] Lepage C, Rachtel B, Coleman MP. Survival from malignant digestive endocrine tumors in England and Wales: a population-based study. *Gastroenterology* 2007;132:899–904. <https://doi.org/10.1053/j.gastro.2007.01.006>.
- [3] Lepage C, Bouvier AM, Favier J. Endocrine tumours: epidemiology of malignant digestive neuroendocrine tumours. *Eur J Endocrinol* 2013;168:R77–83. <https://doi.org/10.1530/EJE-12-0418>.
- [4] Panzuto F, Boninsegna L, Fazio N, Campana D, Pia Brizzi M, Capurso G, et al. Metastatic and locally advanced pancreatic endocrine carcinomas: analysis of factors associated with disease progression. *J Clin Oncol* 2011;29:2372–7. <https://doi.org/10.1200/JCO.2010.33.0688>.
- [5] de Mestier L, Lepage C, Baudin E, Coriat R, Courbon F, Couvelard A, et al. Digestive Neuroendocrine Neoplasms (NEN): French Intergroup clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, GTE, RENATEN, TEN-PATH, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR). *Dig Liver Dis* 2020;52:473–92. <https://doi.org/10.1016/j.dld.2020.02.011>.
- [6] Pavel M, O’Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 2016;103:172–85. <https://doi.org/10.1159/000443167>.
- [7] Bajetta E, Catena L, Procopio G, De Dosso S, Bichisao E, Ferrari L, et al. Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumours? *Cancer Chemother Pharmacol* 2007;59:637–42. <https://doi.org/10.1007/s00280-006-0306-6>.
- [8] Dussol A-S, Joly M-O, Vercherat C, Forestier J, Hervieu V, Scoazec J-Y, et al. Gemcitabine and oxaliplatin or alkylating agents for neuroendocrine tumors: comparison of efficacy and search for predictive factors guiding treatment choice: GEMOX or alkylating agents for NETs? *Cancer* 2015;121:3428–34. <https://doi.org/10.1002/ncr.29517>.
- [9] Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:501–13. <https://doi.org/10.1056/NEJMoa1003825>.
- [10] Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:514–23. <https://doi.org/10.1056/NEJMoa1009290>.
- [11] Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. *Endocr Relat Cancer* 2016;23:191–9. <https://doi.org/10.1530/ERC-15-0490>.
- [12] Arnold R, Chen Y-J, Costa F, Falconi M, Gross D, Grossman AB, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: follow-up and documentation. *Neuroendocrinology* 2009;90:227–33. <https://doi.org/10.1159/000225952>.
- [13] Lepage C, Dahan L, Bouarioua N, Toumpanakis C, Legoux J-L, Le Malicot K, et al. Evaluating lanreotide as maintenance therapy after first-line treatment in patients with non-resectable duodeno-pancreatic neuroendocrine tumours. *Dig Liver Dis* 2017;49:568–71. <https://doi.org/10.1016/j.dld.2017.02.004>.
- [14] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16:139–44. <https://doi.org/10.1200/JCO.1998.16.1.139>.
- [15] Harris AL, Carmichael J, Farndon J, Dawes P, Ghani S, Evans RGB, et al. Comparison of short-term and continuous chemotherapy (mitozantrone) for advanced breast cancer. *Lancet* 1990;335:186–90. [https://doi.org/10.1016/0140-6736\(90\)90277-C](https://doi.org/10.1016/0140-6736(90)90277-C).
- [16] Labianca R, Sobrero A, Isa L, Cortesi E, Barni S, Nicoletta D, et al. Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised ‘GISCAD’ trial. *Ann Oncol* 2011;22:1236–42. <https://doi.org/10.1093/annonc/mdq580>.
- [17] Chibaudel B, Maindrault-Goebel F, Lledo G, Mineur L, André T, Bennamoun M, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMO2 study. *J Clin Oncol* 2009;27:5727–33. <https://doi.org/10.1200/JCO.2009.23.4344>.
- [18] Landau DA, Tausch E, Taylor-Weiner AN, Stewart C, Reiter JG, Bahlo J, et al. Mutations driving CLL and their evolution in progression and relapse. *Nature* 2015;526:525–30. <https://doi.org/10.1038/nature15395>.
- [19] Amin NA, Seymour E, Saiya-Cork K, Parkin B, Shedden K, Malek SN. A quantitative analysis of subclonal and clonal gene mutations before and after therapy in chronic lymphocytic leukemia. *Clin Cancer Res* 2016;22:4525–35. <https://doi.org/10.1158/1078-0432.CCR-15-3103>.

- [20] Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med* 2012; 366:883–92. <https://doi.org/10.1056/NEJMoa1113205>.
- [21] Swanton C. Intratumor heterogeneity: evolution through space and time. *Cancer Res* 2012;72:4875–82. <https://doi.org/10.1158/0008-5472.CAN-12-2217>.
- [22] Davis A, Gao R, Navin N. Tumor evolution: linear, branching, neutral or punctuated? *Biochim Biophys Acta Rev Cancer* 2017; 1867:151–61. <https://doi.org/10.1016/j.bbcan.2017.01.003>.
- [23] Meng Y, McCarthy G, Berthon A, Dinét J. Patient-reported health state utilities in metastatic gastroenteropancreatic neuroendocrine tumours – an analysis based on the CLARINET study. *Health Qual Life Outcomes* 2017;15:131. <https://doi.org/10.1186/s12955-017-0711-z>.
- [24] Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen D-T, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer* 2011;117:268–75. <https://doi.org/10.1002/cncr.25425>.
- [25] Ducreux M, Dahan L, Smith D, O'Toole D, Lepère C, Dromain C, et al. Bevacizumab combined with 5-FU/streptozocin in patients with progressive metastatic well-differentiated pancreatic endocrine tumours (BETTER trial) – a phase II non-randomised trial. *Eur J Cancer* 2014;50:3098–106. <https://doi.org/10.1016/j.ejca.2014.10.002>.